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# Increased estrogen level can be associated with depression in males

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ABSTRACT

*Background:* Several studies have shown a positive association between depression and obesity; however the underlying mechanisms are not fully understood. It is not known if this association is driven by altered sex hormone levels in men due to increased BMI.

*Patients and methods:* Data were obtained from the LIFE-Adult-Study, a population-based cohort study. A total of 3925 men (2244 < 60 years and 1681 > 60 years) were included into analyses. Associations between BMI, sex hormones and depressive symptomatology according to CES-D score were evaluated.

*Results:* Obese men had compared to normal weight controls lower total testosterone (12.6 ± 4.7 vs 19.4 ± 5.5 nmol/L, $p < 0.001$ in < 60 years, and 13.8 ± 6.9 vs 18.3 ± 5.9 nmol/L, $p < 0.001$ in > 60 years group) and free testosterone (249.0 ± 73.9 vs 337.2 ± 82.0 pmol/L, $p < 0.001$, and 217.8 ± 71.2 vs 263.4 ± 72.2 pmol/L, $p < 0.001$), and increased estradiol in older group only (97.3 ± 43.0 vs 82.3 ± 34.2 pmol/L, $p < 0.001$ in obese). Men < 60 years old with depressive symptomatology had higher estradiol levels compared to those without depressive symptomatology (96.3 ± 40.7 vs 84.4 ± 36.6 pmol/L, $p < 0.001$), however no association with BMI was observed.

*Conclusions:* Selected sex hormone parameters were significantly different in overweight and obese compared to normal weight males and certain differences could be seen between younger and older males. Depressive symptomatology was associated with increased estradiol levels in younger men, regardless of BMI.

## 1. Introduction

According to World Health Organization (WHO), by 2020, depression will be the second leading cause of disability worldwide (WHO, 2001). Depression is one of the most common, serious and recurrent disorders. It is associated with diminished role functioning and poorer quality of life as well as with increased medical morbidity and mortality (Kessler and Bromet, 2013). Understanding of the etiology of depression is of key importance to developing and determining more focused and effective treatment strategies.

Although human and animal research has provided some information about etiology, the underlying mechanisms of depression are still subject to debate. Several psychosocial and biological factors have been shown to play a role in the etiopathogenesis of depression. Among psychosocial factors, lower socioeconomic status, financial, occupational and legal stressful life events and prior history of major depression were shown to be associated with depression in men (Kendler and Gardner, 2014). Among often-discussed biological factors are hormonal changes, particularly changes of sex hormones.

The important role of androgens and estrogens in the etiology of mental disorders is supported by several observations. One observation is that females are more than twice as likely as males to be afflicted by mood disorders (Kessler et al., 2005) with a higher incidence in times of hormonal flux such as puberty, perimenstrual and postpartum periods or menopause, mostly driven by changes in estrogen levels (Ahokas et al., 2001; Solomon and Herman, 2009). On the other hand, there is a lower incidence of depression in postmenopausal women connected to pituitary attenuance. Contrary to depression in females, depression

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prevalence in males increases with age and with a drop in plasma testosterone (Khera, 2013).

Testosterone is a major male sex hormone that plays a key role in the development of male reproductive tissues, sexual secondary characteristics, muscle and bone mass and well-being (Bassil et al., 2009). Testosterone levels decline gradually with age (Basaria, 2013), although several other factors (including obesity) contribute to its diminution also in younger men (Khera, 2013). It has been shown that a low testosterone level in hypogonadal men is associated with numerous non-specific symptoms including depression and anxiety (Alkamel et al., 2014; Khera, 2013). Among them, testosterone-replacement therapy has been shown to greatly improve mood, alleviate anxiety and mitigate symptoms of depression (Kanayama et al., 2007; Zarrouf et al., 2009). Jovanovic et al. also showed that testosterone modulates serotoninergic transmission playing a crucial role in the development of depression (Jovanovic et al., 2015). On the other hand, standard antidepressant treatment leads to the normalization of testosterone (Pope et al., 2003). These findings suggest a strong and also reciprocal relationship between testosterone and depression; not only that lower testosterone can lead to depression but also that depression can lower testosterone.

Estrogen, normally considered as a female hormone, plays a crucial role in a number of physiological functions in men, including bone metabolism, cardiovascular, testicular and sexual functions (Rambhatla et al., 2016). In men, the majority of circulating estradiol is primary derived from the peripheral aromatization of circulating testosterone by adipocytes (Lakshman et al., 2010), but also by certain tissues requiring the hormone for its normal tissue homeostasis, such as bones and the brain (Arevalo et al., 2015). The role of estradiol in the explanation of gender differences in schizophrenia prevalence (estrogen-protection hypothesis) is widely accepted (Bratek et al., 2016).

The association between estrogen and depression in men is not so far described.

