# *The relationshop between physical exercise, clinical and cognitive characteristics and BDNF levels in patients with severe mental disorders*

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**ABSTRACT**

**Background:** Human and animal studies suggest that physical exercise improves cognitive function and mood, potentially via an increase of Brain-derived-neurotrophic factor (BDNF). However, studies have been small and potentially underpowered. Here, we aimed to clarify the role of physical exercise on cognitive function and current mood in severe mental disorders in the most extensive sample to date. Secondly, we aimed to investigate the relationship between physical exercise and BDNF mRNA levels

**Methods:** Three hundred and six patients with a DSM-IV Schizophrenia (SZ) or Bipolar Disorder spectrum (BD) diagnosis were included. Clinical characteristics were assessed using the Structured Clinical Interview for DSM-IV. All patients underwent neuropsychological assessment. Physical exercise was measured as hours spent on any regular physical activity (≥ or < 90 min) per week. BDNF mRNA was measured using standardized procedures.

**Results:** Patients with ≥90 min of exercise per week had fewer depressive symptoms ($p<0.001$, Cohen's $d=0.48$) and performed significantly better on working memory ($p<0.001$, $d=0.44$) and executive functioning ($p<0.001$, $d=0.50$) compared to the <90 min group. Findings remained significant after adjusting for premorbid cognitive functioning, age, and sex. BDNF mRNA was positively associated with physical exercise ($p=0.046$) and cognitive functioning ($p=0.037$).

**Limitations:** As our study is a cross-sectional study, we cannot infer causality, only associations.

**Conclusions:** Our findings of increased levels of mRNA BDNF associated with improved clinical characteristics and high physical exercise suggest an underlying mechanistic link. Further studies of the mechanisms underlying the beneficial effects of physical exercise in severe mental illness are warranted.

## INTRODUCTION

Severe mental disorders, including schizophrenia spectrum disorders (SZ) and bipolar spectrum disorders (BD) are severe mental disorders characterised by psychosis and changes in mood often followed by cognitive dysfunction, including difficulties with problem solving, memory and executive functioning (Aas *et al.*, 2014a, Bourne *et al.*, 2013). At average people with SZ function at a cognitive level of approximately one standard deviation below that of healthy comparison groups (Aas *et al.*, 2014a, Bozikas and Andreou, 2011, Lewandowski *et al.*, 2011, Simonsen *et al.*, 2011). Cognitive function also predicts current and later functional outcome, providing a rationale for attempts to find psychopharmacological or psychological interventions to ameliorate cognitive dysfunction in SZ (Green *et al.*, 2004, Lystad *et al.*, 2014, Tandberg *et al.*, 2013). To date, cognitive deficits persist after successful treatment of psychotic symptoms (Rund *et al.*, 2007, van Os and Kapur, 2010). Most individuals with SZ are not working but depend on social benefits with an estimation of 55 000 pounds per person per year (UK) (Mangalore and Knapp, 2007). Thus, investigations of new treatment regimens are of great importance, especially new alternative of low cost and easily assessable treatments.

In addition to the global cognitive impairment, specific domains present greater dysfunction, including episodic memory, working memory and executive function (Flashman and Green, 2004, Reichenberg *et al.*, 2009). It is important to note that there are also patients with SZ with cognitive functioning in the normal or above-normal range (Allen et al., 2003;Goldstein, 1990;Heinrichs and Awad, 1993;Reichenberg et al., 2009;Silverstein and Zerwic, 1985). However, also in the high cognitive function subgroup, the majority (64%) still have abnormal scores on at least one cognitive domain (Vaskinn *et al.*, 2014), with brain volume correlates (Vaskinn *et al.*, 2015). Recent review papers show that cognitive impairment is also

found in BD particularly in specific areas of working memory, executive functioning, attention, and processing speed (Bourne *et al.*, 2013, Lewandowski *et al.*, 2011, Simonsen *et al.*, 2011).

