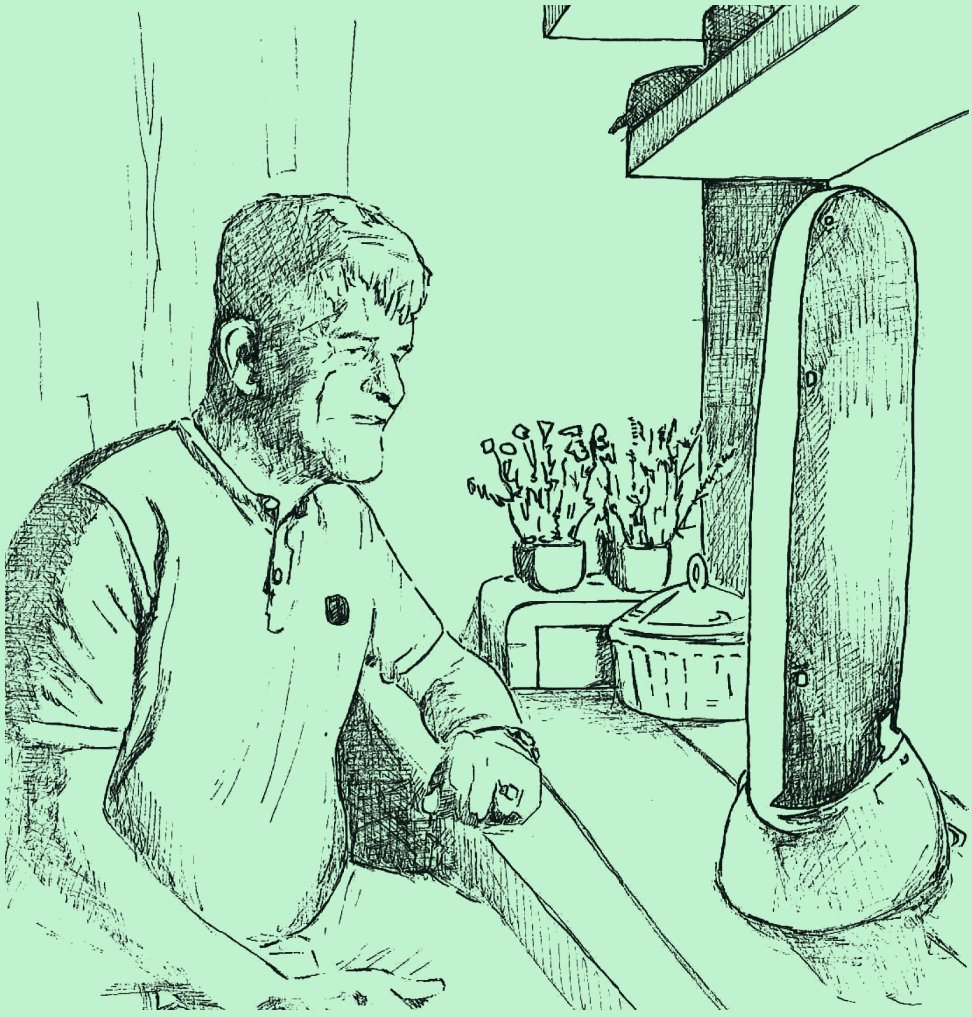
# Shine a light on depressive symptoms in adults with intellectual disabilities

## Diagnostics and non-pharmacological treatment



Pauline Hamers

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# Shine a Light on Depressive Symptoms in Adults with Intellectual Disabilities

## *Diagnostics and Non-pharmacological Treatment*

Depressieve symptomen bij volwassenen met een verstandelijke beperking in de schijnwerpers

*Diagnostiek en niet-farmacologische behandeling*

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# Chapter 1

General introduction

# GENERAL INTRODUCTION

### Healthy ageing and Intellectual disabilities Study (HA-ID study)

In 2008, a large cross-sectional epidemiological study on health and health-related factors in elderly with intellectual disabilities (ID) was started in a consortium of three Dutch health care provider services for adults with intellectual disabilities (Amarant, Ipse de Bruggen and Abrona), and two universities (Erasmus University Medical Center Rotterdam and Groningen University) (1). In this large study, in which 1050 elderly adults (50 years and older) with ID participated, three main themes were investigated: "Physical activity and fitness", "Nutrition and nutritional state", and "Depression and anxiety". Besides these three main themes, research on cardiovascular risk factors, multimorbidity, polypharmacy, frailty, sleep-wake rhythm and a physical activity program was done as well. One of the main goals of the HA-ID study was to expand the knowledge on prevalence and risk factors on these health problems, and the relationships between them. In this way, a clinically relevant inside could be given into the care and support needs for elderly people with ID in the Netherlands. Since the start of the HA-ID study, an impressive number of international articles has been published, and the study has provided important results to further improve the care for elderly with an intellectual disability. Research outcomes of the "Depression and anxiety" theme (2), form the basis of my thesis.

### Depressive symptoms in adults with ID

In the population of adults with ID, the point prevalence of Major Depressive Disorder (MDD) is high (up to 8%) (3-6). In the large cohort study (n=1023) of Cooper et al. (2007), point prevalence rates of adults with affective disorder ranged from 3.6% to 6.6%, depending on the different used diagnostic criteria (7). In the HA-ID study, it was shown that 16.8% (95% CI: 14.4–19.1) of the elderly participants had elevated depressive symptoms, and 7.6% (95% CI: 5.2–11.0) of the participants could be diagnosed with MDD (8). Besides elevated depressive symptoms, 16.3% (95% CI: 14.0–18.6) of the participants had increased anxiety symptoms of whom 4.4% (95% CI: 2.6–7.0) could be diagnosed with an anxiety disorder (8). Furthermore, almost 8% (95% CI: 6.1–9.5) of the participants had elevated depressive symptoms as well as elevated symptoms of anxiety (8). In the population of adults with ID, depressive

symptoms are positively associated with age (8, 9), chronic diseases (9) and increased anxiety symptoms (9). Depressive symptoms are also more prevalent in adults with moderate ID compared to other levels of ID (10). Adults with ID and depressive or anxiety symptoms experience significantly more life events compared to those without these symptoms (11). Furthermore, Hermans and colleagues (2012) found that almost all elderly with ID experienced two or more life events in the past year, and 72% of this group experienced one or more negative life events in that same year (11).

**Difficulties in recognizing depressive symptoms in adults with ID**

Depression has a negative impact on the quality of life (12-19) and therefore, it is essential to recognize depressive symptoms. Previous research showed that depressive symptoms are often not recognized in adults with ID, leading to an underestimation in clinical practice (8, 20, 21). The HA-ID study showed that only 37.5% of the MDD diagnoses during the study were previously reported by clinicians (8). This means that almost two-thirds of the participants with a MDD were not previously recognized. In clinical practice, depressive symptoms can be hard to recognize in adults with ID because depressive symptoms can be presented in a different way compared to those in the general population. The verbal and cognitive limitations in adults with ID make recognizing depressive symptoms challenging, because a part of the population of adults with ID cannot recognize and/or express their (changing) thoughts and feelings, or communicate about physical and mental complaints. Consequently, a large part of adults with ID and depressive symptoms must depend on their caregivers to notice their depressive symptoms and other physical and mental complaints. Consequently, diagnoses of MDD are missed, and these patients are not treated for their mental illness. Specific clinical characteristics of depression presented in adults with ID are signs of irritability, challenging behavior, withdrawal from social interactions and crying (20, 22, 23). In addition, these expressions of symptoms can vary between the different levels of impairment (24). These specific characteristics in adults with ID are not part of the diagnostic criteria for depression, such as defined in the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (25). These specific characteristics can be found in the adapted criteria and accompanying notes of MDD as described in the Diagnostic Manual-Intellectual Disability 2 (DM-ID-2) (26).

### Measuring depressive symptoms in adults with ID

Reliable and valid instruments for depressive symptoms are necessary to recognize depression and measure depressive symptoms in adults with ID. In clinical practice, the use of a questionnaire for depressive symptoms can help to identify those who need further diagnostic evaluation. Further, reliable and valid instruments can also be used to evaluate the effectiveness of treatment of depressive symptoms in individual patients, when used pre and post intervention. In the past few years, more attention has been paid to developing and studying instruments to screen for depressive symptoms in adults with ID (27-31), but there are still some gaps. In 2012, the Dutch translation of the Anxiety, Depression And Mood Scale (ADAMS) was studied as part of the HA-ID study (27). This instrument, specifically developed for the ID-population, was originally developed by Esbensen and colleagues in 2003 (30). The Dutch ADAMS is found to be a reliable and valid instrument to screen for depression and anxiety symptoms in elderly with ID, but was not investigated in adults with ID younger than 50 years of age (27).

### (non-) Pharmacological treatment of depressive symptoms in adults with ID

Depressive symptoms are usually treated with antidepressants, mainly Selective Serotonin Reuptake Inhibitors (SSRI) and tricyclic antidepressants (TCA) (32, 33). In the HA-ID study, 10% of the participants used antidepressants (8). The indication for the prescription of these antidepressants was not described, so it is possible that these antidepressants were prescribed for other clinical symptoms such as anxiety. A retrospective study showed that half of adults with ID benefit from antidepressants, which were often used in combination with other psychotropic drugs (33). Antidepressants were used for a variety of diagnoses, but primarily for depression, generalized anxiety disorder or obsessive-compulsive disorder (33). A systematic literature review showed that the effect of antidepressants in adults with ID is low, but the amount of adverse events is high (34). In the included studies of this review, antidepressants were prescribed for various reasons: depressive symptoms, problem behavior, stereotype and repetitive behavior, compulsive behavior and self-injurious behavior. Given the high number of polypharmacy, side effects and interaction effects, pharmacological treatment is not always desirable (35-37). Besides, finding the most suitable antidepressant and dosage to treat depressive symptoms in adults with ID

can be difficult, because not all adults with ID can communicate about treatment and/or adverse effects.

In clinical practice, (adapted) Cognitive Behavioral Therapy is sometimes used to treat depressive symptoms, predominantly in the sub-population of adults with ID with minor verbal and intellectual limitations. A meta-analysis on this kind of treatment showed moderate effect sizes in adults with mild or moderate ID and depressive symptoms, and overall more effect with individual therapy than with group-based therapy (38). A recent study on behavioral activation and self-help for depression in adults with mild ID showed that both interventions decreased depressive symptoms, but unfortunately, a control group was lacking (39). In general, there are limited non-pharmacological treatment options known in clinical practice for adults with ID and depressive symptoms that are effective. Therefore, a systematic review of all non-pharmacological interventions to treat depressive symptoms in adults with ID was needed.



**Light and Bright Light Therapy in the general population**

In the general population, depression is associated with circadian rhythm disturbances (40-44). Particularly, the sleep-wake cycle and hormone cycles are frequently disturbed in adults with depressive symptoms (40-42, 45). These circadian rhythms are regulated by biological clocks in our body and our master biological clock, the suprachiasmatic nucleus (SCN), which is located in our brain (46, 47). Light (via retinal input) has a major impact on this master biological clock in the SCN, and therefore influences the circadian rhythms (44, 47). Although recent research in mice showed that the effect of light (via retinal input) on mood, can also take place independently of the SCN (48). It was shown that not the SCN, but the perihabenular nucleus in the brain region of the thalamus was involved in regulating mood via light (48).

The impact of light on (mental) health is not a novel concept. Already in previous centuries, the influence of light has been associated with influencing (mental) health and circadian rhythms (49). For example, ancient Egyptians, Chinese and Indians used light in the treatment of many diseases, including psychosis (50). In the 1980s, the use of bright light to treat depressive symptoms in seasonal depression was studied for the first time (51-53). Nowadays, Bright Light Therapy (BLT) is widely studied and

proven to be effective in the general population, both in patients with seasonal and non-seasonal depression (54-58). Although it is not yet clear to what amount of daily light people with (mental) health problems are generally exposed. It is possible, for example, that people with (mental) health problems are less exposed to light during the day because they spend more time indoors than people without (mental) health problems. Another question is if there is an association between natural light exposure during the day, mood and/or sleep problems. Therefore, this topic needed to be further investigated to fill this gap in knowledge.

**Light and Bright light therapy in adults with ID**

Studies regarding the influence of natural light on (mental) health in adults with ID are lacking. Generalization of the results of light and BLT studies of the general population to the population of adults with ID is not possible. The reason lies in the working mechanism of BLT, which is located in the brain. Patients with ID have congenital brain malformations or brain damage which caused the ID, and as a result may respond differently to BLT. Other factors in lives of adults with ID may also contribute to a different response on BLT. For example, the amount of time spent outside in daylight. Adults with ID are often dependent on their caregiver to go outside, and therefore may be exposed to less natural daylight during the day than adults of the general population. Another factor are circadian sleep-wake disturbances in adults with ID. These sleep-wake disturbances occur frequently in this population, even more frequent than in the general population, and these sleep-wake disturbances are, like in the general population, associated with depression (59, 60). As BLT influences the release of the hormone melatonin in the brain, which has influence on the sleep-wake rhythm, BLT may therefore have a different effect in adults with ID.

In the population of adults with ID, the use of BLT was first described in 1998 by Cooke & Thomson (61), followed by two other papers containing case reports (62, 63). These case reports showed that depressive symptoms decreased after BLT, which lead to a pilot feasibility study of BLT in adults with ID and depressive symptoms by Hermans and colleagues (64). In this pilot study (n=14), feasibility of BLT in adults with (moderate, severe or profound) ID was good, and BLT decreased the level of depressive symptoms in six of nine participants who scored above the clinical cut-off point prior to BLT (64). These positive results, but also the lack of a control group and the small sample size

of the pilot study, made it essential to further investigate this non-pharmacological intervention to decrease depressive symptoms in adults with ID. Especially for those with a severe or profound ID, as there are little alternative treatments to decrease depressive symptoms in this group. A multicenter randomized controlled study was needed to expand the knowledge on the use of BLT to treat depressive symptoms in the population of adults with ID.



**Depression and stress**

Besides associations with circadian rhythm disturbances, depressive symptoms are also associated with life events and stress. This applies for patients with and without ID (11, 65-68). In the field of endocrinology, scalp hair cortisol concentrations (HCC) are used as a biomarker to retrospectively examine stress in patients (69-73). This non-invasive reliable and valid method can measure integrated long-term glucocorticoids (74-76). Studies in the general population have shown associations between depressive symptoms and HCC. These results are inconclusive, as both positive and negative associations were found (72). As far as we know, HCC had not previously been studied in adults with ID. In the general population, BLT appears to influence the level of cortisol (57, 77, 78), but this was also not yet investigated in the population of people with ID. Research into this type of biomarkers in the population of adults with ID is of great importance, because in this way, subjective complaints on stress that are difficult to identify in this population can be partially objectified. Therefore, research on this topic was needed to expand our knowledge about the use of hair glucocorticoids (cortisol and cortisone) as a biomarker to retrospectively examine stress in adults with ID.

## STUDY AIMS AND OUTLINE OF THIS THESIS

For clinical practice, it is essential that there are valid and reliable questionnaires to detect depressive symptoms in adults with ID. These instruments will contribute to better recognition of depressive symptoms in this population. With better recognition, more adults with a depression will get proper treatment. If appropriate, these instruments can be used to monitor the effectiveness of antidepressant interventions as well. In the Netherlands, there was a lack of instruments for adults below 50 years of age. Therefore, the first aim of this thesis was to investigate the reliability and validity

of the Dutch Anxiety, Depression And Mood Scale (ADAMS) in adults aged <50 years with intellectual disabilities. The ADAMS can now be used in the whole Dutch adult ID population. This reliability and validity study of the ADAMS is described in **Chapter 2.** The second aim of this thesis was to investigate the associations between light exposure during the day, mood and sleep in adults with (mental) health problems. This was studied with a systematic review and described in **Chapter 3.** Although depressive symptoms can be treated with antidepressants, this is not always the most desirable method. The third aim of this thesis was to expand the knowledge on non-pharmacological interventions for adults with intellectual disabilities and depressive symptoms. We investigated this with a systematic review, and the results are discussed in **Chapter 4**. In the next chapter, **Chapter 5**, the study protocol of our multicenter randomized controlled trial for bright light therapy in adults with intellectual disabilities and depressive symptoms is described. In this chapter, we also give an overview of the obstacles we faced during the preparation and execution of our study, and how we tried to manage these obstacles. As mentioned above, we aimed to improve the recognition of depressive symptoms in adults with ID. But when those symptoms are recognized, the number of possibilities to treat these depressive symptoms in the population of adults with ID is rather small, especially in those with severe ID. In **Chapter 6**, we present the results of our multicenter randomized controlled trial to treat depressive symptoms in adults with ID. With this study we want to expand the knowledge on a potential intervention to decrease depressive symptoms in adults with ID, including those with severe ID. In **Chapter 7**, we explored the use of hair glucocorticoids in adults with intellectual disabilities and depressive symptoms. In this study, we examined the associations between hair glucocorticoids and depressive symptoms, and co-morbid anxiety symptoms. Besides, we investigated the influence of light therapy on hair glucocorticoids. In the general discussion, **Chapter 8**, we reflect on the main findings of this thesis. Implications for clinical practice and directions for future research are discussed.

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# Chapter 2

## Reliability and validity of the Dutch Anxiety, Depression And Mood Scale in adults aged <50 years with intellectual disabilities

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## ABSTRACT

**Background:** Reliable and valid screening instruments for depression and anxiety are needed for adults with intellectual disabilities (ID).

**Methods**: Internal consistency (n=198), interrater reliability (n=41), test-retest reliability (n=37) and criterion validity (n=43) were studied. Internal consistency was also studied in a sample with epilepsy (n=98).

**Results:** Internal consistencies of the Dutch ADAMS total scale and subscales were satisfactory to good (α: 0.76 to α: 0.92). Internal consistency in the subgroup with epilepsy was satisfactory to good (α: 0.74 to α: 0.88). Interrater reliability and test-retest reliability were fair to excellent for the total scale (ICC's: 0.57-0.84) and subscales (ICC's: 0.43 – 0.86). The criterion validity of the Dutch ADAMS Depressive Mood subscale was good with a sensitivity of 88% (95% CI: 53%-98%) and a specificity of 80% (95% CI: 64%-90%).

**Conclusions:** The Dutch ADAMS is a reliable and valid instrument and can be used in research and clinical practice in adults with ID.

## INTRODUCTION

In the population of adults with intellectual disabilities (ID), the prevalence of depression ranges from 2.2% to 8.3% and the prevalence of anxiety disorders varies from 1.7% to 7.8%, depending on the study population and which (clinical) diagnostic criteria are used (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Deb, Thomas, & Bright, 2001; Hermans, Beekman, & Evenhuis, 2013; Elita Smiley, 2005; E. Smiley et al., 2007). Depressive symptoms can be hard to recognize and are often missed in people with ID (Hermans et al., 2013). Limited cognitive and verbal abilities make diagnosing depression challenging. Therefore, accurate screening and diagnostic instruments, specifically developed for the ID population, are important to detect depressive symptoms and also to monitor the effectiveness of interventions. Unfortunately, the number of reliable and valid screening instruments to detect psychopathology, such as depression, in the adult ID population is limited (Hermans & Evenhuis, 2010; Matson, Belva, Hattier, & Matson, 2012).



Having epilepsy is associated with an even higher prevalence of depressive symptoms in adults with ID (van Ool et al., 2016). Moreover, Van Ool and colleagues suggest that more severe epilepsies are risk factors for behavioral problems and psychiatric disorders (van Ool et al., 2016). Depressive and anxiety symptoms may result from epilepsy due to seizure-related or psychosocial factors, such as increased dependence, experienced stigma, restrained activity, and poor seizure control (Peterson, Walker, & Shears, 2014; Reisinger & Dilorio, 2009), or may come from the same underlying neurobiological mechanism (Kanner et al., 2012). Depression in patients with epilepsy seems under-diagnosed (Kanner, 2006) and depressive symptoms may be partly hard to distinguish from epilepsy related symptoms, such as fatigue and concentration problems. Therefore, proper screening instruments for adults with ID and comorbid epilepsy are needed as well.

In 2003, Esbensen and colleagues published the Anxiety, Depression And Mood Scale (ADAMS) which is specifically developed for the ID population (Esbensen, Rojahn, Aman, & Ruedrich, 2003). Hermans and colleagues investigated the reliability and validity of the Dutch translation in adults with ID aged 50 years and older (Healthy Ageing and Intellectual Disabilities Study, HA-ID study) (Hermans, Jelluma, van der

Pas, & Evenhuis, 2012). The authors concluded that the feasibility, test-retest reliability and internal consistency of the Dutch translation of the ADAMS are fair to good, with exception of a poor interrater reliability of the Social Avoidance subscale in the borderline/mild ID subgroup. The clinical manual of the Dutch ADAMS was published in 2013 including new data and reordered subscales (Hermans & Evenhuis, 2013). Nowadays, this version of the Dutch ADAMS is used in many different care provider services of people with ID in the Netherlands. As the HA-ID study focused on people of 50 years and older, no conclusions can be drawn about the reliability and validity of the Dutch ADAMS within a younger adult population (18-49 years). Therefore, the aim of this study is to investigate the validity and reliability of the Dutch ADAMS in adults with ID in a sample of adults younger than 50 years of age.

## METHODS

### Study population

Participants were recruited by behavioral scientists, psychologists and physicians of different care provider services for adults with ID in in the Netherlands. The only exclusion criterion of this study was age below 18 or above 49 years. The legal guardians of the participants gave informed consent to participate if the participant was not able to give informed consent. Adapted information letters were used for the people with ID who gave permission themselves. The questionnaires were completed by professional caregivers of the participants who knew the participants for at least 3 months. The Medical Ethical Testing Committee of the Erasmus University Medical center concluded that the rules laid down in the Dutch Medical Research Involving Human Subjects Act (WMO) do not apply to the current study (MEC-2015-587 and MEC-2016-408).

### Instrument characteristics

*ADAMS*

The Anxiety, Depression And Mood Scale (ADAMS) is a by proxy instrument for adults with ID (Esbensen et al., 2003). This instrument consists of 28 items (4-point scale) and five subscales ('Manic/Hyperactivity Behavior', 'Depressive Mood', 'Social Avoidance', 'General Anxiety' and 'Obsessive/Compulsive behavior'). The minimum total score is 0 and the maximum score is 84.

In 2012, the ADAMS was translated into Dutch and feasibility, reliability and validity of the Dutch version of the ADAMS was studied as part of the HA-ID study (Hermans et al., 2012). In total, 975 participants of 50 years and older were screened with the ADAMS. Internal consistency was tested in a sample of 127 participants and was good (Cronbach's alpha 0.80-0.88 for the five different subscales). Test-retest reliability was tested in a sample of 93 participants and was good as well (ICC total ADAMS: 0.83, ICC subscales: 0.75-0.86). The test-retest reliability of the total score and subscales was also studied in different subgroups based on level of ID. Good test-retest reliability was found in all level of ID subgroups, with exception of a fair test-retest reliability in the severe/profound ID group (0.52, 95% CI: 0.11-0.78). Interrater reliability, measured in a sample of 83 participants, was fair to good for all subscales (ICC total ADAMS: 0.76, ICC subscales: 0.57-0.78). Interrater reliability was fair to good for all levels of ID subgroups except for the borderline/mild ID subgroup where a poor interrater reliability was found (0.38, 95% CI: 0.02-0.66). Criterion validity of the ADAMS Depressive Mood Subscale was tested in a sample of 288 participants by studying the sensitivity and specificity rates compared to the outcome of the PAS-ADD interview (Moss, 2011). Sensitivity and specificity ranged from sufficient to good (Hermans et al., 2012).



After the study of Hermans et al. was published in 2012, more data has been collected in clinical practice. In 2013, Hermans and colleagues published the manual of the Dutch ADAMS which included this new data (Hermans & Evenhuis, 2013). In response to an explorative factor analyses and to what extent a subscale is indicative of a depression or anxiety disorder, the 'Depressive Mood' subscale was extended with six items, the 'Manic/Hyperactivity Behavior' and 'Obsessive/Compulsive behavior' subscales have been removed and a subscale labeled 'Other problems' has been added. The anxiety subscale and social avoidance subscale are unchanged. The current 'Depressive Mood' subscale covers the following topics: 'Sleeps more', 'Depressed', 'Sad', 'Worried', 'Attention', 'Fatigued', 'Lacks energy', 'Distracted', 'Facial expression', 'Starting routine tasks', 'Listless', 'Trembles' and 'Tearfull'. The Anxiety subscale includes the original topics: 'Nervous', 'Does not relax', 'Tense', 'Worried', Anxious', 'Panic attacks' and 'Trembles'. As the previous subscale, the 'Social Avoidance' subscale covers the same topics as the original subscale: 'Communication', 'Withdraws', 'Shy', 'Avoids others', 'Facial expression', 'Avoids eye contact', 'Avoids peers'. The fourth subscale of the Dutch ADAMS, 'Other Problems', consists of some items included in

the 'Manic/Hyperactive Behavior' and the 'Compulsive Behavior' subscales of the original ADAMS complemented by other items. The following topics are included in the 'Other Problems' subscale of the Dutch ADAMS: 'Communication', 'Overactive', 'Ritualistic behavior', 'Attention', 'Checker', 'Distracted', 'Rituals', 'Facial Expression', 'Starting routine tasks', 'Panic attacks', 'Avoid eye contact'.

*PAS-ADD*

The Psychiatric Assessment Schedule for Adults with Developmental Disability (PAS-ADD) is a semi-structured clinical interview which provides full diagnoses under both ICD-10 and DSM-IV (TR) for several disorders, including depression and anxiety disorders (Moss, 2011). The PAS-ADD can be used for the patient, as well as with an informant when the patient's language or verbal level is poor (Moss, 2011). The test-retest and interrater reliability analysis of the PAS-ADD show moderate to high kappa values (Gonzalez-Gordon, Salvador-Carulla, Romero, Gonzalez-Saiz, & Romero, 2002). The PAS-ADD has a good interrater reliability as well (mean Kappa of 0.65 for individual items) (Costello, Moss, Prosser, & Hatton, 1997). Criterion validity of the PAS-ADD was investigated with psychiatric diagnoses of experts. The validity of the PAS-ADD in relation to depressive symptoms was good (Moss et al., 1997) .

**Procedure**

After informed consent, the main professional caregiver of the participant was asked to fill out the Dutch ADAMS (baseline, T1, n= 198). For the participants in sample A, a second professional caregiver of the participant was asked to fill out the Dutch ADAMS at baseline as well, independent of the main professional caregiver (interrater reliability sample). In sample A, the main professional caregiver was also asked to fill out the Dutch ADAMS four weeks after baseline (T2) (test-retest sample). Further, a random part (n= 43) of sample A was assessed with the PAS-ADD interview as well (only the Depression section). Personal characteristics (gender, age, level of ID) and type of care setting of the participants were retrieved from the personal files. The interrater reliability, test-retest reliability and criterion validity were not studied at the tertiary epilepsy center (sample B).

**Statistical analyses**

For the reliability analyses, we calculated that the sample size must be at least 39 participants (minimal 95% confidence interval (CI)) (Esbensen et al., 2003; Hermans et al., 2012; Walter, Eliasziw, & Donner, 1998). In order to be able to examine the reliability for subgroups based on the degree of ID (mild, moderate, severe/profound), we needed at least 117 participants. IBM SPSS Statistics version 22 was used to perform the statistical analyses with a significance level of $\alpha = 0.05$. Differences on baseline in means of the total Dutch ADAMS score and four Dutch ADAMS subscales were studied in the whole sample with t-tests for gender and two age groups (18-34 and 35-49) and with One-way ANOVA for level of ID. Differences between sample A and sample B were studied with Pearson's Chi-square tests for independence for gender, the two age groups and level of ID. The Yates Continuity Correction is used with 2 by 2 tables. Besides, we used a two-way between-groups ANOVA to explore the impact of two independent variables (level of ID and sample A/B) on the total Dutch ADAMS score.



Pearson's Chi-square tests for independence were used to study if the three subsamples (the interrater reliability sample, test-retest reliability sample and criterion validity sample) are representative for sample A. The Yates Continuity Correction is used with 2 by 2 tables. The following characteristics of the participants were used to determine representativeness: gender, age and level of ID. Our hypothesis was that the participants in sample A and the interrater reliability, test-retest reliability and criterion validity are not significantly different.

Cronbach's alpha was used to analyze internal consistency of the Dutch ADAMS (total scale and the subscales). Correlations below 0.40 are considered to be poor, between 0.40 and 0.59 fair and between 0.60 and 0.74 are considered as good. Excellent correlations are those above 0.75 (Cicchetti & Sparrow, 1981). With item analysis we studied if one or more items decreased the internal consistency. Test-retest reliability was used to measure stability and reliability of the Dutch ADAMS over time. Intraclass Correlation Coefficients (ICCs) were used to examine if professional caregivers scores were correlated. The scores of the Dutch ADAMS can be influenced by an occurrence of a major event. If a major event occurred between T1 and T2, the scores of the participant were not included into the analyses. To measure the interrater reliability, the T1 scores of the main professional caregiver and the second professional caregiver

were examined. ICCs were used to measure the interrater reliability. Both test-retest reliability and interrater reliability were measured for the total test-retest and interrater reliability samples as well as for subgroups (mild ID, moderate ID and severe / profound ID). The criterion validity of the Dutch ADAMS Depressive mood subscale was studied with sensitivity and specificity rates. The PAS-ADD interview (Depression section) was used as the reference standard.

## RESULTS

### Participants characteristics

The total study population consisted of 198 adults aged between 18 - 49 years with mild, moderate, severe or profound ID and were recruited from different care provider services in the Netherlands. The participants of sample A (n=100) lived in different care provider services for people with ID. The participants of sample B (n=98) lived in residential facilities of a tertiary epilepsy center. All the participants of sample B had epilepsy. Details of the participants characteristics can be found in Table 1.

In the total sample (n=198), we did not find significant differences in mean total score and subscale scores for gender, age and level of ID. There were no significant differences in gender and age between sample A and sample B. There were significant differences in level of ID between sample A and sample B: less participants with mild ID and more participants with profound ID were included in sample B. The interaction effect between group (sample A/B) and level of ID was not significant ($p = 0.10$). A significant main effect was found for 'group' ($p = 0.027$), but the effect size was small (partial eta squared = 0.03). The main effect of level of ID was not significant ($p = 0.632$).

### Representativeness

*Interrater reliability sample*

No significant differences in gender ($p = 0.566$) and age ($p = 0.416$) between sample A and the interrater reliability sample were found. There were significant differences in level of ID ($p = 0.000$), because no adults with mild ID were included in the interrater reliability sample.

**Table 1.** Participants characteristics

| | Total sample n= 198* | Sample A n= 100 | Sample B n= 98 | Interrater reliability sample** n= 41 | Test-retest reliability sample** n= 37 | Criterion validity sample** n= 43 |
|---|---|---|---|---|---|---|
| Gender | | | | | | |
| Male/female | 108/90 | 51/49 | 57/41 | 19/22 | 25/12 | 17/26 |
| Age (%) | | | | | | |
| 18-34 | 97 (49.0) | 50 (50.0) | 47 (48.0) | 18 (43.9) | 18 (51.4) | 19 (44.2) |
| 35-49 | 101 (51.0) | 50 (50.0) | 51 (52.0) | 23 (56.1) | 19 (48.6) | 24 (55.8) |
| Level of ID (%) | | | | | | |
| Mild ID | 44 (22.2) | 28 (28.0) | 16 (16.3) | 0 (0.0) | 13 (35.1) | 9 (20.9) |
| Moderate ID | 46 (23.2) | 21 (21.0) | 25 (25.5) | 11 (26.8) | 8 (21.6) | 11 (25.6) |
| Severe ID | 57 (28.8) | 30 (30.0) | 27 (27.6) | 18 (43.9) | 13 (35.1) | 12 (27.9) |
| Profound ID | 41 (20.7) | 11 (11.0) | 30 (30.6) | 11 (26.8) | 2 (5.4) | 11 (25.6) |
| Unknown | 10 (5.1) | 10 (10.0) | 0 (0.0) | 1 (2.4) | 1 (2.7) | 0 (0.0) |
| Residential setting (%) | | | | | | |
| Central location | 129 (65.2) | 53 (53.0) | 76 (77.6) | 41 (100) | 25 (67.6) | 32 (74.4) |
| Community-based | 33 (16.7) | 15 (15.0) | 18 (18.3) | 0 (0.0) | 7 (18.9) | 8 (18.6) |
| Independent with support | 12 (6.1) | 8 ( 8.0) | 4 (4.1) | 0 (0.0) | 5 (13.5) | 3 (7.0) |
| Unknown | 24 (12.1) | 24 (24.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Epilepsy (%) | | | | | | |
| Diagnoses of epilepsy | 98 (49.5) | 0 (0.0) | 98 (100.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Epilepsy data not collected | 100 (50.5) | 100 (100.0) | 0 (0.0) | 41 (100.0) | 37 (100) | 43 (100) |

* Total sample = sample A + sample B, ** Part of sample A.

*Test-retest reliability sample*

There was a significant difference in gender (less women) (p = 0.020) and no significant differences in age (p= 1.000) and level of ID (p = 0.418) between sample A and the test-retest reliability sample.

*Criterion validity sample*

There were no significant differences in gender (p = 0.073) and age (p = 0.419) between sample A and the criterion validity sample. Significant differences were found in level of ID between sample A and the criterion validity sample (p = 0.001) due to less adults with mild ID and more adults with profound ID in the criterion validity sample.

### Reliability

In the total sample (n=198), the alpha coefficient of the total Dutch ADAMS scale was 0.91. The alpha coefficients of the four subscales ranged from 0.76 to 0.87. The internal consistency was also calculated for sample A. The alpha coefficient of the total Dutch ADAMS scale in sample A was 0.92. The alpha coefficients of the four subscales of sample A ranged from 0.77 to 0.90. The internal consistency was calculated for the subgroup with epilepsy as well (sample B). The alpha coefficient for the total Dutch ADAMS in this subgroup was 0.88 and the alpha coefficient for the four subscales ranged from 0.74 to 0.84. Details of the internal consistency results can be found in Table 2. For the interrater reliability, 41 second professional caregivers also completed the Dutch ADAMS at baseline. The interrater reliability of the total Dutch ADAMS was 0.64 (ICC; 95% CI: 0.42 -0.79). The interrater reliability of the four subscales ranged from 0.64 to 0.77. Interrater reliability was also measured for the different levels of ID. These, and the details of the overall interrater reliability, are presented in Table 2.

To measure the stability and reliability of the Dutch ADAMS over time (test-retest reliability), professional caregivers completed the Dutch ADAMS at T1 and T2. Sixteen participants who experienced major life events between T1 and T2 were not included into the test-retest analyses, resulting in a sample of 37 participants. The test-retest period (T1-T2) ranged from 27 to 72 days. The test-retest reliability of the whole Dutch ADAMS was 0.71 (ICC; 95% CI: 0.51-0.84). The test-retest reliability of the four subscales varied from 0.72 to 0.79. The details of the test-retest reliability of the Dutch ADAMS, as well as the results in the level of ID subgroups, can be found in Table 2.

