

An Exploratory Cohort Study of the Association Between the Level of Testosterone and Suicidal Ideation in the Hospitalized Adolescent Female With Depression in China

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Abstract

Background

To date, around 4 per 100,000 adolescent committed suicide within the 29 OECD countries. The suicidal behavior is related to psychological factors, genetics, neurobiology, and other biomarkers. We aimed to investigate the risk factors for the suicidal ideation, especially the association between suicide ideation and different levels of testosterone in the adolescent female with depression. The goal of this study is to aid the development of strategies to intervene the suicidal behavior for the depressed female adolescent.

Method

In this single center, prospective cohort study, we enrolled adolescent female with depression. We collected baseline demographic data, age adjusted level of testosterone, Symptom Self-rating Scale, and information about the suicidal ideation, non-suicidal self-injury (NSSI), and suicide attempt. We used multivariate logistic regression to determine the risk factors for the suicidal ideation.

Results

Total 113 hospitalized adolescent female enrolled with a mean age of 13.5 (1.20). Among these patients, there were 86 (76.1%) subjects suffered from the suicidal ideation, while 59 (52.2%) of them had NSSI and 23 (20.4%) had suicide attempt behavior. In the final model, higher level of testosterone ($p = 0.04$) and higher age ($p = 0.02$) were associated with the higher odds of having suicidal ideation.

Conclusion

In this exploratory cohort study, suicidal ideation was prevalent. It is important to assess the level of testosterone in the adolescent female with depression. This study is consistent with the other studies. It shows the age is a potential predictor for the suicidal ideation in the hospitalized adolescent female with depression.

Background

The adolescent suicide problem is becoming a public health issue in recent years. According to the survey among 10–19 years old adolescent from 29 OECD countries, the average suicide rate is 3.9 (1.80) per 100,000 person [1]. In childhood, the prevalence of mood disorders is relatively low (< 1%) [2], but the prevalence will increase greatly after presenting puberty, up to 14% [3]. And in childhood, there is no gender difference in the incidence of mood disorders, and the incidence of boys is even slightly higher. However, in the adolescence period, the incidence gradually increases in adolescent female, and the ratio of male to female is about 1:2 [4]. The reason for the soaring prevalence of adolescence may be related to the physiological, hormonal, and psychological changes and the shift of social roles during the adolescence [5].

Unlike adult depression, adolescent depression is characterized by extreme irritability, rather than low mood or anhedonia [6]. In addition, compared with adult depression, the adolescent patients are more likely to experience extreme irritability, self-harm, and impulsive suicidal behaviors [7]. During the adolescence, compared with male, females are more prone to self-harm and suicidal behavior, especially between the ages of 12–15, the ratio of males to females reaches 1:5–6. However, as the age increases, the incidence of self-harm between male and female tends to be equal [8, 9]. Adolescent depression can seriously affect patients' academic performance and occupational capability [10, 11], and increase the risk of smoking and drug abuse [12]. Although most adolescents can recover from the initial depressive episode, 50%-70% will relapse within 5 years [13, 14]. Furthermore, the depression in adolescence is related to anxiety, drug abuse, suicidal behavior, and unemployment in the adulthood [15, 16].

Adolescence is a period characterized by rapid changes in the brain, during which excitatory synapses are reduced, and the myelin sheaths in the frontal, temporal, and parietal regions increase to promote mood regulation, impulse control, and executive functions, which are more likely to occur High-risk impulsive behaviors such as self-harm and suicidal behavior [17, 18, 19]. And compared to before puberty, the testosterone level during puberty will increase significantly and have a direct impact on the function of the central nervous system [20].

Testosterone is also known as male hormone because its concentration in men is more than ten times that in women. The level of Testosterone drastically changes during the adolescence and closely related to adolescents' mood disorder, self-harm, and suicidal behaviors [21]. Testosterone can cross the blood-brain barrier and affect the brain; testosterone can regulate many neurotransmitters or their receptors, including GABA, dopamine and serotonin (5-HT), etc., thereby affecting mood and Behavior [22]. Previously, it seems that high testosterone levels and low levels of testosterone are both associated with the suicidal behavior [23, 24, 25, 26, 27, 28]. There is argument that the age is the factor for the difference [25]. However, the gender difference and the association between adolescent female patients with depression and the level of testosterone are not clear.

