A Comprehensive Exploration of the Gender-Specific Clinical, Hematological, and Physiological Effects of Eating Disorders

BY

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Thesis

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This thesis by ***Annalisa Barca-Hall*** is accepted in its present form by the Brown University School of Public Health as satisfying the thesis requirements for the degree of Master of Public Health.

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Introduction:

Background:

Eating disorders (EDs), especially anorexia nervosa (AN), are vastly understudied and highly stigmatized in males. Research, diagnostic criteria, and treatment paradigms have historically been centered around the female population[1,2,3,4]. Though complete data on psychiatric trends remain limited, psychiatric disorders are the most common form of illness experienced among children under the age of eighteen years[5]. The rates of EDs in males appears to be increasing, particularly within the younger population, and more males appear to be seeking treatment than in previous decades[2,4]. Males constitute approximately 25% of AN/bulimia nervosa cases in the general population, and up to 67% of patients with adolescent avoidant restrictive food intake disorder (ARFID), but a significantly lower proportion of patients with EDs in the clinical setting [1,2]. Male ED patients have been found to present with lower BMIs, older ages at admission, and longer durations of illness[4,6]. Evidence also suggests that male AN patients may be more likely to engage in excessive exercise and more likely to be diagnosed with a co-morbid anxiety disorder[4]. Bradycardia is the most common medical complication seen in males upon initial assessment and post-treatment mortality appears to be higher in males than females[2,4]. Male patients are also more likely to report a drive for muscularity rather than thinness, have a higher chance of receiving an incorrect diagnosis than females, and are less likely to be diagnosed with an ED than females, despite reporting similar symptoms[3]. Given the increasing prevalence of mental illness among U.S. adolescents and the physical, social, and emotional vulnerability of this population, further research on EDs among males is essential in order to finesse the current diagnostic criteria, reduce misdiagnoses, increase early detection in the clinical setting, and ultimately, reduce morbidity

and mortality.

Objective:

Due to the lower prevalence and lack of focus on adolescent males within the eating disorder research community, little is known about the specific risk factors for EDs in males or the impact of EDs on male hormone levels, electrolyte levels, or hematologic factors.

Statement of Purpose:

This study will compare male and female ED patients using a wide range of variables with the aim of addressing a gap in the current literature regarding the gender specific adverse health effects of EDs. Additionally, in a secondary analysis, we will compare male and female subjects at least six months post-baseline in an effort to identify factors associated with relapse.

Hypothesis:

Based on the present literature, we hypothesize that males will present with more significant adverse health outcomes than their female counterparts at both baseline and follow-up. Specifically, we expect males in our study to be older at baseline and at diagnosis, have lower BMIs, BMI z-scores, weight z-scores, body fat percentages, heart rates and systolic and diastolic blood pressures at both baseline and follow-up compared to females.

Methods:

Data Source:

A retrospective chart review was performed using data obtained from the Research Patient Data Registry (RPDR) with IRB approval. All analyses were performed at the Massachusetts General Hospital Neuroendocrine Unit. Only subjects between the ages of 10

and 25 at baseline, who had been seen in the MGH ambulatory setting, were included in the analysis. Subjects were included in the analysis if they had a valid diagnosis of either AN, eating disorder not otherwise specified (EDNOS) (a DSM-IV diagnostic group; included because DSM-5 diagnoses were not available before 2013), or avoidant restrictive food intake disorder (ARFID). Due to less complete data, subjects with a diagnosis of bulimia nervosa or binge eating disorder were excluded from the study. Subjects with a history of any diseases known to affect bone or mineral metabolism and/or were pregnant or nursing were also excluded from the study. The final study sample included 97 total subjects, with 48 males and 49 females.