**Table 2.** Reliability of the Dutch ADAMS

| | Total Dutch ADAMS | Depressive mood | Anxiety | Social Avoidance | Other Problems |
|---|---|---|---|---|---|
| **Total sample (n=198)** | | | | | |
| Mean score (SD) | 24.69 (14.24) | 10.95 (7.88) | 6.28 (4.48) | 5.34 (4.26) | 10.07 (5.88) |
| Min-max score | 0- 69 | 0-34 | 0-20 | 0-19 | 0-24 |
| **Internal consistency** (Cronbach's alpha) | | | | | |
| Total Sample (n=198) | 0.91 | 0.87 | 0.83 | 0.80 | 0.76 |
| Sample A (n=100) | 0.92 | 0.90 | 0.84 | 0.81 | 0.77 |
| Sample B (n=98) | 0.88 | 0.84 | 0.76 | 0.77 | 0.74 |
| **Interrater reliability *** | | | | | |
| (ICC (95% CI)) n= 41** | 0.64 (0.42 -0.79) | 0.77 (0.61 -0.87) | 0.64 (0.42 -0.79) | 0.69 (0.49 -0.82) | 0.66 (0.45 -0.81) |
| Moderate ID (n= 11) | 0.70 (0.19 -0.91) | 0.68 (0.17 -0.90) | 0.78 (0.35 -0.93) | 0.59 (0.01 -0.87) | 0.74 (0.28 -0.93) |
| Severe/profound ID (n= 29) | 0.57 (0.28 -0.77) | 0.81 (0.64 -0.91) | 0.49 (0.16 -0.72) | 0.60 (0.31 -0.79) | 0.62 (0.34 -0.80) |
| **Test-Retest reliability*** | | | | | |
| (ICC (95% CI)) n=37** | 0.71 (0.51 -0.84) | 0.72 (0.52 -0.84) | 0.75 (0.57-0.87) | 0.79 (0.63 -0.89) | 0.72 (0.53 -0.85) |
| Mild ID (n=13) | 0.64 (0.15 -0.87) | 0.59 (0.07 -0.86) | 0.77 (0.41 -0.92) | 0.61 (0.11 -0.87) | 0.43 (-0.17 -0.79) |
| Moderate ID (n=8) | 0.59 (-0.11 -0.90) | 0.82 (0.35 -0.96) | 0.58 (-0.20 -0.90) | 0.52 (-0.15 -0.88) | 0.75 (0.22 -0.94) |
| Severe/profound ID (n=15) | 0.84 (0.58 -0.94) | 0.75 (0.40 -.90) | 0.85 (0.61 -0.95) | 0.86 (0.63 -0.95) | 0.85 (0.60 -0.95) |

* Analyzed in sample A, ** one participant's level of ID is missing.

### Validity

The criterion validity was studied in a sample of 43 participants. A cut-off score of ≥14 on the Depressive Mood subscale was used for the sensitivity and specificity analyses based on the manual of the Dutch ADAMS (Hermans & Evenhuis, 2013). When a participant was diagnosed with a major depressive disorder (MDD) according to the DSM criteria of the PAS-ADD clinical interview, this participant was marked as 'positive' on the PAS-ADD. When a participant did not reach the required number of symptoms on the PAS-ADD clinical interview to be diagnosed with a MDD, the participant was marked as 'negative' on the PAS-ADD. Of the 43 participants, 28 participants scored 'negative' on the PAS-ADD clinical interview as well as on the ADAMS Depressive Mood subscale (true negatives). Seven out of the 43 participants scored 'positive' on the PAS-ADD clinical interview (MDD diagnosed) and also positive on the ADAMS Depressive Mood subscale (true positives). Seven out of the 43 participants were not diagnosed with an MDD according to the PAS-ADD clinical interview, but scored above the cut-off point of the ADAMS Depressive Mood subscale (false positives). One out of the 43 participants had a MDD according to the PAS-ADD clinical interview, but did not have a score above the cut-off point of the ADAMS Depressive Mood subscale (false negative).

The sensitivity of the Dutch ADAMS Depressive Mood subscale is 88% (95% CI: 53%-98%). The specificity of the Dutch ADAMS Depressive Mood subscale is 80% (95% CI: 64%-90%). As the criterion validity sample is small, sensitivity and specificity rates of the Dutch ADAMS Depressive Mood subscale were not measured for the level of ID groups separately.

## DISCUSSION

Depressive and anxiety symptoms can be difficult to recognize in adults with ID. Therefore, reliable and valid screening instruments are needed for this population. The results of our study show a good internal consistency of the Dutch ADAMS total scale and satisfactory to good internal consistency of the subscales, for adults younger than 50 years of age. In the subgroup of participants with epilepsy (sample B), the internal consistency of the Dutch ADAMS total scale is good and the internal consistency of the subscales is satisfactory to good. Thus, including participants with epilepsy did not have consequences for the internal consistency of the Dutch ADAMS.



Furthermore, our results suggest a good interrater reliability of the total Dutch ADAMS scale and a good to excellent interrater reliability for the subscales. In the level of ID subgroups, the interrater reliability is fair to good for the total scale and fair to excellent for the subscales (Cicchetti & Sparrow, 1981). The stability over time of the Dutch ADAMS (measured with test-retest reliability) is good for the total scale and good to excellent for the subscales. In the level of ID subgroups, the test-retest reliability of the total scale is excellent for the severe/profound subgroup and fair to good for the mild and moderate subgroups. The test-retest reliability of the subscales in the ID subgroups ranges from fair tot excellent (Cicchetti & Sparrow, 1981). The criterion validity of the Dutch ADAMS Depressive Mood subscale, expressed with sensitivity and specificity rates, is good. In summary, our results show that the Dutch ADAMS is a reliable and valid screening instrument for detecting anxiety and depressive symptoms in adults aged between 18-49 years.

Previous research by Hermans and colleagues in an elderly sample showed a good internal consistency of all subscales of the Dutch ADAMS (Hermans et al., 2012). Moreover, they also found a good test-retest reliability for the total group and good test-retest reliability in the level of ID subgroups (except for the Social avoidance subscale in their severe/profound ID subgroup which had a fair test-retest reliability) (Hermans et al., 2012). Furthermore, they also mentioned a fair to good interrater reliability for the total scale and subscales. In their level of ID subgroups, the interrater reliability was fair to good, with exception of a poor interrater reliability in the borderline/mild ID subgroup (Hermans et al., 2012). Besides, their criterion validity

analyses of the Dutch ADAMS showed a sufficient to good sensitivity and specificity. Rojahn and colleagues mention in their study an excellent internal consistency of the total ADAMS, which is comparable to ours (Rojahn, Rowe, Kasdan, Moore, & van Ingen, 2011). The French version of the ADAMS was evaluated in 2004 (Methot, 2004). They found a satisfactory to excellent internal consistency and an excellent test-retest reliability. The results in the studies of Hermans and colleagues (Hermans et al., 2012) and Rojahn and colleagues (Rojahn et al., 2011) are based on the ADAMS with five subscales and the study of Methot and colleagues (Methot, 2004) is based on an ADAMS with three subscales. As the Dutch ADAMS in the present study has four subscales, results of the previous studies are not completely comparable with the current study.

The first strength of the present study is the large sample used in the internal consistency analyses. A second strength of the current study is the significant amount of adults with intellectual disabilities and comorbid epilepsy who are included. Third, the mean age of the participants of the current study (34.8 years) is almost 30 years below the mean age of the previous study in 2012 by Hermans and colleagues (62.2 years). As a result, the current study adds valuable information to the existing literature about the reliability and validity of the Dutch ADAMS.

The small sample sizes of the subgroups used in the reliability and validity analyses is a limitation of this study. A second limitation of this study is that the three subsamples of this study (interrater reliability sample, test-retest reliability sample and criterion validity samples ) are not a complete representation of sample A. There was a difference between the interrater reliability sample and sample A because no adults with mild ID were included in the interrater reliability sample. In the test-retest reliability sample there was a underrepresentation of women and in the criterion validity sample, the overrepresentation of participants with profound ID and the underrepresentation of participants with mild ID caused significant differences. A third limitation is the rather large range of the test-retest period.

In conclusion, the Dutch ADAMS is a reliable and valid screening instrument which can be used to screen for depressive symptoms and anxiety symptoms in the adult population with ID in clinical practice and to monitor the effectiveness of interventions.

Routinely screening is recommended in order to prevent underdiagnosis, especially among those with epilepsy. In the future, larger subgroups based on level of ID are needed and more research can be done in analyzing the underlying factors in the Dutch ADAMS in the ID population aged between 18-49 years.

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## CONFLICT OF INTEREST

None.

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# Chapter 3

## The influence of personal light exposure on mood and sleep in patients with (mental) health problems: a systematic review

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## ABSTRACT

**Background:** Chronotherapeutic interventions are used to improve (mental) health problems such as depression and sleep disorders, without knowing how personal light exposure prior to these interventions is related to the outcome measures. In this study, we aimed to give an overview of studies focusing on the relationship between personal light exposure and mood and/or sleep in patients with (mental) health problems.

**Methods:** In June 2019, five databases were searched with an electronic search strategy. Inclusion criteria were defined prior to the start of the study, PRISMA guidelines have been followed, and the quality of the included papers was assessed.

**Results:** In total, 8140 papers were found with the electronic literature search. After applying the inclusion criteria, 12 papers were included in the final database. The quality of the studies was mostly assessed as 'fair'. Patients' personal light exposure was usually measured with a wrist worn device. Some patient groups were less exposed to light during the day compared to control subjects. In patients with different kinds of (mental) health problems, in some, but not in all included studies, less exposure to light was associated with more depressive symptoms and more sleep problems.

**Conclusions:** The associations between personal light exposure (natural and artificial light), sleep and mood in patients with different kinds of (mental) health problems are inconclusive. In all included studies, personal light exposure was measured in an inaccurate way, and therefore, the results must be interpreted with caution. More research, for instance with large longitudinal studies using appropriate light measurements, is needed.

## 1. INTRODUCTION

Natural light is important for human health. Back in the seventies, French scientist Michel Siffre experienced that a lack of natural light exposure can have a major impact on humans. In his experiment, where he stayed in a cave for 205 days, the lack of natural light caused him major depressive symptoms as well as suicidal thoughts (Siffre 1975). The lack of light also affected his biological sleep-wake rhythm, now free-running, causing a sleep-wake cycle of up to 50 hours instead of the regular approximately 24 hours (Siffre 1975). Regular exposure to light as well as darkness are necessary to adjust the biological clock to the 24-hour light-dark rhythm (Duffy and Czeisler 2009). Darkness is a necessity during sleeping hours to sleep well, and we need enough light in the morning to wake up and start a number of processes in our body (Chellappa et al. 2013; Foster 2010; Czeisler et al. 1986; Figueiro, Nagare, and Price 2018; Duffy and Czeisler 2009; Touitou, Reinberg, and Touitou 2017; Cho et al. 2015; Ohayon and Milesi 2016; Bedrosian and Nelson 2017). In the pineal gland, the hormone melatonin is produced, and its release is increased by input of the suprachiasmatic nucleus (SCN) when the amount of light exposure decreases (Griefahn, Kuenemund, and Robens 2006). Hereby, the circadian sleep-wake rhythm is regulated (Arendt 2006). Sleep disturbances often co-occur with mental health problems such as mood disorders (Riemann and Voderholzer 2003; Tsuno, Besset, and Ritchie 2005). For example, polysomnographic studies have shown associations between major depressive disorder and abnormal sleep architecture (Peterson and Benca 2006), decreased REM sleep latency and longer REM sleep periods early at night (Benca et al. 1992).



The specific role of light in the development of (mental) health problems is still inconclusive. One hypothesis is that there are disturbances in the amount of light exposure, resulting in malsynchronization of circadian rhythms (Monteleone, Martiadis, and Maj 2011; Germain and Kupfer 2008; Wirz-Justice 2006). Increasing natural light exposure in daily lives of people by increasing (morning) outdoor activities can improve mood (Wirz-Justice et al. 1996). Morning light can decrease the release of melatonin in the morning, and phase shift this release in such a way that the release of melatonin is more synchronized with the regular 24hr cycle (Griefahn, Kuenemund, and Robens 2006).

Multiple studies on light therapy show good results in improving health outcomes, in particular mood and sleep, in different patient groups (Even et al. 2008; Golden et al. 2005; Lieverse et al. 2011; Tuunainen, Kripke, and Endo 2004; Fifel and Videnovic 2019; Schroeder and Colwell 2013; Videnovic et al. 2017; Beauchamp and Lundgren 2016). Chronotherapeutic interventions, such as bright light therapy and dynamic lighting systems, are used to improve circadian rhythms in patients with various (mental) health problems like depressive symptoms, dementia and sleep problems (Zhou et al. 2018; Sit et al. 2018; Münch et al. 2017; Hermans, Soerokromo, and Evenhuis 2017; Lam et al. 2001; Engwall et al. 2015; Brouwer et al. 2015). These interventions are applied without knowing how personal light exposure prior to these interventions is related to the outcome measures, such as mood or sleep.

In the current systematic review, we studied the associations between personal light exposure (which includes natural light and artificial light), sleep and mood in patients with different kinds of (mental) health problems without specific light interventions. Our secondary aim was to examine the personal light exposure of the different study populations of the included studies, and the way the personal light exposure was measured.

## 2. METHODS

Prior to the start of this study, we registered this review in the PROSPERO database (PROSPERO: CRD42016039107). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) guidelines were followed during this study (Moher et al. 2009).

### 2.1. Data sources

Five databases (Embase, Medline Epub, Web of Science, PsycINFO and Google scholar) were searched with an electronic search strategy (Appendix 1) on June 14, 2019. Additionally, references lists of included papers were examined by hand to check for other relevant papers.

### 2.2. Study selection

*2.2.1. Inclusion criteria and outcomes*

The inclusion criteria were defined prior to the start of the study and were as follows: published before the 14th of June 2019, English language, adult patients with mental health problems and/or medical problems, outcome measures regarding mood and/or sleep, and studies must have investigated the relationship between light and mood and/or sleep under naturalistic conditions. Patients personal light exposure (natural and artificial light) must have been measured for at least a full waking day to be included. Only when the light exposure was measured on the patient himself (e.g. wearables or attached on patients clothes), the study could be included. In addition, studies focusing on patients who were bedbound during the study were excluded, because these patients were not able to go outside to be exposed to natural light. Narrative papers without results, letters to the editor, conference abstracts and grey literature were not included in this systematic review.



*2.1.2. Study selection and data extraction*

After the electronic search in five databases, duplicate papers have been removed. Two reviewers (PH and MB) screened all remaining papers on title and abstract independently. The predefined inclusion criteria were used, and any disagreement was discussed. Full texts of all remaining papers have been read and assessed with use of the predefined criteria by the same two reviewers independently. Reference lists of included papers were scanned for potentially relevant papers and these papers were screened by both reviewers on the inclusion criteria before adding them in the final database. Figure 1 shows the flowchart of the study selection. The quality of the studies in the final database was checked by both reviewers (PH and MB) independently, and finalized in a consensus meeting.

### 2.2. Quality assessments

We used the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the NIH National Heart, Lung and Blood Institute to examine the quality of the included studies (The National Heart Lung and Blood Institute 2018). Besides, the included studies have also been screened for mentioning conflicts of interest.

## 3. RESULTS

In total, 13.818 papers were identified by the electronic search, and 8140 papers were left after duplicates were removed. After screening on title and abstract, 303 papers have been read in full text, and screened with the in- and exclusion criteria. Reasons for exclusion can be found in Figure 1. No additional papers were found with the hand search in the reference lists of the included papers. In total, 12 papers were included in the final database of this systematic review. Five studies focused on light exposure, mood and sleep (Ancoli-Israel et al. 1997; Martin et al. 2001; Sun et al. 2014; Joo et al. 2017; Nioi et al. 2017), three studies on light exposure and mood (Oren et al. 1994; Haynes, Ancoli-Israel, and McQuaid 2005; Te Lindert et al. 2018) and four studies focused on light exposure and sleep (Shochat et al. 2000; Martin, Jeste, and Ancoli-Israel 2005; Martin et al. 2006; Sharkey, Pearlstein, and Carskadon 2013).

### 3.1. Personal light exposure measurements

In nine out of the 12 included studies, only a wrist worn device with a light sensor was used to measure participants' personal light exposure (Ancoli-Israel et al. 1997; Martin et al. 2001; Martin, Jeste, and Ancoli-Israel 2005; Martin et al. 2006; Shochat et al. 2000; Haynes, Ancoli-Israel, and McQuaid 2005; Joo et al. 2017; Nioi et al. 2017; Sun et al. 2014). In one study, personal light exposure was measured in nine of the twelve participants with the use of a light sensor attached to their shirt, and in the other three participants a wrist worn device with a light sensor was used (Sharkey, Pearlstein, and Carskadon 2013). In one study, participants wore two brooches where a light sensor was integrated. In this study, one of the brooches was worn on chest level on indoor clothing, and one was attached on chest level on outdoor clothes (Te Lindert et al. 2018). One study used a lapel light sensor in addition to a wrist worn device with a light sensor in all participants (Oren et al. 1994). There were major differences between the included studies regarding the number of days on which participants personal light exposure was measured. Three studies measured personal light exposure during 7 days (Oren et al. 1994; Joo et al. 2017; Te Lindert et al. 2018). In one study, 7 days of personal light exposure was measured at three time points (33 weeks pregnancy and weeks 2 and 6 postpartum) (Sharkey, Pearlstein, and Carskadon 2013). One study reported a four days measurement (Nioi et al. 2017), and seven studies reported a 3 day personal light exposure measurement (Ancoli-Israel et al. 1997; Martin et al. 2001;

Martin, Jeste, and Ancoli-Israel 2005; Martin et al. 2006; Shochat et al. 2000; Haynes, Ancoli-Israel, and McQuaid 2005; Sun et al. 2014).

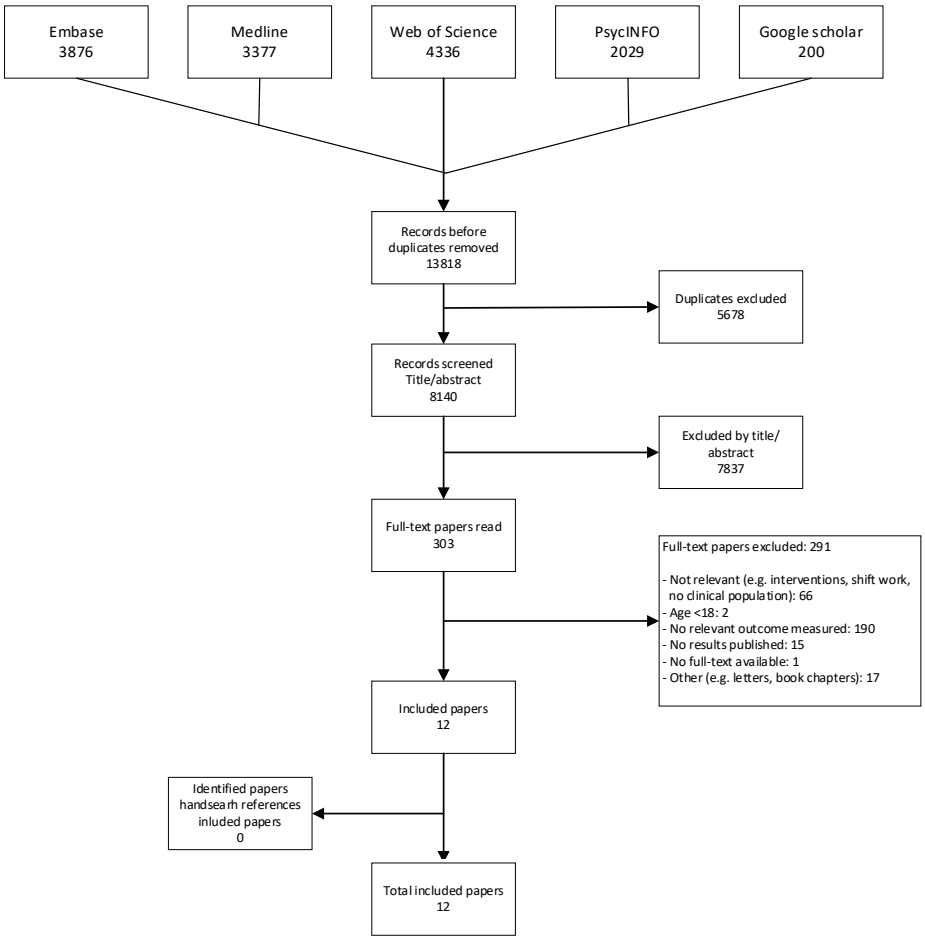


**Figure 1.** Flow chart of study selection

### 3.2. Description of the included study populations

Various types of study populations are included in this review. Three studies were focusing on patients with depressive symptoms (seasonal and non-seasonal) (Oren et al. 1994; Haynes, Ancoli-Israel, and McQuaid 2005; Sharkey, Pearlstein, and Carskadon 2013). Two studies included nursing home patients with dementia (Ancoli-Israel et al. 1997; Shochat et al. 2000), and two studies were on patients with schizophrenia (Martin et al. 2001; Martin, Jeste, and Ancoli-Israel 2005). Fragile elderly living in nursing

homes were studied in two studies (Nioi et al. 2017; Martin et al. 2006). We included one study on patients with delayed sleep-wake phase disorder (DSWPD) (Joo et al. 2017), one study on patients with insomnia disorder (Te Lindert et al. 2018), and one study on outpatients with cancer (Sun et al. 2014).

### 3.3. Quality assessment of the included studies

The quality of the studies was assessed with the Study Quality Assessment tool of the NIH National Heart, Lung and Blood Institute (The National Heart Lung and Blood Institute 2018) by two researchers (PH and MB), and any disagreement was solved in a consensus meeting. None of the included studies had no risk of bias on all items. In summary, one study was rated as 'good' (Te Lindert et al. 2018), 10 studies were rated as 'fair' (Ancoli-Israel et al. 1997; Haynes, Ancoli-Israel, and McQuaid 2005; Joo et al. 2017; Martin et al. 2001; Martin et al. 2006; Oren et al. 1994; Shochat et al. 2000; Sun et al. 2014; Sharkey, Pearlstein, and Carskadon 2013; Nioi et al. 2017), and one study was rated as 'poor' (Martin, Jeste, and Ancoli-Israel 2005). Details of the results of the quality assessment can be found in Appendix 2 (Table 3). Conflicts of interest were declared in five of the 12 included studies (Nioi et al. 2017; Joo et al. 2017; Sun et al. 2014; Sharkey, Pearlstein, and Carskadon 2013; Te Lindert et al. 2018).

### 3.4. Personal light exposure and mood

The eight included studies on personal light exposure and mood are described in Table 1. Two of these studies were focusing on patients with depressive symptoms (Oren et al. 1994; Haynes, Ancoli-Israel, and McQuaid 2005). In the study of Oren et al. (1994), similar amounts of light exposure were found in patients with Seasonal Affective Disorder (SAD) and unaffected control subjects (Oren et al. 1994). In patients with SAD, they found a significant inverse correlation between photoperiod and the severity of depression. Haynes and colleagues (2005) included patients with a major depressive disorder without a seasonal pattern and a similar amount of control subjects (Haynes, Ancoli-Israel, and McQuaid 2005). They found that lower levels of light exposure during the day were associated with an increased chance of depression. Moreover, they found that the association between habitual behaviors and depression was partially mediated by light exposure (Haynes, Ancoli-Israel, and McQuaid 2005). Patients with less habitual behaviors were exposed to less light during the day, and the lack of light exposure increased the probability of depression (Haynes, Ancoli-

Israel, and McQuaid 2005). Ancoli-Israel and colleagues (1997) found that patients with severe dementia were exposed to less bright light (<1000lux) than patients with less severe or no dementia (Ancoli-Israel et al. 1997). In the total group, those with elevated depressive symptoms, were less exposed to light above 1000 lux (Ancoli-Israel et al. 1997). Nioi and colleagues (2017) examined a group of elderly living in a care home and found overall low levels of light exposure in summer and particularly in winter (Nioi et al. 2017). In this study, no significant correlations were found between light exposure and mental health variables.



Martin et al. (2001) included patients with schizophrenia (Martin et al. 2001). In this study, patients exposed to more bright light had less psychiatric symptoms and lower depression scores. Patients with delayed sleep-wake phase disorder (DSWPD) were included in the study of Joo et al. (2017). In this study, which also included control subjects, a later mean light exposure above 200lux was associated with more depressive symptoms (Joo et al. 2017). Te Lindert et al. (2018) studied patients with insomnia disorder and control subjects. They found no differences regarding overall light exposure between both groups, and the positive and negative mood ratings in both groups did not change due to more light exposure (Te Lindert et al. 2018). Only in patients with insomnia disorder, the variability of light exposure increased the experience of "Liking" (*"the subjective experience of pleasantness"*), but this was not found for "Wanting" (*"desires for incentives or declarative goals"*) (Te Lindert et al. 2018). The largest study on light exposure and mood of our systematic review included a large group of outpatients with cancer (Sun et al. 2014). In this study, the amount of personal light exposure (minutes) and the intensity of light exposure were significantly and negatively correlated with depression in outpatients with cancer (Sun et al. 2014).

**Table 1.** Characteristics of included studies focusing on personal light exposure and mood.

| Author (year) | Country | Sample size | Participants | Light measurements Number of light measurement days |
|---|---|---|---|---|
| Oren et al. (1994) | USA | n= 26 | 13 outpatients with winter seasonal affective disorder (SAD), 11F/2M, mean age: 38 years.<br>13 unaffected subjects, 11F/2M, mean age: 38 years. | Actillume (wrist and lapel light sensors), one week. |
| Ancoli-Israel et al. (1997) | USA | n= 77 | Nursing-home patients: severely dementia (n=55) and a group of patients with moderate, mild, or no dementia (n=22)<br>58F/19M, mean age:<br>85.7 years | Actillume (wrist worn),<br>3 days |
| Martin et al. (2001) | USA | n= 28 | Patients with schizophrenia.<br>14M/14F, mean age:<br>58.3 years | Actillume (wrist worn),<br>3 days. |
| Haynes et al. (2005) | USA | n=78 | 39 patients with MDD and 39 never-depressed subjects.<br>54M/24F, mean age:<br>43.7 years | Actillume (wrist worn),<br>3 days |
| Sun et al. (2014) | Taiwan | n=163 | 163 outpatient subjects with cancer, 68M/95F, mean age: 56.7 years | Mini Mitter (wrist worn),<br>3 days |
| Joo et al. (2017) | USA | n= 68 | 42 patients with delayed sleep-wake phase disorder (DSWPD): 22F/20M, mean age: 34.5<br>26 control subjects: 12F/14M , mean age 33.4 | Mini Mitter (wrist worn),<br>7 days |
| Nioi et al. (2017) | Scotland | n=16 | 16 older subjects living in a care home, 3M/13F, mean age: not reported (subjects aged between 72 and 99 years) | Philips Respironics Actiwatch (wrist worn),<br>4 days |
| te Lindert et al. (2018) | the Net-herlands | n= 35 | 17 patients with insomnia disorder, 5M/12F, mean age: 56.8.<br>18 matched control patients, 5M/12F, mean age: 57.0. | Daysimeter-D, 2 sensors integrated in a brooch: one attached on indoor clothing on chest level and one attached to an outdoor jacket,<br>7 days. |

*Abbreviations: F: female; M: Male; DSM: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder.*

| **Mood outcome measurements** | **Results** | **Quality Rating** (Good, Fair, or Poor) |
|---|---|---|
| Hamilton Depression Rating Scale | Similar light exposure between outpatients with SAD and controls without SAD. In patients with SAD, the severity of depression was inversely related to photoperiod. | Fair |
| The Geriatric Depression Scale (GDS) | Patients with severe dementia were less exposed to bright light (≥1000 lux) than those with mild dementia, moderate dementia and nursing-home patients without dementia. Mental status and light exposure were significantly correlated. Patients with higher levels of depression were significantly less exposed to light of ≥1000 lux. | Fair |
| Structured Clinical Interview for DSM-III-R<br>Hamilton Depression Rating Scale (HDRS)<br>Brief Psychiatric Rating Scale (BPRS) | 45% of the patients with schizophrenia were exposed to less than 1 hr of bright light (>1000 lux) a day. 32% of the patients with schizophrenia were exposed to less than 30 minutes bright light (>1000 lux) a day.<br>Patients with schizophrenia who were exposed to more bright light had lower BPRS and lower Hamilton depression scores. | Fair |
| Structured Clinical Interview for the DSM-IV (SCID)<br>Hamilton Depression Rating Scale (HDRS) | Exposure to light mediated (partially) the relationship between habitual behaviors and depression.<br>Lower levels of light exposure during the day were associated with an increased probability of depression. | Fair |
| Beck Depression Inventory II-Taiwan version (BDI-II-T) | Minutes of light exposure and the intensity of light exposure were significantly negatively correlated with depression. | Fair |
| Beck Depression Index (BDI) | Compared to controls, patients with DSWPD had more light exposure at night and less light exposure in the morning compared, but the total 24h light exposure levels were not different between groups.<br>Total sample: later mean light exposure above 200 lux was correlated with higher depression scores. | Fair |
| Warwick Edinburgh Mental Well-Being Scale | Low levels of light exposure in summer and especially in winter. No significant relation between health and exposure to light. | Fair |
| Daytime Insomnia Symptom Scale (DISS) (the factors Negative Mood, and Positive Mood were used).<br>Liking and Wanting scores | No differences in overall daily light exposure between both groups.<br>The mood ratings in both groups did not change due to more light exposure.<br>Only in patients with insomnia disorder, the variability of light exposure increased the experience of "Liking" (*"the subjective experience of pleasantness"*). | Good |

### 3.5. Personal light exposure and sleep

Table 2 shows the nine included studies on personal light exposure and sleep. Sharkey and colleagues (2013) included pregnant women with a history of major depressive disorder without a current mood episode. In this study, no correlation was found between light exposure and circadian phase shift or changes in phase angle, the time between Dim Light Melatonin Onset (DLMO) and sleep onset (Sharkey, Pearlstein, and Carskadon 2013). Two studies focused on patients with dementia (Ancoli-Israel et al. 1997; Shochat et al. 2000). Patients with severe dementia had different sleep patterns and less light exposure of bright light above 1000 lux compared to patients with mild, moderate or no dementia (Ancoli-Israel et al. 1997). In the other study, patients exposed to higher levels of light during the day had less night awakenings, but the severity of dementia and not overall light exposure predicted more sleep and less time awake during the day (Shochat et al. 2000). Martin et al. (2006) examined a large group of nursing home residents who stayed at long-term care wards. Overall, mean bright light exposure (≥1000 lux) per day was 10 minutes. A significant correlation was found between more light exposure and a later circadian rhythm acrophase, and light exposure was not correlated with the circadian rhythm strength (Martin et al. 2006). Nioi and colleagues (2017) studied a group of elderly living in a care home (Nioi et al. 2017). They also found overall low levels of light exposure especially in winter, but no significant correlations between sleep and light exposure.

Martin and colleagues (2001) found that light exposure was not related to the sleep-wake rhythm variables of the patients with schizophrenia. In 2005, Martin and colleagues found no difference in mean daytime light exposure and no difference in minutes of light exposure > 1000 lux per day between patients with schizophrenia and control subjects (Martin, Jeste, and Ancoli-Israel 2005). In this study, controls without schizophrenia were more regularly, but during a shorter amount of time, exposed to bright light than patients with schizophrenia (Martin, Jeste, and Ancoli-Israel 2005). Further, in contrast to the study of 2001, in patients with schizophrenia in 2005, later acrophase of the light exposure rhythm was associated with more sleep during the day, less time awake out of bed and more daytime sleep occurrences (Martin, Jeste, and Ancoli-Israel 2005).

In one study, outpatients with cancer were included (Sun et al. 2014). Significant correlations were found between minutes of light exposure and sleep quality, sleep onset latency, sleep efficiency and awakenings during the night. Patients who were exposed to more light during the day had a better sleep quality compared to those with less light exposure (Sun et al. 2014).

In the study of Joo et al. (2017), patients with DSWPD had more light exposure at night and less light exposure in the morning compared to control subjects, but the total 24h light exposure levels were not different in both groups. They also found that a later mean light exposure above 200 lux during the day was correlated with worse sleep quality and more depressive symptoms (even when adjusted for sleep duration) (Joo et al. 2017).

**Table 2.** Characteristics of included studies focusing on personal light exposure and sleep.

| Author (year) | Country | Sample size | Participants | Light measurements Number of light measurement days |
|---|---|---|---|---|
| Ancoli-Israel et al. (1997) | USA | n= 77 | Nursing-home patients: severely dementia (n=55) and a group of patients with moderately, mild, or no dementia (n=22) 58F/19M, mean age: 85.7 years | Actillume (wrist worn), 3 days |
| Shochat et al. (2000) | USA | n= 77 | Institutionalized elderly (nursing home): 44 patients with severe dementia, 9 patients with mild dementia, 10 with moderate dementia and three patients with no dementia. 58F/19M, mean age: 85.8 years. | Actillume (wrist worn), 3 days. |
| Martin et al. (2001) | USA | n= 28 | Patients with schizophrenia. 14M/14F, mean age: 58.3 years | Actillume (wrist worn), 3 days. |
| Martin et al. (2005) | USA | n=56 | 28 patients with schizophrenia: 14M/14F, mean age: 58.3* Normal comparison subjects: 14M/14F, mean age: 57.3 years ** These patients are also studied in Martin et al. (2001)* | Actillume (wrist worn), 3 days |
| Martin et al. (2006) | USA | n= 492 | Nursing home residents (long-stay wards, not bedbound). 396F/96M, mean age: not reported. | Actillume (wrist worn), 3 days |

| | **Sleep outcome measurements** | **Results (light and sleep)** | **Quality Rating** (Good, Fair, or Poor) |
|---|---|---|---|
| | Sleep/wake activity: Actillume | Patients with severe dementia had different sleep patterns and were less time exposed to bright light (≥1000 lux) compared to patients with mild or moderate dementia or no dementia. | Fair |
| | Sleep/wake activity: Actillume | Fewer night awakenings were found in patients exposed to higher levels of light during the day. Severity of dementia (and not the overall light exposure) predicted more sleep and less time awake during the day. | Fair |
| | Sleep logs<br>Sleep/wake activity: Actillume | Exposure to light was not related to sleep-wake rhythm in patients with schizophrenia. | Fair |
| | Sleep diaries<br>Sleep interview questionnaire<br>Sleep/wake activity: Actillume | No significant difference in mean daytime light exposure between both groups.<br>No significant difference in amount of minutes of light exposure >1000 lux per day between both groups.<br>In patients with schizophrenia, lower light exposure rhythm minimum was related to less daytime total sleep and more time spent out of bed awake. Later light exposure rhythm acrophase was associated with: more sleep during the day, less time awake out of bed and more daytime sleep occurrences. | Poor |
| | Behavioral observations of daytime sleep versus wakefulness and in-bed vs. out-of-bed.<br>Mini-motion logger, 2 nights (to screen for nighttime sleep disturbance).<br>Sleep/wake activity: Actillume (residents who were screened positive for nighttime sleep disturbances) | A significant correlation between a greater exposure to light and a later circadian rhythm acrophase time. Exposure to light was not associated with circadian rhythm strength. | Fair |

**Table 2.** Continued

| Author (year) | Country | Sample size | Participants | Light measurements Number of light measurement days |
|---|---|---|---|---|
| Sharkey et al. (2013) | USA | n=12 | Pregnant subjects fulfilled DSM-IV criteria for history of MDD (no mood episode at enrollment),12F, mean age: 26.9 years | Micro Light Sensor worn continuously pinned/ clipped to the shirt. In 3 participants, the built-in light sensor of the Micro Motion logger Watch was used . 7 days at 33 weeks gestation and postpartum weeks 2 and 6. |
| Sun et al. (2014) | Taiwan | n=163 | 163 outpatient subjects with cancer, 68M/ 95F, mean age: 56.7 years | Mini Mitter (wrist worn), 3 days |
| Joo et al. (2017) | USA | n= 68 | 42 patients with delayed sleep-wake phase disorder (DSWPD): 22F/20M, mean age: 34.5 26 control subjects: 12F/14M, mean age 33.4 | Mini Mitter (wrist worn), 7 days |
| Nioi et al. (2017) | Scotland | n=16 | 16 older subjects living in a care home, 3M/13F, mean age: not reported (subjects aged between 72 and 99 years) | Philips Respironics Actiwatch (wrist worn), 4 days. |

*Abbreviations: F: female; M: Male; DSM: Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder*

| Sleep outcome measurements | Results (light and sleep) | Quality Rating (Good, Fair, or Poor) |
|---|---|---|
| Sleep/wake activity: Octagonal Basic or Micro Motion logger Watch, 7 days at 33 weeks gestation and postpartum weeks 2 and 6.<br>Dim light salivary melatonin onset (DLMO)<br>Sleep/wake diaries<br>Time-stamped voicemail for wake-up times. | No significant correlation between light exposure and circadian phase shifts . Besides, no significant correlation between light exposure and changes in phase angle between DLMO and sleep onset. | Fair |
| Sleep/wake activity: Mini Mitter<br>Pittsburgh Sleep Quality Index-Taiwan form (PSQI-T) | Minutes of light exposure was significantly correlated with sleep quality, sleep onset latency, sleep efficiency and waking after sleep onset.<br>Patients with more light exposure experienced improved sleep quality compared to patients exposed to less light. Minutes of light exposure and the intensity of light exposure were significantly negatively correlated with sleep quality. | Fair |
| Sleep/wake activity: Mini Mitter<br>The Pittsburgh Sleep Quality Index (PSQI)<br>Sleep log | DSWPD patients had more light exposure between 2:00am-4:00am and less light exposure between 8:00am-10:00am than controls.<br>There were no differences in total 24h light levels between the two groups.<br>The midpoint of the average time spent above 200 lux took place later in DSWPD patients than in control subjects, but is significantly earlier with regard to time since awakening.<br>Later mean light exposure above 200 lux during the day was correlated with evening types and higher PSQI scores. | Fair |
| Pittsburgh sleep quality index (PSQI)<br>Sleep/wake activity: Philips Respironics Actiwatch | Low levels of light exposure in summer and especially in winter. No significant relations between sleep quality and sleep and exposure to light. | Fair |

## 4. DISCUSSION

In this systematic review, we give an overview of studies focusing on the association between personal light exposure and mood and/or sleep in patients with (mental) health problems. In patients with different kinds of (mental) health problems, in some, but not in all included studies, less exposure to natural light was associated with more depressive symptoms and more sleep problems. Some patient groups were less exposed to light during the day compared to control subjects. The quality assessment of the included papers revealed a risk of bias in all studies. This must be taken into account when interpreting the results.

