A randomized controlled trial to assess if changing sleep timing can improve glucose metabolism in people with (pre)diabetes

SOCIAL JETLAG TRIAL

Protocol ID	**A randomized controlled trial to assess if changing sleep timing can improve glucose metabolism in people with (pre)diabetes**
Short title	**Social jetlag trial**
EudraCT number	***Not applicable***
Version	**3**
Date	**21-02-2024**
Coordinating investigator/project leader	***E.J. (Emma) Bouman, MSc*** ***PhD candidate*** ***Department of Epidemiology & Data Science*** ***e.bouman1@amsterdamumc.nl*** ***R. (Romy) Slebe, MSc*** ***PhD candidate*** ***Department of Epidemiology & Data Science*** ***r.slebe@amsterdamumc.nl***
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	***Dr. F. (Femke) Rutters*** ***Assistant professor and researcher*** ***Department of Epidemiology & Data Science*** ***f.rutters@amsterdamumc.nl***
Sponsor (in Dutch: verrichter/opdrachtgever)	***Prof. Hans Berkhof,*** ***J.Berkhof@amsterdamumc.nl*** ***VU University Medical Centre*** ***Epidemiology and Data Science*** ***Van der Boechorstraat 7*** ***1081 BT Amsterdam***

Subsidising party	***Diabetes Fonds***
Independent expert (s)	***Prof. Giel Nijpels*** ***Department of General Practice and Elderly Medicine*** ***g.nijpels@amsterdamumc.nl***
Laboratory sites <*if applicable*>	***Coos Molenaar*** ***Senior Unithoofd Klinisch Chemisch Laboratorium at Diagnost-IQ B.V*** ***Hoorn, C.S.Molenaar@westfriesgasthuis.nl***

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: **Hans Berkhof, head of department of Epidemiology & Data Science**		
[Coordinating Investigator/Project leader/Principal Investigator]: ***Dr. F. (Femke) Rutters*** ***Assistant professor and researcher*** ***Department of Epidemiology & Data Science***		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
BMI	**Body Mass Index**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
CRF	**Case Record Form**
DLMO	**Dim Light Melatonin Onset**
DSMB	**Data Safety Monitoring Board**
ECG	**Electrocardiogram**
FPG	**Fasting plasma glucose**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HbA1c	**Glycated haemoglobin**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NFU	**The Netherlands Federation of University Medical Centres; in Dutch: Nederlandse Federatie van Universitair Medische Centra**
OGTT	**Oral Glucose Tolerance Test**
RNA	**Ribonucleic acid**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
T2D	**Type 2 diabetes**

UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
VAS	**Visual Analog Scale**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
ZT	**Zeitgeber time**

SUMMARY

Rationale: Social jetlag is a chronic disruption of sleep timing that is characterized by different sleep timing during workdays and free days. Social jetlag has been associated with disturbed glucose metabolism, insulin resistance and an increased risk of metabolic syndrome and Type 2 Diabetes (T2D).
Objective: To investigate whether a combination of bright light therapy in the morning, bright light reduction in the evening and sleep advance instructions for 3 weeks reduces social jetlag and if this results in improvement of glycemic and metabolic control, sleep, mood and quality of life after 4 and 12 weeks in people with (pre)diabetes and to assess possible mediators, compared to regular sleep habits.
Study design: A randomized controlled trial.
Study population: 60 people with pre-diabetes or diabetes with >1 hour social jetlag from our groups cohorts.
Intervention: Bright light therapy (5000 lux) emitted by Vitamine-L (Lumie, UK) for 30 minutes each morning, following sleep advance instructions, and wearing bright light dimming goggles every evening for a period of 3 weeks. The control group adheres to their regular sleep habits and conditions.
Main study parameters/endpoints: The primary outcome is social jetlag measured using questionnaires and objective measurements and insulin sensitivity measured as HOMA-IR after 4 and 12 weeks and HbA1c after 12 weeks comparing the intervention and control in an intention to treat analysis. Secondary outcomes at 4 and 12 weeks are 1) fasting blood glucose, glucose lowering medication use, frequency of hypoglycemic sensation, 2) metabolic outcomes, including BMI, waist circumference, body fat percentage, blood pressure, (para)sympathetic nervous system activity from ECGs and electrochemical skin conductance tests, 3) sleep measured as sleep times, sleep quality and sleep phases using a sleep measuring headband, 4) mood including depression, fatigue and anxiety measured using questionnaires and 5) quality of life measured using the SF-36 questionnaire. Additionally, to assess other factors that might play a role as possible mediators, we will assess at 4 and 12 weeks the Dim Light Melatonin Onset (DLMO) in saliva samples (in a subgroup), feeling of satiety and satiation is assessed using a 10-cm VAS scale, diet is assessed using a food frequency questionnaire and physical activity using an accelerometer. A subgroup of 20 participants who also fulfill the inclusion criteria of a similar observational study (Extreme phenotype social jetlag study, ABR: NL80321.029.22 METC: 2022.0062) will be selected and asked to participate in both studies. By performing only 4 extra measurements during the baseline visit, these participants can participate in both studies. This will reduce the total number of inclusions for the observational study.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: At baseline, people will be asked to come to the research center twice for a visit of 1 and one of 1,5 hours subsequently. In between the visits they will be asked to perform some measurements themselves from home (in total this takes 2 hours) and to wear an accelerometer and sleep measuring headband for 7 days. During the second visit, we will draw a small amount of blood (10ml total), in the subgroup that takes part in both studies an OGTT will also be performed and blood will be drawn for the biobank. At the baseline visit, 30 participants will be allocated to the intervention group and will be asked to follow a minimally invasive study protocol to reduce their social jetlag. The control group retains their regular sleeping habits. During the intervention period, the participants will be asked to wear an accelerometer and light sensor for one week to assess compliance to the protocol. After 4 weeks, people will wear an accelerometer and sleep measuring headband at home for 7 days again and will come back to the research center for a 1,5 hour visit again. 12 weeks after the start of the intervention, they will come back for one more visit of 1.5/3h.

1. INTRODUCTION AND RATIONALE

Social jetlag is a chronic disruption of sleep timing. It is caused by a discrepancy between biological rhythms and social engagements and is characterised by different sleep timing during workdays and free days (1). Unlike sleep disruption caused by performing shift work or by travelling through different time zones, social jetlag is subtle but highly prevalent: in over 70% of the student and over 50% in the working population (2, 3). Social jetlag usually starts during adolescence and remains present throughout the working career (1-4).

Social jetlag is known to be associated with several pathologies such as mental health, cardiovascular disease, and type 2 diabetes (2). In our recent meta-analysis, with data from over 68 studies, we found that social jetlag is significantly associated with higher HbA1c levels, higher odds of obesity and increased body mass index (BMI) (5). In our cross-sectional study in people with type 2 diabetes, we showed that in working people, a high social jetlag was associated with a higher HbA1c (1.87 mmol/mol [95% CI: 0.75 to 2.99]) and blood pressure (5.81 mm Hg [95% CI: 4.04 to 7.59]) (6).

In other words, social jetlag can contribute to poorer glycaemic control and metabolic control in those with type 2 diabetes. As type 2 diabetes is a highly prevalent disease that affects glucose metabolism through insulin sensitivity and causes a high burden of disease with over 400 million people affected worldwide (7), reducing social jetlag could offer a way to reduce this disease burden and improve overall population health. Previous research has shown that it is possible to reduce social jetlag, for example the study by Geerdink et al. 2016 (8). In this study, 42 participants with >1h social jetlag were either exposed to a high intensity blue light (intervention) or amber light exposure (placebo) in the morning for 9 days. This was combined with a sleep advancing scheme to advance bed times with at least 45 minutes and wake up times with at least 30 minutes, thereby changing the timing of sleep but not the duration, resulting in a reduction of social jetlag. Moreover, blue light was more effective in advancing the circadian clock, assessed through Dim Light Melatonin Onset (DLMO), compared to placebo and still had a significant effect 1 week after the intervention was stopped, with participants from the blue light group still waking up 30 minutes earlier. Overall, this study showed that blue light combined with a sleep advancing scheme for only 1 week is effective in reducing social jetlag (8).