Variables:

The baseline covariates of interest included age at diagnosis, height, weight, BMI, comorbid anxiety diagnosis, calcium, phosphorus, potassium, TSH, estradiol, vitamin D, WBC, hemoglobin (HGB), hematocrit (HCT), heart rate, blood pressure, and pulse pressure. Z-scores and percentiles were calculated for height, weight, BMI, diastolic and systolic blood pressure for subjects less than 20 years of age based on guidelines from the Centers for Disease Control and the National Institutes of Health. In a secondary analysis, mean heart rate and pulse pressure were analyzed at follow-up within a small sample of subjects, in addition to percentiles for weight, BMI, systolic blood pressure, and diastolic blood pressure.

Statistical Analyses:

All statistical analyses were completed using the 13th version of the JMP Statistical Software data program. The student T-test was used at the 0.05 significance level to compare the means of two groups when data followed the normal distribution and the Wilcoxon Rank Sum test was used to compare the two samples when data were not normally distributed. The

Chi-square test was used to examine categorical variables and crude odds ratios were obtained for binary variables.

Results:

Baseline Characteristics:

Table 1 displays baseline characteristics for the study population. All parametric variables are expressed as mean ± standard deviation, non-parametric variables are expressed as median (IQR), and categorical variables are expressed as % (n). The p-values from the significance tests are displayed in the third column of Table 1.

48 male and 49 female subjects between the ages of 10 and 25 years with an ED diagnosis were included in the final analysis. There was a significant difference (p=0.0042) in age, as the males had a mean age of 14.76 ± 2.98 years compared to a mean age of 16.62 ± 3.26 years for the females. Males and females differed significantly in regard to ED diagnosis (p=0.0014). 73.47% of the females had a diagnosis of AN, compared to only 39.58% of the males. Only 14.29% of the females had a diagnosis of EDNOS compared to 35.42% of the males and only 12.46% of the females had a diagnosis of ARFID compared to 25.00% of the males. The two genders also differed significantly in regard to both age at baseline and age at diagnosis. The mean age at baseline for males was 14.76 ± 2.98 years compared to 16.62 ± 3.26 years for females (p=0.0042). As shown in Figure 1, the mean age at diagnosis for males was 14.67 ± 3.14 years compared to 16.51 ± 3.38 years for females (p=0.0066).

Male and female subjects did not differ significantly in regard to height, weight, or BMI at baseline. Though the difference was not significant, the male group presented with height z-scores and height percentiles that were noticeably lower than female group (-0.71 ± 1.57 vs. -

0.19 ± 1.06 and 31% vs 44%). The male group had moderately higher weight z-scores and BMI z-scores than the female group but, again, the differences were not significant. These results are displayed in Figure 2. A greater portion of female subjects (51.28%) presented with weight percentiles below the 15% compared to male subjects (45.24%) but, again, the p-value was not significant. Male subjects presented with significantly higher median hemoglobin levels (14.15 vs. 13.1, p=0.0017) and mean hematocrit levels at baseline than the females (41.42 ± 3.40 vs. 39.23 ± 2.64, p=0.0280).

As shown in Figure 3, males and females differed significantly in regard to comorbid mental illness. A greater proportion of the female group had an anxiety diagnosis compared to the male group (25% vs. 40.82%) and a greater proportion of the female group had a depression diagnosis compared to the male group (20.83% vs. 28.57%). A greater proportion of the male subjects, however, were diagnosed with an anxiety disorder and/or depressive disorder prior to being diagnosed with an eating disorder than the female subjects.

Hemodynamic Parameters:

As displayed in Table 2, the male group presented with higher heart rates at baseline compared to the female group, however, the difference was not statistically significant (83.85 BPM ± 25.00 vs. 74.11 BPM ± 20.50). 25.0% of female subjects presented with bradycardia, a heart rate less than 60 BPM, compared to 18.52% of male subjects, however, the p-value was greater than 0.05. The two groups did not differ significantly for mean systolic blood pressure (mmHg), systolic blood pressure Z-scores, or systolic blood pressure percentiles. Though the p-values were not statistically significant, the male group did present with moderately higher systolic blood pressure Z-scores (-0.58 ± 1.20 vs. -0.69 ± 1.28) and moderately higher systolic blood pressure percentiles (32.5% (12.5-59.25) vs. 20.0% (5.0-55.0%)). The male group also

