Diplomarbeit

BIPOLAR DISORDER AND PHYSICAL ACTIVITY
Correlation between physical activity and clinical parameters in bipolar disorder

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Eidesstattliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe, andere als die angegebenen Quellen nicht verwendet habe und die den benutzten Quellen wörtlich oder inhaltlich entnommenen Stellen als solche kenntlich gemacht habe.

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Zusammenfassung

Einleitung: Die bipolare Störung (BD) wird von einer großen Zahl an Komorbiditäten (Ko-M) und erhöhter Mortalität begleitet. Speziell Übergewicht und Adipositas, sowie systemische Entzündung und kognitive Defizite zeigen eine hohe Prävalenz und nehmen im Verlauf der Erkrankung zu. Es wurde gezeigt, dass Bewegung einen positiven Effekt sowohl auf diese Ko-M, als auch auf psychiatrische Symptome hat.

Ziel: Das Ziel dieser Studie war es, Korrelate von Bewegung, die den Verlauf der bipolaren Störung beeinflussen, zu identifizieren. Darüber hinaus wurde das Bewegungsverhalten mit gesunden Kontrollpersonen verglichen.

Methode: Im Rahmen der BIPFAT Studie an der Univ.-Klinik für Psychiatrie und Psychotherapeutische Medizin der Medizinischen Universität Graz füllten 119 bipolare PatientInnen, welche zum Zeitpunkt der Testung euthym waren, und 71 gesunde Kontrollpersonen den "International Physical Activity Questionnaire (IPAQ)", welcher das Bewegungsverhalten der vergangenen sieben Tage erfasst, aus. Des Weiteren wurden Blutwerte und klinische Parameter erhoben.

Ergebnisse: PatientInnen und Kontrollpersonen wiesen keine Unterschiede im selbst-berichteten Bewegungsverhalten auf. Body Mass Index (BMI), das globale Funktionsniveau (GAF), sowie die Kognitionsparameter für Aufmerksamkeit, Gedächtnis und exekutive Funktionen korrelierten mit Bewegung. Inflammation, klinische Parameter und andere kognitive Werte zeigten keinen Zusammenhang mit Sport.

Diskussion: Ein positiver Zusammenhang zwischen Bewegung und BMI, Aufmerksamkeit, Gedächtnisleistung, Exekutivfunktionen und dem GAF konnte reproduziert werden. Es konnte kein Zusammenhang zwischen Bewegung und Entzündung, sowie klinischen Parametern gefunden werden. Bewegung stellt demnach eine geeignete Therapieunterstützung dar, da sie im Zusammenhang mit Ko-M der

bipolaren Störung wie kognitiver Leistungsfähigkeit und Gewicht steht. Zur genaueren Verifizierung wären weitere Daten aus besser objektivierbaren Quellen, die über einen längeren Zeitraum erhoben werden, sinnvoll.

Abstract

Introduction: A high number of co-morbidities (Co-M) and increased mortality accompany bipolar disorder (BD). Especially Overweight and Obesity, systemic inflammatory processes and cognitive deficits are highly prevalent and increase within the course of illness. Physical activity (PA) was found to have beneficial effects not only on psychiatric symptoms, but also on Co-M such as reduced weight, better neurocognitive performance and reduced inflammation in former studies.

Aim: The aim of the study is to identify correlates of PA in patients suffering from BD that influence the course of the disease. Moreover, the PA behaviour of patients was compared to healthy controls.

Methods and Participants: 119 patients, euthymic at point of testing, and 71 healthy controls completed the self-reported "International Physical Activity Questionnaire (IPAQ)" interrogating PA of the past seven days. Furthermore, inflammatory biomarkers and clinical parameters were gathered.

Results: There was no difference in the self-reported PA behaviour between patients and controls. Body Mass Index (BMI), global functioning (GAF) and cognitive parameters such as attention, memory and executive functioning correlate with PA in BD. Inflammatory markers, clinical presentation of BD and premorbid IQ are not correlated to PA in the cohort.

Conclusion: A positive correlation between PA and BMI, attention, memory, executive functioning and GAF were found. However, the study could not support previous findings suggesting that PA correlates with inflammatory state of body and clinical parameters. In conclusion, sport seems to offer a concomitant therapy, as it is ncorrelated to cognitive functioning and weight. However, further data concerning PA

from a less subjectivity prone questionnaire investigating PA behaviour over a longer period are necessary to verify past findings.

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Abbreviations

APA…..American Psychiatric Association

BD…..Bipolar Disorder

BD-I…..Bipolar-I Disorder

BD-II…..Bipolar-II Disorder

BDNF…..Brain-Derived Neurotrophic Factor

BMI…..Body Mass Index

Co-M…..Co-Morbidities

CNS…..central nervous system

CRP…..C-reactive Protein

CVD…..cardiovascular disease

CVLT…..California Verbal Learning Test

DM…..Diabetes Mellitus

DSM-IV.....Diagnostic and Statistical Manual of Mental Disorders IV

GCS-F…..Granulocyte Colony Stimulating Factor (GCS-F)

HAMD…..Hamilton Rating Scale for Depression

HPA…..Hypothalamus-Pituitary-Adrenal Axis

HPT…..Hypothalamus-Pituitary-Thyroid Axis

I-IP…..Immune-Inflammatory Processes

IGF-1…..Insulin-Like Growth Factor

IL-6…..Interleukine-6

KYA…..Kynurenic Acid

KYN…..Kynurenin

MWT-B…..multiple word choice test

NS…..Nitrosaminic Stress

OB…..Obesity

OS…..Oxidative Stress

OW…..Overweight

PA…..Physical Activity

PIA…..Physical Inactivity

SCID…..Structural Clinical Interview

TMT-A…..Trail Making Test – A

TMT-B…..Trail Making Test - B

TNF-alpha…..Tumor Necrosis Factor - Alpha

TRY..…Tryptophan

3-HK…..3-hydroxykynurenin

WHO…..World Health Organisation

YMRS…..Young Mania Rating Scale

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1 Introduction

In the EU the tremendous amount of over one third (38.2%) of the population suffers from mental problems (Wittchen et al., 2011). However, even though acceptance and understanding of these illnesses are growing, patients suffering from psychiatric illness still have to face a big stigmatisation.

Just like with most psychiatric diagnoses, the exact mechanism and pathologies underlying bipolar disorder (BD) are still greatly unknown and receive increasing interest of international research. Furthermore, BD is a severe psychiatric diagnosis influencing the lives of the affected greatly, not only due to the mood symptoms but also due to the high number of co-morbidities (Co-M) accompanying BD.

The psychopharmacological treatment of BD is based on the individual response to the various substances and therefore sometimes results in a process of trying out different substances until the correct one for the patient is found. In addition, medication often leads to an increase in Co-M, especially overweight (OW), resulting in non-compliance and worsening of the course of BD. As a result, concomitant therapies targeting Co-M of BD should be established.

Physical activity (PA) was found to have beneficial effect on numerous of the Co-M accompanying BD. Neurocognitive deficits, systematic inflammation and mood episodes could be targeted using PA. Therefore, the following thesis analysed PA in a Styrian cohort of patients suffering from BD with the aim of identifying PA correlates. Moreover, it tried to offer a basis for further investigations, hoping to gain data allowing exercise interventions to be accepted as concomitant therapy not only by doctors, but also by patients.

1.1 Bipolar Disorder

Even though BD has gained increasing interest from international research in the last years, the aetiology is still not completely clarified. However, the great number of Co-M and the elevated mortality accompanying BD is very well documented.

The World Health Organization (WHO) states that BD is the "sixth most disabling" diagnosis in the world (Murray & Lopez, 1997 cited in Alsuwaidan, Kucyi, Law & Mcintyre, 2009; Janney et al., 2014). Furthermore, BD is a diagnosis that causes high costs for society (Janney et al., 2014). This indicates that research on BD is crucial to improve the personal situation of patients affected but also to decrease the financial and social burden of BD on society.

1.1.1 Definition, Symptoms and Diagnosis

BD is an affective disorder. It is characterised by a repeated switch between depressive and manic episodes. Since a great variety in course and symptoms of BD has been identified, these are being summarized into the so-called "bipolar spectrum" (Möller, Laux & Kapfhammer, 2011; Bauer, 2012; Tölle & Windgassen, 2012).

The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) of the American Psychiatric Association (APA) differentiates between Bipolar-I- (BD-I) and Bipolar-II-disorder (BD-II). Furthermore, a single manic episode and cyclothymia are counted among the BD spectrum. Beside depression, BD-I shows manic episodes, while BD-II shows hypomanic episodes (Möller et al., 2011; Tölle & Windgassen, 2012; Rothenhäusler & Täschner, 2013; Young & Oldani, 2013). Möller et al. (2011) states that patients generally might experience more depressive, than manic episodes (ratio of 3:1), BD-II even shows 37 times more depressive than manic symptoms.

1.1.1.1 Mania and Hypomania

Mania is an inadequately elevated mood, a euphoric mental state. The following table summarizes the DSM-IV criteria necessary for the diagnosis of a manic phase:

Criterion A	1a. euphoric/elevated and/or b. irritable mood 2a. for at least one week and/or b. hospitalization necessary due to the severity of the symptoms
Criterion B	In addition: at least three (with 1a.) or four (with 1b.) of the following symptoms must be present: - elevated drive/ psychomotorical restlessness - logorrhoea - fast thinking - insomnia - megalomania - distraction - loss of social inhibition (increased money spending with ensuing debt, risky behaviour, increased libido)
Criterion C	Moreover, stated symptoms must lead to: a. hospitalization and/or b. impairment of social or occupational life and/or c. be accompanied by psychotic symptoms However note that psychosis must not occur separately from the affective episodes
Criterion D	organic reasons or substance abuse as cause for mania must be excluded

Table 1: DSM-IV Criteria for Mania (Möller et al., 2011; Bauer, 2012; Tölle & Windgassen, 2012)

Typical for manic episodes is also the lost insight within the disease. Hypomania in comparison is defined as a mild to moderate state of manic symptoms. The euphoric or irritated mood only has to be present for a minimum of four days. Furthermore, the symptoms must not lead to impairment in daily life or to hospitalization (Möller et al., 2011; Bauer, 2012; Tölle & Windgassen, 2012; Wittchen, Zaudig & Fydrich, 1997).