Significant associations between personal light exposure and mood were found in some study populations (Haynes, Ancoli-Israel, and McQuaid 2005; Ancoli-Israel et al. 1997; Oren et al. 1994; Martin et al. 2001; Joo et al. 2017; Sun et al. 2014), whereas no associations between personal light exposure and mood were found in other studies, including the only study of good quality (Nioi et al. 2017; Te Lindert et al. 2018). In that good quality study, the variability of light exposure did increase the experience of "Liking" (which is *"the subjective experience of pleasantness"*) in patients with insomnia disorder. In studies focusing on the relationship between personal light exposure and sleep-wake variables, significant associations between personal light exposure and sleep were found in some studies (Martin, Jeste, and Ancoli-Israel 2005; Joo et al. 2017; Ancoli-Israel et al. 1997; Martin et al. 2006; Sun et al. 2014), but no associations on this matter were found in other studies (Nioi et al. 2017; Shochat et al. 2000; Martin et al. 2001; Sharkey, Pearlstein, and Carskadon 2013). Most studies where no association between personal light and mood and/or sleep was found included less than 30 patients, and therefore, these studies may be underpowered.

In the current systematic review, some patient groups with (mental) health problems were exposed to little amounts of natural light (>1000lux) during the day. Differences in the amount or timing of personal light exposure between patients and controls were found in patients with severe dementia (Ancoli-Israel et al. 1997), and patients with DSWPD (Joo et al. 2017). In the latter, the total 24h level of light exposure did not differ between DSWPD patients and control subjects, but there was difference in the timing of the light exposure: patients with DSWPD had more light exposure at night

and less in the morning compared to control subjects (Joo et al. 2017). This can be caused by the fact that these patients are more awake and sleep later at night due to their DSWPD. Patients with dementia may not be able to go outside by themselves because of the cognitive problems, resulting in less exposure to natural light. Similar amount of light exposure between patients and control subject was found in patients with insomnia disorder (Te Lindert et al. 2018) and patients with seasonal mood variations (Oren et al. 1994). Based on this systematic review, an overall conclusion on the possible differences of personal light exposure between patients groups and controls can not be drawn because not all included studies compared the personal light exposure of patients with those of control patients. Besides, in the studies where personal light exposure of patients was compared with those of controls, contrasting results were found.



In most of the included studies, personal light exposure was measured with a light sensor on a wrist-worn device. Previous research has shown that this way of measuring personal light exposure is not always reliable, because light sensors may be covered by the clothes of patients (Burkhalter et al. 2015) and, furthermore, there is a 11% (measured outdoor) and 27% (measured indoor) difference between personal light exposure measured with a wrist worn device and light captured with the eye (Aarts et al. 2017). Personal light exposure measured on chest level shows an inaccuracy of 6% to 17% (Aarts et al. 2017). Therefore, it is possible that personal light exposure measurements of the included studies of this systematic review are not accurate enough, and therefore, results of the included studies must be interpreted with caution.

A limitation of our systematic review is that we did not included 'grey literature', and only included papers in English. Conducting a meta-analysis was considered to be not feasible because the great heterogeneity in outcome measures used in the studies included in our final database. Strengths of our systematic review are the duplicate study selection and quality assessment, performed by two researchers independently. Further, we did not include a restriction on publication date, and therefore all relevant papers published before our literature search date were screened.

As a result of the, most often cross-sectional, design of the studies included in this systematic review, causal relationships were not studied. Therefore, it is not clear whether less exposure to light leads to (mental) health problems or whether (mental) health problems lead to less time spent outside, and therefore lead to less personal light exposure during the day. For example, there is a possibility that timing of light exposure can cause DSWPD (Lingjaerde, Bratlid, and Hansen 1985), but other factors can influence the sleep-wake rhythm as well, for example, biological factors, (mental) health problems or sleep habits. For that reason, more studies, with large longitudinal studies investigating daily light exposure of patients with (mental) health problems, for example in those who are normally less exposed to natural light or patients vulnerable to develop mood or sleep problems, are needed. In this way, we can investigate the causal relationship between personal light exposure and (mental) health variables.

In future research, personal light exposure should be measured with valid instruments, preferably with sensors placed near the eyes (for example attached to a pair of glasses), instead of using a light sensor of a wrist worn device (Aarts et al. 2017). In this way, more reliable levels of personal light exposure will be measured. Further, it is necessary in intervention studies to measure personal light exposure prior to the start of the intervention, during the intervention and after the intervention to gain more knowledge on the associations between personal light exposure, mood and sleep. We suggest that personal light exposure should be measured for at least three full days, and ideally for one week, including a weekend, to gain optimal inside in the amount of daily personal light exposure. A variety of questionnaires to measure mood were used in the included studies of this review. To be able to draw clear conclusions, it is important that valid and reliable (preferably comparable) questionnaires are used, which was not the case in all of the included studies.

## 5. CONCLUSION

We conclude that the associations between personal light exposure (natural and artificial light), sleep and mood in patients with different kinds of (mental) health problems are inconclusive. The results must be interpreted with caution regarding the unreliable way the personal light exposure was measured, and the risk of bias in all studies. More research (longitudinal studies with large samples and appropriate

light measurements) is needed to expand our knowledge on the associations between personal light exposure, mood and sleep.

## CONFLICT OF INTEREST

The authors report no conflicts of interest.

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## APPENDIX 1

### Search strategies

*Embase.com: 3876*

('light exposure'/exp OR 'latitude'/de *OR 'sunbathing'/de OR 'sunlight'/de* OR (((light) NEAR/3 (exposur*)) OR sunbath* OR sun OR sunlight OR daylight OR Antarctic* OR arctic *OR 'north-pole' OR 'south-pole'* OR ((high* OR increas*) NEAR/3 (latitude*))):ab,ti) **AND** (wellbeing/de OR 'psychological well-being'/de OR 'psychological wellbeing assessment'/de OR 'emotion'/exp OR 'sleep'/exp *OR 'sleep waking cycle'/de OR 'sleep disorder'/de* OR 'circadian rhythm'/de OR 'depression'/exp OR (*wellbeing OR ((well) NEXT/1 (being)) OR* emotion* OR mood* OR happiness* OR unhappiness* OR fear* *OR anxi** OR *affective* OR affection** OR apath* OR anger OR sleep* OR circadian* OR (('day night' OR diurnal) NEXT/1 (rhythm* OR cycle OR pattern* OR variation*)) OR depressi* *OR optimism* OR pessimism**):ab,ti) **NOT** (([animals]/lim *OR plant/exp)* NOT [humans]/lim) **NOT** ('Conference Abstract' OR 'Letter' OR 'Note' OR 'Editorial')/it **AND** [english]/lim

*Medline EPub (Ovid): 3377*

(*"Sunbathing"/ OR exp "Sunlight"/* OR (((light) ADJ3 (exposur*)) OR sunbath* OR sun OR sunlight OR daylight OR Antarctic* OR arctic *OR "north-pole" OR "south-pole"* OR ((high* OR increas*) ADJ3 (latitude*))).ab,ti.) **AND** (exp "Emotions"/ OR exp "Sleep"/ *OR exp "Sleep Wake Disorders"/* OR "Circadian Rhythm"/ OR "Depression"/ OR (*wellbeing OR ((well) ADJ1 (being)) OR* emotion* OR mood* OR happiness* OR unhappiness* OR fear* *OR anxi** OR *affective* OR affection** OR apath* OR anger OR sleep* OR circadian* OR (("day night" OR diurnal) ADJ1 (rhythm* OR cycle OR pattern* OR variation*)) OR depressi* *OR optimism* OR pessimism**).ab,ti.) **NOT** ((exp Animals/ *OR exp Plants/)* NOT Humans/) **NOT** (congresses OR letter OR editorial).pt. **AND** (English).lg.

*PsycInfo (Ovid): 2029*

((((light) ADJ3 (exposur*)) OR sunbath* OR sun OR sunlight OR daylight OR Antarctic* OR arctic *OR "north-pole" OR "south-pole"* OR ((high* OR increas*) ADJ3 (latitude*))).ab,ti.) **AND** (exp "Emotions"/ OR exp "Sleep"/ *OR exp "Sleep Disorders"/ OR "Sleep Deprivation"/* OR "Human Biological Rhythms"/ OR exp "Emotions"/ *OR "Well Being"/* OR (*wellbeing OR ((well) ADJ1 (being)) OR* emotion* OR mood* OR happiness* OR unhappiness* OR

fear* *OR anxi** OR *affective* OR affection** OR apath* OR anger OR sleep* OR circadian* OR (("day night" OR diurnal) ADJ1 (rhythm* OR cycle OR pattern* OR variation*)) OR depressi* *OR optimism* OR pessimism**).ab,ti.) **NOT** (congresses OR letter OR editorial).pt. **AND** (English).lg.

*Web of Science: 4336*

TS=(((((light) NEAR/2 (exposur*)) OR sunbath* OR sun OR sunlight OR daylight OR Antarctic* OR arctic *OR "north-pole" OR "south-pole"* OR ((high* OR increas*) NEAR/2 (latitude*)))) **AND** ((*wellbeing OR ((well) NEAR/1 (being)) OR* emotion* OR mood* OR happiness* OR unhappiness* OR fear* *OR anxi** OR *affective* OR affection** OR apath* OR anger OR sleep* OR (("day night" OR diurnal OR circadian*) NEAR/1 (rhythm*)) OR depressi* *OR optimism* OR pessimism**)) **NOT** ((animal* OR mouse OR mice OR murine OR rat OR rats OR insect* OR plants OR plant) NOT (human* OR patient*))) **AND** DT=Article AND LA=English

*Google Scholar: 200 (top relevant refs)*

"lightexposure"|sunlight|daylight
*wellbeing*|emotions|emotional|mood|anxiety|sleep|circadian|depression|depressive

## APPENDIX 2

**Table 3.** Quality assessment of the studies (NIH National Heart, Lung and Blood Institute Study quality assessment tool)

| | Oren et al. (1994) | Ancoli-Israel et al. (1997) | Shochat et al. (2000) | Martin et al. (2001) | Haynes et al. (2005) | Martin et al. (2005) | Martin et al. (2006) | Sharkey et al. (2013) | Sun et al. (2014) | Joo et al. (2017) | Nioi et al. (2017) | te Lindert et al. (2018) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Was the research question or objective in this paper clearly stated? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 2. Was the study population clearly specified and defined? | No | Yes | No | No | No | No | Yes | No | No | No | Yes | No |
| 3. Was the participation rate of eligible persons at least 50%? | NR | NR | NR | NR | NR | NR | Yes | NR | Yes | NR | NR | NR |
| 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? | NR | NR | NR | Yes | Yes | No | No | Yes | Yes | No | NR | Yes |
| 5. Was a sample size justification, power description, or variance and effect estimates provided? | Yes | No | No | No | No | No | No | Yes | Yes | No | No | No |
| 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? | Yes | No | No | No | No | No | No | No | No | No | No | Yes |
| 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? | No | No | Yes | No | Yes | No | No | No | No | Yes | No | Yes |
| 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

**Table 3.** Continued

| | Oren et al. (1994) | Ancoli-Israel et al. (1997) | Shochat et al. (2000) | Martin et al. (2001) | Haynes et al. (2005) | Martin et al. (2005) | Martin et al. (2006) | Sharkey et al. (2013) | Sun et al. (2014) | Joo et al. (2017) | Nioi et al. (2017) | te Lindert et al. (2018) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10. Was the exposure(s) assessed more than once over time? | No | No | No | No | No | No | No | Yes | No | No | Yes | Yes |
| 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes |
| 12. Were the outcome assessors blinded to the exposure status of participants? | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| 13. Was loss to follow-up after baseline 20% or less? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? | No | No | Yes | No | Yes | No | Yes | No | No | Yes | No | Yes |
| Quality Rating (Good, Fair, or Poor) | Fair | Fair | Fair | Fair | Fair | Poor | Fair | Fair | Fair | Fair | Fair | Good |

*NR: not reported*

# Chapter 4

## Non-pharmacological interventions for adults with intellectual disabilities and depression: a systematic review

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## ABSTRACT

**Background** Although high rates of depression symptoms are reported in adults with intellectual disabilities (ID), there is a lack of knowledge about non-pharmacologic treatment options for depression in this population. The first research question of this paper is: Which non-pharmacological interventions have been studied in adults with ID and depression? The second research question is: What were the results of these non-pharmacological interventions?

**Method** Systematic review of the literature with an electronic search in six databases completed with hand searches. PRISMA guidelines have been followed. Selected studies met pre-defined inclusion criteria.

**Results** Literature search resulted in 4267 papers of which 15 met the inclusion criteria. Five different types of non-pharmacological interventions have been studied: Cognitive Behavioral Therapy, behavioral therapy, exercise intervention, Social Problem-Solving Skills Program and Bright Light Therapy.

**Conclusion** There are only a few studies of good quality evaluating non-pharmacological interventions for adults with ID and depression. Some of these studies, especially studies on CBT, show good results in decreasing depressive symptoms. High-quality randomized controlled trials evaluating non-pharmacological interventions with follow-up are needed.

## BACKGROUND

Since the 1980's there is awareness that psychiatric disorders can co-occur with intellectual disabilities (ID) (Sovner and Hurley, 1983, Cooper et al., 2007, Hermans et al., 2013, Marston et al., 1997, Hurley, 2008). Nowadays, we know that depression is a common psychiatric disorder in adults with ID. The prevalence range of depression in the ID population varies from 2.2% to 7.6% (Cooper et al., 2007, Deb et al., 2001, Hermans et al., 2013, Smiley, 2005). The prevalence is higher compared to the general population, despite the fact that depressive symptoms can be difficult to recognize in this population (Hurley, 2008, Marston et al., 1997, Hermans et al., 2013). Depression is mainly characterised by sadness and loss of interest or pleasure (American Psychiatric Association, 2013). Depression has a major impact on the quality of life (QoL) and leads to cognitive, social and physical problems (Bijl and Ravelli, 2000, Beekman et al., 2002, Sprangers et al., 2000, Hays et al., 1995, Alonso et al., 2004, Coryell et al., 1993, Judd et al., 2008, Rand and Malley, 2017, Kober, 2010, Horovitz et al., 2014). Horovitz and colleagues found a significantly higher QoL in a group of adults with ID without Axis I diagnosis compared to adults with ID in the anxiety/mood disorder diagnosis group (Horovitz et al., 2014). Furthermore, adults with ID with higher levels of anxiety/depression are more likely to report a poor QoL (Rand and Malley, 2017).



In the general population, antidepressants are frequently prescribed to treat depressive symptoms. Psychoactive medications, including antidepressants, are regularly prescribed in adults with ID, primarily to reduce challenging behavior (Lott et al., 2004, Matson and Mahan, 2010, Sheehan et al., 2015, Deb et al., 2009). There is some evidence that antidepressant medication can decrease depressive symptoms in adults with ID (Janowsky et al., 2005, Masi et al., 1997, Verhoeven et al., 2001). For example, in a group of 20 participants, Verhoeven and colleagues found Citalopram effective in decreasing depressive symptoms (Verhoeven et al., 2001). Many adults with ID use more than one medication and polypharmacy is common in adults with ID (Bowring et al., 2017, Häβler et al., 2015, Haider et al., 2014). Negative side effects (short term and long term) can appear when psychoactive medications are used in adults with ID (Matson and Mahan, 2010, Mahan et al., 2010, Häβler et al., 2015, Eady et al., 2015, Deb et al., 2009). For example, physical complaints, neurological damage, movement side effects and physiological problems are mentioned (Matson and Mahan, 2010, de Leon et al., 2009, Sheehan et al., 2017). Besides, adults with ID seem to be more amenable to develop side

effects compared to the general population when psychoactive medications are used (Arnold, 1993, Matson and Mahan, 2010, Sheehan et al., 2017). Moreover, it can take a while for a psychoactive medication to work in the right daily dosage and adults with ID may experience even more side effects when more than one psychotropic medication is used (Matson and Mahan, 2010). Therefore, there is a need for evidence based non-pharmacological treatments for depression in adults with ID.

In the general population, a wide range of systematic reviews on non-pharmacological interventions for depression have been published over the last couple of years (Catalan-Matamoros et al., 2016, Cox et al., 2012, Merry et al., 2011, Kvam et al., 2016, Lee et al., 2016, Stubbs et al., 2016). Unfortunately, the conclusions of these reviews (both positive and negative) cannot be generalized to the ID population because a large part of the non-pharmacological interventions for depression of the general population are not suitable for adults with ID. Next to cognitive limitations, adults with ID frequently have verbal limitations. Psychological interventions, for example CBT, are too difficult for adults with a more severe ID and for those with verbal limitations. Furthermore, a large part of people with ID have physical limitations as well (Cooper et al., 2015). Consequently, exercise interventions can be too complicated to perform or physically impossible.

A few systematic reviews concerning non-pharmacological interventions for depression for adults with ID have been published. Some studies are investigating interventions for a part of the ID population. For example, Osugo & Cooper (2016) focused on interventions for adults with mild ID and mental ill-health (Osugo and Cooper, 2016). They concluded that there was some evidence for Group CBT (although larger trials are needed), but that in general the evidence based interventions for people with mild ID and mental problems were limited. Koslowski and colleagues (2016) investigated in their systematic review and meta-analyses the effectiveness of interventions on mental health problems in adults with mild to moderate ID (Koslowski et al., 2016). They found no strong evidence for interventions aimed at improving mental health problems, including depression, and found a non-significant moderate effect size (d=0.49, 95% CI - 0.05 to 1.03; P=0.08) for depression interventions (psychotherapy only). The focus of other reviews in this research area are on specific treatments only. For instance, Vereenooghe & Langdon (2013) did a meta-analysis on psychological therapies for people with ID and mental health problems and found an overall moderate between-group effect size (g = 0.682, 95% CI [0.379, 0.985]). Furthermore, a subgroup meta-analysis indicated that individually psychological therapy (g = 0.778, 95% CI [0.110, 1.445]) was more effective than

group-based psychological therapy (g = 0.558, 95% CI [0.212, 0.903]) and psychological interventions for depression had a moderate effect size (g = 0.742, 95% CI [-0.116, 1.599]).

Depression can occur in all levels of ID. Hence, an overview of evidence based non-pharmacological interventions for depression for the whole ID population is needed, as the severe and profound ID population got no or little attention in previous reviews. Therefore, the aim of this review is to evaluate non-pharmacological treatments for adults with ID (all levels) and depression. Our first research question is: Which non-pharmacological interventions have been studied in adults with ID and depression? Our second research question is: What were the results of these non-pharmacological interventions?

## 2. METHOD



We have used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to perform this study (Moher et al., 2009). The study is registered in the PROSPERO database (PROSPERO 2016: CRD42016051524).

### 2.1 Data sources

An electronic search in six databases, Embase, Medline, Web of Science, Cochrane, PsycINFO and Google scholar, has been performed on October 3rd 2016. The search strategy (for the databases mentioned above) are included in Appendix 1. The electronic search has been completed with hand searches in reference lists of recent systematic reviews (published between January 2012- October 3rd 2016) and in reference lists of included papers.

### 2.2 Study selection

*2.2.1 Inclusion criteria*

Inclusion criteria have been clearly defined before the start of the study. All papers published in English before October 3rd 2016, mentioning non-pharmacological interventions for treating depression (of any type) or depressive symptoms in adults (aged ≥16 years) with ID (IQ ≤70) have been selected. Outcome measures on depressive symptoms must be mentioned in the paper to be included. Because the aim of this study is to find all non-pharmacological interventions for adults with ID and depression, no exclusion on type of study-design has been made. Therefore, all different kinds of study designs, from case study to RCT, were included. The choice to include all study designs

contributes to the presentation of the current state of evidence for the different types of non-pharmacological interventions and possible gaps of knowledge can be exposed.

When a combined population of children and adults was described in a paper, the results of the adult population must be separately presented to be included. The same applies to level of ID: when the study population also contained adults with an IQ of more than 70, the population with IQ ≤70 must be separately presented to be included. In some papers, combined interventions (pharmacological and non-pharmacological) are described. Papers are only included when the results of both of these interventions are studied separately. (Systematic) reviews of nonpharmacological interventions, as well as narrative papers without results and congress abstracts, were not included in the current review.

*2.2.2. Process of the study selection*

After identifying papers through the electronic search, duplicates have been removed. Then, title and abstract of the papers have been scanned by two reviewers (PH and HH) independently, according to the predefined inclusion criteria mentioned above. After the selection of all relevant records on title and abstract, the databases of the two reviewers were merged to see if there was any disagreement about included papers. Any disagreement was solved by discussion in a consensus meeting. Reference lists of recent systematic reviews were studied by both reviewers (PH and HH) for relevant studies. Hereafter, full texts of all remaining papers have been assessed for eligibility by two reviewers (PH and HH) independently. Hand searches in reference lists of included papers was done to search for relevant papers to include. The potential relevant papers of both hand searches were discussed by both reviewers (PH and HH) before including the papers in the final database. After this step, the final database was created. See Figure 1 for the flow chart of the selection of studies. Data extraction of the included studies has been performed by one reviewer (PH) and checked by the second reviewer (HH).

### 2.3 Quality assessment of the included studies

To evaluate the quality of the included studies, the Cochrane Risk Of Bias Tool (Higgins and Green, 2011) has been used by two reviewers independently (PH and HH) and any disagreement has been discussed in a second consensus meeting. With this tool, six domains were assessed to evaluate the quality of the included studies: selection bias, performance bias, detection bias, attrition bias, reporting bias and possible other bias. Low risk of a specific

bias is rated with a '+'. For example, there is a low risk of performance bias when participants and researchers do not know which intervention the participant will receive (blinding). When there is a high risk of a specific bias, that bias is marked with a '-'. For example, when there is a high risk of selection bias due to inadequate concealment of allocations. A question mark is used when not enough information is given in the paper to make a clear judgement. The included studies have also been screened for mentioning conflicts of interest.

### 2.4 Quality assessment of the current systematic review

AMSTAR (which stands for: A MeaSurement Tool to Assess systematic Reviews) is used by an independent researcher to assess the methodological quality of the current review (Shea et al., 2007). The goals of the AMSTAR include creating valid, reliable and useable instruments to differentiate between systematic reviews. Besides, the AMSTAR facilitates the development of high-quality reviews. The AMSTAR checklist consists of eleven questions and seems to be a valid and reliable instrument (Shea et al., 2009).



## 3. RESULTS

The electronic search identified 6023 papers. After removing duplications, 4267 papers have been included in the initial database. These 4267 papers have been screened on title and abstract by two reviewers independently (PH and HH). The reference lists of recent systematic reviews (Chen, 2013, Flynn, 2012, Sturmey, 2012, Matson, 2013, Hwang and Kearney, 2013, Vereenooghe and Langdon, 2013, Jennings and Hewitt, 2015, Koslowski et al., 2016, Maber-Aleksandrowicz et al., 2016, Osugo and Cooper, 2016, Unwin et al., 2016) were studied for relevant papers by these two reviewers as well. One relevant new paper was found. Both reviewers read 113 full text articles and screened these papers on the inclusion criteria. The main exclusion reason was the absence of study results (for example: narrative articles or study results on depressive symptoms were not published), see Figure 1. A total of 15 papers have been included after full text screening. Hand searches in reference lists of these included papers (also done by reviewers PH and HH) did not reveal other relevant papers to include in the final database. Therefore, the final database contained 15 papers.

### 3.1 Description of the included studies

Five different types of non-pharmacological interventions are identified in the included studies of this review: Cognitive Behavioral Therapy, behavioral therapy, exercise

intervention, Social Problem-Solving Skills Program and Bright Light Therapy. Some of these interventions are developed for the ID population, others are adjusted versions of interventions of the general population. The interventions will be discussed in sections 3.3.1 - 3.3.5 and the characteristics of the studies are presented in Table 1a and Table 1b.

### 3.2 Quality assessment of the included studies

According to the Cochrane Risk of Bias Tool, none of the included papers had a low risk of bias on all domains and much is unclear due to a lack of reporting. Two studies scored a low risk of bias on five out of seven criteria (Hassiotis et al., 2013, Carraro and Gobbi, 2014). Only one study mentioned no conflicts of interest (Hassiotis et al., 2013). In the other papers nothing was mentioned about any conflicts on this matter. In Table 2, the details of the quality assessment are shown.

#### *3.3.1. Cognitive behavioral therapy*

Cognitive Behavioral Therapy (CBT) is the most common studied intervention to decrease depressive symptoms. CBT is a psychotherapy in which thoughts, beliefs and attitudes are discussed. In CBT, thoughts are modified in order to change mood and behavior. Eight studies focused on CBT (Lindsay et al., 1993, McCabe et al., 2006, McGillivray et al., 2008, Ghafoori et al., 2010, Hassiotis et al., 2013, McGillivray and Kershaw, 2013, McGillivray and Kershaw, 2015, Lindsay et al., 2015). Three studies were RCT's with follow-up (McCabe et al., 2006, McGillivray et al., 2008, Hassiotis et al., 2013). Three studies were controlled trials with pre-, post- and follow-up (Lindsay et al., 2015, McGillivray and Kershaw, 2015, McGillivray and Kershaw, 2013). The study of Ghafoori et al. (2010) was a pilot study with one group with pre, post and follow-up measurements (Ghafoori et al., 2010). Two cases were described in the study of Lindsay and colleagues (Lindsay et al., 1993).

Seven of these studies reported significantly decreased depression symptoms after CBT, one high quality study (Hassiotis et al., 2013) did not find significant treatment effects. In the study of Lindsay et al. (2015) no significant effect was found in the BSI (Brief Symptom Inventory) depression scale, but they did found significant reductions in self-reported depression (Glasgow Depression Scale, GDS) and carer-reported depression (GDS). In six of the seven studies with positive results, the improvement maintained at follow-up. Based on the results and quality of the included studies, CBT seems to be an effective intervention to decrease depressive symptoms in adults with ID, although there are some conflicting results.

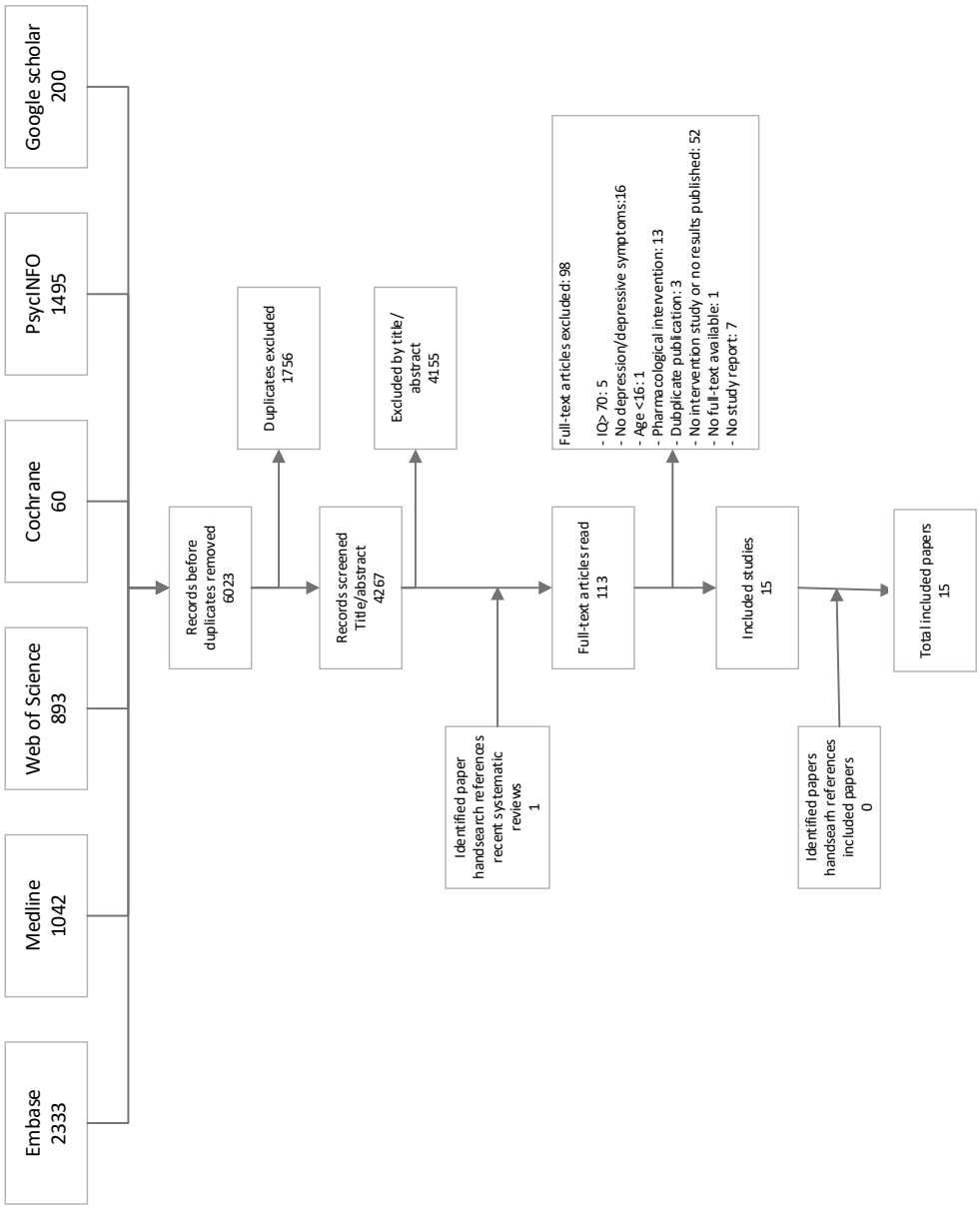


**Figure 1.** Flow chart of study selection

**Table 1a.** Characteristics of included studies.

| Author (year) | Study design | Sample size | Participants (age, gender and level of ID) |
|---|---|---|---|
| McCabe et al. (2006) | RCT | n= 34: 19 EG, 15 CG. (The CG group later also took part of the EG). Total EG: 34 | Mean age: 34.1 (EG), 39.8 (CG)<br>22M (16 EG + 6 CG)/27F (18 EG+9 CG)<br>Mild-moderate ID |
| McGillivray et al. (2008) | RCT | n= 47: 20 TG, 27 CG. (Control group received treatment as well after follow-up (TG 2). | Mean age: 38.4 (TG) and 31.2 (CG)<br>32 M (TG 13, CG19)/ 15 F (TG7, CG 8)<br>Mild ID |
| Ghafoori et al. (2010) | Pilot study, one group (pre, post and follow-up) | n= 8 | Mean age: 20.0<br>2M/6F<br>Mild-moderate ID |
| Hassiotis et al. (2013) | RCT | n= 32: 16 TG, 16 CG. | Mean age: 33.7 (M-iCBT) 38.3 (TAU)<br>12M/20F,<br>Mild-moderate ID |
| McGillivray & Kershaw (2013) | Controlled trial (pre, post and follow-up) | n= 82: 32 G1, 24 G2, 26 G3. | Mean age overall = 37*<br>47M/35F *<br>Mild ID |
| McGillivray & Kershaw (2015) | Controlled trial (pre, post and follow-up) | n= 70: 23 G1, 23 G2, 24 G3 | Mean age overall: 36.0*<br>42M/28F*<br>Mild ID |

| Intervention | Measured depression outcome | Results on depressive symptoms |
|---|---|---|
| Group CBT, 5 weeks, 2h sessions. Control group: waiting list | BDI-II, ATQ-R | Intervention significantly decreased depressive symptoms and negative automatic thoughts. Follow-up (3 months, n=18): impact of the intervention on depressive symptoms sustained over time, no further improvement found. |
| Staff administered group CBT program, 12 weeks, 2h sessions. | BDI-II, ATQ-R | Significant decrease in depressive symptoms and negative automatic thoughts in the CBT group. Follow-up (3 months): positive effects maintained. |
| Cognitive Behavioral Group Therapy Program, 9 weeks, 1.5h sessions | SCL-90-R | Significant improvements in six primary dimensions of the SCL-90-R, including 'Depression'. Follow-up (4 months): no significant treatment effects maintained at follow-up. |
| M-iCBT, 16 weeks, 1h sessions. Control: Treatment as usual | BDI-Y | No significant treatment effect. Follow-up (6 months): no significant effects on depression. |
| Staff administered group CBT program + with a staff-initiated referral to a GP (1), Staff administered group CBT program only (2), referral to GP only (3) | BDI-II, ATQ-R | CB-only group and CB with GP referral group: greatest reduction in depression symptoms directly after the program. Significant reduction in frequency of negative automatic only in the CB-only group. Follow-up (8 months): CB strategies (particularly CB with referral to GP) appeared effective in reducing depressive symptoms and negative automatic thoughts. |
| Cognitive and behavioral strategies (group 1), cognitive focused strategies (group 2), behavioral focused strategies (group 3). | BDI-II, ATQ-R. | The mean depression scores decreased in all three interventions groups after the intervention. No significant difference between groups. Follow-up (6 months): group 1: all individuals indicated improvement, group 2: 67% maintained improvement, group 3: 47% maintained improvement. |