The only other study assessing methods to reduce social jetlag was the study by Zerbini et al 2018 (9). For two weeks, they exposed 76 participants with at least 1.5h social jetlag to either the control intervention (no intervention) or to the blue light reduction in the evening condition

[30]. They showed a significant change in sleep timing on workdays, but not on free days, an advanced DLMO and a trend towards people in the intervention group to sleep longer (17 ± 34 minutes), compared to the control group although social jetlag was nog reduced (9). In an unpublished study by researchers from the Amsterdam UMC, they showed that wearing blue-light-blocking glasses for two weeks in the evening, sleep onset time was earlier and sleep onset time was earlier in teenagers (10).

To date, there are no studies on the metabolic effects of these types of social jetlag reduction interventions. Therefore, our aim is to investigate whether a reduction in social jetlag for 3 weeks can improve glycaemic and metabolic control, sleep, mood and quality of life in people with (pre)diabetes.

2. OBJECTIVES

We established the following two objectives:

Primary Objective:

To investigate whether a combination of bright light therapy in the morning, bright light reduction in the evening and sleep advance instructions for 3 weeks reduces social jetlag and if this results in improvement of insulin sensitivity and glucose control in people with (pre)diabetes, compared to regular sleep habits.

Secondary Objective:

To investigate if a combination of bright light therapy in the morning, bright light reduction in the evening and sleep advance instructions for 3 weeks compared to regular sleep habits reduces social jetlag and if this results in improvement of glycemic outcomes, metabolic control, sleep, mood and quality of life in people with (pre)diabetes and to assess possible mediators.

3. STUDY DESIGN

The proposed study entails a randomized controlled intervention study with two conditions as depicted in figure 1:
(1) the active condition: a combination of evidence-based techniques to realign social jetlag. Participants will be exposed to 30 minutes of bright light therapy in the morning (5000 lux) by using a lamp, they will receive sleep advance instructions, and will be asked to wear light dimming goggles in the evening to reduce bright light exposure in the hours before they go to bed.
(2) the control condition: participants will receive advice on sleep hygiene and remain the same sleeping conditions and habits. Due to the nature and design of the study, blinding of the researchers or participants is not possible. However, since the primary outcomes are social jetlag and glycemic parameters, we do not expect large placebo effects on these outcomes.

Up to 20 participants who also fulfill the inclusion criteria of a similar observational study (Extreme phenotype social jetlag study, ABR: NL80321.029.22 METC: 2022.0062) will be asked to participate in both studies. By performing only 4 extra measurements during the baseline visits, these participants can participate in both studies. This will reduce the total burden for the participants as this will reduce the needed inclusions for the Extreme phenotype social jetlag study by half. Only 20 participants are needed to complete the data collection Extreme phenotype social jetlag study. These measurements include one extra ECG and SUDO scan, non-invasive saliva collection during one evening six times (dim light melatonin onset) and one morning three times (cortisol awakening response) and an oral glucose tolerance test on the second study day at baseline.

Participants are invited to the research center in the afternoon and informed consent is signed. In the subgroup that participates in both studies, an ECG and electrochemical skin conductance test will be performed. Then participants will go home and will fill out VAS scales about satiety and satiation before and after having dinner. The subgroup that participates in both studies will be asked to wear light dimming goggles for one evening and collect six saliva samples for melatonin onset assessment. Additionally, a subgroup of 15 participants will be asked to take part in extra non-invasive saliva collection measurements. After that, all participants will wear an activity tracker at home during regular activities and a sleep monitoring headband at night for a period of 7 days and they will fill in a sleep diary during this period. During the second study day at baseline, anthropometrics and blood pressure will be measured and blood will be drawn to determine HbA1c levels as well as fasting insulin and glucose levels. Additionally, the subgroup that participates in both studies

will collect another three saliva samples for morning cortisol determination as well as an OGTT and 20ml extra blood will be drawn for the biobank (belonging to the existing protocol of the Extreme Phenotype Social Jetlag study ABR: NL80321.029.22 METC: 2022.0062 and under biobank number: 2019.272) with their consent. Participants will also fill in a VAS scale on satiety and satiation and several questionnaires. After that, an ECG and electrochemical skin conductance test will be performed. At the end of the visit and after the participants received breakfast, the participants will be randomly assigned to either the control or intervention group and they will receive information on the intervention program or control condition.

To improve adherence to the protocol and assess compliance, after 1 week, participants will send in a sleep diary of seven days and wear an accelerometer as well as a light tracker for seven days.

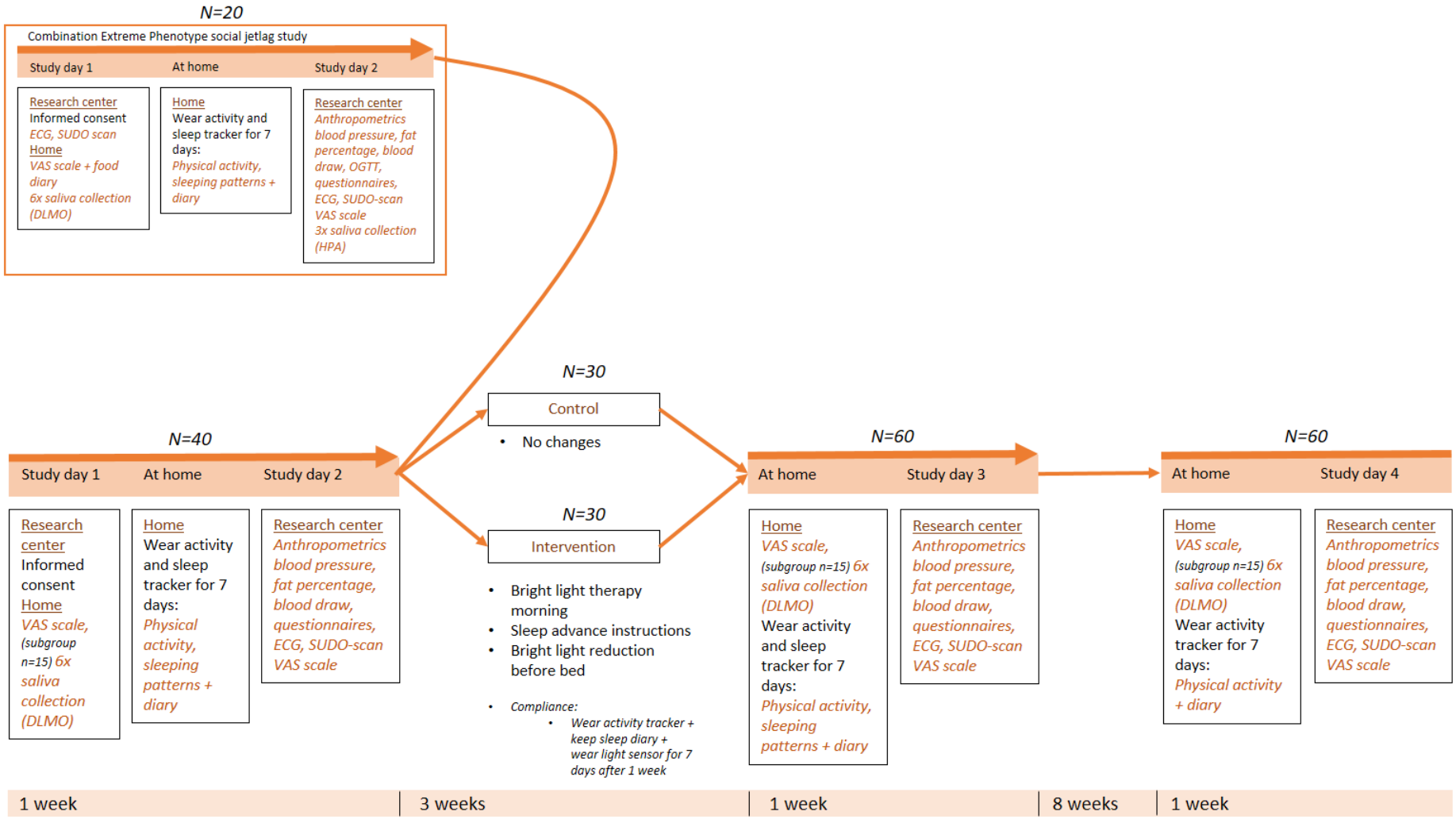
After a period of 3 weeks, all participants will wear an activity tracker and a sleep monitoring headband at for 7 days and fill in a sleep diary. After that, participants will be invited back to the research center once for the same measurements as the second day of the baseline visit (anthropometrics, blood pressure, blood draw, ECG and SUDO and questionnaires). Twelve weeks after the start of the intervention, they will come back one more time for the same measurements and they will wear an activity tracker for one more week. See table 1 below for an overview of the different measurements in the different subgroups and figure 1 for an overview of the study protocol.

