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# Immune System Function and its Relation to Depression: How Exercise can Alter the Immune System-Depression Dynamics

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## Abstract

Using data of 2,057 participants in the Dutch Lifelines database we explore the relationship between innate immune system response and acute (depressed for 2 weeks) or chronic (depressed for 2 years) depression in people. We then explore how riding a bicycle, a popular sport and mode of transport in the Netherlands, moderates this relationship. Focusing on acute depression, we found it associated with higher eosinophil, neutrophil and basophilic granulocyte cell counts but not with monocyte cell count. Increased cell count in innate immune responses in the case of depressed people comes from the fact that depression increases pro-inflammatory cytokines (e.g., IL-1, IL-6 and TNF-α) which are secreted by innate immune system cells. However, when a depressed person regularly rides a bike, the cell counts of both eosinophil and neutrophil granulocyte increased to secrete anti-inflammatory cytokines like IL-6 and IL-10 which help to reduce the effects of depression. Chronic depression is associated with increased cell counts of basophilic, eosinophil, neutrophil granulocytes and monocytes. Again, regular cycling increases cell counts of eosinophil and neutrophil granulocytes and monocytes which leads to the secretion of anti-inflammatory cytokines to lessen the effects of depression. These findings allow us to better understand how depression, innate immune system and exercise (cycling) are related.

**Keywords:** Immune system response; Short- and Long-term Depression; Exercise; Cycling; Interventions

## Introduction

In the world today, depression has become one of the most common and difficult social illness affecting about 4.4% to 25% of the population worldwide. Depression may have various symptoms, but some of them are changes in behavior, loss of interest or pleasure in daily activities, fatigue, insomnia, constant weight gain or weight loss etc. [1]. Symptoms of depression include feelings of sadness, decreased interest or pleasure in activities, insomnia or hypersomnia, loss of energy, feelings of worthlessness or inappropriate guilt, diminished concentration and thoughts about death or suicide [1]. The relationship between the activation of inflammatory immune system responses and depression has been known for a long time [2]. Depressive symptoms and related stress was first associated with a decline in natural killer (NK) cells and T cells in the learned immune system, leading to the assumption that reduction of NK activity is a reliable indicator of depression [3].

Reasons for these effects are elevated levels of corticotrophin-releasing hormone (CRH) in the CNS that reduces immune responses, especially NK cell count, and activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis (HPA), where cortisol suppresses immune responses. Later, depression was found to be directly related to pro-inflammatory cytokine secretion, such as IL-1, IL-6 and TNF-α secreted by the innate immune system that includes eosinophil, neutrophil and basophilic granulocyte and monocyte cells. These cytokines increase both CRH and the HPA axis and disrupt glucocorticoid receptor functioning thus creating a self-reinforcing inflammatory cascade. Other molecular mechanisms caused by cytokines such as IL-2, IFN-α lead to the depletion of tryptophan known as the precursor of serotonin and thus the cause of depression [4].

Here we use data based on epidemiological research to study the relationship between innate immune system responses and depression. First, using the Lifelines database (a large Dutch dataset of epidemiological data), we focus on the distinction between acute depression (experienced in the last 14 days) and chronic depression (experienced in the last two years). The literature bases the difference between acute and chronic depression on the recurrence of acute episodes (generally up to two to three weeks) which build up to chronic depression (lasting two years or more) [5]. Secondly, because pro-inflammatory cytokines secreted by innate immune system responses are found to be a major cause of depression, we focus on the cell counts of innate immune system: eosinophil, neutrophil and basophilic granulocytes and monocytes. Each of these cells secrete specific cytokines which escalate the process of depression [4]. As the difference between acute and chronic depression is based on duration and severity, we expect that these immune system responses will affect acute and chronic depression differentially [5].

Evidence is rising for complex reciprocal communication in the pathways in the nervous, endocrine and immune systems. This complex communication also might appear in depression dynamics. In line with this, researchers have proposed various theories on the relation between immune system functioning and depression [6,7]. Most theories and findings point to how the balance or interaction between anti-inflammatory and pro-inflammatory cytokines affect the emergence of depression [4,8,9]. A recent theory conjectures that depression comes with a shift in Th1/Th2 immune response balance toward Th1 (pro-inflammatory) [10] where Th2 are the anti-

inflammatory cytokines. Th2 immune response starts the depression process by secreting IL-5 (an anti-inflammatory cytokine secreted by monocytes) which is involved in the activation of Th1 immune response, including eosinophil granulocytes. Other researchers find a similar function for IL-6 which also triggers Th1 immune response [11].

Evidently Th1 immune response in depressed people secrete higher levels of pro-inflammatory cytokines IL-1, IL-2, IL-12, IL-13, GM-CSF, INF-g, and TNF-α. However, in depressed people, Th2 immune response secrete low concentrations of the anti-inflammatory cytokines IL-4, IL-5, IL-6, IL-10, and IL-13. Th2 immune response is reduced during depression due to the increased production of pro-inflammatory cytokines by Th1 immune response. This rise in pro-inflammatory cytokines comes with other effects in different pathways. For instance, it has been shown that lower IL-5 levels in depression comes with reduced serotonin (5-HT) and norepinephrine levels [4]. Experimentally induced allergy leads to overexpression of IL-5 in the brain as well as to depressive symptoms [12]. Therefore, IL-5 may function as a mediator in the pathway from inflammation to depressive symptoms upstream of the changes in the neurotransmitter metabolism of depressed patients [4].

In the depression cascade, the pro-inflammatory cytokines affect behavioral, neuroendocrine and neurochemical dynamics of the body and also act as neuromodulator for the brain [6]. HPA axis is highly sensitive to the secretion levels of pro-inflammatory cytokines. High levels of pro-inflammatory cytokines disturb the negative feedback inhibition of circulating corticosteroids (CSs) on the HPA axis.

High levels of pro-inflammatory cytokines in depression, create deficiency in serotonergic (5-HT) neurotransmission, thus lowering the 5-HT levels. Pro-inflammatory cytokines reduce the availability of serotonin precursor, tryptophan (TRP) through activation of the TRP-metabolizing enzymeindoleamine-2, 3-dioxygenase (IDO) [6].

Although the high levels of pro-inflammatory cytokines are believed to produce most of the symptoms occurring in depression, it remains to be established whether pro-inflammatory cytokines play a causal role in depressive illness or represent epiphenomena without major significance. Repeated recurrence of acute depression periods leads to chronic depression. We test whether the innate immune cell count is related to both kinds of depressions [5].

From here we hypothesize that in depressed people the cell count of pro-inflammatory cytokines (Th1 immune response) secreted by the neutrophil, eosinophil and basophilic granulocytes will be higher than anti-inflammatory cytokines (Th2 immune response). However, Th1 immune response may possibly show more prominent effects in acute depression whereas in chronic depression both Th1 and Th2 immune response may show their respective effects distinctly [4].

One meta-study on depression and pro-inflammatory cytokines found TNF-α and IL-6 (which are both Th1 immune response) to be the major cause of depression [1]. IL-6 is responsible for the activation of neutrophils [11]. An important caveat is that IL-6 has both pro- and anti-inflammatory properties in special cases. Finally, it is well known that physical activity or the lack of it has a substantial influence on the immune system [13]. IL-6 acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine (cytokine released from muscle). Exercise has extensive anti-inflammatory effects on immune system and depression as it increases the level of anti- inflammatory myokine IL-6, IL-1 receptor antagonist (IL-1 re), and IL-10 anti-inflammatory cytokine. The amount and magnitude of exercise determines the level of these anti-inflammatory effects on depression [13].