**Table 1a.** Continued

| Author (year) | Study design | Sample size | Participants (age, gender and level of ID) |
|---|---|---|---|
| Lindsay et al. (2015) | Controlled trial (pre, post and follow-up) | n= 24: 12 TG, 12 CG | Mean age: 28.9 (TG), 33.1 (CG)<br>12 M (6 TG + 6 CG)/ 12 F (6 TG + 6 CG)<br>Mild ID |
| Jahoda et al. (2015) | Feasibility study (one group: pre, post and follow-up) | n= 21 | Mean age= 42.2<br>12M/ 9F<br>Mild-moderate-severe ID |
| Heller et al. (2004) | RCT | n= 53: 32 TG, 21 CG | Mean age: 39.41 (TG), 40.22 (CG)<br>24M/29F<br>Mild - moderate ID. |
| Carraro & Gobbi (2014) | RCT | n= 27: 14 EG, 13 CG | Mean age overall: 40.1*<br>16M/11 F*<br>Mild-moderate ID |

*Note. *: not specified per group. #: measurements especially developed for people with ID. Abbreviations: ATQ-R, Automatic Thoughts Questionnaire-Revised; BDI, Beck Depression Inventory; BDI-Y, Beck Depression Inventory Youth; BSI, Brief Symptom Inventory; CBT, Cognitive Behavior Therapy; CDI, Children's Depression Inventory; F, female; GDS-LD, Glasgow Depression Scale for people with Learning Disabilities; ID, intellectual disabilities; IDDS, the Intellectual Disabilities Depression Scale; M, male; M-iCBT, Manualized Individual Cognitive Behavioral Therapy; SCL-90-R, Symptom Checklist-90-Revised; TAU: treatment as usual.*

| Intervention | Measured depression outcome | Results on depressive symptoms |
|---|---|---|
| Experimental group: Individual CBT<br>Control group: waitlist (TAU) | BSI, GDS | No significant effect on BSI depression score.<br>Statistically significant reductions in self-reported depression (GDS) and carer-reported depression (GDS).<br>Follow-up: 3 to 6 months follow-up (treatment group only): Significant decrease on the GDS maintained. |
| Behavioral activation, 10-12 sessions. | GDS-LD #<br>IDDS # | Significant reduction in self-report depressive symptoms. Positive change for informant reports on depressive symptoms.<br>Follow-up (3 months): reduction depressive symptoms maintained. |
| TG: 12 weeks, 3 days per week health promotion program, 2 hrs a day (1h exercise + 1h health education). CG: no training. | CDI | Participants in the intervention group were less depressed than those in the control group (marginally significant).<br>No follow-up. |
| Short-term group-base exercise program, 12 weeks, two times a week, 1h sessions.<br>Control group: painting activities | Zung Self-Rating Depression Scale | Significant reduction of depressive symptoms in the exercise group compared with the control group.<br>No follow-up. |

**Table 1b.** Characteristics of included case studies.

| Author (year) | Study design | Sample size | Participants (age, gender and level of ID) | Intervention | Measured depression outcome | Results on depressive symptoms |
|---|---|---|---|---|---|---|
| Lindsay et al. (1993) | Case studies | n= 2 | Mean age: 24<br>1M/1F<br>Mild ID | Cognitive therapy (Duration/frequency of therapy is unclear). | The Zung Depression Scale | Both subjects improved on the Zung Depression scale. Suicidal thoughts decreased in one participant.<br>Follow-up (6 weeks): reductions on depression scores maintained. |
| Matson (1982) | Case studies | n= 4 | Mean age: 33.5<br>3F/1M<br>Mild-moderate ID | Behavioral therapy, 10-35 sessions | Self-Rating Depression scale BDI | Significant decrease of depressive symptoms on both scales.<br>Follow-up (4-6 months): treatment effect maintained. |
| Stuart et al. (2014) | Case study | n= 1 | Age: 40.0<br>1F<br>Mild ID | Seven sessions of therapy over 3 months (simplified behavioral activation and daily audio-bases progressive muscular relaxation). | GDS-LD # | Decrease in depressive symptoms on the GDS-LD but still above the cut-off point.<br>No follow-up |
| Anderson & Kazantzis (2008) | Case studies | n= 3 | Age range: 19-52 (no mean published)<br>2M/1F<br>Mild ID | Social Problem-Solving Skills training, 15 individual sessions. | Adapted Zung Depression Scale # | Pretreatment - follow-up: Depression showed a 40% change in one case and 31% change in another case.<br>Follow-up (4 weeks): improvement maintained. |
| Altabet et al. (2002) | Case studies | n= 3 | Mean age: 57<br>1M/2F<br>Profound ID | LT sessions, 30 minutes (between 8-10 am), 10.000 lux, 5 days per week for 12 weeks. | DASH # (depression subscale)<br>ABC # (lethargy and irritability subscale)<br>Mood chart. | Positive effects on mood and sleep patterns.<br>Follow-up (3 weeks): treatment gains maintained, (8 weeks): increased depressive symptoms. |

*Note. #: measurements especially developed for people with ID. Abbreviations: ABC, Aberrant Behavior Checklist; BDI, Beck Depression Inventory; DASH, the Diagnostic Assessment for the Severely Handicapped; F, female; GDS-LD, Glasgow Depression Scale for people with Learning Disabilities; ID, intellectual disabilities; LT, Light Therapy; M, male.*

**Table 2.** Quality assessment of the included studies

| | Selection bias (Random sequence generation) | Selection bias (Allocation concealment) | Performance bias (Blinding of participants and personnel) | Detection bias (Blinding of outcome assessment) | Attrition bias (Incomplete outcome data) | Reporting bias (Selective reporting) | Other sources of bias |
|---|---|---|---|---|---|---|---|
| **Matson (1982)** | - | - | - | - | + | ? | - |
| **Lindsay et al. (1993)** | - | - | - | - | + | ? | - |
| **Altabet et al. (2002)** | - | - | - | - | + | ? | - |
| **Heller et al. (2004)** | ? | ? | + | + | + | ? | + |
| **McCabe et al. (2006)** | ? | ? | + | + | + | ? | - |
| **Anderson & Kazantzis (2008)** | - | - | - | + | + | ? | ? |
| **McGillivray et al. (2008)** | ? | ? | + | + | + | ? | - |
| **Ghafoori et al. (2010)** | ? | ? | - | + | + | ? | - |
| **Hassiotis et al. (2013)** | ? | + | + | + | + | ? | + |
| **McGillivray & Kershaw (2013)** | ? | ? | ? | + | ? | ? | ? |
| **Carraro & Gobbi (2014)** | + | - | + | + | + | ? | + |
| **Stuart et al. (2014)** | - | - | - | + | + | ? | - |
| **Jahoda et al. (2015)** | - | - | + | - | + | ? | - |
| **McGillivray & Kershaw (2015)** | - | - | - | + | + | ? | + |
| **Lindsay et al. (2015)** | - | - | + | + | + | ? | + |

*Note. + = low risk, - = high risk, ? = unclear.*

### *3.3.2 Behavioral therapy*

In three studies the effect of behavioral therapy on depressive symptoms has been investigated (Matson, 1982, Stuart et al., 2014, Jahoda et al., 2015). Behavioral therapy is based on the theory that a large part of human behavior is learnt from the environment. In all three studies participants with mild ID have been included, Matson (1982) and Jahoda et al. (2015) also included participants with moderate or severe ID. None of these three studies on behavioral therapy used control groups next to the experimental groups. In the feasibility study of Jahoda et al., 21 participants were included in a one group study with pre, post and follow-up measurements. Matson (1982) and Stuart et al. (2014) reported case studies (respectively n=4 and n=1). Depressive symptoms were (significantly) decreased after behavioral therapy in all three studies. The patient in the study of Stuart et al. (2014) still had a depression score above the cut-off point after the intervention. In the studies of Matson (1982) and Jahoda et al. (2015) the reduction of depressive symptoms maintained at follow-up. Because of the small sample sizes and no use of control groups in the above studies, the results on behavioral therapy on decreasing depressive symptoms in adults with ID must be interpreted with caution.

### *3.3.3 Exercise intervention*

In two RCTs, the effect of exercise on depressive symptoms has been investigated (Heller et al., 2004, Carraro and Gobbi, 2014). Participants in the study of Heller et al. (2004) participated in a 12 weeks (3 day per week, 2hrs a day), health promotion program which consisted of 1h exercise and 1h health education per day. The participants in the study of Carraro et al. (2014) participated in a short-term group-base exercise program (12 weeks, 2 times a week, 1h sessions). Both studies contained an intervention group and a control group and reported significant reductions on depressive symptoms in the intervention group. Unfortunately, both studies did not mention any follow-up measurements. Based on these two studies, we can conclude that exercise interventions to decrease depressive symptoms are promising.

### *3.3.4 Social Problem-Solving Skills Program*

The only study which focused on social problem-solving skills was a multiple single-case study with three participants (Anderson and Kazantzis, 2008). Participants in this study had mild ID and got 15 individual sessions of Social Problem-Solving Skills

training where they were trained to solve the problems that they encountered in daily life. No control group has been used in this study. Reduction of depressive symptoms was seen in two out of three participants, in whom improvement maintained at the 4 weeks follow-up. This study should be seen as a first exploration of the potential of problem-solving skills programs, because of the poor design of this study.

*3.3.5 Bright Light Therapy*

Altabet et al. (2002) published three case studies investigating the effect of Bright Light Therapy (BLT) on depressive symptoms (Altabet et al., 2002). The participants had a profound ID and participated in a 12 weeks, five days a week, BLT program (no control group). Participants got BLT in the morning with a 10.000 lux light box. Positive effects on mood were found, but beneficial treatment effects were not uniform. At 3-week follow-up, treatment gains maintained. The 8-week follow-up showed increased depressive symptoms. As this study only contains case reports, it should be seen as a first consideration of the use of BLT to decrease depressive symptoms in adults with ID.



### 3.4 Quality assessment of the current systematic review

The current study was evaluated by an independent researcher and scored 8 out of 11 points. According to AMSTAR, the strengths of this review are the use of an 'a priori' design, the duplicate study selection and data extraction, and tables 1a-1b providing characteristics of the included studies.

## 4. DISCUSSION

The current systematic review contains 15 studies evaluating the effect of a total of five different non-pharmacological interventions to decrease depressive symptoms in adults with ID. These five different types of non-pharmacological interventions are similar to those found by Holvast and colleagues in the elderly population with depression in primary care (Holvast et al., 2017). Based on our study, we can conclude that CBT is an effective non-pharmacological intervention to decrease depressive symptoms in adults with mild or moderate ID (Lindsay et al., 2015, McCabe et al., 2006, McGillivray and Kershaw, 2015, McGillivray and Kershaw, 2013, McGillivray et al., 2008). However, these results must be interpreted with caution because of the methodological problems of some studies as seen in the quality assessment. In the

general population, CBT is a widely used effective treatment for depression (Butler et al., 2006). CBT can be used in the mild to moderate ID population to decrease depressive symptoms as well, although more RCTs are needed to establish its usefulness in clinical practice. The main part of the included studies in this paper include interventions for people with mild or moderate ID. In only two studies people with severe or profound ID have been included, even though it is known that they can suffer from depression as well (Hermans et al., 2013, Cooper et al., 2007). In general, conducting intervention studies in the ID population is challenging. For instance, ethical dilemmas, specific living conditions of people with ID, dependence on professional staff, a difficult informed consent procedure, the burden of the measurements and challenging behavior are issues researchers are confronted with when conducting intervention studies in this population (Oliver et al., 2002, Hamers et al., 2017). This might be an explanation why intervention studies with adults with severe ID are even more scarce. In the 1980s, Matson already published about behavioral therapy for adults with ID and depression. Unfortunately, none of the studies on behavioral therapy included in this review used control groups (Matson, 1982, Stuart et al., 2014, Jahoda et al., 2015). Therefore, we cannot conclude with certainty that behavioral therapy is responsible for the decrease in depressive symptoms. However, as positive results are published in these papers, it seems promising.

In the two studies (RCTs) investigating exercise as a non-pharmacological treatment to decrease depressive symptoms, intervention groups as well as control groups have been used (Carraro and Gobbi, 2014, Heller et al., 2004). Both studies reported positive results in decreasing depressive symptoms. In the study of Heller et al. (2004) participants got health education and exercise and in the study of Carraro & Gobbi (2004) participants got exercise only, which makes it hard to compare these two exercise studies. Despite this fact, exercise interventions seem promising interventions to decrease depression in adults with ID without psychical limitations and should be further studied.

The study of Anderson & Kazantzis (2008) was the only study in this review focusing on Social Problem-Solving Skills Program. Unfortunately, this was a multiple single-case study with only three participants which makes it hard to draw any conclusions about the effect of this intervention on decreasing depressive symptoms (Anderson and Kazantzis, 2008). Bright Light Therapy (BLT) in adults with profound ID is studied by

Altabet and colleagues in 2002. Positive effects were seen on mood, but no conclusions can be drawn because of the small sample size and no control group (Altabet et al., 2002), so more research is needed. The recent published pilot study with promising results of Hermans and colleagues (Hermans et al., 2017) is the first step towards more insight into the effect of BLT as a treatment for depression in adults with ID.

A large part of the 15 included studies of this review are case reports or studies with a small sample size. Some of the reviewed studies also have methodological problems, for example: no control group or no follow-up. Despite the fact that a large number of adults with ID suffer from depressive symptoms, limited well conducted studies are carried out to evaluate the effect of non-pharmacological interventions to decrease depressive symptoms.



The strength of the current systematic review is that the whole study selection (from title/abstract to full text) and the quality assessment is done by two reviewers independently. Another strength of this study is that there was no restriction on publication year, so all relevant studies published before the start of this study are screened. Besides, the study protocol of this systematic review was registered at the start of the study, which makes the current systematic review transparent. The methodological quality of the current study was assessed with the AMSTAR checklist (Shea et al., 2007) by an independent researcher and received an AMSTAR score of 8 (out of 11).

A limitation of the current systematic review is the small number of papers which could be included due to the inclusion criteria. Many studies were excluded because of lack of data on study methods and outcome measures. For example, in several papers the IQ level of participants was not mentioned. Further, depressive outcome measures were not reported in quite a few papers, for example in the case series of Tsiouris (Tsiouris, 2007). Because of the small number of papers included in our review which are spread over five different kind of interventions, a meta-analyses on the effect of the non-pharmacological treatments was unfortunately not possible. We did not use the 'grey literature' in this systematic review. So, papers could have been missed. Third, this review is limited by only including papers published in English. Fourth, the included studies are very different in study design which makes them hard to compare with each other.

The used tool to evaluate the quality of the studies (the Cochrane Risk Of Bias Tool) is actually designed for (randomized) controlled trials. As for a more pragmatic approach, we used it to evaluate all the study designs of the included papers. Eventually, the use of this specific tool emphasized the poor quality of most of the studies. It is well known that there is a possibility of publication bias of papers with positive outcomes (Easterbrook et al., 1991, Dickersin et al., 1987, Turner et al., 2008, Luijendijk and Koolman, 2012) and therefore, papers with negative outcomes can be missed which may have influenced the results of the current review.

In conclusion, currently CBT is the most well studied non-pharmacological intervention for depression in people with ID, which seems to be effective as well in the mild and moderate ID population. Other promising interventions are exercise and possibly behavioral therapy and bright light therapy. Although it is known that performing a RCT in adults with ID (and depression) can be challenging, we emphasize that further research, preferably RCTs, are needed to grow the evidence-base for non-pharmacological interventions for people with ID and depression. In this way, the non-pharmacological treatment options in this population can be expanded, which is especially important for those with severe or profound ID who can often only rely on pharmacological treatments.

## 5. CONFLICTS OF INTEREST

There are no conflicts of interest.

## 6. ACKNOWLEDGEMENTS

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## APPENDIX 1

### Search strategies

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('depression'/exp OR 'mental health'/exp OR 'mental disease'/de OR 'mental patient'/de OR 'mood disorder'/de OR 'major affective disorder'/de OR 'minor affective disorder'/de OR (depressi* OR bipolar* OR (season* NEAR/3 affecti*) OR dysphori* OR dysthymi* OR melancholi* OR pseudodementi* OR psychopatholog* OR ((mental* OR psychiatr*) NEAR/3 (health* OR disorder* OR disease* OR difficult* OR comorbid* OR co-morbid*)) OR ((mood OR affect*) NEAR/3 disorder*)):ab,ti) AND ('psychiatric treatment'/de OR 'electroconvulsive therapy'/exp OR 'psychotherapy'/exp OR 'physical medicine'/exp OR 'exercise'/exp OR 'chronotherapy'/exp OR ((non NEXT/1 pharmac*) OR nonpharmac* OR psychotherap* OR physiotherap* OR phototherap* OR kinesiotherap* OR kinesitherap* OR exercis* OR dramatherap* OR storytell* OR mindfulness* OR ((psychiatr* OR behav* OR cognit* OR psycho* OR dance OR activit* OR activat* OR running OR movement* OR physical* OR light OR group OR electroconvuls* OR drama OR socioemotion* OR emotion* OR mental*) NEAR/3 (treat* OR therap* OR interven*)) OR psychoeducat* OR 'therapeutic work' OR chronotherap* OR CBT):ab,ti) AND ('intellectual impairment'/de OR 'mental deficiency'/exp OR 'developmental disorder'/de OR (((intellectual* OR mental* OR learning) NEXT/1 (impair* OR disab* OR deficien* OR handicap* OR retard*)) OR (developmental* NEXT/1 (disorder* OR disab*)) OR (Down* NEAR/3 syndrome*)):ab,ti) AND [english]/lim NOT ('juvenile'/exp NOT adult/exp)

*Medline Ovid*

(exp "Depression"/ OR exp "Mood Disorders"/ OR "mental health"/ OR "Mental Disorders"/ OR "Mentally Ill Persons"/ OR "Bipolar Disorder"/ OR (depressi* OR bipolar* OR (season* ADJ3 affecti*) OR dysphori* OR dysthymi* OR melancholi* OR pseudodementi* OR psychopatholog* OR ((mental* OR psychiatr*) ADJ3 (health* OR disorder* OR disease* OR difficult* OR comorbid* OR co-morbid*)) OR ((mood OR affect*) ADJ3 disorder*)).ab,ti.) AND ("Psychiatric Somatic Therapies"/ OR exp "Convulsive Therapy"/ OR exp "Psychotherapy"/ OR "Physical and Rehabilitation Medicine"/ OR "Psychiatric Rehabilitation"/ OR exp "Physical Therapy Modalities"/ OR exp "exercise"/ OR "chronotherapy"/ OR ((non ADJ pharmac*) OR nonpharmac* OR psychotherap* OR physiotherap* OR phototherap* OR kinesiotherap* OR kinesitherap*

OR exercis* OR dramatherap* OR storytell* OR mindfulness* OR ((psychiatr* OR behav* OR cognit* OR psycho* OR dance OR activit* OR activat* OR running OR movement* OR physical* OR light OR group OR electroconvuls* OR drama OR socioemotion* OR emotion* OR mental*) ADJ3 (treat* OR therap* OR interven*)) OR psychoeducat* OR "therapeutic work" OR chronotherap* OR CBT).ab,ti.) AND (exp "Intellectual Disability"/ OR "Developmental Disabilities"/ OR (((intellectual* OR mental* OR learning) ADJ (impair* OR disab* OR deficien* OR handicap* OR retard*)) OR (developmental* ADJ (disorder* OR disab*)) OR (Down* ADJ3 syndrome*)).ab,ti.) AND english.la. NOT ((exp child/ OR exp infant/ OR Adolescent/) NOT exp adult/)

*PsycINFO Ovid*

(exp "Depression (emotion)"/ OR exp "Affective Disorders"/ OR "mental health"/ OR "Mental Disorders"/ OR "Bipolar Disorder"/ OR (depressi* OR bipolar* OR (season* ADJ3 affecti*) OR dysphori* OR dysthymi* OR melancholi* OR pseudodementi* OR psychopatholog* OR ((mental* OR psychiatr*) ADJ3 (health* OR disorder* OR disease* OR difficult* OR comorbid* OR co-morbid*)) OR ((mood OR affect*) ADJ3 disorder*)).ab,ti.) AND ("Physical Treatment Methods"/ OR exp "Phototherapy"/ OR exp "Electroconvulsive Shock Therapy"/ OR exp "Psychotherapy"/ OR exp "Physical Therapy"/ OR exp "exercise"/ OR ((non ADJ pharmac*) OR nonpharmac* OR psychotherap* OR physiotherap* OR phototherap* OR kinesiotherap* OR kinesitherap* OR exercis* OR dramatherap* OR storytell* OR mindfulness* OR ((psychiatr* OR behav* OR cognit* OR psycho* OR dance OR activit* OR activat* OR running OR movement* OR physical* OR light OR group OR electroconvuls* OR drama OR socioemotion* OR emotion* OR mental*) ADJ3 (treat* OR therap* OR interven*)) OR psychoeducat* OR "therapeutic work" OR chronotherap* OR CBT).ab,ti.) AND (exp "Intellectual Development Disorder"/ OR "Developmental Disabilities"/ OR (((intellectual* OR mental* OR learning) ADJ (impair* OR disab* OR deficien* OR handicap* OR retard*)) OR (developmental* ADJ (disorder* OR disab*)) OR (Down* ADJ3 syndrome*)).ab,ti.) AND english.la. NOT ((100.ag. OR 200.ag.) NOT 300.ag.)

*Cochrane*

((depressi* OR bipolar* OR (season* NEAR/3 affecti*) OR dysphori* OR dysthymi* OR melancholi* OR pseudodementi* OR psychopatholog* OR ((mental* OR psychiatr*) NEAR/3 (health* OR disorder* OR disease* OR difficult* OR comorbid*

OR co-morbid*)) OR ((mood OR affect*) NEAR/3 disorder*)):ab,ti) AND (((non NEXT/1 pharmac*) OR nonpharmac* OR psychotherap* OR physiotherap* OR phototherap* OR kinesiotherap* OR kinesitherap* OR exercis* OR dramatherap* OR storytell* OR mindfulness* OR ((psychiatr* OR behav* OR cognit* OR psycho* OR dance OR activit* OR activat* OR running OR movement* OR physical* OR light OR group OR electroconvuls* OR drama OR socioemotion* OR emotion* OR mental*) NEAR/3 (treat* OR therap* OR interven*)) OR psychoeducat* OR 'therapeutic work' OR chronotherap* OR CBT):ab,ti) AND ((((intellectual* OR mental* OR learning) NEXT/1 (impair* OR disab* OR deficien* OR handicap* OR retard*)) OR (developmental* NEXT/1 (disorder* OR disab*)) OR (Down* NEAR/3 syndrome*)):ab,ti) NOT ((child* OR infan* OR adolescen*) NOT adult*)



*Web of Science*

TS=(((depressi* OR bipolar* OR (season* NEAR/2 affecti*) OR dysphori* OR dysthymi* OR melancholi* OR pseudodementi* OR psychopatholog* OR ((mental* OR psychiatr*) NEAR/2 (health* OR disorder* OR disease* OR difficult* OR comorbid* OR co-morbid*)) OR ((mood OR affect*) NEAR/2 disorder*))) AND (((non NEAR/1 pharmac*) OR nonpharmac* OR psychotherap* OR physiotherap* OR phototherap* OR kinesiotherap* OR kinesitherap* OR exercis* OR dramatherap* OR storytell* OR mindfulness* OR ((psychiatr* OR behav* OR cognit* OR psycho* OR dance OR activit* OR activat* OR running OR movement* OR physical* OR light OR group OR electroconvuls* OR drama OR socioemotion* OR emotion* OR mental*) NEAR/2 (treat* OR therap* OR interven*)) OR psychoeducat* OR "therapeutic work" OR chronotherap* OR CBT)) AND ((((intellectual* OR mental* OR learning) NEAR/1 (impair* OR disab* OR deficien* OR handicap* OR retard*)) OR (developmental* NEAR/1 (disorder* OR disab*)) OR (Down* NEAR/2 syndrome*))) NOT ((child* OR infan* OR adolescen*) NOT adult*)) AND LA=(english)

*Google scholar*

Depression|depressive
"nonpharmaceutical"|psychotherapy|phototherapy|"psychiatric|behavior|
cognitive|light therapy" "intellectual|intellectually|mental|mentally
impairment|disabled|disability|deficiency|handicap|retarded|retardation"

# Chapter 5

## A multicenter randomized controlled trial for bright light therapy in adults with intellectual disabilities and depression: study protocol and obstacle management

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## ABSTRACT

Due to the limited cognitive and communicative abilities of adults with intellectual disabilities (ID), current treatment options for depression are often limited to lifestyle changes and pharmacological treatment. Bright light therapy (BLT) is an effective intervention for both seasonal and non-seasonal depression in the general population. BLT is an inexpensive, easy to carry out intervention with minimal side effects. However, knowledge on its anti-depressant effect in adults with ID is lacking. Obstacles in realizing a controlled intervention study in this particular study population may have contributed to this lack. To study the effect of BLT on depression in this population, it is necessary to successfully execute a multicenter randomized controlled trial (RCT). Therefore, the study protocol and the management of anticipated obstacles regarding this trial are presented.

## 1. INTRODUCTION

Depression can be difficult to recognize and diagnose in people with intellectual disabilities (ID) because of their cognitive and verbal limitations and different manifestations of depression in this group compared to the general population (Hurley, 2008; Marston, Perry, & Roy, 1997). For example: crying, expressions of irritability, withdrawal and challenging behavior are common characteristics in adults with ID and depression (Charlot L., 2007; Hurley, 2008; S. Moss et al., 2000), but not part of standard diagnostic criteria (American Psychiatric Association, 2013). As a result, depression is poorly recognized in adults with ID (Hermans, Beekman, & Evenhuis, 2013). Nevertheless, depression is a common psychiatric disorder among adults with ID (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Hermans et al., 2013), which can lead to social, cognitive and physical problems and has a negative impact on their quality of life (Alonso et al., 2004; Beekman et al., 2002; Bijl & Ravelli, 2000; Coryell et al., 1993; Hays, Wells, Sherbourne, Rogers, & Spritzer, 1995; Judd et al., 2008; Murray & Lopez, 1997; Sprangers et al., 2000). However, there are barely any treatment options besides pharmacological treatment, especially for adults with severe or profound ID. In the Netherlands, cognitive behavioral therapy is one of the most regular therapies for depression, besides medication. Cognitive behavioral therapy can only be used in a small proportion of adults with ID due to their intellectual and verbal impairments. As a result, the current treatment options for adults with ID and depression are often limited to lifestyle changes (such as increasing activities) and pharmacological treatment. Because there is a high prevalence of polypharmacy in adults with ID (Haider, Ansari, Vaughan, Matters, & Emerson, 2014), the use of (an extra) medication is not preferred. Besides, the known side effects of anti-depressants are also inconvenient and, unfortunately, it can take some time for the anti-depressants work sufficiently.

Several studies indicate that depression is associated with disturbances in the circadian rhythms (Boyce & Barriball, 2010; Bunney & Potkin, 2008; Germain & Kupfer, 2008; McClung, 2007; Monteleone, Martiadis, & Maj, 2011; Wirz-Justice, 2006). Circadian rhythms (for example: sleep-wake cycle, hormone levels and body temperature) are primarily controlled and regulated endogenously by several biological clocks which are located at different places in the body (Hastings, Maywood, & Reddy,

2008). The main biological clock is located in the hypothalamus brain region in the suprachiasmatic nucleus (SCN). Light is the major Zeitgeber of this main biological clock and influences the circadian rhythms via retinal light input (Wirz-Justice, 2006) if there is no eye disease (Reme, Rol, Grothmann, Kaase, & Terman, 1996). Other external factors, such as (social) activities, mealtimes, work schedules and rules and habits of a care institution, can influence these circadian rhythms as well (Boivin & Boudreau, 2014; Kazemi et al., 2016; Naylor et al., 2000).

It is known that light exposure influences the level of the hormone melatonin in a healthy brain (Griefahn, Kuenemund, & Robens, 2006). When the amount of light decreases, the production of the hormone melatonin, which is created by the pineal gland and which influences feelings of sleepiness, increases by input of the SCN. Melatonin itself has also influence on the melatonin receptors in the SCN (Arendt, 2006; Stehle, von Gall, & Korf, 2003; Wirz-Justice, 2013). Thus, the release of melatonin follows a circadian rhythm and changes in this release may occur due to a disrupted circadian sleep-wake rhythm. It is known, that many adults with depression experience tiredness and sleeping difficulties like insomnia (Almeida & Pfaff, 2005; Kaneita et al., 2006; Murphy & Peterson, 2015) and older people with ID have a significantly less stable and more fragmented sleep-wake rhythm than the general population (Maaskant, van de Wouw, van Wijck, Evenhuis, & Echteld, 2013).

The hormone cortisol is released during stress and the level of cortisol is associated with depression (Dettenborn et al., 2012; Hardeveld et al., 2014; Vreeburg et al., 2009). A chronically elevated cortisol secretion is associated with psychological and physical health problems such as high blood pressure, diabetes mellitus and depression (Schoorlemmer, Peeters, van Schoor, & Lips, 2009; Vreeburg et al., 2009). Treatment of depression may lead to a decrease in stress, which can lead to a decrease of the level of cortisol.

In the general population, Bright Light Therapy (BLT) is an effective intervention for both seasonal and non-seasonal depression and has been studied widely since the 1980s (Even, Schroder, Friedman, & Rouillon, 2008; Golden et al., 2005; Kripke, 1998; Lieverse et al., 2011; Morgan & Jorm, 2008; Pail et al., 2011; Rosenthal et al., 1984; Schwartz & Olds, 2015; Thaler et al., 2011; Tuunainen, Kripke, & Endo, 2004; Wirz-Justice, 2013).

Golden and colleagues showed in their review and meta-analyses that the effects of BLT are comparable to those of anti-depressants (Golden et al., 2005). However, in a recent systematic review, Mårtensson and colleagues argued that the evidence of the effectiveness of BLT is inconclusive, partially because of methodological shortcomings of several studies (Martensson, Pettersson, Berglund, & Ekselius, 2015). Nevertheless, the overall experience with BLT for treatment of depression is positive. Another advantage of BLT is that it hardly causes side-effects as opposed to pharmacological treatment of depression. Besides, it will also reduce the costs of depression-treatment because BLT is relatively inexpensive and seems easy to deploy.

Although BLT has been studied since a couple of decades in the general population, only a few case reports have been published on its effect in adults with ID (Altabet, Neumann, & Watson-Johnston, 2002; Cooke & Thompson, 1998; Tsiouris, 2007). The results of these case reports seem promising, as BLT decreased the number of depressive symptoms. A pilot study into feasibility of BLT and using actigraphy in adults with ID was recently conducted (Hermans et al, 2015, submitted). Fourteen participants (eight men, average age 52) with moderate to profound ID were included. Hermans and colleagues concluded that caregivers indicated that BLT and the use of actigraphy was feasible for all participants. Also the severity of depressive symptoms had been decreased, but the results should be interpreted with caution because of the small sample size and the lack of a control group.



As BLT seems to influence the biological clock in the brain, it may have a different effect on depression in adults with ID, due to impaired brain development or brain damage. Consequently, research outcomes of BLT studies in the general population cannot be generalized to adults with ID. Furthermore, also environmental variables, for example time spent outside in daylight, may differ from the general population and can interfere with the effect of BLT in adults with ID. As a consequence, it is unclear whether BLT has the same anti-depressant effect in adults with ID as in the general population.

Although it is of great importance to investigate non-pharmacological treatment for depression in adults with ID it is quite understandable that so far, no high-quality effect studies have been performed. Indeed, apart from meeting general

requirements for randomized controlled trials (RCT) (sample size with adequate power, representativeness, randomization, blinding, adequate statistics, budget), research in populations with ID generally has to meet specific challenges. Each study requires its own scenario with a detailed identification of potential obstacles, solutions, responsibilities and time slots. In this paper, we will describe the study protocol and how we have managed the anticipated obstacles.

## 2. METHODS

### 2.1 Objectives

The primary objective of this study is to investigate the effect of BLT on depressive symptoms in both intervention groups compared to regular care (control group). Our secondary objectives are: investigating if there is a significant difference in effect of BLT with lightbox I compared to lightbox II and if the effect of BLT is still visible four weeks after the end of the BLT (follow-up). Besides, we will investigate the effect of BLT on circadian rhythms (DLMO and actigraphy) and stress (level of cortisol) in the intervention groups.

### 2.2 Study protocol

The current study is a multicenter randomized controlled trial (RCT) with measurements taken at three different time points: baseline (T0), directly after BLT (T1) and four weeks after BLT (T2). Participants will be randomized into three groups. Group I: this group will receive two weeks of BLT in the morning before noon with a 10.000 lux bright white lightbox, additional to their care as usual. Group II: this group will receive two weeks of BLT in the morning before noon with a bright white lightbox of < 499 lux (placebo group), additional to their care as usual. Group III: this group continues getting regular care with no additional intervention (control group). Randomization takes place through a computerized program which has been created by an independent data manager. Block stratification will be used to ensure that the participants are properly distributed over the study groups within each participating center. Blinding will be applied to the researchers, participants and caregivers. The researchers do not know which type of lightbox is distributed to the participant. This study is introduced by the participants and caregivers as a study where we compare two lightboxes with a different amount of lux. The participants and the care providers

do not know if lightbox type I or type II is distributed for the BLT. Besides, we make sure that participants of the same living area do not get BLT simultaneously. Participants and their caregivers are instructed not to mention details of the amount of light of the lightbox with the investigators.

*2.2.1 Study population, recruitment and inclusion*

The study will be conducted in three care provider services in collaboration with the research group of Intellectual disability Medicine of the Erasmus University Medical Center Rotterdam in the Netherlands. The three care provider services (Amarant Group, Abrona and Ipse de Bruggen) are located in three different regions in the Netherlands and provide support or care to a large group of clients (approximately 12,000 clients) with borderline to profound ID. Recruitment will mainly be focused on clients who get long-term specialized care. Long-term specialized care refers to the living facilities of the health care provider services where people with ID live who depend on specialized care their whole life. To be included, participants must be 18 years or older, have an intellectual disability (IQ ≤ 70) and have severe enough depressive symptoms (score of ≥ 14 on the depressive mood subscale of the Dutch version of the Anxiety, Depression And Mood Scale (ADAMS) (Hermans & Evenhuis, 2013; Hermans, Jelluma, van der Pas, & Evenhuis, 2012). Exclusion criteria are a diagnosis of bipolar disorder, prepartum and/or postpartum depression, dementia, current delirium, hypomanic, manic or psychotic episode, current suicidal behavior or suicidal expressions and if the lens of the eye is missing (aphakia). If a client has been treated with BLT, the last treatment must have ended more than four weeks ago. Because BLT may cause side effects if a participant uses certain photosensitizing medications or has certain diseases (for example porphyria, urticaria solaris or recent eye surgery), the participants' physician will decide if it is safe to include the client in the study.



