

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Effects of bright light therapy for depression during pregnancy: a randomized, double-blind controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038030
Article Type:	Original research
Date Submitted by the Author:	26-Feb-2020
Complete List of Authors:	Bais, Babette; Erasmus Medical Center, Psychiatry Kamperman, Astrid M.; Erasmus MC, Psychiatry Bijma, Hilmar; Erasmus Medical Center, Obstetrics and Gynaecology Hoogendijk, Witte; Erasmus Medical Center, Psychiatry Souman, Jan; Signify NV, Lighting Applications Knijff, Esther; Erasmus Medical Center, Psychiatry Lambregtse-van den Berg, Mijke; Erasmus MC, Psychiatry; Erasmus MC, Child and Adolescent Psychiatry/Psychology
Keywords:	Depression & mood disorders < PSYCHIATRY, OBSTETRICS, PSYCHIATRY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Effects of bright light therapy for depression during pregnancy: a randomized, double-blind**
4
5 2 **controlled trial**
6

7 3
8
9 4 Babette Bais, MSc^{1*}, Astrid M Kamperman, PhD², Hilmar H Bijma, MD, PhD³, Witte JG Hoogendijk, MD,
10
11 5 PhD⁴, Jan L Souman, PhD⁵, Esther Knijff, MD, PhD⁶, Mijke P Lambregtse-van den Berg, MD, PhD⁷
12
13 6

14 7 ¹ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

15 8 ² Epidemiological and Social Psychiatric Research Institute, Department of Psychiatry, Erasmus
16
17 9 University Medical Centre Rotterdam, Rotterdam, The Netherlands

18
19
20 10 ³ Department of Obstetrics and Gynaecology, Erasmus University Medical Centre Rotterdam, Rotterdam,
21
22 11 The Netherlands

23
24 12 ⁴ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

25
26 13 ⁵ Department Lighting Applications, Signify Research, Eindhoven, The Netherlands;

27
28 14 ⁶ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

29
30 15 ⁷ Department of Child and Adolescent Psychiatry/Psychology, department of Psychiatry, Erasmus
31
32 16 University Medical Centre Rotterdam, Rotterdam, The Netherlands

33
34 17 *Corresponding author: P.O. Box 2040, 3000CA Rotterdam, The Netherlands; b.bais@erasmusmc.nl
35
36 18

1
2
3 19 **Abstract**

4
5 20 **Objectives** Approximately 11-13% of pregnant women suffer from depression. Bright light therapy (BLT)
6
7 21 is a promising treatment, combining direct availability, sufficient efficacy, low costs and high safety for
8
9 22 both mother and child. Here, we examined the effects of BLT on depression during pregnancy.

10
11 23 **Design** Randomized, double-blind controlled trial.

12
13 24 **Setting** Primary and secondary care in The Netherlands, from November 2016 to March 2019.

14
15 25 **Participants** 67 pregnant (12-32 weeks gestational age) with a DSM-5 diagnosis of depressive disorder.

16
17 26 **Interventions** Participants were randomly allocated to treatment with either BLT (9,000 lux, 5,000 K) or
18
19 27 dim red light therapy (DRLT, 100 lux, 2,700 K), which is considered placebo. For six weeks, both groups
20
21 28 were treated daily at home for 30 minutes upon awakening. Follow-up took place weekly during the
22
23 29 intervention, after six weeks of therapy, three and ten weeks after treatment and two months postpartum.

24
25 30 **Primary and secondary outcome measures** Depressive symptoms were measured primarily with the
26
27 31 Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder. Secondary
28
29 32 measures were the Hamilton Rating Scale for Depression and the Edinburgh Postnatal Depression Scale.
30
31 33 Changes in rating scale scores of these questionnaires over time were analysed using generalized linear
32
33 34 mixed models.

34
35 35 **Results** Median depression scores decreased by 40.6-53.1% in the BLT group and by 50.9-66.7% in the
36
37 36 DRLT group. We found no statistically significant difference in symptom change scores between BLT and
38
39 37 DRLT. Sensitivity and post-hoc analyses did not change our findings.

40
41 38 **Conclusions** BLT and DRLT were both effective in reducing depressive symptoms in pregnant women
42
43 39 with depression. More research is necessary to determine whether these responses represent true
44
45 40 treatment effects, non-specific treatment responses, placebo effects or a combination hereof.

45
46 41 **Trial Registration** Bright Up, NTR5476, <http://www.trialregister.nl>
47
48 42

49 43 **Strengths and limitations of this study**

- 50
51 44
 - We conducted various follow up measurements, including postpartum, to study the effects of
52
53 45 withdrawal of treatment and to study whether treatment during pregnancy would protect against
54
55 46 postpartum depression.

- 1
2
3 47 • The setting of treatment was within a real world setting.
4
5 48 • A strength of this study was the comprehensive assessment of side effects, as well as
6
7 49 acceptability and satisfaction of treatment.
8
9 50 • An unforeseen lack of resources prevented us from including 150 participants, as we aimed to do
10
11 51 according to our sample size calculation.
12
13 52 • Depressive symptoms during the study are assessed by questionnaires, rather than diagnostic
14
15 53 criteria.
16
17 54

55 Introduction

56 Antepartum depression is a common and high impact disease, with approximately 11-13% of pregnant
57 women suffering from depression ¹. Antepartum depression is not only seen in autumn and winter, but is
58 a year-round phenomenon, with certain subgroups even showing more symptoms in summer ². Many risk
59 factors for antepartum depression have been identified ^{3,4}, inflammation is mentioned amongst others as
60 possible cause ^{5,6}. Women who suffer from antepartum depression are more likely to suffer from
61 postpartum depression as well ⁷. Children who are exposed to maternal depression during pregnancy
62 have a higher risk of adverse birth outcomes, such as prematurity and being small for gestational age ^{8,9}.
63 Additionally, children show more often cognitive, emotional and behavioral problems in childhood,
64 adolescence and adulthood ^{10,11} and they have a higher risk of suffering from depression later in life ¹².
65 During pregnancy, fetal programming of the hypothalamus-pituitary-adrenal gland (HPA) axis takes place,
66 which can be affected by maternal depression during pregnancy and may have long-lasting effects on
67 stress response ¹³. Possible mechanisms are 1) maternal cortisol crossing the placenta and thus
68 increasing fetal cortisol levels, 2) placental secretion of corticotropin-releasing factor, which stimulates
69 both maternal and fetal cortisol, and 3) reduced blood flow to the fetus, causing fetal growth restriction ^{8,14-}
70 ¹⁷. In addition, epigenetic programming takes place within the antepartum period, which influences not
71 only the health of the (unborn) infant, but also that of following generations ¹⁸. Therefore, early detection
72 and treatment of antepartum depression is highly important for both mother and infant.
73 In non-pregnant women, guidelines propose psychotherapy, antidepressant medication or a combination
74 of both as treatment. However, psychotherapy might not be readily available and the safety of maternal
75 use of antidepressants, which cross the placenta, still remains to be established. The use of
76 antidepressants is controversial, because of potential teratogenicity ^{19,20}. For example, increased risks
77 have been found for persistent pulmonary hypertension of the neonate ²¹ and cardiovascular
78 malformations ²². Furthermore, pregnant women express a strong preference for non-pharmacologic
79 treatment because of the possible harm for their unborn child ^{23,24}. Moreover, current adherence to
80 national guidelines by midwives and gynaecologists is low ²⁵ and international guidelines on the
81 pharmacological treatment of antepartum depression are not consistent ²⁶, which might result in
82 unwanted variation in practice. Despite this, antidepressant use during pregnancy is increasing, not only

1
2
3 83 in the Netherlands ^{27,28}, but in other European countries and the United States as well ²⁹⁻³¹. In the
4
5 84 Netherlands, approximately 2-3% of pregnant women use antidepressants ^{28,32,33}. In the United States,
6
7 85 this prevalence is approximately 6-7% ³⁴⁻³⁶, but could even be as high as 15% in some states ³⁷.
8
9 86 Therefore, it is urgent and clinically relevant to investigate alternative approaches to treat antepartum
10
11 87 depression, such as bright light therapy (BLT) ³⁸.
12
13 88 Light synchronizes the suprachiasmatic nucleus (SCN), or the 'biological clock', with the environmental
14
15 89 day-night rhythm ³⁹. Light hits the retina and intrinsically photosensitive retinal ganglion cells (ipRGCs) in
16
17 90 the retina project, via the retino-hypthalamic tract to the SCN and thus influences circadian rhythm ³⁹⁻⁴¹,
18
19 91 which may indirectly benefit depressive symptoms ⁴². However, not only do ipRGCs project to the SCN,
20
21 92 but also directly to brain regions important in the regulation of mood, such as the medial amygdala and
22
23 93 the lateral habenula ³⁹⁻⁴¹.
24
25 94 Although BLT is the first-choice treatment for seasonal affective disorder, a condition of reoccurring
26
27 95 depressions during fall and winter, with remissions in spring and summer ^{43,44}, the effects of BLT have
28
29 96 been shown both in seasonal affective disorder and in non-seasonal depression, which is not only shown
30
31 97 by a Cochrane review ⁴⁵, but also by more recent systematic reviews and meta-analyses ⁴⁶⁻⁴⁹. An open
32
33 98 trial of BLT in pregnant women showed improvement of mean depression ratings by 49% ⁵⁰. Two small
34
35 99 randomized controlled trials showed significant improvement of depression among pregnant women
36
37 100 exposed to BLT compared to placebo ^{51,52}. Although these results seem promising, the sample sizes of
38
39 101 these studies were small, making them at risk for chance-findings ⁵³.
40
41 102 In this study, we compared the effectiveness of BLT compared to placebo light among pregnant women
42
43 103 with a depressive disorder in a larger randomized clinical trial. Moreover, we followed women until the
44
45 104 postpartum period, to study whether treatment with light therapy during pregnancy might protect against
46
47 105 postpartum depression. We hypothesized that daily treatment with six weeks of morning BLT will improve
48
49 106 depressive symptoms during pregnancy.

107

108 **Material and Methods**

109 *Design*

1
2
3 110 This study was a randomized, double-blind, placebo-controlled clinical trial (Bright Up, NTR5476,
4
5 111 <http://www.trialregister.nl>). A detailed protocol can be found elsewhere ⁵⁴. In short, the aim of the Bright
6
7 112 Up study was to evaluate the effectiveness of BLT for pregnant women with a depressive disorder,
8
9 113 compared to placebo light.

10
11 114

12 115 *Participants*

14 116 Eligible participants were pregnant women (12-32 weeks of gestational age, confirmed by ultrasound)
15
16 117 diagnosed with a depressive disorder, confirmed by a Structured Clinical Interview for DSM disorders
17
18 118 (SCID) by one trained assessor ⁵⁵. The specific inclusion and exclusion criteria are listed in Table 1.

19
20 119 In the earlier published study protocol ⁵⁴, we aimed to include women who were 12-18 weeks pregnant.
21
22 120 For pragmatic reasons, in particular the fact that a substantial number of women was referred after 18
23
24 121 weeks of pregnancy, we later decided to widen our inclusion criteria to 12-32 weeks pregnancy.

25
26 122 In the Netherlands, maternity care for low-risk pregnancies is provided by midwives (primary care). High-
27
28 123 risk pregnancies are cared for by gynaecologists in a general hospital (secondary care) or fetal-maternal
29
30 124 medicine unit (tertiary care).

31
32 125 In this study, women were recruited not only via health care professionals, such as general practitioners,
33
34 126 midwives, gynaecologists, psychiatrists and psychologists, but also via (social) media. A complete flow-
35
36 127 chart of the recruitment can be found in Figure 1.

37
38 128 Initially, we calculated the number of women to be included, based on the results and research
39
40 129 methodology of previous studies ^{50,51,56}. We expected a true treatment effect in the range of a 10-15%
41
42 130 symptom reduction over the full course of treatment, reflecting a small to medium effect size. To
43
44 131 demonstrate this, with an α of 0.05 and a β of 0.8, a total sample size of 126 participants, 63 per arm was
45
46 132 needed. To account for loss to follow up during and after treatment, we aimed at including 150 women.
47
48 133 Power calculations were performed using GLIMMPSE 2.1.5. software ⁵⁷. Inclusion took place in The
49
50 134 Netherlands and started on 9 November 2016 and lasted until 15 March 2019. By then, 67 women were
51
52 135 included. However, due to limiting resources, we decided to stop the inclusion.

53 136

54 137 *Patient and Public Involvement*

1
2
3 138 No patients involved.
4

5 139

6
7 140 *Ethics*

8
9 141 All procedures performed involving human participants were in accordance with the ethical standards of
10
11 142 the institutional and/or national research committee and with the 1964 Helsinki declaration and its later
12
13 143 amendments or comparable ethical standards. Written informed consent was obtained from all
14
15 144 participants. The study protocol and later amendments were approved by the medical ethical committee
16
17 145 of the Erasmus University Medical Centre, Rotterdam, The Netherlands (registration number MEC-2015-
18
19 146 731).

20 147

21
22 148 *Blinding*

23
24 149 Participants were blinded to allocation. Participants were informed that the study aimed to investigate the
25
26 150 efficacy of different light colours. They were not informed that one treatment arm was considered placebo
27
28 151 treatment. This was in accordance with approval of the medical ethical committee.

29
30 152 Outcome assessors were blinded to the allocation of the participants. Participants were asked not to
31
32 153 share any details regarding their treatment towards the assessors. When blinding was broken, the
33
34 154 assessor was replaced. The researcher performing the primary statistical analyses (AK) was blinded to
35
36 155 the allocation. The field researcher (BB) was not blinded to the allocation for practical reasons. This
37
38 156 researcher made sure lamps of the correct allocation were delivered to the participants. Also, this
39
40 157 researcher asked participants about any side effects, keeping the independent assessors blinded to any
41
42 158 adverse effects that might break the blinding, e.g. strained eyes, and answered any questions from the
43
44 159 participants regarding their lamps.

45 160 At baseline, we asked about any expectations concerning the treatment with regards to their depressive
46
47 161 symptoms. Women could choose whether they expected a negative effect, a small negative effect, no
48
49 162 effect, a small positive effect or a positive effect. After the intervention period, the participants were asked
50
51 163 whether they were aware of their allocation.

52
53 164

54
55 165 *Light therapy*

1
2
3 166 Light treatment consisted of either active BLT (9,000 lux, color temperature 5,000 K) or dim red light
4
5 167 therapy (DRLT, 100 lux, color temperature 2,700 K). The photobiological characterizations of these
6
7 168 treatments are shown in Supplementary Table 1. The original lamps were adjusted in the factory where
8
9 169 these are produced (EnergyUp HF3419/01, Philips, Eindhoven, The Netherlands). To ensure that
10
11 170 participants are exposed to the same light intensity, the output of the lamps was fixed. For the control
12
13 171 condition, the standard LED's in the lamp were replaced by LED's with a lower intensity and a different
14
15 172 color temperature. The lamps in the control condition were positioned at the same distance from the
16
17 173 participant as in the experimental condition.

18 174 The active light therapy was shown to be effective in other studies^{51,52,56,58}. DRLT can be considered to
19
20 175 be biologically inactive and thus as placebo treatment⁴⁵. In line with two previous RCT's among pregnant
21
22 176 women, we chose six weeks of daily light exposure^{51,52}.

23
24 177 The lamps were delivered at the participants' home by one researcher (BB) who was not blinded to the
25
26 178 allocation of the participants. This researcher did not share anything about the allocation with the
27
28 179 participants. After delivery of the lamps and instructions, participants commenced their daily treatment
29
30 180 with light for 30 minutes within 30 minutes of habitual wake up time for a six weeks period. This took
31
32 181 place at the participants' home. Participants sat in front of two lamps with a distance of approximately 40
33
34 182 cm (15.8 inches). They received a plastic ruler of this length to ensure of the correct distance. The light
35
36 183 boxes were placed in a custom-made scaffolding, so that the height of the light boxes could be adjusted
37
38 184 per person and glare was avoided. Apart from the light treatment, participants in both treatment arms
39
40 185 received treatment as usual: women were free to visit their general practitioner, obstetric care provider or
41
42 186 mental health care worker and start additional treatment, whenever they felt a need for this.

43 187 During the intervention period, self-reported compliance with the light treatment was checked weekly.
44
45 188

47 189 *Method*

48
49 190 A baseline interview was conducted by telephone by one researcher (BB). The baseline interview
50
51 191 collected sociodemographic information (age, ethnicity, educational level, marital status, body mass index
52
53 192 (BMI)), obstetric information (gestational age, whether the pregnancy was planned, parity), psychiatric
54
55 193 information (substance use (smoking, alcohol, drugs), present and past medication use, present
56
57
58
59
60

1
2
3 194 depressive symptoms and psychiatric history) and information on somatic conditions. Also, participants
4
5 195 were screened with the SCID for depressive disorder and various potential co-morbidities, such as
6
7 196 generalized anxiety disorder and panic disorder. Previous depressive episodes were also assessed with
8
9 197 the SCID. The general practitioner was contacted to verify present medication use and whether the
10
11 198 participant met any exclusion criteria.

12
13 199 After baseline measurements and receiving written informed consent, the participants were randomly
14
15 200 allocated to either receive BLT or DRLT in a 1:1 ratio. Randomization was done with the web-based
16
17 201 computer-generated schedule ALEA (software for randomization in clinical trials, version 2.2) using
18
19 202 random block sizes of 2-6⁵⁹ by an independent researcher. Stratification factors were the use of any
20
21 203 current antidepressant medication and the number of previous depressive episodes. The latter was
22
23 204 dichotomized to three or less versus four or more⁶⁰.

24 205 Follow up took place at the following time points:

- 26 206 ▪ weekly during the intervention period (T0+1, T0+2, etc.)
- 27
28 207 ▪ after 6 weeks of treatment (T1)
- 29
30 208 ▪ 3 weeks after end of treatment (T2)
- 31
32 209 ▪ 10 weeks after end of treatment (T3)
- 33
34 210 ▪ 2 months postpartum (P1)
- 35
36 211 ▪ 6 months postpartum (P2)
- 37
38 212 ▪ 18 months postpartum (P3)

39 213 At these time points, questionnaires were assessed and body material was collected. We collected urine,
40
41 214 hair and cortisol from the participants, as can be found in our earlier published protocol⁵⁴.

42
43 215 This paper reports the short term effectiveness, i.e. up to two months postpartum.

44
45 216

47 217 *Primary and secondary outcome measures*

48
49 218 The primary outcome measure was the average change in depressive symptoms between the two
50
51 219 groups, as measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal
52
53 220 Affective Disorder version (SIGH-SAD). Secondary outcome measures were these changes as measured

1
2
3 221 by the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Edinburgh Depression Scale
4
5 222 (EPDS).
6
7 223 In the earlier published protocol ⁵⁴, we were primarily interested in the effects of light therapy on
8
9 224 depressive symptoms. Secondly, we were interested in the effects on various other outcomes, such as
10
11 225 maternal hormonal levels, maternal sleep quality and infant outcomes. Depressive symptoms were
12
13 226 measured by two questionnaires: the SIGH-SAD and the EPDS, with the HAM-D being part of the SIGH-
14
15 227 SAD. Therefore, in the original protocol ⁵⁴, we mentioned these two questionnaires together as the
16
17 228 primary outcome, as opposed to the other outcomes (maternal hormonal levels and others). However, it is
18
19 229 not technically possible to have more than one primary outcome. Our power calculation was based on the
20
21 230 SIGH-SAD, which makes this our true primary outcome. The HAM-D and the EPDS are the secondary
22
23 231 outcomes for this manuscript. In the current manuscript, we only report our findings regarding the
24
25 232 depressive symptoms. We will report the other outcomes elsewhere.

26 233 The SIGH-SAD is a 29-item structured interview, consisting of 21 HAM-D items and 8 atypical items. We
27
28 234 used the entire SIGH-SAD questionnaire as primary measure, since this is the current benchmark for
29
30 235 assessment of depression severity in light therapy trials. We chose the original 17-item HAM-D
31
32 236 questionnaire as a secondary measure, since it is more commonly used in clinical practice and research.

33
34 237 Blinded assessors conducted the SIGH-SAD interviews (including HAM-D questions) by telephone
35
36 238 weekly in the intervention period and at follow up.

37
38 239 The EPDS is a structured 10-item questionnaire and was used as a self-report measure of depression
39
40 240 during pregnancy and postpartum ⁶¹. Items are scored with a value 0-3, resulting in a sum score of 0-30
41
42 241 ⁶¹. The EPDS was developed for the detection of postpartum depression, but has been validated for
43
44 242 screening depression during pregnancy as well ⁶². The EPDS was assessed weekly in the intervention
45
46 243 period and at follow up. Participants received a link by e-mail to fill out the questionnaire.

244

245 *Side effects, acceptability and satisfaction*

246 During the intervention period, participants were asked weekly about any possible side effects.
247 Acceptability was assessed by asking participants about their subjective treatment experiences after the
248 intervention period. Women could choose whether they experienced a negative effect, a small negative

1
2
3 249 effect, no effect, a small positive effect or a positive effect. Women were asked how easy or difficult they
4
5 250 could implement the therapy in their daily schedule and how easy or difficult the lamp was in use: very
6
7 251 difficult, difficult, neutral, easy or very easy. Women could answer whether they found the light therapy
8
9 252 very unpleasant, unpleasant, neutral, pleasant or very pleasant. Women were asked whether they would
10
11 253 like to use the light therapy outside of the study (yes/no). Finally, women were asked how likely they
12
13 254 would recommend light therapy to others on a scale of 1 to 10.

14 255

16 256 *Confounders*

18 257 The baseline interview collected information on various confounders, such as sociodemographic,
19
20 258 obstetric and psychiatric information and information on somatic conditions (see Method for further
21
22 259 specifications).

24 260 The participant's chronotype was assessed at inclusion with the Munich Chronotype Questionnaire
25
26 261 (MCTQ), a structured 19-item self-report questionnaire⁶³, since evening types are more prone to
27
28 262 depression compared to morning types^{64,65}. The participant can be classified into one of seven
29
30 263 chronotypes: extremely, moderately or slightly early, normal or slightly, moderately or extremely late. Sum
31
32 264 scores range from 16 to 86, with low scores indicating extremely late chronotypes.

33 265

35 266 *Statistical analysis*

37 267 Continuous participant characteristics were summarized using mean and standard deviation (SD).
38
39 268 Categorical variables, such as educational level, were summarized by count and percent. In line with the
40
41 269 CONSORT statement, baseline differences between the two treatment arms were not tested⁶⁶.

43 270 For treatment effect analyses, we applied an intention-to-treat procedure, since none of the participants
44
45 271 could switch to a different condition, and we included all observations of all participants until the study
46
47 272 ended or the participant(s) dropped out of the study.

49 273 The primary outcome was changes in SIGH-SAD rating scale scores over time. Secondary outcomes
50
51 274 were changes in HAM-D and EPDS rating scale scores over time. Analyses were conducted using
52
53 275 general linear mixed modelling analyses. In a series of random-intercept models, we included time,
54
55 276 allocation and time x allocation interaction-term as an effect measure of allocation on the course of

1
2
3 277 depression rating scale scores. The standardized baseline score was included in the model, since
4
5 278 baseline depression severity is an important predictor for treatment outcome⁶⁷. We studied the treatment
6
7 279 effect for both the intervention period and follow-up period (two months postpartum).

8
9 280 Primary analyses were first crude, then adjusted. As adjusted primary analyses, we calculated propensity
10
11 281 scores based on patient characteristics (psychiatric history, ethnicity, level of education, an unplanned
12
13 282 pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or
14
15 283 psychotherapeutic treatment interventions). Next, we adjusted separately for chronotype and the month of
16
17 284 treatment. By means of sensitivity analyses, we repeated the primary analyses with last observation
18
19 285 carried forward data imputation. As post-hoc analyses, we repeated the crude analyses for women with
20
21 286 good compliance (<7 missed treatments) and for women with most severe depressive symptomatology
22
23 287 (based on median split baseline SIGH-SAD scores). Effect parameters were supplied with a 95%
24
25 288 confidence interval (CI).

26 289 Additionally, we tested responders versus non-responders with Fisher's exact test, where response was
27
28 290 defined as a $\geq 50\%$ decrease to a final score of ≤ 8 on the 17-item HAM-D and ≤ 5 on the EPDS at the end
29
30 291 of the intervention period.

31
32 292 Data was analyzed using SPSS 21.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was
33
34 293 defined as $p < .05$.

35
36 294

37 295 **Results**

38 296 *Demographic and clinical characteristics*

39
40 297 In total, 283 women were referred to the study. The majority of the participants (82%) was recruited via
41
42 298 (social) media. Of these referrals, we included and randomized 67 women, with 33 allocated to BLT and
43
44 299 34 to DRLT. In total, eleven women dropped out during the study, of whom five in the BLT group. Ten
45
46 300 women dropped out in the intervention period, one at ten weeks after treatment. Figure 1 shows a flow-
47
48 301 chart of the entire study sample.

49
50
51 302 Table 2 shows the participant characteristics at the time of inclusion. At inclusion, the mean (SD) of the
52
53 303 SIGH-SAD was 26.5 (7.2), of the 17-item HAM-D was 16.9 (5.3) and of the EPDS was 16.1 (4.8). Median
54
55 304 scores were respectively 27, 17 and 16.

1
2
3 305 The most common comorbidity was anxiety (25.4%), followed by obsessive compulsive disorder (17.9%),
4
5 306 PTSS (11.9%) and social phobia (11.9%). Various somatic comorbidities were reported, such as asthma,
6
7 307 Guillain-Barré syndrome and fibromyalgia.

8
9 308 During the course of this study, as part of the care as usual, eleven additional women started with
10
11 309 psychotherapy: three women in the intervention period, one after the intervention period during pregnancy
12
13 310 and seven in the postpartum period. During the entire study, four additional women started with
14
15 311 psychotropic medication: one woman started with an SSRI in the intervention period and one woman in
16
17 312 the postpartum period (both sertraline), one with an antipsychotic (quetiapine) and one with a
18
19 313 benzodiazepine (temazepam) postpartum. Of one participant, the dose of the SSRI was increased in the
20
21 314 postpartum period (escitalopram).

22 315

23 24 316 *Compliance*

25
26 317 Self-reported compliance was somewhat higher in the BLT group, compared to the DRLT group. Amongst
27
28 318 the women treated with BLT, eight women (24.2%) never missed a treatment, in contrast to three women
29
30 319 (8.8%) in the DRLT group. Sixteen women (48.5%) treated with BLT missed a maximum of six
31
32 320 treatments, compared to twenty women (58.9% in the DRLT group. In both groups, two women missed
33
34 321 seven to thirteen treatments in the intervention period. One woman treated with BLT and two with DRLT
35
36 322 missed fourteen or more treatments. One woman treated with BLT and two with DRLT missed the final
37
38 323 two weeks of treatment, the first one due to complete remission of her symptoms.

39 324

40 41 325 *Maintaining blinding*

42
43 326 Before treatment, three women (4.8%) did not expect any effect from light therapy for their depressive
44
45 327 symptoms. All other participants expected a (small) positive effect. After treatment, one participant treated
46
47 328 with BLT (3.0%) and three women in the group treated with DRLT (8.8%) thought they were treated with
48
49 329 placebo treatment. All other women had no specific ideas about their allocation.