Depression is a core symptom of BD, and a diagnostic criteria. Depression is also commonly reported in patients with psychosis (Sonmez *et al.*, 2013, Romm *et al.*, 2010), with an increased risk of suicide during the early phases of psychotic illness (Nordentoft *et al.*, 2011, Sim *et al.*, 2004). Thus, low-cost treatments to improve depressive symptoms could have significant benefits in both BD and SZ populations. Depression is also related to cognitive dysfunction (ref), which may be seen in both disorders (ref). Further, mood episodes are also an independent predictior of functional impairments (ref)

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Another major issue in modern psychiatry is the poor physical health and increased suicide rate in patients with SZ and BD, which are causing a reduction in life expectancy by 10-15 years (Bitter *et al.*, 2017, Firth *et al.*, 2015, Osby *et al.*, 2016). Recent studies indicate that physical exercise can benefit cognitive function, mood symptoms, and functional recovery, in addition to improving general physical health in severe mental disorder (Firth *et al.*, 2015, Bitter *et al.*, 2017 ). Thus, regular physical exercise in SZ and BD has the potential as a low cost and an easily assessable treatment option. Studies show that interventions of at least ≥90 min of moderate to vigorous physical exercise, such as aerobic exercise, fast walking, cycling, or football playing have a positive effect on cognitive function (mostly studied is memory) and improved general mental, mood or physical health (Firth et al., 2015). Indeed, physical exercise is known to protect neurons from various brain insults, promote neurogenesis and potentially enhance cognitive function (Collins *et al.*, 2009).

Brain-Derived Neurotrophic Factor (BDNF) is a Nerve Growth Factor protein essential for growth and differentiation of neurons during brain development as well as

synaptic plasticity and maintenance of neurons in adult life. BDNF has been linked to cognitive functioning in animals; however, studies in humans are sparse (Piepmeier & Etnier 2015). Patients with mental disorders including SZ have reduced BDNF levels compared to healthy controls (HC) in the brain (Durany *et al.*, 2001), and in the blood (Buckley *et al.*, 2011, Durany *et al.*, 2001, Ikeda *et al.*, 2008). Interestingly, several animal studies have found that physical exercise increases BDNF mRNA levels in the brain (Zoladz and Pilc, 2010). Hence, physical exercise could potentially improve cognitive function in severe mental illness by a BDNF pathway (Kim *et al.*, 2015, Park *et al.*, 2014, Archer *et al.*, 2014). The knowledge about the role of physical exercise on cognitive functioning and symptom severity, as well as on BDNF mRNA levels in severe mental disorders is limited. Previous studies may have been hampered by small studies (N<100) reducing the ability to appropriately adjust for key factors, including premorbid functioning, age, sex or variation in BDNF levels based on differences in BDNF *Val66Met* genotype (Aas et al., 2014).

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The aim of the present study was to gain more knowledge about the relationship between physical exercise and cognitive and clinical characterstics, and the association with mRNA BDNF levels. We investigated the following hypotheses:1) At least 90 min of physical exercise per week will be associated with better cognitive function and less severe mood symptoms (focus on depressive symptoms). 2) Higher blood BDNF mRNA levels will be associated with better cognitive functioning and more hours exercising per week.

## METHODS

### Participants

The participants were recruited consecutively from psychiatric units (outpatient and inpatient) of 4 major hospitals in Oslo, as part of the larger NORMENT, Thematically

Organized Psychosis (TOP) Research study. A total of three hundred and six participants (schizophrenia [n=177] or bipolar disorders [n=129]) were recruited to the study. Two hundred and nineteen (71.6%) of the participants were taking at least one type of antipsychotic medication; 104 (34.0%) used antidepressants. The mean age of the patients was 29.9±10.4, and 51% were males. Mean age at first received treatment for psychosis was 23.7±9.2 years. Physical exercise was defined as hours spent on any physical activity per week. Exclusion criteria for all groups were: hospitalized head injury, neurological disorder, unstable or uncontrolled medical condition that interferes with brain function, IQ below 70 and age outside the range of 18–65 years. The Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. All participants gave written informed consent.

**Clinical Assessment**

Trained physicians, psychiatrists, and clinical psychologists carried out the clinical assessment. The diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I). Diagnostic reliability was found satisfactory (Ringen *et al.*, 2008) with an overall agreement for DSM-IV diagnostic categories of 82% and the overall κ 0.77 (95% CI: 0.60-0.94). Medication at time of testing was determined through clinical interview and medical charts. Depressive symptomatology was measured using the Inventory of Depressive Symptoms (IDS-C) and the Calgary Depression Scale for Schizophrenia (CDSS). Symptom severity and function were rated separately using a split version of the Global Assessment of Functioning Scale (GAF, Pedersen *et al.*, 2007)

**Neurocognitive Assessment**

Included in this study are measures previously found sensitive to dysfunction in SZ and BD (Aas et al., 2014a; Bozikas and Andreou, 2011; Lewandowski et al., 2011). The following domains were assessed: 1) Memory, 2) Working memory, 3) Executive function and 4) IQ (verbal and performance subtests). To examine performance by domain, raw scores within each domain were standardized into z-scores (for further details, see Aas *et al.*, 2014).