Table 1. Overview of study measurements per subgroup

	Measurement	**Regular trial group (N=40)**	**Combination extreme phenotype (N=20)**
Visit 1	Informed consent	X	X
	ECG		X
	SUDO-scan		X
After visit 1 (at home)	VAS scale + food diary	X	X
	Wear dark goggles and collect 6x saliva sample		X
	Additional measurement (n=15, randomly selected): wear dark goggles and collect 6x saliva sample	X	
	Wear activity tracker	X	X
	Wear sleep headband	X	X
	Fill out sleep diary	X	X
Visit 2	Anthropometrics	X	X
	Blood pressure	X	X
	Fat percentage	X	X
	Waist circumference	X	X
	Saliva collection 3x		X
	Blood draw	X	X
	Oral glucose tolerance test		X
	ECG	X	X
	SUDO-scan	X	X
	VAS scale	X	X
	Questionnaires	X	X
1 week before visit 3 (at home)	VAS scale + food diary	X	X
	Additional measurement (n=15, randomly selected): wear dark goggles and collect 6x saliva sample	X	
	Wear activity tracker	X	X
	Wear sleep headband	X	X
	Fill out sleep diary	X	X
Visit 3	Anthropometrics	X	X
	Blood pressure	X	X
	Fat percentage	X	X
	Waist circumference	X	X
	Blood draw	X	X
	ECG	X	X
	SUDO-scan	X	X
	VAS scale	X	X
	Questionnaires	X	X

1 week before visit 4 (at home)	VAS scale + food diary	X	X
	Additional measurement (n=15, randomly selected): wear dark goggles and collect 6x saliva sample	X	
	Wear activity tracker	X	X
	Fill out sleep diary	X	X
Visit 4	Anthropometrics	X	X
	Blood pressure	X	X
	Fat percentage	X	X
	Waist circumference	X	X
	Blood draw	X	X
	ECG	X	X
	SUDO-scan	X	X
	VAS scale	X	X
	Questionnaires	X	X

Figure 1. Overview of study protocol



4. STUDY POPULATION

4.1 Population (base)

60 participants with (pre)diabetes and >1h of social jetlag are recruited from our cohorts. They will be recruited from the ENvironmental DEterminants of lifestyle behAViORs and risk of type 2 diabetes and cardiovascular diseases', also called the ENDEAVOR study cohort (METC protocol 2017.027), the DIRECT (Diabetes Research on Patient Stratification) study (METC protocol 2012.222), the New Hoorn Study (Prevalence and determinants of impaired glucose regulation) (including METC protocol 2021.0177), Early detection of diastolic dysfunction and heart failure with preserved ejection fraction in people with type 2 diabetes (EARLY-HFpEF, 2018/064) and the Biobank 3 (Hoorn Diabetes Care System Cohort follow up 2023, METC protocol 2023.0144). We will recruit participants from these studies who previously consented to being (re)-approached for additional research. If these recruitment options are not sufficient, we will start recruiting by advertisements via Facebook or local newspapers. Participants will be invited to our clinical trial unit at the research center in Hoorn, which is part of the Amsterdam UMC.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Social jetlag (>1h) (calculated as difference between midpoint of sleep during week days and free weekend days)
- (Pre) diabetes: HbA1c >39 mmol/mol (5.7%), fasting plasma glucose >5.6 mmol/l, or 2-hour OGTT >7.8mmol/l (according to the American Diabetes Association) including the use of any glucose-lowering medication
- Informed consent to be contacted for future research
- Willing to comply with the study procedures

4.2.1 Inclusion criteria with overlap Extreme phenotype social jetlag study

In order to be eligible to participate in this study simultaneously with the extreme phenotype social jetlag study, subjects must meet these additional criteria:

- Prediabetes: HbA1c between 5.7% and 6.5%, fasting plasma glucose between 5.6 mmol/l and 7.0 mmol/l or OGTT between 7.8 mmol/l and 11.0 mmol/l.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Excessive alcohol use (>21 alcoholic consumptions per week);
- Having crossed more than 1 time zone in the month prior to participation;
- Working shifts more than once per month;
- Unable to provide written informed consent;
- Visually impaired (partial or total inability of visual perception);

4.4 Sample size calculation

We calculated the sample size on one of the primary outcomes, namely HbA1c after 12 weeks. To date, no previous study investigating these social jetlag reducing interventions has assessed metabolic outcomes. Previous lifestyle interventions in the target population show a change in HbA1c over a period of 3-6 months of 0.2-0.75% (11, 12). We hypothesize a difference of -0.25% in HbA1c level between the two groups from the current intervention. To assess a change of -0.25% ± 0.25 in HbA1c level, with an α of 0.05 and β of 0.1 the (corrected) number of participants needed is 23 persons per group, with a 25% drop-out this results in 30 participants per group.

Our recent studies showed that 65% of all people with T2DM have >1 social jetlag (5) and 39% of the general population (13) of which about 40% have (pre)diabetes. We expect to be able to include 35% of all earlier participants presenting with social jetlag (about 500 participants). These numbers suggests it should be feasible to reach our sample size of 60 participants.

5. TREATMENT OF PARTICIPANTS

The intervention consists of three components: bright light therapy in the morning, sleep advance instructions, and bright light reduction in the evening.

5.1 Investigational treatment

Bright light therapy

In the bright light condition, a Vitamine-L lamp (Lumie, UK) will be placed at 30 cm before the participant, yielding 5000 lux (https://www.lumie.com/products/vitamin-l), which is similar to outside light levels on a clouded day. The participant does not have to look straight into the light. Participants are requested to expose themselves to 30 minutes of bright light each morning by sitting in front of the lamp, working on their computer or reading. When requested, participants can receive a reminder by text to start the bright light therapy. Participants are not liable for loss or damage to the equipment.

Participants will receive a Vitamine-L lamp together with instructions for use. The Vitamine-L lamp is certified to ISO 13485 Medical Devices, QMS standard. Lights must pass rigorous safety tests and be supported by clinical research to meet the Medical Devices Directive EC93/42/EEC. They are approved for use for light therapy at home. Thus, in the present protocol the lights will be used for the purpose they are designed for (i.e. administration of light). Due to recent insights about possible interactions of different photoreceptors in the non-visual effects of light (14), we believe that it is probably most efficient to use full spectrum bright light in the morning, rather than select a certain specific wavelength, such as blue light only. By exposing people to full spectrum bright light in the morning and a reduction of light intensity in the evening combined with sleep advance instructions, we will try to reduce social jetlag.