Obesity can also be associated with changes in sex hormone levels (Lee et al., 2013). A study of obese men showed that BMI is negatively correlated with total testosterone concentration and positively correlated with estradiol (Vermeulen et al., 1993). These abnormalities are mediated by excessive adipose tissue leading to increased aromatase activity with the increased peripheral conversion of androgens to estrogens (Zumoff et al., 2003). The adipose tissue also affects hypothalamic-pituitary-testicular axis, reducing the release of gonadotropin. Also through other mechanisms adipose tissue and androgens influence each other in a bidirectional and reciprocal way (Lee et al., 2013).

A positive association between obesity and depression has been shown in several large studies and meta-analyses (Simon et al., 2006; Zhao et al., 2009). Luppino et al. showed that obese men have a 31% increased risk of developing depression over time, whereas depressive men do not have a significant risk of becoming obese (Luppino et al., 2010).

We suggest that obesity, sex hormones and depression are strongly interconnected; nevertheless the role of sex hormone alterations associated with increased BMI in men *per se* on depression is still not understood.

The aim of this study was to investigate the associations between 1. BMI and sex hormone levels, 2. depressive symptomatology and sex hormone levels, and 3. the role of BMI and altered sex hormone levels in depressive symptomatology in men.

## 2. Patients and methods

### 2.1. Study cohort

Data included to this study were obtained from the LIFE-Adult-Study, a population-based cohort study with more than 10,000 randomly selected deeply phenotyped adults aged 40–79 years. The LIFE-Adult-Study aimed to investigate the prevalences, early onset markers, genetic predispositions and role of lifestyle factors of major civilization diseases, particularly focused on obesity. This study was conducted by the Leipzig Research Centre for Civilization Diseases (LIFE) over 3 years (2011–2014). Written informed consent was obtained from all participants. The study was approved by the responsible institutional ethics board of the Medical Faculty of the University of Leipzig. The data privacy and safety concept of the study was approved by the responsible data protection officer (Loeffler et al., 2015).

From total male sample of 4706, we excluded those who were (1) underweight (BMI of $< 18.5\ kg/m^2$), because of small numbers, (2) using medications possibly influencing either sex-hormones, BMI or mental status, including ATC categories: G03 (sex hormones and genital modulators), H02 (systemic corticosteroids), L02 (endocrine therapy), N03 (antiepileptics), N04 (antiparkinsonics), N05 (psycholeptics), N06 (psychoanaleptics), N07 (other CNS drugs), (3) individuals with hypo- and hyperthyreosis, severe chronic renal, hepatic or neurological diseases, or cancer during the last year prior recruitment to the study, and (4) individuals who had already been diagnosed and treated (pharmacologically or non-pharmacologically) for depression in the last year.

After all abovementioned exclusions, 3925 men were included into statistical analyses.

In hormonal analyses, men were split according to BMI and age. A cut-off of 60 years was used to divide the sample into two main categories, as a natural rapid drop of testosterone in males can be observed in the sixth decade of life (Basaria, 2013) and also due to the fact that several differences in the prevalence and factors associated with depression of younger vs. older men have been published (Balsis and Cully, 2008; Wuthrich et al., 2015).

### 2.2. Anthropometry

Anthropometric measurements were taken by trained study nurses according to standardized protocols. Body weight was measured with an electronic scale (SECA 701, Seca Gmbh & Co KG) with a precision of 0.01 kg; height was assessed by means of a stadiometer (SECA 240) to the nearest 0.1 cm (Loeffler et al., 2015). Body mass index was calculated as weight divided by the square of body height. Categories were defined as follows: underweight as a body mass index (BMI) $\leq 18.5\ kg/m^2$, normal weight as BMI $> 18.5$ to $< 25\ kg/m^2$, overweight as BMI $> 25$ to $< 30\ kg/m^2$ and obese as BMI $\geq 30\ kg/m^2$.

### 2.3. Assessing depressive symptoms

The level of depressive symptomatology was assessed using a self-report questionnaire, the updated German version of the Center for Epidemiological Studies Depression Scale (CES-D) known in Germany as the Allgemeine Depressionsskala – Langform (ADS-L). The ADS-L is a reliable and valid instrument for detecting depressive symptoms (Stein et al., 2014) with wide applicability in general population. It is a 20-item scale where participants rate statements from “0–not at all or less than 1 day” to “4–nearly every day for the last week.” A cutoff score of 23 or greater was assessed as presence of depressive symptomatology (Stein et al., 2014), indicating a probable clinically manifest depression.

### 2.4. Medical history, medications

Participants of the study were asked about medical diagnoses previously confirmed by a physician. The interview contained more than 70 common diagnoses, including hormonal and mental disorders. Data on all medications taken within seven days prior to the interview were gathered. Medications were identified by bar codes (Loeffler et al., 2015), following ATC classification.

### 2.5. Socioeconomic status

Socioeconomic status was obtained in a structured interview and