A cross-sectional study to assess night-shift work related exposures and their association with markers of biological perturbation

Published: 02-02-2015
Last updated: 21-04-2024

This study aims at, first, assessing the most relevant exposure aspects of night-shift work and, second, identifying biomarkers for both acute and chronic circadian disruption associated to these specific nightshift work aspects. By applying…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON43599

Source
ToetsingOnline

Brief title
CLOCKWORK

Condition

- Other condition

Synonym
stress markers (cortisol) and 24-hour rhythm markers (melatonin)

Health condition

Biomarkers, circadian and biological disruption markers

Research involving

Human

Sponsors and support

Primary sponsor: Universiteit Utrecht
Source(s) of monetary or material Support: Rijksinstituut voor Volksgezondheid en Milieu (ministerie van Volksgezondheid;Welzijn en Sport)

Intervention

Keyword: Biomarker, Circadian rhythm, Exposure assessment, Night work

Outcome measures

Primary outcome

We will assess the following night-shift work dimensions: disturbed social pattern, behavioral changes including diet and physical activity, disturbed sleep, nutrition at night, light at night, and sun exposure. We have developed a suite of tools to measure these dimensions including traditional epidemiological methods (questionnaires and logs), objective exposure measurement devices (actimetry sensors, Psychomotor Vigilance Task (PVT) using a smartphone, and light sensors). Study parameters that will be assessed in blood are traditional circadian biomarkers (cortisol and melatonin), aspects of metabolic syndrome, expression of the known clock genes, inflammatory markers, reproductive hormones, metabolism biomarkers, complete blood counts (CBC), and vitamin D status. Urine samples will be used to assess melatonin.

Primary study parameters are:

* Lifestyle aspects

* 24hr activity pattern

* 24hr exposure pattern

* 24hr dietary pattern

* Sleep quality

* 24hr exposure to light

* Behavioral and social changes

* Psychomotor Vigilance Task test

* Clock gene expression in peripheral blood

* Markers of metabolic syndrome in peripheral blood

* Chronotype

* Blood pressure

* Body Mass Index

* Waist circumference

* Melatonin in 24hr urine

* Complete blood counts (CBC, infections, immune system)

In the sub-study:

Primary study parameters are:

* Clock gene expression in peripheral blood

* Markers of metabolic syndrome in peripheral blood

* Complete blood counts (CBC, infections, immune system)

* Cellular biomarkers of functional response to infection in peripheral blood

Secondary outcome

In addition to the primary study parameters we will assess a suite of OMICs

markers in the blood samples to conduct

exploratory analyses of short- and long- term markers of night-shift work. The

gut microbiome will be assessed in a feces

sample and hair samples will be used to assess cortisol levels (secondary

parameters).

Secondary study parameters are:

* Cortisol determined in hair sample

* OMICS markers determined in blood sample

* Microbiome markers determined in feces

In the sub-study:

In addition to the primary study parameters we will assess a suite of OMICs

markers in the blood samples to conduct exploratory

analyses of short- and long-term markers of night-shift work.

Study description

Background summary

Night-shift work impact

Night work has become an unavoidable part of our industrial society. In developed countries approximately 15-20% of the working population is working in shifts and this percentage is increasing. There is growing evidence that shift work, and especially night-shift work, disrupts lifestyle and circadian rhythm and therefore contributes to the development of chronic disorders, including cardio-metabolic diseases and cancer. In 2007, the IARC (International Agency for Research on Cancer) classified shift work involving circadian disruption as probably carcinogen in humans.

Previous research

In the last decades many studies have assessed the effects of night-shift work on health-related outcomes, with inconsistent results. In most cohort studies that have been conducted to date night work is assessed using simple metrics (e.g. *ever done night work* , or *duration of years of night work*). Also, previous research has been performed on effects of night-work on intermediate markers, including hormonal levels, clock gene expression, and alertness. So far, not much research has been performed on long-term or chronic disruptions in response to night work between recently started and more experienced night workers. Effects of night work on reproductive hormones and clock gene expression is still a matter of debate since findings vary between previously conducted studies.