Sleep advance instructions

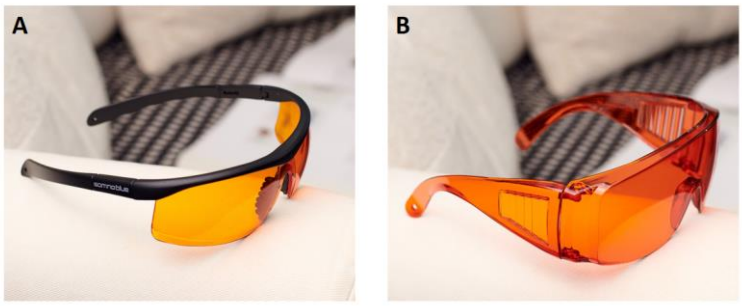
Study participants are told to sleep more regularly, with similar sleep onset and sleep offset times on weekdays and weekend days. To support them with this, participants will follow a sleep-advancing scheme (8). Based on self-report of the participant, the habitual sleep onset and habitual sleep offset will be calculated as the average of all days (week and weekend days). Then participants are asked to give their preferred sleep offset for all days of the week (similar for week and weekend days); preferred sleep onset is calculated as sleep offset – preferred sleep duration between 7-8h. To sleep advance every day on average 20 minutes, the first 3 days, the light therapy have been scheduled 10h after

preferred sleep onset. Days 4-6, the light therapy is scheduled 9h after preferred sleep onset and days 7-9 the light therapy 8h after preferred sleep onset, if the earlier sleep onset is 3 hours earlier. After the preferred sleep offset and onset are reached, the new schedule will be continued during the rest of the 3 weeks intervention.

Bright light reduction evening

As final part of the intervention, participants receive blue-light dimming goggles (figure 2) with instructions to wear them every evening from 18.00 hours until they go to sleep (15). When wearing the goggles they can still perform their usual activities, such as watching television or reading, with screens of electronic devices in dimmed modus (15, 16) as well as room lighting being < 10 m-EDI lux (dim lighting of the room, curtains closed).

Figure 2. Blue-light dimming goggles (Somnoblue) A. Regular goggles B. Goggles for people who wear glasses.



Control group

The control group remains under their normal conditions and receives information on sleep hygiene (website https://www.thuisarts.nl/slecht-slapen/ik-wil-beter-slapen). However, no specific instructions to change their sleep habits or conditions will be provided. After the trial has finished, the control group will also be offered to follow the intervention protocol if they wish.

5.2 Use of co-intervention

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable, the intervention does not include an investigational product.

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies

Not applicable

6.4 Summary of known and potential risks and benefits

Not applicable

6.5 Description and justification of route of administration and dosage

Not applicable

6.6 Dosages, dosage modifications and method of administration

Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7 NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

Not applicable.

7.2 Summary of findings from non-clinical studies

Not applicable.

7.3 Summary of findings from clinical studies

Not applicable,

7.4 Summary of known and potential risks and benefits

Not applicable.

7.5 Description and justification of route of administration and dosage

Not applicable.

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

Not applicable .

8 METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

- Social jetlag measured using questionnaires and objective measurements after 4 and 12 weeks;
- HOMA-IR determined from fasting insulin levels determined using an anti-body kit (AutoDELFIA Insulin kit; Wallac Oy) and fasting blood glucose determined in fluorinated plasma with the UV test using hexokinase (Cobas c501, Roche Diagnostics) after 4 and 12 weeks;
- HbA1c (mmol/mol) determined with turbidimetric inhibition immunoassay (Cobas c501, Roche diagnostics, Mannheim, Germany) after 12 weeks.

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary study parameters are:

1) Other Measures of glycaemic control:
   - Fasting blood glucose determined in fluorinated plasma with the UV test using hexokinase (Cobas c501, Roche Diagnostics);
   - Self-reported Hypoglycaemic sensations are determined using a questionnaire;
   - Diabetes medication use is assessed from the participants medication overview and described as type (ATC code), timing and dosage);

2) Metabolic parameters including anthropometrics, assessed as weight, body fat percentage and waist circumference; Blood pressure (is assessed using a hematomator and described as a continuous variable or dichotomous as hypertension, defined as systolic blood pressure and diastolic blood pressure >= 140/90 and/or use of hypertensive medication); Nervous system activity assessed using an electrochemical skin conductance test; Cardiovascular health is assessed using a standard resting 12-lead ECG and coded according to the Minnesota coding system;
3) Sleep including sleeping rhythms, sleep quality and sleep phases assessed using wearables, sleep diaries and questionnaires;
4) Mood including depression, fatigue and anxiety measured using questionnaires;
5) Quality of life is assessed using the SF-36 questionnaire;

Outcome parameters for the combination with Extreme Phenotype Social jetlag study

1) Dim Light Melatonin Onset, measured from 6 saliva samples collected in the evening of study day 1.
2) HPA axis activity from the Cortisol Awakening Response (CAR) measured from 3 timed saliva samples at study day 2.
3) 2h Glucose levels after an Oral Glucose tolerance test (OGTT) determined in fluorinated plasma with the UV test using hexokinase (Cobas c501, Roche Diagnostics)
4) Nervous system activity from SUDO scan (neuropathy) and heart rate variability (HRV)v and cardiovascular health (Minnesota coding) from 5 minute ECG recordings

8.1.3 Other study parameters (if applicable)

Possible confounders and mediators will be assessed. Participants will self-report: age, sex, education status, stress level, work status and other medication use, diet, alcohol consumption, smoking, feeling of satiety and satiation. Additionally, Dim Light Melatonin onset assessed using a 6 point saliva measurements and 3 point saliva measurements for cortisol awakening reaction (in a subgroup) and physical activity measured using an accelerometer.

8.2 Randomization, blinding and treatment allocation

Randomization will be performed automatically by the Electronic Data Capturing software (Castor EDC). Blocked randomization will be used to ensure good balance of participant characteristics in each group. Randomization will be stratified on sex, two strata of age and two strata of social jetlag to prevent misbalance. Allocation will be determined by using a computerized random number generation process.
Due to the nature of the intervention, blinding is not possible. However, since the primary outcomes are social jetlag and glycemic parameters, we do not expect large placebo effects on these outcomes.

8.3 Study procedures

The study procedures will be performed by the two coordinating researchers together with several research assistants and all measurements will be performed at the research location in the Diabetes Research Center in Hoorn (location of Amsterdam UMC).

Participants from previous studies who meet the inclusion criteria and have given consent to be invited for additional research, will receive written study information. After two weeks they will be contacted to discuss participation and any questions regarding the study.

First study day

Participants are invited to the clinical trial unit at the research center in Hoorn in the afternoon. At the start of the first study visit, before any of the study procedures, the informed consent form is presented to the participant. The investigator will explain the aim of the study, the procedures and the consent to the participant. The participant will be given sufficient time to ask questions regarding the study. Written informed consent will be obtained with the participant's dated name and signature or by the participant's legally acceptable representative's dated name and signature along with the dated name and signature of the investigator conducting the informed consent procedure. A copy of the consent form will be given to the participant before the start of the study procedures.

The following procedures will be performed:

ECG and electrochemical skin conductance test

The participants with overlap with the Extreme Phenotype social jetlag study will undergo an ECG and electrochemical skin conductance test will be performed in the afternoon of study day 1. They will be used to determine (para)sympathetic activity and cardiac health.

From the ECG, we will assess Heart Rate Variability (HRV). We will determine: the root mean square of successive differences (RMSSD) between heart beats as a measure of short term autonomic nervous system activity (17), the proportion of intervals between the successive R-peaks (RR intervals) of the ECG that differ more than 50ms divided by the total number of RR intervals (PNN50) as a measure of vagal activity, and low frequency/high frequency (LF/HF) ratio as a measure for sympathovagal balance (18). Furthermore, from the ECG, we will determine heart rate (19), QT intervals (20), and QRS duration and PR-interval, and we will detect premature ventricular complexes (20-22).

