## ORIGINAL RESEARCH

# High Rates of Depression and Depressive Symptoms among Men Referred for Borderline Testosterone Levels

Christopher J. Westley, BSc,* Richard L. Amdur, PhD,† and Michael S. Irwig, MD†‡

*School of Medicine and Health Sciences, The George Washington University, Washington, DC, USA; †Medical Faculty Associates, Washington, DC, USA; ‡Center for Andrology and Division of Endocrinology, The George Washington University, Washington, DC, USA

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**ABSTRACT**

***Introduction.*** Men referred for borderline testosterone levels represent an increasingly common clinical scenario, yet there is little literature on this population.

***Aim.*** We hypothesized that men referred for borderline testosterone levels would have higher rates of depression and depressive symptoms than the general population.

***Methods.*** Subjects included 200 adult men (mean age of 48 years old) referred for borderline total testosterone levels between 200 and 350 ng/dL (6.9–12 nmol/L). Collected data included demographic information, medical histories, medication use, signs and symptoms of hypogonadism, and assessments of depressive symptoms and/or a known diagnosis of depression or use of an antidepressant.

***Main Outcome Measures.*** The main outcome measure was a combination of known depression, current use of an antidepressant, and/or depressive symptoms according to the Patient Health Questionnaire 9 (PHQ-9) with scores ≥10 considered positive.

***Results.*** Depression and/or depressive symptoms were present in 56% of the subjects. This rate was significantly higher than rates of 6–23% (PHQ-9 scores ≥10) seen in general populations. Antidepressant use was 25%. The population was notable for high rates of overweight/obesity and physical inactivity. Common symptoms were erectile dysfunction, decreased libido, fewer AM erections, low energy, and sleep disturbances.

***Conclusions.*** While sexual and nonspecific symptoms (i.e., fatigue) likely prompted measurements of testosterone in this selected population, clinicians should recognize the high rates of depression and depressive symptoms in men referred for borderline testosterone levels. Clinicians should consider screening for depression/depressive symptoms and overweight and unhealthy lifestyle risk factors in men referred for tertiary care for potential hypogonadism.

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***Key Words.*** Depression; Erectile Dysfunction; Libido; Obesity; Testosterone

### Introduction

Over the past decade, there has been a dramatic increase in the frequency of measuring testosterone levels in men and in testosterone supplementation. This trend corresponds to increased direct-to-consumer marketing in which a disease awareness campaign for "Low T" leads men to believe that their low energy and decline in sexual function are due to lower levels of testosterone [1]. Not surprisingly, from 2001 to 2011, prescriptions for testosterone tripled among one of the largest commercial health insurance populations in the United States [2].

Among the many men who have their testosterone levels checked, a substantial number will have

borderline levels close to the lower limit of the reference range. What constitutes a "low testosterone" is unclear as the effects of testosterone in various target tissues such as the brain, muscle, bone and reproductive organs are more important than serum testosterone levels. There is no universally accepted lower limit of normal for serum testosterone which reflects different opinions by experts, different assay methodologies, and a lack of standardization among the assays [3]. Furthermore, the signs and symptoms of male hypogonadism are quite nonspecific and overlap with many signs and symptoms of depression. A bidirectional association exists between sexual dysfunction and depression among middle-aged men [4]. A clinical practice guideline and a consensus statement on late-onset hypogonadism therefore recommend against using case-finding instruments for the detection of hypogonadism [3,5].

In the European Male Aging Study (EMAS), the authors suggest that borderline total testosterone levels range between 8 and 11 nmol/L (230–320 ng/dL) [6]. In this population-based study, men with borderline testosterones had adjusted mean scores which showed poorer general health, decreased physical function, decreased hemoglobin, and a slight increase in the risk of cardiovascular disease as compared with the normal testosterone group [7]. It is well established that decreased levels of testosterone are associated with aging, development of comorbid health conditions, and lifestyle factors [8,9].

Large studies examining the relationship between testosterone levels and depression or depressive symptoms have shown no association. In the Massachusetts Male Aging Study (MMAS) and Tromso study, total testosterone levels were not associated with depressive symptoms as assessed by the Center for Epidemiologic Studies-Depression Scale and Hopkins Symptom Checklist-10, respectively [10,11]. In the Coronary Artery Risk Development in young Adults (CARDIA) Male Hormone Study, only black men in the lowest quartile of total testosterone had a higher adjusted odds ratio of depressive symptoms as assessed by the Center for Epidemiologic Studies-Depression Scale [12].

