MOODSTRATIFICATION IMMUNOSTRATA Groningen
Premature immune ageing to predict the effect of physical training intervention in mood disorders

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Primary objective:To assess whether the state of premature immune aging (senescent CD8+ T cells) predicts treatment response to physical endurance intervention therapy in depressed patients. We will compare the mood-beneficial effects of physical...

Ethical review	Not approved
Status	Will not start
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON54984

Source
ToetsingOnline

Brief title
IMMUNOSTRATA Groningen

Condition

- Mood disorders and disturbances NEC

Synonym
mood disorders; bipolar disorder & major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: mood disorders, physical training, premature immune aging

Outcome measures

Primary outcome

High and low senescent CD8 T cells (either determined by CD28 negativity or CD57 positivity), i.e. higher or lower than the mean of the senescent CD8+ T cells in the total depression group at base-line. Response to treatment will be analysed via HDRS-17 score improvement and responders and non-responders will be defined via the 50% improvement in HDRS-17 score

Secondary outcome

Other immune senescence markers

1. High and low number of *senescent* CD4+ T cells in the effector memory (EM) and effector memory re-expressing CD45RA (EMRA) populations

2. High and low signs of monocyte senescence: Monocyte gene expression of mitochondrial apoptosis (BAX, BCL10, EGR1, EGR2) and the SASP related gene TNF

3. High and low signs of the monocyte inflammatory pyroptosis state: Monocyte gene expression of the inflammatory genes IL-1A, IL-1B, IL-6, CCL20 and TNFAIP3

4. Correlates of high and low signs of the monocyte senescent and inflammatory state in whole blood material TEMPUS): The gene expression of

amongst others BAX, SERPINE1, TGFBR3, NFATC2, TNFAIP3, FOXP3 and CD8

5. High or low levels of the T cell senescence related growth serum

factor IL-7

6. High or low levels of the inflammaging serum factors hsCRP and IL-6

Study description

Background summary

Physical training intervention is hypothesized to alleviate signs of premature aging of the immune system in mood disorder (MD) patients and has concomitantly beneficial effects on the depression severity.

The premature immune aging state can predict treatment response to physical training.
Therefore, MD patients with the most outspoken premature immune aging (i.e. those with signs in the highest tertile) respond better than those with weak or absent premature immune aging (i.e. those with signs in the lowest tertile).

The signs used for the definition of premature immune aging are:
1. an increased monocyte apoptotic/SASP gene expression (or a correlate thereof in a whole blood preparation),
2. a positive CMV antibody status
3. reduced serum levels of IL-7
4. increased serum levels of hsCRP and IL-6.

Study objective

Primary objective:
To assess whether the state of premature immune aging (senescent CD8+ T cells) predicts treatment response to physical endurance intervention therapy in depressed patients. We will compare the mood-beneficial effects of physical endurance training in all depressed patients and in those with high versus those with low signs of premature aging of the immune system.

Secondary objectives:
To compare the longer term socio-economic beneficial effects of physical endurance training in all depressed patients and those with high versus those with low signs of premature aging of the immune system.
To compare the signs of a premature aging of the immune system before and after physical endurance training in mood disorder patients.

To assess whether the state of chronic inflammation indeed predicts treatment response to TAU with first-line antidepressants (serotonergic/noradrenergic) in depressed patients as it did in our previous studies and in the literature. We will therefore compare the mood-beneficial effects of the first line TAU drugs in all depressed patients and in those with
a) high versus low levels of hsCRP,
b) high versus low levels of IL-6,
c) high versus low levels of pro-inflammatory monocytes and leukocytes.
To construct easy and clinical applicable (finger prick) assay to measure immune senescence and chronic inflammation in depressed patients

Study design

We will include 2 groups in this study to assess the role of exercise training on the immune system in MD. The MD patients will be randomized into 2 groups: Treatment as usual (TAU) and TAU combined with exercise training.

Intervention

Participants in group 1 will receive treatment as usual (TAU), i.e. pharmacotherapy plus clinical management.

Participants in group 2 will receive TAU combined with exercise training, consisting of a cycling exercise. The participants in the exercise groups will do a cycling exercise of 30 minutes, 3 times every week, during a period of 8 weeks.
In the training program, the Functional Threshold Power (measured with ergometry) will be used to choose the optimal heart rate range for each patient. The intensity level will increase from 45-50% to 50-60% in the second week, to 60-65% in the third week and up to 65-70% from the fifth week on. These increases are necessary to ensure a high enough intensity.

Study burden and risks

Burden
Baseline measurement (including interview, questionnaires, blooddraw, ergometry) for patients will take approximately 120 minutes.
End of treatment measurement (including questionnaires, blooddraw, ergometry)) for patients will take approximately 90 minutes.
The follow op meeting for patients will take approximately 60 minutes.
The physical training intervention, for half of the patients, will take 35 minutes, 3 times per week, during 8 weeks.

Risks
We do not expect major safety problems related to the study parameters. During the blood sample drawing and fitness test qualified study personal will be

present. As the study is conducted in the hospital, participants can receive medical attention if required.

Benefit
The study provides no benefits for the participating participants.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients
- A depressive episode in the course of unipolar or bipolar disorder with a HDRS-17 score >13
- Meets DSM criteria for MDD or BD established by MINI interview.
- Age 18-65 years

- Preferably already on an anti-depressant and/or mood stabilizer apparently without success
- Signed informed consent, able to understand, speak and write the national language

Exclusion criteria

- Use of beta blockers or other medication affecting hearth frequency
- Abnormalities on ECG (other than normal sinus rhythm)
- Chronic use of anti-inflammatory drugs
- Existing cancer or history of cancer in the last 5 years (except skin epidermoid cancer or in-situ cervix cancer)
- Existing or planned pregnancy or lactation
- Schizoaffective disorders, schizophrenia
- Immediate risk for suicidal behavior (3 on HamD-17 rating scale
- Known current uncontrolled systemic disease (e.g. LE, RA).
- Known major uncontrolled metabolic disorder (e.g. diabetes, hyper- or hypothyroidism, Cushing disease of Addison disease).
- Known other significant uncontrolled somatic/organic/neurological disorder, such as or diabetes or stroke which may affect mood.
- Current or recent (last 4 weeks) use of somatic medication which may affect mood or the immune system (e.g. corticoids, anti-inflammatory drugs, immune suppressive drugs).
- Participation in a study of an investigational drug or device concomitantly or within 30 days prior to this study
- Patients thought to be unreliable or incapable of complying with the requirements of the protocol
- Patient is relative of, or staff directly reporting to the investigator

Healthy controls:
- Chronic use of anti-inflammatory drugs
- Existing cancer or history of cancer in the last 5 years (except skin epidermoid cancer or in-situ cervix cancer)
- Known current uncontrolled systemic disease (e.g. LE, RA).
- Known major uncontrolled metabolic disorder (e.g. diabetes, hyper- or hypothyroidism, Cushing disease of Addison disease).
- Known other significant uncontrolled somatic/organic/neurological disorder, such as or diabetes or stroke which may affect mood.
- Current or recent (last 4 weeks) use of somatic medication which may affect mood or the immune system (e.g. corticoids, anti-inflammatory drugs, immune suppressive drugs).
- Pregnancy

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	125
Type:	Anticipated

Ethics review

Not approved

Date:	31-05-2021
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
Other	Ingediend bij NTR, nog niet toegewezen.
CCMO	NL74885.042.20