presented with significantly lower mean diastolic blood pressure compared to the female group (61.30 ± 7.62 vs. 66.00 ± 9.45, p=0.02). The two groups did not differ significantly in regard to diastolic blood pressure Z-scores or diastolic blood pressure percentile at baseline, but the male group presented with moderately lower scores for both (-0.33 ± 0.81 vs. 0.01 ± 1.02 and 37.60 ± 26.42 vs. 50.97 ± 27.40). Lastly, the male subjects presented with significantly wider pulse pressures on average compared to the female subjects (44.23 ± 11.54 vs. 37.29 ± 7.70, p=0.0058).

Secondary Analysis:

Data for subjects at least six months post-baseline were analyzed when available and the results are displayed in Table 3. Follow-up variables of interest included: weight percentile, BMI percentile, heart rate, systolic BP percentile, and pulse pressure, however, availability of data varied greatly among the variables. Of the 24 male subjects with available follow-up data, only 20.83% presented with weights less than the 15th percentile at baseline but greater than or equal to the 15th percentile at follow-up compared to 31.3% of the 16 female subjects. 34.78% of male subjects (n=23) had BMI's less than the 15th percentile at baseline but greater than or equal to the 15th percentile at follow-up compared to 22.2% of female subjects (n=9). Male and female subjects presented with similar heart rates at follow-up, as 77.78% of males (n=9) and 73.9% of females (n=23) had heart rates greater than or equal to 60 BPM at both baseline and follow-up. In regard to systolic blood pressure percentile, 27.27% of male subjects (n=11) and only 10% of female subjects (n=10) presented with systolic blood pressure levels less than the 15th percentile at baseline but greater than the 15th percentile at follow-up. 42.86% of male subjects (n=14) presented with pulse pressures within the normal range (30-50) at baseline and follow-up compared to 73.15% of female subjects (n=26).

Discussion:

The results of this study suggest that male and female adolescents with EDs may present more similarly at both baseline and follow-up than we initially hypothesized. Contrary to what we predicted and what the literature suggests, the male subjects in our study presented with significantly younger ages at baseline and diagnosis[4,6]. This could potentially be explained by the greater prevalence of EDNOS and ARFID among male subjects compared to female subjects in this study, as these diagnoses are more common in younger children.

We were surprised to find that the male subjects presented at baseline with higher weight z-scores and weight percentiles compared to female subjects, as we had hypothesized that, due to factors such as social stigma or misdiagnoses, males would seek treatment later than females. The difference in height z-scores and percentiles between the two genders should be noted and explored further to determine whether this difference is due to age or possible stunting among the males. As hypothesized, male subjects did have lower BMI's and BMI Z-scores at baseline than female subjects, however, the difference was marginal. Male subjects had slightly lower vitamin D and potassium levels than female subjects, but overall, contrary to our hypothesis, the male subjects did not present with more abnormal lab values than their female counterparts. The only two lab values that differed significantly between males and females were HCT and HGB, which is consistent with what is seen within the general population.

The greater prevalence of anxiety disorder diagnoses among the female group in our study is consistent with previous studies examining trends of psychiatric diagnoses between genders[8]. The greater portion of male subjects presenting with an anxiety and/or depressive

disorder prior to being diagnosed with an eating disorder points to the importance of early identification of adolescents at risk of mental illness in the clinical setting.

There was a suggestion, though the difference was not statistically significant, that the mean heart rate of male subjects was slightly (approximately 10 beats) higher than the mean heart rate of female subjects at baseline and a greater proportion of females presented with bradycardia compared to male subjects. These results are surprising given that healthy males tend to have lower resting heart rates than healthy females in the general population. We are unable to determine whether these differences may be influenced by exercise since, due to the nature of this study, we did not measure exercise volume.

