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Research report

# Weight cycling in bipolar disorder

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ABSTRACT

*Background:* An association between excess weight and/or weight fluctuations and cardiovascular morbidity and mortality is amply documented. Individuals with bipolar disorder (BD) are differentially affected by overweight/obesity, chaotic eating patterns (e.g., binge eating), as well as cardiovascular morbidity and mortality. Weight cycling (WCYC) is defined as a pattern of repetitive weight loss and gain.
*Methods:* We sought to determine the relationship between course of illness and BD and WCYC retrospectively as well whether these co-occurring phenotypes identify a biologically distinct subpopulation on the basis of having a unique inflammatory biomarker/biosignature profile. Sociodemographic, clinical, and inflammatory markers were gathered from a well-characterized cohort of actual euthymic adults with BD ($n=101$) and a healthy control group ($n=48$).
*Results:* Individuals with BD with a history of WCYC were provided evidence of a greater frequency of prior episodes (i.e., both manic and depressed), as well as of significantly higher levels of circulating IL-6 concentrations when compared to non-WCYC individuals with BD. The association persisted after adjusting for relevant covariates (e.g., BMI, age, number of prior episodes).
*Limitations:* Include the small control group, differing medication status and that all data relies on personal information. Nevertheless we tried to verify all data as far as clinical disclosure was available.
*Conclusion:* The results of this study indicate that adults with BD excessive in weight are not only more susceptible to a relapse-prone course of illness, but also are more likely to present with WCYC. The finding of elevated pro-inflammatory cytokines in this subpopulation may identify a separate subpopulation with greater susceptibility to cardiovascular disease. The overarching aim of personalized treatment and preventive strategies in BD begins with appropriate, empirically supported patient stratification. Our results provide preliminary support for stratifying BD cardiovascular risk on the basis of anthropometrics and WCYC.


## 1. Introduction

The association between excess weight and adverse health outcomes is well established. In addition weight cycling (WCYC), which is a different phenomenon, is independently associated with adverse health outcomes as increased cardiovascular morbidity/mortality and psychological symptoms (Blair et al., 1993; Diaz et al., 2005; Hamm et al., 1989; Lissner et al., 1991; Peters et al., 1995). Weight loss may be an ideal approach to counteract the negative consequences of obesity. However, even when weight loss is achieved, losses are rarely maintained (Wing and Hill, 2001). After one cycle of gaining and losing weight the second regain is faster than the first increase of weight (Brownell et al., 1986; Field et al., 1999).

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Repeated periods of weight loss and regain have been termed WCYC. In the general population between 29% and 78% of women and about 18% of men show some degree of WCYC (Field et al., 1999; Lahti-Koski et al., 2005).

The pathways from WCYC to an increased cardiovascular mortality are not well understood. However, several cardiovascular risk factors associated with WCYC have already been identified as e.g. total body and visceral body fat accumulation, changes in the fatty acid composition in the accumulated fat, fluctuations in renal function, plasma glucose, insulin, blood lipids, blood pressure and heart rate (Montani et al., 2006). It has been suggested that WCYC might be associated with systemic low grade inflammation—a factor that also significantly contributes to the development of cardiovascular morbidity (Strohacker and McFarlin, 2010). A general association between WCYC and psychological symptoms has been described in the literature—mainly in obese persons—as WCYC was found to be linked with the feelings of loss of control, personal failure, and decreased self-esteem. A recent study gives evidence for WCYC as a key component of interpersonal oversensitivity (Kensinger et al., 1998; Petroni et al., 2007). There is an interest in investigations which aim to verify whether WCYC causes depression or results from it (Luppino et al., 2010; Marchesini et al., 2004). An association between WCYC and depression in obesity in mentally healthy probands has been reported before (Kensinger et al., 1998; Muls et al., 1995; Walfish, 2004; Womble et al., 2001) but has been denied in other settings (Bartlett et al., 1996; Foster et al., 1996; Simkin-Silverman et al., 1998). One reason for the controversial results in previous studies is the failure of a standardized definition of WCYC. Furthermore, intake of mood stabilizers and antipsychotics and also weight loss in the case of incompliance or during depressive and manic episodes might contribute to weight instability.