50 330

51 52 331 *Treatment effect*

1
2
3 332 Supplementary Table 2 shows the observed median SIGH-SAD, HAM-D and EPDS scores over the
4
5 333 course of the study. In the women treated with BLT, median depression scores decreased by 42.6%
6
7 334 (SIGH-SAD), 53.1% (HAM-D) and 40.6% (EPDS) in the intervention period. In the DRLT group, this was
8
9 335 respectively 50.9%, 66.7% and 59.4%. After women stopped with light treatment, median scores
10
11 336 continued to decrease for all questionnaires in both groups, three and ten weeks after treatment. At two
12
13 337 months postpartum, women treated with BLT showed no increase in EPDS scores, whereas women
14
15 338 treated with DRLT showed an increase in EPDS-scores. For both SIGH-SAD and HAM-D scores, a
16
17 339 decrease was observed in both treatment arms.
18
19 340 We also calculated the median improvement scores without the baseline score. For women treated with
20
21 341 BLT, these were 6.1% (SIGH-SAD), 16.7% (HAM-D) and 13.6% (EPDS). For women treated with DRLT,
22
23 342 this was respectively 31.6%, 40% and 45.8%.
24
25 343 No statistically significant difference was found between the two treatment arms for the intervention
26
27 344 period, nor for the entire study (Figure 2 and Table 3). Adjusted primary analyses, where we repeated our
28
29 345 primary analyses adjusted for propensity scores, and sensitivity analyses with imputed data did not show
30
31 346 any other findings (Supplementary Table 3). Adjustment for chronotype and month of treatment did not
32
33 347 change our findings as well. Post-hoc analyses, where we repeated the analyses for women with higher
34
35 348 treatment compliance and for women with higher symptom severity at baseline, did not show a
36
37 349 statistically significant difference between the two treatment arms (Supplementary Table 3).
38
39 350 For the HAM-D, 13 participants in the BLT group and 17 participants in the DRLT group were considered
40
41 351 responders. This was respectively 11 and 9 when measured with the EPDS. When we studied
42
43 352 responders versus non-responders, we found no statistically significant differences for both HAM-D
44
45 353 scores ($p=.46$) and EPDS scores ($p=.60$).

354

355 *Side effects*

49 356 For women treated with BLT, the most frequently reported side effect was headaches (30.3%), followed
50
51 357 by sleep problems (12.1%) and nausea (6.1%). For women treated with DRLT, the most reported side
52
53 358 effect was headaches (20.6%), followed by sleep problems (8.9%) and irritable eyes (5.9%). Side effects
54
55 359 were not reported more often by women treated with BLT, compared to DRLT ($p=0.52$). Most side effects

1
2
3 360 were experienced for a maximum of three days. None of the women suffered from any (hypo)manic
4
5 361 symptoms. We reduced the treatment duration for five women to 20 minutes daily due to their side
6
7 362 effects. Interestingly, two women dropped out of the study due to side effects, but only in the DRLT group.
8

9 363

10 364 *Acceptability and satisfaction*

11
12 365 The majority of women experienced a (small) positive effect for their depressive symptoms (78.6% BLT;
13
14 366 61.5% DRLT; $p=0.58$). All participants found the lamp (very) easy in use. Most women found the light
15
16 367 therapy pleasant (57.1% BLT; 50% DRLT; $p=0.49$). Twenty-six women reported that it was (very) easy to
17
18 368 plan the light therapy in the morning (42.9% BLT; 53.8% DRLT; $p=0.43$). Thirty-two women reported that
19
20 369 they would like to use light therapy outside of the study (57.1% BLT; 61.5% DRLT; $p=0.79$). On average,
21
22 370 women reported it was likely they would recommend the light therapy to others (BLT mean 8.0, SD 1.3;
23
24 371 DRLT mean 7.0, SD 2.7; $p=0.08$).
25

26 372

27 28 373 **Discussion**

29
30 374 We conducted a randomized controlled trial, evaluating the effectiveness of BLT in a sample of 67
31
32 375 pregnant women with major depressive disorder, compared to DRLT. We found no statistically significant
33
34 376 difference between BLT and DRLT on depressive symptoms. Median depression scores decreased by
35
36 377 40.6-53.1% during the intervention in the women treated with BLT and by 50.9-66.7% in the women
37
38 378 treated by DRLT.
39

40 379

41 380 *Effects in the current study*

42
43 381 This level of improvement is comparable to the studies by Oren *et al.*⁵⁰ and Corral *et al.*⁶⁸ who both
44
45 382 found a reduction in mean depression scores of 49%. Oren *et al.* conducted an open trial in an
46
47 383 antepartum population, whereas Corral *et al.* conducted a randomized controlled trial among women with
48
49 384 a postpartum depression. Similar to Corral *et al.*, we did not find a statistically significant difference
50
51 385 between the effective and placebo conditions. The median improvement in the DRLT group can be
52
53 386 explained by placebo effects, which could also be the case in the BLT group. A meta-analysis showed
54
55 387 that the placebo response in antidepressant trials is approximately 68%⁶⁹, although this effect is not clear
56
57
58
59

1
2
3 388 yet in light therapy trials specifically. Secondly, the improvement in both groups can be explained by non-
4
5 389 specific treatment effects such the structure offered by the study ⁴², the interaction with the researchers or
6
7 390 increased awareness and self-care resulting from participating in the study. A systematic review on
8
9 391 various studies in treating antepartum depression with a control condition showed that these trials often
10
11 392 show a considerable reduction in symptom scores in both treatment arms ³⁸. Furthermore, it might be that
12
13 393 symptoms decrease related to the course of pregnancy, spontaneous remission or regression to the
14
15 394 mean. A meta-analysis showed that untreated depressive symptoms could decrease by 10-15%, on
16
17 395 average ⁷⁰. However, untreated depression during pregnancy is an important predictor for postpartum
18
19 396 depression ⁷¹. We calculated the improvement of the depressive symptoms without the baseline scores,
20
21 397 to study whether the improvement was especially notable in the first week of treatment. We found that the
22
23 398 improvement was less, especially in the group treated with BLT, which may pinpoint to regression to the
24
25 399 mean. For example, women may have the feeling of 'finally being heard', or feeling empowered about
26
27 400 doing something about their symptoms, which may explain these findings.

28 401 Corral *et al.* mentioned that several participants commented positively on having 30 minutes of "quiet
29
30 402 time" on a daily basis. Several of our participants mentioned this as well, which could reflect sinking into a
31
32 403 state of more relaxation or more mindfulness which may have contributed to the improvement in both
33
34 404 groups. Two meta-analyses showed that mindfulness-based therapy is an effective treatment for a variety
35
36 405 of psychological problems ^{72,73}. An earlier pilot study and an open study of mindfulness also showed
37
38 406 positive effects on mood specifically in pregnant women ^{74,75}. Corral *et al.* mentioned that many
39
40 407 postpartum women are motivated to access recourses, such as psychological treatment, which could
41
42 408 have exerted non-specific treatment effects. In their study however, no participant took part in any
43
44 409 treatment during the study. In our study, several women started psychotherapy or antidepressant
45
46 410 medication. However, adjustment for any intervention did however not change our findings.

47 411 Finally, it has been shown earlier in healthy volunteers that treatment with similar conditions as our
48
49 412 placebo therapy might actually have some effects in melatonin suppression ⁷⁶, which could explain why
50
51 413 we actually see a decrease of symptoms in the DRLT group.

52
53 41454
55 415 *Differences with literature*

1
2
3 416 The results of this study differ from the randomized controlled trials by Epperson *et al.*⁵¹ and Wirz-Justice
4
5 417 *et al.*⁵², who did find superiority of bright light therapy over placebo in an antepartum population.
6
7 418 Wirz-Justice *et al.* included only clinical patients and found that BLT had more effects in severe patients in
8
9 419 their study. However, mean baseline SIGH-SAD score in the Wirz-Justice *et al.* and Epperson *et al.*
10
11 420 studies were 27.7 and 28.1, respectively, which is not clinically relevant different from the present study
12
13 421 (26.5). Additionally, we included baseline depression scores in our model, which did not change our
14
15 422 findings. Also, post-hoc analyses, where we repeated the analyses for women with higher baseline
16
17 423 severity, did not show any significant findings.
18
19 424 Both Epperson *et al.* and Wirz-Justice *et al.* treated their patients for 1 hour a day and within 10 minutes
20
21 425 of habitual wake-up time, which is different from the present study. Thus far, no studies have been
22
23 426 executed comparing the effectiveness of shorter versus longer exposure to bright light in non-seasonal
24
25 427 depression. Possibly, more light output in the BLT group would be necessary to show superiority of BLT
26
27 428 over DRLT in a pregnant population. However, other studies that treated patients for 30 minutes also did
28
29 429 show a statistical significant difference between the effective and the placebo intervention in non-
30
31 430 seasonal depression⁴⁵. One must keep in mind that these studies have been done in non-pregnant
32
33 431 populations and different – yet unknown – underlying mechanisms may play a part during pregnancy,
34
35 432 such as hormonal fluctuations and a shift in social role.
36
37 433 Our placebo condition, in which the possible effect of DRLT could be questioned, is not a plausible
38
39 434 explanation for not finding a statistically significant effect between the treatment arms. Epperson *et al.*
40
41 435 used a placebo condition with 500 lux white light, which is questionable as a placebo, for white light of
42
43 436 100 lux is able to phase-shift human circadian rhythms⁷⁷. Since this study found a significant
44
45 437 improvement in women treated with BLT when compared to this placebo, it is unlikely that the settings of
46
47 438 our placebo would explain failing to achieve a significant difference between the two treatment arms.
48
49 439 In the study by Corral *et al.*, depression scores worsened after withdrawal of treatment, indicating that
50
51 440 spontaneous remission would be less likely. However, in the present study, median depression scores of
52
53 441 all questionnaires continued to improve after withdrawal of treatment in both groups, indicating that
54
55 442 spontaneous remission in both groups is a possible explanation for this finding.
56
57
58
59
60

1
2
3 444 *Strengths and limitations*
4

5 445 Internationally, we conducted the largest randomized controlled trial studying light therapy in pregnant
6
7 446 women with a depression. Moreover, we conducted various follow up measurements, including
8
9 447 postpartum, to study the effects of withdrawal of treatment and to study whether treatment during
10
11 448 pregnancy would protect against postpartum depression. Another strength is using a single assessor to
12
13 449 diagnose depression. Moreover, the setting of treatment was within a real world setting. Finally, a
14
15 450 strength of this study was the comprehensive assessment of side effects, as well as acceptability and
16
17 451 satisfaction of treatment.

18 452 The main limitation of our study was that an unforeseen lack of resources prevented us from including
19
20 453 150 participants, as we aimed to do according to our sample size calculation⁵⁴, which enables us to find
21
22 454 only large treatment effects⁵⁴. Another limitation is the fact that depressive symptoms during the study
23
24 455 are assessed by questionnaires, rather than diagnostic criteria. Also, information about psychiatric history
25
26 456 was collected via an interview and not through medical records, which may be influenced by recall bias.
27
28 457 Moreover, various covariates are self-reported, such as BMI, substance use and medication. We noticed
29
30 458 a different attrition rate at T3 (10 weeks after treatment) and P1 (2 months postpartum). At T3, this is due
31
32 459 to the fact that more women treated with DRLT already gave birth at T3, which resulted in missing data.
33
34 460 We do not have an explanation for the different attrition rate at P1. We cannot rule out the possibility that
35
36 461 these differences in attrition might have impacted our follow-up results. However, our sensitivity analyses
37
38 462 indicate our follow-up results to be robust for differences between the conditions and data imputation.

39 463

40
41 464 *Conclusions*
42

43 465 BLT has been shown effective in treating non-seasonal depression⁴⁵ and in women with antepartum
44
45 466 depression as well^{51,52}. In the present study, both BLT and DRLT showed improvement in pregnant
46
47 467 women with a depressive disorder after 6 weeks of treatment. Given the very mild and short-lived side
48
49 468 effects, the major improvement in a short time period, the high acceptability of the participants, the low
50
51 469 costs and the direct availability, more studies to the effectiveness of BLT during pregnancy are warranted.
52
53 470 It is important to determine whether the responses observed in the present study represent true treatment
54
55 471 effects, non-specific treatment responses, placebo effects or a combination of these. This could be done
56
57
58
59
60

1
2
3 472 by studying biological outcomes, such as cortisol and melatonin levels, which might show a statistically
4
5 473 significant difference between the two treatment arms irrespective of perceived symptoms of depression.
6
7 474 Additionally, it might show an indication of the positive effects of light therapy on the circadian rhythm and
8
9 475 its inhibiting effects on HPA-axis hyperactivity.

10
11 476

12 477 **Acknowledgements**

14 478 We would like to thank all participants for participating in the study. We would also like to thank all general
15
16 479 practitioners, midwives, gynaecologists, psychiatrists and psychologists for their help with the recruitment.
17
18 480 We are grateful for all co-workers, students and assistants who contributed to the data collection in this
19
20 481 study: Nina Molenaar, PhD, Marlies Brouwer, PhD, Leo Genet, MSc, Sophie de Droog, MSc, Sofie
21
22 482 Koomen, MSc, Diewertje Houtman, MSc, Maria Zepeda, MSc, Nicolle Croes, MSc, Rianne Winters, MSc.
23
24 483 Lisanne van Kesteren, BSc, Finn Stofkoper, BSc, Indira Schouten, MSc and Mieke Roukema, MSc.
25

26 484

28 485 **Funding**

30 486 MLB received funding from the 'Light, Cognition, Behaviour and Health' program of The Netherlands
31
32 487 Organization for Health Research and Development (NWO; The Hague, The Netherlands), in
33
34 488 collaboration with Signify Research (grant number 058-14-003) to fund the current study.
35

36 489

38 490 **Competing interests**

39 491 Author JS is employed by Signify Research. The lamps used in this study were provided by Signify
40
41 492 Research.
42

43 493

45 494 **Author's contributions**

47 495 MLB is the project's principle investigator and initiator of the study, obtained funding and designed the
48
49 496 study. BB was responsible for recruiting and counselling participants, running the study and collecting
50
51 497 data. AK is the project's methodologist and executed the primary statistical analysis. HB and EK were
52
53 498 involved in the recruitment of the study. JS provided support. AK, WH and MLB supervised the study. BB,
54
55 499 AK and MLB prepared the original draft. All authors reviewed, edited and approved the final manuscript.
56
57
58
59

1
2
3 500
45 501 **Data availability statement**6
7 502 The datasets used and/or analysed during the current study are available from the corresponding author8
9 503 MLB on reasonable request.
10

11 504

12
13 505 **Word count**

14 506 5,289

15
16 507
1718 508 **References**

- 19
20 509 1. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-
21 510 regression of the prevalence and incidence of perinatal depression. *J Affect Disord* 2017; **219**: 86-92.
- 22 511 2. Bais B, de Groot N, Grootendorst-van Mil NH, et al. Seasonality of depressive symptoms during
23 512 pregnancy. *Psychiatry Res* 2018; **268**: 257-62.
- 24 513 3. Lancaster CA, Gold KJ, Flynn HA, Yoo H, Marcus SM, Davis MM. Risk factors for depressive
25 514 symptoms during pregnancy: a systematic review. *Am J Obstet Gynecol* 2010; **202**(1): 5-14.
- 26 515 4. Räisänen S, Lehto SM, Nielsen HS, Gissler M, Kramer MR, Heinonen S. Risk factors for and
27 516 perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002-
28 517 2010 in Finland. *BMJ Open* 2014; (11): DOI:10.1136/bmjopen-2014-004883.
- 29 518 5. Leff-Gelman P, Mancilla-Herrera I, Flores-Ramos M, et al. The Immune System and the Role of
30 519 Inflammation in Perinatal Depression. *Neurosci Bull* 2016; **32**(4): 398-420.
- 31 520 6. Osborne LM, Monk C. Perinatal depression--the fourth inflammatory morbidity of pregnancy?:
32 521 Theory and literature review. *Psychoneuroendocrinology* 2013; **38**(10): 1929-52.
- 33 522 7. Milgrom J, Gemmill AW, Bilszta JL, et al. Antenatal risk factors for postnatal depression: a large
34 523 prospective study. *J Affect Disord* 2008; **108**: 147-57.
- 35 524 8. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression
36 525 during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction.
37 526 *Arch Gen Psychiatry* 2010; **67**(10): 1012-24.
- 38 527 9. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal
39 528 depression compared with women without depression: a systematic review and meta-analysis. *JAMA*
40 529 *Psychiatry* 2016: DOI:10.1001/jamapsychiatry.2016.0934.
- 41 530 10. Talge NM, Neal C, Glover V, the Early Stress, Translational Research and Prevention Science
42 531 Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal
43 532 stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry* 2007;
44 533 **48**(3-4): 245-61.
- 45 534 11. Hentges RF, Graham SA, Plamondon A, Tough S, Madigan S. A Developmental Cascade from
46 535 Prenatal Stress to Child Internalizing and Externalizing Problems. *J Pediatr Psychol* 2019.
- 47 536 12. Pearson RM, Evans J, Kounali D, et al. Maternal depression during pregnancy and the postnatal
48 537 period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* 2013;
49 538 **70**(12): 1312-9.
- 50 539 13. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis.
51 540 *Neurosci Biobehav Rev* 2010; **35**(1): 17-22.
52
53
54
55
56
57
58
59
60

- 1
2
3 541 14. Dierckx B, Tulen JH, van den Berg MP, et al. Maternal psychopathology influences infant heart
4 542 rate variability: Generation R Study. *Psychosom Med* 2009; **71**(3): 313-21.
- 5 543 15. Goedhart G, Vrijkotte TG, Roseboom TJ, van der Wal MF, Cuijpers P, Bonsel GJ. Maternal cortisol
6 544 and offspring birthweight: results from a large prospective cohort study. *Psychoneuroendocrinology*
7 545 2010; **35**(5): 644-52.
- 8 546 16. Henrichs J, Schenk JJ, Roza SJ, et al. Maternal psychological distress and fetal growth
9 547 trajectories: the Generation R Study. *Psychol Med* 2010; **40**(4): 633-43.
- 10 548 17. Zijlmans MA, Riksen-Walraven JM, de Weerth C. Associations between maternal prenatal
11 549 cortisol concentrations and child outcomes: A systematic review. *Neurosci Biobehav Rev* 2015; **53**: 1-24.
- 12 550 18. Steegers EA, Barker ME, Steegers-Theunissen RP, Williams MA. Societal Valorisation of New
13 551 Knowledge to Improve Perinatal Health: Time to Act. *Paediatr Perinat Epidemiol* 2016; **30**(2): 201-4.
- 14 552 19. Byatt N, Deligiannidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review
15 553 focused on risks and controversies. *Acta Psychiatr Scand* 2013; **127**(2): 94-114.
- 16 554 20. Hanley GE, Oberlander TF. The effect of perinatal exposures on the infant: antidepressants and
17 555 depression. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**(1): 37-48.
- 18 556 21. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy
19 557 and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the
20 558 five Nordic countries. *BMJ* 2012; **344**: d8012.
- 21 559 22. Simoncelli M, Martin BZ, Berard A. Antidepressant use during pregnancy: a critical systematic
22 560 review of the literature. *Curr Drug Saf* 2010; **5**(2): 153-70.
- 23 561 23. Battle CL, Salisbury AL, Schofield CA, Ortiz-Hernandez S. Perinatal antidepressant use:
24 562 understanding women's preferences and concerns. *J Psychiatr Pract* 2013; **19**(6): 443-53.
- 25 563 24. Kothari A, de Laat J, Dulhunty JM, Bruxner G. Perceptions of pregnant women regarding
26 564 antidepressant and anxiolytic medication use during pregnancy. *Australas Psychiatry* 2019; **27**(2): 117-
27 565 20.
- 28 566 25. Molenaar NM, Brouwer ME, Duvekot JJ, et al. Antidepressants during pregnancy: Guideline
29 567 adherence and current practice amongst Dutch gynaecologists and midwives. *Midwifery* 2018; **61**: 29-
30 568 35.
- 31 569 26. Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal
32 570 depression with antidepressants: An international review. *Aust N Z J Psychiatry* 2018; **52**(4): 320-7.
- 33 571 27. Bakker MK, Kolling P, van den Berg PB, de Walle HE, de Jong van den Berg LT. Increase in use of
34 572 selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort
35 573 study from the Netherlands. *Br J Clin Pharmacol* 2008; **65**(4): 600-6.
- 36 574 28. Molenaar NM, Lambregtse-van den Berg MP, Bonsel GJ. Dispensing patterns of selective
37 575 serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort
38 576 study from the Netherlands. *Arch Womens Ment Health* 2019.
- 39 577 29. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before,
40 578 during and after pregnancy: a population-based study in six European regions. *Bjog-Int J Obstet Gy* 2015;
41 579 **122**(7): 1010-20.
- 42 580 30. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy.
43 581 *American Journal of Obstetrics and Gynecology* 2007; **196**(6): 544-5.
- 44 582 31. Jimenez-Solem E, Andersen JT, Petersen M, et al. Prevalence of Antidepressant Use during
45 583 Pregnancy in Denmark, a Nation-Wide Cohort Study. *Plos One* 2013; **8**(4).
- 46 584 32. van Gelder MMHJ, Bos JHJ, Roeleveld N, de Jong-van den Berg LTW. Drugs associated with
47 585 teratogenic mechanisms. Part I: dispensing rates among pregnant women in the Netherlands, 1998-
48 586 2009. *Hum Reprod* 2014; **29**(1): 161-7.
- 49 587 33. Ververs T, Kaasenbrood H, Visser G, Schobben F, de Jong-van den Berg L, Egberts T. Prevalence
50 588 and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006; **62**(10): 863-70.
- 51
52
53
54
55
56
57
58
59
60

- 1
2
3 589 34. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to
4 590 identify and estimate critical periods in pregnancy: An application to antidepressants. *Birth Defects Res A*
5 591 *Clin Mol Teratol* 2016; **106**(11): 927-34.
- 6 592 35. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs) in
7 593 women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug
8 594 Administration's Mini-Sentinel program. *Arch Womens Ment Health* 2016; **19**(6): 969-77.
- 9 595 36. Taylor LG, Thelus Jean R, Gordon G, Fram D, Coster T. Development of a mother-child database
10 596 for drug exposure and adverse event detection in the Military Health System. *Pharmacoepidemiol Drug*
11 597 *Saf* 2015; **24**(5): 510-7.
- 12 598 37. Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States
13 599 from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth* 2014; **14**: 242.
- 14 600 38. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM.
15 601 Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment
16 602 meta-analysis. *PLoS One* 2017; **12**(3): e0173397.
- 17 603 39. Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood.
18 604 *Somnologie* 2019.
- 19 605 40. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep and
20 606 affect. *Nature Reviews Neuroscience* 2014; **15**(7): 443-54.
- 21 607 41. Prayag AS, Münch M, Aeschbach D, Chellappa SL, Gronfier C. Light modulation of human clocks,
22 608 wake and sleep. *Clocks & Sleep* 2019; **1**: 193-208.
- 23 609 42. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol*
24 610 2008; **23**(7): 571-85.
- 25 611 43. Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder: a review. *J Psychiatry*
26 612 *Neurosci* 2000; **25**(5): 469-80.
- 27 613 44. Magnusson A, Boivin D. Seasonal affective disorder: an overview. *Chronobiol Int* 2003; **20**(2):
28 614 189-207.
- 29 615 45. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database*
30 616 *Syst Rev* 2004.
- 31 617 46. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood
32 618 disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; **162**(4): 656-62.
- 33 619 47. Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical
34 620 trials. *J Affect Disord* 2016; **198**: 64-71.
- 35 621 48. Perera S, Eisen R, Bhatt M, et al. Light therapy for non-seasonal depression: systematic review
36 622 and meta-analysis. *BJPsych Open* 2016; **2**(2): 116-26.
- 37 623 49. Martensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: A
38 624 critical review of the evidence. *J Affect Disord* 2015; **182**: 1-7.
- 39 625 50. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of
40 626 antepartum depression. *Am J Psychiatry* 2002; **159**(4): 666-9.
- 41 627 51. Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for
42 628 antepartum depression: preliminary findings. *J Clin Psychiatry* 2004; **65**(3): 421-5.
- 43 629 52. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of
44 630 light therapy for antepartum depression. *J Clin Psychiatry* 2011; **72**(7): 986-93.
- 45 631 53. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; **2**(8): e124.
- 46 632 54. Bais B, Kamperman AM, van der Zwaag MD, et al. Bright light therapy in pregnant women with
47 633 major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. *BMC*
48 634 *Psychiatry* 2016; **16**(1): 381.
- 49 635 55. First MB GM, Spitzer RL, Williams JBW. User's guide for the SCID-I. Structured clinical interview
50 636 for DSM-IV TR axis I disorders (research version). New York: New York Psychiatric Institute; 2002.

- 1
2
3 637 56. Lieveerse R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light
4 638 treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-
5 639 controlled trial. *Arch Gen Psychiatry* 2011; **68**(1): 61-70.
- 6 640 57. Kreidler SM, Muller KE, Grunwald GK, et al. GLIMPSE: Online Power Computation for Linear
7 641 Models with and without a Baseline Covariate. *J Stat Softw* 2013; **54**(10).
- 8 642 58. Meesters Y, Dekker V, Schlangen LJ, Bos EH, Ruiters MJ. Low-intensity blue-enriched white light
9 643 (750 lux) and standard bright light (10,000 lux) are equally effective in treating SAD. A randomized
10 644 controlled study. *BMC Psychiatry* 2011; **11**: 17.
- 11 645 59. Project TAI. ALEA Randomisation Software (Version 2.2). Amsterdam: Netherlands Cancer
12 646 Institute; 2006. p. <http://tenalea.net/>.
- 13 647 60. Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major depressive
14 648 disorder: The contributions of psychological interventions in preventing relapse and recurrence. *Clin*
15 649 *Psychol Rev* 2015; **41**: 16-26.
- 16 650 61. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item
17 651 Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782-6.
- 18 652 62. Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh
19 653 Depression Scale during pregnancy. *J Psychosom Res* 2011; **70**(4): 385-9.
- 20 654 63. Roenneberg T, Wirz-Justice A, Meroz M. Life between clocks: daily temporal patterns of
21 655 human chronotypes. *J Biol Rhythms* 2003; **18**(1): 80-90.
- 22 656 64. Merikanto I, Kronholm E, Partonen M, Laatikainen T, Vartiainen E, Partonen T. Circadian
23 657 preference links to depression in general adult population. *J Affect Disord* 2015; **188**: 143-8.
- 24 658 65. Merikanto I, Lahti T, Kronholm E, et al. Evening types are prone to depression. *Chronobiol Int*
25 659 2013; **30**(5): 719-25.
- 26 660 66. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for
27 661 reporting parallel group randomised trials. *BMC Med* 2010; **8**: 18.
- 28 662 67. Friedman ES, Davis LL, Zisook S, et al. Baseline depression severity as a predictor of single and
29 663 combination antidepressant treatment outcome: results from the CO-MED trial. *Eur*
30 664 *Neuropsychopharmacol* 2012; **22**(3): 183-99.
- 31 665 68. Corral M, Wardrop AA, Zhang H, Grewal AK, Patton S. Morning light therapy for postpartum
32 666 depression. *Arch Womens Ment Health* 2007; **10**(5): 221-4.
- 33 667 69. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo
34 668 response in antidepressant trials. *J Affect Disord* 2009; **118**(1-3): 1-8.
- 35 669 70. Posternak MA, Miller I. Untreated short-term course of major depression: a meta-analysis of
36 670 outcomes from studies using wait-list control groups. *J Affect Disord* 2001; **66**(2-3): 139-46.
- 37 671 71. Yazici E, Kirkan TS, Aslan PA, Aydin N, Yazici AB. Untreated depression in the first trimester of
38 672 pregnancy leads to postpartum depression: high rates from a natural follow-up study. *Neuropsychiatr*
39 673 *Dis Treat* 2015; **11**: 405-11.
- 40 674 72. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: a comprehensive meta-
41 675 analysis. *Clin Psychol Rev* 2013; **33**(6): 763-71.
- 42 676 73. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and
43 677 depression: A meta-analytic review. *J Consult Clin Psychol* 2010; **78**(2): 169-83.
- 44 678 74. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. An open trial of mindfulness-
45 679 based cognitive therapy for the prevention of perinatal depressive relapse/recurrence. *Arch Womens*
46 680 *Ment Health* 2015; **18**(1): 85-94.
- 47 681 75. Vieten C, Astin J. Effects of a mindfulness-based intervention during pregnancy on prenatal
48 682 stress and mood: results of a pilot study. *Arch Womens Ment Health* 2008; **11**(1): 67-74.
- 49 683 76. Nagare R, Plitnick B, Figueiro MG. Effect of exposure duration and light spectra on nighttime
50 684 melatonin suppression in adolescents and adults. *Light Res Technol* 2019; **51**(4): 530-43.