The neurocognitive assessments were carried out by psychologists trained in standardized neuropsychological testing. A 3-hour test battery was administered in a fixed order with two breaks with refreshments. The neuropsychological battery was composed as follows: Working memory was measured using the Letter-Number Sequencing, Digit Span forwards, and Digit Span backwards (Wechsler, 2003); Executive function was measured using the Verbal Fluency Test (Delis-Kaplan Executive Function Scale [D-KEFS]) (Delis 2004) including phonetic fluency and semantic fluency; Memory was measured using Logical Memory test at immediate and delayed (30 minutes) time points (Wechsler, 2007). General intellectual abilities: Performance abilities (perception and visuospatial abilities) were measured using the Block Design task and the Matrix Reasoning from the WASI (Wechsler, 2007); Verbal abilities were measured by Similarities and the Vocabulary from the WASI (Wechsler, 2007). The National Adult Reading Test (NART), was used to assess premorbid cognitive functioning (Vaskinn, A. & Sundet, K. 2001).

**Genotyping**

DNA was extracted from blood and genotyped using the Affymetrix Human SNP Array 6.0 (Affymetrix Inc, Santa Clara, CA, USA), as previously reported (Djurovic et al., 2010). All chips were subjected to the Birdseed-v2 algorithm developed by Affymetrix Inc. and Broad Inst (Kom et al., 2008) and implemented in the software respiratory Affymetrix Power Tools (APT v1.10).

**BDNF mRNA expression Analyses**

Blood samples for gene expression analysis of BDNF were collected using Tempus Blood RNA Tubes (Life Technologies Corporation, Carlsbad, CA, USA), and stored at -80°C until analysis. Total RNA was extracted either automated with the ABI PRISM 6100 Nucleic Acid PrepStation (Life Technologies Corporation, Carlsbad, CA, USA) and the Tempus 12-port RNA Isolation Kit or manually with the Tempus Spin RNA Isolation Kit (Life Technologies Corporation, Carlsbad, CA, USA) according to the manufacturer's protocol. The analyses have been published elsewhere (Aas *et al.*, 2014b).

**Statistics**

Data were analyzed using the IBM SPSS software, Version 25. T-Tests were performed to investigate exercise ≥ or < than 90 min per week and clinical characteristics. Ninty min of exercise per week was both the median of time reported in our sample, as well as the time recommended to have an effect on cognition and physical health in the meta-analysis by Firth et al., (2015). In addition to ≥ or < than 90 min per week, physical exercise was also analyzed as a continuous variable using multiple regression. As age, gender and diagnosis (SZ or BD) may influence the cognitive and clinical features investigated in this study, these variables were added as confounders in the model. To control for the possibility of patients with better cognitive function exercising more than patients with lower cognitive function, we controlled for premorbid IQ (NART). Antidepressants was initially included as a confounder in the analyses due to previous findings of an antidepressant increase in plasma BDNF levels (Zhou *et al.*, 2017) but antidepressant was eventually taken out of from the final model as it did not improve the model. Effect sizes were computed based on comparing the two groups (≥ or < than 90 min of exercise per week) using Cohen's d (Cohen, 1977). According to Rosenthal

and Rosnow (Rosenthal and Rosnow, 1984), effect sizes were considered small for values between 0.20 and 0.50, moderate for values between 0.50 and 0.80, and large for values higher than 0.80.

For the BDNF mRNA analysis, BDNF *Val66Met* genotype was added as a confounder as we have previously reported that different variants of the BDNF *Val66Met* are related to different BDNF mRNA expression (Aas et al., 2014b). As there is no recommended minimum time of physical exercise to influence BDNF levels, physical exercise was also investigated as a continuous variable. The threshold for statistical significance was set at $p < 0.05$ with Post hoc Bonferroni corrections.