The sample size of this study has been calculated with the *SAS/ETS 9.3 user's guide* ("SAS/ETS 9.3 user's guide," 2011) and is based on a clinically relevant difference of four points (decrease) on the depressive mood subscale of the ADAMS (Hermans & Evenhuis, 2013) after the intervention, based on the results of the pilot study (Hermans et al, 2015, submitted). Depressive symptoms in both intervention groups (group I and group II) are compared with depressive symptoms of participants who receive care as usual (group III), resulting in multiple comparisons. Therefore, a Bonferroni

correction will be applied and we will compare the groups at a significance level of 2.5% (α = 0.025) and power of 80% (β= 0.80). Taking this in consideration, each group should contain at least 45 participants. Anticipating on early loss to follow-up of 20% of the participants, our aim is to include 57 participants in each study group, leading to including minimally 135 and maximally 171 participants. For our primary objectives, attrition in this study can be caused by absence of depression subscale scores (caregiver did not fill in the questionnaire(s)). Attrition in our secondary measurements can be caused by no approval of the secondary measurements by the legal guardian (or participants), failure of the material, problems with storage of the melatonin and cortisol samples, no DLMO or cortisol data because of too low values (DLMO) or too short hair (< 3 cm) (cortisol).

### 2.3 Informed consent procedure

Physicians and behavioral scientists of the three care provider services select potential participants who meet the inclusion criteria. The informed consent procedure in this study differs from the procedure in the general population: not all clients are able to give informed consent themselves. The client's behavioral therapist or physician decides whether a client is able to understand the information and to make the decision to give consent for participation. If a client is considered able to understand the adapted information of the current study and to decide whether he wants to participate, the information and consent form are sent to the client. Otherwise, the information and consent form are sent to the legal representative. The professional caregivers of the client will be informed by an information letter sent by mail and e-mail.

### 2.4 Study intervention

Both BLT groups will receive BLT for the duration of 30 minutes per day at 20 centimeters distance for a period of 14 consecutive days, in the morning before 12 a.m. We intend to give BLT as early as possible after wake-up. A tape-measure is distributed together with the lightbox to measure the distance between the participant and the lightbox. Only when a distance of 20 centimeters is not possible, for example due to the use of a wheelchair, the 30 cm distance is allowed. In case of 30 centimeters distance, the duration of each session is extended from 30 to 60 minutes, according to the manual of the lightbox. To ease the burden, the participant may choose an activity he/she

feels comfortable with during the BLT. The participants in group I receive BLT (10.000 lux) with the Philips energy light type HF3319 (UV-filtered lightbox). The participants in group II also receive BLT with the Philips energy light type HF3319, but a LEE filter is installed to significantly reduce the amount of lux to <499. This LEE filter (no. 299) is heat resistant and does not change the color of the light. In order to guarantee the safety of the participants, all lightboxes are checked by the Medical Technology Department of the Erasmus University Medical Center Rotterdam in the Netherlands. This department also measured the number of lux using a lux meter (Konica Minolta T-10A) at 20 centimeters distance and 30 centimeters distance. The average amount of lux produced by lightbox type I at a distance of 20 centimeters appeared 11214 lux (range 10860 - 11640) and the average amount of lux of lightbox type II with the LEE filter appeared 317 lux (range 297 -329). The average amount of lux produced by lightbox type 1 at a distance of 30 centimeters appeared 7122 lux (range 6930-7380) and the average amount of lux of lightbox type II with the LEE filter appeared 198 lux (range 188-209).



All lightboxes are coded (A or B) by an independent researcher who is not involved in this study. The researchers who will distribute the lightboxes do not know which code belongs to which type of lightbox, and neither do participants and professional caregivers. After completion of the total study, the encryption will be broken. We are aware that the placebo (<499 lux) in this study may reduce the depressive symptoms as well as the original lightbox (10.000 lux) due to a placebo effect. For example, because the participant improved due to the extra attention which is given by the professional caregivers due to the BLT. To overcome this issue, we added a care as usual group (Group III). In this way, we can compare both intervention groups with a group of participants who do not get an added intervention and investigate if possible differences can be attributed to the amount of lux.

### 2.5 Diagnostic measures

#### *2.5.1 Participant characteristics*

Participants characteristics (gender, age, ethology of ID, level of ID, residential setting, psychiatric disorders, physical medical conditions, use of medication, BLT in the past, treatment for depression during study intervention) will be collected through participants' medical and psychological files. The professional caregiver is asked how

much time a participant spends outdoors per day, at what time the participant gets up and goes to bed (weekdays and weekends) and whether the participant smokes or drinks alcohol (including the amount).

### *2.5.2 Depression*

Depressive symptoms will be studied with the depressive mood subscale of the ADESS (the Dutch version of the Anxiety, Depression And Mood Scale (ADAMS) (Hermans & Evenhuis, 2013; Hermans et al., 2012) which is completed by a professional caregiver. The internal consistency, test-retest reliability and inter-rater reliability of the Dutch version of this subscale are good ($\alpha = 0.85$, ICC = 0.78 and ICC = 0.78) (Hermans & Evenhuis, 2013; Hermans et al., 2012). Its sensitivity and specificity against the gold standard (the PAS-ADD interview (S. Moss, 2011)) are 83% and 64%, respectively (Hermans & Evenhuis, 2013; Hermans et al., 2012). Depressive symptoms are further investigated with the Dutch Signalizing Depression List for people with Intellectual Disabilities (SDL-ID) (Roeden, 1989) and the subscale "Irritability" of the Aberrant Behavior Scale (ABC) (Aman, Singh, Stewart, & Field, 1985), to be completed by a professional caregiver. The SDL-ID has good internal consistency and inter-rater reliability ($\alpha = 0.77$ and $r = 0.87$) (Roeden, 1989) and shows a high correlation with the ADAMS depressive mood subscale ($r = 0.71$) (Hermans et al., 2012). The ABC consists of five subscales, but only the subscale "Irritability" will be used in this study, because irritability is a characteristic symptom of depression in people with ID. The internal consistency of this subscale is good ($\alpha = 0.89$) (Rojahn, Rowe, Kasdan, Moore, & van Ingen, 2011). Presence of a major depressive disorder according to DSM criteria will be investigated with the Dutch translation of the PAS-ADD (Psychiatric Assessment Schedule for Adults with Developmental Disability) Clinical Interview (S. Moss, 2011) before the start of BLT. The PAS-ADD will be conducted by the researchers with the professional caregiver and, if possible, also with the participant. In participants with a diagnosis of major depression at T0, the PAS-ADD is completed again at T1.

### *2.5.3 Sleep-wake rhythm*

The circadian sleep-wake rhythm will be studied by examining the sleep-wake pattern using actigraphy (AW2 Philips Respironics) four days before the start of BLT (T0), during the last four days of BLT (T1), and for four days four weeks after the end of BLT (T2) in group I and II. Dim Light Melatonin Onset (DLMO) is also a marker to assess the circadian sleep-wake rhythm (Klerman, Gershengorn, Duffy, & Kronauer, 2002; Lewy, 2007; Lewy,

Cutler, & Sack, 1999). DLMO in saliva will be studied at T0 and T1 in group I and II. In both intervention groups, the saliva samples will be collected by the professional caregivers 3 hours before bedtime, 2 hours before bedtime, 1 hour before bedtime and at bedtime. The melatonin samples are analysed using the RIA method. The DLMO will be calculated by the hockey-stick method (Danilenko, Verevkin, Antyufeev, Wirz-Justice, & Cajochen, 2014).

*2.5.4 Stress*

We will longitudinally study stress in both intervention groups by investigating the cortisol level in scalp hair samples (Dettenborn et al., 2012; Manenschijn, Koper, Lamberts, & van Rossum, 2011; Russell, Koren, Rieder, & Van Uum, 2012). A scalp hair sample of at least three centimetres is required to analyse the cortisol level before and after BLT. The scalp hair sample will be collected six weeks after the end of BLT by trained professionals. Because life events are related to depression and stress in adults with ID (Hermans & Evenhuis, 2012), participant's life events in the year prior to this study will be examined using the Checklist Life Events developed by our research group (Hermans & Evenhuis, 2012) and this questionnaire will be completed by the professional caregiver.



The circadian sleep-wake rhythm measurements (Actiwatch and DLMO) and stress (cortisol level) are not primary outcome measures. The researchers have chosen not to burden the 'care-as-usual group' (group III) with measurements whose results are not necessary to answer the primary research question. The following outcome measures are also measured in just the two intervention groups: the expectations of the participant and/or their professional caregiver concerning the effect of BLT will be collected prior to the BLT using a questionnaire, and compliance is registered during the intervention period (two weeks of BLT) by the professional caregivers. As we use the AW2, which has an integrated light sensor, the amount of light to which a participant is exposed could be measured. However, Burkhalter and colleagues found that the data of the light sensor was not reliable due to the fact that the light sensors were covered by the sleeves of the participants (Burkhalter et al., 2015). Therefore, the light data of the AW2 will not be used to evaluate compliance to the intervention. Adherence to the BLT therapy (start time, duration and distance) will be measured using a daily log. The study procedure is presented in Figure 1.

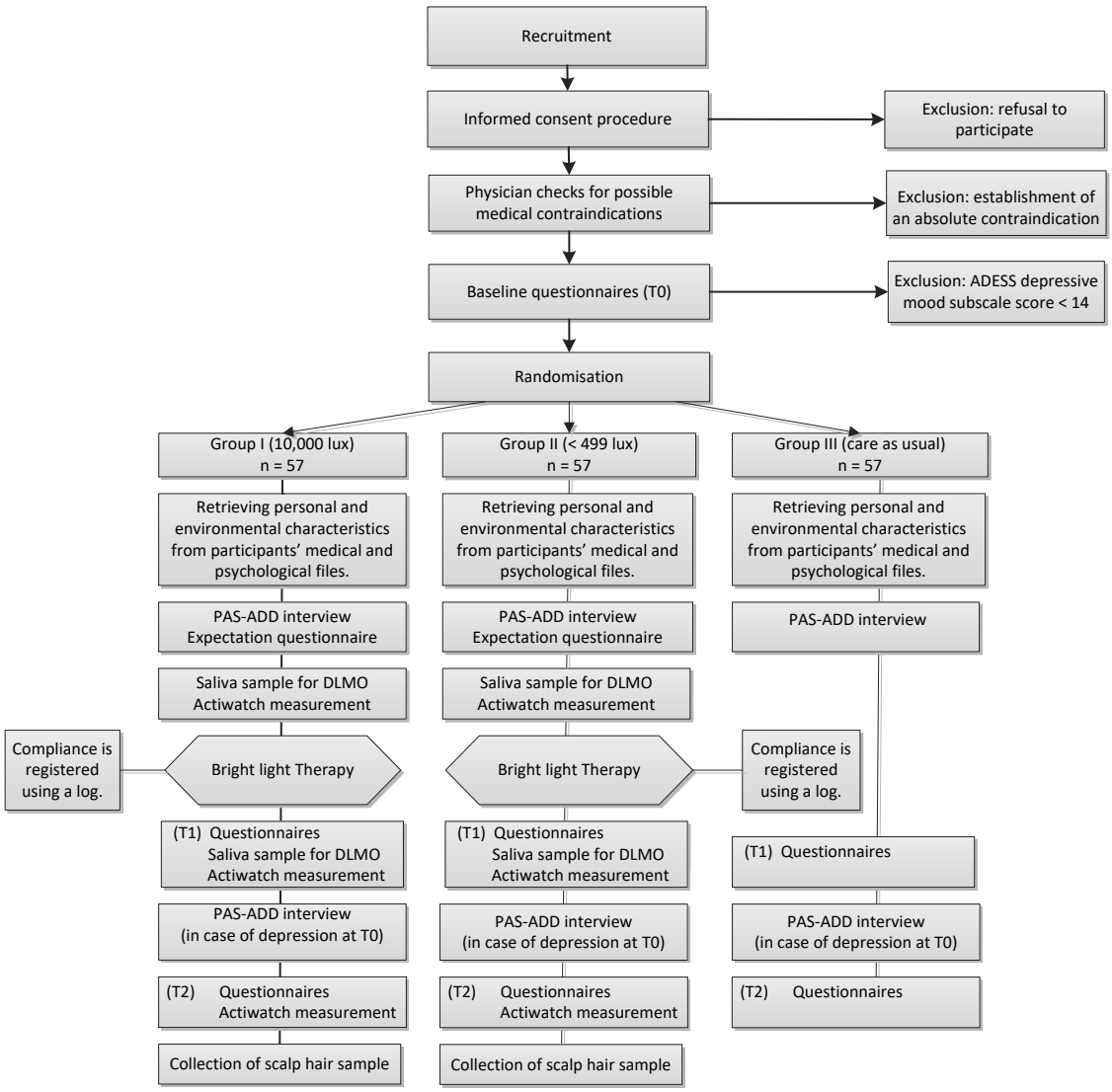


**Figure 1.** Flow chart study procedure

### 2.6 Statistical analyses

Data will be analyzed using IBM SPSS statistics. The intention to treat basis will be used in all analyses: participants are analyzed in the group in which they have been randomized. If the ADESS depressive mood subscale score of T1 is missing, the participant is called a drop-out (loss to follow up). Also a minimum of ten days of

BLT is necessary for the analyses. If a participant has had less than ten days of BLT, the ADESS depressive mood subscale scores of these participant are not included in the analyses. Missing data will not be imputed, but will be reported. Multivariate regression analysis will be used to investigate the effect of BLT on depression. The ADESS depressive mood subscale scores of the three research groups of T1 will be used. The ADESS depressive mood subscale scores of participants in group I and group II will be compared separately with the ADESS depressive mood subscale scores of participants in the care as usual care group. Group differences at T0 will be statistically corrected. For the two primary analyses, a significance level of $p = 0.025$ will be used, to correct for the increased risk of a type 1 error due to multiple comparisons. BLT will be considered effective if depressive symptoms decrease significantly (lower ADESS depressive mood subscale score) after intervention with BLT. Multivariate analysis of variance (MANOVA) will be used to investigate if the effect of BLT with lightbox type I (10.000 lux) is larger than BLT with lightbox type II (<499 lux). MANOVA's will also be used to investigate the changes in circadian rhythms, DLMO and stress. To examine if the possible effect of BLT still exists four weeks after the end of the BLT (follow-up), ANOVA repeated measures will be used. Expectations prior to the BLT, compliance of the BLT and patients characteristics will be taken into account as possible confounders.



### 2.7 Ethical considerations

The Dutch law (the Medical Research Involving Human Subjects Act) applies to the 'no, unless principle' and therefore, scientific research with adults with ID (if they are not able to understand the information of the study and to decide about participation) is in principle forbidden. There is an exception for therapeutic research which may be of direct benefit to the participants and cannot be done in another study population and for non-therapeutic research which is conducted with a selected population (group restricted) and for whom the risks and burden are negligible and with minimal objections. Our intervention study meets the criteria for therapeutic research because BLT may be an antidepressant, as it is in the general population, and can be of great direct benefit for the participants. Further, to participate in our study, a legal representative must provide consent for the participants which are not able to decide for themselves. Participants will maintain their own regular care and treatment and the current study will not interfere with the standard care and treatment. The medication of the participants will not be adjusted. This study is part of the Healthy Ageing and

Intellectual Disability study. Ethical approval for the current study was obtained for all three care provider services by the Ethics Committee of the Erasmus University Medical Center Rotterdam in the Netherlands (MEC-2014-632). This study follows the guidelines of the Declaration of Helsinki (64ste WMA General Assembly, October 2013). This trial is registered (NTR number: NTR5162). Inclusion of the participants started in May 2015 and is still ongoing.

## 3. OBSTACLE MANAGEMENT

Several obstacles were observed prior to the start of this study. First, there are obstacles specific for research in adults with ID. An obstacle results from the specific living conditions of adults with ID because inclusion of participants with ID often takes place through care provider services. Therefore, apart from management consent to perform the study, optimal collaboration and commitment of managers and staff of these care provider services are necessary to successfully complete research in this population. Therefore, managers and staff were informed and motivated by educational sessions and written information prior to the start of the study. In the past, this approach led to good results (Hilgenkamp et al., 2011). Furthermore, clients are not able to sign up themselves because of cognitive and verbal impairments. As a result, an obstacle was how to motivate physicians and behavioral scientists to sign up their clients. In a period of four months prior to the start of the recruitment, all involved professionals and their managers were informed by educational sessions and written information about depression in adults with ID and the study protocol. At the start of the recruitment period, the professionals were informed again by email and an information letter and during the study through quarterly newsletters.

Participants may not be able to give permission to be included themselves. Consequently, the participants may not be motivated to participate, which can be an obstacle during this study. Therefore, the participants will be informed by the professional caregivers by making use of a simplified version of the patient information letter with pictograms. In the current study, participants are dependent on the care of professional caregivers. These professional caregivers are key figures in this study, because they are involved in several diagnostic measurements as well as in arranging BLT in the morning. To inform the professional caregivers, flyers were distributed and

written information letters were sent. In this way, professional caregivers were also motivated to discuss possible participants with the involved physician or behavioral scientist.

Next, the burden of intervention and measurements for both participants and professional caregivers can be an obstacle in this study; this is specifically addressed in Dutch legislation on research in incompetent study groups. To ease the burden, the distribution and information about the lightbox and secondary outcome measures (actigraphy, DLMO and cortisol) by the researcher are combined with the PAS-ADD interview. Some diagnostic measurements required adaption, too. Van Dijk et al. (2012) found that 32% of participants with borderline to profound ID were not able to wear an Actiwatch for measuring sleep-wake rhythm, due to anticipated loss or breakage of the actiwatch, or to fear, resistance or refusal by participants (or as anticipated by professional caregivers) (van Dijk, Hilgenkamp, Evenhuis, & Echteld, 2012). In the study of Hylkema & Vlaskamp it was mentioned that insufficient arm movements were an obstacle in using actigraphy in adults with ID (Hylkema & Vlaskamp, 2009). To succeed in using actigraphy in our study, we have written a detailed information letter with pictograms to explain the measurement with the AW2 for both the participant and the professional caregivers. Also oral information is given when the AW2 is distributed.



The measurement of DLMO in adults with ID was another obstacle in this study, because taking multiple saliva samples can be difficult in our study population. We have added special information for optimising the saliva collection in adults with ID into the regular DLMO instruction letter for the professional caregivers. Furthermore, we diminished the number of saliva samples from the usual five samples to four, because DLMO can also be calculated with four samples. With one sample less, the participants will be hampered less in their daily activities and it also eases the burden on the professional caregivers.

Another obstacle was how to measure the cortisol level over a period of time without subjecting participants to invasive measurements like repeatedly taking blood samples. Measuring cortisol in scalp hair is a relatively new, non-invasive method to determine long-term cortisol levels in humans (Dettenborn et al., 2012; Manenschijn et al., 2011; Russell et al., 2012). Hair cortisol concentrations are not subject to variations

due to acute stress and can reflect cortisol exposure over months to years (Manenschijn et al., 2011; Wester & van Rossum, 2015). Second, there are obstacles specifically for BLT studies. Different contraindications and exclusion criteria for BLT were used in previous BLT studies in the general population (Benedetti et al., 2005; Dallaspezia et al., 2012; Dauphinais et al., 2012; Lam et al., 2006; Lieverse et al., 2008; Oren et al., 2002; Terman, Terman, & Ross, 1998). Therefore, we have made an overview of the photosensitizing medications and relevant diseases and clearly stated if a given medication or disease is an absolute contraindication or a relative contraindication (inclusion is possible), based on relevant literature (Meesters & Letsch, 1998; Terman & Terman, 2005; Wirz-Justice, 2013), the advice of consulted ophthalmologists, and the 'Pharmacotherapeutic Compass' (www.farmacotherapeutischkompas.nl) which contains all medicines available in the Netherlands.

From the beginning, there is a debate about which placebo intervention can be used in BLT studies. Furthermore, each intervention can have a certain degree of effect, regardless whether the intervention contains the appropriate dosage or administration (Andrews, 2001; Khan, Khan, & Brown, 2002). In some BLT studies, a (deactivated) ion generator is used as a placebo treatment (Dauphinais et al., 2012; Eastman, Young, Fogg, Liu, & Meaden, 1998; Flory, Ametepe, & Bowers, 2010). Other BLT studies use dim red light, which is considered to be not anti-depressant (Lieverse et al., 2008; Loving, Kripke, Elliott, Knickerbocker, & Grandner, 2005; Wirz-Justice et al., 2011). We chose to reduce the amount of lux to a point where it is widely considered not to be anti-depressant (<499 lux). The two lightboxes used in this study are identical from the outside and have the same color of light. Professionals involved in this study do not have influence on or knowledge of the randomization sequence; neither do the researchers. As a result, low inclusion or selective loss to follow-up is possible due to the fact that professionals and/or legal representatives may not want clients to get a placebo treatment and still have to undergo effect measurements (Group II) or no intervention at all (Group III). Therefore, the study protocol and the necessity of the three study groups were discussed in the educational sessions prior to the study, in the patient information letters and also further explained if this was requested. Third, there is an obstacle which is specific for depression intervention studies in adults with ID. As mentioned before, depression can be difficult to recognize and diagnose in people with ID because of the cognitive and verbal difficulties and different manifestations of

depression in this group compared to the general population (Hurley, 2008; Marston et al., 1997). Consequently, an obstacle in this study is including enough participants who meet the inclusion criteria of enough depressive symptoms. To optimize inclusion, the different manifestations of depression in adults with ID were discussed in the educational sessions and newsletters mentioned before. As a result of the discussed obstacles, a minimum of six to nine months are required for preparation of the study. An overview of the obstacles and consequences for the organization of the study, as well as obstacle management are presented in Table 1.

**Table 1.** Obstacles, consequences and obstacle management for research in adults with ID, in BLT studies and in depression intervention studies in adults with ID.

| **Obstacles specific in research in adults with ID** | | |
|---|---|---|
| **Obstacles** | **Consequences for the organization of the study** | **Obstacle management in the current study** |
| Specific living conditions of participants: inclusion often through care provider services. | Collaboration, consent and commitment of managers and staff. | Managers and staff are informed and motivated by educational sessions and written information. |
| Clients are not able to sign up themselves because of the cognitive and verbal impairments: Professional staff needs to sign up clients. | Motivate physicians and behavioral scientists to sign up their clients. | Educational sessions and written information about depression in adults with ID and the study protocol prior to the study. Information by email and an information letter at the start of the study. Quarterly newsletters during the study. |
| Study population is partially or completely incompetent to decide to participate. | Motivation of participants who cannot give consent themselves.<br>(Legal) ethical requirements. | Using a simplified version of the patient information letter with pictograms, pointing out the potential direct benefit for participants. |
| Clients are dependent on care of professional caregivers. | Inform and motivate professional caregivers for the study. | Flyers were distributed and written information letters are sent to inform the professional caregivers. |

**Table 1. Continued**

| | | |
|---|---|---|
| Acceptation of intervention and measurements. | Decrease the burden of intervention and outcome measurements for participants and professional caregivers. Some measurements require adaptation for our study population. | Distribution of the light box, explanation of the intervention and measurements as well as the PAS-ADD interview are combined at the same moment.<br>Actigraphy: detailed information letter with pictograms and oral information.<br>DLMO: special instructions into the regular DLMO instruction letter and adjustment of the number of saliva samples<br>Cortisol: hair cortisol is used instead of blood or urine samples. |

| **Obstacles specific in Bright Light Therapy studies** | | |
|---|---|---|
| **Obstacles** | **Consequences for the organization of the study** | **Obstacle management** |
| Various contraindications and exclusion criteria were used in previous BLT studies in the general population. | Figuring out which contraindications and exclusion criteria apply to our study population. | Developing a list of relative and absolute contra-indications for BLT in adults with ID. |
| Placebo bright light therapy differs across BLT studies. | Choosing the right placebo condition for this study. | Two (at the outside) identical light boxes are used. Adjustment of the amount of lux (<499) in the placebo condition. |
| Low motivation to sign up or give consent because of the randomization procedure (RCTs).<br>(Risk of being selected for a non-intervention group). | Low or selective inclusion / selective loss to follow-up. | Information about the study protocol is given in the educational sessions and patient information letters and further explained if requested. |

| **Obstacle specific in depression intervention studies in adults with ID** | | |
|---|---|---|
| **Obstacle** | **Consequence for the organization of the study** | **Obstacle management** |
| Depression is not recognized in a large part of the ID population. | (Risk of) low inclusion. | Specific manifestations of depression in adults with ID are discussed in the educational sessions and newsletters. |

## 4. DISCUSSION

This first multicenter Bright Light Therapy (BLT) randomized controlled trial (RCT) in adults with intellectual disabilities (ID) and depression may provide an opportunity to improve our knowledge of BLT in this population. The information of the preparation period of this study can be of great interest for other researches for designing and performing their study. In this paper, we discussed that it is difficult to carry out a high quality multicenter RCT on the effects of BLT in adults with ID and depression because of the obstacles in research in adults with ID, obstacles specifically for BLT studies and an obstacle specifically for depression intervention studies in adults with ID. It is necessary to measure the hormones melatonin and cortisol objectively to investigate the effect of BLT on the circadian rhythms and stress. Unfortunately, investigating the effect of BLT in a study population of adults with ID is challenging due to obstacles in measuring depressive symptoms, circadian rhythm (DLMO and actigraphy) and stress (cortisol). In addition, other obstacles may arise during the study. For instance, in a BLT study a low baseline melatonin secretion was found which may have influenced the limited intervention effects (Burkhalter et al., 2015). Besides, Martensson and colleagues suggest that the effect of BLT could not be confirmed in several studies due to methodological problems like a small study population (Martensson et al., 2015). After the inclusion period, it will come clear whether we have successfully managed all anticipated obstacles prior to the start of the study and if new obstacles did appear during the study. When BLT is effective in our study population it may enlarge the treatment options for depression in this population. BLT can then become a non-pharmacological treatment for decreasing depressive symptoms in adults with ID. Especially, for those who not benefit from pharmacological treatment, those with polypharmacy and adults with ID who cannot tolerate or refuse medication.



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## TRIAL REGISTRATION AND TRIAL STATUS

This trial is registered (NTR number: NTR5162). Inclusion of the participants started in May 2015 and is still ongoing.

## CONFLICT OF INTEREST

None.

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# Chapter 6

## The effect of Bright Light Therapy on depressive symptoms in adults with intellectual disabilities: results of a multicenter randomized controlled trial

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*Under review*

## ABSTRACT

**Background:** Although a large number of adults with intellectual disabilities (ID) have depressive symptoms, non-pharmacological treatments are scarce. We investigated whether bright light therapy (BLT) is effective in decreasing depressive symptoms compared to care as usual.

**Methods:** This multicenter randomized controlled trial consisted of three study groups (10.000 lux BLT, dim light BLT and a no-BLT group). Participants received BLT for 30 minutes in the morning (14 consecutive days), additional to their regular care. Primary outcome: depressive symptoms measured with the ADAMS Depressive Mood subscale one week after the end of BLT (same time period in the no-BLT group).

**Results:** 41 participants were included in our trial. In both BLT groups a significant decrease in depressive symptoms was seen. No significant differences were found between 10.000 lux BLT and no-BLT ($p = 0.199$), and no significant differences between dim light BLT and no-BLT ($p = 0.451$). A minimum amount of side effects and no adverse events were reported.

**Conclusions:** In both BLT interventions a decrease in depressive symptoms was seen. With 10.000 lux BLT, depressive symptoms decreased even below the clinical cut-off point, which makes BLT a promising intervention for clinical practice.

## INTRODUCTION

Depression is common in the general population and has a large impact on functioning in daily life (Wittchen et al., 2011). Compared to the general population, even higher numbers of depression and depressive symptoms are found in the population of adults with intellectual disabilities (ID) (Cooper, Smiley, Morrison, Williamson, & Allan, 2007; Hermans, Beekman, & Evenhuis, 2013). Despite the large number of adults with ID and depressive symptoms, treatment options, especially for those with severe ID, are scarce (Hamers, Festen, & Hermans, 2018). Some adults with mild or moderate ID and without major verbal limitations, may benefit from psychological interventions, for example Cognitive Behavioral Therapy (CBT) (Vereenooghe & Langdon, 2013), but a large part of adults with ID and depressive symptoms get pharmacological treatment or no treatment at all. Pharmacological side effects, high numbers of polypharmacy, the lack of non-pharmacological interventions for those with severe ID, together with the high prevalence of depressive symptoms in adults with ID, makes investigating other non-pharmacological interventions extremely important.



### Bright light therapy

In the general population, Bright Light Therapy (BLT) is broadly studied and used in clinical practice to treat seasonal affective disorder and non-seasonal depression (Even, Schroder, Friedman, & Rouillon, 2008; Golden et al., 2005; Lieverse et al., 2011; Martiny, 2004; Nussbaumer et al., 2015; Tuunainen, Kripke, & Endo, 2004). The working mechanism is not fully understood, but it is suggested that disturbances in the circadian rhythms are involved (Germain & Kupfer, 2008; Monteleone, Martiadis, & Maj, 2011; Wirz-Justice, 2006). Our main biological clock, which controls our circadian rhythms, is situated in the hypothalamus in the suprachiasmatic nucleus (SCN). Retinal light input is the main influencer of the biological clock (Wirz-Justice, 2006). Neural pathways from the SCN lead to the pineal gland where melatonin is produced. In this way, light can influence the secretion of melatonin: when the amount of light increases, the production of the hormone melatonin is decreased (Griefahn, Kuenemund, & Robens, 2006). The effect of BLT is comparable to those of pharmacological interventions to decrease depressive symptoms (Golden et al., 2005) and BLT can even be more effective when combined with antidepressants (Lam et al., 2016). Besides, BLT seems

to be a safe intervention without major side effects (Brouwer et al., 2017; Kogan & Guilford, 1998; Meesters & Letsch, 1998).

Unfortunately, the results of BLT studies in the general population cannot be generalized to the population of adults with ID, because many adults with ID have some kind of brain damage that might interfere with the abovementioned neural pathways; for example, congenital brain damage, progressive brain damage or damage caused by traumatic injury. Furthermore, a large amount of adults with ID are care dependent and have physical and/or mobility problems. Therefore, it is possible that they benefit less from direct daylight because they do not spend the same amount of time outside compared to the general adult population.

In the ID population, BLT did not get much attention yet. Since 1998, some case reports were published (Altabet, Neumann, & Watson-Johnston, 2002; Cooke & Thompson, 1998; Tsiouris, 2007). These first explorations of BLT in the ID population showed promising results. However, systematic report of the results and control groups were lacking. A feasibility study in the Netherlands showed that BLT is a feasible intervention for adults with ID. Besides, they found a decrease in depressive symptoms after BLT in almost all patients and in nearly half of the sample a clinical relevant improvement was found (Hermans, Soerokromo, & Evenhuis, 2017). As larger studies with control groups are needed to expand the knowledge of the effect of BLT in the ID population, the primary objective of our study was to investigate whether BLT is effective in decreasing depressive symptoms in two BLT intervention groups compared to no-BLT (control group). Our secondary objective was to examine if there is a significant difference in the effect of BLT between the two BLT intervention groups. Besides, we examined if the effect of BLT is still visible four weeks after the end of BLT.

## METHOD

### Participants

Potential participants were recruited in three large care provider centers in the Netherlands that are part of the Healthy Ageing and Intellectual Disabilities Consort (HA-ID Consort). Physicians, psychologists and behavioral scientists of the care provider centers selected potential participants and decided whether a potential participant

was able to understand the information of the study and to make the decision to give informed consent for participation. If the participant was not able to decide, the legal guardian was informed and gave written consent. Recruitment and inclusion of the participants started in May 2015 and ended in September 2017. The data collection ended in November 2017.

### Inclusion and exclusion criteria

Adults with ID (IQ ≤ 70) and with depressive symptoms were included in this study. To be included, a minimum score of 14 (clinical cut-off point) was needed on the Depressive Mood subscale of the Dutch version of the Anxiety, Depression And Mood Scale (ADAMS; range 0 - 39) (Hamers, van Ool, et al., 2018; Hermans & Evenhuis, 2013). Exclusion criteria were checked by a physician and behavioral scientist who were involved with the care of the participant. Exclusion criteria were: a diagnosis of bipolar disorder, prepartum and/or postpartum depression, dementia, current delirium, hypomanic, current manic or psychotic episode, current suicidal behavior or suicidal expressions and aphakia (the lens of the eye is missing). In addition, because of possible side effects in combination with BLT, the physician excluded participants who used specific photosensitizing medications, had recent eye surgery or certain diseases, for example porphyria, urticaria solaris. Previous BLT sessions must have ended more than four weeks prior to the inclusion.



### Ethical regulation and trial registration

Written informed consent was retrieved from each participant or from their legal guardian if the participant was not able to decide for himself due to the ID. The study did not interfere with the usual care and treatment of the participants. Ethical approval for all three care provider centers was given by the Ethics Committee of the Erasmus University Medical Center Rotterdam in the Netherlands. Guidelines of the Declaration of Helsinki (64th WMA General Assembly, October 2013) were followed. Besides, this study is registered prior to the start of the study (NTR number: NTR5162) and CONSORT guidelines regarding Randomized Trials of Nonpharmacologic Treatments were followed (Boutron, Altman, Moher, Schulz, & Ravaud, 2017).

## Study design

*Randomization and masking*

We conducted a multicenter randomized controlled trial (RCT) with three study groups to investigate the effect of BLT in adults with depressive symptoms. Block stratification was used to ensure that participants were properly distributed over the three study groups within each of the three participating centers. Block stratification was performed by a computerized program developed by an independent data-manager. One researcher (PH) enrolled the participants and used the outcomes of the digital randomization to assign the participants to the right group. To ensure blinding of the researchers, lightboxes were coded before the start of the study by an independent researcher. Furthermore, the researchers and the professional staff were not informed about which type of lightbox was distributed to the participants. The participants and their professional caregivers were not blinded and were told that two lightboxes with different amount of lux were tested in the current study. They were instructed not to share details of the lightboxes and the amount of lux with the researchers. Participants living together at the same residence did not get BLT at the same time. When data-collection was finished, the blinding was broken. No changes to methods were made after trial commencement.

*Sample size*

Prior to this study, the ideal sample size was calculated based on a clinically relevant decrease of four points on the Depressive Mood subscale of the ADAMS (Hermans & Evenhuis, 2013; Hermans, Jelluma, van der Pas, & Evenhuis, 2012). Details of the sample size calculation are previously published (Hamers, Evenhuis, & Hermans, 2017). Our aim was to include at least 57 participants in each group. Hence, a maximum of 171 participants would be included in our study. Unfortunately, after an inclusion period of almost two and a half years (May 2015- September 2017), the intended sample size was not reached. A large screening with the inclusion criteria of this study among adults with ID (>1000 participants) in the three participating care provider centers from October 2016 to March 2017 revealed some potential participants, but did not give enough perspective to extent the inclusion period longer than September 2017. Detailed information of our study protocol and the different obstacles we faced in this study are published previously (Hamers et al., 2017).

*Intervention*

In group I, participants received BLT with a 10.000 lux bright white UV-filtered lightbox (Philips Energy lightbox, type HF3319), additional to their care as usual. Participants in group II received BLT with a bright white lightbox with on average 317 lux, additional to their care as usual. In group II we used the same lightbox as in group I, but a LEE filter (no. 299) was installed. This heat resistant filter did not change the colour of the light. On the outside, the two lightboxes looked the same when they were turned off. The participants in group III got no BLT only care as usual (control group). Participants in the two intervention groups received 30 minutes BLT in the morning as early as possible after wake-up (at least before 12 a.m.), for a period of 14 consecutive days. Usually, BLT was given during breakfast. Besides oral information, a detailed BLT manual with pictograms was given to the participant and the professional caregiver before the start of the intervention. The professional caregivers were asked to report adherence in a daily log. The distance between the participant and the lightbox was 20 cm (tape-measures were distributed). A distance of 30 cm was only allowed when the 20 cm distance was not possible, for example because of wheelchair use. When a 30 cm distance was used, BLT was extended with 30 minutes per day according to the manual of the lightbox. The treatment distances in group I and group II were the same. The amount of lux of all lightboxes was measured by the Medical Technology Department of the Erasmus University Medical Center Rotterdam in the Netherlands with use of a lux meter (Konica Minolta T-10A). The average amount of lux at 20 cm of the lightboxes used in group I was 11214 lux (range 10860 - 11640) and 317 lux (range 297 -329) in group II. At a distance of 30 cm, the average amount of lux of lightboxes type I was 7122 lux (range 6930-7380) and the average amount of lux of lightboxes type II was 198 lux (range 188-209). The Medical Technology Department checked all lightboxes used in this trial on safety. Physicians, psychologists and behavioral scientists were asked, but not obligated, not to make changes in (medication) treatment four weeks prior to enrollment and up to six weeks after the end of the intervention if this was not considered necessary. Caregivers were asked to report changes in treatment during the study.



**Objectives and outcomes**

The primary objective of this study was to examine if BLT is effective in decreasing depressive symptoms in two BLT intervention groups compared to no BLT, one

week after the end of BLT. The Depressive Mood subscale (13 items) of the Anxiety, Depression And Mood Scale (ADAMS) was used to study these depressive symptoms prior to BLT (Baseline, T0) and one week after BLT (T1) (Hamers, van Ool, et al., 2018; Hermans & Evenhuis, 2013; Hermans et al., 2012). The measurements in the control group (no BLT) had the same frequency.

Our secondary objectives were to examine if there is a significant difference in effect of BLT between both intervention groups. The ADAMS Depressive Mood subscale scores on T0 and T1 of group I and group II were used to investigate this objective. Further, we examined if the effect of BLT is still visible four weeks after the end of the BLT intervention with use of the Dutch ADAMS Depression subscale scores of group I and II at T0 and T2. Additionally, subgroup analyses were used to examine depressive symptoms in the three different groups on T1 and T2.

In addition to the ADAMS Depressive Mood subscale, the Dutch Signalizing Depression List for people with Intellectual Disabilities (SDL-ID) (Roeden, 1989) was used to evaluate the effectiveness of BLT as well, because this measurement contains items that are complementary to the Dutch ADAMS Depressive Mood subscale. Besides, a subscale of the Aberrant Behavior Checklist (ABC) (Aman, Singh, Stewart, & Field, 1985) was used to measure "Irritability", because it is known that a large part of adults with ID and depressive symptoms have symptoms of irritability. In the Netherlands, these measurements are often used in clinical practice to evaluate the effectiveness of interventions. The questionnaires were completed by a professional caregiver at T0, T1 and T2. ABC scores were only available on baseline.

The presence of a major depression disorder according to the criteria of DSM-IV was investigated with the PAS-ADD Clinical Interview, which is a semi-structured psychiatric interview developed for adults with ID (Moss, 2011). Prior to the start of the study, the participants (if possible) and the professional caregivers of those in both BLT groups were asked to complete a questionnaire about the expectations of the BLT intervention. Besides, the professional caregivers were asked to report compliance, adverse events and side effects in a daily log during the intervention. In case of a serious adverse event (SAE), such as hospitalizations, serious illness or death, professional caregivers were asked to report to the researchers immediately.

We retrieved information on sex, age, level of ID, use of medication, residential setting, treatment during study intervention and BLT in the past by participants' medical and psychological files.

*Statistical analyses*

Data were analyzed using IBM SPSS Statistics 24. Prior to the start of the study, we stated in our study protocol that the intention to treat basis shall be used. None of the participants assigned to one of the three study groups switched to another study arm. Missing data on T1 and T2 were not imputed but reported. Baseline characteristics of the participants, baseline depression scores, baseline ABC Irritability scores were checked for any significant differences between the three groups. Expectations prior to the BLT, total amount of BLT days, compliance with the intervention and date of the intervention/control group period (quarter) were analyzed with One-way ANOVA (2-sided) for continuous data and Chi-squared tests for categorical data to check for confounders. Baseline differences between the groups were taken as a confounder into the analyses.



To investigate the effect of BLT on depressive symptoms, multivariate regression analyses were used. The ADAMS depressive mood subscale of group I and group II were compared separately with those of group III (control group). Independent t-tests were used to investigate if there was a significant difference in effect of BLT between both intervention groups. ANOVA repeated measures were used to investigate the effect of BLT at follow-up (four weeks after the end of BLT). For the subgroup analyses, paired samples T-tests were used to investigate the ADAMS depression subscale scores on T1 and T2 in the three different study groups. A Bonferroni correction resulted in a significant level of $p$ =0.017 (.05/3). A Bonferroni correction corrects for increased risk of a type 1 error due to multiple comparisons. Effect sizes were measured using Cohen's *d*. All statistical analyses mentioned above were also conducted with the SDL-ID total scores.

## RESULTS

### Patient characteristics

Between May 2015 and September 2017, 41 participants were included in our trial. Twelve participants were randomly assigned to group I, 15 participants to group II and 14 participants to group III. Figure 1 shows the flow diagram of our study. One participant of group II was excluded after the intervention, because there was no compliance to the study protocol (14 days of BLT were given in a six week period, instead of in a two week period). The characteristics of the participants of the three groups are presented in Table 1. The participants were aged between 24 and 81 years and all levels of ID were covered in this study. According to norms of Zeilinger et al. (2011), 60.0% of our total sample had an ABC Irritability percentile ranking score above 80% (Zeilinger, Weber, & Haveman, 2011), which means these participants had a considerable amount of challenging behavior.

On baseline, there were significant differences in 'sex' between the three groups ($p$ =0.024) and we corrected for this baseline difference as appropriate. Expectations prior to the BLT ($p$ =0.056), total amount of BLT days ($p$ = 0.060), compliance with the intervention ($p$ = 0.420), and date of the intervention/control group period (quarter of the year) ($p$ = 0.058), were checked for the possibility of influencing the T1 depression scores. None of these variables were confounders. At baseline, none of the participants was classified with a Major Depressive Disorder. There were no significant differences between the three groups on baseline ADAMS depressive symptoms ($p$=*0*.390) and SDL-ID total score ($p$ =0.709).

### Primary outcomes

Table 2 shows the clinical outcomes on depressive symptoms measured on baseline (T0), one week after the intervention (T1) and four weeks after the end of the intervention (T2). The multivariate regression analyses showed no significant differences between groups I and III on depressive symptoms measured with the ADAMS depression subscale on T1 ($p$ = 0.199), and no significant differences between group II and group III on T1 ($p$ = 0.451).

**Secondary outcomes**

Independent Samples t-test revealed no significant differences between group I T1 and group II T1 ADAMS depression subscale scores ($p = 0.394$). Likewise, there were no significant differences between group I T1 and group II T1 SDL-ID scores ($p = 0.101$). ANOVA repeated measures were used to examine if the effect of BLT was still visible four weeks after the end of BLT. We used the ADAMS depression subscale scores at Time 1 (baseline, T0), Time 2 (one week after BLT, T1) and Time 3 (four week follow-up, T2). In group I, Mauchly's test, $\mathcal{X}^2(2) = 4.70$, $p = 0.095$ did not indicate any violation of sphericity. There was a significant effect for time in this group ($p= 0.008$). Post hoc tests using the Bonferroni correction for multiple comparisons revealed significant differences on ADAMS depression subscale scores between Time 1 and Time 3 in group I ($p = 0.004$). In group II, Mauchly's test, $\mathcal{X}^2(2) = 1.72$, $p =0 .423$ did not indicate any violation of sphericity and there was a significant effect for time as well ($p= 0.013$). Post hoc tests using the Bonferroni correction showed significant differences between Time 1 and Time 3 ($p =0.008$) in this group.

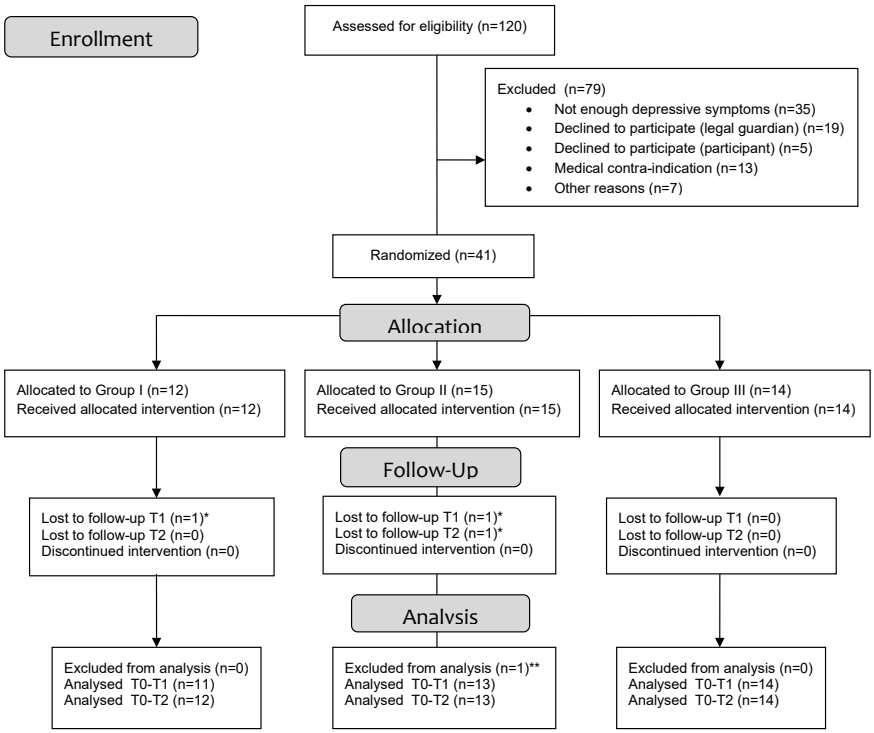


**Figure 1.** Flow diagram participants. *Professional caregiver did not complete the questionnaires at this time point. **No compliance to the study protocol.

**Table 1.** Participants characteristics

| | **Group I BLT 10.000 lux n=12** | **Group II BLT dim light n=14** | **Group III Control group n=14** | ***p*- value[a]** |
|---|---|---|---|---|
| Sex | | | | **.024** |
| Male (%) | 5 (41.7) | 4 (28.6) | 11 (78.6) | |
| Female (%) | 7 (58.3) | 10 (71.4) | 3 (21.4) | |
| Age, years | | | | .531 |
| Mean (SD) | 56.17 (11.33) | 57.14 (11.41) | 52.07 (14.29) | |
| Level of ID (%) | | | | .076 |
| Mild | 5 (41.7) | 2 (14.3) | 2 (14.3) | |
| Moderate | 2 (16.7) | 2 (14.3) | 8 (57.1) | |
| Severe | 3 (25.0) | 7 (50.0) | 2 (14.3) | |
| Profound | 2 (16.7) | 3 (16.7) | 2 (14.3) | |
| Medication use (%)[b] | | | | |
| Antidepressants | 6 (50.0) | 6 (42.9) | 6 (42.9) | .728 |
| Antipsychotics | 9 (75.0) | 9 (64.3) | 8 (57.1) | .650 |
| Benzodiazepines | 4 (33.3) | 5 (35.7) | 3 (21.4) | .653 |
| Anti-epileptics | 5 (41.7) | 4 (28.6) | 2 (14.3) | .404 |
| Contraception | 2 (16.7) | 2 (14.3) | 1 (7.1) | .665 |
| Beta blockers | 1 (8.3) | 0 (0.0) | 1 (7.1) | .540 |
| Anxiolytics | 0 (0.0) | 0 (0.0) | 0 (0.0) | .386 |
| Melatonin | 0 (0.0) | 1 (7.1) | 0 (0.0) | .440 |
| No medication used | 1 (8.3) | 3 (21.4) | 2 (14.3) | .596 |
| Missing data | 0 (0.0) | 0 (0.0) | 1 (7.1) | |
| ABC Irritability subscale | | | | .530 |
| Mean (SD) | 9.17 (4.49) | 10.36 (7.62) | 12.00 (6.45) | |
| Total BLT days | | | | .249 |
| Mean (SD) | 13.00 (1.54) | 12.14 (2.07) | n.a. | |
| Date of BLT intervention/ control group period, *n* (%) | | | | .164 |
| 1st Quarter of the year | 6 (50.0) | 2 (14.3) | 6 (42.9) | |
| 2nd Quarter of the year | 4 (33.3) | 4 (28.6) | 4 (28.6) | |
| 3rd Quarter of the year | 1 (8.3) | 2 (14.3) | 3 (21.4) | |
| 4th Quarter of the year | 1 (8.3) | 6 (42.9) | 1 (7.1) | |

*Abbreviations: BLT: Bright Light Therapy; SD: standard deviation; ID: Intellectual Disability; ABC: the Aberrant Behavior Checklist; n.a.: not applicable. a Calculated as comparisons of the three groups, using ANOVA for continuous variables or Chi-square tests for discrete variables. The comparison of total BLT days was only calculated for the two intervention groups. [b] Some participants used more than 1 medication. Significant test values are in bold type.*

**Table 2.** Outcomes ADAMS Depression subscale and SDL-ID Totalscore

| | **Group I 10.000 lux** | **Group II BLT dim light** | **Group III Control group** |
|---|---|---|---|
| **ADAMS Depression subscale T0** | | | |
| *Mean (SD)* | 21.83 (5.49) | 19.86 (3.70) | 19.43 (4.70) |
| **ADAMS Depression subscale T1** | | | |
| *Mean (SD)* | 13.73 (5.68)[a] | 16.00 (6.92) | 18.86 (7.38) |
| **ADAMS Depression subscale Change T0-T1** | | | |
| *Mean (95%CI)* | 8.36 (3.50-13.23) [b] | 3.54 (0.82-6.26)[b] | 0.57 (-3.91-5.05) |
| **Cohen's *d* Effect size T0-T1** | 1.52 | 0.73 | 0.10 |
| (*95%CI)* | (-0.66-3.70) | (-1.26-2.72) | (-2.11-2.30) |
| **ADAMS Depression subscale T2** | | | |
| *Mean (SD)* | 11.25 (7.03)[a] | 14.85 (7.70) | 16.29 (8.42) |
| **ADAMS Depression subscale Change T0-T2** | | | |
| *Mean (95%CI)* | 10.58 (5.61-15.55)[b] | 5.39 (2.13-8.64)[b] | 3.14 (-1.62-7.91) |
| **Cohen's *d* Effect size T0-T2** | 1.75 | 0.87 | 0.48 |
| (*95%CI)* | (-0.67-4.17) | (-1.29-3.04) | (-1.96-2.91) |
| **SDL-ID Total scores T0** | | | |
| *Mean (SD)* | 38.17 (6.63) | 39.29 (3.41) | 37.57 (6.16) |
| **SDL-ID Total scores T1** | | | |
| *Mean (SD)* | 30.82 (6.23)[a] | 35.15 (6.14) | 38.07 (7.98) |
| **SDL-ID Total scores Change T0-T1** | | | |
| *Mean (95%CI)* | 8.00 (3.43-12.57) [b] | 4.00 (.060-7.94) | -0.50 (-4.24-3.24) |
| **Cohen's *d* Effect size T0-T1** | 1.19 | 0.88 | -0.07 |
| *(95%CI)* | (-1.32-3.71) | (-0.91-2.66) | (-2.62-2.47) |
| **SDL-ID Total scores T2** | | | |
| *Mean (SD)* | 29.33 (5.94)[a] | 32.69 (6.03)[a] | 35.50 (7.62) |
| **SDL-ID Total scores Change T0-T2** | | | |
| *Mean (95%CI)* | 8.83 (3.35-14.32)[b] | 6.85 (3.37-10.33)[b] | 2.07 (-1.91-6.06) |
| **Cohen's *d* Effect size T0-T2** | 1.47 | 1.42 | 0.31 |
| (*95%CI)* | (-0.95-3.88) | (-0.35-3.17) | (-2.16-2.78) |

*T0: baseline, T1: one week after intervention, T2: follow-up 4 weeks. Clinical cut-off point ADAMS Depression subscale = 14. Clinical cut-off point SDL-ID Total score = 35. a Mean score below clinical cut-off point. b Significant difference (a significant level of p=0.017 (.05/3) was used to correct for increased risk of a type 1 error due to multiple comparisons).*

The results of the subgroup analyses (paired samples t-tests) including the effect sizes measured with Cohen's *d* can be found in Table 2. In group I, we found a significant difference with a very large effect size (*d* = 1.52*)* between T0 and T1 ADAMS depression subscale scores (*p* =0.003). We also found a significant difference with a very large effect size (*d* = 1.75*)* between T0 and T2 ADAMS depression subscale scores in group I (*p* = 0.001). In group II, a significant difference with a medium effect size (*d* = 0.73) was found between T0 and T1 ADAMS depression subscale scores (*p* =0.015). Furthermore, we found a significant difference with a large effect size (*d*= 0.87*)* between T0 and T2 ADAMS depression subscale scores (*p*= 0.004). In group III, no significant differences were found between T0 and T1 ADAMS depression subscale scores (*p* = 0.787). Likewise, we found no significant differences between T0 and T2 ADAMS depression subscale scores (*p* = 0.178). Table 2 also shows the subgroup analysis with paired samples t-tests of the SDL-ID scores and the effect sizes measured with Cohen's *d*.

Figure 2 shows the mean change in ADAMS Depression subscale scores over time in the three groups. In group I, the mean ADAMS depression subscale score and the mean SDL-ID score on T1 and T2 decreased below the clinical cut-off points. In group II, only the mean SDL-ID score on T2 was below the clinical cut-off point. In group III, no mean scores on T1 and T2 decreased below the clinical cut-off points.



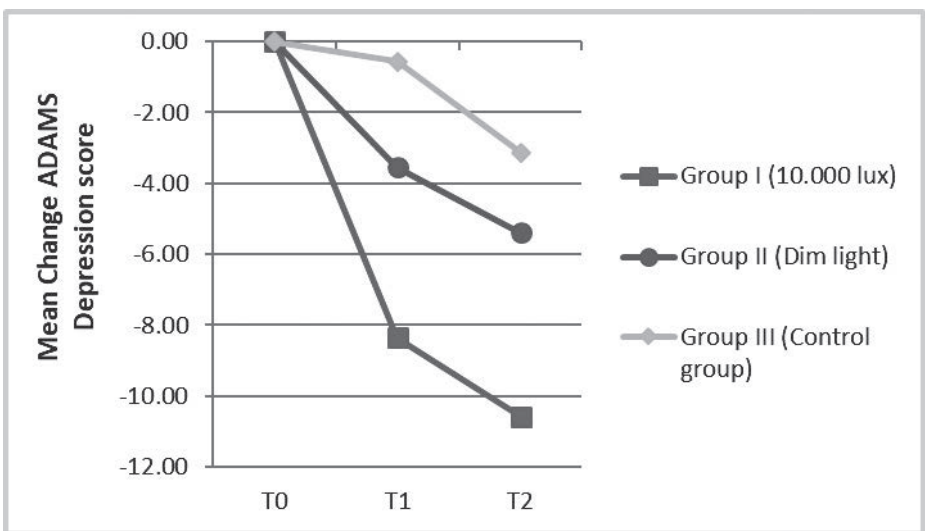


**Figure 2.** Mean change in ADAMS Depression subscale score (13 items) in patients randomly assigned to one of the three study groups.

In group I, 75.0% of the participants had a decreased ADAMS depression subscale score on T1. In group II and group III this was 71.4% and 57.1% respectively. When further examined, the depression scores of 45.5% of the participants in group I and 7.7% of the participants in group II, were decreased 40% or more after BLT. In group III, 14.3% of the participants had 40% or more decreased depression scores after their control group period.

The multivariate regression analyses with the SDL-ID scores on T1 showed significant differences between group I and group III ($p$ = 0.046). It was found that 'group' significantly predicted the T1 SDL-ID scores ($p$= 0.014). There were no significant differences on T1 SDL-ID scores between group II and group III ($p$ = 0.401).

After the analyses for the whole sample (n=40), we checked if BLT with less than 10 days (in a period of 14 days) influenced the outcomes. Therefore, we repeated all analyses in a sample excluding the participants who had less than 10 BLT days in the 14 day period. In total, one participants of group I and three participants of group II were excluded for this sample analyses (n=36). The patient characteristics of this sample can be found in Table 3 and depression outcomes of this sample can be found in Table 4, both placed in the supplement. In this sample, we did not find significant differences between the BLT groups and control group or between both BLT groups on our primary outcome measure.

**Adverse events and side effects**

No serious adverse events or adverse events were reported during this trial. A minimum amount of side effects were registered in the daily logs. Headache was reported twice in group II and fatigue or drowsiness was mentioned three times in group I and once in group II. In the daily logs other striking behavior regarding the BLT was reported as well: some participants turned away their face or body from the lightbox. In group I, this was reported four times, and in group II six times.

## DISCUSSION

Non-pharmacological treatment options for adults with ID and depressive symptoms are limited. As far as we know, this is the first multicenter randomized controlled trial investigating the effect of BLT on depressive symptoms in adults with ID. We found no significant effect between the three trial groups on our primary outcome. However, the results of our secondary analyses suggest that BLT with 10.000 lux decreases depressive symptoms directly after the intervention period and at follow-up, showing very large effect sizes. In the dim light group, there are also significant decreases in depressive symptoms directly after the intervention and at follow-up with medium to large effect sizes. We did not find significant decrease of depressive symptoms in our control group.

Prior to the current study, only a couple of case reports (Altabet et al., 2002; Cooke & Thompson, 1998; Tsiouris, 2007) and one feasibility study (Hermans et al., 2017) were published on BLT for adults with ID and depressive symptoms. Positive results were found in these first explorations of BLT to decrease depressive symptoms in adults with ID, but these must be interpreted with caution because of the lack of a randomization procedure and control groups. Therefore, the strengths of the current study, for example, the block randomization and blinding procedures, and the strictly protocolled intervention, makes this study adding important information to the existing literature (Hamers, Festen, et al., 2018). As most studies, our study has a couple of limitations which must be mentioned. The first limitation is the small sample sizes of the three groups. During our study, we faced a number of obstacles (Hamers et al., 2017). From the 120 potential participants who were signed up for the study, only 41 could be included in our trial. The strict inclusion criteria of our trial, for example, the exclusion of people with bipolar disorder and people who use specific photosensitizing medications, contributed to the safety of our trial, but also lowered the number of participants enrolled in our study. With our small sample size, significant differences between the intervention groups and the control group, and between both intervention groups may be hard to find, due to a lack of power. The confidence intervals of the mean change between baseline and T1 and between baseline and T2 in group I, suggest that in a larger sample it is likely that significant differences could be found. The second limitation of our study is the high prevalence of psychotropic

medication used in all three groups. Consequently, the BLT intervention in this study cannot completely be seen as a monotherapy, but more as an add-on treatment. Since it is known that in the population of adults with ID (and depressive symptoms), high numbers of psychotropic medication are used, our sample seems quite representative.

It is interesting to note that in our study, antipsychotics are used more frequently than antidepressants, which was quite unexpected because exclusion criteria of our study prevented including participants with psychotic symptoms or bipolar disorder. Furthermore, in our sample, antipsychotics are used more often than in samples of adults with ID without depressive symptoms. From existing literature, we know that a large part of adults with ID use antipsychotics off-label for challenging behavior (de Kuijper et al., 2010). It is possible that in our study, a large part of the participants who use antipsychotics have depressive symptoms which are being expressed with challenging behavior (also regarding the high scores on the ABC Irritability subscale at baseline), and therefore treated with off-label antipsychotics.

Except for a significant difference in depressive symptoms between group I and group III after the intervention measured with one questionnaire in our secondary outcomes, we did not find any significant differences in depressive symptoms between the 10.000 lux condition, dim light condition and care as usual. However, we did find that half of the participants recovered for at least 40% from their depressive symptoms after 10.000 lux BLT and less than 15% recovered for at least 40% after dim light BLT or no BLT (control group). Overall, we do see a positive trend in decreasing depressive symptoms in our 10.000 lux BLT group, with the number of depressive symptoms even beneath the clinical cut-off points after the intervention. This makes BLT a promising intervention to decrease depressive symptoms in clinical practice. Therefore, RCTs with lager sample sizes (also with and without used psychotropic medication), are needed to further investigate the (direct) effect of BLT on depressive symptoms of adults with ID.

In summary, to the best of our knowledge, this is the first multicenter RCT investigating the effect of BLT on depressive symptoms in adults with ID. Our results show significant decreases of depressive symptoms in both intervention groups, but not in the control group. Overall, significant differences between both intervention groups, and between

the intervention groups and control group were not found, which is possibly due to a sample size problem. Trial replications with larger samples are needed. Compared to psychotropic medication, BLT has limited side effects, is not expensive and can have immediate effect after a short period. This makes BLT a promising non-pharmacological treatment option to decrease depressive symptoms in adults with ID.

## DATA SHARING

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

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## SUPPLEMENTARY MATERIAL

**Table 3.** Participants characteristics (n=36)

| | **Group I BLT 10.000 lux n=11** | **Group II BLT dim light n=11** | **Group III Control group n=14** | ***p*- value[a]** |
|---|---|---|---|---|
| Sex | | | | **.022** |
| Male (%) | 4 (36.4) | 3 (27.3) | 11 (78.6) | |
| Female (%) | 7 (63.6) | 8 (72.7) | 3 (21.4) | |
| Age, years | | | | .408 |
| Mean (SD) | 57.64 (10.61) | 58.82 (9.72) | 52.07 (14.29) | |
| Level of ID (%) | | | | **.026** |
| Mild | 5 (45.5) | 1 (9.1) | 2 (14.3) | |
| Moderate | 2 (18.2) | 1 (9.1) | 8 (57.1) | |
| Severe | 3 (27.3) | 7 (63.6) | 2 (14.3) | |
| Profound | 1 (9.1) | 2 (18.2) | 2 (14.3) | |
| Medication use (%)[b] | | | | |
| Antidepressants | 6 (54.5) | 5 (45.5) | 6 (42.9) | .763 |
| Antipsychotics | 8 (72.7) | 6 (54.5) | 8 (57.1) | .657 |
| Benzodiazepines | 4 (36.4) | 5 (45.5) | 3 (21.4) | .565 |
| Anti-epileptics | 4 (36.4) | 3 (27.3) | 2 (14.3) | .558 |
| Contraception | 2 (18.2) | 1 (9.1) | 1 (7.1) | .670 |
| Beta blockers | 1 (9.1) | 0 (0.0) | 1 (7.1) | .621 |
| Anxiolytics | 0 (0.0) | 0 (0.0) | 0 (0.0) | .446 |
| Melatonin | 0 (0.0) | 1 (9.1) | 0 (0.0) | .420 |
| No medication used | 1 (9.1) | 3 (27.3) | 2 (14.3) | .516 |
| Missing data | 0 (0.0) | 0 (0.0) | 1 (7.1) | |
| ABC Irritability subscale | | | | .473 |
| Mean (SD) | 8.64 (4.30) | 12.00 (7.64) | 12.00 (6.45) | |
| Total BLT days | | | | .501 |
| Mean (SD) | 13.36 (0.92) | 13.09 (0.94) | n.a. | |
| Date of BLT intervention/ control group period, *n* (%) | | | | **.026** |
| 1st Quarter of the year | 6 (54.5) | 2 (18.2) | 6 (42.9) | |
| 2nd Quarter of the year | 4 (36.4) | 3 (27.3) | 4 (28.6) | |
| 3rd Quarter of the year | 0 (0.0) | 0 (0.0) | 3 (21.4) | |
| 4th Quarter of the year | 1 (9.1) | 6 (54.5) | 1 (7.1) | |

*Abbreviations: BLT: Bright Light Therapy; SD: standard deviation; ID: Intellectual Disability; ABC: the Aberrant Behavior Checklist; n.a.: not applicable. a Calculated as comparisons of the three groups, using ANOVA for continuous variables or Chi-square tests for discrete variables. The comparison of total BLT days was only calculated for the two interventiongroups. b Some participants used more than 1 medication. Significant test values are in bold type.*

**Table 4.** Outcomes ADAMS Depression subscale and SDL-ID (n=36)

| | **Group I 10.000 lux** | **Group II BLT dim light** | **Group III Control group** |
|---|---|---|---|
| **ADAMS Depression subscale T0** | | | |
| *Mean (SD)* | 22.36 (5.43) | 19.36 (3.64) | 19.43 (4.70) |
| **ADAMS Depression subscale T1** | | | |
| *Mean (SD)* | 13.60 (5.97) [a] | 15.45 (7.44) | 18.86 (7.38) |
| **ADAMS Depression subscale Change T0-T1** | | | |
| *Mean (95%CI)* | 9.10 (3.96 – 14.24) [b] | 3.91 (0.84-6.98) | 0.57 (-3.91-5.05) |
| **Cohen's *d* Effect size T0-T1** | 1.62 | 0.70 | 0.10 |
| (*95%CI*) | (-0.70-3.93) | (-1.63-3.03) | (-2.11-2.30) |
| **ADAMS Depression subscale T2** | | | |
| *Mean (SD)* | 11.91 (6.98) [a] | 14.10 (8.08) | 16.29 (8.42) |
| **ADAMS Depression subscale Change T0-T2** | | | |
| *Mean (95%CI)* | 10.46 (4.95-15.96) [b] | 5.70 (1.57-9.83) [b] | 3.14 (-1.62-7.91) |
| **Cohen's *d* Effect size T0-T2** | 1.75 | 0.88 | 0.48 |
| (*95%CI*) | (-0.74-4.24) | (-1.62-3.38) | (-1.96-2.91) |
| **SDL-ID Total scores T0** | | | |
| *Mean (SD)* | 38.55 (6.82) | 39.36 (3.70) | 37.57 (6.16) |
| **SDL-ID Total scores T1** | | | |
| *Mean (SD)* | 30.90 (5.56) [a] | 35.73 (6.53) | 38.07 (7.98) |
| **SDL-ID Total scores Change T0-T1** | | | |
| *Mean (95%CI)* | 8.40 (3.37-13.43) [b] | 3.64 (-1.11-8.38) | -0.50 (-4.24-3.24) |
| **Cohen's *d* Effect size T0-T1** | 1.20 | 0.72 | -0.07 |
| *(95%CI)* | (-1.52-3.93) | (-1.40-2.83) | (-2.62-2.47) |
| **SDL-ID Total scores T2** | | | |
| *Mean (SD)* | 30.00 (5.75) [a] | 33.10 (6.19) [a] | 35.50 (7.62) |
| **SDL-ID Total scores Change T0-T2** | | | |
| *Mean (95%CI)* | 8.55 (2.50 -14.59) [b] | 6.60 (2.07-11.13) [b] | 2.07 (-1.91 -6.06) |
| **Cohen's *d* Effect size T0-T2** | 1.42 | 1.31 | 0.31 |
| (*95%CI*) | (-1.09-3.93) | (-0.74-3.36) | (-2.16-2.78) |

*T0: baseline, T1: one week after intervention, T2: follow-up 4 weeks. Clinical cut-off ADAMS Depression subscale = 14. Clinical cut-off point SDL-ID Total score = 35. a Mean score below clinical cut-off point. b Significant difference (a significant level of p= 0.017 (.05/3) was used to correct for increased risk of a type 1 error due to multiple comparisons).*

# Chapter 7

## Effect of bright light therapy on long-term stress levels in adults with intellectual disabilities and depressive symptoms.

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## ABSTRACT

The aim of this study was to explore long-term biological stress levels, as assessed by hair cortisol (HairF) and hair cortisone (HairE) concentrations, in adults with intellectual disabilities (ID) and depressive symptoms, and to investigate whether bright light therapy (BLT) could influence these concentrations. Scalp hair samples were used to retrospectively examine HairF and HairE levels in adults with ID and depressive symptoms on baseline and post bright light therapy (with 10.000 lux) and dim light (300 lux). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to measure hair glucocorticoid concentrations. Hair glucocorticoids of 14 participants (seven with 10.000 lux BLT and seven with dim light 300 lux intervention) were included in our analyses. A significant moderate positive correlation was found between baseline HairF and baseline scores on depression (ADAMS: $p$=0.028 and SDL-ID: $p$=0.028). HairE levels, but not HairF, were significantly increased after light intervention in our total sample (geometric baseline mean: 10.0 pg/mg [95% CI 7.2-13.9] vs post intervention: 14.0 pg/mg [95% CI: 11.2-17.4], $p$= 0.003), and in particular after dim light (geometric baseline mean: 9.3 pg/mg [95% CI 6.1-14.1] vs post intervention: 13.5 pg/mg [95% CI: 10.0-18.3], $p$=0.020). This is the first study on hair glucocorticoids in adults with an ID and depressive symptoms. The use of hair glucocorticoids to retrospectively examine biological levels of stress in adults with ID seems a promising method. It is a more objective method to gain insight in the level of stress adults with ID may have experienced.

## 1. INTRODUCTION

A large part of the population of adults with intellectual disabilities (ID), IQ < 70 and significant problems with adaptive functioning, is diagnosed with a major depressive disorder (MDD) or has depressive symptoms (Cooper et al., 2007b; Hermans et al., 2013). It is known that many adults with ID also experience negative life events (Hermans, H. & Evenhuis, H. M., 2012; Hove et al., 2016). Depressive symptoms are associated with life events and stress (Cooper et al., 2007a; Hermans, H. & Evenhuis, H. M., 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). In the general population, a chronically elevated level of cortisol is not only associated with mental health problems such as depression, but also with physical problems such as cardiovascular disease, obesity and diabetes mellitus (Manenschijn et al., 2013; Schoorlemmer et al., 2009; Stetler & Miller, 2011; Vreeburg et al., 2009). Long-term stress can not reliable be measured with serum, saliva or urine samples. The active glucocorticoid cortisol and the biologically inactive cortisone can be reliably measured in scalp hair (Wester & van Rossum, 2015). Scalp hair assessment is a non-invasive reliable and valid method to measure long-term exposure to glucocorticoids (Manenschijn et al., 2011; Noppe et al., 2014; Stalder & Kirschbaum, 2012). Hair cortisol has been used as a biomarker to retrospectively examine stress over periods of months to even years (Gow et al., 2010; Karlen et al., 2011; Kirschbaum et al., 2009; Staufenbiel et al., 2014; Staufenbiel et al., 2013).



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). With regard to depression and anxiety, both positive and negative associations between related symptoms and HairF are observed (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, which is the inactive metabolite of cortisol and can be re-activated to cortisol by the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) in skin and hair follicles (Baudrand & Vaidya, 2015), in diseases and mental health 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., 2011; Wirz-Justice et al., 1993). 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 24h 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 ID, cortisol concentrations have so far only 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). No study has yet investigated long-term cortisol as well as cortisone concentrations in adults with ID. Therefore, the aim of the current study was to explore HairF and HairE in adults with ID and depressive symptoms, and to investigate whether BLT could alter these long-term glucocorticoid levels. 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.

## 2. METHODS

### 2.1. Participants

All participants of the current study were included in a multicenter randomized controlled trial which investigated the effect of BLT on depressive symptoms in adults with ID. Details of the study can be found in the published study protocol (Hamers et al., 2017). 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 with ID in the Netherlands and the research group of Intellectual Disability Medicine of the Erasmus University Medical Center Rotterdam in the Netherlands.