685 77. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian
 686 pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol* 2000; **526 Pt 3**: 695-
 687 702.

688

689 **Table 1.** Inclusion and exclusion criteria for the Bright Up Study.

Inclusion criteria	Women
	18-45 years of age
	12-32 weeks pregnant (as confirmed by ultrasound)
	Current DSM-5 diagnosis of depressive disorder (as assessed by the SCID*)
Exclusion criteria	Insufficient proficiency in Dutch or English
	Multiple pregnancy
	Current use of antidepressants shorter than 2 months
	Lifetime diagnosis of bipolar I or II disorder
	Any psychotic episode
	Current substance abuse
	Current primary anxiety disorder
	Recent history of suicide attempt
	Current shift-work
	Somatic and/or obstetric conditions that override study participation
	Previous treatment with BLT
	Eye condition (macular degeneration, eye diseases, recent eye surgery)

690 * SCID = Structured Clinical Interview for DSM disorders

691

692 **Table 2.** Overview of participant characteristics at inclusion.

	BLT (n=33)	DRLT (n=34)
Age in years, mean (SD)	31.9 (4.4)	31.9 (5.3)
Gestational age in weeks, mean (SD)	20.6 (6.2)	19.7 (6.3)

Ethnicity		
Dutch	27 (81.8%)	26 (76.5%)
Other	6 (19.2%)	8 (33.5%)
Marital status		
Married or cohabiting	33 (100%)	32 (94.1%)
Committed relationship, not cohabiting	0 (0%)	1 (2.9%)
Single	0 (0%)	1 (2.9%)
Education		
Elementary or (pre-)vocational education	11 (33.3%)	13 (38.2%)
Higher professional education	8 (24.2%)	11 (32.4%)
(Pre-) academic education	14 (42.4%)	10 (29.4%)
Parity		
Nulliparous	15 (45.5%)	20 (58.8%)
Primiparous	13 (39.4%)	9 (26.5%)
Multiparous	5 (15.2%)	5 (14.7%)
BMI in kg/m² or st/ft², mean (SD)	25.5 (4.5)	26.3 (5.4)
Planned pregnancy	22 (66.7%)	22 (64.7%)
Antidepressant medication	3 (9.1%)	5 (14.7%)
Sleep medication	3 (9.1%)	2 (5.9%)
Psychotherapy	14 (48.5%)	16 (47.1%)
Comorbidities		
0	17 (51.5%)	13 (38.2%)
1	9 (27.3%)	13 (38.2%)
>1	7 (21.2%)	8 (23.5%)
Duration of depression in weeks, mean (SD)	24.6 (16.9)	45.1 (121.9)
Depressive episodes in past		
0	12 (36.4%)	11 (32.4%)
1	9 (27.2%)	14 (41.2%)

>1	12 (36.4%)	9 (26.5%)
Chronotype		
Early (extremely, moderately and slightly)	20 (80%)	25 (92.6%)
Normal	1 (4%)	1 (3.7%)
Late (extremely, moderately and slightly)	4 (16%)	1 (3.7%)

693 BLT = bright light therapy; DRLT = dim red light therapy

694

695 **Table 3.** Effects of allocation on the course of depressive symptoms through the intervention period and
696 follow-up (until two months postpartum): crude analysis

	β (95% CI) of intervention*	β (95% CI) of follow-up**
SIGH-SAD	-0.68 (-1.84, 0.49)	-0.16 (-0.82, 0.51)
HAM-D	-0.18 (-0.74, 0.37)	0.04 (-0.29, 0.37)
EPDS	0.01 (-0.51, 0.53)	-0.05 (-0.35, 0.24)

697 * From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum

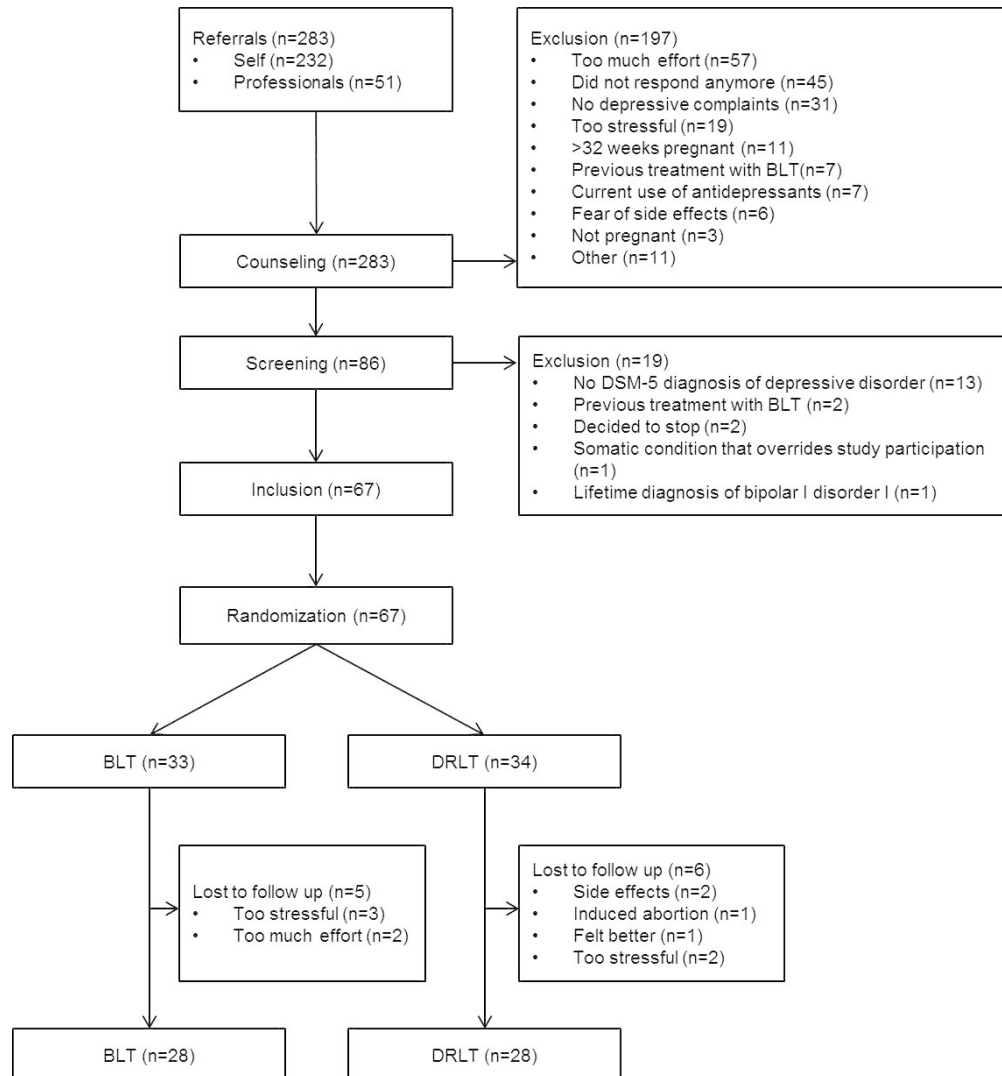
698

699 Figure legends

700 **Figure 1.** Flow-chart of the Bright Up study.

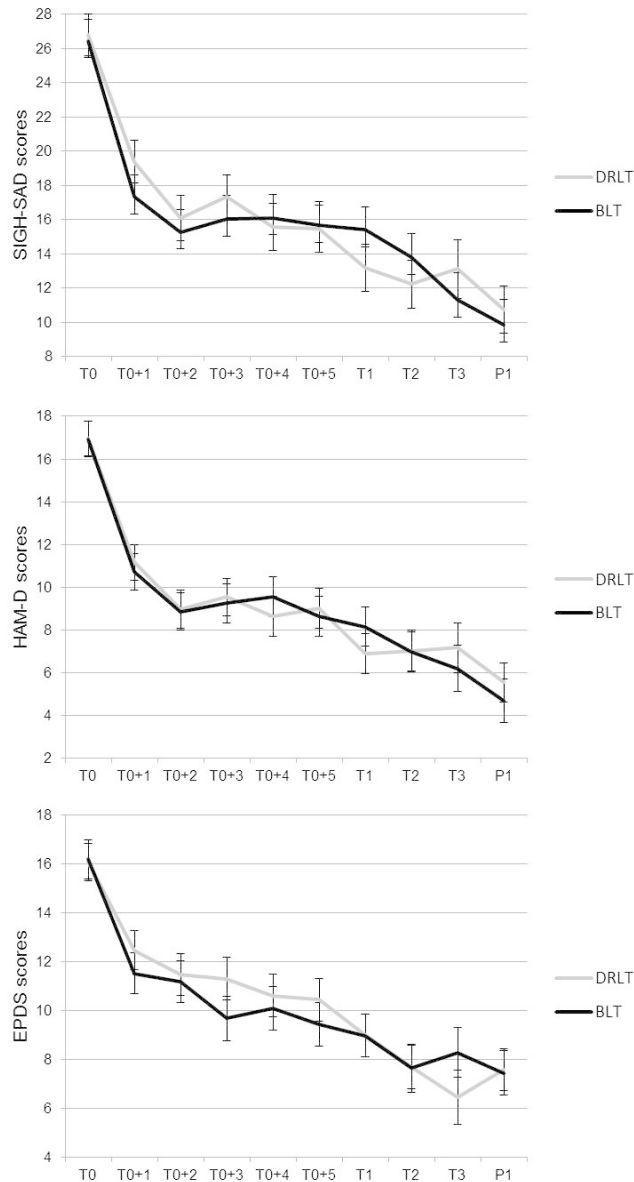
701 **Figure 2.** Estimated marginal means of depression scores in women with antepartum depression until
702 two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent
703 treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.

704 BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the
705 Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for
706 Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1,
707 T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of
708 treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum



Flow-chart of the Bright Up study.

193x207mm (150 x 150 DPI)



Estimated marginal means of depression scores in women with antepartum depression until two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.

BLT = bright light therapy; DRLT = dim red light therapy; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum

127x228mm (150 x 150 DPI)

Supplementary Table 1. Photobiological characterizations of light therapy in both treatment arms.

	BLT	DRLT
Cyanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	578.7	2.24
Melanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	891	5.53
Chloropic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1032.3	7.23
Erythroopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1212.3	11.37
Rhodopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	16.61	16.61

BLT = bright light therapy; DRLT = dim red light therapy

Supplementary Table 2. Observed median SIGH-SAD, HAM-D and EPDS scores with ranges and number of participants over the course of the study for both treatment arms.

Measure	T0	T0+1	T0+2	T0+3	T0+4	T0+5	T1	T2	T3	P1
SIGH-SAD										
BLT (mdn, range, N)	27 (14-44; 33)	16.5 (1-33; 30)	16 (2-43; 29)	15 (0-41; 25)	18 (0-32; 25)	17.5 (1-37; 24)	15.5 (0-29; 26)	13 (1-26; 25)	11 (0-29; 17)	8 (1-23; 20)
DRLT (mdn, range, N)	26.5 (13-42; 34)	19 (8-33; 31)	17 (2-35; 27)	18 (4-30; 29)	15 (3-28; 24)	16 (2-31; 25)	13 (2-34; 25)	11.5 (1-26; 24)	9.5 (1-31; 14)	8 (0-28; 25)
HAM-D										
BLT (mdn, range, N)	16 (7-29; 33)	9 (0-25; 30)	9 (1-30; 29)	8 (0-28; 25)	10 (0-22; 25)	10 (0-21; 24)	7.5 (0-20; 26)	8 (0-17; 25)	5 (0-16; 17)	3 (0-11; 20)
DRLT (mdn, range, N)	18 (4-29; 34)	10 (3-20; 31)	9 (1-22; 27)	9 (2-20; 29)	8 (0-18; 24)	8 (1-20; 25)	6 (1-18; 25)	4.5 (0-20; 24)	4 (0-15; 14)	4 (0-19; 25)
EPDS										
BLT (mdn, range, N)	16 (7-25; 31)	11 (3-23; 26)	11 (0-23; 26)	10 (0-19; 21)	8 (0-25; 23)	7 (0-18; 23)	9.5 (1-18; 26)	8.5 (0-15; 18)	8.5 (1-24; 16)	7 (0-13; 22)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

DRLT (mdn, range, N)	16 (3-25; 34)	12 (6-19; 28)	12 (3-20; 25)	11.5 (3-21; 24)	10 (1-18; 24)	10 (2-19; 23)	6.5 (1-22; 24)	6 (0-21; 23)	4 (1-10; 12)	7 (0-18; 26)
-----------------------------	---------------	---------------	---------------	-----------------	---------------	---------------	----------------	--------------	--------------	--------------

BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum; mdn = median

Supplementary Table 3. Effects of allocation on the course of depressive symptoms through the intervention period and follow-up (until two months postpartum): sensitivity analyses.

	β (95% CI) of intervention*	β (95% CI) of follow-up**
Adjusted analysis^a		
SIGH-SAD	-0.24 (-1.68, 1.20)	-0.24 (-1.68, 1.20)
HAM-D	0.13 (-0.49, 0.75)	0.13 (-0.49, 0.75)
EPDS	0.25 (-0.38, 0.89)	0.25 (-0.38, 0.89)
Data imputation^b		
SIGH-SAD	-0.45 (-1.44, 0.53)	-0.08 (-0.63, 0.46)
HAM-D	-0.09 (-0.63, 0.44)	0.06 (-0.25, 0.37)
EPDS	0.19 (-0.30, 0.68)	0.04 (-0.24, 0.32)
Post-hoc analysis: high treatment compliance^c		
SIGH-SAD	-0.40 (-1.36, 0.55)	-0.32 (-0.88, 0.24)
HAM-D	-0.12 (-0.79, 0.54)	-0.06 (-0.43, 0.31)
EPDS	0.03 (-0.58, 0.65)	-0.05 (-0.40, 0.30)

Post-hoc analysis: high symptom severity^d

SIGH-SAD	-0.84 (-2.33, 0.65)	-0.20 (-1.14, 0.75)
HAM-D	-0.16 (-1.12, 0.87)	0.13 (-0.48, 0.73)
EPDS	-0.05 (-0.92, 0.82)	0.20 (-0.33, 0.74)

* From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum; ^a Propensity score composed of psychiatric history, ethnicity, level of education, an unplanned pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions; ^b Last observation carried forward; ^c <7 missed treatments; ^d Based on median split baseline SIGH-SAD scores



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p. 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 4-5
	2b	Specific objectives or hypotheses	p. 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p. 6
Participants	4a	Eligibility criteria for participants	p. 6; Table 1
	4b	Settings and locations where the data were collected	p. 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 8-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	p. 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 7-9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p. 7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 11-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 12, Fig. 1, Supp. Table 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 6
	14b	Why the trial ended or was stopped	p. 6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Sup. Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Sup. Table 2, Fig. 2, p.13-15, Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	p. 14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	p. 14, Sup. Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 15-17
Other information			
Registration	23	Registration number and name of trial registry	p. 2, 6
Protocol	24	Where the full trial protocol can be accessed, if available	p. 6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effects of bright light therapy for depression during pregnancy: a randomized, double-blind controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038030.R1
Article Type:	Original research
Date Submitted by the Author:	27-Aug-2020
Complete List of Authors:	Bais, Babette; Erasmus Medical Center, Psychiatry Kamperman, Astrid M.; Erasmus MC, Psychiatry Bijma, Hilmar; Erasmus Medical Center, Obstetrics and Gynaecology Hoogendijk, Witte; Erasmus Medical Center, Psychiatry Souman, Jan; Signify NV, Lighting Applications Knijff, Esther; Erasmus Medical Center, Psychiatry Lambregtse-van den Berg, Mijke; Erasmus Medical Center, Child and Adolescent Psychiatry/Psychology; Erasmus Medical Center, Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Depression & mood disorders < PSYCHIATRY, OBSTETRICS, PSYCHIATRY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Effects of bright light therapy for depression during pregnancy: a randomized, double-blind**
4
5 2 **controlled trial**
6

7 3
8
9 4 Babette Bais, MSc^{1*}, Astrid M Kamperman, PhD², Hilmar H Bijma, MD, PhD³, Witte JG Hoogendijk, MD,
10
11 5 PhD⁴, Jan L Souman, PhD⁵, Esther Knijff, MD, PhD⁶, Mijke P Lambregtse-van den Berg, MD, PhD⁷
12
13 6

14
15 7 ¹ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

16
17 8 ² Epidemiological and Social Psychiatric Research Institute, Department of Psychiatry, Erasmus
18
19 9 University Medical Centre Rotterdam, Rotterdam, The Netherlands

20
21 10 ³ Department of Obstetrics and Gynaecology, Erasmus University Medical Centre Rotterdam, Rotterdam,
22
23 11 The Netherlands

24
25 12 ⁴ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

26
27 13 ⁵ Department Lighting Applications, Signify Research, Eindhoven, The Netherlands;

28
29 14 ⁶ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

30
31 15 ⁷ Department of Child and Adolescent Psychiatry/Psychology, department of Psychiatry, Erasmus
32
33 16 University Medical Centre Rotterdam, Rotterdam, The Netherlands

34
35 17 *Corresponding author: P.O. Box 2040, 3000CA Rotterdam, The Netherlands; b.bais@erasmusmc.nl
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 19 **Abstract**

4
5 20 **Objectives** Approximately 11-13% of pregnant women suffer from depression. Bright light therapy (BLT)
6
7 21 is a promising treatment, combining direct availability, sufficient efficacy, low costs, and high safety for
8
9 22 both mother and child. Here, we examined the effects of BLT on depression during pregnancy.

10
11 23 **Design** Randomized, double-blind controlled trial.

12
13 24 **Setting** Primary and secondary care in The Netherlands, from November 2016 to March 2019.

14
15 25 **Participants** 67 pregnant women (12-32 weeks gestational age) with a DSM-5 diagnosis of depressive
16
17 26 disorder.

18
19 27 **Interventions** Participants were randomly allocated to treatment with either BLT (9,000 lux, 5,000 K) or
20
21 28 dim red light therapy (DRLT, 100 lux, 2,700 K), which is considered placebo. For six weeks, both groups
22
23 29 were treated daily at home for 30 minutes upon awakening. Follow-up took place weekly during the
24
25 30 intervention, after six weeks of therapy, three and ten weeks after treatment, and two months postpartum.

26
27 31 **Primary and secondary outcome measures** Depressive symptoms were measured primarily with the
28
29 32 Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder. Secondary
30
31 33 measures were the Hamilton Rating Scale for Depression and the Edinburgh Postnatal Depression Scale.
32
33 34 Changes in rating scale scores of these questionnaires over time were analysed using generalized linear
34
35 35 mixed models.

36
37 36 **Results** Median depression scores decreased by 40.6-53.1% in the BLT group and by 50.9-66.7% in the
38
39 37 DRLT group. We found no statistically significant difference in symptom change scores between BLT and
40
41 38 DRLT. Sensitivity and post-hoc analyses did not change our findings.

42
43 39 **Conclusions** BLT and DRLT both reduced depressive symptoms in pregnant women with depression.
44
45 40 More research is necessary to determine whether these responses represent true treatment effects, non-
46
47 41 specific treatment responses, placebo effects, or a combination hereof.

48
49 42 **Trial Registration** Bright Up, NTR5476, <http://www.trialregister.nl>

50
51 44 **Strengths and limitations of this study**

- 1
2
3 45 • We conducted various follow up measurements, including postpartum, to study the effects of
4
5 46 withdrawal of treatment and to study whether treatment during pregnancy would protect against
6
7 47 postpartum depression.
8
9 48 • The setting of treatment was within a real world setting.
10
11 49 • A strength of this study was the comprehensive assessment of side effects, as well as
12
13 50 acceptability and satisfaction of treatment.
14
15 51 • An unforeseen lack of resources prevented us from including 150 participants, as we aimed to do
16
17 52 according to our sample size calculation.
18
19 53 • Depressive symptoms during the study are assessed by questionnaires, rather than diagnostic
20
21 54 criteria.
22
23 55

56 Introduction

57 Antepartum depression is a common and high impact disease, with approximately 11-13% of pregnant
58 women suffering from depression¹. Antepartum depression is not only seen in autumn and winter, but is
59 a year-round phenomenon, with certain subgroups even showing more symptoms in summer². Many risk
60 factors for antepartum depression have been identified^{3,4}. Possible causes for antepartum depression
61 may include alterations in endocrine systems, such as the hypothalamus-pituitary-adrenal axis⁵, and
62 inflammation^{6,7}. Women who suffer from antepartum depression are more likely to suffer from postpartum
63 depression as well⁸. Children who are exposed to maternal depression during pregnancy have a higher
64 risk of adverse birth outcomes, such as prematurity and being small for gestational age^{9,10}. Additionally,
65 children of mothers with antepartum depression show more often cognitive, emotional, and behavioral
66 problems in childhood, adolescence, and adulthood^{11,12} and they have a higher risk of suffering from
67 depression later in life¹³. During pregnancy, fetal programming of the hypothalamus-pituitary-adrenal
68 gland (HPA) axis takes place, which can be affected by maternal depression during pregnancy and may
69 have long-lasting effects on stress response¹⁴. Possible mechanisms are 1) maternal cortisol crossing
70 the placenta and thus increasing fetal cortisol levels, 2) placental secretion of corticotropin-releasing
71 factor, which stimulates both maternal and fetal cortisol, and 3) reduced blood flow to the fetus, causing
72 fetal growth restriction^{9,15-18}. In addition, epigenetic programming takes place within the antepartum
73 period, which influences not only the health of the (unborn) infant, but also that of following generations¹⁹.
74 Therefore, early detection and treatment of antepartum depression is highly important for both mother
75 and infant.

76 In non-pregnant women, guidelines propose psychotherapy, antidepressant medication, or a combination
77 of both as treatment. However, psychotherapy might not be readily available and the safety of maternal
78 use of antidepressants, which cross the placenta, still remains to be established. The use of
79 antidepressants is controversial, because of potential teratogenicity^{20,21}. For example, increased risks
80 have been found for persistent pulmonary hypertension of the neonate²² and cardiovascular
81 malformations²³. Furthermore, pregnant women express a strong preference for non-pharmacologic
82 treatment because of the possible harm for their unborn child^{24,25}. Moreover, current adherence to
83 national guidelines by midwives and gynaecologists is low²⁶ and international guidelines on the

1
2
3 84 pharmacological treatment of antepartum depression are not consistent ²⁷, which might result in
4
5 85 unwanted variation in practice. Despite this, antidepressant use during pregnancy is increasing, not only
6
7 86 in the Netherlands ^{28,29}, but in other European countries and the United States as well ³⁰⁻³². In the
8
9 87 Netherlands, approximately 2-3% of pregnant women use antidepressants ^{29,33,34}. In the United States,
10
11 88 this prevalence is approximately 6-7% ³⁵⁻³⁷, but could even be as high as 15% in some states ³⁸.
12
13 89 Therefore, it is urgent and clinically relevant to investigate alternative approaches to treat antepartum
14
15 90 depression, such as bright light therapy (BLT) ³⁹.
16
17 91 Light synchronizes the suprachiasmatic nucleus (SCN), or the 'biological clock', with the environmental
18
19 92 day-night rhythm ⁴⁰. Light hits the retina and intrinsically photosensitive retinal ganglion cells (ipRGCs) in
20
21 93 the retina project, via the retino-hypthalamic tract to the SCN and thus influences circadian rhythm ⁴⁰⁻⁴²,
22
23 94 which may indirectly benefit depressive symptoms ⁴³. However, not only do ipRGCs project to the SCN,
24
25 95 but also directly to brain regions important in the regulation of mood, such as the medial amygdala and
26
27 96 the lateral habenula ⁴⁰⁻⁴².
28
29 97 Although BLT is the first-choice treatment for seasonal affective disorder, a condition of reoccurring
30
31 98 depressions during fall and winter, with remissions in spring and summer ^{44,45}, the effects of BLT have
32
33 99 been shown both in seasonal affective disorder and in non-seasonal depression, which is not only shown
34
35 100 by a Cochrane review ⁴⁶, but also by more recent systematic reviews and meta-analyses ⁴⁷⁻⁵⁰. An open
36
37 101 trial of BLT in pregnant women showed improvement of mean depression ratings by 49% ⁵¹. Two small
38
39 102 randomized controlled trials showed significant improvement of depression among pregnant women
40
41 103 exposed to BLT compared to placebo ^{52,53}. Although these results seem promising, the sample sizes of
42
43 104 these studies were small, making them at risk for chance-findings ⁵⁴.
44
45 105 In this study, we compared the effectiveness of BLT compared to placebo light among pregnant women
46
47 106 with a depressive disorder in a larger randomized clinical trial. Moreover, we followed women until the
48
49 107 postpartum period, to study whether treatment with light therapy during pregnancy might protect against
50
51 108 postpartum depression. We hypothesized that daily treatment with six weeks of morning BLT will improve
52
53 109 depressive symptoms during pregnancy.

110

111 **Material and Methods**

112 *Design*

113 This study was a randomized, double-blind, placebo-controlled clinical trial (Bright Up, NTR5476,
114 <http://www.trialregister.nl>). A detailed protocol can be found elsewhere ⁵⁵. In short, the aim of the Bright
115 Up study was to evaluate the effectiveness of BLT for pregnant women with a depressive disorder,
116 compared to placebo light.

117

118 *Participants*

119 Eligible participants were pregnant women (12-32 weeks of gestational age, confirmed by ultrasound)
120 diagnosed with a depressive disorder, confirmed by a Structured Clinical Interview for DSM disorders
121 (SCID) by one trained assessor ⁵⁶. The specific inclusion and exclusion criteria are listed in Table 1.

122 In the earlier published study protocol ⁵⁵, we aimed to include women who were 12-18 weeks pregnant.

123 For pragmatic reasons, in particular the fact that a substantial number of women were referred after 18
124 weeks of pregnancy, we later decided to widen our inclusion criteria to 12-32 weeks pregnancy.

125 In the Netherlands, maternity care for low-risk pregnancies is provided by midwives (primary care). High-
126 risk pregnancies are cared for by gynaecologists in a general hospital (secondary care) or fetal-maternal
127 medicine unit (tertiary care).

128 In this study, women were recruited not only via health care professionals, such as general practitioners,
129 midwives, gynaecologists, psychiatrists, and psychologists, but also via (social) media. A complete flow-
130 chart of the recruitment can be found in Figure 1.

131 Initially, we calculated the number of women to be included, based on the results and research
132 methodology of previous studies ^{51,52,57}. We expected a true treatment effect in the range of a 10-15%
133 symptom reduction over the full course of treatment (6 weekly assessments), reflecting a small to medium
134 effect size. To demonstrate this, with an α of 0.05 and a β of 0.8, time included as a continuous factor, a
135 total sample size of 126 participants, 63 per arm was needed. To account for loss to follow up during and
136 after treatment, we aimed at including 150 women. Power calculations were performed using GLIMMPSE
137 2.1.5. software ⁵⁸. Inclusion took place in The Netherlands and started on 9 November 2016 and lasted
138 until 15 March 2019. By then, 67 women were included. However, due to limiting resources, we decided
139 to stop the inclusion.