## Overview of the Study

We gathered epidemiological data from self-reports of acute and chronic depression forms by 2,057 participants in the Lifelines dataset. We studied whether these self-reports are related to cell counts of the innate immune system. While most of the literature focuses on learned immunity system cell count and depression, in recent years attention has shifted to the innate immune system mainly because the innate immune system secretes pro-inflammatory cytokines which are the triggers of depression. Specifically, it increases the level of anxiety that induces the pro-inflammatory cytokine cascade which leads to depression (IL-1 to IL-6 and TNF-α) [14]. After that we also studied effects of cycling in reducing the depression, due to secretion of anti-inflammatory myokine IL-6, IL-1 receptor antagonist (IL-1 re), and IL-10 anti-inflammatory cytokine by innate immune system cells [14].

## Research Methodology

### Data source

Data were collected from the Lifelines Cohort Study Biobank in Groningen, the Netherlands [15]. This large-scale longitudinal study collects data and biological samples and makes them available for research on healthy aging, based on a standard application procedure. Every five years, participants visit one of the Lifelines sites in the north of the Netherlands for a follow-up examination. This study is coded under Proposal no. OV16_0366 -- https://www.lifelines.nl/ and considered the data with the permission of the ERIM ethics commission of the Erasmus University Rotterdam (no. 2016/02/11-05483wve).

### Sample size

We selected a segment of the adult group in the Lifelines database, comprising 2057 participants (18–65 years of age) that had complete epidemiological information for the study of acute and chronic depression, innate immune system responses, and listed bicycling as a physical activity [16]. Note all these measures were collected simultaneously as done in most of epidemiological studies. The data is based on cross-sectional study and samples were collected in year 2016-2018 from the participants visiting Lifelines cohort.

### Depression

Responses to the cognitive mental status examination, the Mini-Mental State (MMS) scale, which includes “Did you feel depressed in the past 2 weeks?” and “Have you felt depressed in the past 2 years?”, were considered to study acute and chronic depression respectively. Both items were moderately correlated (r=0.61, p=0.03). ‘Yes’ responses were coded 1 (‘depressed’) and ‘No’ responses were coded 2 (‘not depressed’) [17]. Since the study is based on epidemiological data and not the experimental data, no ‘control group’ was formed, instead self-reported ‘depressed’ and ‘not depressed’ groups were compared against each other for both acute and chronic depression forms.

### Immune system cells

For the innate immune system cells, we selected monocytes, basophilic granulocytes, eosinophil granulocytes and neutrophil

granulocytes. Unit of count of immunity cells was 10E9/L. Blood sample were collected using EDTA Sysmex tube was used from XE2100 - System kit (Diagnostic Kompas 2003 as provided by https://www.lifelines.nl/) [18]. (Appendix Table 1).

## Cycling

The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) was used. Self-reported cycling activity was considered. People who do not perform regular cycling were coded as "1" (no cycling) and people who perform regular cycling were coded as "2" (regular cycling) [19]. In case of chronic depression form, cycling was considered for 2 years. In case of acute depression form, cycling was considered for 2 weeks.

| Variables | Total N=2057 | | Total N=2057 | |
|---|---|---|---|---|
| | Acute depression: Depressed (N=397) | Acute depression: Not-depressed (N=1660) | Chronic depression: Depressed (N=228) | Chronic depression: Not-depressed (N=1829) |
| Monocytes | 0.495 (0.169) | 0.485 (0.170) | 0.508 (0.171) | 0.485 (0.170) |
| Basophilic granulocytes | 0.035 (0.001) | 0.032 (0.000) | 0.351 (0.021) | 0.322 (0.020) |
| Eosinophil granulocytes | 0.196 (0.006) | 0.181 (0.003) | 0.206 (0.181) | 0.181 (0.119) |
| Neutrophil granulocytes | 3.556 (0.068) | 3.371 (0.033) | 3.573 (1.427) | 3.386 (1.338) |

**Table 1:** Means and standard deviations (in parentheses) of system responses for acute and chronic depression.

## Research tool

We used multivariate analysis of variance (MANOVA) with a confidence interval as 95% and followed basic assumptions such as independence of observations, dependent variable on interval measurement, dependent variables multivariate normally distributed and equal population covariance matrices for each group [20].

The analysis was conducted in two stages to understand the pro-inflammation cytokine effect of depression and anti-inflammatory cytokine effect of physical activity on depression.

**Stage 1:** Innate immune system cell counts were taken as dependent variables and acute and chronic depression were taken as independent variables.

**Stage 2:** Cycling was used as fixed factor/moderator while keeping innate immune system cell counts as dependent variables and acute and chronic depression as independent variables.

Please note that we computed MANOVA of innate immune system cell counts for acute and chronic depression separately, since both the forms of depression differ from each other based on the severity and duration of occurrence.

## Results

In first phase of the study we tested whether the means of innate immune system cell counts differed significantly between self-reported 'depressed' and 'not-depressed' groups for acute and chronic depression form, we computed MANOVA of acute and chronic depression forms separately as the independent variable and innate immunity as dependent variable.

First talking about acute depression (AD) form, self-reported 'depressed' group from showed significantly different means for innate immune system cell count compared to self-reported 'non-depressed' group for basophilic granulocytes ('Depressed'(AD) M=0.035, SD=0.001; 'Non-Depressed'(AD) M=0.032, SD=0.0; F=9.564, p=0.002, η2=0.005), eosinophil granulocytes ('Depressed'(AD) M=0.196, SD=0.006; 'Non-Depressed'(AD) M=0.181, SD=0.003; F=4.690, p=0.030, η2=0.002) and neutrophil granulocytes ('Depressed'(AD) M=3.556, SD=0.068; 'Non-Depressed'(AD) M=3.371, SD=0.033; F=6.022, p=0.014, η2=0.003) but not for monocytes ('Depressed'(AD) M=0.495, SD=0.169; 'Non-Depressed'(AD) M=0.485, SD=0.170; F=0.981, p=0.322, η2=0.0). In short, the mean value of self-reported 'depressed' group for innate immune system cell counts was found higher compared to self-reported 'non-depressed' group.

| Variables | | Acute depression | Chronic depression |
|---|---|---|---|
| Monocytes | F-value | 0.981 | 3.771 |
| | p-value | 0.322 | 0.052 |
| | η2 | 0 | 0.002 |
| Basophilic granulocytes | F-value | 9.564 | 4.103 |
| | p-value | 0.002 | 0.043 |
| | η2 | 0.005 | 0.002 |
| Eosinophil granulocytes | F-value | 4.69 | 8.038 |
| | p-value | 0.03 | 0.005 |
| | η2 | 0.002 | 0.004 |
| Neutrophil granulocytes | F-value | 6.022 | 3.927 |
| | p-value | 0.014 | 0.048 |
| | η2 | 0.003 | 0.002 |

**Table 2:** MANOVA results for innate immune system responses to acute and chronic depression.

Next talking about chronic depression (CD) from self-reported 'depressed' group showed significantly different means all innate immune system cell count compared to self-reported 'non-depressed' group for basophilic granulocytes ('Depressed'(CD) M=0.351, SD=0.021; 'Non-Depressed'(CD) M=0.322, SD=0.020; F=4.103,

p=0.043, η2=0.002), eosinophil granulocytes ('Depressed'(CD) M=0.206, SD=0.181; 'Non-Depressed'(CD) M=0.181, SD=0.119; F=8.038, p=0.005, η2=0.004), neutrophil granulocytes ('Depressed' (CD) M=3.573, SD=1.427; 'Non-Depressed'(CD) M=3.386, SD=1.338; F=3.927, p=0.048, η2=0.002) and monocytes ('Depressed'(CD) M=0.508, SD=0.171; 'Non-Depressed'(CD) M=0.485, SD=0.170; F=3.771, p=0.052, η2=0.002). Table 1 shows the mean values of the innate immune system cell counts for acute and chronic depression. Table 2 lists the MANOVA results for innate immune system cell counts for acute and chronic depression.