The sympathetic skin response will be assessed using the sudoscan©. The sudoscan© is a method for sudomotor function assessment that measures sweat

composition to detect deviations in the ionic balance of the sweat. A low voltage of variable amplitude is applied to electrodes on the skin and the electrical potential difference caused by the electrochemical reaction on these electrodes is measured. The sudoscan uses electrodes placed on body regions with a high density of sweat glands (palms, feet). The sudoscan will last between 2 and 3 minutes (23).

At home study days (8 days)

During the first study visit, the participants with overlap with the Extreme Phenotype social jetlag study and an additional subgroup of 15 participants from the trial will receive a pair of light dimming goggles and saliva collection swabs with instructions to wear the goggles and collect their own saliva samples in the evening.
All study participants will receive an activity tracker (Actigraph) and sleep tracking device (ZMax) with instructions for wearing and using them for the coming 7 days. Additionally, they will receive paper VAS scale questionnaires and a sleep diary with instructions how and when to fill them out.

VAS scale

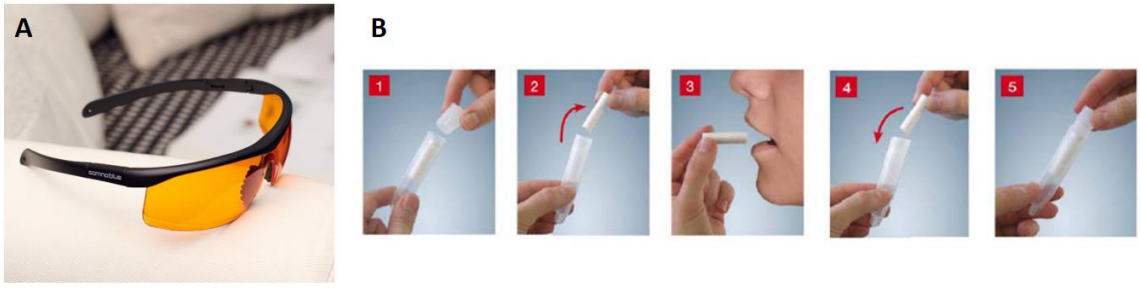
Before and directly after and their regular at-home dinner on study day 1, participants will fill out VAS scales on their feeling of satiety and satiation. The scales consist of four questions to assess feeling of hunger, fullness, satiety, and desire for prospective consumption. All questions can be answered on a scale from ‘not at all’ to ‘extremely high’ (24, 25). This non-invasive short questionnaire will take up to five minutes to fill out. The VAS scale is a validated and frequently used method to measure subjective appetite (24). The first assessment will be performed on study day 1 before and after dinner independently by the participants. The participants will also report what they ate for dinner that day. The second assessment will be at the research center on day 2.

Dim light melatonin onset (DLMO)

The subgroup with overlap with the Extreme Phenotype social jetlag study (ABR: NL80321.029.22 METC: 2022.0062) and an additional 15 participants will undergo measurements for DLMO. Five hours before their regular bedtime on the first study day, participants will remain in dimmed light conditions (<10 lux), using blue light blocking goggles (Somnoblue). They can still perform their usual activities, such as watching television or reading, with screens of electronic devices in dimmed modus (15, 16). During this period, they will collect saliva samples with a swab six times every hour until one hour after their regular bed time (26).

Participants will be instructed not to eat, drink, or brush their teeth 20 minutes before taking a sample and will be asked to write down the sample times. They will store their samples in their fridge and send the samples back to the research center by post with an envelope they received (26). The sampling of saliva using a swab is non-invasive as they only have to chew on them and will take a few minutes including storing of the sample and writing down the time of sampling. Melatonin levels will be assessed in the saliva samples to assess the dim light melatonin onset.

Figure 3. (A) Dimmed blue light goggles (Somnoblue) and (B) saliva collection swab set



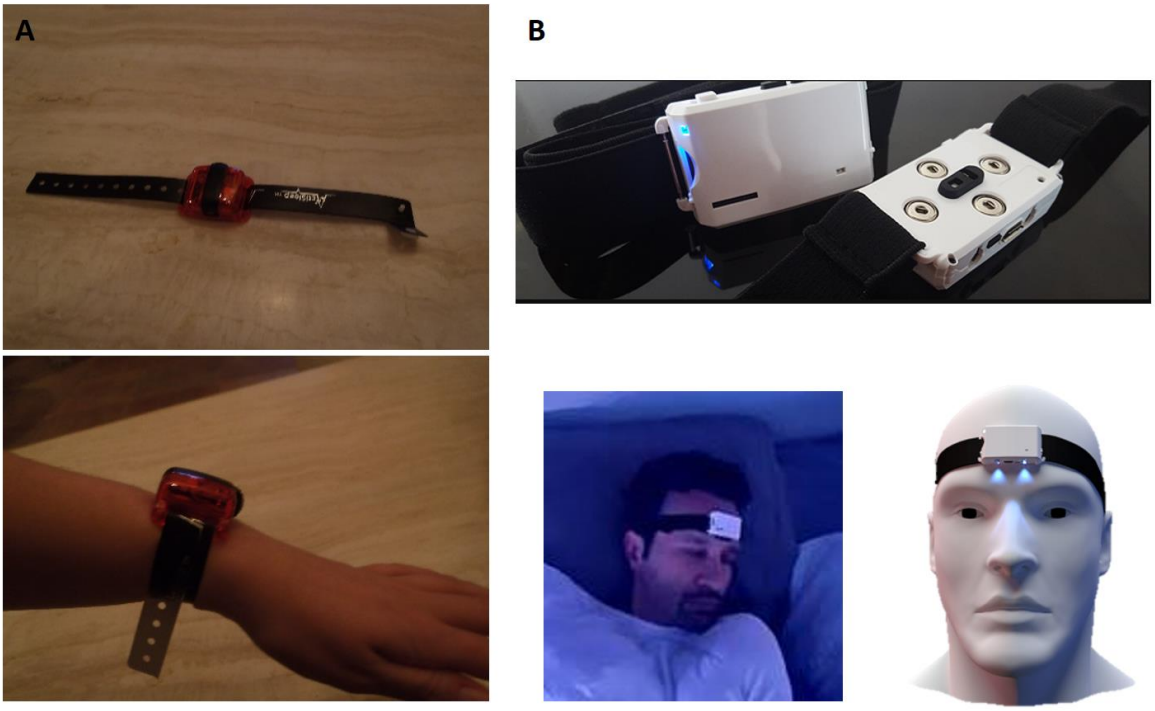
Sleep and activity tracking

From the second at-home study day, participants are asked to wear a wrist-worn triaxial accelerometer (T3x Actigraph, during all activities for a period of 7 days. The accelerometer has a narrow strap wrist band that is easy to wear and should not cause any significant discomfort. The participants will be instructed wear the accelerometer all the time and to remove it only when swimming, or undertaking other water-based activities, they can be worn when taking a shower. Data that will be collected are total activity, moderate to vigorous physical activity, sleep-related behavior and sedentary time.

Additionally, participants will receive a headband (Zmax lite), which they are asked to wear at night for the same period of 7 days. The Zmax lite comprises two frontal EEG channels (F7-Fpz, F8-Fpz), a tri-axial accelerometer, and a PPG sensor, all with a sampling frequency of 256 Hz. The Zmax headband will collect data on sleep phases (deep, light or REM sleep). The headband is composed of foam and fabric and the elastic band behind the head makes it adjustable to sit tight enough to be secure, but loose enough to minimize discomfort. Several studies have confirmed the capacity of

the Zmax headband for sleep staging as alternative to gold standard polysomnography (27). Participants are not liable for loss or damage to the equipment. Also participants will be asked to fill in a sleep diary during these days, which asks about time went to bed, time went to sleep, time woken up, time out of bed, sleep quality (1-10 rate) as well as leaves room for comments regarding sleep. The sleep diary take about 7 minutes to fill out (1 minute per day).

Figure 4A-B Activity tracker and sleep headband. A: Accelerometer (T3x Actigraph). B: Sleep monitor (Zmax headband).