Method

Study Design

This study is a convenience sampling, single-center, cohort study. The adolescent female subjects between the ages of 10 and 16 who were diagnosed with depressive disorder according to the International Classification of Diseases 10 (ICD 10) were eligible for this study.

Study Setting

The Seventh People's Hospital of Hangzhou (Mental Health Center of Zhejiang University School of Medicine) is a tertiary A-level psychiatric hospital. It is a teaching hospital of Zhejiang University and Anhui Medical University, with 1,100 beds. Among them, the Pediatric and Adolescent Psychiatry Department is the only ward in Zhejiang Province with a child psychiatric inpatient department. The

service scope covers the entire Zhejiang and extends to Anhui, Jiangsu, Jiangxi and other provinces (the total adolescent population exceeds 10 million). The number of outpatient visits is over 30000 each year, of which adolescent depression patients account for 20-25%. The department has 9 doctors and 15 nurses.

It was found in outpatient clinics that compared with male, female adolescent depression patients who went to the clinic for the first time were more likely to have suicidal ideas and self-harm and suicidal behaviors. According to related literature, testosterone level is closely related to impulsive behavior; therefore, this study intends to explore the association between suicidal ideation and testosterone level in such patient population.

Measures

The primary outcome is the incidence of suicidal ideation, which is based on the Beck scale for suicide ideation (BSS) [29] and the non-suicidal self-injury behavior rating questionnaire [30]. A scale was compiled to assess the patients' suicidal conception, NSSI and suicide attempt within one week.

This study used the "General Situation Questionnaire" to investigate the general information and self-harm and suicide of the research objects. Items include age, diagnosis, whether it is an only child, whether the parents are divorced, family history of mental disorders, and menstrual cycle.

The revised version of the Symptom Self-rating Scale (Symptom Checklist 90, SCL-90) [31] was used to assess the clinical symptoms of patients. The scale includes 10 factors: somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, terror, paranoia, psychosis, and others (factors that reflect sleep and diet). A 5-point scale of 1 to 5 is used. If the total score exceeds 160 points, or any factor score exceeds 2, the individual is likely to have mental health problems in this sub-section.

The level of testosterone was determined by the blood sample. Five mL of early morning venous blood from the patients on the 3rd to 5th day of the menstrual cycle (if not yet menarche, there is no requirement for this time), the patients will collect blood samples around 6:00 am and used SIEMENS (ADVIA Centaru XP) to evaluate the testosterone level. The test kit (direct chemiluminescence method) measures the serum level of testosterone (sensitivity range: 0.35-52.1nmol/L). The level of testosterone was adjusted by age, and the normal range is 0.5-2.6nmol/L.

Study participants

This study collected the first untreated adolescent female patients with depression who were hospitalized in the Seventh People's Hospital of Hangzhou from January 2018 to December 2019. Enrollment criteria: 1. Female; 2. Between the ages of 10-16 years [32]; 3. After admission, a senior attending physician and an associate chief physician performed regular psychiatric examination, in line with ICD-10 Diagnostic criteria for depression. 4. The initial depression occurred without antipsychotic medication. Exclusion criteria: 1. Suffered from polycystic ovary syndrome, abnormal thyroid function, adrenal disease, pituitary

tumor or other major physical diseases; 2. Neurodevelopmental Disorders, Autism Spectrum Disorder, and Asperger Syndrome; 3. With impulse control disorder such as concomitant conduct disorder, hyperactivity disorder; 4. Combined substance abuse of alcohol, tobacco, drugs; 5. Pre-existed psychotherapy.

This study was reviewed and approved by the ethics committee of the Mental Health Center of Zhejiang University School of Medicine (IRB number hzqy_2018_003). All subjects and their legal guardians gave informed consent to this study. Informed consent forms were obtained.