1.1.1.2 Depression

Depression is marked by decreased mood and drive. The following table summarizes the DSM-IV criteria necessary for the diagnosis of a depressive phase:

Criterion A	1. depressive mood 2. for at least two weeks 3. during the major time of the day
Criterion B	In addition: 1. loss of interest and 2. lost pleasure of activities that normally were considered positive
Criterion C	Furthermore at least five out of the 7 following criteria must be fulfilled: 1. lack of energy/fatigue 2. feeling of guilt/worthlessness 3. thoughts of death/suicide 4. reduced concentration/thinking ability/ decision making 5. psychomotorical restlessness or reduction 6. sleep dysbalance 7. change in appetite and weight (gain or loss)
Criterion D	must not be as a result to substance abuse, organic reasons or sorrow

Table 2: DSM-IV Criteria for Depression (Möller et al., 2011; Bauer, 2012; Wittchen et al. 1997)

1.1.2 Epidemiology

BD-II and major depressive disorder seem to lie on a continuous spectrum (Akiskal & Benazzi, 2006) and around 70% present with depressive primary symptoms (Möller et al, 2011). Therefore, correct diagnosis of BD still remains difficult and under-diagnosis can be the consequence (Möller et al., 2011; Young & Oldani, 2013).

Rothenhäusler and Täschner (2013) state that lifetime prevalence for BD-I lies at 0.3-1.5%, for BD-II at 5.5%. However, data concerning the prevalence of BD is diverse.

Moreover, the onset of BD usually occurs in early adulthood or late adolescence, and occurs at a mean of 25-30 years (Möller et al., 2011; Bauer, 2012; Rothenhäusler & Täschner, 2013).

1.1.3 Prognosis and Course of Illness

While the course of BD is very diverse, it can generally be said, that it is a chronic illness with a periodic course and recurrent symptoms (Möller et al., 2011; Young & Oldani, 2013). Bauer (2012) states that 10% of the patients experience over ten episodes during their lifetime. Furthermore, Fagiolini et al. (2013) stated that up to 35% of patients never completely recover from their episodes and that residual and prodromal symptoms are common. Therefore, BD seems to have a continuous impact on the life of the affected patients.

It is being reported, that BD is a progressive illness resulting in a permanent change in neural activity and brain structure. This phenomenon is called "neuroprogression" and is marked by increasing cognitive deficits. This degeneration of the central nervous system (CNS) might be driven by several mechanisms such as chronic inflammatory and oxidative processes (Kucyi, Alsuwaidan, Liauw & Mcintyre, 2010; Fries et al., 2012; Anderson & Maes, 2015).

„Neuroprogression refers to the changes occurring over time with recurrent episodes being associated with increased apoptosis, neurotoxicity, decreased neuroplasticity and neurogenesis and increased OS (oxidative stress) and NS (nitrosaminic stress)-driven oxidative damage, leading to lipid peroxidation, protein oxidation, DNA damage and autoimmunity, and hypernitrosylation." (Anderson & Maes, 2015, page 2)

Neuroprogression allows staging of BD. Kapczinski et al. (2009) have created a staging method based on neuroprogressive symptoms, allowing for the separation of the patients into 5 different groups of growing severity of disability. It could be shown, that

several abnormalities in biomarkers seem to increase with these groups (Kapczinski et al., 2009; Fries et al., 2012).

Furthermore, Möller et al. (2011) state that 25-50% of the patients commit a suicide attempt during the course of the illness and 30-60% show a handicap in their psychosocial functions. This shows that BD is a severe mental illness, demanding better understanding and treatment.

1.1.4 Aetiology

The question of the aetiology of BD is still not completely answered. Numerous models indicating a multifactorial genesis exist. While a strong genetic basis is being discussed, the environmental factors must not be underestimated (Möller et al., 2011; Bauer, 2012). However, Barbour, Edenfield and Blumenthal (2007) state that the cause of BD is primarily biological, indicating that external influences can only trigger the illness when pre-existing susceptibility for BD exists, but not cause it.

1.1.4.1 Genetics

Möller et al. (2011) state that BD seems to have a heritability of up to 80%, and that first-degree relatives of patients suffering from BD have a 10 times elevated risk of being diagnosed with BD themselves. Several genes have been identified leading to susceptibility for BD (Möller et al., 2011; Bauer, 2012).

1.1.4.2 Neuroanatomy

Moreover, studies have shown that patients with BD have pathologies concerning their brain anatomy. To name only some examples - a reduction of mass in the hippocampus, frontal and prefrontal cortex, have been identified. Furthermore, white

matter hyper-intensities were reported in structural imaging studies (Birner et al., 2015). However, while these abnormalities seem to increase with progression, it is not yet certain whether the abnormalities drive the course or the episodes lead to the abnormalities (Möller et al., 2011; Fries et al., 2012).

1.1.4.3 Biochemistry

The neurotransmitter hypothesis, which is common in psychiatric diseases, also comes up in the explanation of BD. In BD the neurotransmitter being discussed as relevant for the genesis of the illness are serotonin, noradrenaline and dopamine (Alsuwaidan et al., 2009; Möller et al., 2011). While during mania noradrenaline seems to be elevated, in depression serotonin, dopamine and noradrenaline seem to be reduced (see table 2; Alsuwaidan et al. 2009).

1.1.4.4 Neuroendocrinology

Most importantly, the hypothalamus-pituitary-adrenal axis (HPA) and the hypothalamus-pituitary-thyroid axis (HPT) have to be named when talking about endocrinological aetiology of BD. The over-activation of the HPA leads to an increased secretion of cortisol and adrenergic hormones. This results in a constant activation of stress and change in immunological processes. These processes have been named to be causes for neurocognitive dysfunction and depression (Möller et al., 2011; Kucyi et al., 2010).

1.1.4.5 Neuroplasticity

The neuroplasticity is reduced in BD. This results from the fact, that neurotrophins such as brain-derived neurotrophic factor (BDNF) seem to be altered in BD (Möller et al., 2011; Fries et al., 2012; Barbosa et al., 2012).

1.1.5 Treatment

Geddes and Miklowitz (2013) state that even under psychiatric treatment, a big number of patients show recurrent symptoms. This indicates that the current treatment possibilities are not satisfying and new or supportive options have to be found. Moreover, treatment targeting the numerous Co-M of BD should be established. The treatment of BD is based on three main areas:

A. Treatment of acute phase

B. Stabilization of symptoms after an episode

C. Long-term relapse prophylaxes

(Möller et al., 2011; Geddes & Miklowitz, 2013; Bauer, 2012).

1.1.5.1 Pharmacological Treatment

The medication that has been proven most efficient as a mood stabilizer is lithium. However, the side effects and risks of this treatment must not be underestimated. Moreover, anticonvulsants, antipsychotics and antidepressants are used to treat BD (Möller et al., 2011; Geddes & Miklowitz, 2013). Generally, it can be seen that medication, especially psychotropic substances, has a broad range of side effects, such as increased appetite and weight gain.

1.1.5.2 Psychotherapy

In addition to the psychopharmalogical treatment the concomitant psychotherapy ist of great importance. As a supportive method to medication psycho-education and cognitive-behavioural therapy have shown to be effective (Möller et al., 2011; Geddes & Miklowitz, 2013).

1.1.6 Co-Morbidities and Mortality

BD is not only associated with numerous Co-M but also with elevated mortality compared to the general population (Barbour et al., 2007; Kucyi et al., 2010; Swartz & Fagiolini, 2012). The rates of Co-M tend to increase with the progression of the illness (Fries et al., 2012), and deteriorate the prognosis of the illness (Swartz & Fagiolini, 2012). It is interesting to note, that people with BD are twice more likely to suffer from another psychiatric illness than to suffer solely from BD (McElroy, 2001, cited in Fagiolini et al., 2013).

Reasons for the increased prevalence of medical CO-M seem to be an unhealthy lifestyle, pharmacological treatment and mood episodes (Kilbourne et al., 2007; Goodrich & Kilbourne, 2010). Nevertheless, other factors as for example common inflammatory pathways linking obesity (OB), diabetes mellitus (DM) and BD have been discussed (Reininghaus et al., 2014).

1.1.6.1 Overweight and Obesity

OW and OB are the best studied CO-M of BD. It was shown that OW/OB are more prevalent in BD than in the general population (Elmslie, Silverstone, Mann, Williams & Romans, 2000; Elmslie, Mann, Silverstone, Williams and Romans, 2001; Fagiolini, Kupfer, Houck, Novick & Frank, 2003). Reininghaus et al. (2014) identified, that 70% of patients with BD are OW. Side effects of the medication is one reason for the elevated occurrence of OW/OB in BD (Maina, Salvi, Vitalucci, D'ambrosio & Bogetto, 2008; Kucyi et al., 2010; Gurpegui et al., 2012; Geddes & Miklowitz, 2013; Young & Oldani, 2013; McElroy et al., 2002).

However, Maina et al. (2008) showed, that OB and OW is already more prevalent in drug naive BD population compared to healthy controls and other drug naive mentally

ill populations. Therefore, unhealthy lifestyle, accompanying especially depressive episodes, but also mania, might be further reasons for the high occurrence of OW (Swartz & Fagiolini, 2012; Young & Oldani, 2013).

Moreover, it is interesting to note, that OB and OW are associated with a more severe course of BD, higher relapse rates and non-recovery (Fagiolini et al., 2003; Silveira et al., 2014, Reininghaus et al. 2014). This results in the hypothesis, that BD and OB have a common pathogenetical pathway leading to a reciprocal amplification of the diseases. OB, just as BD, has been shown to be associated with a chronic inflammatory state of the body (Wolowczuk et al., 2012). While it was shown that there is an association between OB, inflammation and depression, the pathogenetic direction and exact pathways still remain uncertain (Miller, Freedland, Carney, Stetler & Banks, 2003; Luppino et al., 2010).

1.1.6.2 Immune Inflammatory Processes

BD shows an activation of immune-inflammatory processes (IIP). T-cell activation and pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-alpha) and interleukine-6 (IL-6) and acute-phase proteins for example C-reactive protein (CRP) are raised whereas anti-inflammatory cytokines are reduced (Breunis et al., 2003; Alsuwaidan et al., 2009; Anderson & Maes, 2015). Alterations in OS and NS, and tryptophan (TRY) pathway have been shown leading to the belief that BD is a multisystemic illness resulting in numerous Co-M (Berk et al., 2011; Anderson & Maes, 2015; Reininghaus et al., 2014;). Leboyer et al. (2012) even state that BD can be viewed as a "systemic multi inflammatory disease" and that this systemic inflammation might be the connection between BD and high prevalence of CVD in BD.

IL-6 elevation, especially during mania, and TNF-alpha increase has been identified, but other pro-inflammatory cytokines also seem to play a role. While pro-

inflammatory markers are elevated in BD during every phase, even in remission, these alterations are especially present during acute phases (Langan & McDonald, 2009; Anderson & Maes, 2015).