### 2.2. Light intervention

We used two light interventions in this study: 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 installed to reduce the amount of lux to 317 lux (mean), without changing the color of the light. All participants received the light intervention in the morning before 12 a.m., 30 minutes a day for a period of 14 consecutive days. The lightbox was placed at 20 centimeters distance in order to receive the right amount of lux.

### 2.3. Hair glucocorticoids

We collected three centimeters of scalp hair (proximal) from participants to analyze 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 Wester and colleagues (Wester & van Rossum, 2015). As scalp hair grows approximately one centimeter a month (Wennig, 2000), the scalp hair samples in our study were cut six 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 centimeter closest to the scalp was assumed to reflect the period of approximately four weeks after the end of the intervention, since we took also into account the days needed for hair to grow out of the scalp from the hair follicle. The second centimeter of the sample, which is not used in the analyses of this study, contained the intervention period. The third centimeter of the hair sample was our baseline measurement. 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 hours. Then methanol was added for the 18 hours 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. This method is described in detail elsewhere (Noppe et al., 2015). All hair samples were analyzed 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 (Hermans & Evenhuis, 2013; Hermans et al., 2012). This proxy instrument contains 28 items and is specially developed for adults with ID. The Anxiety subscale contains 7 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., 2018; Hermans & Evenhuis, 2013; Hermans et al., 2012). 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 ID), 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 amount of life events of the participant in the year prior to enrollment in the study (Hermans, H. & Evenhuis, H.M., 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 is retrieved from medical files. All questionnaires are filled in by the professional caregiver of the participant. Other participant characteristics (sex, age, level of ID and genetic syndrome) are 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 the Netherlands (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, Chicago, Illinois) 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 are excluded as well. Other corticosteroid use was included in our analyses as a confounder (Wester et al., 2017). Group comparisons on baseline characteristics were analyzed 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 and T1, and between T0 and T2. The same analyses were used to examine the differences in anxiety subscale scores. The Kolmogorov–Smirnov tests showed that our hair glucocorticoid data were not normally distributed, and therefore $\log_{10}$ transformations were used in our analyses. To examine if there were baseline difference 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 and post intervention, 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.



## 3. RESULTS

### 3.1. Hair samples

Scalp hair samples with sufficient length of three centimeters were available in 17 out of 26 participants 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 participants 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.

**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# | 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## | 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# | >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 |

*HairF: cortisol; HairE: cortisone. #Patient 4 and 13 were excluded from the analyses because their results were extreme outliers. ##Patient 8 was excluded because of corticosteroid use on the head hair area. Intervention A: 10.000 lux bright light therapy, Intervention B: dim light intervention.*

### 3.2. Participant characteristics

Finally, 14 participants were included in our analyses: seven participants were exposed to BLT with 10.000 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 ID (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), indicating clinically significant depressive symptoms. None of the participants met the diagnostic criteria of a Major Depressive Disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). On baseline, we found no significant differences between the groups on age, sex, level of ID, 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.

**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 ID (%) | | | |
| 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) |

**Table 2.** Continued

| | Total group n=14 | Group A (10.000 lux) n=7 | group B (Dim light) n=7 |
|---|---|---|---|
| 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 (-0.8-14.5) | 3.3 (-0.1-6.7) |
| 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 -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(-0.6-7.1) | 2.6 (-0.5-5.7) |
| 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 (-1.8-8.3) | 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 (-0.6-15.2) | 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 (-1.8-18.4) | 7.6 (1.1-14.1) |

*SD: standard deviation; ID: intellectual disability; IQ: intelligence quotient; [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= 0.025 (.05/2) was used to correct for increased risk of a type 1 error due to multiple comparisons. * Significant difference.*

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

We found a moderate correlation between baseline HairF and baseline ADAMS Depressive Mood subscale scores (r= 0.605, *p*=0.028), and baseline SDL-ID Total scores (r= 0.605, *p*=0.028), which both were statistically significant. We did not find significant correlations between baseline HairF and baseline ADAMS Anxiety subscale scores (r=0.355, *p*=0.234), life events in the past year (r= -0.275, p=0.362), and negative life events in the past year (r=-0.124, *p*=0.687).

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

There were no significant associations between baseline HairE and baseline ADAMS Depressive Mood subscale scores (r= -0.120, *p*=0.696), and baseline SDL-ID Total scores (r= -0.143, *p*=0.641). We found a trend towards an inverse correlation between baseline HairE and baseline ADAMS Anxiety subscale scores (r= -0.512, *p*=0.073). We did not find significant correlations between HairE and life events in the previous year (r= -0.356, *p*=0.233), and negative life events in the previous year (r= -0.397, *p*=0.179).

### 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 are shown. In the total sample, we did not find significant differences between pre and post intervention in HairF (*p*=0.802), but we found a significant increase in HairE (geometric baseline mean: 10.0 pg/mg [95% CI: 7.2-13.9] vs post intervention: 14.0 pg/mg [95% CI: 11.2-17.4], *p*= 0.003). In group A (10.000 lux BLT), we found no significant differences between pre and post intervention in HairF (*p*=0.619) and HairE (*p*=0.108). In group B (dim light intervention), we found no significant change in HairF (*p*=0.682). However, we found a significant increase in HairE in this group (Geometric baseline mean : 9.3 pg/mg [95% CI: 6.1-14.1] vs post intervention: 13.5 pg/mg [95% CI: 10.0-18.3], *p*=0.020).



### 3.6. HairE/HairF ratio

We found a significant increase in mean HairE/HairF ratio after the light intervention in the total sample (baseline: 3.1 [95% CI: 1.8-4.3] vs post intervention: 4.0 [95% CI: 2.4-5.5], *p*= 0.10). In group A, we also found a significant increase in mean HairE/HairF ratio after the light intervention (baseline: 2.9 [95% CI: 0.97-4.9] vs post intervention: 3.8 [95% CI: 1.3-6.2], *p* =0.036). In group B, no significant difference was found between baseline and post intervention mean HairE/HairF ratio (baseline: 3.2 [95% CI: 0.9-5.4] vs post intervention: 4.2 [95% CI: 1.3-7.1], *p*=0.143).

**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 |
|---|---|---|---|
| **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 | 4.9 (2.8 - 8.7) | 5.8 (2.0 - 16.6) | 4.2 (1.9- 9.4) |
| **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 | 14.0 (11.2 - 17.4)* | 14.5 (9.5 - 22.0) | 13.5 (10.0 - 18.3)* |
| **Ratio HairE/HairF** | | | |
| Baseline | 3.1 (1.8-4.3) | 2.9 (0.97-4.9) | 3.2 (0.9-5.4) |
| Post intervention | 4.0 (2.4-5.5)* | 3.8 (1.3-6.2)* | 4.2 (1.3 -7.1) |

*CI: confidence interval; HairF: cortisol; HairE: cortisone; Geometric mean and 95% CI of the Log10 transformed data are shown. We corrected for corticosteroid use in the pre-post intervention analyses. *Significant change.*

## 4. DISCUSSION

We performed a first small explorative study on long-term glucocorticoid exposure in adults with ID and depressive symptoms. Collecting hair samples for investigating hair glucocorticoids in adults with ID seems feasible in the majority of participants. 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. 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. 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 24h 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 nine years higher than in the general population study (median age 51 (range 40-65) vs median age 42 (range 18-85), respectively). Previous research showed that HairF can increase with age, which can be caused by changes in HPA axis function related to aging (Kudielka et al., 2004). So, 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 a 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 due to the fact that we included participants with elevated depressive symptoms, but without a diagnosis of MDD.

It is known, that depressive symptoms are positively associated with stress (Constance, 2005). In the adult ID population, a large part 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, H. & Evenhuis, H. M., 2012). In a recent study in adults with ID, 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 colleagues also reported that more (negative) life events were associated with a greater incidence of depressive and anxiety symptoms and MDD in elderly with ID (Hermans, H. & Evenhuis, H. M., 2012). In our study, higher HairF was associated with more depressive symptoms.

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 ID must be interpreted with caution. Besides, all our participants had elevated depressive symptoms and, consequently, the results of our study cannot be generalized to adults with ID without depressive symptoms. Previous research has shown that natural light can decrease glucocorticoids in scalp hair (Wester et al., 2016). Therefore, 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.

Retrospectively examining stress in adults with ID 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 ID, but these results can be biased because a proxy has to make a judgement of the stress of the adult with ID. 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 ID population, especially for those with severe ID.

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 ID may be different from that of the general population (Hilgenkamp & Baynard, 2018), and therefore, more studies on hair glucocorticoids in adults with ID, with and without depressive symptoms, are needed. Furthermore, attention must be paid to the variety of syndromes causing ID, which may influence the working mechanism of the HPA axis. Additionally, HairF is associated with cardiovascular disease and type 2 diabetes in the general population (Manenschijn et al., 2013). Both diseases occur frequently in elderly with ID, 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 the ID population to fill the gaps of knowledge. In this way, more will be known about hair glucocorticoids in adults with ID, 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 comorbid 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 ID.

In conclusion, this first explorative study on hair glucocorticoids in adults with ID and depressive symptoms showed that at baseline higher HairF was significantly correlated with more depressive symptoms. We also found a trend towards an inverse correlation between baseline HairE and anxiety symptoms. HairE was significantly increased after light therapy in our total study population. The use of hair glucocorticoids to retrospectively examining biological stress in adults with ID may be a promising method to gain more insight in the level of stress adults with ID may have experienced.

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## DECLARATION OF INTERESTS

All authors declare no conflicts of interest.

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# Chapter 8

General discussion

## GENERAL DISCUSSION

High point prevalence rates of depressive symptoms are found in adults with intellectual disabilities (ID), even though depressive symptoms can be hard to recognize in this population (1-5). The overall aim of this thesis was to add knowledge on diagnostics of depressive symptoms and long-term stress, and on non-pharmacological treatment options to treat depressive symptoms in adults with ID. In this final chapter, the main findings of this thesis, opportunities and implications for future research, and implications for clinical practice are discussed.

### Main findings

*The Dutch ADAMS is applicable in adults with intellectual disabilities of all ages*

Symptoms of depression in adults with ID are often expressed differently compared to those in the general population, which may be a reason why these specific symptoms are not always recognized as being part of a Major Depressive Disorder (MDD) in adults with ID (5-8). Frequently expressed clinical representations of depression in adults with ID are crying, signs of irritability, challenging behavior and withdrawal from social interactions (6, 9). These specific characteristics are not included in the characteristics of MDD such as defined in the fifth Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (10), but these specific characteristics can be found in the adapted criteria and accompanying notes of MDD described in the Diagnostic Manual-Intellectual Disability 2 (DM-ID-2) (8). Because depressive symptoms can be hard to recognize in adults with ID, current prevalence numbers regarding MDD in adults with ID seem an underestimation, even though the numbers are already high (11). Further, when depressive symptoms are not recognized, patients might not getting proper treatment. In order to further improve the recognition of depressive symptoms in adults with ID, reliable and valid instruments are needed. Research regarding the reliability and validity of the Dutch Anxiety, Depression And Mood Scale (ADAMS) in adults aged 50 years or older was published by Hermans and colleagues in 2012 (12). Therefore, we investigated the reliability and validity of the Dutch ADAMS in adults with ID aged <50 years (13). Our study (Chapter 2), together with the results of the study in 2012, showed that the Dutch ADAMS is a reliable and valid instrument to screen for depressive and anxiety symptoms in adults with ID (12, 13). In the Netherlands, this instrument is now used in many different health care organizations for adults with ID.

*Non-pharmacological interventions to treat depressive symptoms in adults with intellectual disabilities*

In the stepped-care model of the Dutch Multidisciplinary Guideline for Depression (2013), treatment of MDD usually starts with less invasive treatment options, depending on the duration and severity of the depression (14). Basic interventions to treat depressive symptoms included in this stepped care model are e.g. psychoeducation, structuring of daily life and active monitoring of the patient. These basic interventions can be combined with low-intensity interventions such as bibliotherapy, self-help and self-management, physical activity or psychosocial interventions (14). When these interventions do not have enough effect, higher intensity treatment options can be used, such as psychotherapy and/or pharmacological treatment (14). Non-pharmacological interventions to treat depressive symptoms are widely studied and used in the general population (15-20). In clinical practice, depressive symptoms in adults with ID are usually treated with psychotropic medications, and there is some evidence that antidepressants in this population are effective (21-23). Most of the non-pharmacological interventions recommended in the guideline for depression of the general population are not suitable for all adults with ID because of verbal, cognitive and physical limitations. Unfortunately, pharmacological treatment is not always the most desirable way to treat depressive symptoms in adults with ID. For example because of the short and long term negative side effects which are reported regularly in research and clinical practice in this population (24-29). In addition, negative side effects of psychotropic medications seem to occur more frequent in adults with ID compared to without ID (25, 29, 30). Therefore, other treatment options are needed for adults with ID.



In the stepped-care model of the Dutch Multidisciplinary Guideline for Depression (2013), non-pharmacological treatment for depressive symptoms with the use of Bright Light Therapy (BLT) is mentioned as a possible intervention for seasonal depression (14). This is one of the few potentially suitable non-pharmacological interventions for adults with ID because no level of communication or self-reflection is needed. Unfortunately, this section of the stepped-care guideline was published in 2005 and not revised in 2013, and therefore not adapted with recent study results of BLT for non-seasonal depression (31-33), including findings about comparable effect sizes between pharmacological treatment for depression and BLT (34).

In clinical practice, more knowledge was needed into the effectiveness of non-pharmacological treatments for depressive symptoms in adults with ID. Therefore, we conducted a systematic review, which is described in Chapter 4 (35). This review contained 15 studies (describing five different types of interventions) on non-pharmacological interventions to decrease depressive symptoms in adults with ID. Cognitive Behavioral Therapy (CBT) was the most studied non-pharmacological intervention in adults with ID (36-43). CBT is effective in reducing depressive symptoms in adults with mild or moderate ID. Other types of non-pharmacological interventions presented in our systematic review, all with limited number of studies and participants, were: behavioral therapy (44-46), exercise interventions (47, 48), a social problem solving skills program (47), and Bright Light therapy (BLT) (49). Some of these interventions, for example the exercise interventions, showed positive results. An important finding of our review was that a large part of the included studies showed methodological problems (e.g. small sample sizes or the lack of a control group). Therefore, we concluded that not only more research is needed, but also more well designed studies are needed to draw reliable conclusions about the effectiveness of these non-pharmacological interventions.

In the studies of our systematic review, predominantly adults with mild or moderate ID were included (35). As a consequence, adults with severe or profound ID are underrepresented. In most of these interventions to decrease depressive symptoms, a relative high level of communication and self-reflection is needed, and therefore, these interventions cannot be used in adults with severe or profound ID (35). Bright Light Therapy could be a promising non-pharmacological intervention for people with ID (including for those with severe or profound ID), because no level of communication or self-reflection is needed (35). However, only three case studies (49-51) on BLT in adults with ID were published. Therefore, Hermans et al. (2017) conducted a small pilot study (n=14) on BLT in adults with ID, which gave more insight in the feasibility of BLT in adults with ID (52). They showed that BLT was applicable and decreased depressive symptoms in the majority of the adults with ID, even in those with severe or profound ID, and those with challenging behavior (52). Because of the small sample size of this pilot study, and because no control patients were included, a randomized controlled trial (RCT) with a larger sample size was needed to expand our knowledge on this type of non-pharmacological intervention in this specific population.

*Bright light therapy to decrease depressive symptoms in adults with ID*

As far as we know, we conducted the first multicenter randomized controlled trial to examine the effect of BLT on depressive symptoms in adults with ID (Chapter 6). BLT with 10.000 lux showed a significant decrease in depressive symptoms with a very large effect size one week after the end of the 14 day BLT period, and at four week follow-up. In 45.5% of the participants of this group, depressive symptoms were decreased with 40% or more. In our dim light group (300 lux), a significant decrease in depressive symptoms was found as well, although in this group a medium (T1) to large effect size (T2) was found, and only 7.7% of the participants recovered 40% or more. In the care as usual group, no significant decrease in depressive symptoms was found. We did not find significant differences in decrease of depressive symptoms between the three study groups after the intervention (or care as usual period). This may be due to our rather small sample size, resulting in a lack of power.

An interesting finding of our RCT is that antipsychotics were used more often by the participants than antidepressants. As a diagnosis of psychoses and bipolar disorder were exclusion criteria for our trial, our hypothesis is that these antipsychotics were prescribed off-label for challenging behavior. Behavior that can be caused by underlying depressive symptoms, and this was probably not recognized as such. In our RCT, we found high baseline numbers on the Aberrant Behavior Checklist Irritability scale (53). Irritability is a frequently expressed clinical representation of depression and listed as challenging behavior in adults with ID, supporting our hypothesis.



*Hair glucocorticoids in adults with ID and depressive symptoms*

To gain more inside in long-term stress in adults with ID and depressive symptoms, we performed the first small explorative study on long-term hair glucocorticoids, which may be a potential non-invasive biomarker for long-term stress in this population (Chapter 7). Significant positive correlations were found between depressive symptoms and hair cortisol, and we found a trend towards a negative correlation between hair cortisone and anxiety symptoms. The increase in mean cortisone after BLT could point towards an increased conversion of the active cortisol into the inactive cortisone. We could only include 14 participants in our study, and for that reason, our results must be seen as a first exploration on this biomarker which, in the future, may be a potential tool to investigate long-term stress in adults with ID. This kind of objective markers

is especially needed in those adults with ID who cannot communicate about their health and health related factors.

## STUDY LIMITATIONS

In research in adults with ID, especially in clinical trials, several difficulties are faced (54-56). In Chapter 5 of this thesis, we described the study protocol of our RCT on the effect of BLT in adults with ID, and we gave an overview of the obstacles we encountered during the preparation and execution of our study. Besides, we gave an overview of how we tried to manage these difficulties. The main obstacle we faced during our RCT was finding and recruiting enough participants with ID and elevated depressive symptoms who could participate in our study. After one year of recruitment, when the inclusion number remained low, we extended the inclusion period with another year, and actively screened adults with ID, living in the three participating health care organizations, for depressive symptoms. This screening identified adults with ID and elevated depressive symptoms that were not recognized prior to the screening. This added screening slightly elevated the inclusion number of our study. Unfortunately, after an inclusion period of almost 2.5 years, we could include 41 participants. Although this is the highest number of included patients in a BLT study in this population, we faced a lack of statistical power. This major inclusion obstacle might be the reason why large intervention studies in this population are lacking.

## OPPORTUNITIES AND IMPLICATIONS FOR FUTURE RESEARCH

*Biomarkers and other objective instruments to measure long-term stress in adults with ID*

At this moment, the Academic Collaboration Center for people with ID 'Healthy Ageing and Intellectual Disabilities' (HA-ID, in Dutch 'GOUD') is preparing a 10-year follow-up of the large cross-sectional epidemiological study on health and health related factors in elderly with ID which started in 2008 (57). One of the added measurements in this follow-up study will be the collection of hair samples in adults with ID (with and without depressive symptoms) to investigate hair glucocorticoids. When more research in larger sample sizes on this biological marker is completed, this method, together with relevant questionnaires, may give us more insight in the way hair glucocorticoids can be used as a biomarker to examine long-term stress in adults with ID. In the future,

this could help professionals in clinical practice to examine long-term stress in adults with ID with a more objective marker. This is especially helpful in those patients who cannot communicate about life events or other stress related factors such as sleep deprivation, diseases or pain. Together with the use of hair glucocorticoids, other innovative technologies to measure (mental) heath related factors such as (long-term) stress, emotions and pain (such as with heart rate and/or skin conductance) need to be investigated in adults with ID. In the future, it would be interesting to combine outcomes of objective biomarkers which retrospectively measure long-term stress with objective stress measurements that are used in the present. In this way, more will be known about (chronic) stress in adults with ID, and this knowledge can contribute to care for those (previously unknown) people suffering from (chronic) stress.

**Research in the population of adults with ID**

In order to manage one of the main obstacles in research in adults with ID, including enough participants with ID in a study, especially in randomized controlled trials, international collaborations are needed. We invite international colleagues to replicate our BLT study to expand the knowledge on this non-pharmacological treatment option to treat depressive symptoms in adults with ID. We published the study protocol of our trial and the obstacles we faced, including corresponding obstacle management (58). Recently, a systematic review was published on the obstacles faced in conducting RCTs in adults with ID (55). Our study and this recent review, can be helpful in optimizing research in this population of adults with ID. If more results of high quality studies investigating non-pharmacological interventions for adults with ID and depressive symptoms are available, we can work towards more evidence-based care in this field.

**Funding for research**

Obtaining funding for research in adults with ID can be difficult and challenging, which may also be part of the reason why large trials are not performed. Studies in the population of adults with ID, especially intervention studies, frequently take more time both in preparation and execution of the study compared to the same kind of studies in the general population. Therefore, funding agencies should take these challenges into account when funding intervention in adults with ID. Without high quality research (were obstacles are tackled), there will still be gaps in knowledge, for

example regarding the best way that depressive symptoms in adults with ID can be diagnosed and treated.

Three Dutch health care provider services for adults with ID (Amarant, Ipse de Bruggen and Abrona), in collaboration with Erasmus University Medical Center Rotterdam, form the Academic Collaboration Center for people with ID 'Healthy Ageing and Intellectual Disabilities'(HA-ID, in Dutch 'GOUD'), to make research in adults with ID possible. Their large financial and organizational support in times of government cutbacks, shows their recognition of the need for more knowledge on health-related factors, diagnostic instruments and evidence-based interventions in adults with ID. Important topics that all will contribute to optimizing care for this vulnerable population. The Dutch government recently acknowledged the need for more funding for further development of the infrastructure of the Academic Collaboration Centers for people with ID. In these Academic Collaboration Centers, many different disciplines (care organizations for people with ID and their staff, researchers, policy makers and educational settings), all involved in the care of people with ID, work together to gain more knowledge on how to optimize the care for people with ID. Six already existing and successful Academic Collaborations centers for people with ID in the Netherlands, including the Academic Collaboration center HA-ID, are currently funded on a structural basis by the Dutch Government. With this structural funding, in combination with the financial and organizational support of health care provider services for adults with ID, more resources are available to bring research in this population to a higher level. In this way, we can further develop inclusive research, optimize implementation of results in regular care, and further collaborate with educational settings, which all contributes to optimizing care for people with ID.

## IMPLICATIONS FOR CLINICAL PRACTICE

### Screening for depressive symptoms

To prevent underdiagnoses of depression in adults with ID, regular screening, especially for those who are at risk for developing a depression, is recommended. For example, adults with ID who experienced negative life events, who have sleep problems or other (mental) health symptoms related to depression, should be screened for depressive symptoms twice a year. The results of this screening should

be discussed in a multidisciplinary team and, if elevated depressive symptoms are found, more diagnostic research is necessary. We recommend the use of (The Dutch version of) the Anxiety Depression and Mood Scale (ADAMS, in Dutch: ADESS), that can be used in all adults with ID, to screen for depressive symptoms. The Dutch ADAMS manual and questionnaire are available free of charge (downloads are available at www.goudonbeperktgezond.nl). The use of the DM-ID-2 depression section (Chapter 12) (8), with adapted criteria of the DSM-5 and accompanying notes on the different expressions of depression in adults with ID, is recommended for diagnosing depression in clinical practice. Especially for adults with moderate to profound ID.

### Education of care professionals

As mentioned before, depressive symptoms in adults with ID are frequently missed. In order to recognize the specific symptoms of depression in adults with ID, and to identify those who are vulnerable for developing depressive symptoms, more education for (future) care professionals on this topic is needed.

### Bright light therapy in adults with ID

The results of the effect of BLT to treat depressive symptoms in adults with ID are still inconclusive, most probably due to our small sample size. Nevertheless, this non-pharmacological treatment has been used increasingly in adults with ID in clinical practice in recent years. Therefore, an instruction will be made in the near future to share our knowledge of BLT in adults with ID. One should be aware that BLT, in combination with specific photosensitizing medications, can cause (severe) damage to the eye or skin. Further, BLT can worsen suicidal expressions and cause or severe mania. As a consequence, BLT should not be used in adults with ID without consulting a physician, preferably a physician for people with ID or a psychiatrist with relevant knowledge of this specific population.



## CONCLUSION OF THIS THESIS

Knowledge about health-related factors, such as depression and stress (and associated interventions), with regard to adults with ID, lags behind knowledge about these subjects in adults without ID. This thesis contributes to the knowledge on the psychometric properties of the Dutch Anxiety, Depression And Mood Scale (ADAMS), and a novel

potential biomarker to examine long-term stress in adults with ID. Further, we looked into the theoretical construct of the influence of light on mood and sleep. Non-pharmacological interventions for adults with (all levels of) ID and depressive symptoms, especially bright light therapy, are evaluated. With the novel and innovative knowledge on various themes that emerged from this thesis, an attempt was made to further close the knowledge gap, and to contribute to optimizing care for adults with ID.

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# Chapter 9

Summary

Samenvatting

Dankwoord

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PhD Portfolio

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## SUMMARY

### Chapter 1 General introduction

The point prevalence rates of depressive symptoms in adults with intellectual disabilities (ID) are high, even though depressive symptoms can be hard to recognize in this population. Diagnoses of major depressive disorder are often missed, leading to undertreatment of those in need. Further, there is a lack of non-pharmacological interventions to treat depressive symptoms in adults with ID. Therefore, we studied the literature on this topic, and investigated the effect of a potential non-pharmacological intervention to treat depressive symptoms in adults with ID: bright light therapy (BLT). The overall aim of this thesis was to add knowledge on diagnostics of depressive symptoms and long-term stress, and on non-pharmacological treatment options to treat depressive symptoms in adults with ID.

### Chapter 2 Reliability and validity of the Dutch Anxiety, Depression And Mood Scale in adults aged <50 years with intellectual disabilities

To prevent underdiagnoses of depression in adults with ID, instruments with good psychometric quality are needed to adequately detect depressive symptoms in adults with ID. In the past, the reliability and validity of the Dutch Anxiety, Depression And Mood Scale (ADAMS, in Dutch: ADESS) was investigated in elderly with ID (aged 50 years and older). This instrument was found to be feasible, reliable and valid in that population. The Dutch ADAMS was not investigated in adult with ID below the age of 50 years. In chapter 2 of this thesis, the study on the reliability and validity of the Dutch ADAMS in adults with ID aged <50 years is described. This study showed that the Dutch ADAMS is a reliable instrument to measure depressive symptoms and anxiety symptoms in adults with ID (<50 years). The scale is consistent in measuring over time and between different raters. It is also a valid instrument because the scale investigates the concept of interest, namely depressive symptoms and anxiety symptoms in adults with ID. These results, together with previous research on elderly with ID, confirm that the Dutch ADAMS can now be used in the whole adult ID population.

### Chapter 3 The influence of personal light exposure on mood and sleep in patients with (mental) health problems: a systematic review

This study gains more insight in the working mechanism of light on mood and sleep. This was necessary as chronotherapeutic interventions, such as bright light therapy, are used to treat depressive symptoms although little is known about the influence of personal light exposure prior to these interventions. In this study, we aimed to give an overview of the studies focusing on this topic. After a systematic literature search, 12 papers focusing on light, mood and sleep could be included. Overall, the quality of the included studies was fair and many methodological problems, e.g. small sample sizes and inaccurate personal light exposure measurements, were found. In some studies, less exposure to light, was associated with more depressive symptoms and sleep problems. In some other studies, these associations were not found. Some groups of patients with (mental) health problems were exposed to less personal light compared to healthy control subjects. No strong conclusions could be drawn on the association between personal light exposure, sleep and mood in patients with (mental) health problems because of contrasting results. Some studies found associations between light, mood and sleep but others did not find these associations. Further, there is a lack of high quality papers with large sample sizes, and personal light exposure was measured in a unreliable way.

### Chapter 4 Non-pharmacological interventions for adults with intellectual disabilities and depression: a systematic review

There was limited knowledge of non-pharmacological interventions for depressive symptoms in adults with ID, especially for those with severe or profound ID. Therefore, a systematic review has been performed to increase knowledge into the effectiveness of these interventions in adults with ID. After an electronic search in six databases, we have included 15 studies in our systematic review. These 15 studies described five types of non-pharmacological interventions. Cognitive Behavioral Therapy was the most studied intervention (eight studies), and is found to be effective in decreasing depressive symptoms in adults with mild or moderate ID. Other studies, generally with small sample sizes or other methodological problems, focused on behavioral therapy (three studies), exercise intervention (two studies), social problem-solving skills intervention (one study), and bright light therapy (one study). Because of the small number of studies on these types of interventions, we concluded that some of

these interventions show promising results, but more studies are needed to further expand our knowledge into the effectiveness of these interventions. Overall, we concluded that there is a lack of high quality studies investigating the effect of non-pharmacological interventions to treat depressive symptoms in adults with ID.

**Chapter 5 A multicenter randomized controlled trial for bright light therapy in adults with intellectual disabilities and depression: study protocol and obstacle management**

As seen in Chapter 4, there are limited non-pharmacological interventions to treat depressive symptoms in adults with ID. Therefore, more research regarding this topic was needed. In this chapter, we described the study protocol of our randomized controlled trial (RCT) into the effectiveness of bright light therapy (BLT) in adults with ID. Besides, the obstacles which we faced during our RCT, and the management of these obstacles are described. For example obstacles regarding recruitment and the informed consent procedure. In addition, we had to deal with low motivation to sign up to participate in the study because of the risk of being randomized into the control group, the medical contraindications for bright light therapy, and finding the optimal placebo treatment option. Information on the study protocol, the obstacles we faced and their management, can be helpful for researchers who, for example, want to replicate our study on the effect of BLT on depressive symptoms in adults with ID.

**Chapter 6 The effect of Bright Light Therapy on depressive symptoms in adults with intellectual disabilities: results of a multicenter randomized controlled trial**

To evaluate the effectiveness of bright light therapy (BLT) in adults with ID, we conducted a multicenter randomized controlled trial. Adults with ID were eligible for the study when they had a Depressive Mood subscale score of 14 or more on the ADAMS. A Depressive Mood subscale score of 14 or more is an indication of the presence of a major depressive disorder. Those who were eligible and gave consent, were randomized into one of the three study arms: BLT with 10.000 lux, BLT with 300 lux (dim light: a filter was installed without changing the color of the light), or a control condition without BLT. In the general population, BLT with 10.000 lux is used to treat depressive symptoms, and 300 lux is considered to be not anti-depressant. For example, 300 lux to 500 lux light intensities are regularly found in offices. In both

BLT groups, participants received BLT additional to their care as usual. BLT was given for a period of two weeks, with a duration of 30 minutes in the morning as soon as possible after wake up.

In a period of 2.5 years, 41 participants were included in this study. Their age ranged from 24 to 81 years, and by chance an even amount of males and females were included. Minimal side effects and no (serious) adverse events were reported. We found no significant differences in effect between both BLT groups and the control condition. In both intervention groups, BLT decreased the amount of depressive symptoms, and no significant decrease of depressive symptoms was found in the control group. Only with 10.000 lux BLT, the amount of depressive symptoms decreased below the clinical cut-off point. Although we could only include 41 participants, this is, as far as we know, the largest study into the effectiveness of BLT in adults with ID. This study showed that BLT might be a promising intervention to treat depressive symptoms in adults with ID, but (larger) trial replications are needed.

### Chapter 7 Effect of bright light therapy on long-term stress levels in adults with intellectual disabilities and depressive symptoms

To the best of our knowledge, we were the first to use head hair samples to retrospectively examine hair cortisol and hair cortisone in adults with ID and depressive symptoms. We also examined whether BLT influenced hair cortisol and hair cortisone concentrations. To measure hair cortisol and hair cortisone, Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used. A scalp hair sample was available in 17 out of 26 participants who received BLT. Scalp hair samples of 14 participants could be included in our analyses: seven were randomized in our 10.000 lux BLT group and seven were randomized in our dim light BLT group (300 lux). Moderate significant correlations were found between hair cortisol and baseline depression scores, and hair cortisone was significantly elevated after BLT, particularly after BLT with 300 lux (dim light). The use of scalp hair samples to retrospectively investigate long-term stress levels in adults with ID seems to be a promising method to objectify the stress level in the past.

**Chapter 8 General discussion**

In this final chapter, the main findings, opportunities and implications for future research, and implications for clinical practice are summarized. In general, more high quality randomized controlled trials on non-pharmacological interventions to treat depressive symptoms in adults with ID are needed. We must work towards more evidence-based interventions in this field to optimize care, and to contribute to increase the quality of life for adults of this population. In order to perform high quality studies, the main obstacle (including enough participants) must be tackled, and more funding is needed for research in this group of adults with ID. In clinical practice, we must be alert on adults with ID who are vulnerable for developing depressive symptoms. More training in this area is necessary for (future) healthcare professionals.

## SAMENVATTING

### Hoofdstuk 1 Algemene inleiding

Er zijn veel volwassenen met een verstandelijke beperking (VB) en depressieve klachten. Depressieve klachten zijn lastig te herkennen bij deze groep. De diagnose 'Depressieve stoornis' wordt regelmatig niet gesteld terwijl ze wel aanwezig is en hierdoor wordt diegene er ook niet voor behandeld. Ook zijn er maar weinig niet-farmacologische interventies om depressieve symptomen bij volwassenen met een VB te behandelen. Daarom hebben we de literatuur bekeken op dit gebied, en onderzochten we wat het effect is van lichttherapie op depressieve klachten bij volwassenen met een VB. Het algemene doel van dit proefschrift was om bij te dragen aan kennis omtrent het herkennen van depressieve klachten en lange termijn stress bij volwassenen met een VB, en om meer te weten te komen over niet-farmacologische behandelmogelijkheden voor depressieve klachten bij volwassenen met een VB.

### Hoofdstuk 2 De betrouwbaarheid en validiteit van de Nederlandse vertaling van de Angst, Depressie en Stemming Schaal voor volwassenen (<50 jaar oud) met een VB

Meetinstrumenten met goede psychometrische eigenschappen zijn noodzakelijk om depressieve symptomen bij volwassenen met een VB op een adequate manier te detecteren. In het verleden is de betrouwbaarheid en validiteit van de Nederlandse Angst, Depressie en Stemming Schaal (ADESS) onderzocht bij ouderen met een VB (50 jaar en ouder). Uit dat onderzoek bleek dat het gebruik van de ADESS haalbaar, betrouwbaar en valide is in die populatie. De ADESS was niet onderzocht bij volwassenen met een VB jonger dan 50 jaar. In hoofdstuk 2 van dit proefschrift, is het onderzoek naar de betrouwbaarheid en validiteit van de ADESS bij volwassenen met een VB jonger dan 50 jaar beschreven. Deze studie toonde aan dat de ADESS een betrouwbaar meetinstrument is om angst- en stemmingsklachten te meten bij volwassenen met een VB onder de 50 jaar. De schaal is betrouwbaar in herhaalde metingen over de tijd en ook wanneer verschillende beoordelaars de schaal invullen. Dit meetinstrument is ook een valide meetinstrument omdat de schaal het te meten concept (angst- en stemmingsklachten) ook daadwerkelijk meet. Deze resultaten, samen met het onderzoek bij ouderen met een VB, bevestigen dat de ADESS gebruikt kan worden in de gehele populatie van volwassenen met een VB.