In second phase of the study, we tested the interactive effect between acute and chronic depression forms with cycling (as physical activity) on the innate immune system cell counts. Here, we computed MANOVA with acute and chronic depression forms and cycling interaction as independent variables and the innate immunity variables of basophilic granulocytes, eosinophil granulocytes, neutrophil granulocytes and monocytes as dependent variables. We computed MANOVA results for acute and chronic depression forms separately. The mean values and standard deviations of the innate immunity variables for the interaction between acute and chronic depression forms and cycling can be found in Tables 3 and 4.

| | **Total N=2057** | | | | **Total N=2057** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Acute depression: Depressed (N=397)** | | **Acute depression: Not-depressed (N=1660)** | | **Chronic depression: Depressed (N=228)** | | **Chronic depression: Not-depressed (N=1829)** | |
| **Variables** | No cycling (N=174) | Regular cycling (N=223) | No cycling (N=704) | Regular cycling (N=956) | No cycling (N=99) | Regular cycling (N=129) | No cycling (N=779) | Regular cycling (N=1050) |
| Monocytes | 0.489 (0.182) | 0.499 (0.160) | 0.474 (0.168) | 0.494 (0.171) | 0.485 (0.177) | 0.526 (0.164) | 0.476 (0.170) | 0.491 (0.170) |
| Basophilic granulocytes | 0.036 (0.024) | 0.034 (0.020) | 0.031 (0.019) | 0.032 (0.020) | 0.035 (0.022) | 0.034 (0.019) | 0.032 (0.020) | 0.032 (0.020) |
| Eosinophil granulocytes | 0.195 (0.146) | 0.197 (0.140) | 0.174 (0.113) | 0.185 (0.131) | 0.193 (0.124) | 0.216 (0.215) | 0.177 (0.120) | 0.184 (0.118) |
| Neutrophil granulocytes | 3.486 (1.582) | 3.610 (1.328) | 3.308 (1.389) | 3.417 (1.272) | 3.378 (1.50) | 3.723 (1.355) | 3.339 (1.422) | 3.420 (1.273) |

**Table 3:** Means and standard deviations (in parentheses) of innate immunity system responses for acute and chronic depression X cycling as physical exercise.

| | | **Acute Depression MANOVA** | | | **Chronic Depression MANOVA** | | |
|---|---|---|---|---|---|---|---|
| **Variables** | | **Acute depression** | **Cycling** | **Acute depression X Cycling** | **Chronic depression** | **Cycling** | **Chronic depression X Cycling** |
| | F-value | 1.163 | 2.6 | 0.275 | 3.244 | 5.499 | 1.079 |
| | p-value | 0.281 | 0.107 | 0.6 | 0.002 | 0.019 | 0.03 |
| Monocytes | η2 | 0.001 | 0.001 | 0 | 0.002 | 0.003 | 0.001 |
| | F-value | 10.174 | 0.113 | 0.874 | 4.244 | 0.017 | 0.152 |
| | p-value | 0.001 | 0.737 | 0.35 | 0.04 | 0.896 | 0.697 |
| Basophilic granulocytes | η2 | 0.005 | 0 | 0 | 0.002 | 0 | 0 |
| | F-value | 5.058 | 0.689 | 0.421 | 7.325 | 2.635 | 0.705 |
| | p-value | 0.025 | 0.054 | 0.052 | 0.007 | 0.047 | 0.04 |
| Eosinophil granulocytes | η2 | 0.002 | 0.003 | 0.001 | 0.004 | 0.001 | 0.001 |
| | F-value | 5.961 | 2.331 | 0.011 | 3.203 | 4.979 | 1.928 |
| | p-value | 0.015 | 0.027 | 0.017 | 0.004 | 0.026 | 0.017 |
| Neutrophil granulocytes | η2 | 0.003 | 0.001 | 0.002 | 0.002 | 0.002 | 0.001 |

**Table 4:** MANOVA results for innate immunity system responses to acute and chronic depression X cycling as physical exercise.