The inflammatory state promotes the TRY breakdown, leading to reduced levels of TRY and serotonin (Johnson, El-Khoury, Aberg-Wistedt, Stain-Malmgren & Mathe, 2001; Miller, Llenos, Cwik, Walkup & Weis, 2008; Capuron et al., 2011; Myint, 2012; Anderson & Maes, 2015). This high turnover was being associated with depression and corresponding symptoms such as pessimism, and reduced motivation (Capuron et al., 2011), probably due to the reduced serotonin levels. This dysbalance in TRY breakdown leads to an increased Kynurenine (KY) to TRY ratio (Myint et al., 2007; Wolowczuk et al., 2012; Reininghaus et al., 2014; Anderson & Maes, 2015).

TRY catabolites have been identified as important components in neural activity and neurodegeneration. While in BD neurotoxic 3-hydroxykynurenine (3-HK) and neuroprotective kynurenic acid (KYA) are increased, the ratio is increased towards a more neurotoxic effect (Berk et al., 2011; Myint, 2012; Anderson & Maes, 2015, Reininghaus et al. 2014). This is another pathway, why IIP leads to neuroprogression and thus to a progressive course of the illness.

Among the factors increasing chronic inflammation in depressive subjects OB, stress and diet have been identified. On the other hand, this chronic inflammation might further lead to DM, depression and cardiovascular disease (CVD) risk factors (Haroon, Raison & Miller, 2012). Therefore, there seems to be a bidirectional cause of IIP in mental illnesses.

1.1.6.3 Risk Factors for Cardiovascular Disease

Moreover, BD is accompanied by risk factors leading to CVD. These risk factors include OB, smoking, hypertension, DM and dyslipidaemia (Möller et al., 2011; Young & Oldani, 2013; Janney et al., 2014).

A bad lifestyle (e.g. sedentary behaviour and bad nutrition) that is especially seen during depressive episodes combined with the severe side effects of psychopharmacological drugs, such as weight gain, lead to a high mortality associated with CVD in BD (Swartz & Fagiolini, 2012; Young & Oldani, 2013). Shah et al. 2007 showed, that BD patients engage less in PA (reduced exercise tolerance) compared to persons without mental illness. This fact supports the appearance of CVD risk factors.

It has to be noted, that the chronic inflammatory state of BD seems to support the creation of CVD, as inflammation is a crucial pathophysiological mechanism in the development of coronary heart disease. For example, IL-6 and CRP have been identified as cardiac mortality predictors (Miller et al., 2003; Swartz & Fagiolini, 2012).

Moreover, it is interesting to note, that CVD was found to develop earlier in life in BD than in healthy controls (Swartz & Fagiolini, 2012). Studies reported the occurrence of CVD in BD 15 years earlier than in healthy controls, and 6 years earlier than in major depressive patients (Goodrich & Kilbourne, 2010).

1.1.6.4 Neuropsychological abnormalities

There is growing evidence, that BD is accompanied by cognitive impairment. While this is especially present during mania and depression (Dixon, Kravariti, Frith, Murray & Mcguire, 2004) it is also detectable during euthymia/remission (Gurpegui et al., 2012; Buoli, Caldiroli, Caletti, Zugno & Altamura et al., 2014; Lackner et al. 2015). The main domains affected are executive functions, processing speed, attention, verbal learning

and memory (Robinson et al., 2006; Kucyi et al., 2010; Silveira et al., 2014; Bauer et al., 2015; Lackner et al., 2015). Lackner et al. (2015) found that people with BD differed from healthy controls in verbal learning and memory.

The number of past episodes and the duration of the illness seem to positively correlate with the cognitive deficits (Martinez-Aran et al., 2004; Barbosa et al., 2012; Buoli et al., 2014; Rosa et al., 2014). When considering the Kapczinski scale, there seems to be evidence, that individuals at a later stage of illness show worse cognitive functioning than healthy controls, while BD individuals at an earlier stage of disease have fewer cognitive deficits (Kapczinski et al., 2009; Rosa et al., 2014). While some data indicates that patients with BD-I perform worse in memory than BD-II (Bora, Yucel, Pantelis & Berk, 2011), others found that BD-II performs worse than BD-I in memory, IQ and executive functions (Summers, Papadopoulou, Bruno, Cipolotti & Ron, 2006).

It becomes more evident, that OB/OW is associated with neurocognitive impairment (Yim et al., 2012; Lackner et al. 2015). While there are hypotheses circulating, that the high prevalence of OB in BD advance the neurocognitive impairment, the findings still remain controversial. Lackner et al. (2015) found that OW BD subjects perform worse than normal weight BD patients. Furthermore, Yim et al. (2012) found that Body Mass Index (BMI) was negatively correlated with cognitive measures in BD. However, Silveira et al. (2014) found that OB as comorbidity was not shown to worsen neurocognition.

As there is data, identifying neurocognitive impairments even during euthymia, these deficits cannot simply be explained by depressive and manic symptoms. For example, Fries et al. (2012) explains that changes in the prefrontal cortex might be the explanation for mood instability and cognitive dysfunction. Another possible reason for these cognitive impairments is the imbalance of pro-inflammatory and neurotrophic factors (Barbosa et al., 2012). Increased IIP levels have been associated with cognitive

dysfunction in BD (Anderson & Maes, 2015; Berk et al. 2011). Moreover, the phenomenon of neuroprogression as a reason for these impairments is also getting growing interest (Torres, Boudreau & Yatham et al., 2007).

1.2 Physical Activity

PA is defined as skeletal muscle movement leading to energy usage (McCormick et al., 2008). There exist data that recommends 30 minutes of activity on most days of the week to achieve beneficial health effects (Ross, Freeman & Janssen, 2000b; Ng, Dodd, Jacka, Leslie & Berk 2007b; McCormick et al., 2008; Vancampfort et al., 2013). Warburton, Nicol & Bredin (2006) state that energy expenditure of 1000 kcal reduces mortality and that however, also lower expenditures lead to beneficial health effect. Therefore the WHO recommendations for PA for people aged 18 to 64 are at least 150 minutes of moderate-intensity or 75 minutes of vigorous intensity aerobic PA per week, each session lasting at least ten minutes (WHO, 2011).

While physical inactivity (PIA) is a risk factor for several diseases, it has been shown, that PA has a beneficial effect on various diagnosis including OB, DM, cardiovascular pathologies and dementia. Moreover, it seems to positively affect cognition and has effects on brain plasticity (Ross et al., 2000a; Warburton et al., 2006; Barbour et al., 2007; Alsuwaidan et al., 2009; Wright, Armstrong, Taylor & Dean, 2012).

1.2.1 Bipolar Disorder

BD is commonly accompanied by PIA and bad nutrition. This is connected with the high number of Co-M, worsening the course of BD. Especially by altering PA behaviour, positive effects on the course can be viewed (Sylvia et al., 2013).

As stated before, it was shown that patients suffering from BD lead an inactive lifestyle. Janney et al. (2014) investigated PA behaviour with the help of an accelometer and found, that patients with BD spend 78% of their time with sedentary (≤ 100 counts) behaviour. On the other hand, only 1.4% of the time is spent with vigorous/moderate (≥ 1952 counts) activity and 21% with light intensity activities (101 - 1951 counts) (Janney et al., 2014). Wright et al. (2012) state that the mood state, due to low motivation during depression, has been identified as a barrier for patients with BD to do PA. Furthermore, PA was found to be negatively correlated with educational status, medical Co-M, social isolation and self-efficacy in BD, while correlation with age and BMI are still inconsistent (Vancampfort et al., 2012).

The pathway of the beneficial effect of sport on mental problems is still not completely identified. However, models such as the thermogenesis, neocortical activation and amine as well as serotonin metabolism are thought to play a role. Moreover, the influence of the HPA and endorphins offer an explanation. Furthermore the psychological effects of sport such as self-efficacy and -motivation, distraction of negative thinking and stress tolerance, must not be denied. The structure regular activity induces in ones life and the reduced stress reactivity have to be named as well (Salmon, 2001; Barbour et al., 2007; Ng, Dodd & Berk, 2007a; Ng et al., 2007b; Blake, 2012; Wright et al., 2012).

While people leading an inactive lifestyle are at higher risk for depression (Barbour et al., 2007), Sylvia, Ametrano and Nierenberg (2010) indicate that PA might lead to mood stability by increasing the tolerance towards stress and decreasing the allostatic load. However, data indicates, that intensity of exercise seems to play an even bigger role than regularity (Warburton et al., 2006; Ng et al., 2007a).

So far, most studies focus on the effects of sport on depression and anxiety, which show that exercise has an anti-depressant and anxiolytic effect (Salmon, 2001; Martinsen, 2008; Vancampfort et al., 2013).

The effect of exercise in a manic phase still remains unclear. While it is believed that sport allows to get rid of excessive energy it is also believed that it could increase manic symptoms and cardiovascular strain due to a further physiological arousal (Baxter et al., 2010; Wright et al., 2012; Sylvia et al., 2013).

An intervention study focusing on nutrition, exercise and wellness showed a positive effect of PA on nutrition behaviour, Co-M, depressive symptoms and daily functioning. However, an increase in manic symptoms was also shown (Sylvia et al., 2013).

While the number of studies dealing with the effect of PA on BD and other mental diseases is ever growing, there are a lot of limitations concerning the study design. Therefore further investigations and better study protocols are necessary (Baxter et al., 2010).

1.2.2 Effects on Inflammation

PA seems to have a great influence on the immune system. Exercise affects alterations in the cytokine levels beneficially and reduces the inflammatory state of the body, due to the commonly known immune suppressant effect of exercise (Gleeson, 2006; Alsuwaidan et al., 2009; Rosa et al., 2011). However, it has to be noted, that inflammatory processes are activated and levels of pro-inflammatory cytokines such as IL-6 are raised right after a workout. IL-6 then seems to activate anti-inflammatory cytokines and the body adapts to the physical stress of exercise. It seems to be regular activity, by adapting to the

post exercise inflammation, that reduces the systemic inflammation (Pedersen & Hoffmann-Goetz, 2000; Pedersen 2000; Rosa et al., 2011, Petersen & Pedersen, 2005)

1.2.3 Effects on Neuroplasticity and Cognition

As explained before, it was shown that neural plasticity and cognition is reduced in BD. Exercise is associated with an increase in BDNF, insulin-like growth factor (IGF-1), and granulocyte colony stimulating factor (GCS-F) and therefore promotes neural plasticity and genesis. Thus, exercise could have beneficial effects on neuroprogression and thus, on cognition in BD (Kramer, Erickson & Colcombe, 2006; Barbour et al., 2007; Alsuwaidan et al., 2009; Kucyi et al., 2010; Sylvia et al., 2010; Vancampfort et al., 2013). However, data is not consistent. Kucyi et al. (2010) state that exercise has a positive impact on neurocognition, especially on domains like executive functions and verbal memory. Kramer et al. (2006) even reviews that exercise might have a beneficial effect on cognition in later life by neuroprotection. Barbour et al. (2007) reviewed that exercise improved cognitive functioning of individuals with cognitive deficits. Moreover, it is interesting to note, that especially the hippocampus, which is affected by atrophy in depression, seems to be stimulated to grow due to exercise (Alsuwaidan et al., 2009; Kucyi et al. 2010). The following figure taken from Kucyi et al. (2010) illustrates the ways in which PA beneficially influences cognition.