**Hoofdstuk 3 Een systematisch literatuur onderzoek naar de invloed van persoonlijke lichtblootstelling op stemming en slaap bij patiënten met (mentale) gezondheidsproblemen**

Deze studie geeft ons meer inzicht in het werkingsmechanisme van licht op stemming en slaap. Dit was noodzakelijk omdat chronotherapeutische interventies, zoals lichttherapie, worden gebruikt om depressieve symptomen te verminderen, hoewel er weinig bekend is over de invloed van persoonlijke blootstelling aan licht voorafgaand aan deze interventies. In deze studie wilden we een overzicht geven van de studies die zich op dit onderwerp richten. Na een systematische literatuurstudie konden uiteindelijk 12 artikelen over licht, stemming en slaap worden geïncludeerd. Over het algemeen was de kwaliteit van deze studies redelijk, maar er werden ook veel methodologische problemen gevonden zoals een klein aantal geïncludeerde patiënten, en de onnauwkeurige manier van het meten van de persoonlijke lichtblootstelling. In sommige studies werd minder blootstelling aan licht geassocieerd met meer depressieve symptomen en slaapproblemen, maar in sommige andere studies werden deze associaties niet gevonden. Sommige groepen patiënten werden blootgesteld aan minder licht in vergelijking met gezonde controle patiënten. Vanwege de tegengestelde resultaten, konden er geen sterke conclusies getrokken worden over het verband tussen persoonlijke lichtblootstelling, slaap en stemming bij patiënten met diverse gezondheidsproblemen. Daarnaast is er op dit gebied een gebrek aan studies van hoge kwaliteit met grote steekproefgroottes, en wordt de persoonlijke lichtblootstelling in de meeste onderzoeken op een onnauwkeurige manier gemeten.

**Hoofdstuk 4 Een systematisch literatuur onderzoek naar niet-farmacologische interventies voor volwassenen met een verstandelijke beperking en depressieve klachten**

Er was weinig bekend over niet-farmacologische interventies om depressieve klachten te behandelen bij volwassenen met een VB, vooral voor de groep met een (zeer) ernstige VB. Daarom hebben we een systematisch literatuuronderzoek uitgevoerd om meer kennis te vergaren over de effectiviteit van niet-farmacologische interventies om depressieve symptomen te behandelen bij volwassenen met een VB. Na een elektronische zoekopdracht in zes databases konden we uiteindelijk 15 studies includeren. Deze 15 studies beschrijven vijf soorten niet-farmacologische

interventies. Cognitieve gedragstherapie (CGT) was de meest bestudeerde interventie (acht studies), en CGT is effectief gebleken bij het verminderen van depressieve symptomen bij volwassenen met een lichte of matige VB. Andere studies, over het algemeen met een laag aantal deelnemers en ook andere methodologische problemen, waren gericht op gedragstherapie (drie studies), fysieke interventies (twee studies), sociale probleemoplossende vaardigheden (één studie) en lichttherapie (één studie). Sommige van deze interventies behaalden veelbelovende resultaten. Het totaal aantal studies naar niet-farmacologische behandeling voor depressieve klachten bij volwassenen met een VB is gering en studies met een hoge mate van kwaliteit ontbreken. Daarom zijn er meer studies van hoge kwaliteit nodig zijn om onze kennis over de effectiviteit van niet-farmacologische behandeling voor depressie bij volwassenen met een VB verder uit te breiden.

**Hoofdstuk 5 Studieprotocol en obstakelmanagement van een multicenter gerandomiseerd onderzoek met controlegroep naar het effect van lichttherapie voor depressieve klachten bij volwassenen met een VB**

In hoofdstuk 4 van dit proefschrift is beschreven dat er maar weinig niet-farmacologische interventies zijn om depressieve klachten bij volwassenen met VB te behandelen. Daarom was meer onderzoek naar dit onderwerp nodig. In dit hoofdstuk beschrijven we het onderzoeksprotocol van de studie naar het effect van lichttherapie op depressieve klachten bij volwassenen met een VB, de obstakels die wij tegen kwamen, en de manier waarop wij daarmee zijn omgegaan. Obstakels die we tegenkwamen lagen op het gebied van: de werving en het includeren van volwassenen met een VB, de toestemmingsprocedure, de lage motivatie om deel te nemen aan het onderzoek vanwege het risico gerandomiseerd te worden in de controlegroep, het feit dat depressieve symptomen regelmatig gemist worden bij volwassenen met een VB, de medische contra-indicaties voor lichttherapie en het vinden van de optimale placebo-behandeloptie. Informatie over het studieprotocol, de obstakels die wij tegen kwamen en daarnaast de manier waarop wij die hebben aangepakt, kunnen nuttig zijn voor onderzoekers die ook onderzoek willen doen naar het effect van lichttherapie op depressieve klachten bij volwassenen met een VB.

### Hoofdstuk 6 Het effect van lichttherapie op depressieve symptomen bij volwassenen met een VB: resultaten van een multicenter gerandomiseerd onderzoek met controle groep

Met behulp van een multicenter gerandomiseerd onderzoek met controlegroep hebben we onderzocht wat het effect is van lichttherapie op depressieve klachten bij volwassenen met een VB. Volwassenen met VB kwamen in aanmerking voor de studie wanneer ze een score van 14 of hoger hadden op de Depressieve stemming subschaal van de ADESS. Een score van 14 of hoger op deze subschaal is een aanwijzing voor het hebben van een depressieve stoornis. Wanneer er naast genoeg depressieve symptomen toestemming was voor deelname aan de studie, werd de cliënt gerandomiseerd in een van de drie studiegroepen: lichttherapie met 10.000 lux (fel licht), lichttherapie met 300 lux (gedimd licht: er werd gebruik gemaakt van een ingebouwde filter die de kleur van het licht niet veranderde) of de controle groep zonder lichttherapie. Lichttherapie met 10.000 lux wordt bij de algemene bevolking gebruikt om depressieve klachten te verminderen en 300 lux wordt gezien als niet effectief om depressieve klachten te verminderen. 300 lux lichtintensiteit kan vergeleken worden met het aantal lux dat normaliter gevonden wordt in kantoren (300-500 lux). In beide lichttherapie groepen ontvingen de deelnemers lichttherapie naast hun reguliere zorg. Lichttherapie werd aangeboden voor een periode van twee aaneengesloten weken, 30 minuten per dag, in de ochtend zo snel mogelijk na ontwaken. In een periode van 2.5 jaar hebben uiteindelijk 41 deelnemers deelgenomen aan dit onderzoek. Hun leeftijd varieerde van 24 tot 81 jaar en evenveel mannen als vrouwen deden mee. Tijdens het onderzoek werden er maar weinig bijwerkingen gezien, en deze waren niet ernstig van aard. We vonden geen significante verschillen in het effect van de lichttherapie tussen beide lichttherapie groepen en de controleconditie. In beide lichttherapie groepen verminderde de hoeveelheid depressieve symptomen. In de controle groep werd geen significante afname van depressieve symptomen gezien. Alleen met 10.000 lux lichttherapie daalde de hoeveelheid depressieve symptomen onder het klinische afkappunt. Hoewel we slechts 41 deelnemers konden includeren, is dit onderzoek, voor zover wij weten, het grootste onderzoek naar de effectiviteit van lichttherapie bij volwassenen met een VB. Deze studie toont aan dat lichttherapie een veelbelovende interventie kan zijn om depressieve symptomen te behandelen bij volwassenen met VB, maar herhaling van dit onderzoek (met grotere onderzoeksgroepen) is noodzakelijk.

**Hoofdstuk 7 Het effect van lichttherapie op het langdurige stressniveau van volwassenen met een VB en depressieve symptomen**

Voor zover wij weten, hebben wij de eerste studie verricht waarbij plukjes hoofdhaar gebruikt worden om het haarcortisol- en haarcortisongehalte te onderzoeken bij volwassenen met een VB en depressieve symptomen. We onderzochten ook of lichttherapie invloed had op het haarcortisol- en haarcortisongehalte. Hierbij werd gebruik gemaakt van vloeistofchromatografie met massaspectrometer (LC-MS / MS). Een pluk hoofdhaar was beschikbaar bij 17 van de 26 deelnemers die lichttherapie ontvingen tijdens de studie. De plukjes hoofdhaar van 14 deelnemers hebben we kunnen analyseren: zeven cliënten kregen lichttherapie met 10.000 lux en zeven cliënten kregen lichttherapie met gedimd licht (300 lux). We vonden een significante samenhang tussen haarcortisol en baseline depressiescores. Haarcortison was significant verhoogd na lichttherapie, vooral na lichttherapie met gedimd licht. Bij volwassenen met een VB lijkt het gebruik van plukjes hoofdhaar een veelbelovende objectieve methode om het stressniveau in het verleden te onderzoeken.

**Hoofdstuk 8 Algemene discussie**

In dit laatste hoofdstuk, worden de belangrijkste bevindingen, kansen en implicaties voor toekomstig onderzoek en implicaties voor de klinische praktijk beschreven. Er zijn meer gerandomiseerde, gecontroleerde onderzoeken van hoge kwaliteit nodig naar niet-farmacologische interventies voor de behandeling van depressieve symptomen bij volwassenen met een VB. We moeten toewerken naar meer evidence-based interventies op dit gebied om de zorg voor deze kwetsbare groep te optimaliseren. Op die manier kunnen we bijdragen aan de verbetering van de kwaliteit van leven voor volwassenen in deze populatie. Om studies van hoge kwaliteit uit te voeren, moet het belangrijkste obstakel (voldoende deelnemers includeren) worden aangepakt en daarnaast is er meer financiering nodig. In de klinische praktijk moeten we alert zijn op volwassenen met een VB die kwetsbaar zijn voor het ontwikkelen van depressieve symptomen. Meer scholing op dit gebied is noodzakelijk voor (toekomstige) zorgprofessionals.

## DANKWOORD

*Dit proefschrift werd mede mogelijk gemaakt door….*

Een promotietraject doorloop je niet alleen. Daar zijn veel verschillende mensen, ieder op hun eigen manier, bij betrokken. Op deze pagina's wil ik hen graag bedanken.

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De drie zorgorganisaties die samen met de vakgroep Geneeskunde voor Verstandelijk gehandicapten van het Erasmus MC de Academische Werkplaats GOUD vormen, investeren gezamenlijk in wetenschappelijk onderzoek. Ik ben hen dankbaar dat ik deel mag uitmaken van deze inspirerende academische werkplaats. Graag wil ik de (voormalig) bestuurders van deze zorgorganisaties ten tijde van mijn onderzoek bedanken: Ronald Helder (Amarant), Marc Bindels (Amarant), Jan van Hoek (Ipse de Bruggen), Jan Duenk (Abrona) en Toke Piket (Abrona). Daarnaast wil ik de leden van de GOUD-stuurgroep bedanken: Frank Brouwers (Amarant), Marcel Schellart (Ipse de Bruggen) en Ineke Bootsman (Abrona). Tijdens mijn onderzoek heb ik regelmatig praktische zaken rondom mijn onderzoek besproken met de interne coördinatoren van GOUD. Hartelijk dank Erwin van den Hout (Amarant), Ineke Bootsman (Abrona) en Joris van Erp (en later Cor van Rongen). Wat fijn om korte lijntjes te hebben met de praktijk! Natuurlijk vergeet ik de huidige interne GOUD-coördinator van Amarant niet: Patricia Smit-Brekelmans. Patricia, ik wil jou bedanken voor de fijne samenwerking

tijdens mijn onderzoek, de gezellige lunch overleggen, de vele autoritjes naar diverse vergaderingen in het land, en het feit dat jij je betrokkenheid en bezorgdheid toonde in zaken die speelden in mijn privé leven. Dit alles heb ik ontzettend gewaardeerd. Ook wil ik graag de implementatiecoaches van GOUD bedanken. Wat fijn dat wij een beroep op jullie kunnen doen en jullie ons helpen met het implementeren van kennis en producten in de praktijk. Daarnaast wil ik Yvonne Swaans bedanken voor het regelen van allerlei praktische zaken.

Beste em. prof. dr. Evenhuis, beste Heleen, in de eerste jaren van mijn promotietraject was jij mij promotor. Jouw passie voor onderzoek in de VB-sector is enorm inspirerend. Dank voor het pionieren, je bereidheid om mee te denken en kritische blik op mijn eerste manuscripten.

Beste prof. dr. Bindels, beste Patrick, wat fijn dat jij in de laatste helft van mijn promotietraject mijn promotor was. Het was prettig om met jou te sparren over mijn onderzoek en de artikelen die ik schreef, en om feedback te krijgen vanuit een andere invalshoek.

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Dederieke, manager van de vakgroep en mijn copromotor vanaf de 2e helft van mijn promotieonderzoek. Ik wil jou bedanken voor het feit dat ik altijd bij terecht kan met vragen of om even te sparren. Niet alleen over werk, maar ook over zaken daarbuiten. Ik waardeer het zeer dat jouw deur altijd open staat en dat we altijd een beroep op je kunnen doen wanneer nodig.

Thessa, samen met Dederieke vorm jij het management van de vakgroep. Sinds een aantal jaar ben jij werkzaam in het buitenland en hierdoor heb jij mijn

promotieonderzoek vanaf een afstand meegemaakt. Hartelijk dank voor jouw input tijdens de beginperiode van mijn promotietraject.

Geachte leden van de beoordelingscommissie – prof. dr. Jan van Busschbach, prof. dr. Petri Embregts en prof. dr. Anita Hokken-Koelega, graag wil ik jullie bedanken voor het lezen en beoordelen van mijn proefschrift.

In 2014 begonnen Renske G. en ik ieder aan ons promotietraject binnen het GOUD2 onderzoek. Graag wil Renske bedanken voor het jaar dat wij samen zijn opgetrokken als de nieuwe lichting promovendi binnen GOUD. In 2016 startte Sylvie Beumer binnen GOUD2. Sylvie, ik wil je graag bedanken voor de fijne overlegmomenten over zowel onderzoek als de klinische praktijk. Ook heb ik mooie herinneringen aan de tijd in Barcelona tijdens het EAMHID Congres. Ook andere (oud) GOUD-collega's wil ik bedanken: Heidi, Thessa, Alyt, Stijn, Luc, Marieke, Josje, Channa en Ellen. De uitkomsten van jullie onderzoeken vormen de basis voor de latere GOUD onderzoeken. Alyt, wat fijn dat ik altijd een beroep op jou kan doen om mee te denken met de statistische analyses van mijn onderzoek.

Inmiddels is GOUD 3 gestart, en zijn er veel nieuwe collega's bijgekomen. Bedankt M&M&M (Marleen, Mireille, Marie-Louise), Theodore, Roy, Anne-Marie, Cor, Annemieke, Kim en Laura. Binnen de vakgroep Geneeskunde voor Verstandelijk Gehandicapten wil ik Mylène, Sandra, Renske, Marlies en Marieke bedanken. Dank allen voor de prettige tijd op de afdeling, de gezellige borrels, etentjes en fijne lunchwandelingen. Ook wil ik Miriam bedanken voor de secretariële ondersteuning. Mylène, wat goed dat we samen hebben gewerkt aan het systematic review over licht en gezondheid, en wat fijn dat ik een beroep kan doen op jouw kennis omtrent de actiwatch data. Bedankt ook voor de gezellige tijd tijdens de SLTBR congressen die we bezocht hebben. Over de SLTBR congressen gesproken: dank ook aan Erasmus MC collega Babette Bais voor de gezellige tijd in Berlijn en Groningen!

Binnen Amarant maak ik deel uit van de Commissie Wetenschappelijk onderzoek. In eerste instantie met Heidi Hermans en later Moniek Voermans als voorzitter. Wat leuk om samen met jullie en de andere leden van de commissie de lopende onderzoeken binnen Amarant te bespreken, en deel te mogen nemen aan de onderzoeksymposia

van Amarant. Graag zou ik een aantal gedragskundigen binnen Amarant willen bedanken voor het feit dat ik deel uit mocht maken van de intervisiegroep tijdens mijn promotietraject: Petra, Michelle, Heidi, Mirjam en collega's die tijdelijk aangesloten zijn. En wat leuk Mirjam, dat ook jij inmiddels onderzoek doet binnen een academische werkplaats voor mensen met een verstandelijke beperking!

Oud-collega's van het dr. Leo Kannerhuis Brabant (LKHB, destijds onderdeel van Amarant) wil ik bedanken voor de gezellige etentjes en belangstellende berichtjes. En in het bijzonder Claudia, die mij in 2014 de vacature voor de promotieplek binnen GOUD stuurde, omdat ze vond dat die baan echt bij mij zou passen. Goed gezien Claudia! Verder wil ik mijn voormalig manager van het LKHB bedanken. Sussiel, wat fijn dat jij, ondanks dat ik tijdens de sollicitatieprocedure voor de baan als gedragskundige bij het LKHB een heftige periode doormaakte, mij toch hebt aangenomen. Beste Katinka, mijn werkbegeleider destijds, dank voor de fijne gesprekken en wandelingen. Ik denk nog regelmatig terug aan de jaren bij het LKHB, waar we met een fijn en bevlogen team goed werk hebben verzet.

Tijdens mijn promotietraject heb ik ook samen mogen werken met mensen van buiten onze academische werkplaats. Voor het artikel over de betrouwbaarheid en validiteit van de ADESS werkte ik samen met dr. Jans van Ool en dr. Jos Hendriksen van Kempenhaeghe. Ik wil jullie beiden hartelijk danken voor de fijne en efficiënte samenwerking. Daarnaast kwam ik Jans regelmatig tegen bij verschillende congressen op diverse werelddelen, en daar heb ik fijne herinneringen aan!

Voor het artikel over cortisol in hoofdhaar heb ik binnen het Erasmus MC samengewerkt met prof. dr. Liesbeth van Rossum, prof. dr. Yolanda de Rijke en Drs. Mesut Savas. Hartelijk dank voor de fijne samenwerking en het feit dat wij van jullie expertise gebruik mogen maken. Hopelijk zetten we de samenwerking in de toekomst voort, er is immers nog een hoop te ontdekken op het gebied van cortisol in hoofdhaar bij mensen met een verstandelijke beperking.

Mijn lieve vriendinnen Debby, Judith, Debbie C. en Anika wil ik bedanken! We go long way back, soms wel >30 jaar! En ook alle andere vrienden en kennissen wil ik graag bedanken voor alle gezellige theetjes, borrels, etentjes, (NS)wandelingen, dagjes

en weekendjes weg, theatervoorstellingen, film- en docu avonden, en bezoeken aan concerten en festivals. Wat fijn dat jullie er waren, ook in moeilijkere tijden. De afgelopen jaren stak ik veel tijd en energie in mijn promotieonderzoek, en moest ik daarnaast dealen met heftige zaken in mijn privéleven. Hierdoor zag ik sommigen van jullie minder dan dat ik zou willen, en moest ik soms ook afspraken afzeggen. Ik vind het fijn dat jullie desondanks nog steeds deel uit maken van mijn leven!

Graag wil ik mijn schoonouders Harrie en Marly bedanken voor het feit dat we altijd een beroep op jullie kunnen doen wanneer we oppas nodig hebben voor onze dochter.

Wanneer een kind opgevoed wordt door een jurist en een verpleegkundige, wat voor effect heeft die opvoeding dan op het latere leven van het kind? De 'cure' en de 'care' als het ware in een mooie mix. Bij mij kwam het tot uiting in grondig en gestructureerd werken volgens (strenge zelf opgelegde) structuren, planningen en deadlines, met daarnaast een groot verantwoordelijkheidsgevoel en de drang om daadwerkelijk iets bij te dragen aan de maatschappij. Dankjewel pap en mam, dat jullie mij mijn eigen keuzes lieten maken, mij vrijheid gaven en mijn nieuwsgierig, eigenwijs en zelfstandig de wereld lieten ontdekken, en dat jullie op onze dochter konden passen wanneer dat nodig was.

Mam, in de jaren voor mijn geboorte werkte jij als Z-verpleegkundige en groepshoofd in de zorg voor mensen met een verstandelijke beperking op het 't Hooge Veer in Tilburg. Hoe bijzonder is het dat ik, nu bijna 40 jaar later, meer dan 10 jaar in dienst ben bij diezelfde zorgorganisatie. Tijdens mijn jeugd raakte ik door jouw werk bekend met mensen met een verstandelijke beperking, en ben ik opgegroeid met jouw passie voor dit vakgebied. Wat ben trots op jou, dat jij tot aan jouw pensioen hebt gewerkt binnen de zorg, waar je steeds zocht naar manieren om het leven van de cliënten te veraangenamen. En mijn naamgenoot waarbij je nu vrijwilligerswerk doet: die boft zeker met zo'n betrokken en bevlogen maatje!

Pap, van jou heb ik de pragmatische manier van werken, perfectionisme, doorzettingsvermogen en het plannen en organiseren meegekregen. Deze eigenschappen kwamen tijdens mijn klinische werk en promotieonderzoek ontzettend

goed van pas. Wat fijn dat je regelmatig vroeg hoe de stand van zaken was m.b.t. mijn promotieonderzoek. Ik hoop dat je geniet van je welverdiende pensioen.

Mijn zusje Nicolle, dank dat jij in de afgelopen jaren, samen met jouw man Oscar, in kon springen als oppas voor Frédérique wanneer dat nodig was. Ook dank voor het feit dat ik jou meerdere keren als taxi kon inzetten wanneer de NS mij weer eens op station ergens in het land liet stranden.

Mijn lieve dochter Frédérique, toen ik in 2014 aan dit promotietraject begon was je net 6 jaar geworden en zat je in groep 3. Nu, wanneer ik dit dankwoord schrijf, ben jij een mooie spontane en sociale tiener die geniet van het leven, altijd vrolijk is en die na de zomervakantie naar het voortgezet onderwijs gaat. Wat ben ik toch ontzettend trots op jou! Je tovert altijd weer een lach op mijn gezicht en je laat mij zien waar het in het leven echt om gaat. Dikke knuffel van mij voor jou! Gaan we binnenkort weer samen een weekendje weg?

Lieve Bart, al 20 jaar ben jij mijn maatje, mijn tegenpool, de rust in mijn leven en mijn plek om thuis te komen. Een promotietraject vraagt niet alleen van de promovendus veel tijd en energie, ook van een partner. Wat ben ik blij dat jij taken van mij over kon nemen wanneer dat nodig was, vakanties wilde verzetten wanneer ik weer eens de wereld over wilde vliegen om een presentatie te geven op een interessant congres, mij in alle stilte liet werken wanneer dat nodig was, en niks wat ik vraag te veel voor jou is. Ik waardeer je enorme geduld, rust en het feit dat je zo'n lieve vader bent voor onze dochter. De afgelopen jaren waren, door omstandigheden waarop wij geen invloed hebben gehad, verre van makkelijk, en daarbij vergeleken is promoveren 'a piece of cake'. Ik ben zo blij dat ik samen met jou belangrijke en moeilijke beslissingen in ons leven heb kunnen maken. Ik hoop dan ook dat we, samen met onze dochter Frédérique, nog lang en vooral ook in goede gezondheid van het leven mogen genieten. Ik houd heel veel van jou! X

Pauline

## CURRICULUM VITAE

Pauline Hamers werd geboren op 20 mei 1980 in Tilburg. In 1992 startte zij in de brugklas HAVO/VWO van het Cobbenhagen College. Na haar HAVO eindexamen ging zij naar het VWO. In 1998 ging Pauline Sociaal Pedagogische Hulpverlening (SPH) studeren aan de Fontys Hogeschool in Eindhoven. Tijdens het 4e jaar liep zij haar jaarstage bij de medisch-orthopedagogische dagbehandeling 'De Vlinder' in Goirle. Na het behalen van haar SPH diploma in 2002, besloot Pauline om een aantal maanden te gaan werken en reizen. In september 2003 startte Pauline met de opleiding Pedagogische Wetenschappen en Onderwijskunde aan de Radboud Universiteit Nijmegen. Zij koos de richting 'Orthopedagogiek: Gezin en gedrag', en na twee jaar behaalde zij in 2005 haar Bachelor Orthopedagogiek. Gedurende haar Masterjaar liep zij haar klinische stage als orthopedagoog i.o. bij SG De Keyzer (Cluster 4 SO/VSO) in Goirle. Tevens behaalde zij daar haar diagnostische aantekening. Haar masteronderzoek verrichtte zij in hetzelfde jaar voor Stichting de Waarden te Nijmegen. Pauline richtte zich tijdens dit onderzoek op het validiteits- en betrouwbaarheidsonderzoek van een meetinstrument om de sociaal-emotionele ontwikkeling van kinderen in een residentiele setting in kaart te brengen. In 2006 behaalde Pauline haar masterdiploma Orthopedagogiek (Cum Laude). Hierna ging Pauline wederom een aantal maanden op reis en werkte zij vanaf februari 2007 voor een periode van 6 maanden als testleider bij een onderzoek naar leesproblemen en dyslexie (CITO).

Vanaf mei 2007 tot april 2009 werkte Pauline als orthopedagoog bij het Team Inhoudelijke Screening van REC Chiron in Boxtel. Hier behandelde zij dossiers voor Cluster 4 indicaties ten behoeve van het speciaal onderwijs. Vanaf november 2007 tot februari 2009 werkte Pauline ook als onderzoeker bij de afdeling Maatschappelijke Gezondheidszorg van het Erasmus MC. Daar voerde zij, onder supervisie van Prof. Dr. Agnes van der Heide, onderzoek uit naar consultaties binnen de palliatieve zorg. Van april 2009 tot september 2014 was Pauline werkzaam als gedragskundige bij zorgorganisatie Amarant op locatie Dr. Leo Kannerhuis Brabant (LKHB). Bij dit expertise centrum richtte Pauline zich met name op consultatietrajecten en diagnostiek bij kinderen, jongeren en jongvolwassenen met een autismespectrumstoornis

en comorbiditeit. In september 2014 startte Pauline als promovenda binnen de Academische werkplaats 'Gezond ouder worden met een verstandelijke beperking' (GOUD). Vanaf 1 juli 2019 werkt Pauline als postdoc onderzoeker bij deze academische werkplaats.

## PHD PORTFOLIO

**Erasmus MC Department:** General Practice, Intellectual Disability Medicine
**PhD period:** 01-09-2014 - 30-06-2019 (wtf: 0.89)
**Promotor:** Prof. Dr. P.J.E. Bindels
**Copromotoren:** Dr. H. Hermans
Dr. D.A.M. Maes-Festen

| **1. PhD training** | | |
|---|---|---|
| | **Year** | **Workload (ECTS)** |
| **General courses** | | |
| - Medical library courses (searching and EndNote) | **2014** | **1.0** |
| - BROK (Good Clinical Practice) | **2015, 2019** | **2.0** |
| - Research Integrity | **2015** | **0.3** |
| - Biomedical English Writing and Communication | **2018** | **4.0** |
| **Specific courses** | | |
| - Anxiety and depression in adults with ID, GITP | **2016** | **1.0** |
| - NIHES Biostatistical Methods I: Basic Principles, part A (CC02A) | **2017** | **2.0** |
| **Seminars and workshops** | | |
| - PAOK Section EAA Behavior and sleep disturbances Training, Rotterdam, the Netherlands | **2017** | **0.3** |
| - NVO congress, Amsterdam, the Netherlands | **2018** | **0.3** |
| - NVO congress, Ede, the Netherlands | **2019** | **0.3** |
| **Presentations** | | |
| - Department oral presentations | **2014-2019** | **2.0** |
| - Study oral presentations (managers, physicians, caregivers, psychologists, and behavioral scientists) | **2014-2016** | **4.0** |
| - Oral and poster presentations Amarant Research symposium, Rijsbergen and Tilburg, the Netherlands | **2016-2019** | **1.0** |
| - Research symposia Ipse de Bruggen, Zwammerdam, the Netherlands | **2017 + 2019** | **0.6** |
| **National and international conferences** | | |
| - Symposium Colors of the Future (Developments in ID-medicine), Rotterdam, the Netherlands (attendance) | **2014** | **0.3** |
| - Symposium NPG "Focus op kennis en onderzoek", Utrecht, the Netherlands (oral presentation) | **2015** | **1.0** |
| - 15th IASSIDD World Congress, Melbourne, Australia (oral presentation) | **2016** | **2.0** |
| - 4th Tranzo AWVB Symposium, Tilburg, the Netherlands (attendance) | **2017** | **0.3** |

| | | |
|---|---|---|
| - 4th Chronotherapy Network the Netherlands (CNN), symposium, Leiden, the Netherlands (attendance)<br>- 29th Society of Light Treatment and Biological Rhythms Congress (SLTBR), Berlin, Germany (poster presentation)<br>- 11th European Congress Mental Health in Intellectual Disability, Luxembourg, Luxembourg (EAMHID) (2 oral presentations)<br>- 30th Society of Light Treatment and Biological Rhythms Congress (SLTBR), Groningen, the Netherlands (poster presentation)<br>- 18th IASSIDD European Congress, Athens, Greece (oral presentation + chair mental health symposium)<br>- Vilans Congress 'Zoek het uit', Nieuwegein, the Netherlands (poster presentation)<br>- 3rd Implementation Science Conference, Utrecht, the Netherlands (attendance)<br>- 5th Tranzo AWVB Symposium, Tilburg, the Netherlands (attendance)<br>- 12th European Congress Mental Health in Intellectual Disability (EAMHID), Barcelona, Spain (oral presentation) | **2017**<br>**2017**<br>**2017**<br>**2018**<br>**2018**<br>**2019**<br>**2019**<br>**2019**<br>**2019** | **0.3**<br>**2.0**<br>**2.0**<br>**2.0**<br>**2.0**<br>**1.0**<br>**0.3**<br>**0.3**<br>**2.0** |
| **2. Teaching** | **Year** | **Workload (Hours/ECTS)** |
| **Lecturing**<br>- Guest lectures: "Depression in adults with ID and light therapy", Intellectual Disability physicians alumni network | **2015 + 2016** | **1.0** |
| **Supervising Masters theses**<br>- 1 Medical Science master student<br>- 2 Pedagogical Science master students<br>- Supervising student session 'How to judge a paper' | **2015**<br>**2015-2016**<br>**2018** | **4.0**<br>**8.0**<br>**0.3** |
| **3. Other** | **Year** | |
| - Member of the Scientific Research Committee Amarant<br>- Best Poster Award (30th Society of Light Treatment and Biological Rhythms Congress (SLTBR), Groningen, the Netherlands) | **2015 - 2018** | **1.0**<br>**-** |

# LIST OF PUBLICATIONS

### This thesis

*International publications (peer reviewed journals)*

**Hamers, P.C.M.,** Evenhuis, H.M, and Hermans, H. (2017). A multicenter randomized controlled trial for bright light therapy in adults with intellectual disabilities and depression: Study protocol and obstacle management. *Research in Developmental Disabilities*, *60*, 96–106. (5 Year Impact Factor: 2.376, 14/69 Rehabilitation, 9/41 Special Education).

**Hamers, P.C.M.,** Festen, D.A.M., and Hermans, H. (2018). Non-pharmacological interventions for adults with intellectual disabilities and depression: a systematic review. *Journal of Intellectual Disability Research*, *62(8),* 684-700. (5 Year Impact Factor: 2.637, 13/69 Rehabilitation, 8/41 Special Education).

**Hamers, P.C.M.**, van Ool, J.S., Festen, D.A.M., Hendriksen, J.G.M., Bindels, P.J.E., Hermans, H. (2019). Reliability and validity of the Dutch Anxiety, Depression And Mood Scale in adults aged <50 years with intellectual disabilities. *J Appl Res Intellect Disabil*.; 32: 568– 574. (5 Year Impact Factor: 2.575, 18/69 Rehabilitation, 26/59 Educational Psychology).

**Hamers, P.C.M.,** Festen, D.A.M., Bindels, P.J.E., Hermans, H. The effect of Bright Light Therapy on depressive symptoms in adults with intellectual disabilities: results of a multicenter randomized controlled trial. *Under review*

**Hamers, P.C.M.**, Savas, M., van Rossum, E.F.C., de Rijke, Y.B., Bindels, P.J.E., Festen, D.A.M., Hermans, H. Effect of bright light therapy on long-term stress levels in adults with intellectual disabilities and depressive symptoms. *Submitted*

**Hamers, P.C.M.,** Böhmer, M.N., Festen, D.A.M., Bindels, P.J.E., and Hermans, H. The influence of personal light exposure on mood and sleep in patients with (mental) health problems: a systematic review. *Submitted*

**Other publications**

*International publications (peer reviewed journals)*

Böhmer, M.N., **Hamers, P.C.M.,** Bindels, P.J.E., Oppewal, A., van Someren, E.J.W., Festen, D.A.M. Are we still in the dark? A systematic review on personal daily light exposure, circadian rhythm, sleep and mood in healthy adults from the general population. *Submitted*

*National publications*

**Hamers, P.C.M.,** Festen, D., Hermans, H. (2017). Achtergrond en onderzoeksdesign van onderzoek naar niet-farmacologische behandeling van depressieve klachten bij volwassenen met een verstandelijke beperking. *Tijdschrift voor Artsen voor Verstandelijk Gehandicapten, Jaargang 35, nummer 4,* 168-171.

**Hamers, P.C.M.,** Festen, D., Hermans, H. (2018). Niet-farmacologische behandeling bij volwassenen met een verstandelijke beperking en een depressieve stoornis: een systematisch literatuuronderzoek. *Tijdschrift voor Artsen voor Verstandelijk Gehandicapten, Jaargang 36, nummer 3,* 105-108.

*Congress abstracts*

Bohmer, M.N., **Hamers**, **P.C.M.,** Oppewal, A., Maes-Festen, D.A.M. (2019). Are we still in the Dark? A Systematic Review on Light Exposure, Sleep and Mood in the General Population. *Neuropsychobiology;78*: 157. (5 Year Impact Factor: 1.891, 101/146 Psychiatry, 52/77 Psychology, 224/267 Neurosciences).

**Hamers**, **P.C.M.,** Festen, D.A.M., Hermans, H. (2018). A multicenter randomised controlled trial for bright light therapy in adults with intellectual disabilities and depressive symptoms: first results. *Journal of Applied Research in Intellectual Disabilities*, *volume 31*, Issue 4, 557. (5 Year Impact Factor: 2.575, 18/69 Rehabilitation, 26/59 Educational Psychology).

**Hamers, P.C.M.**, Festen, D.A.M., Hermans, H. (2018). A Multicenter Randomised Controlled Trial with Bright Light Therapy to decrease depressive symptoms in Adults with Intellectual Disability: preliminary results. *Neuropsychobiology ;76*: 18-19. (5 Year Impact Factor: 1.891, 101/146 Psychiatry, 52/77 Psychology, 224/267 Neurosciences).

**Hamers, P.C.M.,** Festen, D.A.M., Hermans, H. (2017) A Systematic Review of Non-Pharmacological Interventions for Adults With ID and Depression. *Journal of Mental Health Research in Intellectual Disabilities, Volume 10,* Supplement 1, 156. (5 Year Impact Factor: 1.525, 27/41 Special Education, 50/69 Rehabilitation, 113/142 Psychiatry).

**Hamers, P.C.M.,** Evenhuis, H.M., Hermans, H. (2017). A Multicenter Randomized Controlled Trial for Bright Light Therapy in Adults With Intellectual Disability and Depression: Obstacles and Challenges. *Journal of Mental Health Research in Intellectual Disabilities, Volume 10,* Supplement 1, 157-158. (5 Year Impact Factor: 1.525, 27/41 Special Education, 50/69 Rehabilitation, 113/142 Psychiatry).

**Hamers, P.C.M.**, Evenhuis, H.M., Hermans, H. (2017). A Multicenter Randomized Controlled Trial for Bright Light Therapy in Adults with Intellectual Disability and Depression: Study Protocol. *Neuropsychobiology;74*: 238-239. (5 Year Impact Factor: 1.891, 101/146 Psychiatry, 52/77 Psychology, 224/267 Neurosciences).

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*Letter to the editor*

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# GOUD

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