1
2
3 140
45 141 *Patient and Public Involvement*6
7 142 No patients involved.
8
9 14310
11 144 *Ethics*

12 145 All procedures performed involving human participants were in accordance with the ethical standards of
13 146 the institutional and/or national research committee and with the 1964 Helsinki declaration and its later
14 147 amendments or comparable ethical standards. Written informed consent was obtained from all
15 148 participants. The study protocol and later amendments were approved by the medical ethical committee
16 149 of the Erasmus University Medical Centre, Rotterdam, The Netherlands (registration number MEC-2015-
17 150 731).
18
19
20
21
22
23

24 151

25
26 152 *Blinding*

27
28 153 Participants were blinded to allocation. Participants were informed that the study aimed to investigate the
29 154 efficacy of different light colours. They were not informed that one treatment arm was considered placebo
30 155 treatment. This was in accordance with approval of the medical ethical committee.

31
32
33 156 Outcome assessors were blinded to the allocation of the participants. Participants were asked not to
34 157 share any details regarding their treatment towards the assessors. When blinding was broken, the
35 158 assessor was replaced. The researcher performing the primary statistical analyses (AK) was blinded to
36 159 the allocation. The field researcher (BB) was not blinded to the allocation for practical reasons. This
37 160 researcher made sure lamps of the correct allocation were delivered to the participants. Also, this
38 161 researcher asked participants about any side effects, keeping the independent assessors blinded to any
39 162 adverse effects that might break the blinding, e.g. strained eyes, and answered any questions from the
40 163 participants regarding their lamps.
41
42
43
44
45
46
47
48

49 164 At baseline, we asked about any expectations concerning the treatment with regards to their depressive
50 165 symptoms. Women could choose whether they expected a negative effect, a small negative effect, no
51 166 effect, a small positive effect or a positive effect. After the intervention period, the participants were asked
52
53 167 whether they were aware of their allocation.
54
55
56
57
58
59
60

168

169 *Light therapy*

170 Light treatment consisted of either active BLT (9,000 lux, color temperature 5,000 K) or dim red light
171 therapy (DRLT, 100 lux, color temperature 2,700 K). The photobiological characterizations of these
172 treatments are shown in Supplementary Table 1. The original lamps were adjusted in the factory where
173 these are produced (EnergyUp HF3419/01, Philips, Eindhoven, The Netherlands). To ensure that
174 participants are exposed to the same light intensity, the output of the lamps was fixed. For the control
175 condition, the standard LED's in the lamp were replaced by LED's with a lower intensity and a different
176 color temperature. The lamps in the control condition were positioned at the same distance from the
177 participant as in the experimental condition.

178 The active light therapy was shown to be effective in other studies ^{52,53,57,59}. DRLT can be considered to
179 be biologically inactive and thus as placebo treatment ⁴⁶. In line with two previous RCT's among pregnant
180 women, we chose six weeks of daily light exposure ^{52,53}.

181 The lamps were delivered at the participants' home by one researcher (BB) who was not blinded to the
182 allocation of the participants. This researcher did not share anything about the allocation with the
183 participants. After delivery of the lamps and instructions, participants commenced their daily treatment
184 with light for 30 minutes within 30 minutes of habitual wake up time for a six weeks period. This took
185 place at the participants' home. Participants sat in front of two lamps with a distance of approximately 40
186 cm (15.8 inches). They received a plastic ruler of this length to ensure of the correct distance. The light
187 boxes were placed in a custom-made scaffolding, so that the height of the light boxes could be adjusted
188 per person and glare was avoided. Apart from the light treatment, participants in both treatment arms
189 received treatment as usual: women were free to visit their general practitioner, obstetric care provider, or
190 mental health care worker and start additional treatment, whenever they felt a need for this.
191 During the intervention period, self-reported compliance with the light treatment was checked weekly.

192

193 *Method*

194 A baseline interview was conducted by telephone by one researcher (BB). The baseline interview
195 collected sociodemographic information (age, ethnicity, educational level, marital status, body mass index

1
2
3 196 (BMI)), obstetric information (gestational age, whether the pregnancy was planned, parity), psychiatric
4
5 197 information (substance use (smoking, alcohol, drugs), present and past medication use, present
6
7 198 depressive symptoms, psychiatric history), and information on somatic conditions. Also, participants were
8
9 199 screened with the SCID for depressive disorder and various potential co-morbidities, such as generalized
10
11 200 anxiety disorder and panic disorder. Previous depressive episodes were also assessed with the SCID.
12
13 201 The general practitioner was contacted to verify present medication use and whether the participant met
14
15 202 any exclusion criteria.

16
17 203 After baseline measurements and receiving written informed consent, the participants were randomly
18
19 204 allocated to either receive BLT or DRLT in a 1:1 ratio. Randomization was done with the web-based
20
21 205 computer-generated schedule ALEA (software for randomization in clinical trials, version 2.2) using
22
23 206 random block sizes of 2-6⁶⁰ by an independent researcher. Stratification factors were the use of any
24
25 207 current antidepressant medication and the number of previous depressive episodes. The latter was
26
27 208 dichotomized to three or less versus four or more⁶¹.

28 209 Follow up took place at the following time points: weekly during the intervention period (T0+1, T0+2, etc.),
29
30 210 after 6 weeks of treatment (T1), 3 weeks after end of treatment (T2), 10 weeks after end of treatment
31
32 211 (T3), 2 months postpartum (P1), 6 months postpartum (P2), 18 months postpartum (P3).

33
34 212 At these time points, questionnaires were assessed and body material was collected. We collected urine,
35
36 213 hair, and saliva from the participants, as can be found in our earlier published protocol⁵⁵.

37
38 214 This paper reports the short term effectiveness, i.e. up to two months postpartum.

39
40 215

41 216 *Primary and secondary outcome measures*

42
43 217 The primary outcome measure was the average change in depressive symptoms between the two
44
45 218 groups, as measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal
46
47 219 Affective Disorder version (SIGH-SAD). Secondary outcome measures were these changes as measured
48
49 220 by the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Edinburgh Depression Scale
50
51 221 (EPDS).

52
53 222 In the earlier published protocol⁵⁵, we were primarily interested in the effects of light therapy on
54
55 223 depressive symptoms. Secondly, we were interested in the effects on various other outcomes, such as

1
2
3 224 maternal hormonal levels, maternal sleep quality and infant outcomes. Depressive symptoms were
4
5 225 measured by two questionnaires: the SIGH-SAD and the EPDS, with the original 17-item HAM-D being
6
7 226 part of the SIGH-SAD, which consists of 21 HAM-D items and 8 atypical items. Therefore, in the original
8
9 227 protocol ⁵⁵, we mentioned these two questionnaires together as the primary outcome, as opposed to the
10
11 228 other outcomes (maternal hormonal levels and others). However, it is not technically possible to have
12
13 229 more than one primary outcome. Our power calculation was based on the SIGH-SAD, which makes this
14
15 230 our true primary outcome. The HAM-D and the EPDS are the secondary outcomes for this manuscript. In
16
17 231 the current manuscript, we only report our findings regarding the depressive symptoms. We will report the
18
19 232 other outcomes elsewhere.

20 233 The SIGH-SAD is a 29-item structured interview, consisting of 21 HAM-D items and 8 atypical items. We
21
22 234 used the entire SIGH-SAD questionnaire as primary measure, since this is the current benchmark for
23
24 235 assessment of depression severity in light therapy trials. We chose the original 17-item HAM-D
25
26 236 questionnaire as a secondary measure, since it is more commonly used in clinical practice and research.
27
28 237 Blinded assessors conducted the SIGH-SAD interviews (including HAM-D questions) by telephone
29
30 238 weekly in the intervention period and at follow up.

31
32 239 The EPDS is a structured 10-item questionnaire and was used as a self-report measure of depression
33
34 240 during pregnancy and postpartum ⁶². Items are scored with a value 0-3, resulting in a sum score of 0-30
35
36 241 ⁶². The EPDS was developed for the detection of postpartum depression, but has been validated for
37
38 242 screening depression during pregnancy as well ⁶³. The EPDS was assessed weekly in the intervention
39
40 243 period and at follow up. Participants received a link by e-mail to fill out the questionnaire.

41
42 244

43 245 *Side effects, acceptability and satisfaction*

44
45 246 During the intervention period, participants were asked weekly about any possible side effects.

46
47 247 Acceptability was assessed by asking participants about their subjective treatment experiences after the
48
49 248 intervention period. Women could choose whether they experienced a negative effect, a small negative
50
51 249 effect, no effect, a small positive effect, or a positive effect. Women were asked how easy or difficult they
52
53 250 could implement the therapy in their daily schedule and how easy or difficult the lamp was in use: very
54
55 251 difficult, difficult, neutral, easy, or very easy. Women could answer whether they found the light therapy

1
2
3 252 very unpleasant, unpleasant, neutral, pleasant, or very pleasant. Women were asked whether they would
4
5 253 like to use the light therapy outside of the study (yes/no). Finally, women were asked how likely they
6
7 254 would recommend light therapy to others on a scale of 1 to 10.
8

9 255

10 256 *Baseline characteristics*

11
12 257 The baseline interview collected information on various potential confounders, such as
13
14 258 sociodemographic, obstetric, and psychiatric information, and information on somatic conditions (see
15
16 259 Method for further specifications).
17
18 260 The participant's chronotype was assessed at inclusion with the Munich Chronotype Questionnaire
19
20 261 (MCTQ), a structured 19-item self-report questionnaire⁶⁴, since evening types are more prone to
21
22 262 depression compared to morning types^{65,66}. The participant can be classified into one of seven
23
24 263 chronotypes: extremely, moderately or slightly early, normal or slightly, moderately or extremely late. Sum
25
26 264 scores range from 16 to 86, with low scores indicating extremely late chronotypes.
27

28 265

29 266 *Statistical analysis*

30
31 267 Continuous participant characteristics were summarized using mean and standard deviation (SD).
32
33 268 Categorical variables, such as educational level, were summarized by count and percent. In line with the
34
35 269 CONSORT statement, baseline differences between the two treatment arms were not tested⁶⁷.
36
37 270 For treatment effect analyses, we applied an intention-to-treat procedure, since none of the participants
38
39 271 could switch to a different condition, and we included all observations of all participants until the study
40
41 272 ended or the participant(s) dropped out of the study.
42
43 273 The primary outcome was changes in SIGH-SAD rating scale scores over time. Secondary outcomes
44
45 274 were changes in HAM-D and EPDS rating scale scores over time. Analyses were conducted using
46
47 275 general linear mixed modelling analyses. In a series of random-intercept models, we included time
48
49 276 (continuous), allocation, and time x allocation interaction-term as an effect measure of allocation on the
50
51 277 course of depression rating scale scores. The standardized baseline score was included in the model,
52
53 278 since baseline depression severity is an important predictor for treatment outcome⁶⁸. We studied the
54
55 279 treatment effect for both the intervention period and follow-up period (two months postpartum).
56
57
58
59
60

1
2
3 280 Primary analyses were first crude, then adjusted. As adjusted primary analyses, we calculated propensity
4
5 281 scores based on patient characteristics (psychiatric history, ethnicity, level of education, an unplanned
6
7 282 pregnancy, maternal age, parity, gestational age, duration of actual depression, and other psychiatric or
8
9 283 psychotherapeutic treatment interventions). Next, we adjusted separately for chronotype and the month of
10
11 284 treatment. By means of sensitivity analyses, we repeated the primary analyses with last observation
12
13 285 carried forward data imputation. As post-hoc analyses, we repeated the crude analyses for women with
14
15 286 good compliance (<7 missed treatments) and for women with most severe depressive symptomatology
16
17 287 (based on median split baseline SIGH-SAD scores). Effect parameters were supplied with a 95%
18
19 288 confidence interval (CI).

20 289 Additionally, we tested responders versus non-responders with Fisher's exact test, where response was
21
22 290 defined as a $\geq 50\%$ decrease to a final score of ≤ 8 on the 17-item HAM-D and ≤ 5 on the EPDS at the end
23
24 291 of the intervention period.

25
26 292 Data was analyzed using SPSS 21.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was
27
28 293 defined as $p < .05$.

29
30 294

31 32 295 **Results**

33 34 296 *Demographic and clinical characteristics*

35
36 297 In total, 283 women were referred to the study. The majority of the participants (82%) were recruited via
37
38 298 (social) media. Of these referrals, we included and randomized 67 women, with 33 allocated to BLT and
39
40 299 34 to DRLT. In total, eleven women dropped out during the study, of whom five in the BLT group. Ten
41
42 300 women dropped out in the intervention period, one at ten weeks after treatment. Figure 1 shows a flow-
43
44 301 chart of the entire study sample.

45 302 Table 2 shows the participant characteristics at the time of inclusion. At inclusion, the mean (SD) of the
46
47 303 SIGH-SAD was 26.5 (7.2), of the 17-item HAM-D was 16.9 (5.3) and of the EPDS was 16.1 (4.8). Median
48
49 304 scores were respectively 27, 17 and 16.

50
51 305 The most common comorbidity was anxiety (25.4%), followed by obsessive compulsive disorder (17.9%),
52
53 306 PTSS (11.9%), and social phobia (11.9%). Various somatic comorbidities were reported, such as asthma,
54
55 307 Guillain-Barré syndrome, and fibromyalgia.

1
2
3 308 During the course of this study, as part of the care as usual, eleven additional women started with
4
5 309 psychotherapy: three women in the intervention period, one after the intervention period during
6
7 310 pregnancy, and seven in the postpartum period. During the entire study, four additional women started
8
9 311 with psychotropic medication: one woman started with an SSRI in the intervention period and one woman
10
11 312 in the postpartum period (both sertraline), one with an antipsychotic (quetiapine) and one with a
12
13 313 benzodiazepine (temazepam) postpartum. Of one participant, the dose of the SSRI was increased in the
14
15 314 postpartum period (escitalopram).

16 315

18 316 *Compliance*

20 317 Self-reported compliance was somewhat higher in the BLT group, compared to the DRLT group. Amongst
21
22 318 the women treated with BLT, eight women (24.2%) never missed a treatment, in contrast to three women
23
24 319 (8.8%) in the DRLT group. Sixteen women (48.5%) treated with BLT missed a maximum of six
25
26 320 treatments, compared to twenty women (58.9%) in the DRLT group. In both groups, two women missed
27
28 321 seven to thirteen treatments in the intervention period. One woman treated with BLT and two with DRLT
29
30 322 missed fourteen or more treatments. One woman treated with BLT and two with DRLT missed the final
31
32 323 two weeks of treatment, the first one due to complete remission of her symptoms.

33 324

35 325 *Maintaining blinding*

37 326 Before treatment, three women (4.8%) did not expect any effect from light therapy for their depressive
38
39 327 symptoms. All other participants expected a (small) positive effect. After treatment, one participant treated
40
41 328 with BLT (3.0%) and three women in the group treated with DRLT (8.8%) thought they were treated with
42
43 329 placebo treatment. All other women had no specific ideas about their allocation.

44 330

46 331 *Treatment effect*

48 332 Supplementary Table 2 shows the observed median SIGH-SAD, HAM-D, and EPDS scores over the
49
50 333 course of the study. In the women treated with BLT, median depression scores decreased by 42.6%
51
52 334 (SIGH-SAD), 53.1% (HAM-D), and 40.6% (EPDS) in the intervention period. In the DRLT group, this was
53
54 335 respectively 50.9%, 66.7%, and 59.4%. After women stopped with light treatment, median scores

55 336

56 337

57 338

58 339

59 340

60 341

1
2
3 336 continued to decrease for all questionnaires in both groups, three and ten weeks after treatment. At two
4
5 337 months postpartum, women treated with BLT showed no increase in EPDS scores, whereas women
6
7 338 treated with DRLT showed an increase in EPDS-scores. For both SIGH-SAD and HAM-D scores, a
8
9 339 decrease was observed in both treatment arms.

10
11 340 We also calculated the median improvement scores without the baseline score. For women treated with
12
13 341 BLT, these were 6.1% (SIGH-SAD), 16.7% (HAM-D), and 13.6% (EPDS). For women treated with DRLT,
14
15 342 this was respectively 31.6%, 40%, and 45.8%.

16
17 343 No statistically significant difference was found between the two treatment arms for the intervention
18
19 344 period, nor for the entire study (Figure 2 and Table 3). Adjusted primary analyses, where we repeated our
20
21 345 primary analyses adjusted for propensity scores, and sensitivity analyses with imputed data did not show
22
23 346 any other findings (Supplementary Table 3). Adjustment for chronotype and month of treatment did not
24
25 347 change our findings as well. Post-hoc analyses, where we repeated the analyses for women with higher
26
27 348 treatment compliance and for women with higher symptom severity at baseline, did not show a
28
29 349 statistically significant difference between the two treatment arms (Supplementary Table 3).

30
31 350 For the HAM-D, 13 participants in the BLT group and 17 participants in the DRLT group were considered
32
33 351 responders. This was respectively 11 and 9 when measured with the EPDS. When we studied
34
35 352 responders versus non-responders, we found no statistically significant differences for both HAM-D
36
37 353 scores ($p=.46$) and EPDS scores ($p=.60$).

38 354

39 355 *Side effects*

40
41 356 For women treated with BLT, the most frequently reported side effect was headaches (30.3%), followed
42
43 357 by sleep problems (12.1%) and nausea (6.1%). For women treated with DRLT, the most reported side
44
45 358 effect was headaches (20.6%), followed by sleep problems (8.9%) and irritable eyes (5.9%). Side effects
46
47 359 were not reported more often by women treated with BLT, compared to DRLT ($p=0.52$). Most side effects
48
49 360 were experienced for a maximum of three days. None of the women suffered from any (hypo)manic
50
51 361 symptoms. We reduced the treatment duration for five women to 20 minutes daily due to their side
52
53 362 effects. Interestingly, two women dropped out of the study due to side effects, but only in the DRLT group.

54
55 363

364 *Acceptability and satisfaction*

365 The majority of women experienced a (small) positive effect for their depressive symptoms (78.6% BLT;
366 61.5% DRLT; $p=0.58$). All participants found the lamp (very) easy in use. Most women found the light
367 therapy pleasant (57.1% BLT; 50% DRLT; $p=0.49$). Twenty-six women reported that it was (very) easy to
368 plan the light therapy in the morning (42.9% BLT; 53.8% DRLT; $p=0.43$). Thirty-two women reported that
369 they would like to use light therapy outside of the study (57.1% BLT; 61.5% DRLT; $p=0.79$). On average,
370 women reported it was likely they would recommend the light therapy to others (BLT mean 8.0, SD 1.3;
371 DRLT mean 7.0, SD 2.7; $p=0.08$).

372

373 **Discussion**

374 We conducted a randomized controlled trial, evaluating the effectiveness of BLT in a sample of 67
375 pregnant women with major depressive disorder, compared to DRLT. We found no statistically significant
376 difference between BLT and DRLT on depressive symptoms. Median depression scores decreased by
377 40.6-53.1% during the intervention in the women treated with BLT and by 50.9-66.7% in the women
378 treated by DRLT.

379

380 *Effects in the current study*

381 This level of improvement is comparable to the studies by Oren *et al.*⁵¹ and Corral *et al.*⁶⁹ who both
382 found a reduction in mean depression scores of 49%. Oren *et al.* conducted an open trial in an
383 antepartum population, whereas Corral *et al.* conducted a randomized controlled trial among women with
384 a postpartum depression. Similar to Corral *et al.*, we did not find a statistically significant difference
385 between the effective and placebo conditions. The median improvement in the DRLT group can be
386 explained by placebo effects, which could also be the case in the BLT group. A meta-analysis showed
387 that the placebo response in antidepressant trials is approximately 68%⁷⁰, although this effect is not clear
388 yet in light therapy trials specifically. Secondly, the improvement in both groups can be explained by non-
389 specific treatment effects such the structure offered by the study⁴³, the interaction with the researchers,
390 or increased awareness and self-care resulting from participating in the study. A systematic review on
391 various studies in treating antepartum depression with a control condition showed that these trials often

1
2
3 392 show a considerable reduction in symptom scores in both treatment arms ³⁹. Furthermore, it might be that
4
5 393 symptoms decrease related to the course of pregnancy, spontaneous remission, or regression to the
6
7 394 mean. A meta-analysis showed that untreated depressive symptoms could decrease by 10-15%, on
8
9 395 average ⁷¹. However, untreated depression during pregnancy is an important predictor for postpartum
10
11 396 depression ⁷². We calculated the improvement of the depressive symptoms without the baseline scores,
12
13 397 to study whether the improvement was especially notable in the first week of treatment. We found that the
14
15 398 improvement was less, especially in the group treated with BLT, which may pinpoint to regression to the
16
17 399 mean. For example, women may have the feeling of 'finally being heard', or feeling empowered about
18
19 400 doing something about their symptoms, which may explain these findings.
20
21 401 Corral *et al.* mentioned that several participants commented positively on having 30 minutes of "quiet
22
23 402 time" on a daily basis. Several of our participants mentioned this as well, which could reflect sinking into a
24
25 403 state of more relaxation or more mindfulness which may have contributed to the improvement in both
26
27 404 groups. Two meta-analyses showed that mindfulness-based therapy is an effective treatment for a variety
28
29 405 of psychological problems ^{73,74}. An earlier pilot study and an open study of mindfulness also showed
30
31 406 positive effects on mood specifically in pregnant women ^{75,76}. Corral *et al.* mentioned that many
32
33 407 postpartum women are motivated to access recourses, such as psychological treatment, which could
34
35 408 have exerted non-specific treatment effects. In their study however, no participant took part in any
36
37 409 treatment during the study. In our study, several women started psychotherapy or antidepressant
38
39 410 medication. However, adjustment for any intervention did however not change our findings.
40
41 411 Finally, it has been shown earlier in healthy volunteers that treatment with similar conditions as our
42
43 412 placebo therapy might actually have some effects in melatonin suppression ⁷⁷, which could explain why
44
45 413 we actually see a decrease of symptoms in the DRLT group.

46 414

47 415 *Differences with literature*

48
49 416 The results of this study differ from the randomized controlled trials by Epperson *et al.* ⁵² and Wirz-Justice
50
51 417 *et al.* ⁵³, who did find superiority of bright light therapy over placebo in an antepartum population.
52
53 418 Wirz-Justice *et al.* included only clinical patients and found that BLT had more effects in severe patients in
54
55 419 their study. However, mean baseline SIGH-SAD score in the Wirz-Justice *et al.* and Epperson *et al.*

1
2
3 420 studies were 27.7 and 28.1, respectively, which were not clinically relevant different from the present
4
5 421 study (26.5). Additionally, we included baseline depression scores in our model, which did not change our
6
7 422 findings. Also, post-hoc analyses, where we repeated the analyses for women with higher baseline
8
9 423 severity, did not show any significant findings.

10 424 Both Epperson *et al.* and Wirz-Justice *et al.* treated their patients for 1 hour a day and within 10 minutes
11
12 425 of habitual wake-up time, which is different from the present study. Thus far, no studies have been
13
14 426 executed comparing the effectiveness of shorter versus longer exposure to bright light in non-seasonal
15
16 427 depression. Possibly, more light output in the BLT group would be necessary to show superiority of BLT
17
18 428 over DRLT in a pregnant population. However, other studies that treated patients for 30 minutes also did
19
20 429 show a statistical significant difference between the effective and the placebo intervention in non-
21
22 430 seasonal depression ⁴⁶. One must keep in mind that these studies have been done in non-pregnant
23
24 431 populations and different – yet unknown – underlying mechanisms may play a part during pregnancy,
25
26 432 such as hormonal fluctuations and a shift in social role.

27
28 433 Our placebo condition, in which the possible effect of DRLT could be questioned, is not a plausible
29
30 434 explanation for not finding a statistically significant effect between the treatment arms. Epperson *et al.*
31
32 435 used a placebo condition with 500 lux white light, which is questionable as a placebo, for white light of
33
34 436 100 lux is able to phase-shift human circadian rhythms ⁷⁸. Since this study found a significant
35
36 437 improvement in women treated with BLT when compared to this placebo, it is unlikely that the settings of
37
38 438 our placebo would explain failing to achieve a significant difference between the two treatment arms.
39
40 439 In the study by Corral *et al.*, depression scores worsened after withdrawal of treatment, indicating that
41
42 440 spontaneous remission would be less likely. However, in the present study, median depressions scores of
43
44 441 all questionnaires continued to improve after withdrawal of treatment in both groups, indicating that
45
46 442 spontaneous remission in both groups is a possible explanation for this finding.

47 443

48 444 *Strengths and limitations*

49
50
51 445 Internationally, we conducted the largest randomized controlled trial studying light therapy in pregnant
52
53 446 women with a depression. Moreover, we conducted various follow up measurements, including
54
55 447 postpartum, to study the effects of withdrawal of treatment and to study whether treatment during
56
57
58
59
60

1
2
3 448 pregnancy would protect against postpartum depression. Another strength is using a single assessor to
4
5 449 diagnose depression. Moreover, the setting of treatment was within a real world setting. Finally, a
6
7 450 strength of this study was the comprehensive assessment of side effects, as well as acceptability and
8
9 451 satisfaction of treatment.

10
11 452 The main limitation of our study was that an unforeseen lack of resources prevented us from including
12
13 453 150 participants, as we aimed to do according to our sample size calculation⁵⁵, which enables us to find
14
15 454 only large treatment effects⁵⁵. Another limitation is the fact that depressive symptoms during the study
16
17 455 are assessed by questionnaires, rather than diagnostic criteria. Also, information about psychiatric history
18
19 456 was collected via an interview and not through medical records, which may be influenced by recall bias.
20
21 457 Moreover, various covariates are self-reported, such as BMI, substance use and medication. We noticed
22
23 458 a different attrition rate at T3 (10 weeks after treatment) and P1 (2 months postpartum). At T3, this is due
24
25 459 to the fact that more women treated with DRLT already gave birth at T3, which resulted in missing data.
26
27 460 We do not have an explanation for the different attrition rate at P1. We cannot rule out the possibility that
28
29 461 these differences in attrition might have impacted our follow-up results. However, our sensitivity analyses
30
31 462 indicate our follow-up results to be robust for differences between the conditions and data imputation.

32 463

33 34 464 *Conclusions*

35
36 465 BLT has been shown effective in treating non-seasonal depression⁴⁶ and in women with antepartum
37
38 466 depression as well^{52,53}. In the present study, both BLT and DRLT showed improvement in pregnant
39
40 467 women with a depressive disorder after 6 weeks of treatment. Given the very mild and short-lived side
41
42 468 effects, the major improvement in a short time period, the high acceptability of the participants, the low
43
44 469 costs, and the direct availability, more studies to the effectiveness of BLT during pregnancy are
45
46 470 warranted. It is important to determine whether the responses observed in the present study represent
47
48 471 true treatment effects, non-specific treatment responses, placebo effects, or a combination of these. This
49
50 472 could be done by studying biological outcomes, such as cortisol and melatonin levels, which might show
51
52 473 a statistically significant difference between the two treatment arms irrespective of perceived symptoms of
53
54 474 depression. Additionally, it might show an indication of the positive effects of light therapy on the circadian
55
56 475 rhythm and its inhibiting effects on HPA-axis hyperactivity.

1
2
3 4764
5 477 **Acknowledgements**6
7 478 We would like to thank all participants for participating in the study. We would also like to thank all general
8
9 479 practitioners, midwives, gynaecologists, psychiatrists and psychologists for their help with the recruitment.10
11 480 We are grateful for all co-workers, students and assistants who contributed to the data collection in this
12
13 481 study: Nina Molenaar, PhD, Marlies Brouwer, PhD, Leo Genet, MSc, Sophie de Droog, MSc, Sofie
14
15 482 Koomen, MSc, Diewertje Houtman, MSc, Maria Zepeda, MSc, Nicolle Croes, MSc, Rianne Winters, MSc.
16
17 483 Lisanne van Kesteren, BSc, Finn Stofkoper, BSc, Indira Schouten, MSc and Mieke Roukema, MSc.