Research gap

Even though the term night-shift work encompasses a wide range of different *exposure* aspects, night-shift work is in previous studies often not further defined, leading to a knowledge gap in actual mechanisms through which night-shift work might have an impact on health. To better assess the potential causal link between shift work and chronic disorders, we will need to appreciate details of night work. The following night-shift work aspects (potential mechanisms) have been hypothesized: light at night, nutrition at night, disturbed sleep pattern, disturbed social pattern, altered amount of sun exposure, and behavioral changes (diet, physical activity). Hypothesis on mechanisms relating night-shift work to health are mainly generated in animal research and it is often unclear how to translate these findings to human studies. More information on these mechanisms, and more specific methods to measure shift-work aspects in studies researching the effects of shift work, would likely increase the statistical power to identify associated health effects, and would provide a possible solution for inconsistency in results of shift work research.

Another important research gap is the lack of long-term circadian disruption biomarkers. Chronic circadian disruption is considered an important mechanism between night-shift work and adverse health effects, yet, no biomarkers are available to assess long-term or chronic circadian disruption. Long-term markers would be useful for cohort studies and would possibly identify high risk groups or behaviors related to night work. Moreover, when researching both night-shift work aspects and biomarkers, biomarkers can be related to specific aspects of night work instead of night work in general, resulting in more informative conclusions about which aspects are most disruptive (reflect most disruptions in biomarkers). We will use OMICs techniques (i.e. transcriptomics, epigenetics, proteomics) to agnostically investigate perturbations on a molecular level to generate new hypotheses for future research. Animal studies using OMICs technologies have already identified potential long-term/chronic disruption biomarkers. These results provide support for using these technologies in identifying chronic disruption biomarkers.

Study objective

This study aims at, first, assessing the most relevant exposure aspects of night-shift work and, second, identifying biomarkers for both acute and chronic circadian disruption associated to these specific nightshift work aspects. By applying detailed questionnaires and objective monitors we will be able to quantify specific aspects of the complex mixture of exposures together defined as *night-shift work*. We will associate these aspects with intermediate health outcomes, including known biomarkers of circadian disruption, to identifying which aspects contribute most to biological perturbations. In addition, we aim to identify new biomarkers reflecting chronic circadian disruption due to night-shift work.

In the sub-study:

The goal of the Klokwerk-licht study is to identify new biomarkers reflecting chronic circadian disruption due to night-shift work.

Study design

The design of the study will be cross-sectional. We will include 300 female nurses. The participants will be divided into three groups: recently started night-shift workers (<2 year), long-term night-shift workers (working in night shifts for over 5 years) and non-shift workers (controls* did not perform night or shift work >10 years). Night-shift workers and controls will be included in our study for six (2x two consecutive days and 1x two consecutive nights) and four (2 x two consecutive days) days, respectively. Exposure measurements will be conducted continuously for the duration of the study, while biological sampling will be conducted at the end of each two day (night) session.

After inclusion in the study, participants will receive a baseline questionnaire via regular mail. Via the questionnaire we will assess baseline characteristics of the study participants and previous exposure to night-shift work. At the beginning of the study we will distribute an actimetry device and a light sensor. We will ask participants to keep a short daily log, including questions regarding sleep behavior, work (shift) schedule, activity and other health behavior for the full duration of the study.

In addition, on the second day of each two-day session we will ask participants to keep a log regarding their dietary pattern as well. We will distribute a smart phone (used to conduct a psychomotor vigilance task (PVT) test). On the second day of each two-day session biological sampling will take place. Biological sampling will consist of whole blood, 24hour urine, hair and a feces spot sample.

Collection of biological samples for a day-shift session will take place during

an afternoon shift, because during this shift participants are least disrupted. Biomarker sampling after a night shift will take place at 8.00 AM, directly after the night shift. Participants will fill out a biological questionnaire for each two-day session to assess recent disease and medication use among other parameters that might potentially disturb biomarker measurements.