There is little published literature on adult men referred for management of borderline testosterone levels, although this is a very common clinical scenario. Clinicians face a difficult challenge in how best to manage these men in the absence of data from large randomized controlled trials. This study seeks to compare the rates of depression and depressive symptoms in men referred for borderline testosterone levels with large reference populations that used the same validated instrument. Based on clinical observation, we hypothesized that men referred for borderline testosterone levels would have higher rates of depression and depressive symptoms than the general population.

## Subjects and Methods

### *Subjects and Study Design*

A chart review was performed on adult men 18 years and older who were referred to the senior author's tertiary academic endocrinology practice from September 2007 to August 2014 for management of borderline testosterone levels. Patients were typically referred for interpretation of ambiguous levels of testosterone and for assessment of potential hypogonadism. Inclusion criteria were a baseline total testosterone between 6.9 and 12 nmol/L (200–350 ng/dL), a repeat measurement of total testosterone, and an assessment of depressive symptoms and/or an established self-reported diagnosis of depression or current use of an antidepressant. We defined the borderline total testosterone range as 6.9–12 nmol/L as it included the lower limit of the reference interval for most major commercial assays and it was similar to the 8–12 nmol/L range from a consensus statement [5]. Exclusion criteria included exogenous testosterone within the prior 3 months, medications that lower testosterone (i.e., GnRH agonists), or clearly documented causes of hypogonadism (i.e., Klinefelters' Syndrome, hypopituitarism, etc).

### *Collected Data*

Medical histories were obtained by self-report and by chart review during the initial clinic visit. An inventory of medical conditions and medication use was collected as chronic conditions are associated with depression and many medications are associated with adverse sexual effects and other nonspecific symptoms. Self-identified race or ethnicity was not assessed, but the clinic population is primarily Caucasian and African-American. Exercise amount was reported as the number of nonwalking exercise sessions per week. The five-item abridged international index of erectile function assessed for the presence of erectile dysfunction with scores 21 and under indicative of this condition [13]. Two blood pressure readings were averaged over two separate visits. Metabolic syndrome was defined according to the criteria of the

International Diabetes Federation using body mass index (BMI) ≥ 30 kg/m$^2$ to define obesity [14]. The mean testicular volume was an average of both testicles and was assessed during physical examination using a Prader orchidometer.

### Depressive Symptoms and Depression Assessment

Patients were asked whether they had a known diagnosis of depression, were suffering from depressed mood, or were taking an antidepressant. Patients without a known diagnosis of depression were asked to complete the validated Patient Health Questionnaire 9 (PHQ-9), with a score of 10 or more considered positive [15]. The PHQ-9 was chosen because it is widely used in primary care settings, is simple to complete, and has a sensitivity of 88% and a specificity of 88% for major depression using independent structured mental health professional interviews as the standard.

### Assays

The majority of initial total testosterones were measured by electrochemiluminescence immunoassays (ECLIA), and the assay methodologies were not known for some of the initial values as they were done at outside facilities. The majority (>60%) of repeat total testosterones were measured by liquid chromatography-mass spectrometry. Repeat testosterone measurements (94%) were performed at either LabCorp/Esoterix (Burlington, NC, and Calabasas Hills, CA, USA) or Quest Diagnostics (Chantilly, VA, USA). For testosterone measurements, the coefficients of variation were 3–6% at LabCorp and 6–8% at Quest. The timing of initial testosterone measurements was not available, but men under age 50 were advised to have their repeat testosterone measurements checked in the morning. Serum FSH, LH, prolactin, and sex hormone binding globulin were measured by ECLIA.

### Statistical Analyses

Distributions of all variables were examined for normalcy. Univariate associations were tested using chi-squared or Fishers Exact Test for categorical variables and independent *t*-tests or one-way analysis of variance for continuous variables. Comparison of age groups was made using chi-squared for categorical variables and analysis of variance for continuous variables. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analysis (with the Freq, *t*-test, GLM, and Corr procedures), and $P < 0.05$ was considered statistically significant.

### Ethics

The Institutional Review Board of George Washington University approved this study for analysis of deidentified data. The study had no external funding.