Here acute depression (AD) form consisted of self-reported 'depressed' and 'non-depressed' group. Cycling consisted 'no cycling' and 'regular cycling' groups. The interaction between the acute depression form and cycling resulted in 4 groups namely 'Depressed-

no cycling (AD)', 'Depressed-regular cycling (AD)', 'Not depressed- no cycling (AD)' and 'Not depressed- regular cycling (AD)'. All 4 groups had a significantly different means for cell counts of eosinophil granulocytes (Depressed-no cycling (AD) M=0.195, SD=0.146; Depressed-regular cycling (AD) M=0.197, SD=0.140; Not depressed-no cycling(AD) M=0.174, SD=0.113; Not depressed- regular cycling (AD) M=0.185, SD=0.131; F=0.421, p=0.052, η2=0.001) and neutrophil granulocytes (Depressed-no cycling (AD) M=3.486, SD=1.582; Depressed-regular cycling (AD) M=3.610, SD=1.328; Not depressed- no cycling(AD) M=3.308, SD=1.389; Not depressed-regular cycling(AD) M=3.417, SD=1.272; F=0.011, p=0.017, η2=0.002) but not on basophilic granulocytes (Depressed-no cycling (AD) M=0.036, SD=0.024; Depressed-regular cycling (AD) M=0.034, SD=0.020; Not depressed- no cycling(AD) M=0.031, SD=0.019; Not depressed- regular cycling (AD) M=0.032, SD=0.020; F=0.874, p=0.035, η2=0.0) or monocytes (Depressed-no cycling (AD) M=0.489, SD=0.182; Depressed-regular cycling (AD) M=0.499, SD=0.160; Not depressed- no cycling (AD) M=0.474, SD=0.168; Not depressed-regular cycling (AD) M=0.494, SD=0.171; F=0.275, p=0.6, η2=0.0). Amongst all 4 groups, Depressed-regular cycling (AD) had highest mean value for innate immunity cell counts.

However, chronic depression (CD) form also consisted of self-reported 'depressed' and 'non-depressed' group. Here also cycling consisted 'no cycling' and 'regular cycling' groups. The interaction between the chronic depression form and cycling resulted in 4 groups namely 'Depressed-no cycling (CD)', 'Depressed-regular cycling (CD)', 'Not depressed- no cycling (CD)' and 'Not depressed- regular cycling (CD)'. The interaction between chronic depression and cycling showed a significant difference on means of cell counts of eosinophil granulocytes (Depressed-no cycling (CD) M=0.193, SD=0.124; Depressed-regular cycling (CD) M=0.216, SD=0.215; Not depressed-no cycling (CD) M=0.177, SD=0.120; Not depressed- regular cycling (CD) M=0.184, SD=0.118; F=0.705, p=0.004, η2=0.001), neutrophil granulocytes (Depressed-no cycling (CD) M=3.378, SD=1.50; Depressed-regular cycling (CD) M=3.723, SD=1.355; Not depressed-no cycling (CD) M=3.339, SD=1.422; Not depressed- regular cycling (CD) M=3.420, SD=1.273; F=1.928, p=0.017, η2=0.001) and monocytes (Depressed-no cycling (CD) M=0.485, SD=0.177; Depressed-regular cycling (CD) M=0.526, SD=0.164; Not depressed-no cycling (CD) M=0.476, SD=0.170; Not depressed- regular cycling (CD) M=0.491, SD=0.170; F=1.079, p=0.03, η2=0.001) but not on basophilic granulocytes (Depressed-no cycling (CD) M=0.035, SD=0.022; Depressed-regular cycling (CD) M=034, SD=0.019; Not depressed- no cycling(CD) M=0.032, SD=0.020; Not depressed-regular cycling (CD) M=0.032, SD=0.020; F=0.152, p=0.0.697, η2=0.0). Amongst all 4 groups, Depressed-regular cycling (CD) had highest mean value for innate immunity cell counts.