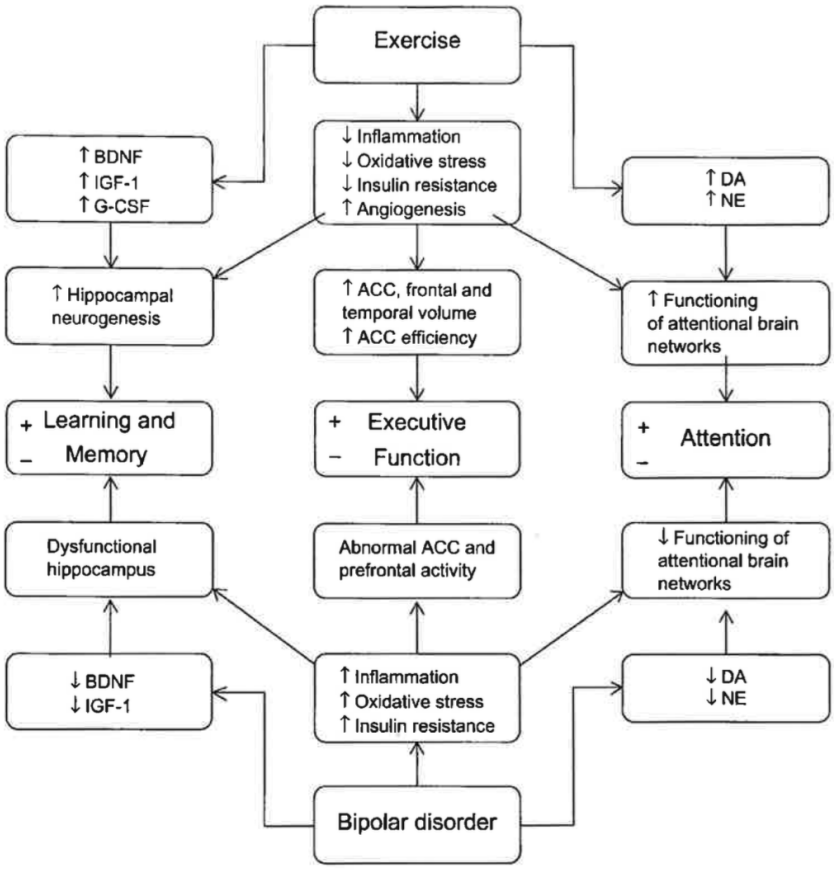

Figure 1: Effects of PA and BD on Neurocognition (Kucyi et al., 2010, page 113)

Legend: ACC…anterior cingulate cortex; BDNF…brain-derived neurotrophic factor; DA…dopamine; IGF-1… insulin-like growth factor-I; G-CSF…granulocyte colony stimulating factor; NE… norepinephrine;

1.2.4 Noradrenaline, Serotonin, Dopamine

As has been discussed earlier the monoaminergic neurotransmitters are dysregulated in BD. It was shown that these alterations could be positively influenced by exercise, as it increases the levels of the neurotransmitter in the brain and the blood (Alsuwaidan et al., 2009).

The following table summarizes the data taken from Alsuwaidan et al. (2009) and should give an overview over the pathologies in BD that could be targeted with PA.

	exercise	bipolar disorder
noradrenaline	acute: increase in plasma	in mania ↑ in depression↓
serotonin	peripheral: TRY increase central: serotonin increase	binding potential ↓
dopamine	DA synthesis increased (mouse models)	in depression ↓ in cerebrospinal fluid
inflammation	chronic: robust anti inflammation due to acute inflammatory response	pro-inflammatory cytokines ↑ anti-inflammatory cytokines ↓in mania and depression

Table 3: Effects of PA and BD on Neurotransmitters and Inflammation

1.2.5 Effects on Cardiovascular Disease

Stress leads to CVD by cardiovascular reactions and hypertension. Regular sport has been shown to reduce the effect of mental stress on the circulatory system (Blumenthal et al., 1990; Barbour et al., 2007). It is important to notice, that a decrease of relative risk for death can be achieved by increasing one's level of activity, even when suffering from other risk factors for CVD (Warburton et al., 2006). Moreover, it was shown, that PA leads to a reduction of risk factors for CVD by decreasing arterial pressure and systemic inflammation and by improving glucose levels as well as insulin sensitivity (Warburton et al., 2006; Kucyi et al., 2010).

However, an intervention study showed, that exercise in cardiac rehabilitation only showed slight improvements in CVD risk factors. Men had a bigger change in body composition than women. Moreover, the effect of training increased with the severity of lipid and glucose metabolism pathologies at the start of rehabilitation (Brochu et al., 2000).

1.3 Research Questions and Hypotheses

Based on the literature research the following research questions and hypotheses evolved in order to study the association of PA and BD.

Literature showed that BD is accompanied by PIA and sedentary behaviour leading to numerous Co-M like OB/OW (Kilbourne et al., 2007; Janney et al., 2014). Therefore the question arises whether Styrian patients with BD are less active than the healthy controls.

Research question 1: Are patients less active than controls?

Hypothesis 1a: Patients are significantly less active than the control group.

Hypothesis 1b: Patients spend significantly more time with sedentary behaviour than the control group.

OB is common in the BD population and a bad prognostic factor for the course of the illness (Maina et al., 2008; Gurpegui et al., 2012; Young & Oldani, 2013). It is commonly known, that exercise has a beneficial effect on the weight and leads to weight loss. Therefore, it is being examined, whether there exists a correlation between PA and BMI in the Styrian BD population.

Research Question 2: Is there a negative correlation between PA and BMI in patients with BD?

Hypothesis 2: BMI and PA are negatively correlated in the BD cohort.

While BD is accompanied by an activation of IIP, seen for example by an elevation of IL-6 and CRP (Langan & McDonald, 2009; Fries et al., 2012; Anderson & Maes, 2015), it was shown, that exercise has an anti-inflammatory effect (Gleeson, 2006; Alsuwaidan et al., 2009). Thus, the question arises, whether PA has an effect on IIP, marked by IL-6 and CRP, in the study population.

Research question 3: Is PA correlated to inflammatory markers, such as IL-6 and CRP, in the study population?

Hypothesis 3a: PA and IL-6 are negatively correlated.

Hypothesis 3b: PA and CRP are negatively correlated.

Some studies found alterations in the TRY breakdown in BD e.g reflected in an increased KY/TRY ratio. The catabolites increased due to this change are being identified as neurotoxic. Since OB/OW was shown to have a negative effect on this alteration, the question arises, whether PA positively affects the KYN/TRY ratio (Myint et al., 2007; Wolowczuk et al., 2012; Reininghaus et al., 2014; Anderson & Maes, 2015).

Research question 4: Is KYN/TRY ratio lower in more active patients with BD?

Hypothesis 4: PA is negatively correlated with KYN/TRY ratio.

Serotonin, noradrenalin and dopamine seem to be altered in BD. A positive effect on these alterations of PA was shown (Alsuwaidan et al., 2009; Möller et al., 2011).

Research question 5: Is there a correlation between PA and serotonin, noradrenalin and dopamine in BD?

Hypothesis 5: It is being hypothesized that there exists a positive correlation between noradrenalin, serotonin and dopamine and PA in BD.

The anxiolytic and antidepressant effect of PA is well studied (Salmon, 2001; Martinsen, 2008; Vancampfort et al., 2013). However, the effect on mania remains uncertain. Therefore, the question arises whether PA has a beneficial effect on the number of acute episodes in BD.

Research question 6: Are the number of depressive and manic episodes, such as depression/mania ratio correlated with PA in the study cohort?

Hypothesis 6a: The expectation arises, that the more active patients are, the less depressive episodes they experience.

Hypothesis 6b: Furthermore, it is being assumed, that PA and number of manic episodes correlate negatively.

Hypothesis 6c: The depression/mania ratio is negatively correlated with PA.

Since PA seems to have a beneficial effect on depressive mood (Salmon, 2001; Martinsen, 2008; Vancampfort et al., 2013) the question arises, whether PA. also beneficially influences suicidal behaviour.

Research question 7: Is there a connection between suicidal behaviour and PA in patients with BD?

Hypothesis 7: Patients who are more active are less likely to commit suicide attempts.

It was found that, PA offers patients a feeling of self-efficacy and –motivation. Moreover, PA allows a distraction of negative thinking and increases stress tolerance. In addition PA gives structure (Salmon, 2001; Barbour et al., 2007; Ng et al., 2007a; Ng et al., 2007b; Blake, 2012; Wright et al., 2012). Therefore, the question arises, whether patients performing more PA show a higher GAF than patients performing less PA.

Research question 8: Are PA and the global function level of patients with BD connected?

Hypothesis 8: GAF and PA are positively correlated.

It was found that, PA has a positive effect on neurocognition. As staging after Kapczinski et al. (2009) is based on neuroprogression the question arises whether PA and Staging are connected.

Research question 9: Are PA and Staging of BD (Kapczinski, 2009) associated?

Hypothesis 9: PA and Staging are positively connected.

The neurocognitive deficits of BD should not be underestimated. Exercise is associated with an increase in BDNF promoting neural plasticity and genesis. Thus, exercise could have a beneficial effect on neuroprogression and thus on cognition in BD (Barbour et al., 2007; Alsuwaidan et al., 2009; Kucyi et al., 2010; Sylvia et al., 2010; Vancampfort et al., 2013) Therefore, the association between exercise and neurocognition should be identified.

Research question 10: Is there a correlation between PA and cognitive markers?

Hypothesis 10a: Attention, measured by the Trail Making Test A (TMT-A), the d2 test and the Stroop Test, is positively correlated with PA.

Hypothesis 10b: Memory, measured by the California Verbal Learning Test (CVLT), is positively correlated with PA.

Hypothesis 10c: Executive functions, measured by the Stroop test and thr Trail Making Test B (TMT-B), are positively correlated to PA**.**

Hypothesis 10d: Premorbid verbal IQ, measured by the multiple word choice test (MWT-B), and PA are positively correlated.