As we hypothesized, males presented with significantly lower diastolic blood pressure levels compared to females. This is noteworthy as females in the general population tend to have lower diastolic blood pressure levels than males[7]. Contrary to our hypothesis, however, the females in our study presented with more narrow pulse pressures than the males in our study.

Due to the minimal follow-up data, the results of Table 3 are largely inconclusive. The only significant difference between the two genders was found when comparing pulse pressure, however, this is likely due to the inadequate sample size. We do believe that this table is still worthwhile, as it provides an outline for future studies examining treatment outcomes among male and female ED patients.

Strengths and Limitations:

This study adds to the minimal existing literature comparing male and female ED patients. Our data are derived from an outpatient setting, whereas most studies involving male ED patients utilize data from the inpatient setting. This makes our results generalizable to a

wider patient population. It should be noted, however, that it is estimated that only 20% of U.S. children and adolescents with a diagnosable mental illness actually receive treatment[5]. Therefore, it is unclear whether our results are generalizable to a non-treatment-seeking population. Strengths of our study include our reasonably large sample size and wide range of variables. Although we focused exclusively on descriptive statistics, the sampling strategy and size, as well as the exploration of longitudinal data, set our study apart from the previous studies examining treatment-seeking males with EDs.

As anticipated, the primary limitations of this study are related to the retrospective method of data collection. The lack of complete data and consistent sample sizes across all variables for both genders constrained some of our analyzes and limits the generalizability of our study. Additionally, because our data were derived from the charts of patients seen in the ambulatory setting, there is likely variation in the way in which certain values, e.g. heart rate, blood pressure, weight, were measured. Selection bias is also a possible limitation, particularly in regard to follow-up data, as subjects with more complete data may have had more severe symptoms at baseline than subjects with less complete data.

Conclusion:

Recommendations and Future Directions

The results of the present study have interesting potential clinical implications but would be strengthened by more complete data. Thus, continued efforts should be made within the research community to involve and examine male ED patients, particularly in longitudinal studies. It may be worthwhile to (1) repeat this study using more recent data considering that Other Specified Feeding or Eating Disorder (OSFED) is now used instead of EDNOS, (2)

stratify male and female subjects by diagnosis, and (3) control for age. The higher rates of EDNOS among the males in our study may support the relatively recent shift to OSFED, as patients with very different symptoms may have been receiving the same broad diagnosis. Overall, the present study emphasizes the continued importance of involving male ED patients in research and development of treatment paradigms and supports the notion that eating disorders may present more similarly in males and females than once thought. This may aid in the early diagnosis and treatment of males in the clinical setting, as previous studies suggested that symptoms may appear more severe in males.