<u>Second study day</u>

After wearing the accelerometer and sleep headband, the participants are invited for the second study day at the research centre. In the morning, they return to the research centre in fasting state. Anthropometric measurements (weight, waist, fat percentage and height) will be taken using a Tanita scale, tape measure and stadiometer. Blood pressure will be assessed using a hematomator. After that, a blood draw will be performed to determine fasting plasma insulin and glucose levels, HbA1c, and OGTT (in the Extreme Phenotype subgroup) and participants will fill out several questionnaires. This is followed by an ECG and electrochemical skin conductance test as described above. After this, the participants will receive a snack and fill in the VAS scales about satiety and satiation before and after eating. After this

the participant are randomly assigned to the intervention and control groups. They will receive information about the study procedures and will be free to leave.

The following measurements will be executed:

HPA axis

The subgroup with overlap with the Extreme Phenotype social jetlag study (ABR: NL80321.029.22 METC: 2022.0062) will be asked to collect saliva with a synthetic swab three times in the morning of study day 2 at ZT 0:30, ZT 1:00 and ZT 2:00. The participants will collect the first sample at home, the same way they collected the saliva sample during the at-home study days. They will bring this sample to the research centre and the other two collections will be done by the researchers. The collection of saliva will be non-invasive and quick. The samples will be used to determine cortisol levels in the morning (the cortisol awakening response (CAR)). This is a validated measure for activation of the hypothalamus-pituitary-adrenal (HPA) axis (28-30). HPA axis activation from cortisol measures has been assessed before in people with social jetlag (3). The swabs will be centrifuged and saliva will be collected, and will be stored at -80 Celsius as soon as possible after collection. For cortisol level assessment, the defrosted samples will be assessed using a radioimmunoassay (Buhlmann Laboratories) with an intra-assay coefficient variation of <6% (3).

Anthropometry

Height (cm), weight (kg), body fat percentage (%) and waist circumference (cm) will be measured with patients being barefoot and only wearing light clothes. Waist circumference will be measured using a tape measure at the level midway between the lowest rib margin and the iliac crest.

Blood pressure

Blood pressure, systolic and diastolic, will be measured three times on the right arm, in sitting position after a ten-minute resting period, by means of a Welch Allyn 3400 series hematomator.

Blood sampling

Levels of glucose levels, insulin, and HbA1c will be assessed by collecting a blood draw to determine the fasting blood. In total 4ml insuline (serum), 2ml glucose (NaF), and 4ml HbA1c (EDTA), will be drawn. P8000 tubes (Becton Dickinson, Wokingham,

UK) will be used to protect the samples from intrinsic proteolysis. The subgroup with overlap with the Extreme Phenotype social jetlag study (ABR: NL80321.029.22 METC: 2022.0062) will also undergo an OGTT. They will drink a glucose solution and blood will be drawn (2ml glucose (NaF)), after 2 hours post load from a cannula to determine blood glucose levels. Additionally, 20ml blood(10ml EDTA +10ml serum) will also be collected to be stored in the biobank (Biobank number 2019.272).

Questionnaires

General

Information on age, sex, education status, and work status will be obtained from the general questionnaire. It will take approximately 10 minutes to fill out.

Depression, fatigue, physical functioning, pain, sleep problems, participation, and anxiety questionnaires

To assess patient reported outcomes, copious and lengthy questionnaires need to be administered, resulting in a large patient burden, reduced compliance and missing data. Recently, an innovative methodology was introduced, called Computerized Adaptive Testing (CAT), which allows for selection of specific questions based on the answer(s) to previous questions. For example, if you answer to the first item of a physical functioning questionnaire that you are not able to walk at normal speed, questions on running are omitted. By asking questions tailored to the responses of each patient, CAT reduces patient and administration burden by up to 75%, compared to fixed-item questionnaires.

Currently, CATs are available for measuring depression, sleep problems, physical functioning, pain, participation, fatigue and anxiety. It will take approximately 7 minutes to fill out the questionnaires, which are presented within the Kwaliteit van Leven in Kaart (KLIK) online portal. The KLIK website is located in a secure, protected web environment and the VUMC has a user agreement with KLIK (31). Convergent validity and discriminant validity were previously tested (32). Convergent validity showed strong correlations between CAT and existing tools to measure anxiety. Discriminant validity was higher for CAT than for other measures. More details are described elsewhere (32). Short form versions of the questionnaires are attached (F1 supplements) as representative examples of these questions.

Hypoglycaemic sensations questionnaire

Hypoglycaemic sensations will be determined using the following questions: did you experience hypoglycaemia in the past three months (yes/no)? If yes, what kind of symptoms did you experience: dizziness, dreaming, feeling restless, headache when getting out of bed, hunger, mood swings, palpitations, snoring, sweating during the night, tingling sensations around the mouth, trembling or other? Also, if yes, how many hypoglycaemic events did you experience where help from others was not needed (number per month/per week/per day)? How many hypoglycaemic events did you experience that required help from others (number per month/per week/per day)? If help was required, was medical assistance needed or was assistance of others needed?

Mild hypoglycaemic sensations will be defined as hypoglycaemic events not requiring help from others. Severe hypoglycaemic sensations will be defined as events requiring help from others, that is, either medical assistance or assistance of others (33). It will take approximately 3 minutes to fill out the questionnaire, which are presented within the Castor eCRF.

Food Frequency Questionnaire

Dietary intake will be assessed with a self-administered food frequency questionnaire (FFQ). The 81-item FFQ is developed and validated by Wageningen University and Research. The FFQ was validated against a dietary history in 128 men and women. This showed the ability of the FFQ to rank participants was acceptable to good, for most nutrients and foods. Pearson correlation coefficients ranged from 0.69 for nutrients and 0.65 for foods (34). The FFQ obtains information on frequency, portion size, and preparation. Intake of the FFQ food item is calculated using the Dutch food composition table (NEVO). The FFQ will be assessed in collaboration with Wageningen University and they will process the data. A data processing agreement is signed for this (K3). It will take approximately 30 minutes to fill out and will only be asked at baseline and after 12 weeks.

Medication

Participants will either bring their boxes of medication with them on the visit or a report from their pharmacy listing the medication, timing and dosage they use. Medication will be coded according to the ATC code and timing and dosage will be reported.

Stress

Stress will be measured as subjective stress on a ten point scale.

Quality of life by the EuroQol (EQ-5D-5L)

EQ-5D-5L is a standardized instrument to assess quality of life at five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. A weighted health index can be derived from the questionnaire. Furthermore, the participant must indicate how he perceives his health status on a scale from 0 to 100. The EQ-5D has been widely tested and used in both general population and patient samples. The EQ-5D-5L is both valid and reliable (68), and sensitivity and ceiling effects are improved compared to the EQ-5D-3L (which had three levels). Furthermore, findings regarding initial content and face validity were consistent across dimensions and countries (68). The questionnaire takes approximately 2 minutes to fill out.

Three week intervention period

Participants in the intervention group will receive the intervention products: a bright light lamp and light dimming goggles along with instructions, and sleep advance instructions. To improve adherence to the protocol and assess compliance, participants will send in a sleep diary of seven days and wear an accelerometer as well as a light logger (Pendant Light 64K Data Logger, HOBO CE) for seven days after one week of the intervention program. The light logger is worn as pendant (2 by 3 cm) on a necklace outside the clothes, only taken of in water-based activities. The control group receives no instructions and will continue with their usual sleep habits and conditions.

First follow-up visit

After three weeks, the intervention period is finished and participants will receive an accelerometer and sleep headband at home to perform one week of sleep and activity measures again. The subgroup taking part in the DLMO measurements will also receive materials for saliva collection. After this they return to the research centre for study day 3. They will return the bright light therapy lamp and will be allowed to keep the light dimming goggles. Then, the same study protocol is followed as on study day 2 as described above (apart from the extra measurements for the group

with overlap with the Extreme Phenotype social jetlag study and apart from the blood measurement of HbA1c).

Second follow-up visit

Twelve weeks after the start of the intervention, a final follow-up visit will take place. All participants will receive an activity tracker at home, the DLMO subgroup will also receive materials for saliva collection and all participants will return to the research centre for study day 4 (same as day 2 and 3). This time HbA1c will also be determined in the blood.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

Not applicable

8.7 Premature termination of the study

No reasons for premature termination are currently foreseen.

9 SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedures or the intervention. Given the non-invasive nature of the study procedures and intervention, only significant adverse events that are observed by the investigator and are related to the performed measurements, will be recorded. A list of the findings that will be recorded given in the Manual of Procedures of the study and possible AE cases will be discussed in the study team. Furthermore, events reported spontaneously by participants or observed by the investigator that have a prolonged effect on the physical wellbeing of the participant (e.g. sustained injury caused by a conducted study measurement or sustained injury incurred during the study visit but unrelated to the study measurements) will be reported.

Light therapy is deemed a safe treatment for the eyes (38). Use of a Vitamine-L lamp may cause minor temporal complaints, such as headache or tired eyes. A Vitamine-L lamp should be used with caution by people with eye problems. Therefore this condition is an exclusion criteria for this study (see paragraph 1.3).

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or

- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs yearly in a line listing through the web portal *ToetsingOnline* to the accredited METC that approved the protocol.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

Not applicable

9.4 Follow-up of adverse events

AEs related to unexpected findings of the performed study measurements will be reported to the participant and their general practitioner. After reporting the findings, the general practitioner will be responsible for the follow up and treatment of the abnormality. No follow up actions from the study team will take place. All other AEs (as defined in paragraph 6.1.2) will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

10 STATISTICAL ANALYSIS

Baseline characteristics will be described by intervention arm as mean ± SD, as median and interquartile range (if not normally distributed) or as numbers and percentages if categorical. Missing data will be investigated for all variables and multiple imputation by predictive mean matching will be used to address missing data if the prevalence exceeds 5%.10 imputation sets with 50 iterations will be performed and results will be gained from pooled estimates.

10.1 Primary study parameter(s)

Statistical analysis will be performed using RStudio version 4.3.0. We will conduct intention to treat analysis as well as per protocol analysis (participants with at least 80% adherence according to the sleep diary + accelerometer + light tracker scores), using linear regression analysis, adjusting for baseline values. We will assess effect modification by age, working status and chronotype. If there is (despite randomization) a misbalance in participant characteristics, a sensitivity analysis will be conducted to assess the effect of the misbalance by adjusting for these variables.

10.2 Secondary study parameter(s)

We will conduct intention to treat analysis and per protocol analysis, using linear or logistic regression analysis, adjusting for baseline values for the secondary outcomes. To determine the magnitude of the possible mediating processes (DLMO, satiety, physical activity and/or energy intake) between the intervention and the outcomes, parallel multiple mediation analysis is used (3).

10.3 Other study parameters

Not applicable

10.4 Interim analysis

Not applicable

11 ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (revised by the 64th WMA General Assembly in Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

Participants from previous studies as mentioned above, who gave consent for future research and who are eligible for this study will be invited. Eligible people will receive detailed written information. They will receive an invitation letter together with the participant information. After 2 weeks, participants will be contacted by telephone by the researcher to discuss participation and plan the study visit. Before the start of the first measurements the researcher will discuss the study procedures: the purpose, nature and duration of the research and the related risks and benefits, as well as the consent. The researcher will answer all questions and obtain a written informed consent before the start of the study. This informed consent form will have to be signed at the research centre in the presence of the one of the investigators or research nurses. The participant will receive a copy of the signed informed consent. Before signing of the informed consent, no measurements will be performed and no invasive questions will be asked.

We expect that 40%-60% of the participants has >1h social jetlag, resulting in a selection of about 1700-2600 people from the New Hoorn Study and subset of the Diabetes Care System cohort. These people are already part of a research cohort and familiar with research, which will reduce recruitment problems.

If we cannot recruit enough participants from our existing cohorts, we will also start recruiting through advertisements via Facebook or local newspapers.

11.3 Objection by minors or incapacitated subjects

Not applicable

11.4 Benefits and risks assessment, group relatedness

The time investment of the participants is 4.5 hours for the baseline measurement and another 3 and 3,5 hours for both the follow-up measurements, distributed over four visits and some measurements at home. At home they will wear an activity tracker and sleep

tracker for 7 days as well as fill out VAS questionnaires and a sleep diary and a subgroup will collect some saliva samples.

During the two visit days, a total amount of 22ml blood will be drawn by means of vena puncture. Vena puncture can cause discomfort and can result in bruising that continues up to a few days after the examinations. The OGTT can lead to nausea and vomiting.

Participants allocated to the intervention group have to adhere to the minimally invasive intervention protocol. They are asked to expose themselves to a bright light for 30 minutes each morning, to adhere to sleep instructions, and to wear light dimming goggles in the evening. While following this intervention protocol, participants can remain participating in their usual activities as much as possible.

Participants have no direct benefit from this study. We hope to find that participants in the intervention group will have an improved sleep timing, and that they have lower blood glucose levels. Additionally, also participants in the control group will receive instructions on sleep hygiene and all participants will be able to receive or keep the blue light blocking goggles after the study has ended. By participating in the study, new data on the health of the participant can also be detected. If clinically relevant health information is discovered, a participants general practitioner will be informed. Participants who do not want to be informed about incidental findings cannot participate in the study.

In relation to the possibility of damage, the severity of potential harm and the vulnerability of the participants, it is concluded that the conduct of the research involves a negligible risk to human participants and, although it might cause some burden, is therefore still justified.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. Dispensation from research subject insurance is requested, as participating in the study is without risk.

11.6 Incentives (if applicable)

Participants will receive parking tickets, reimbursement for travel costs as well as a VVV certificate of €40 for participation in the study.

12 ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The handling of personal data complies with the Dutch Personal Data Protection Act (AVG/GDPR). The data of all participants that will participate in the present study will be coded. All participants have already an identification number, consisting of four numbers, obtained during previous research. Numbering started at '0001' and increased with inclusion of participants. These numbers cannot be traced to the person without the key, which is stored separately. The key document is only available to the participating investigators. The data of each participant will be stored into a Case Record Form (CRF, patient data file) and into a computer file for analysis. The participants will be informed in writing about these data storing and handling procedures. Participants can request the information stored in their CRF. The investigators will perform the administration of the study. Data will be kept for 15 years at the research center in Hoorn (location of the Amsterdam UMC department of Epidemiology and Data Science) and will be used by the researchers to answer similar research questions.

12.2 Monitoring and Quality Assurance

The study qualifies as a negligible risk study. Monitoring of the study will be performed according to the NFU guidelines.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

12.4 Annual progress report

The start date of the study will be communicated to the METC. The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.
In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

This trial will be registered in a public trial registry before the first patient is recruited. Publication will be in accordance with the basic principles of Central Committee on Research Involving Human Subjects (CCMO) statement on publication policy.

13 STRUCTURED RISK ANALYSIS

Not applicable

13.1 Potential issues of concern

No issues of concern are reported for the use of a registered product within the indication and not in combination with other products.

13.2 Synthesis

The OGTT can possibly lead to nausea and vomiting, however, these are rare and manageable side effects. When participants are familiar with these side effects of the OGTT, they will be exempt from the measurement.

In relation to the possibility of damage, the severity of potential harm and the vulnerability of participants, it is concluded that the conduct of the research involves a negligible risk to the participants and is therefore justified.

14 REFERENCES

1. Wittmann M, Dinich J, Merrow M, Roenneberg T. Social jetlag: misalignment of biological and social time. Chronobiology international. 2006;23(1-2):497-509.
2. Caliandro R, Streng AA, van Kerkhof LWM, van der Horst GTJ, Chaves I. Social Jetlag and Related Risks for Human Health: A Timely Review. Nutrients. 2021;13(12).
3. Rutters F, Lemmens SG, Adam TC, Bremmer MA, Elders PJ, Nijpels G, Dekker JM. Is social jetlag associated with an adverse endocrine, behavioral, and cardiovascular risk profile? Journal of biological rhythms. 2014;29(5):377-83.
4. Eisenstein M. Chronobiology: stepping out of time. Nature. 2013;497(7450):S10-2.
5. Bouman EJ, Beulens JWJ, Groeneveld L, de Kruijk RS, Schoonmade LJ, Remmelzwaal S, et al. The association between social jetlag and parameters of metabolic syndrome and type 2 diabetes: a systematic review and meta-analysis. J Sleep Res. 2022:e13770.
6. Bouman EJ, Beulens JWJ, den Braver NR, Blom MT, Remmelzwaal S, Elders PJM, Rutters F. Social jet lag and (changes in) glycemic and metabolic control in people with type 2 diabetes. Obesity (Silver Spring). 2023;31(4):945-54.
7. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes research and clinical practice. 2019;157:107843.
8. Geerdink M, Walbeek TJ, Beersma DG, Hommes V, Gordijn MC. Short Blue Light Pulses (30 Min) in the Morning Support a Sleep-Advancing Protocol in a Home Setting. Journal of biological rhythms. 2016;31(5):483-97.
9. Zerbini G, Kantermann T, Merrow M. Strategies to decrease social jetlag: Reducing evening blue light advances sleep and melatonin. Eur J Neurosci. 2020;51(12):2355-66.
10. van der Meijden WP. Unpublished.
11. Jiang Q, Li JT, Sun P, Wang LL, Sun LZ, Pang SG. Effects of lifestyle interventions on glucose regulation and diabetes risk in adults with impaired glucose tolerance or prediabetes: a meta-analysis. Arch Endocrinol Metab. 2022;66(2):157-67.
12. Glechner A, Keuchel L, Affengruber L, Titscher V, Sommer I, Matyas N, et al. Effects of lifestyle changes on adults with prediabetes: A systematic review and meta-analysis. Prim Care Diabetes. 2018;12(5):393-408.
13. Koopman ADM, Rauh SP, van 't Riet E, Groeneveld L, van der Heijden AA, Elders PJ, et al. The Association between Social Jetlag, the Metabolic Syndrome, and Type 2 Diabetes Mellitus in the General Population: The New Hoorn Study. Journal of biological rhythms. 2017;32(4):359-68.
14. Woelders T, Leenheers T, Gordijn MCM, Hut RA, Beersma DGM, Wams EJ. Melanopsin- and L-cone-induced pupil constriction is inhibited by S- and M-cones in humans. Proc Natl Acad Sci U S A. 2018;115(4):792-7.
15. Sasseville A, Paquet N, Sévigny J, Hébert M. Blue blocker glasses impede the capacity of bright light to suppress melatonin production. J Pineal Res. 2006;41(1):73-8.
16. Burgess HJ, Wyatt JK, Park M, Fogg LF. Home Circadian Phase Assessments with Measures of Compliance Yield Accurate Dim Light Melatonin Onsets. Sleep. 2015;38(6):889-97.
17. Sűdy Á R, Ella K, Bódizs R, Káldi K. Association of Social Jetlag With Sleep Quality and Autonomic Cardiac Control During Sleep in Young Healthy Men. Frontiers in neuroscience. 2019;13:950.
18. Chellappa SL, Vujovic N, Williams JS, Scheer F. Impact of Circadian Disruption on Cardiovascular Function and Disease. Trends in endocrinology and metabolism: TEM. 2019;30(10):767-79.
19. Black N, D'Souza A, Wang Y, Piggins H, Dobrzynski H, Morris G, Boyett MR. Circadian rhythm of cardiac electrophysiology, arrhythmogenesis, and the underlying mechanisms. Heart rhythm. 2019;16(2):298-307.
20. Meloni M, Setzu D, Del Rio A, Campagna M, Cocco P. QTc interval and electrocardiographic changes by type of shift work. American Journal of Industrial Medicine. 2013;56(10):1174-9.

21. Murata K, Yano E, Shinozaki T. Cardiovascular dysfunction due to shift work. Journal of occupational and environmental medicine. 1999;41(9):748-53.
22. Rauchenzauner M, Ernst F, Hintringer F, Ulmer H, Ebenbichler CF, Kasseroler MT, Joannidis M. Arrhythmias and increased neuro-endocrine stress response during physicians' night shifts: a randomized cross-over trial. European heart journal. 2009;30(21):2606-13.
23. Casellini CM, Parson HK, Richardson MS, Nevoret ML, Vinik AI. Sudoscan, a noninvasive tool for detecting diabetic small fiber neuropathy and autonomic dysfunction. Diabetes Technol Ther. 2013;15(11):948-53.
24. Blundell JJJ. Appetite control: Methodological aspects of the evaluation of foods. Obesity Reviews. 2010;11(3):251-70.
25. Hill AJ, Magson LD, Blundell JE. Hunger and palatability: tracking ratings of subjective experience before, during and after the consumption of preferred and less preferred food. Appetite. 1984;5(4):361-71.
26. Pullman RE, Roepke SE, Duffy JF. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). Sleep medicine. 2012;13(6):703-6.
27. Jafarzadeh Esfahani M, D. Weber F, Boon M, Anthes S, Almazova T, van Hal M, et al. Validation of the sleep EEG headband ZMax. bioRxiv. 2023:2023.08. 18.553744.
28. Wilhelm I, Born J, Kudielka BM, Schlotz W, Wüst S. Is the cortisol awakening rise a response to awakening? Psychoneuroendocrinology. 2007;32(4):358-66.
29. Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, et al. Free Cortisol Levels after Awakening: A Reliable Biological Marker for the Assessment of Adrenocortical Activity. Life Sciences. 1997;61(26):2539-49.
30. LAUDAT MH, CERDAS S, FOURNIER C, GUIBAN D, GUILHAUME B, LUTON JP. Salivary Cortisol Measurement: A Practical Approach to Assess Pituitary-Adrenal Function. The Journal of Clinical Endocrinology & Metabolism. 1988;66(2):343-8.
31. Flens G, Smits N, Terwee CB, Dekker J, Huijbrechts I, Spinhoven P, de Beurs E. Development of a Computerized Adaptive Test for Anxiety Based on the Dutch-Flemish Version of the PROMIS Item Bank. Assessment. 2019;26(7):1362-74.
32. Becker J, Fliege H, Kocalevent RD, Bjorner JB, Rose M, Walter OB, Klapp BF. Functioning and validity of a Computerized Adaptive Test to measure anxiety (A-CAT). Depress Anxiety. 2008;25(12):E182-94.
33. Simone PR, Femke R, Brian LT, Michael LW, Giel N, Amber AWAvdH, et al. Self-reported hypoglycaemia in patients with type 2 diabetes treated with insulin in the Hoorn Diabetes Care System Cohort, the Netherlands: a prospective cohort study. BMJ Open. 2016;6(9):e012793.
34. Streppel MT, de Vries JH, Meijboom S, Beekman M, de Craen AJ, Slagboom PE, Feskens EJ. Relative validity of the food frequency questionnaire used to assess dietary intake in the Leiden Longevity Study. Nutr J. 2013;12:75.
35. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5.
36. van der Pal KC, Koopman ADM, Lakerveld J, van der Heijden AA, Elders PJ, Beulens JW, Rutters F. The association between multiple sleep-related characteristics and the metabolic syndrome in the general population: the New Hoorn study. Sleep medicine. 2018;52:51-7.
37. Juda M, Vetter C, Roenneberg T. The Munich ChronoType Questionnaire for Shift-Workers (MCTQShift). Journal of biological rhythms. 2013;28(2):130-40.
38. Brouwer A, Nguyen HT, Snoek FJ, van Raalte DH, Beekman ATF, Moll AC, Bremmer MA. Light therapy: is it safe for the eyes? Acta Psychiatr Scand. 2017;136(6):534-48.