2 Methods

The data for this thesis was gathered as a part of the *BIPFAT* study protocol (EK Nr. 24-123 ex 11/12), which is continuously being conducted at the department of Psychiatry and Psychotherapeutic Medicine at the Medical University of Graz.

2.1 Participants

Exclusion criteria for participants are acute severe medical conditions, such as systematic lupus erythematosus, chronic obstructive pulmonary disease, neurocognitive and neurodegenerative disease, inflammatory bowel disease, active cancer and haemodialysis. Moreover, participants had to be of legal age in order to be included in the study. Before the inclusion into the study, all participants gave their written informed consent.

2.1.1 Patients

The cohort includes 119 patients, recruited inpatients or from the outpatient unit for bipolar affective disorder at the Department of Psychiatry, Medical University of Graz. Patients' BD diagnosis was verified using the *Structural Clinical Interview* (SCID-I; Wittchen et al., 1997), based on the DSM-IV diagnostic criteria. Moreover, the current mental state of the patients was evaluated using standardized external rating systems: *Hamilton Rating Scale for Depression* (HAMD; Hamilton, 1960) and *Young Mania Rating Scale* (YMRS; Young, Biggs, Ziegler & Meyer, 1978). In order for a patient to be included, they had to be euthymic at time of testing. Euthymia was defined as a score of under ten points in the HAMD and under eight points in the YMRS. Current manic or depressive episodes lead to an exclusion of the patient.

2.1.2 Controls

The cohort includes 71 healthy controls. Controls were recruited from the general population. Exclusion Criteria for the controls were past or current psychiatric episodes and diagnosis, severe medical conditions and first-degree relatives suffering from psychiatric diagnosis.

2.2 Procedure

Before participants were included in the study, exclusion and inclusion criteria stated above were evaluated. After outlining the procedure and the risks and benefits of participation, a written informed consent was gathered. Next fasting blood samples were taken followed by a breakfast.

Next a standardized anamnesis gathering demographic, psychiatric and medical information as well as the neuropsychological tests were administered by trained investigators. Subsequent numerous questionnaires, including the IPAQ were filled out by the participants. On a following date a brain MRT and a carotid sonography were conducted.

2.3 Material

The following chapter explains the material used to gather the data for the examination.

2.3.1 Physical Activity Assessment

In order to assess the PA behaviour of the participants, *the long version of the self-administered International Physical Activity Questionnaire* (IPAQ) was used (see

Appendix A). The German version of the IPAQ-Long contains 27 items giving information concerning the duration and frequency in the last seven days of vigorous, moderate and low intensity activities in the four following domains: work, transportation, household and leisure activities. Additionally, sedentary behaviour is examined.

Special algorithms differentiating between the intensities of activity performed allows calculating *MET-Minutes* for each domain, and intensity of activity. MET-Minutes give an estimation of energy expenditure of the activity performed. By multiplying 1.the time spent on each activity, 2.the frequency of this activity in the last week and 3.the METs for the given activity the MET-Minutes per week of the specific activity is obtained. The METs (multiples of resting metabolism) for the calculation are 3.3 for walking, 4.0 for moderate activity and cycling and 8.0 for vigorous activities. By calculating the total MET-minutes in all domains and all intensities, the total activity level of the participant can be put on a continuous score. Moreover, the IPAQ allows separating participants into three categories: low, moderate and high intensity group. These categorical and continuous score are achieved by specific data processing rules found in the *Guidelines for Data Processing and Analysis of IPAQ (www.ipaq.ki.se, 2005)*. While the data cleaning rules were adhered to, the data processing rules were only partly used, as not enough information of how to exactly use them were found. It has to be noted, that IPAQ was established for adults ranging from the age of 18 to 69.

2.3.2 Biological Assays

Fasting blood samples were taken from the participants between 8.00 and 9.30am. These were used to examine several markers including a haemogramm, differentiated blood picture, IL-6, CRP. TRY, KYN, and Neurotransmitters were analysed after a storage at -80°C.

2.3.3 Clinical Parameters

Clinical parameters were gathered during a detailed standardized anamnesis and external rating systems (like BDI, HAMD, YMRS). The number of depressive and manic episodes experienced, psychiatric and medical Co-M, suicidal behaviour and nutrition lifestyle of the participants were explored. Moreover, the severity of BD was identified using staging criteria of Kapczinski et al. (2009) and the Global Functioning was evaluated with the help of the Global Assessment of Function (GAF) (Beltz, 1989).

2.3.4 Cognitive Assessment

Neuropsychological status was evaluated by cognitive test battery, administered by trained investigators, allowing a standardized process. The following table summarizes the neurocognitive spectrum tested and the tests used.

Domain	Cognitive tests
Attention	1. Trail Making Test-A (TMT-A) (Reitan, 1992) 2. d2 test of attention (Brickenkamp, 2002) 3. Stroop Test: word reading and colour naming (Bäumler & Stroop, 1985)
Memory	1. California Verbal Learning Test (CVLT) (Niemann et al., 2008)
Executive Function	1. Stroop Test: interference (Bäumler & Stroop, 1985) 2. Trail Making Test-B (TMT-B) (Reitan, 1992)
Premorbid IQ	1. Multiple word choice test (MWT-B) (Lehrl, 2005)

Table 4: Neurocognitive Test Battery

2.4 Statistical Analyses

The statistical analyses were done using the statistical program IBM SPSS version 22 for windows. The calculations used were t-test for unpaired samples, the chi-squared test and Pearson as well as Spearman correlations and partial correlations. The metrical variable of total MET-minutes/week was correlated to different clinical and laboratory variables using the Pearson or the Spearman correlation coefficient. Whenever the criteria for the Pearson correlation were not fulfilled, the Spearman was calculated. The statistical significance was defined with a p value smaller than 0.05. Due to the fact, that data was collected in a prospective study with multiple parameters, *n* is sometimes smaller than 119.

It is important to state, that categorical separation of the group was not used as IPAQ data processing rules were not sufficiently explained in the guidelines, leading to an ineffective separation.

3 Results

Firstly, the cohort was analysed concerning the basic demographic traits such as gender and age. These were then compared between controls and patients in order to clarify whether the two groups are statistically identical.

Next, the PA behaviour of the patient and the control group were compared using t-tests for unpaired samples. The correlation between PA and various values was only analysed in the patient group using Pearson and Spearman correlation coefficient.

3.1 Cohort description

The following table shows the basic demographic information of the study cohort and offers a comparison between the patient and control group.

	n	**age (*M* ± *SD*)**	**total MET/Minutes per week (*M* ± *SD*)**	**BMI (*M* ± *SD*)**
patients	119	45.06 ± 13.80	5296.32 ± 6361.22	27.95 ± 6.25
controls	71	41.63 ± 16.66	5461.23 ± 4866.26	24.51 ± 3.82

Table 5: Cohort Description

Using the t-test for unpaired samples it can be shown that in the cohort control group and patient group do not differ in age ($t\,(126.472) = 1.46, p = .15$). Moreover, gender does not differ in the two groups (χ^2 (1, N = 190) = 3.13, p = .08). Using the t-test for unpaired samples the BMI differs significantly in the groups ($t\,(182.45) = 4.65, p < 0.05$). Patients have a higher mean BMI than controls.

3.2 PA Behaviour in BD and in the Control Group

First of all, it was examined, whether patients and controls show different PA behaviour.

The t-test for unpaired samples showed no significant result concerning the PA behaviour comparison between patients and controls. The following diagram shows that hypothesis 1a is not confirmed as controls (n = 71) are not more active than patients (n = 119) (t (188) = -.19, p = 0.85).

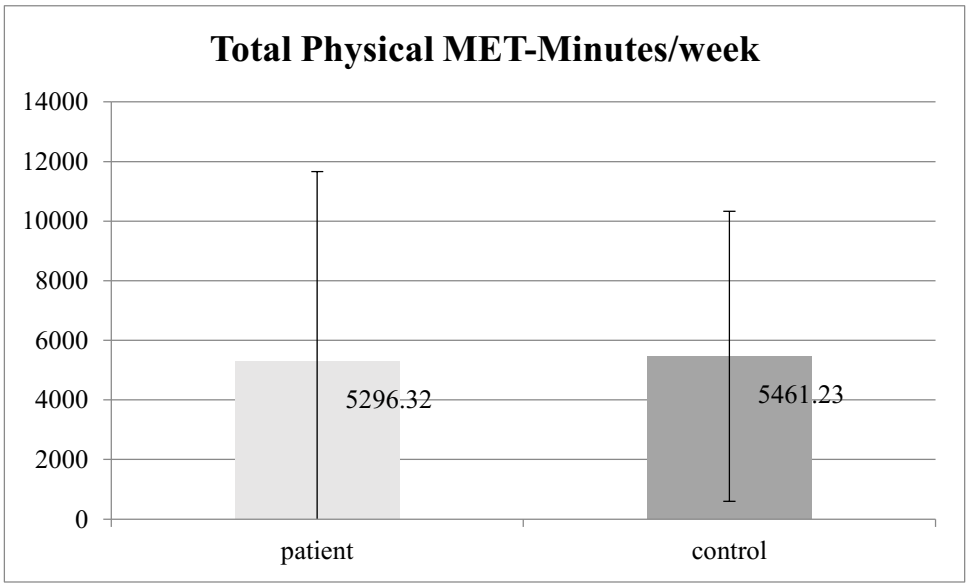

Figure 2: Mean ± SD of Total Physical MET-Minutes of patients (n = 119) and controls (n = 71)

Moreover, the t-test for unpaired samples analysing sedentary behaviour also showed no significant difference between patients and controls. The following figure visualizes the results (t (188) = 0.62, p = 0.54)

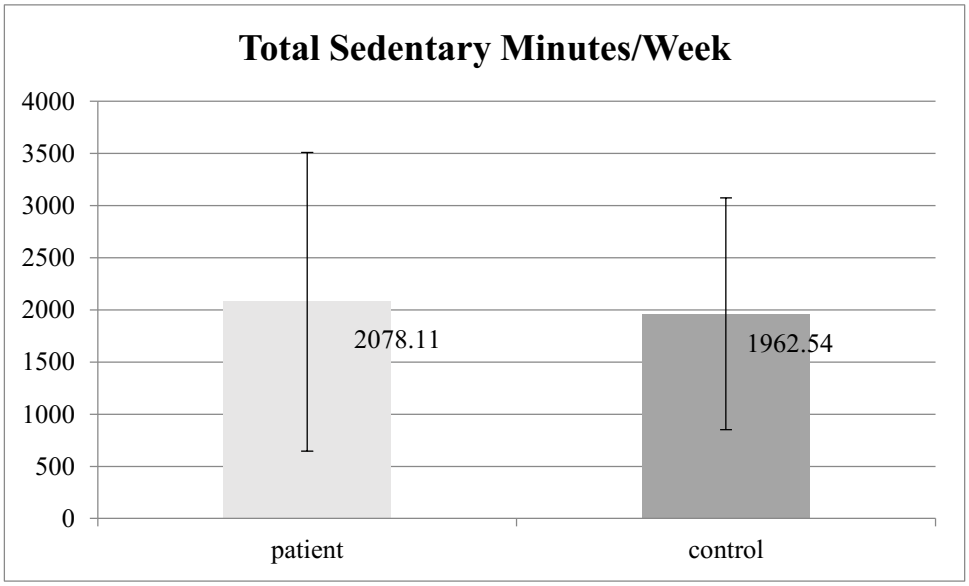

Figure 3: Mean ± SD Total Sedentary Minutes of patients (n = 119) and controls (n = 71)

3.3 Correlation of Physical Activity and Parameters in BD

Before calculating correlations, potential covariates (Vancampfort et al, 2012) were examined. However, neither age (r_s (117) = -.09, p = .34), nor gender (r_s (117) = .02, p = .27) correlate with Total Physical MET-minutes/week. The next step was to calculate the correlations of Total Physical MET-Minutes/week to clinical parameters relevant to the prognosis and course of BD in the patient cohort.