18 484

19
20 485 **Funding**21
22 486 MLB received funding from the 'Light, Cognition, Behaviour and Health' program of The Netherlands
23
24 487 Organization for Health Research and Development (NWO; The Hague, The Netherlands), in
25
26 488 collaboration with Signify Research (grant number 058-14-003) to fund the current study.27
28 48929
30 490 **Competing interests**31
32 491 Author JS is employed by Signify Research. The lamps used in this study were provided by Signify
33
34 492 Research.35
36 49337
38 494 **Author's contributions**39
40 495 MLB is the project's principle investigator and initiator of the study, obtained funding and designed the
41
42 496 study. BB was responsible for recruiting and counselling participants, running the study and collecting
43
44 497 data. AK is the project's methodologist and executed the primary statistical analysis. HB and EK were
45
46 498 involved in the recruitment of the study. JS provided support. AK, WH and MLB supervised the study. BB,
47
48 499 AK and MLB prepared the original draft. All authors reviewed, edited and approved the final manuscript.

49 500

50
51 501 **Data availability statement**52
53 502 The datasets used and/or analysed during the current study are available from the corresponding author
54
55 503 MLB on reasonable request.56
57
58
59
60

1
2
3 5044
5 505 **Word count**6
7 506 5,3728
9 50710
11 508 **References**

- 12 509 1. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-
13 510 regression of the prevalence and incidence of perinatal depression. *J Affect Disord* 2017; **219**: 86-92.
- 14 511 2. Bais B, de Groot N, Grootendorst-van Mil NH, et al. Seasonality of depressive symptoms during
15 512 pregnancy. *Psychiatry Res* 2018; **268**: 257-62.
- 16 513 3. Lancaster CA, Gold KJ, Flynn HA, Yoo H, Marcus SM, Davis MM. Risk factors for depressive
17 514 symptoms during pregnancy: a systematic review. *Am J Obstet Gynecol* 2010; **202**(1): 5-14.
- 18 515 4. Räisänen S, Lehto SM, Nielsen HS, Gissler M, Kramer MR, Heinonen S. Risk factors for and
19 516 perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002-2010
20 517 in Finland. *BMJ Open* 2014; (11): DOI:10.1136/bmjopen-2014-004883.
- 21 518 5. Seth S, Lewis AJ, Galbally M. Perinatal maternal depression and cortisol function in pregnancy
22 519 and the postpartum period: a systematic literature review. *BMC Pregnancy Childbirth* 2016; **16**(1): 124.
- 23 520 6. Leff-Gelman P, Mancilla-Herrera I, Flores-Ramos M, et al. The Immune System and the Role of
24 521 Inflammation in Perinatal Depression. *Neurosci Bull* 2016; **32**(4): 398-420.
- 25 522 7. Osborne LM, Monk C. Perinatal depression--the fourth inflammatory morbidity of pregnancy?:
26 523 Theory and literature review. *Psychoneuroendocrinology* 2013; **38**(10): 1929-52.
- 27 524 8. Milgrom J, Gemmill AW, Bilszta JL, et al. Antenatal risk factors for postnatal depression: a large
28 525 prospective study. *J Affect Disord* 2008; **108**: 147-57.
- 29 526 9. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression
30 527 during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch*
31 528 *Gen Psychiatry* 2010; **67**(10): 1012-24.
- 32 529 10. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal
33 530 depression compared with women without depression: a systematic review and meta-analysis. *JAMA*
34 531 *Psychiatry* 2016: DOI:10.1001/jamapsychiatry.2016.0934.

- 1
2
3 532 11. Talge NM, Neal C, Glover V, the Early Stress, Translational Research and Prevention Science
4 533 Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal
5 534 stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry* 2007;
6 535 **48**(3-4): 245-61.
- 7
8
9
10 536 12. Hentges RF, Graham SA, Plamondon A, Tough S, Madigan S. A Developmental Cascade from
11 537 Prenatal Stress to Child Internalizing and Externalizing Problems. *J Pediatr Psychol* 2019.
- 12
13
14 538 13. Pearson RM, Evans J, Kounali D, et al. Maternal depression during pregnancy and the postnatal
15 539 period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* 2013;
16 540 **70**(12): 1312-9.
- 17
18
19
20 541 14. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis.
21 542 *Neurosci Biobehav Rev* 2010; **35**(1): 17-22.
- 22
23
24 543 15. Dierckx B, Tulen JH, van den Berg MP, et al. Maternal psychopathology influences infant heart
25 544 rate variability: Generation R Study. *Psychosom Med* 2009; **71**(3): 313-21.
- 26
27
28 545 16. Goedhart G, Vrijkotte TG, Roseboom TJ, van der Wal MF, Cuijpers P, Bonsel GJ. Maternal
29 546 cortisol and offspring birthweight: results from a large prospective cohort study.
30 547 *Psychoneuroendocrinology* 2010; **35**(5): 644-52.
- 31
32
33
34 548 17. Henrichs J, Schenk JJ, Roza SJ, et al. Maternal psychological distress and fetal growth
35 549 trajectories: the Generation R Study. *Psychol Med* 2010; **40**(4): 633-43.
- 36
37
38 550 18. Zijlmans MA, Riksen-Walraven JM, de Weerth C. Associations between maternal prenatal cortisol
39 551 concentrations and child outcomes: A systematic review. *Neurosci Biobehav Rev* 2015; **53**: 1-24.
- 40
41
42 552 19. Steegers EA, Barker ME, Steegers-Theunissen RP, Williams MA. Societal Valorisation of New
43 553 Knowledge to Improve Perinatal Health: Time to Act. *Paediatr Perinat Epidemiol* 2016; **30**(2): 201-4.
- 44
45
46 554 20. Byatt N, Deligiannidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review
47 555 focused on risks and controversies. *Acta Psychiatr Scand* 2013; **127**(2): 94-114.
- 48
49
50 556 21. Hanley GE, Oberlander TF. The effect of perinatal exposures on the infant: antidepressants and
51 557 depression. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**(1): 37-48.

- 1
2
3 558 22. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy
4
5 559 and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five
6
7 560 Nordic countries. *BMJ* 2012; **344**: d8012.
- 8
9 561 23. Simoncelli M, Martin BZ, Berard A. Antidepressant use during pregnancy: a critical systematic
10
11 562 review of the literature. *Curr Drug Saf* 2010; **5**(2): 153-70.
- 12
13 563 24. Battle CL, Salisbury AL, Schofield CA, Ortiz-Hernandez S. Perinatal antidepressant use:
14
15 564 understanding women's preferences and concerns. *J Psychiatr Pract* 2013; **19**(6): 443-53.
- 16
17 565 25. Kothari A, de Laat J, Dulhunty JM, Bruxner G. Perceptions of pregnant women regarding
18
19 566 antidepressant and anxiolytic medication use during pregnancy. *Australas Psychiatry* 2019; **27**(2): 117-
20
21 567 20.
- 22
23 568 26. Molenaar NM, Brouwer ME, Duvekot JJ, et al. Antidepressants during pregnancy: Guideline
24
25 569 adherence and current practice amongst Dutch gynaecologists and midwives. *Midwifery* 2018; **61**: 29-35.
- 26
27 570 27. Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal
28
29 571 depression with antidepressants: An international review. *Aust N Z J Psychiatry* 2018; **52**(4): 320-7.
- 30
31 572 28. Bakker MK, Kolling P, van den Berg PB, de Walle HE, de Jong van den Berg LT. Increase in use
32
33 573 of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort
34
35 574 study from the Netherlands. *Br J Clin Pharmacol* 2008; **65**(4): 600-6.
- 36
37 575 29. Molenaar NM, Lambregtse-van den Berg MP, Bonsel GJ. Dispensing patterns of selective
38
39 576 serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study
40
41 577 from the Netherlands. *Arch Womens Ment Health* 2019.
- 42
43 578 30. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before,
44
45 579 during and after pregnancy: a population-based study in six European regions. *Bjog-Int J Obstet Gy* 2015;
46
47 580 **122**(7): 1010-20.
- 48
49 581 31. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy.
50
51 582 *American Journal of Obstetrics and Gynecology* 2007; **196**(6): 544-5.
- 52
53 583 32. Jimenez-Solem E, Andersen JT, Petersen M, et al. Prevalence of Antidepressant Use during
54
55 584 Pregnancy in Denmark, a Nation-Wide Cohort Study. *Plos One* 2013; **8**(4).

- 1
2
3 585 33. van Gelder MMHJ, Bos JHJ, Roeleveld N, de Jong-van den Berg LTW. Drugs associated with
4
5 586 teratogenic mechanisms. Part I: dispensing rates among pregnant women in the Netherlands, 1998-2009.
6
7 587 *Hum Reprod* 2014; **29**(1): 161-7.
- 8
9 588 34. Ververs T, Kaasenbrood H, Visser G, Schobben F, de Jong-van den Berg L, Egberts T.
10
11 589 Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;
12
13 590 **62**(10): 863-70.
- 14
15 591 35. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to
16
17 592 identify and estimate critical periods in pregnancy: An application to antidepressants. *Birth Defects Res A*
18
19 593 *Clin Mol Teratol* 2016; **106**(11): 927-34.
- 20
21 594 36. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs)
22
23 595 in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug
24
25 596 Administration's Mini-Sentinel program. *Arch Womens Ment Health* 2016; **19**(6): 969-77.
- 26
27 597 37. Taylor LG, Thelus Jean R, Gordon G, Fram D, Coster T. Development of a mother-child database
28
29 598 for drug exposure and adverse event detection in the Military Health System. *Pharmacoepidemiol Drug*
30
31 599 *Saf* 2015; **24**(5): 510-7.
- 32
33 600 38. Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States
34
35 601 from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth* 2014; **14**: 242.
- 36
37 602 39. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM.
38
39 603 Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment
40
41 604 meta-analysis. *PLoS One* 2017; **12**(3): e0173397.
- 42
43 605 40. Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and
44
45 606 mood. *Somnologie* 2019.
- 46
47 607 41. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep
48
49 608 and affect. *Nature Reviews Neuroscience* 2014; **15**(7): 443-54.
- 50
51 609 42. Prayag AS, Münch M, Aeschbach D, Chellappa SL, Gronfier C. Light modulation of human
52
53 610 clocks, wake and sleep. *Clocks & Sleep* 2019; **1**: 193-208.
- 54
55 611 43. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol*
56
57 612 2008; **23**(7): 571-85.

- 1
2
3 613 44. Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder: a review. *J Psychiatry*
4
5 614 *Neurosci* 2000; **25**(5): 469-80.
6
7 615 45. Magnusson A, Boivin D. Seasonal affective disorder: an overview. *Chronobiol Int* 2003; **20**(2):
8
9 616 189-207.
10
11 617 46. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database*
12
13 618 *Syst Rev* 2004.
14
15 619 47. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood
16
17 620 disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; **162**(4): 656-62.
18
19 621 48. Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical
20
21 622 trials. *J Affect Disord* 2016; **198**: 64-71.
22
23 623 49. Perera S, Eisen R, Bhatt M, et al. Light therapy for non-seasonal depression: systematic review
24
25 624 and meta-analysis. *BJPsych Open* 2016; **2**(2): 116-26.
26
27 625 50. Martensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: A
28
29 626 critical review of the evidence. *J Affect Disord* 2015; **182**: 1-7.
30
31 627 51. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of
32
33 628 antepartum depression. *Am J Psychiatry* 2002; **159**(4): 666-9.
34
35 629 52. Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for
36
37 630 antepartum depression: preliminary findings. *J Clin Psychiatry* 2004; **65**(3): 421-5.
38
39 631 53. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of
40
41 632 light therapy for antepartum depression. *J Clin Psychiatry* 2011; **72**(7): 986-93.
42
43 633 54. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; **2**(8): e124.
44
45 634 55. Bais B, Kamperman AM, van der Zwaag MD, et al. Bright light therapy in pregnant women with
46
47 635 major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. *BMC*
48
49 636 *Psychiatry* 2016; **16**(1): 381.
50
51 637 56. First MB GM, Spitzer RL, Williams JBW. User's guide for the SCID-I. Structured clinical interview
52
53 638 for DSM-IV TR axis I disorders (research version). New York: New York Psychiatric Institute; 2002.
54
55
56
57
58
59
60

- 1
2
3 639 57. Lieveise R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light
4 640 treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-
5 641 controlled trial. *Arch Gen Psychiatry* 2011; **68**(1): 61-70.
- 6
7
8 642 58. Kreidler SM, Muller KE, Grunwald GK, et al. GLIMMPSE: Online Power Computation for Linear
9 643 Models with and without a Baseline Covariate. *J Stat Softw* 2013; **54**(10).
- 10
11
12 644 59. Meesters Y, Dekker V, Schlangen LJ, Bos EH, Ruiters MJ. Low-intensity blue-enriched white light
13 645 (750 lux) and standard bright light (10,000 lux) are equally effective in treating SAD. A randomized
14 646 controlled study. *BMC Psychiatry* 2011; **11**: 17.
- 15
16
17 647 60. Project TAI. ALEA Randomisation Software (Version 2.2). Amsterdam: Netherlands Cancer
18 648 Institute; 2006. p. <http://tenalea.net/>.
- 19
20
21 649 61. Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major
22 650 depressive disorder: The contributions of psychological interventions in preventing relapse and
23 651 recurrence. *Clin Psychol Rev* 2015; **41**: 16-26.
- 24
25
26 652 62. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item
27 653 Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782-6.
- 28
29
30 654 63. Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh
31 655 Depression Scale during pregnancy. *J Psychosom Res* 2011; **70**(4): 385-9.
- 32
33
34 656 64. Roenneberg T, Wirz-Justice A, Mrosovsky M. Life between clocks: daily temporal patterns of human
35 657 chronotypes. *J Biol Rhythms* 2003; **18**(1): 80-90.
- 36
37
38 658 65. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Partonen T. Circadian
39 659 preference links to depression in general adult population. *J Affect Disord* 2015; **188**: 143-8.
- 40
41
42 660 66. Merikanto I, Lahti T, Kronholm E, et al. Evening types are prone to depression. *Chronobiol Int*
43 661 2013; **30**(5): 719-25.
- 44
45
46 662 67. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for
47 663 reporting parallel group randomised trials. *BMC Med* 2010; **8**: 18.
- 48
49
50 664 68. Friedman ES, Davis LL, Zisook S, et al. Baseline depression severity as a predictor of single and
51 665 combination antidepressant treatment outcome: results from the CO-MED trial. *Eur*
52 666 *Neuropsychopharmacol* 2012; **22**(3): 183-99.

- 667 69. Corral M, Wardrop AA, Zhang H, Grewal AK, Patton S. Morning light therapy for postpartum
668 depression. *Arch Womens Ment Health* 2007; **10**(5): 221-4.
- 669 70. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo
670 response in antidepressant trials. *J Affect Disord* 2009; **118**(1-3): 1-8.
- 671 71. Posternak MA, Miller I. Untreated short-term course of major depression: a meta-analysis of
672 outcomes from studies using wait-list control groups. *J Affect Disord* 2001; **66**(2-3): 139-46.
- 673 72. Yazici E, Kirkan TS, Aslan PA, Aydin N, Yazici AB. Untreated depression in the first trimester of
674 pregnancy leads to postpartum depression: high rates from a natural follow-up study. *Neuropsychiatr Dis*
675 *Treat* 2015; **11**: 405-11.
- 676 73. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: a comprehensive meta-
677 analysis. *Clin Psychol Rev* 2013; **33**(6): 763-71.
- 678 74. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and
679 depression: A meta-analytic review. *J Consult Clin Psychol* 2010; **78**(2): 169-83.
- 680 75. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. An open trial of mindfulness-
681 based cognitive therapy for the prevention of perinatal depressive relapse/recurrence. *Arch Womens*
682 *Ment Health* 2015; **18**(1): 85-94.
- 683 76. Vieten C, Astin J. Effects of a mindfulness-based intervention during pregnancy on prenatal
684 stress and mood: results of a pilot study. *Arch Womens Ment Health* 2008; **11**(1): 67-74.
- 685 77. Nagare R, Plitnick B, Figueiro MG. Effect of exposure duration and light spectra on nighttime
686 melatonin suppression in adolescents and adults. *Light Res Technol* 2019; **51**(4): 530-43.
- 687 78. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian
688 pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol* 2000; **526 Pt 3**: 695-
689 702.

691 **Table 1.** Inclusion and exclusion criteria for the Bright Up Study.

Inclusion criteria	Women
	18-45 years of age
	12-32 weeks pregnant (as confirmed by ultrasound)

Current DSM-5 diagnosis of depressive disorder (as assessed by the SCID*)

Exclusion criteria	Insufficient proficiency in Dutch or English
	Multiple pregnancy
	Current use of antidepressants shorter than 2 months
	Lifetime diagnosis of bipolar I or II disorder
	Any psychotic episode
	Current substance abuse
	Current primary anxiety disorder
	Recent history of suicide attempt
	Current shift-work
	Somatic and/or obstetric conditions that override study participation
	Previous treatment with BLT
	Eye condition (macular degeneration, eye diseases, recent eye surgery)

692 * SCID = Structured Clinical Interview for DSM disorders

693

694 **Table 2.** Overview of participant characteristics at inclusion.

	BLT (n=33)	DRLT (n=34)
Age in years, mean (SD)	31.9 (4.4)	31.9 (5.3)
Gestational age in weeks, mean (SD)	20.6 (6.2)	19.7 (6.3)
Ethnicity		
Dutch	27 (81.8%)	26 (76.5%)
Other	6 (19.2%)	8 (33.5%)
Marital status		
Married or cohabiting	33 (100%)	32 (94.1%)
Committed relationship, not cohabiting	0 (0%)	1 (2.9%)
Single	0 (0%)	1 (2.9%)

Education

Elementary or (pre-)vocational education	11 (33.3%)	13 (38.2%)
Higher professional education	8 (24.2%)	11 (32.4%)
(Pre-) academic education	14 (42.4%)	10 (29.4%)

Parity

Nulliparous	15 (45.5%)	20 (58.8%)
Primiparous	13 (39.4%)	9 (26.5%)
Multiparous	5 (15.2%)	5 (14.7%)

BMI in kg/m² or st/ft², mean (SD)

25.5 (4.5) 26.3 (5.4)

Planned pregnancy

22 (66.7%) 22 (64.7%)

Antidepressant medication

3 (9.1%) 5 (14.7%)

Sleep medication

3 (9.1%) 2 (5.9%)

Psychotherapy

14 (48.5%) 16 (47.1%)

Comorbidities

0	17 (51.5%)	13 (38.2%)
1	9 (27.3%)	13 (38.2%)
>1	7 (21.2%)	8 (23.5%)

Duration of depression in weeks, mean (SD)

24.6 (16.9) 45.1 (121.9)

Depressive episodes in past

0	12 (36.4%)	11 (32.4%)
1	9 (27.2%)	14 (41.2%)
>1	12 (36.4%)	9 (26.5%)

Chronotype

Early (extremely, moderately and slightly)	20 (80%)	25 (92.6%)
Normal	1 (4%)	1 (3.7%)
Late (extremely, moderately and slightly)	4 (16%)	1 (3.7%)

695 BLT = bright light therapy; DRLT = dim red light therapy

696

697 **Table 3.** Effects of allocation on the course of depressive symptoms through the intervention period and
 698 follow-up (until two months postpartum): crude analysis

	β (95% CI) of intervention*	β (95% CI) of follow-up**
SIGH-SAD	-0.68 (-1.84, 0.49)	-0.16 (-0.82, 0.51)
HAM-D	-0.18 (-0.74, 0.37)	0.04 (-0.29, 0.37)
EPDS	0.01 (-0.51, 0.53)	-0.05 (-0.35, 0.24)

699 * From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum

700

701 **Figure legends**

702 **Figure 1.** Flow-chart of the Bright Up study.

703 **Figure 2.** Estimated marginal means of depression scores in women with antepartum depression until
 704 two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent
 705 treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.

706 BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the
 707 Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for
 708 Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1,
 709 T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of
 710 treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum

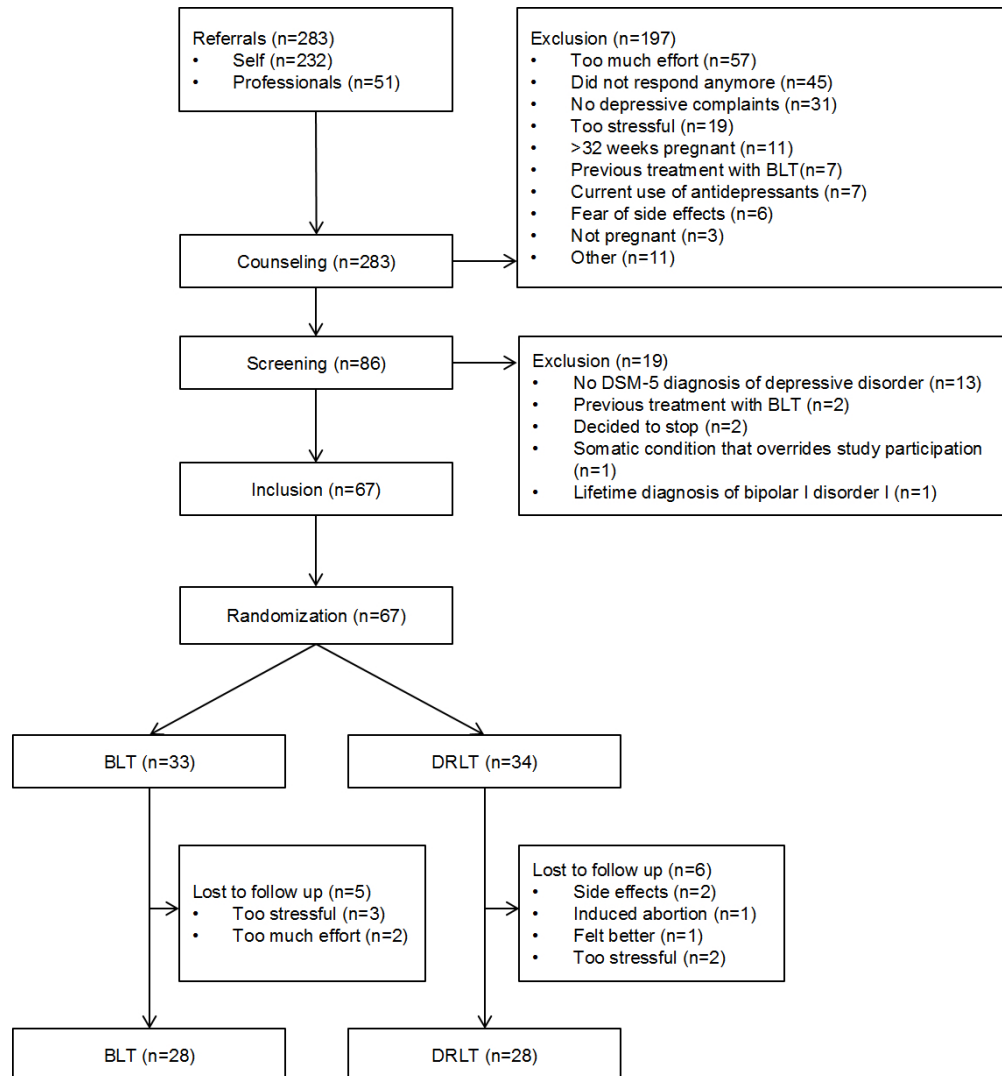


Figure 1. Flow-chart of the Bright Up study.

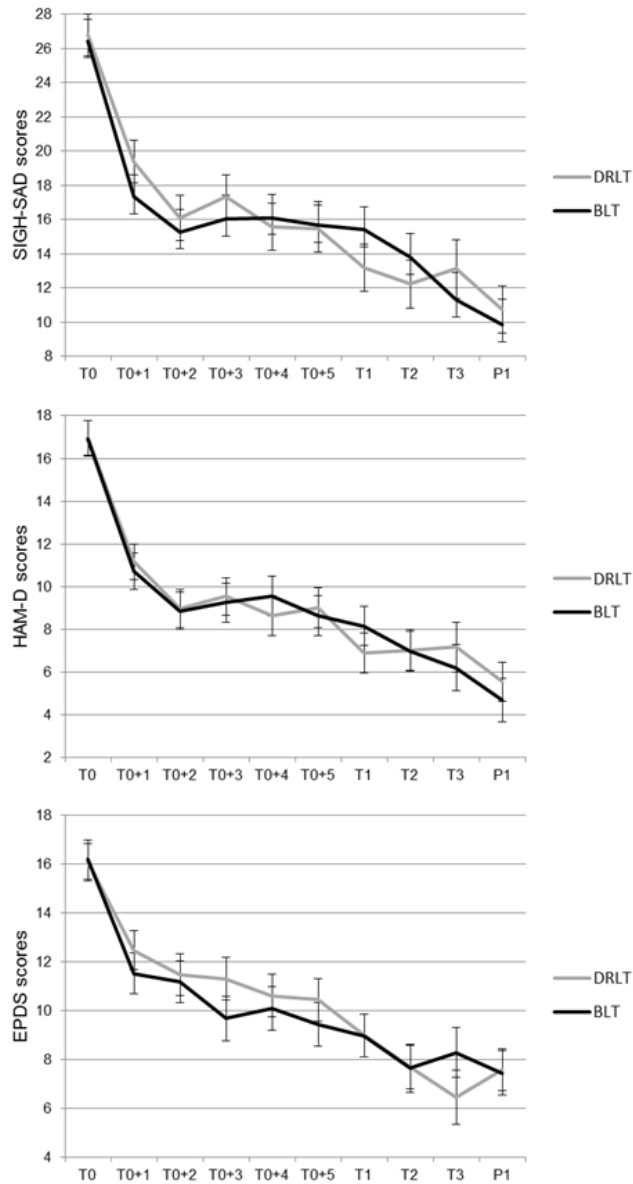


Figure 2. Estimated marginal means of depression scores in women with antepartum depression until two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.
 BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Supplementary Table 1. Photobiological characterizations of light therapy in both treatment arms.

	BLT	DRLT
Cyanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	578.7	2.24
Melanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	891	5.53
Chloropic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1032.3	7.23
Erythropic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1212.3	11.37
Rhodopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	16.61	16.61

BLT = bright light therapy; DRLT = dim red light therapy

For peer review only

Supplementary Table 2. Observed median SIGH-SAD, HAM-D and EPDS scores with ranges and number of participants over the course of the study for both treatment arms.

Measure	T0	T0+1	T0+2	T0+3	T0+4	T0+5	T1	T2	T3	P1
SIGH-SAD										
BLT (mdn, range, N)	27 (14-44; 33)	16.5 (1-33; 30)	16 (2-43; 29)	15 (0-41; 25)	18 (0-32; 25)	17.5 (1-37; 24)	15.5 (0-29; 26)	13 (1-26; 25)	11 (0-29; 17)	8 (1-23; 20)
DRLT (mdn, range, N)	26.5 (13-42; 34)	19 (8-33; 31)	17 (2-35; 27)	18 (4-30; 29)	15 (3-28; 24)	16 (2-31; 25)	13 (2-34; 25)	11.5 (1-26; 24)	9.5 (1-31; 14)	8 (0-28; 25)
HAM-D										
BLT (mdn, range, N)	16 (7-29; 33)	9 (0-25; 30)	9 (1-30; 29)	8 (0-28; 25)	10 (0-22; 25)	10 (0-21; 24)	7.5 (0-20; 26)	8 (0-17; 25)	5 (0-16; 17)	3 (0-11; 20)
DRLT (mdn, range, N)	18 (4-29; 34)	10 (3-20; 31)	9 (1-22; 27)	9 (2-20; 29)	8 (0-18; 24)	8 (1-20; 25)	6 (1-18; 25)	4.5 (0-20; 24)	4 (0-15; 14)	4 (0-19; 25)
EPDS										
BLT (mdn, range, N)	16 (7-25; 31)	11 (3-23; 26)	11 (0-23; 26)	10 (0-19; 21)	8 (0-25; 23)	7 (0-18; 23)	9.5 (1-18; 26)	8.5 (0-15; 18)	8.5 (1-24; 16)	7 (0-13; 22)
DRLT (mdn, range, N)	16 (3-25; 34)	12 (6-19; 28)	12 (3-20; 25)	11.5 (3-21; 24)	10 (1-18; 24)	10 (2-19; 23)	6.5 (1-22; 24)	6 (0-21; 23)	4 (1-10; 12)	7 (0-18; 26)

BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum; mdn = median

Supplementary Table 3. Effects of allocation on the course of depressive symptoms through the intervention period and follow-up (until two months postpartum): sensitivity analyses.