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Table 1: Baseline Characteristics* (n=97)				
	Males (n=48)	**Females** (n=49)	**P-Value:**	**Odds Ratio:**
ED Diagnosis			**0.0014**	--
Anorexia Nervosa	39.58% (n=19)	73.47% (n=36)		
EDNOS	35.42% (n=17)	14.29% (n=7)		
ARFID	25.00% (n=12)	12.24% (n=6)		
Race			NS	--
White	83.33% (n=40)	83.67% (n=41)		
Asian	2.08% (n=1)	6.12% (n=3)		
Black	6.25% (n=3)	4.08% (n=2)		
Hispanic	6.25% (n=3)	0.00 (n=0)		
Other	0.00% (n=0)	2.04% (n=1)		
Age (yrs)	14.76 ± 2.98	16.62 ± 3.26	**0.0042**	--
Age at Diagnosis (yrs)	14.67 ± 3.14	16.51 ± 3.38	**0.0066**	--
Height (cm)	161.65 (149.60-173.23)	161.54 (153.67-165.42)	NS	--
Height Z-Score	-0.71 ± 1.57	-0.19 ± 1.06	NS	--
Height Percentile	31% (8.0-63.0)	44% (12.5-69.5)	NS	--
Weight (kg)	46.65 ± 13.73	45.61 ± 10.57	NS	--
Weight Z-Score	-0.99 (-1.79- -0.1)	-1.07 (-2.01- -0.39)	NS	--
Weight Percentile	17.5% (4.0-46.5)	14% (2.0-35.0)	NS	--
Weight Percentile < 15	45.24% (n=19)	51.28% (n=20)	NS	*0.78 (0.33-1.88)*
BMI (kg/m^2)	17.33 (15.91-19.53)	17.63 (15.80-18.79)	NS	--
BMI Z-Score	-1.18 ± 1.35	-1.24 ± 1.14	NS	--
BMI Percentile	11.0% (3.0-44.0)	11.5% (1.0-40.0)	NS	--
BMI Percentile < 15	51.22% (n=21)	58.33% (n=21)	NS	*0.75 (0.30-1.85)*
Comorbid Anxiety Diagnosis	25% (n=12)	40.82% (n=20)	**0.0976**	*2.10 (0.87-4.92)*
Anxiety Diagnosis Preceded ED Diagnosis	14.58 (n=7)	2.04% (n=1)	**0.0248**	*0.12 (0.01-1.03)*
Comorbid Depression Diagnosis	20.83% (n=10)	28.57% (n=14)	NS	*1.38 (0.55-3.44)*
Depression Diagnosis Preceded ED Diagnosis	6.12% (n=3)	0% (n=0)	NS	--
Calcium (mg%)	9.76 ± 0.35	9.74 ± 0.35	NS	--
Phosphorus (mg/dl)	3.5 ± 0.58	3.47 ± 0.58	NS	--
Potassium (mmol/L)	3.83 ± 2.70	4.00 ± 0.45	NS	--
TSH (uU/ml)	1.80 (1.16-2.15)	1.61 (1.21-2.52)	NS	--
Estradiol	--	36.75 ± 4.79	--	--
Testosterone (ng/dL)	163.33 ± 159.895	38.33 ± 12.51	NS	
Vitamin D (ng/mL)	30.20 ± 9.82	34.94 ± 15.44	NS	--
WBC (th/cumm)	6.30 ± 2.00	5.64 ± 2.09	NS	--
HGB (g/dl)	14.15 (13.28-15.13)	13.1 (12.53-13.9)	**0.0017**	--
HCT (%)	41.42 ± 3.40	39.23 ± 2.64	**0.0280**	--

**Categorical variables are expressed as column % (n), parametric continuous variables are expressed as mean ± SD, and nonparametric continuous variables are expressed as median (IQR).*

**T-test was used for parametric data, Wilcoxon Test was used for non-parametric data, and either the Chi. Sq or Fisher's Exact Test was used for categorical variables.*

Table 2: Hemodynamic Parameters* (n=97)				
	Males (n=48)	**Females** (n=49)	**P-Value:**	**Odds Ratio:**
Heart Rate (BPM)	83.85 ± 25.00	74.11 ± 20.50	NS	--
Bradycardia (< 60 BPM)	18.52% (n=5)	25.0% (n=11)	NS	*1.47 (0.45-4.81)*
Systolic Blood Pressure (mmHg)	105.53 ± 12.28	103.24 ± 12.63	NS	--
Systolic Blood Pressure Z-Score	-0.58 ± 1.20	-0.69 ± 1.28	NS	--
Systolic Blood Pressure Percentile	32.5% (12.5-59.25)	20.0% (5.0-55.0)	NS	--
Diastolic Blood Pressure (mmHg)	61.30 ± 7.62	66.00 ± 9.45	**0.0203**	--
Diastolic Blood Pressure Z-Score	-0.33 ± 0.81	0.01 ± 1.02	NS	--
Diastolic Blood Pressure Percentile	37.60 ± 26.42	50.97 ± 27.40	NS	--
Pulse Pressure (mmHg)	44.23 ± 11.54	37.29 ± 7.70	**0.0058**	--

**Categorical variables are expressed as column % (n), parametric continuous variables are expressed as mean ± SD, and nonparametric continuous variables are expressed as median (IQR).*
**T-test was used for parametric data, Wilcoxon Test was used for non-parametric data, and either the Chi. Sq or Fisher's Exact Test was used for categorical variables.*