3.3.1 PA and BMI

First of all, it has to be noted, that our patient cohort in the mean is OW taking the BMI into consideration (M = 27.95, SD = 6.25). Moreover, PA and BMI in the patient cohort are significantly negatively correlated with r_s (*115*) = -.22, p = .02.

3.3.2 PA and Inflammation

Secondly, the total MET-minutes were correlated to various inflammatory markers.

3.3.2.1 IL-6

However, our study cohort, does not show a significant partial correlation between PA and IL-6 with r_s (55) = -0.01, p = .95. It has to be noted that BMI was kept constant in the calculation, as it is known that OW is associated with systemic inflammation (Wolowczuk et al., 2012).

3.3.2.2 CRP

Moreover, the partial correlation did not show a significant partial correlation between CRP and PA, r_s (108) = .09 p = .36. The constant variable was again BMI.

3.3.2.3 KYN/TRY-ratio

Furthermore, KYN/TRY-ratio was examined. There is no correlation between PA and the TRY breakdown with r_s *(60)* = -.01, p = .95. It hast to be noted, that age, illness duration and BMI were kept constant, as there was a significant correlation between KYN/TRY and these variables in our cohort.

3.3.3 PA and Neurotransmitters

In the table below the examination of the neurotransmitters is summarized. No significant correlation between PA and serotonin, noradrenaline and dopamine was found.

	r_s	p	N
Serotonin	.02	.87	53
Noradrenaline	-.01	.93	57
Dopamine	.16	.25	57

Table 6: Correlation (r) between Neurotransmitters and PA

3.3.4 PA and Clinical Paramters of BD

The following paragraphs display the results of the statistical analysis concernig PA and clinical presentation of BD.

3.3.4.1 Number of Episodes

The following table shows that PA and number of episodes are not correlated in our study cohort. It must be noted, that the illness duration was a controlled variable in the pearson correlation.

	r_s	p	df
Number of depressive episodes	-.09	.37	109
Number of manic episodes	-.01	.93	109
Episode Ratio: Depression/Mania	-.11	.24	106

Table 7: Correlation (r) between episodes and PA

3.3.4.2 Suicidal Behaviour

In our cohort there is no significant correlation between suicidal behaviour and PA (r_s (113) = .01, p = .94.)

3.3.4.3 Global Function

In our cohort there is a significant positive correlation between GAF and PA (r_s (113) = .29, p < 0.01). Note that here the significance cut off was at p < 0.01.This means, that the more PA patients perform, the better their GAF score is.

3.3.4.4 Staging

Furthermore, Hypothesis 9 could not be confirmed. There is no significant correlation between Staging and PA (r_s (111) = -.05, p = .58). Note that illness duration was kept constant.

3.3.5 Cognitive Measures

It has to be noted, that age, illness duration and school educations were kept constant, as it is known, that these three variables have an influence on cognition (Lackner et al., 2015) and they showed a significant correlation with the cognitive values. The following table summarizes the results of the correlation between PA and the neurocognitive tests.

	r_s	*Sig. (p)*	*df*
Attention			
TMT A:	-.06	.54	107
d2:	0.11	.28	105
Stroop:			
Read	-.24	.02*	102
identify	-.28	.00*	102
Memory			
CVLT:			
DG 1-5	.22	.02*	107
Delayed Recall 1	.27	.01*	106
Delayed Recall 2	.26	.01*	107
Executive Functions			
TMT B:	-.13	.19	104
Stroop:			
interference	-.29	.00*	102
Premorbid IQ			
-B:	.08	.42	107

Table 8: Partial Correlation (r_s) between Neurocognition and PA

3.4 Summary of results

The following table summarizes the findings of this analysis.

Hypothesis	*Confirmed*	*Comment*
1 Activity comparison between patients and controls		
1a Patients are less active than controls	no	In our cohort patients and controls have similar activity behaviour.
1b Patients spend more time with sedentary behaviour	no	
2 Correlation between PA and BMI	**yes**	**PA and BMI are negatively correlated in patients with BD.**
3 Correlation between PA and inflammatory markers		
3a Correlation between PA and IL-6	no	In our BD cohort inflammatory markers and PA are not significantly correlated.
3b Correlation between PA and CRP	no	
4 Correlation between KYN/TRY and PA	no	There is no significant correlation between KYN/TRY and PA in our patient group.
5 Correlation between neurotransmitters and PA	no	Our cohort shows no significant correlation between PA and neurotransmitters.
6 Correlation between episodes and PA		
6a depressive	no	There is no correlation between episodes and PA.
6b manic	no	
6c depressive/manic	no	
7 Correlation between suicidal behaviour and PA	no	No correlation found.
8 Correlation between GAF and PA	**yes**	**Patients who are more active score higher in GAF.**
9 Correlation between staging and PA	no	There is no correlation between PA and staging.
10 Correlation between neurocognition and PA		
10a attention	**partial**	**Memory is positively correlated, while results concerning attention and executive functioning are not consistent over all tests;** Premorbid IQ is not correlated to PA.
10b memory	**yes**	
10c executive functioning	**partial**	
10d premorbid IQ	no	

Table 9: Summary of results

4 Discussion

This study investigated PA behaviour of a Styrian cohort of patients suffering from BD and compared it to a group of healthy controls. On the contrary of expectation, patients showed no difference in PA compared to controls. While the literature research revealed some interesting aspects of PA and BD, most of these findings could not be replicated in the study. Therefore, the following section should detect the limitations and offer improvements for future investigations.

4.1 Discussion of the Results

In the next chapter the results of the statistical analysis is being discussed and compared to the results of the literature research.

4.1.1 Comparison of Physical Activity behaviour

When comparing the mean total physical MET-minutes of patients with BD to controls representative for healthy population, no significant difference was found. Thus, hypothesis 1 suggesting, that reduced PA and increased time spent with sedentary behaviour accompanies BD compared to controls was falsified. However, it has to be noted, that when examining the questionnaire inconsistencies were detected. While both patients and controls seemed to report too little time spent with sedentary behaviour, time spent with PA seemed to be exaggerated.

In addition, even though activity between healthy controls and patients suffering from BD is not different, it was not investigated whether the recommendations for PA of the WHO suggesting at least 150 minutes of moderate-intensity OR 75 minutes of vigorous intensity aerobic PA per week (WHO, 2011) are met. Therefore, even though patients are

not less active than patients, this is no indication that they perform enough PA in order for beneficial health effects to occur.

Moreover, PIA seems to be found especially during acute episodes, and particularly during a phase of depression (Wright et al., 2012; Swartz & Fagiolini, 2012). Therefore, further examination should compare activity during euthymia with PA during mania/depression.

4.1.2 Correlates of Physical Activity

While there is a significant correlation between PA in BD and BMI, overall functioning and some aspects of cognition, there is no correlation of PA with clinical presentation, neurotransmitters and inflammation.

4.1.2.1 PA and BMI

Hypothesis 2 stating that BMI and PA in patients with BD are negatively correlated could be verified. However, it has to be noted that the association is not very big supporting the thesis that there are many other factors in BD playing a crucial role in the high prevalence of OW and OB in BD. For sure the crucial effect of medication on weight gain must not be forgotten (Maina et al., 2008; Kucyi et al., 2010; Gurpegui et al., 2012; Geddes & Miklowitz, 2013; Young & Oldani, 2013; McElroy et al., 2002).

Note that, it was found that BMI was already increased in individuals suffering from BD before the onset of BD indicating the similar pathway of BD and OW/OB (Maina et al., 2008). Therefore, the common known beneficial effect of PA on OW/OB might be reduced in individuals with BD suggesting, that for weight control PA is not as effective in BD as in the normal population. Thus, future investigations should evaluate whether PA in BD and in controls show different effects on BMI.

4.1.2.2 PA and Inflammation

PA was shown to have a beneficial effect on the activated I-IP due to an immunosuppressant effect (Alsuwaidan et al., 2009; Gleeson, 2006; Rosa et al., 2011). However, hypothesis 3a and 3b proposing that IL-6 such as CRP and PA are negatively correlated in BD were falsified.

While acute activity leads to an increase in inflammatory markers especially IL-6, it is especially chronic and repeated PA leading to a decrease in I-IP (Pedersen & Hoffmann-Goetz, 2000; Pedersen 2000; Rosa et al., 2011; Petersen & Pedersen, 2005). In addition, CRP is a very unspecific marker, especially increased during acute infection and not identifying chronic inflammation. Therefore, it might be useful to find a questionnaire investigating PA over a longer period and moreover using other inflammatory markers in further examinations. In addition, it would be interesting to identify whether PA intervention leads to a decrease in I-IP markers over time.

Also, hypothesis 4 suggesting that KYN/TRY are negatively correlated with PA could not be verified. This might have the same reasons as of why hypothesis 3 could not be verified and therefore the ratio should also be investigated in a follow up study protocol using a questionnaire interrogating activity over a longer period of time.

4.1.2.3 PA and Neurotransmitters

Furthermore, hypothesis 5 could not be proven. There is no correlation between noradrenaline, dopamine as well as serotonin and PA in our cohort suffering from BD. Noradrenaline rises after acute exercise; such as it is increased during mania. On the contrary, during depressive episodes, it is reduced (Alsuwaidan et al., 2009). This could be one of the reasons why sport in mania is still controversially discussed. Therefore, it would be interesting to evaluate, the effect of sport in the different mood episodes. Moreover,

dopamine and serotonin should rise due to sport (Alsuwaidan et. al, 2009). This was not represented in our cohort.

As there is still no exact intensity of PA leading to these changes defined, it would be interesting to evaluate, whether different intensities of PA lead to different levels of rise in neurotransmitters and therefore, identify the optimal intensity for neurotransmitter level optimisation.

4.1.2.4 PA and Clinical Presentation

The effect of exercise in a manic phase still remains unclear. While it is believed, that sport allows to get rid of excessive energy, it is also believed, that it could increase manic symptoms and cardiovascular strain due to a further physiological arousal (Baxter et al., 2010; Wright et al., 2012; Sylvia et al., 2013).

Literature research identified positive effects of PA on clinical presentation of BD due to an antidepressant effect increased stress tolerance (Sylvia et al., 2009; Salmon, 2001; Barbour et al., 2007; Ng et al., 2007a; Ng et al., 2007b). Neither hypothesis 6 proposing that a the number of depressive episodes and b the number of manic episodes decreases with increasing PA and c that the ratio between depressive and manic episodes decreases with increasing PA, nor hypothesis 7 stating that suicidal attempts decrease with PA could be verified.

This might again be due to the fact that IPAQ interrogates only the last seven days, not taking in consideration whether this behaviour was like this from the onset of the disease. Moreover, the effect of PA on mania is still unclear and leaving the possibility of deterioration due to PA (Baxter et al., 2010; Wright et al., 2012; Sylvia et al., 2013). Further investigations should focus on PA during acute mania and depression. A

prospective analysis must identify whether introducing PA into one's life reduces future episodes.

Hypothesis 8 was verified. The association between sport and the daily functioning level of patients with BD found by Sylvia et al. (2013) was replicated by a positive correlation between PA and GAF in our cohort. This might be due to the fact, that sport leads to self-efficacy and -motivation, distraction of negative thinking and stress tolerance. Furthermore activity induces structure in one's life and reduces stress reactivity (Salmon, 2001; Barbour et al., 2007; Ng, Dodd & Berk, 2007a; Ng et al., 2007b; Blake, 2012; Wright et al., 2012). Therefore, it might motivate individuals to also do other aspects of daily life, which they could normally not be motivated for. Here it would be interesting whether this effect can be replicated during depression and not only during euthymia.

On the contrary, there was no correlation found between PA and staging of BD after Kapczinski. Hypothesis 9 was therefore proven wrong. However, as staging takes a lot of aspects into consideration which are especially long term effects, it must be again said, that IPAQ only interrogates the last week and can therefore not say how patients PA profile of the last year etc. has been.

4.1.2.5 PA and Neurocognition

The study revealed a positive correlation between some domains of neurocognition and PA therefore verifying parts of hypothesis 10. Attention, memory and executive functioning are positively correlated to PA, however note that these results were not replicated in all tests. This supports the findings of Kucyi et al. (2010). Since neurocognition was tested on the same day or close before filling out the IPAQ this correlation shows an acute association between PA and neurocognition. It would however be interesting, whether PA can beneficially influence the common known effect of

increasing cognitive deficits in BD and therefore, a follow up study should focus on whether individuals that are more active show a slower decline than less active individuals with BD.

Neurocognitive decline is one of the well-known Co–M of BD, which needs special attention and treatment targeting this phenomenon of neuroprogression. If further studies can verify our findings and therefore, give basis for PA as a treatment targeting cognitive decline, PA would be a scientifically proven concomitant therapy for BD.

Another point, which was not taken into consideration, is that there are known gender differences concerning cognitive performance in people with BD but also healthy controls. Further analyses correlating PA and cognition in men and women separately are planned.

4.2 Discussion of methods

While the neurocognitive test battery, the laboratory markers and the standardized anamnesis have shown to be very valid in previous investigation; the IPAQ data was evaluated for the first time in the study group.

4.2.1 IPAQ

As stated before it has to be noted, that the IPAQ only interrogates the last seven days and therefore, is just a vast guess of how the PA profile of the participants looks in average. Therefore, it is not ideal to compare the IPAQ data with markers, which show a change over time. Further investigation should prospectively evaluate, whether there is a difference between patients who join concomitant long-term PA therapy, to those who do not join PA.

Moreover, when inserting data it was clear, that first of all many individuals did not understand the questionnaire correct, leading to possibly wrong data. Skipping rules were often ignored. Sometimes participants only inserted frequencies of PA sessions but did not indicate the time spent with these sessions, or vice versa. In addition, time indication often had no logical basis. Moreover, we could not find enough information on the truncation rules in the IPAQ-guidelines as of why we were not able to build the categorical groups provided in the IPAQ (low- , moderate- , highly- active). It is being suggested, that when comparing these three categorical groups with each other there could be more correlations found, as it is believed, that intensity and regularity of sport plays a role in beneficial effects (Warburton et al., 2006; Ng et al., 2007a).

4.3 Limitations and Improvements

As main limitation of the study protocol, the IPAQ has to be stated. Therefore, in future investigations better objectifiable methods interrogating PA over a longer period need to be used. In addition, there should be a separation into groups of PA allowing statements of whether the intensity/regularity of PA is the actual factor influencing the effects of PA. Moreover, a one point analysis was not able to identify whether there is a long term effect of PA on the course of BD which would however, be necessary to correctly integrate PA in the therapy of BD. Therefore, future investigation should compare the effect of PA over time.

Furthermore, it would have been interesting to analyse whether the control group does show correlations to the different variables, leading to the question of whether the effect of sport is not given in BD, as it is believed that I-IP and neuroprogression have common pathways.

Gebder aspects have not been analysed, but are planned as a next step in our study.

4.4 Strengths

It has to be stated, that the cohort size was relatively large and diverse in age and gender, therefore, allowing for a representative statement to be made. In addition, the study protocol, besides the IPAQ, is well established and has proven to be reliable in past examinations. In addition, the statistical analysis was done using suitable tests and considering all prerequisites.

5 Conclusion

In conclusion, while PA seems to have beneficial effects on the course and the Co-M of BD our study could not confirm all of the past findings. However, the IPAQ might not have been the perfect method of investigating PA, as it is self-administered and seems not be completely understood by the participants. Therefore, it would be wise to use an objectified data gathering method, such as a Pedometer or Accelerometer in order for the data to increase in validity. Moreover, the question arises, whether the beneficial effect of PA on the course of BD should also contain measures such as episode severity and not only episode numbers, as the beneficial effect of PA leading to increased self-efficacy might help patients to deal better with the episodes, while number does not decrease. However, while this data does not fully support past findings, it must be said, that the long term effect of PA was not investigated, asking for future investigations combing a better objectifiable source of PA data over a longer period of time. The question arises, whether PA in BD is actually able to show the same effects on IIP and neurocognition as in healthy controls, as a common pathway between BD and IIP/Neuroprogression is being discussed.

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7 Appendix

Appendix A: International Physical Activity Questionnaire (IPAQ) – Long Version

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (Oktober 2002)

SELBSTAUSFÜLLER LANG-VERSION FÜR DIE VERGANGENEN 7 TAGE

ZU VERWENDEN FÜR JUNGENDLICHE UND ERWACHSENE IM MITTLEREN ALTER (15-69 Jahre)

Der International Physical Activity Questionnaire (IPAQ) umfasst eine Zusammenstellung aus 4 Fragebögen. Lange (5 Aktivitätsbereiche unabhängig voneinander befragt) und kurze (4 allgemeine Items) Versionen für die Durchführung von Telefonbefragungen als auch für die selbst zu verwaltende Methode sind verfügbar. Die Absicht der Questionaires ist es einfache Instrumente zur Verfügung zu stellen, die verwendet werden können um international vergleichbare Daten für die gesundheitsfördernde physische Aktivität zu erhalten.

Hintergrund des IPAQ
Die Entwicklung eines internationalen Messinstruments zur Erhebung der physischen Aktivität begann in Genf im Jahr 1998 und wurde im Jahr 2000 durch extensive Reliabilitäts- und Validitätststests in 12 unterschiedlichen Ländern (14 Orte) fortgesetzt. Vom Endergebnis wird behauptet, dass es annehmbare Messeigenschaften für den Einsatz an vielen Orten und in unterschiedlichen Sprachen besitzt und es geeignet ist für landesweite bevölkerungsbezogene Untersuchungen für die Prävalenz der Partizipation in physischer Aktivität.

Verwendung des IPAQ
Es wird empfohlen die IPAQ-Instrumente für Untersuchungen und für Forschungszwecke zu verwenden. Die Anordnung der Fragen sowie die Satzstellungen sollten möglichst unverändert bleiben um die psychometrischen Eigenschaften des Instruments nicht zu beeinflussen.

Übersetzung vom Englischen und kulturelle Anpassung
Übersetzungen aus dem Englischen werden angestrebt um die weltweite Verwendung des IPAQ zu erleichtern. Informationen über die Verfügbarkeit des IPAQ in unterschiedlichen Sprachen können unter www.ipaq.ki.se abgerufen werden. Sollte eine neue Übersetzung vorgenommen werden wird die Verwendung der auf der IPAQ-Website beschriebenen Rückübersetzungsmethoden unbedingt empfohlen. Wenn möglich ziehen sie bitte in Erwägung ihre Übersetzung des IPAQ für andere auf der IPAQ-Website zugänglich zu machen. Weitere Details über Übersetzungen und kulturelle Adaptationen können von der Website gedownloadet werden.

Weitere Entwicklungen des IPAQ
Die internationale Zusammenarbeit beim IPAQ geht weiter und die ***International Physical Activity*** Studie ist in der Entwicklungsphase. Für weitere Informationen steht die IPAQ-Website zur Verfügung.

Weitere Informationen
Detaillierte Informationen über Forschungsmethoden die in der Entwicklung der IPAQ-Instrumente verwendet werden finden Sie unter www.ipaq.ki.se oder bei Booth, M.L. (2000).

Assessment of Physical Activity: An International Perspective. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Weitere wissenschaftliche Publikationen und Präsentationen über die Anwendung des IPAQ sind auf der Website zusammengefasst.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

Wir sind daran interessiert herauszufinden welche Arten von körperlichen Aktivitäten Menschen in ihrem alltäglichen Leben vollziehen. Die Befragung bezieht sich auf die Zeit die Sie während der **letzten 7** Tage in körperlicher Aktivität verbracht haben. Bitte beantworten Sie alle Fragen (auch wenn Sie sich selbst nicht als aktive Person ansehen). Bitte berücksichtigen Sie die Aktivitäten im Rahmen Ihrer Arbeit, in Haus und Garten, um von einem Ort zum anderen zu kommen und in Ihrer Freizeit für Erholung, Leibesübungen und Sport.