In the sub-study:
The original Klokwerk study (running until the end of 2016) is a cross-sectional study conducted among 150 nurses. Within this study population an intensive study protocol (taking a maximum of 6 days to complete) has been applied. The protocol consists of filling out questionnaires, wearing sensors, and donating biological material. Within the Klokwerklicht study a small part of the protocol will be applied among a group of 150 individuals that have not yet participated in the original Klowkerk study. The protocol consists of filling out two questionnaires and donating blood. We will use the same study groups as in the original Klokwerk study: nurses/paramedics that never worked in night shifts, nurses/paramedics that worked less than 2 years in night shifts, and nurses that worked more than 5 years in night shifts. Participants will be recruited from the hospital and healthcare centers where the original Klokwerk study is conducted.

Study burden and risks

As this is an observational study the risk of adverse events due to participation in this study is negligible. Burden for study participants involves filling out questionnaires and logs, conducting Psychomotor Vigilance Task tests, wearing light and activity measuring devices for the duration of the study, and biological sampling. Slight inconvenience for the subjects is expected resulting from wearing devices. Subjects will wear an actigraphy device, day and night for two days in a row (four days in total for control subjects and six days in total for night workers), in order to measure sleep, movement and activity levels. Furthermore, at the same time, they will wear a UV-sensitive light sensor to record UV and light intensity received by a participant. At baseline the participants have to fill in an extensive questionnaire and during the measurement period of two times two days they will also keep a short daily log about their work schedule, sleep and health behavior. On the days we collect blood samples (two times in total for control subjects and three times in total for night workers), we will ask them to fill out a nutritional log as well. This might take some time during work and might therefore be inconvenient as well. Finally, 24-hr urine, feces, hair, and a blood sample (4 tubes, 21 ml in total) will be collected from the subject. Subjects might experience discomfort due to the collection of biological samples. Collecting blood may provoke a hematoma which usually disappears fast. Also the collection of hair might cause reluctant reactions, though this does not lead to any health risk for the participant. Collecting feces and 24-hour urine might make participants uncomfortable. In order to make the study more

feasible, the biomarkers are divided in primary and secondary biomarkers. Primary biomarkers are of high priority, and crucial to answering the main question of the study. Willingness to participate in these measurements are part of the inclusion criteria of the study. Secondary biomarkers are needed to answer additional research questions and of less priority. In total the contact duration between the researchers and the participants regarding the entire study will be approximately 1.5 hours.

The participants have no direct benefit from participating in the CLOCK WORK study. This research can provide useful information for society. It can give a better understanding of the potential adverse effects of night work on humans. Desired, participants will receive a personal report with the most important and interpretable outcome measures. The report will provide data on chronobiology (day / night rhythm), blood pressure, cholesterol, glucose, sleep outcomes, BMI, and complete blood counts. DNA measurements in blood are not in this report, since the measured values only have meaning at group level. However, after the entire research project is finished, the participants will receive a report of the main results of the study. If test results from this study suggest a health hazard for the participant, we will report to the participant (if desired). If
the participant wishes, we will also tell her doctor about this test results.

Contacts

Public
Universiteit Utrecht

Yalelaan 2
Utrecht 3584 CM
NL
Scientific
Universiteit Utrecht

Yalelaan 2
Utrecht 3584 CM
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Subject is between 18 years and 65 years of age by the time of performing the screening questionnaire.
- Subjects are female.
- Subjects are nurse or employed in a paramedic profession.
- Subjects either have not worked in a profession requiring shift work for over 5 years, just started working in night shifts (<2 year) or worked in night-shifts for over 5 years.
- Subjects are willing to give blood, fill out the questionnaires, and wear the sensors.;For the sub-study the same inclusion criteria apply with the exception of the last one. This criterion is replaced with:
- Subjects are willing to give blood and fill out the questionnaires.

Exclusion criteria

- Subject is a smoker or ex-smoker for less than 6 months since baseline of study inclusion. Occasional smokers that have smoked less than 100 cigarettes in their lifetime are considered non-smokers.
- Subject has a doctor diagnosed chronic disease/disorder (i.e. CVD, metabolic syndrome, diabetes).
- Subject has/had cancer excluding non-melanoma skin cancer.
- Subject uses beta-blockers, or melatonin supplementation.
- Subject was pregnant in the last 6 months or is planning to become pregnant in the next 12 months.
- Subject is in fertility treatment.;Exclusion criteria for the sub-study are the same

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-04-2015
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	02-02-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51501.041.14