Statistical analysis

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were implemented in this study. Demographics, admission characteristics, and the SCL-90 results are described using medians and interquartile ranges for continuous variables and frequencies (%) for categorical variables. To evaluate the risk factors associated with the probability of having suicidal ideation within one week, we used multivariate logistic regression to model the suicidal ideation [33], adjusting for the continuous level of testosterone (nmol/L), age, family history of depression, and psychosis components in SCL-90. The adjusted odds ratios were reported. Furthermore, the secondary endpoints NSSI and suicide attempt were both analyzed using multivariate logistic regression, adjusting for the same covariates as listed above. The dependent variables are the self-reported incidence of the NSSI and suicide attempt.

Prior to modeling, redundancy analyses [33] were performed using an adjusted R² cutoff of 0.6 and covariates were reduced based on the least rank in the list of available covariates. Level of statistical significance is 5%. All tests are two-sided. 95% confidence intervals will be reported along with all effect estimates. R software version 3.6.4 (www.r-project.org) and above were used for all the analyses.

Results

From January 2018 through December 2019, we screened 212 adolescent females, of whom 28 (16.1%) met one or more exclusion criteria (Fig. 1). There were 4 (1.9%) patients or their authorized representatives declined to participate for different reasons. Among those, 180 (84.9%) agreed to participate in and signed the informed consent forms. However, 67 (31.6%) of them could not get the sample values of testosterone, due to the limited time window for the sample collection. In total, 113 (53.3%) were included in our final analysis.

Total 113 adolescent female patients were admitted. Of the patients in this cohort, 76.1% of patients suffered from the suicidal ideation, while 52.2% and 20.4% of enrolled subjects have the NSSI and suicide attempt, respectively. The mean level of testosterone is 1.7 (0.65), the suicidal ideation group has higher level of testosterone, comparing with the naïve patients, while the same pattern does not show up in the NSSI and suicide attempts outcomes.

In the self-reported SCL-90-R, the mean of 10 domain scores for the suicidal ideation group range from 2.6 to 3.6, while the none-suicidal ideation group were lower, range from 2.0 to 2.7. In total, the SCL 90 total score shared the same trend of domain score, suicidal ideation had average 66.6 lead in the comparison.

Table 1
Baseline Characteristics of Enrollment across the Status of Suicidal Ideation

	Suicidal Ideation		Overall
	No (n = 27)	Yes (n = 86)	(N = 113)
Age	12.8 (1.28)	13.7(1.09)	13.5 (1.20)
Family Mental Disorder History (Yes)	1 (3.7%)	18 (20.9%)	19 (16.8%)
Divorce (Yes)	4 (14.8%)	9 (10.5%)	13 (11.5%)
Single Child (Yes)	14 (51.9%)	46 (53.5%)	60 (53.1%)
Testosterone (nmol/L)	1.4 (0.50)	1.7 (0.67)	1.7 (0.65)
SCL 90 Total Score	216 (61.86)	282.6 (73.14)	266.7 (75.91)
Number of Positive Items	59.0 (18.43)	72.5 (18.37)	69.3 (19.19)
Somatization	2.0 (0.76)	2.6 (0.99)	2.5 (0.97)
Obsessive Compulsive	2.7 (0.78)	3.3 (0.84)	3.2 (0.86)
Interpersonal Sensitivity	2.5 (0.81)	3.4 (0.95)	3.2 (0.99)
Anxiety	2.7 (0.88)	3.3 (1.02)	3.2 (1.02)
Depression	2.7 (0.90)	3.6 (0.91)	3.4 (0.99)
Horror	2.2 (0.79)	2.7 (0.97)	2.6 (0.95)
Hostile	2.5 (0.94)	3.3 (1.04)	3.1 (1.07)
Paranoid	2.3 (0.80)	3.1 (0.95)	2.9 (0.97)
Psychotic	2.0 (0.75)	2.8 (0.89)	2.7 (0.92)
Others	2.3 (0.79)	3.0 (0.86)	2.8 (0.90)

The odds ratios for the risk factors of being suicidal ideation were presented (Table 2 and Fig. 2). The testosterone level, age, and family mental disorder history are statistically significant in the model. If an adolescent female has 2.03 (nmol/L) testosterone level, the odds of being suicidal ideation has two more times, comparing with the adolescent female with 1.19 (nmol/L) testosterone. The odds ratio is 2.40 (95% CI, 1.03, 5.58), $p = 0.04$. Although the family history was statistically significant, there was only one

patient in the non-suicidal ideation group. It was not conclusive. There were not statistically significant for all the other variables.