Table 3: Secondary Analysis *(≥ 6 Months Post-Baseline)*			
	Males	**Females**	**P-Value:**
Weight Percentile	N=24	N=16	NS
Remained < 15th Percentile	29.17% (n=7)	25% (n=4)	
*<15th Percentile at Baseline **but** ≥ 15th Percentile at Follow-Up*	20.83% (n=5)	31.3% (n=5)	
Remained ≥ 15th Percentile	45.83% (n=11)	43.8% (n=7)	
*≥ 15th Percentile at Baseline **but** < 15th Percentile at Follow-Up*	4.17% (n=1)	0% (n=0)	
BMI Percentile	N=23	N=9	NS
Remained < 15th Percentile	21.74% (n=5)	22.2% (n=2)	
*<15th Percentile at Baseline **but** ≥ 15th Percentile at Follow-Up*	34.78% (n=8)	22.2% (n=2)	
Remained ≥ 15th Percentile	39.13% (n=9)	55.6% (n=5)	
*≥ 15th Percentile at Baseline **but** < 15th Percentile at Follow-Up*	4.35% (n=1)	0% (n=0)	
Heart Rate (BPM)	N=9	N=23	NS
*< 60 at Baseline **and** at Follow-Up*	11.11% (n=1)	4.3% (n=1)	
*<60 at Baseline **but** ≥ 60 at Follow-Up*	11.1% (n=1)	21.7% (n=5)	
*≥ 60 at **both** Baseline and Follow-Up*	77.78% (n=7)	73.9% (n=17)	
Systolic BP Percentile	N=11	N=10	NS
Remained < 15th Percentile	0% (n=0)	30% (n=3)	
*<15th Percentile at Baseline **but** ≥ 15th Percentile at Follow-Up*	27.27% (n=3)	10% (n=1)	
Remained ≥ 15th Percentile	54.55% (n=6)	60% (n=6)	
*≥ 15th Percentile at Baseline **but** < 15th Percentile at Follow-Up*	18.18% (n=2)	0% (n=0)	
Pulse Pressure	N=14	N=26	0.0222
*<30 or >50 at Baseline **but** Between 30 and 50 at Follow-Up*	21.43% (n=3)	19.2% (n=5)	
Remained between 30 and 50	42.86% (n=6)	73.1% (n=19)	
*Between 30 and 50 at Baseline **but** >50 at Follow-Up*	14.29% (n=2)	3.8% (n=1)	
Remained >50	21.43% (n=3)	3.8% (n=1)	