	β (95% CI) of intervention*	β (95% CI) of follow-up**
Adjusted analysis^a		
SIGH-SAD	-0.24 (-1.68, 1.20)	-0.24 (-1.68, 1.20)
HAM-D	0.13 (-0.49, 0.75)	0.13 (-0.49, 0.75)
EPDS	0.25 (-0.38, 0.89)	0.25 (-0.38, 0.89)
Data imputation^b		
SIGH-SAD	-0.45 (-1.44, 0.53)	-0.08 (-0.63, 0.46)
HAM-D	-0.09 (-0.63, 0.44)	0.06 (-0.25, 0.37)
EPDS	0.19 (-0.30, 0.68)	0.04 (-0.24, 0.32)
Post-hoc analysis: high treatment compliance^c		
SIGH-SAD	-0.40 (-1.36, 0.55)	-0.32 (-0.88, 0.24)
HAM-D	-0.12 (-0.79, 0.54)	-0.06 (-0.43, 0.31)
EPDS	0.03 (-0.58, 0.65)	-0.05 (-0.40, 0.30)
Post-hoc analysis: high symptom severity^d		
SIGH-SAD	-0.84 (-2.33, 0.65)	-0.20 (-1.14, 0.75)
HAM-D	-0.16 (-1.12, 0.87)	0.13 (-0.48, 0.73)
EPDS	-0.05 (-0.92, 0.82)	0.20 (-0.33, 0.74)

1
2
3 * From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum; ^a Propensity score composed of psychiatric history, ethnicity, level of education,
4 an unplanned pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions; ^b Last observation
5 carried forward; ^c <7 missed treatments; ^d Based on median split baseline SIGH-SAD scores
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

For peer review only



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p. 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 4-5
	2b	Specific objectives or hypotheses	p. 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p. 6
Participants	4a	Eligibility criteria for participants	p. 6; Table 1
	4b	Settings and locations where the data were collected	p. 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 8-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	p. 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 7-9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p. 7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 11-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 12, Fig. 1, Supp. Table 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 6
	14b	Why the trial ended or was stopped	p. 6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Sup. Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Sup. Table 2, Fig. 2, p.13-15, Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	p. 14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	p. 14, Sup. Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 15-17
Other information			
Registration	23	Registration number and name of trial registry	p. 2, 6
Protocol	24	Where the full trial protocol can be accessed, if available	p. 6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Effects of bright light therapy for depression during pregnancy: a randomized, double-blind controlled trial

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-038030.R2
Article Type:	Original research
Date Submitted by the Author:	30-Sep-2020
Complete List of Authors:	Bais, Babette; Erasmus Medical Center, Psychiatry Kamperman, Astrid M.; Erasmus MC, Psychiatry Bijma, Hilmar; Erasmus Medical Center, Obstetrics and Gynaecology Hoogendijk, Witte; Erasmus Medical Center, Psychiatry Souman, Jan; Signify NV, Lighting Applications Knijff, Esther; Erasmus Medical Center, Psychiatry Lambregtse-van den Berg, Mijke; Erasmus Medical Center, Child and Adolescent Psychiatry/Psychology; Erasmus Medical Center, Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Depression & mood disorders < PSYCHIATRY, OBSTETRICS, PSYCHIATRY

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 1 **Effects of bright light therapy for depression during pregnancy: a randomized, double-blind**
4
5 2 **controlled trial**
6

7 3
8
9 4 Babette Bais, MSc^{1*}, Astrid M Kamperman, PhD², Hilmar H Bijma, MD, PhD³, Witte JG Hoogendijk, MD,
10
11 5 PhD⁴, Jan L Souman, PhD⁵, Esther Knijff, MD, PhD⁶, Mijke P Lambregtse-van den Berg, MD, PhD⁷
12
13 6

14
15 7 ¹ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

16
17 8 ² Epidemiological and Social Psychiatric Research Institute, Department of Psychiatry, Erasmus
18
19 9 University Medical Centre Rotterdam, Rotterdam, The Netherlands

20
21 10 ³ Department of Obstetrics and Gynaecology, Erasmus University Medical Centre Rotterdam, Rotterdam,
22
23 11 The Netherlands

24
25 12 ⁴ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

26
27 13 ⁵ Department Lighting Applications, Signify Research, Eindhoven, The Netherlands;

28
29 14 ⁶ Department of Psychiatry, Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands

30
31 15 ⁷ Department of Child and Adolescent Psychiatry/Psychology, department of Psychiatry, Erasmus
32
33 16 University Medical Centre Rotterdam, Rotterdam, The Netherlands

34
35 17 *Corresponding author: P.O. Box 2040, 3000CA Rotterdam, The Netherlands; b.bais@erasmusmc.nl
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 19 **Abstract**

4
5 20 **Objectives** Approximately 11-13% of pregnant women suffer from depression. Bright light therapy (BLT)
6
7 21 is a promising treatment, combining direct availability, sufficient efficacy, low costs, and high safety for
8
9 22 both mother and child. Here, we examined the effects of BLT on depression during pregnancy.

10
11 23 **Design** Randomized, double-blind controlled trial.

12
13 24 **Setting** Primary and secondary care in The Netherlands, from November 2016 to March 2019.

14
15 25 **Participants** 67 pregnant women (12-32 weeks gestational age) with a DSM-5 diagnosis of depressive
16
17 26 disorder.

18
19 27 **Interventions** Participants were randomly allocated to treatment with either BLT (9,000 lux, 5,000 K) or
20
21 28 dim red light therapy (DRLT, 100 lux, 2,700 K), which is considered placebo. For six weeks, both groups
22
23 29 were treated daily at home for 30 minutes upon awakening. Follow-up took place weekly during the
24
25 30 intervention, after six weeks of therapy, three and ten weeks after treatment, and two months postpartum.

26
27 31 **Primary and secondary outcome measures** Depressive symptoms were measured primarily with the
28
29 32 Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder. Secondary
30
31 33 measures were the Hamilton Rating Scale for Depression and the Edinburgh Postnatal Depression Scale.
32
33 34 Changes in rating scale scores of these questionnaires over time were analysed using generalized linear
34
35 35 mixed models.

36
37 36 **Results** Median depression scores decreased by 40.6-53.1% in the BLT group and by 50.9-66.7% in the
38
39 37 DRLT group. We found no statistically significant difference in symptom change scores between BLT and
40
41 38 DRLT. Sensitivity and post-hoc analyses did not change our findings.

42
43 39 **Conclusions** Depressive symptoms of pregnant women with depression improved in both treatment
44
45 40 arms. More research is necessary to determine whether these responses represent true treatment
46
47 41 effects, non-specific treatment responses, placebo effects, or a combination hereof.

48
49 42 **Trial Registration** Bright Up, NTR5476, <http://www.trialregister.nl>

50
51 44 **Strengths and limitations of this study**
52
53
54
55
56
57
58
59
60

- 1
2
3 45 • We conducted various follow up measurements, including postpartum, to study the effects of
4 withdrawal of treatment and to study whether treatment during pregnancy would protect against
5 46 postpartum depression.
6
7 47
8
9 48 • The setting of treatment was within a real world setting.
10
11 49 • A strength of this study was the comprehensive assessment of side effects, as well as
12 acceptability and satisfaction of treatment.
13 50
14
15 51 • An unforeseen lack of resources prevented us from including 150 participants, as we aimed to do
16 according to our sample size calculation.
17 52
18
19 53 • Depressive symptoms during the study are assessed by questionnaires, rather than diagnostic
20 criteria.
21 54
22
23 55
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

56 Introduction

57 Antepartum depression is a common and high impact disease, with approximately 11-13% of pregnant
58 women suffering from depression¹. Antepartum depression is not only seen in autumn and winter, but is
59 a year-round phenomenon, with certain subgroups even showing more symptoms in summer². Many risk
60 factors for antepartum depression have been identified^{3,4}. Possible causes for antepartum depression
61 may include alterations in endocrine systems, such as the hypothalamus-pituitary-adrenal axis⁵, and
62 inflammation^{6,7}. Women who suffer from antepartum depression are more likely to suffer from postpartum
63 depression as well⁸. Children who are exposed to maternal depression during pregnancy have a higher
64 risk of adverse birth outcomes, such as prematurity and being small for gestational age^{9,10}. Additionally,
65 children of mothers with antepartum depression show more often cognitive, emotional, and behavioral
66 problems in childhood, adolescence, and adulthood^{11,12} and they have a higher risk of suffering from
67 depression later in life¹³. During pregnancy, fetal programming of the hypothalamus-pituitary-adrenal
68 gland (HPA) axis takes place, which can be affected by maternal depression during pregnancy and may
69 have long-lasting effects on stress response¹⁴. Possible mechanisms are 1) maternal cortisol crossing
70 the placenta and thus increasing fetal cortisol levels, 2) placental secretion of corticotropin-releasing
71 factor, which stimulates both maternal and fetal cortisol, and 3) reduced blood flow to the fetus, causing
72 fetal growth restriction^{9,15-18}. In addition, epigenetic programming takes place within the antepartum
73 period, which influences not only the health of the (unborn) infant, but also that of following generations¹⁹.
74 Therefore, early detection and treatment of antepartum depression is highly important for both mother
75 and infant.

76 In non-pregnant women, guidelines propose psychotherapy, antidepressant medication, or a combination
77 of both as treatment. However, psychotherapy might not be readily available and the safety of maternal
78 use of antidepressants, which cross the placenta, still remains to be established. The use of
79 antidepressants is controversial, because of potential teratogenicity^{20,21}. For example, increased risks
80 have been found for persistent pulmonary hypertension of the neonate²² and cardiovascular
81 malformations²³. Furthermore, pregnant women express a strong preference for non-pharmacologic
82 treatment because of the possible harm for their unborn child^{24,25}. Moreover, current adherence to
83 national guidelines by midwives and gynaecologists is low²⁶ and international guidelines on the

1
2
3 84 pharmacological treatment of antepartum depression are not consistent ²⁷, which might result in
4
5 85 unwanted variation in practice. Despite this, antidepressant use during pregnancy is increasing, not only
6
7 86 in the Netherlands ^{28,29}, but in other European countries and the United States as well ³⁰⁻³². In the
8
9 87 Netherlands, approximately 2-3% of pregnant women use antidepressants ^{29,33,34}. In the United States,
10
11 88 this prevalence is approximately 6-7% ³⁵⁻³⁷, but could even be as high as 15% in some states ³⁸.
12
13 89 Therefore, it is urgent and clinically relevant to investigate alternative approaches to treat antepartum
14
15 90 depression, such as bright light therapy (BLT) ³⁹.

16
17 91 Light synchronizes the suprachiasmatic nucleus (SCN), or the 'biological clock', with the environmental
18
19 92 day-night rhythm ⁴⁰. Light hits the retina and intrinsically photosensitive retinal ganglion cells (ipRGCs) in
20
21 93 the retina project, via the retino-hypothalamic tract to the SCN and thus influences circadian rhythm ⁴⁰⁻⁴²,
22
23 94 which may indirectly benefit depressive symptoms ⁴³. However, not only do ipRGCs project to the SCN,
24
25 95 but also directly to brain regions important in the regulation of mood, such as the medial amygdala and
26
27 96 the lateral habenula ⁴⁰⁻⁴².

28
29 97 Although BLT is the first-choice treatment for seasonal affective disorder, a condition of reoccurring
30
31 98 depressions during fall and winter, with remissions in spring and summer ^{44,45}, the effects of BLT have
32
33 99 been shown both in seasonal affective disorder and in non-seasonal depression, which is not only shown
34
35 100 by a Cochrane review ⁴⁶, but also by more recent systematic reviews and meta-analyses ⁴⁷⁻⁵⁰. An open
36
37 101 trial of BLT in pregnant women showed improvement of mean depression ratings by 49% ⁵¹. Two small
38
39 102 randomized controlled trials showed significant improvement of depression among pregnant women
40
41 103 exposed to BLT compared to placebo ^{52,53}. Although these results seem promising, the sample sizes of
42
43 104 these studies were small, making them at risk for chance-findings ⁵⁴.

44
45 105 In this study, we compared the effectiveness of BLT compared to placebo light among pregnant women
46
47 106 with a depressive disorder in a larger randomized clinical trial. Moreover, we followed women until the
48
49 107 postpartum period, to study whether treatment with light therapy during pregnancy might protect against
50
51 108 postpartum depression. We hypothesized that daily treatment with six weeks of morning BLT will improve
52
53 109 depressive symptoms during pregnancy.

54
55 110

55 111 **Material and Methods**

112 *Design*

113 This study was a randomized, double-blind, placebo-controlled clinical trial (Bright Up, NTR5476,
114 <http://www.trialregister.nl>). A detailed protocol can be found elsewhere ⁵⁵. In short, the aim of the Bright
115 Up study was to evaluate the effectiveness of BLT for pregnant women with a depressive disorder,
116 compared to placebo light.

117

118 *Participants*

119 Eligible participants were pregnant women (12-32 weeks of gestational age, confirmed by ultrasound)
120 diagnosed with a depressive disorder, confirmed by a Structured Clinical Interview for DSM disorders
121 (SCID) by one trained assessor ⁵⁶. The specific inclusion and exclusion criteria are listed in Table 1.

122 In the earlier published study protocol ⁵⁵, we aimed to include women who were 12-18 weeks pregnant.

123 For pragmatic reasons, in particular the fact that a substantial number of women were referred after 18
124 weeks of pregnancy, we later decided to widen our inclusion criteria to 12-32 weeks pregnancy.

125 In the Netherlands, maternity care for low-risk pregnancies is provided by midwives (primary care). High-
126 risk pregnancies are cared for by gynaecologists in a general hospital (secondary care) or fetal-maternal
127 medicine unit (tertiary care).

128 In this study, women were recruited not only via health care professionals, such as general practitioners,
129 midwives, gynaecologists, psychiatrists, and psychologists, but also via (social) media. A complete flow-
130 chart of the recruitment can be found in Figure 1.

131 Initially, we calculated the number of women to be included, based on the results and research
132 methodology of previous studies ^{51,52,57}. We expected a true treatment effect in the range of a 10-15%
133 symptom reduction over the full course of treatment (6 weekly assessments), reflecting a small to medium
134 effect size. A sample size calculation was performed using GLIMMPSE 2.1.5. software ⁵⁸, with the
135 following parameters: alpha 0.05; beta 0.80; 6 time assessments (continuous, equally spaced); primary
136 test: time*treatment interaction; SIGH-SAD scores assumed at baseline: M: 28.0 and SD: 7.0, with a
137 linear decrease in symptom scores up to a mean score of 24.0 in the BLT condition. No symptom change
138 was assumed for the DRLT condition; Hotelling-Lawley Trace correction; base correlation 0.4; decay rate
139 0.05; no additional scaling factors included.

1
2
3 140 To demonstrate this a total sample size of 126 participants, 63 per arm was needed. To account for loss
4
5 141 to follow up during and after treatment, we aimed at including 150 women. Inclusion took place in The
6
7 142 Netherlands and started on 9 November 2016 and lasted until 15 March 2019. By then, 67 women were
8
9 143 included. However, due to limiting resources, we decided to stop the inclusion.

10

11 144

12 145 *Patient and Public Involvement*

13
14 146 No patients involved.

15

16 147

17 148 *Ethics*

18
19 149 All procedures performed involving human participants were in accordance with the ethical standards of
20
21 150 the institutional and/or national research committee and with the 1964 Helsinki declaration and its later
22
23 151 amendments or comparable ethical standards. Written informed consent was obtained from all
24
25 152 participants. The study protocol and later amendments were approved by the medical ethical committee
26
27 153 of the Erasmus University Medical Centre, Rotterdam, The Netherlands (registration number MEC-2015-
28
29 154 731).

30

31 155

32 156 *Blinding*

33
34 157 Participants were blinded to allocation. Participants were informed that the study aimed to investigate the
35
36 158 efficacy of different light colours. They were not informed that one treatment arm was considered placebo
37
38 159 treatment. This was in accordance with approval of the medical ethical committee.

39
40 160 Outcome assessors were blinded to the allocation of the participants. Participants were asked not to
41
42 161 share any details regarding their treatment towards the assessors. When blinding was broken, the
43
44 162 assessor was replaced. The researcher performing the primary statistical analyses (AK) was blinded to
45
46 163 the allocation. The field researcher (BB) was not blinded to the allocation for practical reasons. This
47
48 164 researcher made sure lamps of the correct allocation were delivered to the participants. Also, this
49
50 165 researcher asked participants about any side effects, keeping the independent assessors blinded to any
51
52 166 adverse effects that might break the blinding, e.g. strained eyes, and answered any questions from the
53
54 167 participants regarding their lamps.

55

56

57

58

59

60

1
2
3 168 At baseline, we asked about any expectations concerning the treatment with regards to their depressive
4
5 169 symptoms. Women could choose whether they expected a negative effect, a small negative effect, no
6
7 170 effect, a small positive effect or a positive effect. After the intervention period, the participants were asked
8
9 171 whether they were aware of their allocation.

10
11 172

12 173 *Light therapy*

14 174 Light treatment consisted of either active BLT (9,000 lux, color temperature 5,000 K) or dim red light
15
16 175 therapy (DRLT, 100 lux, color temperature 2,700 K). The photobiological characterizations of these
17
18 176 treatments are shown in Supplementary Table 1. The original lamps were adjusted in the factory where
19
20 177 these are produced (EnergyUp HF3419/01, Philips, Eindhoven, The Netherlands). To ensure that
21
22 178 participants are exposed to the same light intensity, the output of the lamps was fixed. For the control
23
24 179 condition, the standard LED's in the lamp were replaced by LED's with a lower intensity and a different
25
26 180 color temperature. The lamps in the control condition were positioned at the same distance from the
27
28 181 participant as in the experimental condition.

29
30 182 The active light therapy was shown to be effective in other studies^{52,53,57,59}. DRLT can be considered to
31
32 183 be biologically inactive and thus as placebo treatment⁴⁶. In line with two previous RCT's among pregnant
33
34 184 women, we chose six weeks of daily light exposure^{52,53}.

35
36 185 The lamps were delivered at the participants' home by one researcher (BB) who was not blinded to the
37
38 186 allocation of the participants. This researcher did not share anything about the allocation with the
39
40 187 participants. After delivery of the lamps and instructions, participants commenced their daily treatment
41
42 188 with light for 30 minutes within 30 minutes of habitual wake up time for a six weeks period. This took
43
44 189 place at the participants' home. Participants sat in front of two lamps with a distance of approximately 40
45
46 190 cm (15.8 inches). They received a plastic ruler of this length to ensure of the correct distance. The light
47
48 191 boxes were placed in a custom-made scaffolding, so that the height of the light boxes could be adjusted
49
50 192 per person and glare was avoided. Apart from the light treatment, participants in both treatment arms
51
52 193 received treatment as usual: women were free to visit their general practitioner, obstetric care provider, or
53
54 194 mental health care worker and start additional treatment, whenever they felt a need for this.
55
56 195 During the intervention period, self-reported compliance with the light treatment was checked weekly.

196

Method

A baseline interview was conducted by telephone by one researcher (BB). The baseline interview collected sociodemographic information (age, ethnicity, educational level, marital status, body mass index (BMI)), obstetric information (gestational age, whether the pregnancy was planned, parity), psychiatric information (substance use (smoking, alcohol, drugs), present and past medication use, present depressive symptoms, psychiatric history), and information on somatic conditions. Also, participants were screened with the SCID for depressive disorder and various potential co-morbidities, such as generalized anxiety disorder and panic disorder. Previous depressive episodes were also assessed with the SCID. The general practitioner was contacted to verify present medication use and whether the participant met any exclusion criteria.

After baseline measurements and receiving written informed consent, the participants were randomly allocated to either receive BLT or DRLT in a 1:1 ratio. Randomization was done with the web-based computer-generated schedule ALEA (software for randomization in clinical trials, version 2.2) using random block sizes of 2-6⁶⁰ by an independent researcher. Stratification factors were the use of any current antidepressant medication and the number of previous depressive episodes. The latter was dichotomized to three or less versus four or more⁶¹.

Follow up took place at the following time points: weekly during the intervention period (T0+1, T0+2, etc.), after 6 weeks of treatment (T1), 3 weeks after end of treatment (T2), 10 weeks after end of treatment (T3), 2 months postpartum (P1), 6 months postpartum (P2), 18 months postpartum (P3).

At these time points, questionnaires were assessed and body material was collected. We collected urine, hair, and saliva from the participants, as can be found in our earlier published protocol⁵⁵.

This paper reports the short term effectiveness, i.e. up to two months postpartum.

219

Primary and secondary outcome measures

The primary outcome measure was the average change in depressive symptoms between the two groups, as measured by the Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version (SIGH-SAD). Secondary outcome measures were these changes as measured

1
2
3 224 by the 17-item Hamilton Rating Scale for Depression (HAM-D) and the Edinburgh Depression Scale
4
5 225 (EPDS).

6
7 226 In the earlier published protocol ⁵⁵, we were primarily interested in the effects of light therapy on
8
9 227 depressive symptoms. Secondly, we were interested in the effects on various other outcomes, such as
10
11 228 maternal hormonal levels, maternal sleep quality and infant outcomes. Depressive symptoms were
12
13 229 measured by two questionnaires: the SIGH-SAD and the EPDS, with the original 17-item HAM-D being
14
15 230 part of the SIGH-SAD, which consists of 21 HAM-D items and 8 atypical items. Therefore, in the original
16
17 231 protocol ⁵⁵, we mentioned these two questionnaires together as the primary outcome, as opposed to the
18
19 232 other outcomes (maternal hormonal levels and others). However, it is not technically possible to have
20
21 233 more than one primary outcome. Our power calculation was based on the SIGH-SAD, which makes this
22
23 234 our true primary outcome. The HAM-D and the EPDS are the secondary outcomes for this manuscript. In
24
25 235 the current manuscript, we only report our findings regarding the depressive symptoms. We will report the
26
27 236 other outcomes elsewhere. Second, in the trial register, we mention the HAM-D and EPDS as primary
28
29 237 outcome, which has been a mistake. The mix-up results from the fact that the SIGH-SAD is in fact the
30
31 238 original 17-item HAM-D with an additional 4 HAM-D and 8 atypical depressive items ⁶², and the inclusion
32
33 239 of women with antepartum depressive mood disorder instead of seasonal affective disorder.

34 240 The SIGH-SAD is a 29-item structured interview, consisting of 21 HAM-D items and 8 atypical items. We
35
36 241 used the entire SIGH-SAD questionnaire as primary measure, since this is the current benchmark for
37
38 242 assessment of depression severity in light therapy trials ⁶³. We chose the original 17-item HAM-D
39
40 243 questionnaire as a secondary measure, since it is more commonly used in clinical practice and research.
41
42 244 Blinded assessors conducted the SIGH-SAD interviews (including HAM-D questions) by telephone
43
44 245 weekly in the intervention period and at follow up.

45 246 The EPDS is a structured 10-item questionnaire and was used as a self-report measure of depression
46
47 247 during pregnancy and postpartum ⁶⁴. Items are scored with a value 0-3, resulting in a sum score of 0-30
48
49 248 ⁶⁴. The EPDS was developed for the detection of postpartum depression, but has been validated for
50
51 249 screening depression during pregnancy as well ⁶⁵. The EPDS was assessed weekly in the intervention
52
53 250 period and at follow up. Participants received a link by e-mail to fill out the questionnaire.

54
55 251

1
2
3 252 *Side effects, acceptability and satisfaction*
4

5 253 During the intervention period, participants were asked weekly about any possible side effects.

6
7 254 Acceptability was assessed by asking participants about their subjective treatment experiences after the
8
9 255 intervention period. Women could choose whether they experienced a negative effect, a small negative
10
11 256 effect, no effect, a small positive effect, or a positive effect. Women were asked how easy or difficult they
12
13 257 could implement the therapy in their daily schedule and how easy or difficult the lamp was in use: very
14
15 258 difficult, difficult, neutral, easy, or very easy. Women could answer whether they found the light therapy
16
17 259 very unpleasant, unpleasant, neutral, pleasant, or very pleasant. Women were asked whether they would
18
19 260 like to use the light therapy outside of the study (yes/no). Finally, women were asked how likely they
20
21 261 would recommend light therapy to others on a scale of 1 to 10.
22
23 262

24 263 *Baseline characteristics*

25
26 264 The baseline interview collected information on various potential confounders, such as
27
28 265 sociodemographic, obstetric, and psychiatric information, and information on somatic conditions (see
29
30 266 Method for further specifications).

31
32 267 The participant's chronotype was assessed at inclusion with the Munich Chronotype Questionnaire
33
34 268 (MCTQ), a structured 19-item self-report questionnaire⁶⁶, since evening types are more prone to
35
36 269 depression compared to morning types^{67,68}. The participant can be classified into one of seven
37
38 270 chronotypes: extremely, moderately or slightly early, normal or slightly, moderately or extremely late. Sum
39
40 271 scores range from 16 to 86, with low scores indicating extremely late chronotypes.
41
42 272

43 273 *Statistical analysis*

44
45 274 Continuous participant characteristics were summarized using mean and standard deviation (SD).
46
47 275 Categorical variables, such as educational level, were summarized by count and percent. In line with the
48
49 276 CONSORT statement, baseline differences between the two treatment arms were not tested⁶⁹.
50
51 277 For treatment effect analyses, we applied an intention-to-treat procedure, since none of the participants
52
53 278 could switch to a different condition, and we included all observations of all participants until the study
54
55 279 ended or the participant(s) dropped out of the study.
56
57
58
59
60

1
2
3 280 The primary outcome was changes in SIGH-SAD rating scale scores over time. Secondary outcomes
4
5 281 were changes in HAM-D and EPDS rating scale scores over time. Analyses were conducted using
6
7 282 general linear mixed modelling analyses. In a series of random-intercept models, we included time
8
9 283 (continuous), allocation, and time x allocation interaction-term as an effect measure of allocation on the
10
11 284 course of depression rating scale scores. The standardized baseline score was included in the model,
12
13 285 since baseline depression severity is an important predictor for treatment outcome⁷⁰. We studied the
14
15 286 treatment effect for both the intervention period and follow-up period (two months postpartum).
16
17 287 Primary analyses were first crude, then adjusted. As adjusted primary analyses, we calculated propensity
18
19 288 scores based on patient characteristics (psychiatric history, ethnicity, level of education, an unplanned
20
21 289 pregnancy, maternal age, parity, gestational age, duration of actual depression, and other psychiatric or
22
23 290 psychotherapeutic treatment interventions). Next, we adjusted separately for chronotype and the month of
24
25 291 treatment. By means of sensitivity analyses, we repeated the primary analyses with last observation
26
27 292 carried forward data imputation. As post-hoc analyses, we repeated the crude analyses for women with
28
29 293 good compliance (<7 missed treatments) and for women with most severe depressive symptomatology
30
31 294 (based on median split baseline SIGH-SAD scores). Effect parameters were supplied with a 95%
32
33 295 confidence interval (CI).
34
35 296 Additionally, we tested responders versus non-responders with Fisher's exact test, where response was
36
37 297 defined as a $\geq 50\%$ decrease to a final score of ≤ 8 on the 17-item HAM-D and ≤ 5 on the EPDS at the end
38
39 298 of the intervention period.
40
41 299 Data was analyzed using SPSS 21.0 (IBM Corporation, Chicago, IL, USA). Statistical significance was
42
43 300 defined as $p < .05$.