## RESULTS

### Demographics and clinical characteristics of the sample divided into ≥ or < than 90 min of exercise per week

No differences between groups were observed for age, gender, or premorbid cognitive function. The group who exercised ≥ 90 min per week were more likely to be BDNF *Val66Met-Val/Val* carriers, and had a better global functioning (GAF scores; $p<0.001$, Cohen's $d=0.33$). The group who exercised ≥ 90 min per week also had higher scores on working memory ($p<0.001$, Cohen's $=0.44$), executive functioning ($p<0.001$, Cohen's $d=0.50$), verbal memory ($p=0.04$, Cohen's $d=0.25$), and general intellectual abililties ($p=0.02$, Cohen's $d=0.27$); see Table 1. The same group had significantly less depressive symptomatology measured by the IDS-C and the CDSS ($p<0.001$, Cohen's $=0.48$ and $p=0.01$,

Cohen's =0.31, respectively). Higher scores on working memory, executive functioning, and verbal memory correlated with better functioning (GAF; ß=0.23, p<0.001, ß=0.25, p<0.001, ß=0.23, and p<0.001, respectively), but not depressive symptoms (CDSS or IDS-C; p>0.1).

Patients with BD had higher scores on BDNF mRNA levels compared to SZ (mean ±SD=1.00±0.39, compared to 1.13± 0.45; t=-2.84, p=0.005). *Met carriers* of the BDNF *Val66Met* also had significantly lower BDNF mRNA levels compared to *Val/Val carriers* (mean±SD=0.92±0.37compared to1.07±0.39; t=3.56, p<0.001, see Table 1).

*-Insert Table 1 here-*

**Physical exercise is associated with better cognitive functioning**

A multiple regression analysis was performed to investigate the association between physical exercise (as a continuous variable) on cognitive function adjusting for age, gender and diagnosis (SZ or BD, see Table 2). There was a positive association between physical exercise and working memory (ß=0.16, p=0.006), and executive functioning (ß=0.15, p=0.006), with no significant findings for verbal memory (ß=0.06, p=0.53).

*-Insert Table 2 here-*

When premorbid cognitive function (NART) was added into the model, a significant link between physical exercise (measured as a continuous variable) and better scores for working memory and executive functioning was still observed (ß=0.12, p=0.01, and ß=0.10, p=0.03, respectively, see Supplementary Material Table S2). Finally, we did not observe any interaction effects between diagnoses (SZ vs. BD) and exercise (see Supplementary Material, Figure S1).

### BDNF mRNA levels, cognitive function, and mood symptoms

A significant association was observed between BDNF mRNA levels and general intellectual abilities measured by WASI (ß=0.12, p=0.037), in the direction of higher BDNF mRNA in the patients who had better cognitive performance. No association was observed for IDS-C and BDNF mRNA (p>0.1).

### BDNF mRNA and physical exercise

No association was observed between physical exercise measured as a dichotomous variable (≥more or < than 90 min per week), and BDNF mRNA levels (p>0.1). Investigating hours spent exercising per week as a continuous variable and BDNF mRNA levels showed a significant association between physical exercise and BDNF mRNA levels (ß=0.11, p=0.046). A significant positive relationship between hours spent on physical exercise on BDNF mRNA levels was also observed after correcting for possible confounders (diagnosis, and BDNF *Val66Met* genotype (ß=0.15, p=0.026)). However, considerable variation in the data was observed (see Supplementary Material Table S3).

## DISCUSSION

Our study gives new knowledge on the role of physical exercise in SZ and BD by showing significant association to better cognitive functioning, fewer symptoms and higher BDNF mRNA levels. Our study demonstrates a positive relationship between physical exercise and better cognitive functioning in patients with SZ or BD, specifically for working memory tasks. This finding was not explained by differences in diagnosis (SZ or BD) or

cognitive functioning before illness onset measured by the NART. Physical exercise of ≥90 min per week was also associated with less severe depressive symptoms, and higher GAF scores supporting a potential multi-target effect of physical exercise in severe mental disorders.

Our large study (N=306) confirms the previous findings by Firth et al., (2015), suggesting that at least 90 minutes of exercise per week is associated with better cognition and less mood symptoms. Previous studies have shown a positive association between exercise and BDNF levels in humans (Aas et al., 2014b), as well as in animals (Kim et al., 2015; Park et al., 2014). In fact, our findings of better cognitive function in the group with regular physical exercise could be related to an increase in BDNF mRNA levels in the brain (Zoladz and Pilc, 2010). Our finding supports an association between regular physical exercise and increased BDNF levels with a moderate effect on cognitive function. However, we only found an association between BDNF mRNA levels and physical exercise analyzed as a continuous variable and not as a dichotomous variable. In fact, it was the participants reporting the highest percentile of time exercising who had the highest BDNF mRNA levels (five hours or more of exercising per week, see Supplementary Material Figure S2). Thus, 90 min of exercise may be at the lower range for having a change in BDNF levels in peripheral blood.

That physical exercise promotes resilience and reduces stress levels is well known (Deuster and Silverman, 2013). About half of patients with SZ or BD report a history of childhood trauma, compared to around 10 % of the general population (Church, 2017). Large meta-analyses confirm childhood trauma to three-fold the risk of developing a psychotic illness (Varese *et al.*, 2012). Patients with SZ or BD who report a history of childhood trauma also have lower BDNF levels measured in peripheral blood, compared to similar patient groups who do not report trauma (Aas *et al.*, 2014b, Mondelli *et al.*, 2011). It has been proposed that a history of childhood trauma sensitize the biological stress system, increases

the subjective stress level, potentially making the individual more vulnerable to develop psychopathology (Aas *et al.*, 2016, Pruessner *et al.*, 2016). We postulate that physical exercise, in conjunction with regular treatment may reduce the physiological and subjective stress response, and potentially reduce the adverse long-term effects of childhood trauma in SZ and BD.

Physical exercise in SZ and BD is a low cost and an easily administered treatment. In our study and other studies, regular physical exercise is associated with better cognitive functioning as well as less severe affective symptomatology, such as depressive symptoms (Firth et al., 2015), supporting exercise as a potential multi-target treatment in SZ and BD.

Some limitations of the current study must be mentioned. First, we used the short-form WASI instead of the full-scale WAIS. Numerous short forms of the WAIS have been developed to reduce administration time while generating a reliable estimate of full-scale IQ (FSIQ) (Cyr, 1984, Silverstein and Zerwic, 1985). Individuals with psychosis tend to show more variations on subtests scores compared to healthy controls (Flashman & Green, 2004), which indicate that using subtests of the battery may decrease the accuracy of the results. On the other hand, patients with psychosis have a limited attention span. Therefore short versions of the WAIS, which are less time consuming, have been found to be beneficial (Allen *et al.*, 1997). Secondly, peripheral BDNF levels were used as a surrogate biomarker of CNS physiology (BDNF was not measured directly in the brain). Reassuringly it has been found plasma BDNF levels reflect brain-tissue BDNF levels (Klein et al., 2011). However, it is still only an estimate of activity in the brain, and not a measure directly from the CNS in itself. Although we found a significant positive correlation between BDNF mRNA levels and physical exercise measured as a continuum variable, large variation in the data was present. Thus our findings should be interpreted with caution until further replications. Finally, we asked participants how many hours of exercise they normally performed each week, without

controlling for specific type of exercise, or using a randomized follow-up study. Reassuringly, the review paper by Firth *et al.*, (2015) concluded that any moderate to vigorous exercise including jogging, cycling, sports or resistance training, independent of type, had a positive effect on mood symptom reduction and cognitive functioning, supporting our broad non-specific approach to exercise. As our study is a cross-sectional study, we cannot infer causality between physical exercise and better mood and cognition, which can only be inferred using longitudinal studies. However, when we corrected for premorbid IQ (NART), those who reported exercising at least 90 minutes per week had better working memory and executive performance, adjusting for the fact that individuals with higher cognitive functioning may exercise more in the first place. However, we can not rule out that those who exercised less than 90 minutes per had a larger reduction in cognitive functioning after illness onset, or if physical exercise could protect from a fall in cognition from premorbid to illness onset. Moreover, no difference in years of education or premorbid functioning (NART) was observed between the groups (<90 min/≥90 min of physical exercise per week).

To conclude, our results of increased levels of mRNA BDNF associated with improved clinical characteristics and high physical exercise suggest an underlying mechanistic link. Further studies of the mechanisms underlying the beneficial effects of physical exercise in severe mental illness are warranted. Physical exercise is a low cost treatment option which can be easily implemented.

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## CONFLICT OF INTEREST

None to declare.

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