## Results

The study population consisted of 200 adult men with a mean age of 48 years old (range 20–77). Demographic and clinical characteristics and selected endocrine test results are shown in Table 1. The sample is notable for low levels of physical activity and a high prevalence of overweight and obesity. Over half (51%) of the men did not engage in regular exercise that did not involve walking. Only 16% of men were normal weight, while 39% were overweight (BMI 25–29.9) and 43% were obese (BMI ≥ 30). Using the lower limit of the reference range for the particular assay used, 75% of men had low initial measurements of total testosterone, and 53% had low repeat measurements.

Over half (56%) of the population had either depressive symptoms according to the PHQ-9 and/or a self-reported diagnosis of depression and/or use of an antidepressant. The rates were 62% for those aged 20–39, 65% for those aged 40–49, 51% for those 50–59, and 45% for those ≥60. The mean and median PHQ-9 scores were 7 and 5, respectively. The PHQ-9 identified depressive symptoms (scores ≥ 10) in 7% of the study population in whom these men denied depressed mood or depression.

The prevalence of hypogonadism symptoms and medical diagnoses are presented in descending order by age group in Table 2. The three most common symptoms were the sexual symptoms: erectile dysfunction, decreased libido, and fewer morning erections. Decreased libido was more common in men under age 50. Other common symptoms were low energy, sleep disturbances, and decreased concentration. As would be expected, older men had increased rates of diseases associated with aging such as prostate conditions, osteoporosis, cardiovascular disease, hypertension, dyslipidemia, and diabetes. Only 3% of subjects had a past history of treated prostate cancer.

Medication use by the study population included phosphodiesterase 5 inhibitors (30%), statins (28%), ACE inhibitors/ARBs (27%), antidepressants (25%), aspirin (21%), thiazides (14%), α blockers (12%), β blockers (12%), calcium channel blockers (12%), anxiety medications (11%), diabetes medications (10%), opiates (7%), other lipid

**Table 1** Demographic and clinical characteristics and endocrine tests stratified by age†

| | Age group | | | | |
|---|---|---|---|---|---|
| Variables | Total n = 200 | 20–39 n = 55 | 40–49 n = 48 | 50–59 n = 53 | ≥60 n = 44 |
| Partnered relationship (%) | 76 | 73 | 69 | 81 | 81 |
| Current smoker* (%) | 8 | 15 | 0 | 10 | 9 |
| ≥10 alcoholic drinks/week (%) | 11 | 11 | 13 | 10 | 16 |
| PHQ-9 score** | 5.0 (2.0–10.0) | 7.5 (2.0–13.0) | 7.0 (3.0–11.0) | 5.0 (3.0–10.0) | 2.5 (1.0–6.0) |
| Exercise sessions/week (%) | | | | | |
| None | 51 | 48 | 57 | 54 | 43 |
| 1–3 | 27 | 26 | 24 | 26 | 32 |
| ≥4 | 22 | 26 | 19 | 20 | 23 |
| Weight status (%) | | | | | |
| Underweight | 2 | 2 | 2 | 0 | 0 |
| Normal | 16 | 33 | 9 | 12 | 11 |
| Overweight | 39 | 38 | 40 | 36 | 43 |
| Obese | 43 | 27 | 49 | 52 | 45 |
| Body mass index, kg/m$^2$ | 30.0 (5.9) | 28.5 (6.7) | 30.2 (5.1) | 31.4 (5.6) | 30.1 (5.5) |
| Systolic blood pressure* (mm Hg) | 128 (14) | 125 (13) | 125 (12) | 131 (15) | 132 (15) |
| Diastolic blood pressure (mm Hg) | 78 (7) | 78 (7) | 78 (7) | 80 (8) | 77 (8) |
| Total cholesterol** (mg/dL) | 179 (38) | 188 (34) | 191 (38) | 181 (39) | 163 (34) |
| HDL cholesterol (mg/dL) | 46 (38–56) | 46 (40–52) | 45 (37–55) | 47 (37–54) | 49 (38–63) |
| Triglycerides (mg/dL) | 127 (91–182) | 122 (91–201) | 132 (87–197) | 134 (94–185) | 124 (81–158) |
| Reproductive variables | | | | | |
| Fathered a child** (%) | 46 | 11 | 45 | 62 | 70 |
| Testicular volume* (cc) | 19 (5) | 19 (5) | 20 (5) | 19 (6) | 16 (4) |
| Total testosterone 1** (ng/dL) | 265 (40) | 269 (42) | 249 (33) | 268 (39) | 275 (41) |
| Total testosterone 2 (ng/dL) | 329 (106) | 355 (110) | 324 (109) | 316 (107) | 318 (94) |
| SHBG** (nmol/L) | 26 (21–35) | 22 (19–26) | 25 (20–33) | 26 (20–40) | 34 (27–45) |
| Low SHBG** (%) | 16 | 26 | 18 | 19 | 0 |
| Luteinizing hormone (%) | | | | | |
| Low | 7 | 12 | 7 | 2 | 8 |
| Normal | 84 | 78 | 89 | 91 | 75 |
| High | 9 | 10 | 5 | 7 | 17 |
| Follicle-stimulating hormone (%) | | | | | |
| Low | 3 | 4 | 2 | 0 | 6 |
| Normal | 86 | 86 | 86 | 89 | 77 |
| High | 11 | 10 | 12 | 11 | 17 |

Significant differences by age group are expressed as *$P < 0.05$ and **$P < 0.01$
†Unless indicated by %, data are presented as mean (SD) or median (interquartile range) for HDL cholesterol, PHQ-9 score, triglycerides, and SHBG (sex hormone binding globulin)
Missing data were present for the following variables: lipids (35%), PHQ-9 (16%), SHBG (16%), FSH (14%), exercise (13%), and LH (13%)

medications (8%), 5α-reductase inhibitors (6%), attention deficit medications (6%), other psychiatric medications (5%), and glucocorticoids (3%). None of the subjects reported using anabolic steroids.

## Discussion

Men referred for borderline total testosterone levels had rates of depression and depressive symptoms that were much higher than those of the general population. One quarter of the men were taking antidepressants. These men also had high rates of obesity and low rates of physical activity. The most common symptoms were erectile dysfunction, decreased libido, fewer morning erections, low energy, and sleep disturbances.

Whereas 56% of the subjects had either a known self-reported diagnosis of depression, use of an antidepressant, and/or PHQ-9 scores ≥10, prevalence rates of depressive symptoms were much lower in general populations using the same validated instrument and scoring system. In an ethnically diverse sample of over 5,000 white, black, Latino, and Chinese-American primary care patients, rates of depressive symptoms (PHQ-9 scores ≥10) ranged from 15% to 22% [16]. Among overweight and obese U.S. adults from the 2005-6 NHANES, only 5.6% had PHQ-9 scores ≥10 [17]. Using a different validated instrument, only 11% of the men in the MMAS were categorized as having depressive symptomatology according to the Center for Epidemiologic Studies-Depression Scale [10].

**Table 2** Symptoms of hypogonadism and medical diagnoses stratified by age†

| Symptom of hypogonadism | Total n = 200 | Age group 20–39 n = 55 | 40–49 n = 48 | 50–59 n = 53 | ≥60 n = 44 |
|---|---|---|---|---|---|
| Erectile dysfunction (by AIIEF) | 89 | 84 | 86 | 95 | 90 |
| Erectile dysfunction** | 78 | 65 | 72 | 87 | 88 |
| Decreased libido* | 69 | 75 | 81 | 64 | 52 |
| Fewer AM erections* | 58 | 41 | 52 | 69 | 72 |
| Low energy* | 52 | 50 | 60 | 60 | 33 |
| Sleep disturbances | 42 | 38 | 50 | 42 | 38 |
| Depressed mood* | 42 | 53 | 50 | 33 | 31 |
| Depression | 39 | 47 | 48 | 31 | 29 |
| Decreased concentration* | 27 | 32 | 40 | 24 | 13 |
| Irritability | 19 | 25 | 24 | 16 | 8 |
| Decreased strength | 19 | 21 | 19 | 20 | 15 |
| Decreasing shaving | 6 | 6 | 9 | 2 | 10 |
| Gynecomastia | 5 | 2 | 7 | 4 | 7 |
| Headache | 4 | 4 | 7 | 0 | 7 |
| Visual field deficits | 2 | 2 | 2 | 0 | 2 |
| Galactorrhea | 1 | 0 | 2 | 0 | 0 |
| General diagnoses | | | | | |
| Depression | 56 | 62 | 65 | 51 | 45 |
| Depression/anxiety | 44 | 51 | 50 | 32 | 41 |
| Sleep apnea** | 22 | 5 | 32 | 28 | 23 |
| BPH*** | 15 | 0 | 10 | 21 | 32 |
| CAD*** | 7 | 2 | 0 | 8 | 20 |
| ADHD | 6 | 9 | 8 | 4 | 0 |
| Osteopenia/osteoporosis*** | 4 | 0 | 0 | 2 | 16 |
| HIV | 4 | 2 | 6 | 6 | 0 |
| Past prostate cancer | 3 | 0 | 0 | 2 | 9 |
| Cancer (except prostate) | 1 | 0 | 0 | 2 | 2 |
| Prostate cancer | 0 | 0 | 0 | 0 | 0 |
| Metabolic diagnoses | | | | | |
| Dyslipidemia*** | 32 | 11 | 25 | 40 | 55 |
| Hypertension*** | 30 | 7 | 23 | 38 | 57 |
| Metabolic syndrome* | 22 | 7 | 23 | 33 | 26 |
| Diabetes*** | 12 | 0 | 6 | 25 | 16 |

Significant differences by age group are expressed as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$

†Data are presented as %

Missing data were present for the following variables: fewer AM erections (32%), metabolic syndrome (14%), irritability (12%), decreased concentration (7%), decreased shaving (7%), decreased strength (7%), and sleep disturbances (7%)

AIIEF = abridged international index of erectile function

Men referred for borderline total testosterone levels also had higher rates of obesity as compared with the U.S. population with data from the most recent National Health and Nutrition Examination Survey (NHANES) [18]. For men aged 20–39, 40–59, and ≥60 years, the prevalence of BMI levels ≥30 in the NHANES survey was 29%, 39%, and 32%, respectively. Corresponding rates for the same age groups in this study were 27%, 50%, and 45%. The higher rates of depression and depressive symptoms in this study are unlikely explained simply by higher rates of obesity as the depressive symptoms rates were considerably higher than those in overweight and obese reference populations. Among a large Australian population, rates of depressive symptoms (PHQ-9 scores ≥10) were 11% among normal weight participants, 12% among overweight participants, and 23% among obese participants [19]. Interestingly, there appears to be a bidirectional relationship between depression and obesity. After adjusting for multiple chronic conditions, U.S. adults with abdominal obesity were 2.5 times as likely to have PHQ-9 scores ≥10 as compared with those without abdominal obesity [17].

The high prevalence of sexual and other nonspecific symptoms (i.e., low energy) in men referred for borderline testosterone levels is not surprising, as these symptoms probably prompted physicians to order the testosterone levels. The self-reported prevalence of erectile dysfunction was 78% as compared with 16% and 30% in populations of randomly selected men in the Boston Area Community Health (BACH) and EMAS studies, respectively [6,20]. Our population also reported a higher rate of low libido (69%) as compared with rates of 12% in the BACH and 28% in the EMAS [6,20]. In the BACH, 24% of the population had a total testosterone <10.4 nmol/L (<300 ng/dL), and in the EMAS, 17% had levels <11 nmol/L (320 ng/dL). In the EMAS, men with a BMI of ≥30 had an increased relative risk ratio of 8.74 for secondary hypogonadism [21].

Over 40% of men referred for borderline testosterone levels in our study reported sleep disturbances. This is likely an underestimate of the true prevalence as many of the men had not had diagnostic sleep studies. Studies have been inconsistent regarding sleep and testosterone levels [22–24]. A study of 12 nonobese older men found that the amount of overnight sleep was an independent predictor of morning testosterone levels [23]. In an interventional study of 10 young healthy men, daytime testosterone levels were 10–15% lower when the men were restricted to 5 hours of sleep vs. 10 hours [24].

Although the focus of this study was to examine depression and depressive symptoms in men referred for borderline testosterone levels, the clinical management of this population is an important issue that deserves comment. Whereas fewer than half of those with depressive symptoms and/or depression were taking antidepressants, many were not receiving any mental health care services, and 7% actually denied having depressive symptoms despite positive scores on the PHQ-9. Use of a validated instrument such as the PHQ-9

was easy to use in a busy clinical setting and allowed us to identify men to refer for mental health services. Furthermore, for the majority of this population who were either overweight or obese, weight loss should be promoted as it translates into increases in testosterone levels proportional to the degree of weight loss [25]. Successful weight loss will also benefit the other co-morbid conditions associated with obesity such as hypertension, insulin resistance, and sleeping disorders. For men with sleep disturbances and short sleep duration, restoring sleep hygiene may be beneficial. According to a consensus statement on late-onset hypogonadism in men that was endorsed by several professional societies, it is unclear whether to recommend testosterone replacement to men with total testosterone concentrations between 8 and 12 nmol/L (230–350 ng/dL) [5]. A systematic review and meta-analysis of 16 RCTS with testosterone therapy found a significant effect on mood in hypogonadal men under 60 years old with a greater effect size in those with subthreshold depression [26]. The long-term benefits and risks of testosterone replacement therapy are unclear due to a lack of a large, long-term randomized controlled trial. Short-term randomized controlled trials of testosterone therapy to obese men with type 2 diabetes found no or minimal changes to Aging Male Symptoms or sexual function [27]. One RCT found increased rates of adverse cardiovascular events in older men with limitations in mobility and with low and borderline testosterone levels (3.5–12.1 nmol/L [100–350 ng/dL]) [28].

The principal strengths of this study include a clinically relevant real-world sample, comprehensive data regarding symptomatology, medication use and medical co-morbidities, and assessments from two validated instruments for depressive symptoms and erectile dysfunction. The limitations to this study are selection bias from a single center, lack of an assessment of depression by a mental health professional, heterogeneity of depression evaluation, and the lack of standardization for total testosterone measurements regarding timing and type of assay. Some subjects had an established diagnosis of depression, whereas others had depressive symptoms according to a self-administered questionnaire. Furthermore, some subjects on antidepressants may not actually have depression as these medications can be prescribed for other indications. Given the different reference ranges for testosterone among particular assays, subjects in this study might be classified as having either borderline testosterone or low testosterone. While mean levels of testosterone in populations of younger men are modestly higher in the morning, the timing of a testosterone level for a given individual is not that helpful as testosterone levels fluctuate significantly throughout the day and a third of men with initial low testosterone readings have normal repeat readings due to this intraindividual variability. Despite the limitations noted, we believe that our findings would be generalizable to other urban Caucasian and African-American men who seek care for borderline testosterone levels. The findings are not generalizable to a general population of men with borderline testosterone levels as our population likely had symptoms that prompted the measurement of testosterone. The purpose of this study was not to examine whether there is an association between borderline testosterone levels and depressive symptoms as this has already been established by three large population-based studies that included men across a broad range of testosterone levels [10–12]. Nonetheless, certain depressed patients seen in clinic have lower testosterone levels with a potential biologic mechanism involving serotonin and corticotrophin-releasing factor which inhibit testicular androgen production [29]. The Tromso study did find that anxiety symptoms were negatively associated with testosterone levels [11].

### Conclusions

Men referred for borderline testosterone levels have higher rates of depressive symptoms and/or depression compared with general populations. There is very little published literature on this selected population that represents a growing common clinical scenario. Clinicians should consider screening for depression/depressive symptoms, overweight, and unhealthy lifestyle risk factors in men referred for tertiary care for potential hypogonadism.

### Take Home Message

Clinicians should consider screening for depression/depressive symptoms, overweight, and unhealthy lifestyle risk factors in men referred for tertiary care for potential hypogonadism.

**Corresponding Author:** Michael S. Irwig, MD, Division of Endocrinology, Medical Faculty Associates, 2150 Pennsylvania Ave NW, Washington, DC 20037, USA. Tel: 202-741-2498; Fax: 202-741-2490; E-mail: mirwig@mfa.gwu.edu

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### Statement of Authorship

*Category 1*

**(a) Conception and Design**
Christopher J. Westley; Richard L. Amdur; Michael S. Irwig

**(b) Acquisition of Data**
Christopher J. Westley; Michael S. Irwig

**(c) Analysis and Interpretation of Data**
Richard L. Amdur; Michael S. Irwig

*Category 2*

**(a) Drafting the Article**
Michael S. Irwig

**(b) Revising It for Intellectual Content**
Christopher J. Westley; Richard L. Amdur; Michael S. Irwig

*Category 3*

**(a) Final Approval of the Completed Article**
Christopher J. Westley; Richard L. Amdur; Michael S. Irwig

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