Results in first stage of study show that the 'depressed' group of chronic depression form had highest mean values for innate immunity cell counts, followed by 'depressed' group of acute depression form. The groups 'not- depressed' for acute and chronic depression forms showed the lowest values for all innate immunity variables indicating that depression leads to inflammation and increase in secretion of pro-inflammatory cytokines (e.g. IL-2, TNF α, IL-6) via increased number of innate immune system cell counts. Results in second stage of study shows that 'depressed group' in acute and chronic depression forms who perform regular cycling have the highest innate immune system cell counts compared to other groups. It is believed physical exercise promotes secretion of anti-inflammatory cytokines (e.g., IL-6, IL-10) through a process of increased innate immune system cell counts and muscle contraction. Anti-inflammatory cytokines are very helpful in the treatment of depression, thus people suffering from acute or chronic depression are advised to take up a physical activity or exercise of their choice.

Seeking to support our findings, we also performed chi-square test and cross-tabulation between cycling and acute and chronic depression groups. First, a significant relation was found between cycling and acute depression, X2 (1, N=2057)=5.419, p=0.020 (Appendix Tables 2 and 3). Similarly, a significant relation was found between cycling and chronic depression, X2 (1, N=2057)=8.172, p=0.004 (Appendix Tables 4 and 5). Cross-tabulation found that the maximum people who do cycling were not depressed (for both acute and chronic forms). This strengthens the conjecture that cycling helps to reduce the effects of depression and might help in the treatment of the depressed (Appendix Tables 2, 3, 4 and 5).

## Discussion

This paper looks at two forms of depression, namely acute and chronic depression [5]. Depression is conceived as a result of different pro-inflammatory and anti-inflammatory cytokines secreted by innate immune cells that show complex communication patterns between the pathways of the nervous, endocrine and immune systems [4,7,21,22]. In order to make the translational implications for this study we studied whether engagement in sports would affect these immune system dynamics and their effects on other systems [2,13,23]. Exploring this holistic view is the main goal of this paper. A review of the literature showed that the findings and conclusions are not always harmonious, which is understandable given the complexity of immune system functioning [4,8,24]. Therefore, our introduction to this paper mainly discussed how pro-inflammatory and anti-inflammatory immune system interaction provokes complex dynamics (in terms of the Th1/Th2 immune response ratio which tends to go to the Th1) [4]. Please also note that we did not study cytokines as such. Given the limitations of the Lifeline dataset, we focused on the innate immune system cells that secrete these cytokines [25].

First, in the case of people with acute depression, innate immune system cells – basophilic, eosinophil and neutrophil granulocytes – exhibit increased cell counts compared to non-depressed people [3,25]. This increase in cell count leads to secretion of pro-inflammatory cytokines such IL-1, IL-6, TNL-α, IFN-ɣ via eosinophil and neutrophil granulocytes [3,26-30]. It also reduces serotonin uptake and increases histamine (which contributes to inflammation) via basophilic granulocytes [31-35]. Note that basophilic granulocytes also secrete IL-4 (an anti-inflammatory cytokine) [36], which reduces production at the time of acute depression [9] and also affects the activation of pro-inflammatory cytokines such as IL-1 and IL6 via which subsequently activate eosinophil and neutrophil granulocytes [37]. Our data in general data substantiates this conjecture. Indeed, in acute depression, basophilic, eosinophil and neutrophil granulocytes showed significantly increased cell counts. However, the monocytes did not [6]. Note that Song et al., [9] have observed that the ratio of IFN-ɣ/IL-4 increased in depressed patients due to activity of eosinophil, neutrophil and basophilic granulocytes; this finding confirms our findings in this paper. Please also note that the non-acutely depressed people (who self-reported the option 'not depressed in the past 14 days') actually had lower innate immune cell counts, thus indicating that they do not secrete pro-inflammatory cytokines and have normal serotonin levels [35].