Bipolar affective disorder (BD) is a severe and lifelong psychiatric disorder defined by recurrent pathological disturbance in mood and the presence of mania. Individuals suffering from BD have an abnormal anthropometric profile. Overweight and the appearance of metabolic syndrome are observed to be overrepresented in this group. Furthermore, there is evidence that the excess weight in BD is hazardous to both mental and physical health outcomes (McIntyre et al., 2010). Overweight/obese individuals with BD have a higher risk of medical co-morbidities, increased mortality as well as an increased frequency of manic and depressive episodes, shorter periods of euthymia and higher rates of suicide attempts compared to normal-weight individuals with BD. This empirical finding is not sufficiently explained by behavioral and/or iatrogenic factors (Bond et al., 2011; Fagiolini et al., 2005; Maina et al., 2008; Wang et al., 2006; Yim et al., 2012). The connection between increased medical co-morbidities and BD is probably mediated by a chronic low-grade inflammatory state. This includes increased stress-activation and alterations in the hypothalamic–pituitary–adrenal axis activation as well as hyperglycemia and hyperinsulinemia leading to an accumulation of chronic allostatic load which may lead to damage in the brain and other body systems (Soczynska et al., 2011).

Mechanistic pathways subserving the relationship between metabolic morbidity and an adverse BD presentation are not sufficiently parsed. Existing studies indicate that chronic stress-sensitive medical conditions, such as cardiovascular disease, obesity and diabetes are found to be the most significant causes of mortality amongst patients with BD; in women, the mortality caused by medical co-morbidity is even higher (Kupfer, 2005; McIntyre et al., 2007).

There is lack of evidence whether simple weight reduction has positive influence on the course of BD and whether regaining weight is associated with a worsening of disease. We therefore evaluated the history of WCYC in a cohort of euthymic individuals with BD. We used the WCYC classification of the Nurses Health Study which defined WCYC as losing at least 4.5 kg for at least three times during the last 4 years (Field et al., 1999).

To date, WCYC in individuals with BD has not been reported in the literature. Nevertheless, we know from previous studies that individuals with BD are differentially affected by binge eating disorder which is directionally consistent with obesity and abnormal weight trajectory (McElroy et al., 2013).

The overarching aim of this investigation was to extend the existing knowledge by reporting on the relationship between anthropometrics and WCYC with a particular emphasis on its association with course of illness variables. In addition, we were interested whether a subpopulation at heightened risk for cardiovascular disease might be identified on the basis of a biomarker that is associated with cardiovascular disease. We hypothesized that weight cycling is associated with clinical parameters (staging, as number of affective episodes and suicide attempts) anthropometric data and inflammatory markers (ultrasensitive C-reactive protein: hsCRP, interleukin-6: IL-6).

## 2. Methods

One hundred and one bipolar individuals were enrolled (52 females). All participants were former in- or outpatients of the department of Psychiatry at the Medical University of Graz (Austria) and were diagnosed with BD according to the DSM-IV criteria. All were euthymic at the time of inclusion and evaluation. All patients ($n=101$) and controls ($n=48$) took part in the BIPFAT study that is an ongoing study that broadly aims to characterize various biological markers that subserve the association between BD and metabolic morbidity (Reininghaus et al., 2014). Measures include complete actual and lifetime psychiatric history (SCID I-interview), anthropometric measure, fasting blood, cognitive testing, magnet resonance tomography, EEG, stool sample and different lifestyle questionnaires. As the BIPFAT study is still ongoing, this report only shows the results on WCYC and clinical parameters. Further information on the sample population, aims and objectives of the BIPFAT study as well as results on tryptophan (TRP), kynurenine (KYN), KYN to TRP ratio (KYN/TRP) and neopterin can be obtained from our previous report (Reininghaus et al., 2014).

For correlation analyses, in the cohort of BD clinical staging (Kapczinski et al., 2009), number of depressive and manic episodes, number of suicide attempts, hsCRP, IL-6 and anthropometric data (body mass index—BMI, waist to hip ratio—WHR, waist to height ratio—WHtR) were included.

Weight cycling was evaluated retrospectively by the amount of weight loss in the last 4 years (2–4 kg, 4–8 kg, 9–22 kg, $>22$ kg). A five tailed scale gave the following answer possibilities: never/1–2 times/3–4 times/5–6 times/$\geq 7$ times (Field et al., 1999). In addition, clinical in- and outpatient data as far as available were included. We used the WCYC classification of the Nurses Health Study which defined WCYC as losing at least 4.5 kg for at least three times during the last 4 years (Field et al., 1999).

For a better conclusion on WCYC in BD and comparison with the general population, data of 48 healthy controls have been additionally obtained (28 females) using the same study design. Controls had to be free of chronic diseases (and without actual or previous history of severe psychiatric disorder) except metabolic syndrome.

## 3. Biological assays

Fasting blood samples were collected between 8.00 a.m. and 9.30 a.m. for measuring serum markers and amino acids. Samples