Denken Sie an all Ihre **anstrengenden** und **moderaten** Aktivitäten in den **vergangenen 7 Tagen**. **Anstrengende** Aktivitäten bezeichnen Aktivitäten die starke körperliche Anstrengungen erfordern und bei denen Sie deutlich stärker atmen als normal. **Moderate** Aktivitäten bezeichnen Aktivitäten mit moderater körperlicher Anstrengung bei denen Sie ein wenig stärker atmen als normal.

TEIL 1: KÖRPERLICHE AKTIVITÄT AM ARBEITSPLATZ

Im ersten Abschnitt geht es um Ihre Arbeit. Das beinhaltet bezahlte Arbeit, Landwirtschaft, freiwillige Tätigkeiten, Seminare und alle anderen unbezahlten Tätigkeiten die Sie außerhalb von zuhause verrichtet haben. Geben Sie hier keine unbezahlten Tätigkeiten an die Sie zuhause verrichtet haben, wie Arbeiten in Haus und Garten, anfallende Instandhaltungsarbeiten und Sorgen für die Familie. Dies wird in Abschnitt 3 befragt.

1. Haben Sie momentan einen Job oder verrichten Sie irgendwelche unbezahlte Arbeiten außerhalb von zuhause?

☐ Ja

☐ Nein → ***Springen Sie weiter zu Teil 2: BEFÖRDERUNG***

Die folgenden Fragen sind über die körperliche Aktivität in den **vergangenen 7** Tagen im Rahmen Ihrer bezahlten und unbezahlten Arbeit. Dies beinhaltet keine Wegstrecken zur oder von der Arbeit.

2. An wie vielen der **vergangenen 7 Tage** haben Sie anstrengende körperliche Aktivitäten wie schweres Heben, Graben, schwere Bauarbeit oder Stiegensteigen **im Rahmen Ihrer Arbeit** verrichtet? Denken Sie dabei nur an körperliche Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben.

_____ **Tage pro Woche**

→ ☐ Keine anstrengenden körperlichen Aktivitäten im Rahmen der Arbeit
Springen Sie weiter zu Frage 4

3. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **anstrengender** körperlicher Aktivität im Rahmen ihrer Arbeit verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

4. Denken Sie erneut nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben Sie moderate körperliche Aktivitäten wie Tragen leichter Lasten **im Rahmen Ihrer Arbeit** verrichtet? Fußwegstrecken bitte nicht mit einbeziehen.

_____ **Tage pro Woche**

☐ Keine moderaten körperlichen Aktivitäten im Rahmen der Arbeit
Springen Sie weiter zu Frage 6

5. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit moderater körperlicher Aktivität im Rahmen Ihrer Arbeit verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

6. An wie vielen der **vergangenen 7 Tage** haben Sie **Fußwegstrecken** von mindestens 10 Minuten ohne Unterbrechung im Rahmen Ihrer Arbeit zurückgelegt? Bitte keine Wegstrecken zur oder von der Arbeit mit einbeziehen.

_____ **Tage pro Woche**

☐ Keine Fußwegstrecken im Rahmen der Arbeit
Springen Sie weiter zu Teil 2: BEFÖRDERUNG

7. Wie viel Zeit haben Sie an einem dieser Tage für gewöhnlich mit **Wegstrecken** im Rahmen Ihrer Arbeit verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

Teil 2: KÖRPERLICHE AKTIVITÄT ZUR BEFÖRDERUNG

In diesen Fragen geht es um die Fortbewegungen von einem Ort zum anderen, wie die Wege zu Arbeit, Geschäften, Kino, usw.

8. An wie vielen der **vergangenen 7 Tage** sind Sie mit einem **motorisierten Verkehrsmittel** wie Zug, Bus, Auto oder Straßenbahn **gefahren**?

_____ **Tage pro Woche**

☐ Keine Fahrten in motorisierten Verkehrsmitteln
→ ***Springen Sie weiter zu Frage 10***

9. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **Fahrten** in Zug, Bus, Auto, Straßenbahn oder irgendeinem motorisierten Verkehrsmittel verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

Denken Sie jetzt nur an das **Fahrradfahren** und **zu Fuß Gehen**, bei dem Sie für Wege zur und von der Arbeit, für Botenwege, sowie für Wegstrecken um von einem Ort zum anderen zurückgelegt haben.

10. An wie vielen der **vergangenen 7 Tage** sind Sie für mindestens 10 Minuten ohne Unterbrechung **fahrradgefahren** um **von einem Ort zum anderen** zu gelangen?

_____ **Tage pro Woche**

☐ Kein Fahrradfahren von einem Ort zum anderen
→ ***Springen Sie weiter zu Frage 12***

11. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage für das **Fahrradfahren** von einem Ort zum anderen verwendet??

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

12. An wie vielen der **vergangenen 7 Tage** sind Sie für mindestens 10 Minuten ohne Unterbrechung **zu Fuß gegangen** um **von einem Ort zum anderen** zu gelangen?

_____ **Tage pro Woche**

☐ Kein zu Fuß Gehen von einem Ort zum anderen
→ ***Springen Sie weiter zu Teil 3: HAUSARBEIT, HAUSINSTANDHALTUNG UND SORGEN FÜR DIE FAMILIE***

13. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage für das **zu Fuß Gehen** von einem Ort zum anderen verwendet?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

TEIL 3: HAUSARBEIT, HAUSINSTANDHALTUNG UND SORGEN FÜR DIE FAMILIE

In diesem Abschnitt geht es um körperliche Aktivitäten die Sie in den **vergangen 7 Tagen** in und um ihr Haus verrichtet haben, wie Hausarbeit, Arbeiten in Hof und Garten, Instandhaltungsarbeiten und Sorgen für die Familie.

14. Denken Sie nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben Sie anstrengende körperliche Aktivitäten wie Tragen schwerer Lasten, Holzhaken, Schneeschaufeln oder Graben **im Hof oder im Garten** verrichtet?

    _____ **Tage pro Woche**

    ☐ Keine anstrengenden körperlichen Aktivitäten im Hof oder im Garten
    → ***Springen Sie weiter zu Frage 16***

15. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **anstrengender** Aktivität in Garten und Hof verbracht?

    _____ **Stunden pro Tag**
    _____ **Minuten pro Tag**

16. Denken Sie erneut nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben Sie moderate Aktivitäten wie Tragen leichter Lasten, Fegen, Fensterputzen und Rechen **im Hof oder im Garten** verrichtet?

    _____ **Tage pro Woche**

    ☐ Keine moderate Aktivität im Garten oder im Hof
    → ***Springen Sie weiter zu Frage 18***

17. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **moderater** körperlicher Aktivität im Garten oder im Hof verbracht?

    _____ **Stunden pro Tag**
    _____ **Minuten pro Tag**

18. Denken Sie erneut nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben Sie moderate Aktivitäten wie Tragen leichter Lasten, Fensterputzen, Bodenaufwaschen und Fegen **zuhause** verrichtet?

    _____ **Tage pro Woche**

    ☐ Keine moderaten Aktivitäten zuhause
    → ***Springen Sie weiter zu Teil 4: KÖRPERLICHE AKTIVITÄTEN IN ERHOLUNG, SPORT UND FREIZEIT***

19. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **moderaten** körperlichen Aktivitäten zuhause verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

TEIL 4: KÖRPERLICHE AKTIVITÄTEN IN ERHOLUNG; SPORT UND FREIZEIT

In diesem Abschnitt geht es um alle körperlichen Aktivitäten die Sie in den **vergangenen 7 Tagen** ausschließlich in Erholung, Sport, Leibesübungen und Freizeit verrichtet haben. Bitte keine Aktivitäten mit einbeziehen die Sie bereits angegeben haben.

20. Ohne die Fußwege die Sie bereits genannt haben, an wie vielen der **vergangenen 7 Tage** sind Sie in ihrer **Freizeit** für mindestens 10 Minuten ohne Unterbrechung **zu Fuß** gegangen?

    _____ **Tage pro Woche**

    ☐ Kein zu Fuß gehen in der Freizeit
    → ***Springen Sie weiter zu Frage 22***

21. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **zu Fuß Gehen** in ihrer Freizeit verbracht?

    _____ **Stunden pro Tag**
    _____ **Minuten pro Tag**

22. Denken sie nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben Sie **anstrengende** körperliche Aktivitäten wie Aerobic, Laufen, schnelles Fahrradfahren oder schnelles Schwimmen in ihrer **Freizeit** verrichtet?

    _____ **Tage pro Woche**

    ☐ Keine anstrengenden Aktivitäten in der Freizeit
    → ***Springen Sie weiter zu Frage 24***

23. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **anstrengender** körperlicher Aktivität in ihrer Freizeit verbracht?

    _____ **Stunden pro Tag**
    _____ **Minuten pro Tag**

24. Denken Sie erneut nur an die körperlichen Aktivitäten die Sie für mindestens 10 Minuten ohne Unterbrechung verrichtet haben. An wie vielen der **vergangenen 7 Tage** haben sie **moderate** körperliche Aktivitäten wie Fahrradfahren bei gewöhnlicher Geschwindigkeit, Schwimmen bei gewöhnlicher Geschwindigkeit und Doppel-Tennis in ihrer **Freizeit** verrichtet?

    _____ **Tage pro Woche**

    ☐ Keine moderaten Aktivitäten in der Freizeit
    → ***Springen Sie weiter zu Teil 5: IM SITZEN VERBRACHTE ZEIT***

25. Wie viel Zeit haben Sie für gewöhnlich an einem dieser Tage mit **moderater** körperlicher Aktivität in ihrer Freizeit verbracht?
_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

TEIL 5: IM SITZEN VERBRACHTE ZEIT

Bei den letzten Fragen geht es um die Zeit die Sie bei der Arbeit, zuhause, bei Seminaren und in der Freizeit in Sitzen verbracht haben. Dies kann Zeit beinhalten wie Sitzen am Schreibtisch, Besuchen von Freunden und vor dem Fernseher sitzen oder liegen. Keine Zeit für Sitzen in einem motorisierten Verkehrsmittel mit einbeziehen von der Sie mir bereits erzählt haben.

26. Wie viel Zeit haben Sie in den **vergangenen 7 Tagen** mit **Sitzen** an **Wochentagen** verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tag**

27. Wie viel Zeit haben Sie an den **vergangenen 7 Tagen** mit **Sitzen** an **Wochenendtagen** verbracht?

_____ **Stunden pro Tag**
_____ **Minuten pro Tags**

Das ist das Ende der Befragung, danke für Ihre Teilnahme.