Second, in the case of chronic depression, which reflects repeated occurrence of acute depression for a period of two or more years [5], all innate immune system cells showed increased cell counts compared to non-depressed people [25]. In the chronically depressed, monocytes secrete IL-5 (an anti-inflammatory cytokine) which activates the production of eosinophil and neutrophil granulocytes [4]. Eosinophil granulocytes secrete pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-13 and TNL-α [28]. On the other hand, basophilic, neutrophil and eosinophil granulocytes together increase the secretion of IL-1, IL-6, TNL-α, IFN-ɣ, chemokines, lectins and other proteins which leads to hyper inflammation [4,11,29]. Monocytes also produce IL-6 which again contributes to further inflammation. Increased pro-inflammatory cytokine level works as a potent modulator of corticotrophin releasing hormones which produce high-lightened HPA axis activity characterized by an increase in adrenocorticotropic hormone (ACTH) and cortisol, which leads to the emergence of chronic depression [4,21]. Again, our data in general substantiate these conjectures. Indeed basophilic, eosinophil, neutrophil granulocytes as well as the monocytes showed significant increased cell count [1,38]. Similar to the non-acute depressed group, here the non-chronically depressed group (who self-reported the option 'not depressed in the past two years') also had lower innate immune cell counts, indicating that the innate immune cells do not provoke the pro-inflammatory responses that lead to depression [4,25].

Some cytokines, however, possess both pro-inflammatory and anti-inflammatory properties, such as IL-6 [13,39]. When people engage in sports, cycling in this case, the innate immune system cells start to secrete anti-inflammatory cytokines like IL-6 and IL-10 [27]. During exercise, contracting skeletal muscles are the main source of production of IL-6 which is accompanied by increased cell count of neutrophil and eosinophil granulocytes in acute depression [27] and additional increase in monocyte cell count for chronic depression [8]. In the case of acute depression, when people do strenuous exercise like cycling, their eosinophil and neutrophil granulocyte cell count increases to secrete anti-inflammatory cytokines IL-6 and IL-10 [9,27]. In the case of chronic depression, cycling however, increased cells count of monocytes, eosinophil and neutrophil granulocytes, which promote secretion of anti-inflammatory cytokines like IL-6, IL-10, IL-4 and IL-5. Additionally, monocytes, which also secrete anti-inflammatory cytokines like IL-5, which facilitate the feedback inhibition of the HPA axis. This results in a lower concentration of pro-inflammatory cytokines [24]. Monocytes also increase the release of endogenous cytokine antagonists such as IL-1 receptor antagonist and IL-10, which reduce the detrimental impact of inflammatory changes on neurotransmitter function [8,9,21].

## Conclusion

In a nutshell, this study shows that when studying how depression relates to immune system functioning, researchers need to distinguish between acute and chronic depression [3,5,40]. In addition, our finding on cycling, both a popular mode of transport and sports in the Netherlands, actually reduced depression via the reduction of pro-inflammatory cytokines [24,41]. In order to gauge whether people who frequently ride bicycles actually feel less depressed, we used chi-square and cross tabulations and found that people who engage in intense cycling indicated via self-reports that they had lower levels of depression than people who do not engage in cycling [42].

## Study Limitations

The relationships found in our research are significant but their adjusted R2 is relatively low. This, however, is a common result in the epidemiological literature. Also note that our data comes from a general population and depression was self-reported. Thus, any differences between healthy and unhealthy participants are minor. Differently put, the participants in the study were not treated for depression and neither did they underwent treatment in a mental institution. Finally, this is not an experimental condition, but an epidemiological study, which might explain the low correlations. This is also why we refrained from considering the exact neuro-endocrine and immune system pathways and chose to build on existing theoretical frameworks proposed for example by Schmidt et al. [4] and Schiepers et al. [6].

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## Disclosures

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