Table 2
The Odds Ratios of Primary Outcome: Suicidal Ideation

	Reference	Comparison	OR (95% CI)	p value
Testosterone (nmol/L)	1.19	2.03	2.40 (1.03, 5.58)	0.04
Age	13	14	1.74 (1.10, 2.74)	0.02
Somatization	1.67	3.25	2.18 (0.65, 7.30)	0.2
Horror	2	3.29	0.87 (0.32, 2.36)	0.78
Hostile	2.33	4	2.06 (0.63, 6.78)	0.23
Family Mental Disorder History	No	Yes	8.95 (1.00, 9.90)	0.05
Divorce	No	Yes	1.11 (0.23, 5.44)	0.89
Single Child	No	Yes	1.50 (0.51, 4.40)	0.46

Note: Differences (point estimates) in the suicidal ideation in the linear regression analyses reflect a comparison between the 25th and the 75th percentile values for each continuous variable among all 113 patients in the cohort.

Discussion

In our analysis, we found that the presence of suicidal ideation is high (76.1%, 86/113). While there are 52.2% (59/113) of NSSI, and 20.4% (23/113) of suicide attempts among adolescent female patients with depression in this cohort. The incidence rate of suicidal ideation among the middle school students was 18.21% [34]. Many studies on suicide ideation among adolescents have suggested that depressive symptoms are highly correlated with suicide [35, 36, 37]. And although adolescent males are more likely to succeed in the suicide, adolescent female suffer more on the suicidal ideation, NSSI, and suicidal behavior [38, 39]. Since the cases included in this study are adolescent female patients with depression. It is not uncommon that the rate of suicidal ideation, non-suicidal self-harm behavior and suicide attempt behavior of this study are higher than the other studies.

Consistent with our results, a suicide data from Poland in 2014 suggested that during adolescence, the suicide rate of children aged 15–19 was much higher than that of children aged 10–14[40]; similarly, Steele and Doey et al. found that in the United States Among adolescent children: 53% of children aged 13–19 have suicidal ideation, while only 12% of children aged 6–12 have suicidal ideation [41]. In summary, it is not difficult to see that in adolescence, whether there is depression or not, older children seem to be more likely to have suicidal ideas, which are closely related to the physiological and psychological changes in this special period [17, 19].

The suicidal ideation of the adolescents is often after experiencing strong negative emotions, including anxiety, restlessness, and anger [42, 43, 44, 45]. Different from the reaction of adults experiencing negative emotions, adolescents are more likely to have suicidal ideations or destructive behaviors related to the imbalance of their emotion regulation system (ER) ability [46]. During adolescence, high levels of testosterone directly up-regulate the emotional system by affecting the orbitofrontal lobe (OFC) and prefrontal cortex (PFC), destroying its stability [47, 48]. It is not difficult to categorize the high levels of testosterone as a risk factor for the suicidal ideation.

The study limitations were also evaluated. Firstly, the sample size was not large enough to attain the statistical power for all variables, such as family mental disorder history; secondly, adolescent patients with depression may modify their diagnosis as bipolar disorder in the follow-up; thirdly, the level of testosterone in adolescents may fluctuate with the menstrual cycle and the anti-depression drug may also affect the quality of the samples in this study; finally, only self-reported assessments were collected. We did not evaluate suicide conception, and the frequency and severity of suicide attempts.

In conclusion, in this single site and prospective cohort study, we found that the high level of testosterone is a potential risk factor for the suicidal ideation for the adolescent female who suffers from depression, especially when they are older.

Declarations

Ethics approval and consent to participate: This study was reviewed and approved by the ethics committee of the Mental Health Center of Zhejiang University School of Medicine (IRB number hzqy_2018_003). All subjects and their legal guardians gave informed consent to this study. Informed consent forms were obtained.

Consent for publication: Not applicable.