**P-values reflect Chi. Square.*

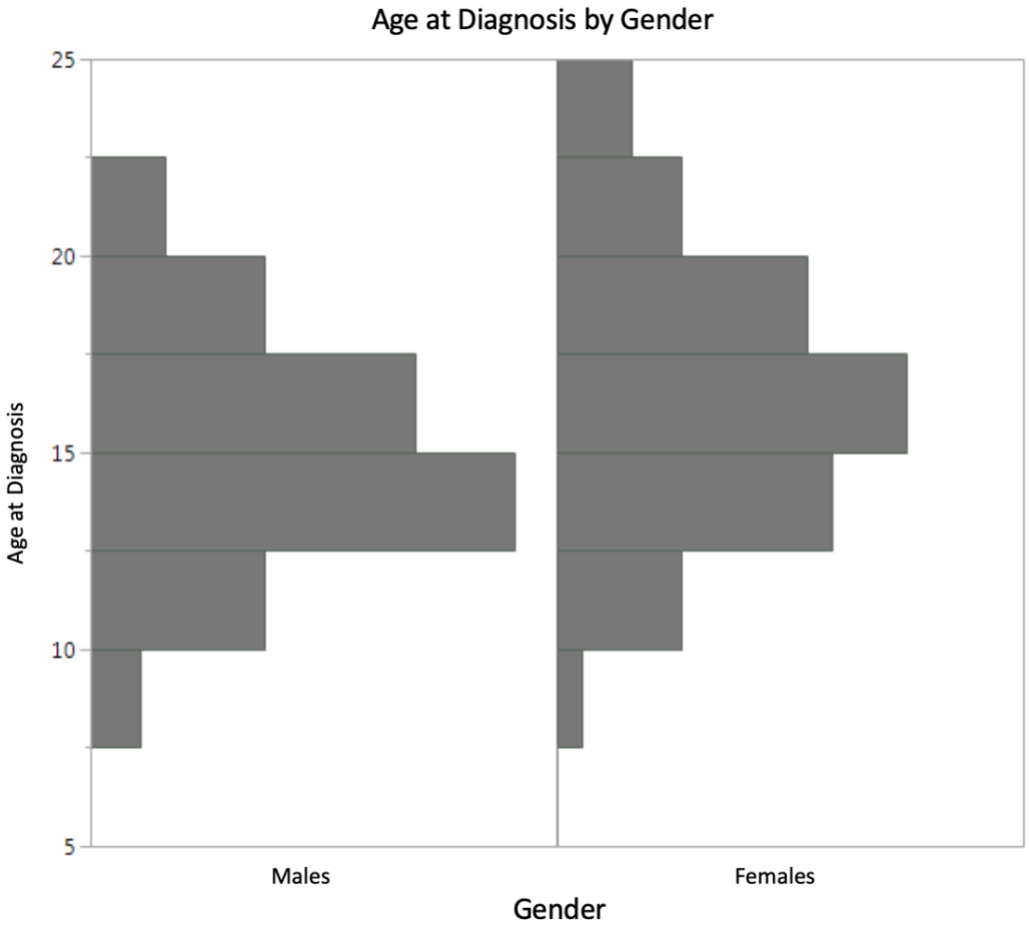
Age at Diagnosis by Gender
25
20
15
10
5
Age at Diagnosis
Males
Females
Gender

Figure 1:

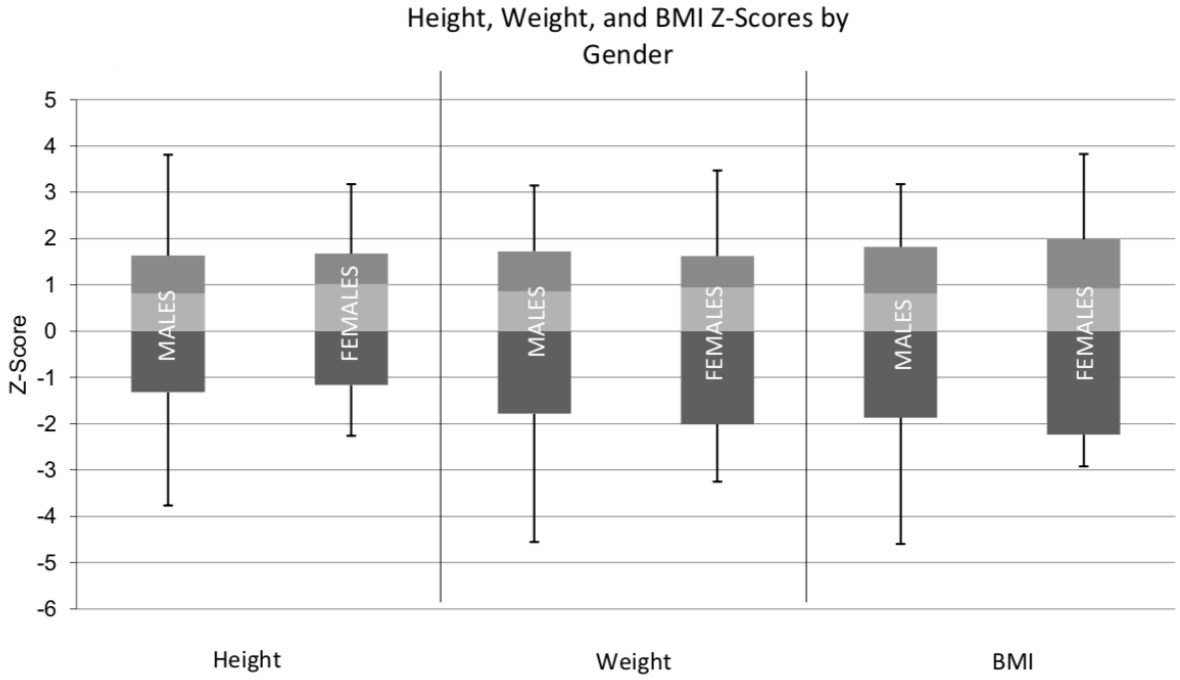
Height, Weight, and BMI Z-Scores by Gender
Z-Score
5
4
3
2
1
0
-1
-2
-3
-4
-5
-6
MALES
FEMALES
MALES
FEMALES
MALES
FEMALES
Height
Weight
BMI