301

302 **Results**

303 *Demographic and clinical characteristics*

49 304 In total, 283 women were referred to the study. The majority of the participants (82%) were recruited via
50
51 305 (social) media. Of these referrals, we included and randomized 67 women, with 33 allocated to BLT and
52
53 306 34 to DRLT. In total, eleven women dropped out during the study, of whom five in the BLT group. Ten

1
2
3 307 women dropped out in the intervention period, one at ten weeks after treatment. Figure 1 shows a flow-
4
5 308 chart of the entire study sample.

6
7 309 Table 2 shows the participant characteristics at the time of inclusion. At inclusion, the mean (SD) of the
8
9 310 SIGH-SAD was 26.5 (7.2), of the 17-item HAM-D was 16.9 (5.3) and of the EPDS was 16.1 (4.8). Median
10
11 311 scores were respectively 27, 17 and 16.

12 312 The most common comorbidity was anxiety (25.4%), followed by obsessive compulsive disorder (17.9%),
13
14 313 PTSS (11.9%), and social phobia (11.9%). Various somatic comorbidities were reported, such as asthma,
15
16 314 Guillain-Barré syndrome, and fibromyalgia.

17
18 315 During the course of this study, as part of the care as usual, eleven additional women started with
19
20 316 psychotherapy: three women in the intervention period, one after the intervention period during
21
22 317 pregnancy, and seven in the postpartum period. During the entire study, four additional women started
23
24 318 with psychotropic medication: one woman started with an SSRI in the intervention period and one woman
25
26 319 in the postpartum period (both sertraline), one with an antipsychotic (quetiapine) and one with a
27
28 320 benzodiazepine (temazepam) postpartum. Of one participant, the dose of the SSRI was increased in the
29
30 321 postpartum period (escitalopram).

31
32 322

33 323 *Compliance*

34 324 Self-reported compliance was somewhat higher in the BLT group, compared to the DRLT group. Amongst
35
36 325 the women treated with BLT, eight women (24.2%) never missed a treatment, in contrast to three women
37
38 326 (8.8%) in the DRLT group. Sixteen women (48.5%) treated with BLT missed a maximum of six
39
40 327 treatments, compared to twenty women (58.9%) in the DRLT group. In both groups, two women missed
41
42 328 seven to thirteen treatments in the intervention period. One woman treated with BLT and two with DRLT
43
44 329 missed fourteen or more treatments. One woman treated with BLT and two with DRLT missed the final
45
46 330 two weeks of treatment, the first one due to complete remission of her symptoms.

47
48 331

49 332 *Maintaining blinding*

50
51 333 Before treatment, three women (4.8%) did not expect any effect from light therapy for their depressive
52
53 334 symptoms. All other participants expected a (small) positive effect. After treatment, one participant treated
54
55
56
57
58
59
60

1
2
3 335 with BLT (3.0%) and three women in the group treated with DRLT (8.8%) thought they were treated with
4
5 336 placebo treatment. All other women had no specific ideas about their allocation.
6

7 337

8
9 338 *Treatment effect*

10
11 339 Supplementary Table 2 shows the observed median SIGH-SAD, HAM-D, and EPDS scores over the
12
13 340 course of the study. In the women treated with BLT, median depression scores decreased by 42.6%
14
15 341 (SIGH-SAD), 53.1% (HAM-D), and 40.6% (EPDS) in the intervention period. In the DRLT group, this was
16
17 342 respectively 50.9%, 66.7%, and 59.4%. After women stopped with light treatment, median scores
18
19 343 continued to decrease for all questionnaires in both groups, three and ten weeks after treatment. At two
20
21 344 months postpartum, women treated with BLT showed no increase in EPDS scores, whereas women
22
23 345 treated with DRLT showed an increase in EPDS-scores. For both SIGH-SAD and HAM-D scores, a
24
25 346 decrease was observed in both treatment arms.

26 347 We also calculated the median improvement scores without the baseline score. For women treated with
27
28 348 BLT, these were 6.1% (SIGH-SAD), 16.7% (HAM-D), and 13.6% (EPDS). For women treated with DRLT,
29
30 349 this was respectively 31.6%, 40%, and 45.8%.

31
32 350 No statistically significant difference was found between the two treatment arms for the intervention
33
34 351 period, nor for the entire study. For the SIGH-SAD, our primary endpoint, we found $\beta=-0.68$ (95% CI -
35
36 352 1.84, 0.49) for the intervention period and $\beta=-0.16$ (95% CI -0.82, 0.51) for the entire study (Figure 2 and
37
38 353 Table 3). Adjusted primary analyses, where we repeated our primary analyses adjusted for propensity
39
40 354 scores, and sensitivity analyses with imputed data did not show any other findings (Supplementary Table
41
42 355 3). Adjustment for chronotype and month of treatment did not change our findings as well. Post-hoc
43
44 356 analyses, where we repeated the analyses for women with higher treatment compliance and for women
45
46 357 with higher symptom severity at baseline, did not show a statistically significant difference between the
47
48 358 two treatment arms (Supplementary Table 3).

49 359 For the HAM-D, 13 participants in the BLT group and 17 participants in the DRLT group were considered
50
51 360 responders. This was respectively 11 and 9 when measured with the EPDS. When we studied
52
53 361 responders versus non-responders, we found no statistically significant differences for both HAM-D
54
55 362 scores ($p=.46$) and EPDS scores ($p=.60$).

1
2
3 3634
5 364 *Side effects*

6
7 365 For women treated with BLT, the most frequently reported side effect was headaches (30.3%), followed
8
9 366 by sleep problems (12.1%) and nausea (6.1%). For women treated with DRLT, the most reported side
10
11 367 effect was headaches (20.6%), followed by sleep problems (8.9%) and irritable eyes (5.9%). Side effects
12
13 368 were not reported more often by women treated with BLT, compared to DRLT ($p=0.52$). Most side effects
14
15 369 were experienced for a maximum of three days. None of the women suffered from any (hypo)manic
16
17 370 symptoms. We reduced the treatment duration for five women to 20 minutes daily due to their side
18
19 371 effects. Interestingly, two women dropped out of the study due to side effects, but only in the DRLT group.

20 372

21
22 373 *Acceptability and satisfaction*

23
24 374 The majority of women experienced a (small) positive effect for their depressive symptoms (78.6% BLT;
25
26 375 61.5% DRLT; $p=0.58$). All participants found the lamp (very) easy in use. Most women found the light
27
28 376 therapy pleasant (57.1% BLT; 50% DRLT; $p=0.49$). Twenty-six women reported that it was (very) easy to
29
30 377 plan the light therapy in the morning (42.9% BLT; 53.8% DRLT; $p=0.43$). Thirty-two women reported that
31
32 378 they would like to use light therapy outside of the study (57.1% BLT; 61.5% DRLT; $p=0.79$). On average,
33
34 379 women reported it was likely they would recommend the light therapy to others (BLT mean 8.0, SD 1.3;
35
36 380 DRLT mean 7.0, SD 2.7; $p=0.08$).

37 381

38
39 382 **Discussion**

40
41 383 We conducted a randomized controlled trial, evaluating the effectiveness of BLT in a sample of 67
42
43 384 pregnant women with major depressive disorder, compared to DRLT. We found no statistically significant
44
45 385 difference between BLT and DRLT on depressive symptoms. Median depression scores decreased by
46
47 386 40.6-53.1% during the intervention in the women treated with BLT and by 50.9-66.7% in the women
48
49 387 treated by DRLT.

50 388

51
52
53 389 *Effects in the current study*

1
2
3 390 This level of improvement is comparable to the studies by Oren *et al.*⁵¹ and Corral *et al.*⁷¹ who both
4
5 391 found a reduction in mean depression scores of 49%. Oren *et al.* conducted an open trial in an
6
7 392 antepartum population, whereas Corral *et al.* conducted a randomized controlled trial among women with
8
9 393 a postpartum depression. Similar to Corral *et al.*, we did not find a statistically significant difference
10
11 394 between the effective and placebo conditions. The median improvement in the DRLT group can be
12
13 395 explained by placebo effects, which could also be the case in the BLT group. A meta-analysis showed
14
15 396 that the placebo response in antidepressant trials is approximately 68%⁷², although this effect is not clear
16
17 397 yet in light therapy trials specifically. Secondly, the improvement in both groups can be explained by non-
18
19 398 specific treatment effects such the structure offered by the study⁴³, the interaction with the researchers,
20
21 399 or increased awareness and self-care resulting from participating in the study. A systematic review on
22
23 400 various studies in treating antepartum depression with a control condition showed that these trials often
24
25 401 show a considerable reduction in symptom scores in both treatment arms³⁹. Furthermore, it might be that
26
27 402 symptoms decrease related to the course of pregnancy, spontaneous remission, or regression to the
28
29 403 mean. A meta-analysis showed that untreated depressive symptoms could decrease by 10-15%, on
30
31 404 average⁷³. However, untreated depression during pregnancy is an important predictor for postpartum
32
33 405 depression⁷⁴. We calculated the improvement of the depressive symptoms without the baseline scores,
34
35 406 to study whether the improvement was especially notable in the first week of treatment. We found that the
36
37 407 improvement was less, especially in the group treated with BLT, which may pinpoint to regression to the
38
39 408 mean. For example, women may have the feeling of 'finally being heard', or feeling empowered about
40
41 409 doing something about their symptoms, which may explain these findings.
42
43 410 Corral *et al.* mentioned that several participants commented positively on having 30 minutes of "quiet
44
45 411 time" on a daily basis. Several of our participants mentioned this as well, which could reflect sinking into a
46
47 412 state of more relaxation or more mindfulness which may have contributed to the improvement in both
48
49 413 groups. Two meta-analyses showed that mindfulness-based therapy is an effective treatment for a variety
50
51 414 of psychological problems^{75,76}. An earlier pilot study and an open study of mindfulness also showed
52
53 415 positive effects on mood specifically in pregnant women^{77,78}. Corral *et al.* mentioned that many
54
55 416 postpartum women are motivated to access recourses, such as psychological treatment, which could
56
57 417 have exerted non-specific treatment effects. In their study however, no participant took part in any

1
2
3 418 treatment during the study. In our study, several women started psychotherapy or antidepressant
4
5 419 medication. However, adjustment for any intervention did however not change our findings.
6
7 420 Finally, it has been shown earlier in healthy volunteers that treatment with similar conditions as our
8
9 421 placebo therapy might actually have some effects in melatonin suppression ⁷⁹, which could explain why
10
11 422 we actually see a decrease of symptoms in the DRLT group.
12
13 423

14 424 *Differences with literature*

15
16 425 The results of this study differ from the randomized controlled trials by Epperson *et al.* ⁵² and Wirz-Justice
17
18 426 *et al.* ⁵³, who did find superiority of bright light therapy over placebo in an antepartum population.
19
20 427 Wirz-Justice *et al.* included only clinical patients and found that BLT had more effects in severe patients in
21
22 428 their study. However, mean baseline SIGH-SAD score in the Wirz-Justice *et al.* and Epperson *et al.*
23
24 429 studies were 27.7 and 28.1, respectively, which were not clinically relevant different from the present
25
26 430 study (26.5). Additionally, we included baseline depression scores in our model, which did not change our
27
28 431 findings. Also, post-hoc analyses, where we repeated the analyses for women with higher baseline
29
30 432 severity, did not show any significant findings.

31
32 433 Both Epperson *et al.* and Wirz-Justice *et al.* treated their patients for 1 hour a day and within 10 minutes
33
34 434 of habitual wake-up time, which is different from the present study. Thus far, no studies have been
35
36 435 executed comparing the effectiveness of shorter versus longer exposure to bright light in non-seasonal
37
38 436 depression. Possibly, more light output in the BLT group would be necessary to show superiority of BLT
39
40 437 over DRLT in a pregnant population. However, other studies that treated patients for 30 minutes also did
41
42 438 show a statistical significant difference between the effective and the placebo intervention in non-
43
44 439 seasonal depression ⁴⁶. One must keep in mind that these studies have been done in non-pregnant
45
46 440 populations and different – yet unknown – underlying mechanisms may play a part during pregnancy,
47
48 441 such as hormonal fluctuations and a shift in social role.

49 442 Our placebo condition, in which the possible effect of DRLT could be questioned, is not a plausible
50
51 443 explanation for not finding a statistically significant effect between the treatment arms. Epperson *et al.*
52
53 444 used a placebo condition with 500 lux white light, which is questionable as a placebo, for white light of
54
55 445 100 lux is able to phase-shift human circadian rhythms ⁸⁰. Since this study found a significant

1
2
3 446 improvement in women treated with BLT when compared to this placebo, it is unlikely that the settings of
4
5 447 our placebo would explain failing to achieve a significant difference between the two treatment arms.
6
7 448 In the study by Corral *et al.*, depression scores worsened after withdrawal of treatment, indicating that
8
9 449 spontaneous remission would be less likely. However, in the present study, median depression scores of
10
11 450 all questionnaires continued to improve after withdrawal of treatment in both groups, indicating that
12
13 451 spontaneous remission in both groups is a possible explanation for this finding.
14

15 452

16 453 *Strengths and limitations*

17
18 454 Internationally, we conducted the largest randomized controlled trial studying light therapy in pregnant
19
20 455 women with a depression. Moreover, we conducted various follow up measurements, including
21
22 456 postpartum, to study the effects of withdrawal of treatment and to study whether treatment during
23
24 457 pregnancy would protect against postpartum depression. Another strength is using a single assessor to
25
26 458 diagnose depression. Moreover, the setting of treatment was within a real world setting. Finally, a
27
28 459 strength of this study was the comprehensive assessment of side effects, as well as acceptability and
29
30 460 satisfaction of treatment.

31
32 461 The main limitation of our study was that an unforeseen lack of resources prevented us from including
33
34 462 150 participants, as we aimed to do according to our sample size calculation⁵⁵, which enables us to find
35
36 463 only large treatment effects⁵⁵. Another limitation is the fact that depressive symptoms during the study
37
38 464 are assessed by questionnaires, rather than diagnostic criteria. Also, information about psychiatric history
39
40 465 was collected via an interview and not through medical records, which may be influenced by recall bias.
41
42 466 Moreover, various covariates are self-reported, such as BMI, substance use and medication. We noticed
43
44 467 a different attrition rate at T3 (10 weeks after treatment) and P1 (2 months postpartum). At T3, this is due
45
46 468 to the fact that more women treated with DRLT already gave birth at T3, which resulted in missing data.
47
48 469 We do not have an explanation for the different attrition rate at P1. We cannot rule out the possibility that
49
50 470 these differences in attrition might have impacted our follow-up results. However, our sensitivity analyses
51
52 471 indicate our follow-up results to be robust for differences between the conditions and data imputation.

53 472

54 473 *Conclusions*

1
2
3 474 BLT has been shown effective in treating non-seasonal depression ⁴⁶ and in women with antepartum
4
5 475 depression as well ^{52,53}. In the present study, depressive symptoms of pregnant women with depression
6
7 476 improved in both treatment arms after 6 weeks of treatment. Given the very mild and short-lived side
8
9 477 effects, the major improvement in a short time period, the high acceptability of the participants, the low
10
11 478 costs, and the direct availability, more studies to the effectiveness of BLT during pregnancy are
12
13 479 warranted. It is important to determine whether the responses observed in the present study represent
14
15 480 true treatment effects, non-specific treatment responses, placebo effects, or a combination of these. This
16
17 481 could be done by studying biological outcomes, such as cortisol and melatonin levels, which might show
18
19 482 a statistically significant difference between the two treatment arms irrespective of perceived symptoms of
20
21 483 depression. Additionally, it might show an indication of the positive effects of light therapy on the circadian
22
23 484 rhythm and its inhibiting effects on HPA-axis hyperactivity.
24
25

26 486 **Acknowledgements**

27
28 487 We would like to thank all participants for participating in the study. We would also like to thank all general
29
30 488 practitioners, midwives, gynaecologists, psychiatrists and psychologists for their help with the recruitment.
31
32 489 We are grateful for all co-workers, students and assistants who contributed to the data collection in this
33
34 490 study: Nina Molenaar, PhD, Marlies Brouwer, PhD, Leo Genet, MSc, Sophie de Droog, MSc, Sofie
35
36 491 Koomen, MSc, Diewertje Houtman, MSc, Maria Zepeda, MSc, Nicolle Croes, MSc, Rianne Winters, MSc.
37
38 492 Lisanne van Kesteren, BSc, Finn Stofkoper, BSc, Indira Schouten, MSc and Mieke Roukema, MSc.
39
40 493

41 494 **Funding**

42
43 495 MLB received funding from the 'Light, Cognition, Behaviour and Health' program of The Netherlands
44
45 496 Organization for Health Research and Development (NWO; The Hague, The Netherlands), in
46
47 497 collaboration with Signify Research (grant number 058-14-003) to fund the current study.
48
49 498

50 51 499 **Competing interests**

52
53 500 Author JS is employed by Signify Research. The lamps used in this study were provided by Signify
54
55 501 Research.
56
57
58
59
60

1
2
3 502
45 503 **Author's contributions**

6
7 504 MLB is the project's principle investigator and initiator of the study, obtained funding and designed the
8
9 505 study. BB was responsible for recruiting and counselling participants, running the study and collecting
10
11 506 data. AK is the project's methodologist and executed the primary statistical analysis. HB and EK were
12
13 507 involved in the recruitment of the study. JS provided support. AK, WH and MLB supervised the study. BB,
14
15 508 AK and MLB prepared the original draft. All authors reviewed, edited and approved the final manuscript.

16 509
1718 510 **Data availability statement**

19
20 511 The datasets used and/or analysed during the current study are available from the corresponding author
21
22 512 MLB on reasonable request.

23
24 513
2526 514 **Word count**27
28 515 5,608
2930 516
3132 517 **References**

- 33
34 518 1. Woody CA, Ferrari AJ, Siskind DJ, Whiteford HA, Harris MG. A systematic review and meta-
35
36 519 regression of the prevalence and incidence of perinatal depression. *J Affect Disord* 2017; **219**: 86-92.
37
38 520 2. Bais B, de Groot N, Grootendorst-van Mil NH, et al. Seasonality of depressive symptoms during
39
40 521 pregnancy. *Psychiatry Res* 2018; **268**: 257-62.
41
42 522 3. Lancaster CA, Gold KJ, Flynn HA, Yoo H, Marcus SM, Davis MM. Risk factors for depressive
43
44 523 symptoms during pregnancy: a systematic review. *Am J Obstet Gynecol* 2010; **202**(1): 5-14.
45
46 524 4. Räisänen S, Lehto SM, Nielsen HS, Gissler M, Kramer MR, Heinonen S. Risk factors for and
47
48 525 perinatal outcomes of major depression during pregnancy: a population-based analysis during 2002-2010
49
50 526 in Finland. *BMJ Open* 2014; (11): DOI:10.1136/bmjopen-2014-004883.
51
52 527 5. Seth S, Lewis AJ, Galbally M. Perinatal maternal depression and cortisol function in pregnancy
53
54 528 and the postpartum period: a systematic literature review. *BMC Pregnancy Childbirth* 2016; **16**(1): 124.
55
56
57
58
59
60

- 1
2
3 529 6. Leff-Gelman P, Mancilla-Herrera I, Flores-Ramos M, et al. The Immune System and the Role of
4
5 530 Inflammation in Perinatal Depression. *Neurosci Bull* 2016; **32**(4): 398-420.
6
7 531 7. Osborne LM, Monk C. Perinatal depression--the fourth inflammatory morbidity of pregnancy?:
8
9 532 Theory and literature review. *Psychoneuroendocrinology* 2013; **38**(10): 1929-52.
10
11 533 8. Milgrom J, Gemmill AW, Bilszta JL, et al. Antenatal risk factors for postnatal depression: a large
12
13 534 prospective study. *J Affect Disord* 2008; **108**: 147-57.
14
15 535 9. Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression
16
17 536 during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Arch*
18
19 537 *Gen Psychiatry* 2010; **67**(10): 1012-24.
20
21 538 10. Jarde A, Morais M, Kingston D, et al. Neonatal outcomes in women with untreated antenatal
22
23 539 depression compared with women without depression: a systematic review and meta-analysis. *JAMA*
24
25 540 *Psychiatry* 2016; DOI:10.1001/jamapsychiatry.2016.0934.
26
27 541 11. Talge NM, Neal C, Glover V, the Early Stress, Translational Research and Prevention Science
28
29 542 Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health. Antenatal maternal
30
31 543 stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry* 2007;
32
33 544 **48**(3-4): 245-61.
34
35 545 12. Hentges RF, Graham SA, Plamondon A, Tough S, Madigan S. A Developmental Cascade from
36
37 546 Prenatal Stress to Child Internalizing and Externalizing Problems. *J Pediatr Psychol* 2019.
38
39 547 13. Pearson RM, Evans J, Kounali D, et al. Maternal depression during pregnancy and the postnatal
40
41 548 period: risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* 2013;
42
43 549 **70**(12): 1312-9.
44
45 550 14. Glover V, O'Connor TG, O'Donnell K. Prenatal stress and the programming of the HPA axis.
46
47 551 *Neurosci Biobehav Rev* 2010; **35**(1): 17-22.
48
49 552 15. Dierckx B, Tulen JH, van den Berg MP, et al. Maternal psychopathology influences infant heart
50
51 553 rate variability: Generation R Study. *Psychosom Med* 2009; **71**(3): 313-21.
52
53 554 16. Goedhart G, Vrijkotte TG, Roseboom TJ, van der Wal MF, Cuijpers P, Bonsel GJ. Maternal
54
55 555 cortisol and offspring birthweight: results from a large prospective cohort study.
56
57
58
59
56 556 *Psychoneuroendocrinology* 2010; **35**(5): 644-52.

- 1
2
3 557 17. Henrichs J, Schenk JJ, Roza SJ, et al. Maternal psychological distress and fetal growth
4
5 558 trajectories: the Generation R Study. *Psychol Med* 2010; **40**(4): 633-43.
6
7 559 18. Zijlmans MA, Riksen-Walraven JM, de Weerth C. Associations between maternal prenatal cortisol
8
9 560 concentrations and child outcomes: A systematic review. *Neurosci Biobehav Rev* 2015; **53**: 1-24.
10
11 561 19. Steegers EA, Barker ME, Steegers-Theunissen RP, Williams MA. Societal Valorisation of New
12
13 562 Knowledge to Improve Perinatal Health: Time to Act. *Paediatr Perinat Epidemiol* 2016; **30**(2): 201-4.
14
15 563 20. Byatt N, Deligiannidis KM, Freeman MP. Antidepressant use in pregnancy: a critical review
16
17 564 focused on risks and controversies. *Acta Psychiatr Scand* 2013; **127**(2): 94-114.
18
19 565 21. Hanley GE, Oberlander TF. The effect of perinatal exposures on the infant: antidepressants and
20
21 566 depression. *Best Pract Res Clin Obstet Gynaecol* 2014; **28**(1): 37-48.
22
23 567 22. Kieler H, Artama M, Engeland A, et al. Selective serotonin reuptake inhibitors during pregnancy
24
25 568 and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five
26
27 569 Nordic countries. *BMJ* 2012; **344**: d8012.
28
29 570 23. Simoncelli M, Martin BZ, Berard A. Antidepressant use during pregnancy: a critical systematic
30
31 571 review of the literature. *Curr Drug Saf* 2010; **5**(2): 153-70.
32
33 572 24. Battle CL, Salisbury AL, Schofield CA, Ortiz-Hernandez S. Perinatal antidepressant use:
34
35 573 understanding women's preferences and concerns. *J Psychiatr Pract* 2013; **19**(6): 443-53.
36
37 574 25. Kothari A, de Laat J, Dulhunty JM, Bruxner G. Perceptions of pregnant women regarding
38
39 575 antidepressant and anxiolytic medication use during pregnancy. *Australas Psychiatry* 2019; **27**(2): 117-
40
41 576 20.
42
43 577 26. Molenaar NM, Brouwer ME, Duvekot JJ, et al. Antidepressants during pregnancy: Guideline
44
45 578 adherence and current practice amongst Dutch gynaecologists and midwives. *Midwifery* 2018; **61**: 29-35.
46
47 579 27. Molenaar NM, Kamperman AM, Boyce P, Bergink V. Guidelines on treatment of perinatal
48
49 580 depression with antidepressants: An international review. *Aust N Z J Psychiatry* 2018; **52**(4): 320-7.
50
51 581 28. Bakker MK, Kolling P, van den Berg PB, de Walle HE, de Jong van den Berg LT. Increase in use
52
53 582 of selective serotonin reuptake inhibitors in pregnancy during the last decade, a population-based cohort
54
55 583 study from the Netherlands. *Br J Clin Pharmacol* 2008; **65**(4): 600-6.
56
57
58
59
60

- 1
2
3 584 29. Molenaar NM, Lambregtse-van den Berg MP, Bonsel GJ. Dispensing patterns of selective
4
5 585 serotonin reuptake inhibitors before, during and after pregnancy: a 16-year population-based cohort study
6
7 586 from the Netherlands. *Arch Womens Ment Health* 2019.
- 8
9 587 30. Charlton RA, Jordan S, Pierini A, et al. Selective serotonin reuptake inhibitor prescribing before,
10
11 588 during and after pregnancy: a population-based study in six European regions. *Bjog-Int J Obstet Gy* 2015;
12
13 589 **122**(7): 1010-20.
- 14
15 590 31. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy.
16
17 591 *American Journal of Obstetrics and Gynecology* 2007; **196**(6): 544-5.
- 18
19 592 32. Jimenez-Solem E, Andersen JT, Petersen M, et al. Prevalence of Antidepressant Use during
20
21 593 Pregnancy in Denmark, a Nation-Wide Cohort Study. *Plos One* 2013; **8**(4).
- 22
23 594 33. van Gelder MMHJ, Bos JHJ, Roeleveld N, de Jong-van den Berg LTW. Drugs associated with
24
25 595 teratogenic mechanisms. Part I: dispensing rates among pregnant women in the Netherlands, 1998-2009.
26
27 596 *Hum Reprod* 2014; **29**(1): 161-7.
- 28
29 597 34. Ververs T, Kaasenbrood H, Visser G, Schobben F, de Jong-van den Berg L, Egberts T.
30
31 598 Prevalence and patterns of antidepressant drug use during pregnancy. *Eur J Clin Pharmacol* 2006;
32
33 599 **62**(10): 863-70.
- 34
35 600 35. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to
36
37 601 identify and estimate critical periods in pregnancy: An application to antidepressants. *Birth Defects Res A*
38
39 602 *Clin Mol Teratol* 2016; **106**(11): 927-34.
- 40
41 603 36. Andrade SE, Reichman ME, Mott K, et al. Use of selective serotonin reuptake inhibitors (SSRIs)
42
43 604 in women delivering liveborn infants and other women of child-bearing age within the U.S. Food and Drug
44
45 605 Administration's Mini-Sentinel program. *Arch Womens Ment Health* 2016; **19**(6): 969-77.
- 46
47 606 37. Taylor LG, Thelus Jean R, Gordon G, Fram D, Coster T. Development of a mother-child database
48
49 607 for drug exposure and adverse event detection in the Military Health System. *Pharmacoepidemiol Drug*
50
51 608 *Saf* 2015; **24**(5): 510-7.
- 52
53 609 38. Hanley GE, Mintzes B. Patterns of psychotropic medicine use in pregnancy in the United States
54
55 610 from 2006 to 2011 among women with private insurance. *BMC Pregnancy Childbirth* 2014; **14**: 242.

- 1
2
3 611 39. van Ravesteyn LM, Lambregtse-van den Berg MP, Hoogendijk WJ, Kamperman AM.
4
5 612 Interventions to treat mental disorders during pregnancy: A systematic review and multiple treatment
6
7 613 meta-analysis. *PLoS One* 2017; **12**(3): e0173397.
8
9 614 40. Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and
10
11 615 mood. *Somnologie* 2019.
12
13 616 41. LeGates TA, Fernandez DC, Hattar S. Light as a central modulator of circadian rhythms, sleep
14
15 617 and affect. *Nature Reviews Neuroscience* 2014; **15**(7): 443-54.
16
17 618 42. Prayag AS, Münch M, Aeschbach D, Chellappa SL, Gronfier C. Light modulation of human
18
19 619 clocks, wake and sleep. *Clocks & Sleep* 2019; **1**: 193-208.
20
21 620 43. Germain A, Kupfer DJ. Circadian rhythm disturbances in depression. *Hum Psychopharmacol*
22
23 621 2008; **23**(7): 571-85.
24
25 622 44. Lam RW, Levitan RD. Pathophysiology of seasonal affective disorder: a review. *J Psychiatry*
26
27 623 *Neurosci* 2000; **25**(5): 469-80.
28
29 624 45. Magnusson A, Boivin D. Seasonal affective disorder: an overview. *Chronobiol Int* 2003; **20**(2):
30
31 625 189-207.
32
33 626 46. Tuunainen A, Kripke DF, Endo T. Light therapy for non-seasonal depression. *Cochrane Database*
34
35 627 *Syst Rev* 2004.
36
37 628 47. Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood
38
39 629 disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; **162**(4): 656-62.
40
41 630 48. Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical
42
43 631 trials. *J Affect Disord* 2016; **198**: 64-71.
44
45 632 49. Perera S, Eisen R, Bhatt M, et al. Light therapy for non-seasonal depression: systematic review
46
47 633 and meta-analysis. *BJPsych Open* 2016; **2**(2): 116-26.
48
49 634 50. Martensson B, Pettersson A, Berglund L, Ekselius L. Bright white light therapy in depression: A
50
51 635 critical review of the evidence. *J Affect Disord* 2015; **182**: 1-7.
52
53 636 51. Oren DA, Wisner KL, Spinelli M, et al. An open trial of morning light therapy for treatment of
54
55 637 antepartum depression. *Am J Psychiatry* 2002; **159**(4): 666-9.
56
57
58
59
60

- 1
2
3 638 52. Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for
4
5 639 antepartum depression: preliminary findings. *J Clin Psychiatry* 2004; **65**(3): 421-5.
6
7 640 53. Wirz-Justice A, Bader A, Frisch U, et al. A randomized, double-blind, placebo-controlled study of
8
9 641 light therapy for antepartum depression. *J Clin Psychiatry* 2011; **72**(7): 986-93.
10
11 642 54. Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; **2**(8): e124.
12
13 643 55. Bais B, Kamperman AM, van der Zwaag MD, et al. Bright light therapy in pregnant women with
14
15 644 major depressive disorder: study protocol for a randomized, double-blind, controlled clinical trial. *BMC*
16
17 645 *Psychiatry* 2016; **16**(1): 381.
18
19 646 56. First MB GM, Spitzer RL, Williams JBW. User's guide for the SCID-I. Structured clinical interview
20
21 647 for DSM-IV TR axis I disorders (research version). New York: New York Psychiatric Institute; 2002.
22
23 648 57. Lieveise R, Van Someren EJ, Nielen MM, Uitdehaag BM, Smit JH, Hoogendijk WJ. Bright light
24
25 649 treatment in elderly patients with nonseasonal major depressive disorder: a randomized placebo-
26
27 650 controlled trial. *Arch Gen Psychiatry* 2011; **68**(1): 61-70.
28
29 651 58. Kreidler SM, Muller KE, Grunwald GK, et al. GLIMPSE: Online Power Computation for Linear
30
31 652 Models with and without a Baseline Covariate. *J Stat Softw* 2013; **54**(10).
32
33 653 59. Meesters Y, Dekker V, Schlangen LJ, Bos EH, Ruiter MJ. Low-intensity blue-enriched white light
34
35 654 (750 lux) and standard bright light (10,000 lux) are equally effective in treating SAD. A randomized
36
37 655 controlled study. *BMC Psychiatry* 2011; **11**: 17.
38
39 656 60. Project TAI. ALEA Randomisation Software (Version 2.2). Amsterdam: Netherlands Cancer
40
41 657 Institute; 2006. p. <http://tenalea.net/>.
42
43 658 61. Bockting CL, Hollon SD, Jarrett RB, Kuyken W, Dobson K. A lifetime approach to major
44
45 659 depressive disorder: The contributions of psychological interventions in preventing relapse and
46
47 660 recurrence. *Clin Psychol Rev* 2015; **41**: 16-26.
48
49 661 62. Williams JBW LM, Rosenthal NE, Amira L, Terman M. Structured Interview Guide for the
50
51 662 Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD). New York: New
52
53 663 York Psychiatric Institute; 1988.
54
55
56
57
58
59
60

- 1
2
3 664 63. Pjrek E, Friedrich ME, Cambioli L, et al. The Efficacy of Light Therapy in the Treatment of
4
5 665 Seasonal Affective Disorder: A Meta-Analysis of Randomized Controlled Trials. *Psychother Psychosom*
6
7 666 2020; **89**(1): 17-24.
- 8
9 667 64. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item
10
11 668 Edinburgh Postnatal Depression Scale. *Br J Psychiatry* 1987; **150**: 782-6.
- 12
13 669 65. Bergink V, Kooistra L, Lambregtse-van den Berg MP, et al. Validation of the Edinburgh
14
15 670 Depression Scale during pregnancy. *J Psychosom Res* 2011; **70**(4): 385-9.
- 16
17 671 66. Roenneberg T, Wirz-Justice A, Mellow M. Life between clocks: daily temporal patterns of human
18
19 672 chronotypes. *J Biol Rhythms* 2003; **18**(1): 80-90.
- 20
21 673 67. Merikanto I, Kronholm E, Peltonen M, Laatikainen T, Vartiainen E, Partonen T. Circadian
22
23 674 preference links to depression in general adult population. *J Affect Disord* 2015; **188**: 143-8.
- 24
25 675 68. Merikanto I, Lahti T, Kronholm E, et al. Evening types are prone to depression. *Chronobiol Int*
26
27 676 2013; **30**(5): 719-25.
- 28
29 677 69. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 Statement: updated guidelines for
30
31 678 reporting parallel group randomised trials. *BMC Med* 2010; **8**: 18.
- 32
33 679 70. Friedman ES, Davis LL, Zisook S, et al. Baseline depression severity as a predictor of single and
34
35 680 combination antidepressant treatment outcome: results from the CO-MED trial. *Eur*
36
37 681 *Neuropsychopharmacol* 2012; **22**(3): 183-99.
- 38
39 682 71. Corral M, Wardrop AA, Zhang H, Grewal AK, Patton S. Morning light therapy for postpartum
40
41 683 depression. *Arch Womens Ment Health* 2007; **10**(5): 221-4.
- 42
43 684 72. Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo
44
45 685 response in antidepressant trials. *J Affect Disord* 2009; **118**(1-3): 1-8.
- 46
47 686 73. Posternak MA, Miller I. Untreated short-term course of major depression: a meta-analysis of
48
49 687 outcomes from studies using wait-list control groups. *J Affect Disord* 2001; **66**(2-3): 139-46.
- 50
51 688 74. Yazici E, Kirkan TS, Aslan PA, Aydin N, Yazici AB. Untreated depression in the first trimester of
52
53 689 pregnancy leads to postpartum depression: high rates from a natural follow-up study. *Neuropsychiatr Dis*
54
55 690 *Treat* 2015; **11**: 405-11.

- 1
2
3 691 75. Khoury B, Lecomte T, Fortin G, et al. Mindfulness-based therapy: a comprehensive meta-
4
5 692 analysis. *Clin Psychol Rev* 2013; **33**(6): 763-71.
6
7 693 76. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and
8
9 694 depression: A meta-analytic review. *J Consult Clin Psychol* 2010; **78**(2): 169-83.
10
11 695 77. Dimidjian S, Goodman SH, Felder JN, Gallop R, Brown AP, Beck A. An open trial of mindfulness-
12
13 696 based cognitive therapy for the prevention of perinatal depressive relapse/recurrence. *Arch Womens*
14
15 697 *Ment Health* 2015; **18**(1): 85-94.
16
17 698 78. Vieten C, Astin J. Effects of a mindfulness-based intervention during pregnancy on prenatal
18
19 699 stress and mood: results of a pilot study. *Arch Womens Ment Health* 2008; **11**(1): 67-74.
20
21 700 79. Nagare R, Plitnick B, Figueiro MG. Effect of exposure duration and light spectra on nighttime
22
23 701 melatonin suppression in adolescents and adults. *Light Res Technol* 2019; **51**(4): 530-43.
24
25 702 80. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C. Sensitivity of the human circadian
26
27 703 pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol* 2000; **526 Pt 3**: 695-
28
29 704 702.

30
31
32 706 **Table 1.** Inclusion and exclusion criteria for the Bright Up Study.

Inclusion criteria	Women
	18-45 years of age
	12-32 weeks pregnant (as confirmed by ultrasound)
	Current DSM-5 diagnosis of depressive disorder (as assessed by the SCID*)
Exclusion criteria	Insufficient proficiency in Dutch or English
	Multiple pregnancy
	Current use of antidepressants shorter than 2 months
	Lifetime diagnosis of bipolar I or II disorder
	Any psychotic episode
	Current substance abuse
	Current primary anxiety disorder

Recent history of suicide attempt

Current shift-work

Somatic and/or obstetric conditions that override study participation

Previous treatment with BLT

Eye condition (macular degeneration, eye diseases, recent eye surgery)

707 * SCID = Structured Clinical Interview for DSM disorders

708

709 **Table 2.** Overview of participant characteristics at inclusion.

	BLT (n=33)	DRLT (n=34)
Age in years, mean (SD)	31.9 (4.4)	31.9 (5.3)
Gestational age in weeks, mean (SD)	20.6 (6.2)	19.7 (6.3)
Ethnicity		
Dutch	27 (81.8%)	26 (76.5%)
Other	6 (19.2%)	8 (33.5%)
Marital status		
Married or cohabiting	33 (100%)	32 (94.1%)
Committed relationship, not cohabiting	0 (0%)	1 (2.9%)
Single	0 (0%)	1 (2.9%)
Education		
Elementary or (pre-)vocational education	11 (33.3%)	13 (38.2%)
Higher professional education	8 (24.2%)	11 (32.4%)
(Pre-) academic education	14 (42.4%)	10 (29.4%)
Parity		
Nulliparous	15 (45.5%)	20 (58.8%)
Primiparous	13 (39.4%)	9 (26.5%)
Multiparous	5 (15.2%)	5 (14.7%)
BMI in kg/m² or st/ft², mean (SD)	25.5 (4.5)	26.3 (5.4)

Planned pregnancy	22 (66.7%)	22 (64.7%)
Antidepressant medication	3 (9.1%)	5 (14.7%)
Sleep medication	3 (9.1%)	2 (5.9%)
Psychotherapy	14 (48.5%)	16 (47.1%)
Comorbidities		
0	17 (51.5%)	13 (38.2%)
1	9 (27.3%)	13 (38.2%)
>1	7 (21.2%)	8 (23.5%)
Duration of depression in weeks, mean (SD)	24.6 (16.9)	45.1 (121.9)
Depressive episodes in past		
0	12 (36.4%)	11 (32.4%)
1	9 (27.2%)	14 (41.2%)
>1	12 (36.4%)	9 (26.5%)
Chronotype		
Early (extremely, moderately and slightly)	20 (80%)	25 (92.6%)
Normal	1 (4%)	1 (3.7%)
Late (extremely, moderately and slightly)	4 (16%)	1 (3.7%)

710 BLT = bright light therapy; DRLT = dim red light therapy

711

712 **Table 3.** Effects of allocation on the course of depressive symptoms through the intervention period and
 713 follow-up (until two months postpartum): crude analysis.

	β (95% CI) of intervention*	β (95% CI) of follow-up**
SIGH-SAD	-0.68 (-1.84, 0.49)	-0.16 (-0.82, 0.51)
HAM-D	-0.18 (-0.74, 0.37)	0.04 (-0.29, 0.37)
EPDS	0.01 (-0.51, 0.53)	-0.05 (-0.35, 0.24)

714 * From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum

715

716 **Figure legends**

1
2
3 717 **Figure 1.** Flow-chart of the Bright Up study.
4

5 718 **Figure 2.** Estimated marginal means of depression scores in women with antepartum depression until
6

7 719 two months postpartum. Shown are SIGH-SAD, HAM-D and EPDS scores. Black lines represent
8

9 720 treatment with BLT, gray lines with DRLT. Bars represent standard error of the mean.

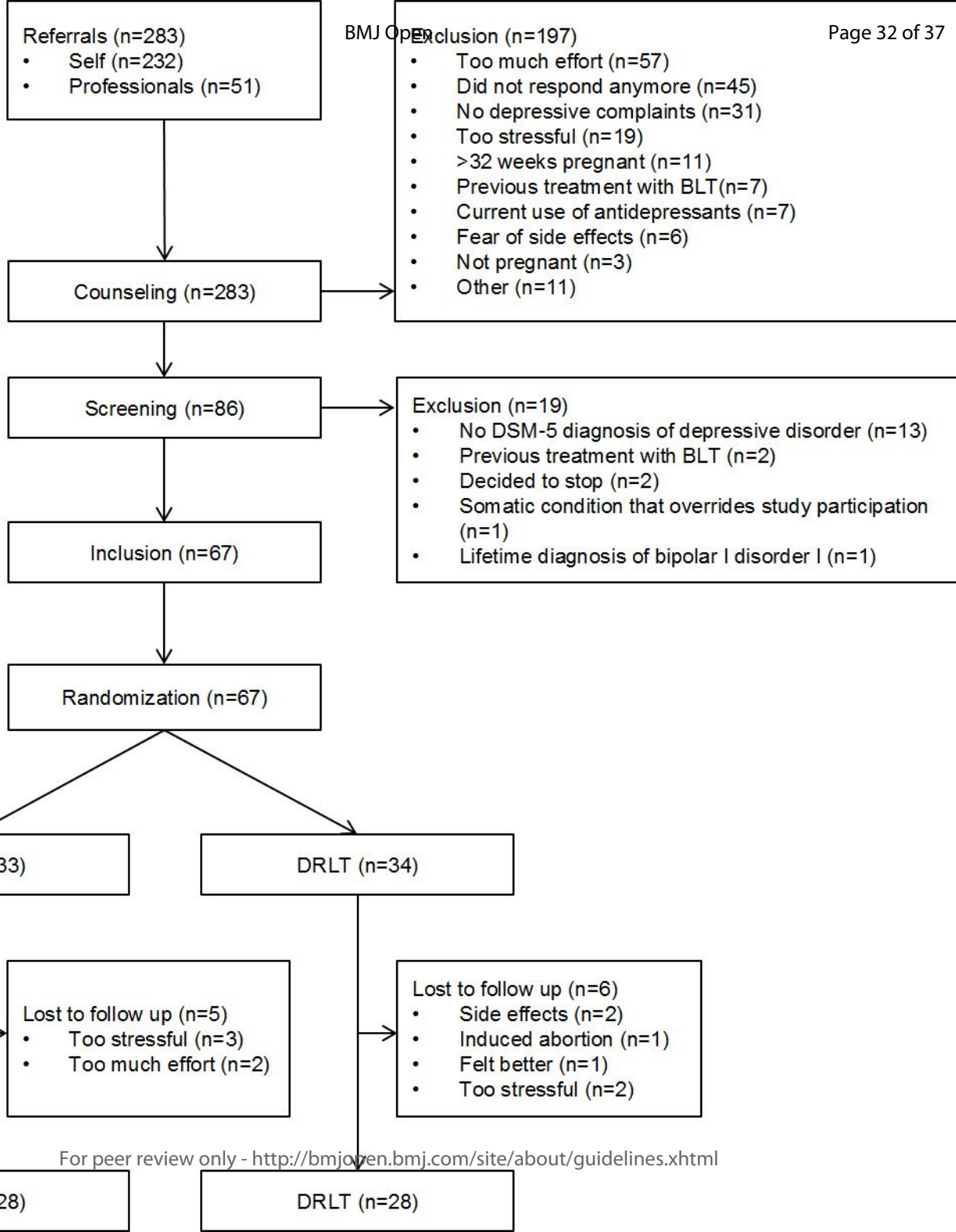
10 721 BLT = bright light therapy; DRLT = dim red light therapy; SIGH- SAD = Structured Interview Guide for the
11

12 722 Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for
13

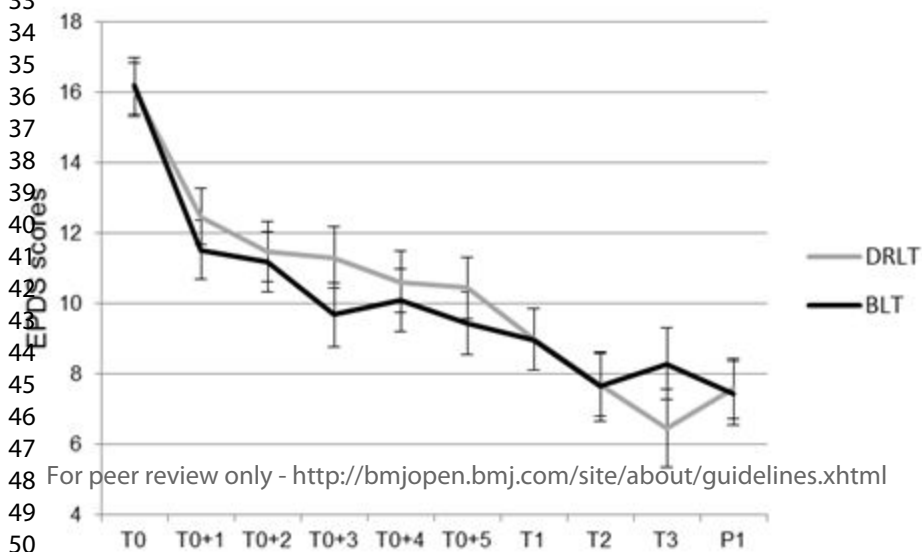
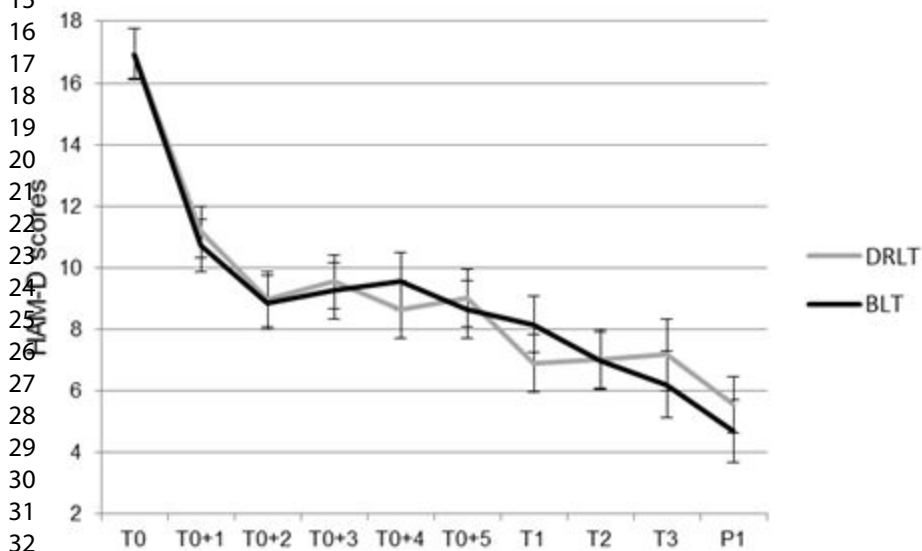
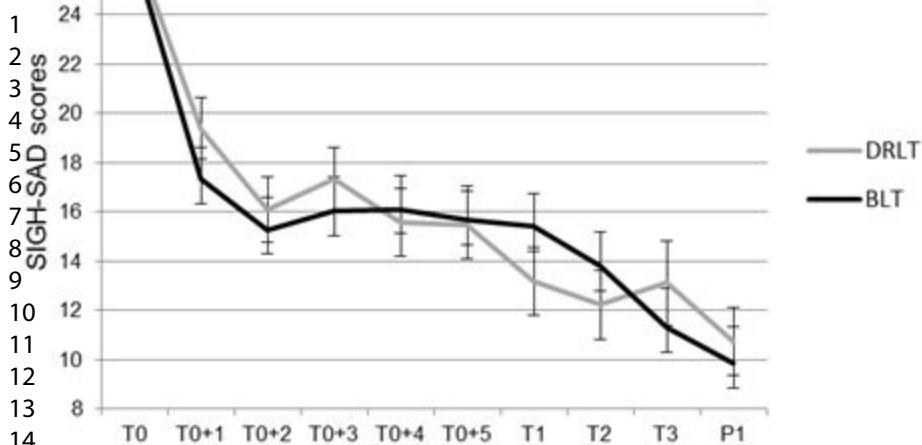
14 723 Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1,
15

16 724 T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of
17

18 725 treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45



Supplementary Table 1. Photobiological characterizations of light therapy in both treatment arms.

	BLT	DRLT
Cyanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	578.7	2.24
Melanopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	891	5.53
Chloropic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1032.3	7.23
Erythroptic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	1212.3	11.37
Rhodopic irradiance ($\mu\text{W} \cdot \text{cm}^{-2}$)	16.61	16.61

BLT = bright light therapy; DRLT = dim red light therapy

Supplementary Table 2. Observed median SIGH-SAD, HAM-D and EPDS scores with ranges and number of participants over the course of the study for both treatment arms.

Measure	T0	T0+1	T0+2	T0+3	T0+4	T0+5	T1	T2	T3	P1
SIGH-SAD										
BLT (mdn, range, N)	27 (14-44; 33)	16.5 (1-33; 30)	16 (2-43; 29)	15 (0-41; 25)	18 (0-32; 25)	17.5 (1-37; 24)	15.5 (0-29; 26)	13 (1-26; 25)	11 (0-29; 17)	8 (1-23; 20)
DRLT (mdn, range, N)	26.5 (13-42; 34)	19 (8-33; 31)	17 (2-35; 27)	18 (4-30; 29)	15 (3-28; 24)	16 (2-31; 25)	13 (2-34; 25)	11.5 (1-26; 24)	9.5 (1-31; 14)	8 (0-28; 25)
HAM-D										
BLT (mdn, range, N)	16 (7-29; 33)	9 (0-25; 30)	9 (1-30; 29)	8 (0-28; 25)	10 (0-22; 25)	10 (0-21; 24)	7.5 (0-20; 26)	8 (0-17; 25)	5 (0-16; 17)	3 (0-11; 20)
DRLT (mdn, range, N)	18 (4-29; 34)	10 (3-20; 31)	9 (1-22; 27)	9 (2-20; 29)	8 (0-18; 24)	8 (1-20; 25)	6 (1-18; 25)	4.5 (0-20; 24)	4 (0-15; 14)	4 (0-19; 25)
EPDS										
BLT (mdn, range, N)	16 (7-25; 31)	11 (3-23; 26)	11 (0-23; 26)	10 (0-19; 21)	8 (0-25; 23)	7 (0-18; 23)	9.5 (1-18; 26)	8.5 (0-15; 18)	8.5 (1-24; 16)	7 (0-13; 22)

DRLT (mdn, range, N)	16 (3-25; 34)	12 (6-19; 28)	12 (3-20; 25)	11.5 (3-21; 24)	10 (1-18; 24)	10 (2-19; 23)	6.5 (1-22; 24)	6 (0-21; 23)	4 (1-10; 12)	7 (0-18; 26)
-----------------------------	---------------	---------------	---------------	-----------------	---------------	---------------	----------------	--------------	--------------	--------------

BLT = bright light therapy; DRLT = dim red light therapy; SIGH-SAD = Structured Interview Guide for the Hamilton Depression Scale – Seasonal Affective Disorder version; HAM-D = Hamilton Rating Scale for Depression; EPDS = Edinburgh Postnatal Depression Scale; T0 = baseline, before treatment; T0+1, T0+2 ... T0+5 = weeks during intervention period; T1 = end of treatment; T2 = 3 weeks after end of treatment; T3 = 10 weeks after end of treatment; P1 = 2 months postpartum; mdn = median

Supplementary Table 3. Effects of allocation on the course of depressive symptoms through the intervention period and follow-up (until two months postpartum): sensitivity analyses.

	β (95% CI) of intervention*	β (95% CI) of follow-up**
Adjusted analysis^a		
SIGH-SAD	-0.27 (-1.70, 1.15)	-0.24 (-1.68, 1.20)
HAM-D	0.10 (-0.51, 0.72)	0.13 (-0.49, 0.75)
EPDS	0.27 (-0.36, 0.90)	0.25 (-0.38, 0.89)
Data imputation^b		
SIGH-SAD	-0.45 (-1.44, 0.53)	-0.08 (-0.63, 0.46)
HAM-D	-0.09 (-0.63, 0.44)	0.06 (-0.25, 0.37)
EPDS	0.19 (-0.30, 0.68)	0.04 (-0.24, 0.32)
Post-hoc analysis: high treatment compliance^c		
SIGH-SAD	-0.40 (-1.36, 0.55)	-0.32 (-0.88, 0.24)
HAM-D	-0.12 (-0.79, 0.54)	-0.06 (-0.43, 0.31)
EPDS	0.03 (-0.58, 0.65)	-0.05 (-0.40, 0.30)

Post-hoc analysis: high symptom severity^d

SIGH-SAD	-0.84 (-2.33, 0.65)	-0.20 (-1.14, 0.75)
HAM-D	-0.16 (-1.12, 0.87)	0.13 (-0.48, 0.73)
EPDS	-0.05 (-0.92, 0.82)	0.20 (-0.33, 0.74)

* From start of study until end of treatment; ** From start of study until follow-up 2 months postpartum; ^a Propensity score composed of psychiatric history, ethnicity, level of education, an unplanned pregnancy, maternal age, parity, gestational age, duration of actual depression and other psychiatric or psychotherapeutic treatment interventions; ^b Last observation carried forward; ^c <7 missed treatments; ^d Based on median split baseline SIGH-SAD scores



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p. 1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p. 2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p. 4-5
	2b	Specific objectives or hypotheses	p. 5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p. 5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p. 6
Participants	4a	Eligibility criteria for participants	p. 6; Table 1
	4b	Settings and locations where the data were collected	p. 6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	p. 7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p. 8-11
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n.a.
Sample size	7a	How sample size was determined	p. 6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n.a.
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p. 9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p. 9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p. 7-9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p. 9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p. 7

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p. 7-8
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p. 11-12
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	p. 11-12
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p. 12, Fig. 1, Supp. Table 2
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p. 6
	14b	Why the trial ended or was stopped	p. 6
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 2
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Sup. Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Sup. Table 2, Fig. 2, p.13-15, Table 3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	p. 14
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	p. 14, Sup. Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	p. 14
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	p. 17-18
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	p. 15-17
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	p. 15-17
Other information			
Registration	23	Registration number and name of trial registry	p. 2, 6
Protocol	24	Where the full trial protocol can be accessed, if available	p. 6
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p. 19

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.