Data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: YL and SW: conceptualization, methodology, data collection, and writing original draft; CX: psychological evaluation; XH: conceptualization and methodology; GZ and YZ: data collection; DF: delivery of the lab results; KD: writing, review & editing; WC: concept, statistical analysis, writing, and reviewing. All authors have read and approved the final manuscript.

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Figures

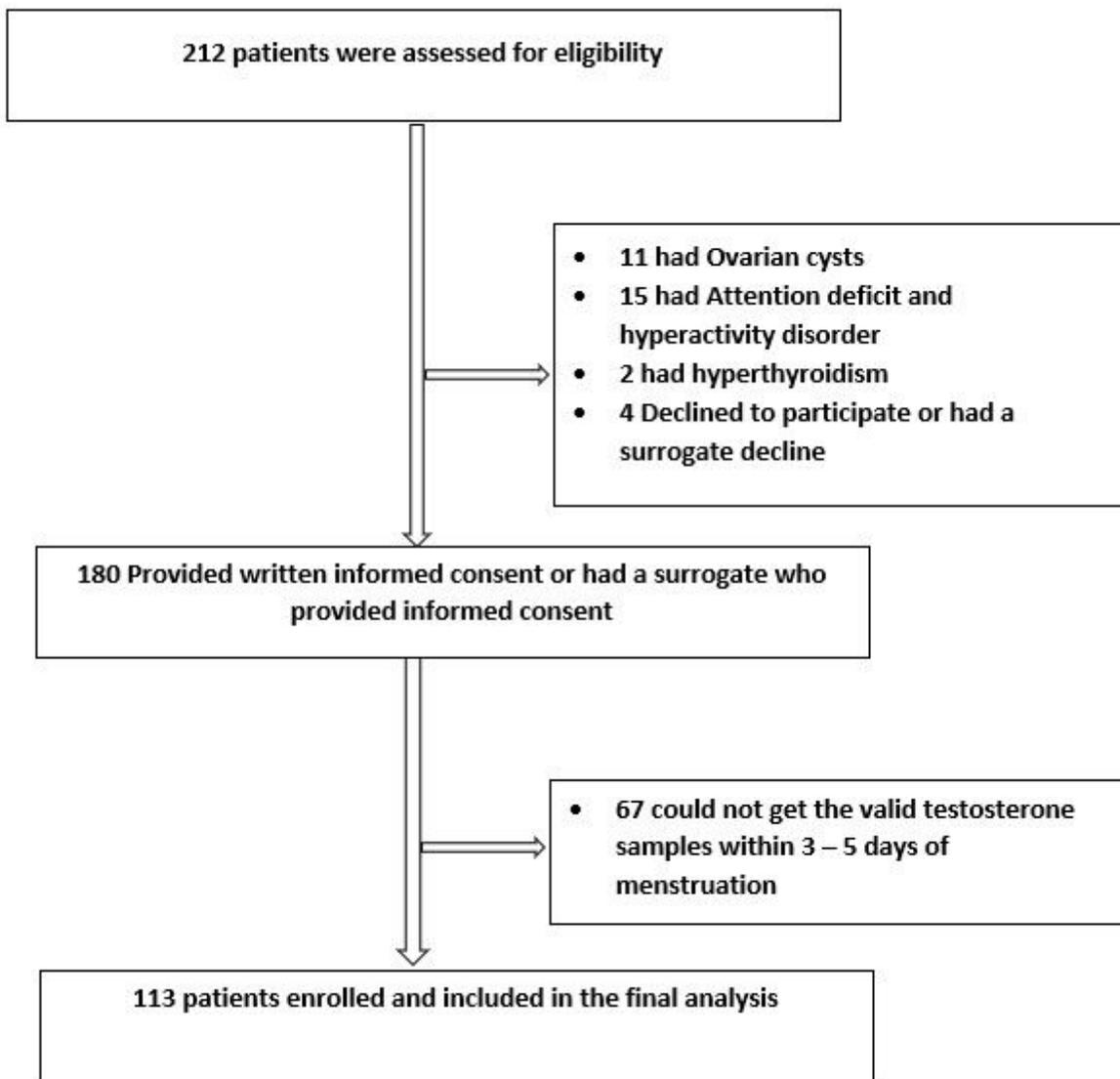


Figure 1

Screen, study exclusion, and enrollment

Odds of Being Suicidal Ideation

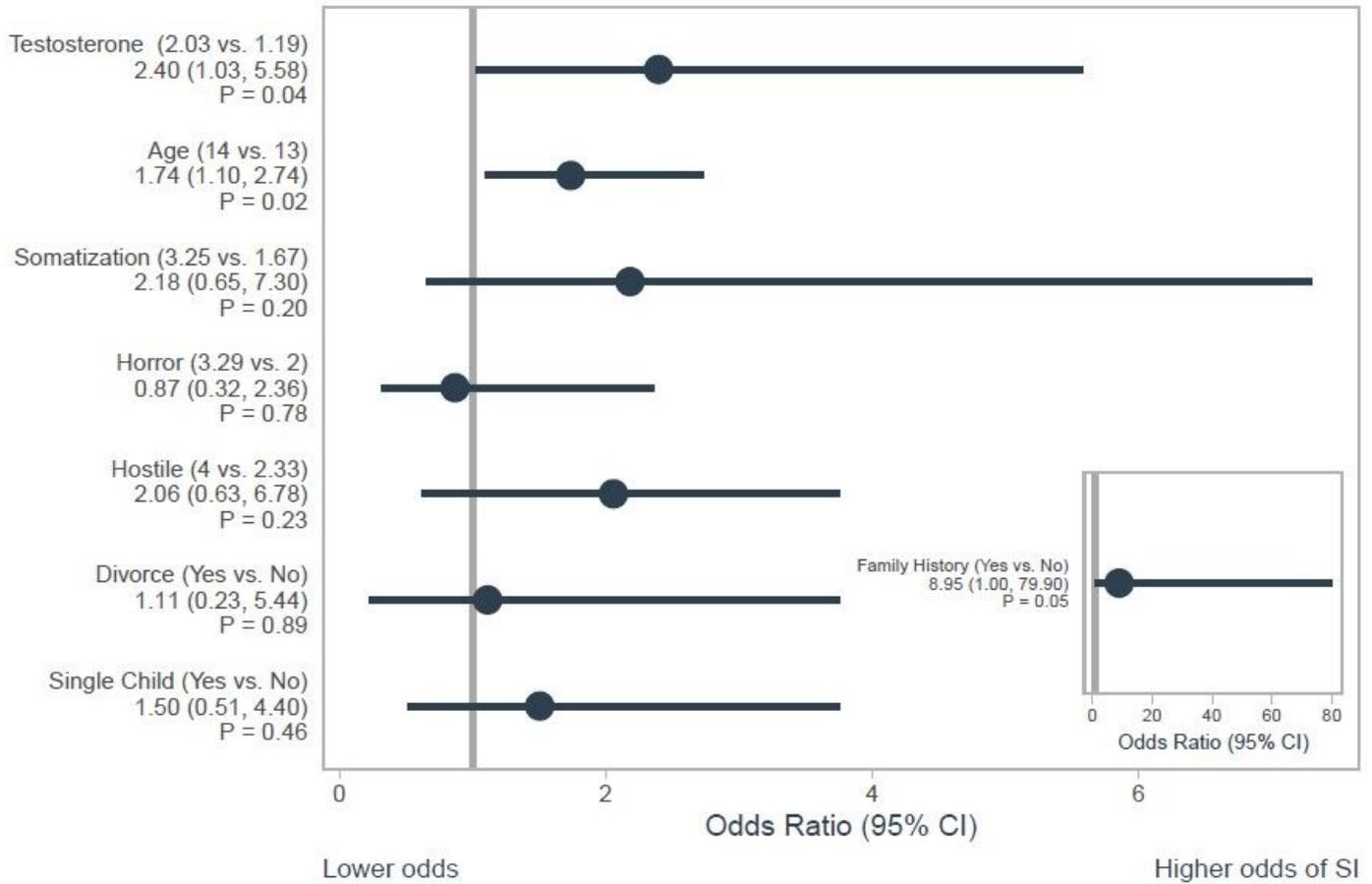


Figure 2

Forest plot of Odds Ratios for Suicidal Ideation

Supplementary Files

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