Figure 2:

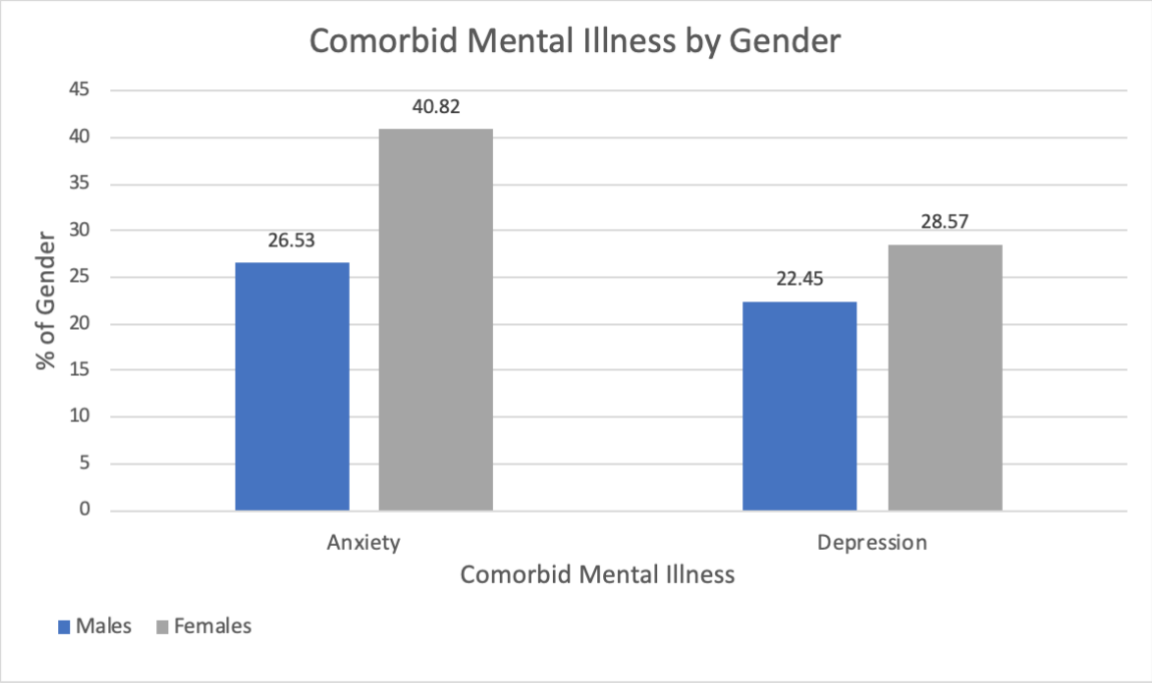
Comorbid Mental Illness by Gender
45
40
35
30
25
20
15
10
5
0
% of Gender
40.82
26.53
28.57
22.45
Anxiety
Depression
Comorbid Mental Illness
Males
Females

Figure 3: