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Plasma prolactin is higher in major depressive disorder and females, and associated with anxiety, hostility, somatization, psychotic symptoms and heart rate

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ABSTRACT

Background: Major Depressive Disorder (MDD) is linked to poor physical health including an increased risk of developing cardiometabolic disease (CMD), yet the underlying physiology of this relationship is not clear. One pathophysiological mechanism that may underlie this relationship is neuroendocrine dysregulation, including that of the hormone prolactin. Prolactin has a role in the regulation of stress, and it is linked to anxiety, hostility, and weight gain, which are all implicated in MDD and increased CMD risk. However, little research has examined plasma prolactin in association with psychological symptoms of MDD or biometric indices of CMD risk. Method: Plasma samples of 120 participants (n = 60 meeting DSM-5 criteria for MDD and n = 60 control; age and sex matched) were analysed to assess prolactin concentration. Biometric data (BMI, waist circumference, blood pressure and heart rate) were collected, and participants completed the Brief Symptom Inventory (BSI) and Depression Anxiety Stress Scale (DASS).

Results: Plasma prolactin was higher in participants with MDD versus controls (8.79 ± 5.16 ng/mL and 7.03 ± 4.78 ng/mL, respectively; $F = 4.528$, $p = 0.035$) and among females versus males (9.14 ± 5.57 ng/mL and 6.31 ± 3.70 ng/mL, respectively; $F = 9.157$, $p = 0.003$). Prolactin was correlated with several psychological symptoms including anxiety, hostility and somatization, and with heart rate, but not with any other biometric measures.

Conclusions: The results of this study indicate that neuroendocrine dysregulation in MDD may extend to the hormone prolactin, with prolactin being specifically associated with a subset of related psychometric and cardiovascular measures.

1. Introduction

Major depressive disorder (MDD) and cardiometabolic disease (CMD) are chronic health conditions, increasing in prevalence worldwide [57]. Both are independently associated with reduced quality of life and increased mortality rate, and are main contributors to the overall global burden of disease [19]. MDD is characterized by low mood and loss of interest in usual activities, accompanied by other symptoms such as changes in appetite and weight, fatigue and feelings of guilt [2], while CMD encompasses cardiovascular disease (CVD) and metabolic syndrome [9]. Individuals with MDD have higher rates of obesity [32], metabolic syndrome [18], and coronary heart disease [14,30], and an increased risk of developing comorbid CMD [18,50]. Neuroendocrine dysregulation may contribute to the pathophysiological mechanisms underlying the links between MDD and CMD, with associations reported between several hormones and different MDD symptom profiles (e.g. Refs. [33,34,52]. Of particular relevance to the increased risk of CMD among those with MDD, but with limited research to-date, is the role of prolactin.

Prolactin is a polypeptide hormone secreted by the acidophilic cells (lactotrophs) of the anterior pituitary gland, under tonic inhibition by hypothalamic dopamine [12]. While the main role of prolactin is stimulation of mammary gland development and milk production during pregnancy and breastfeeding [24], it influences more than 300 diverse

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Table 1
Biometric data (mean ± standard deviation) overall, by group (MDD and control) and sex.

	Overall Cohort	Group		Between groups comparison ^	Effect size partial η^2	Sex		Between sex comparison ^	Effect size partial η^2	Interaction (Group by Sex)	Effect size partial η^2
		MDD	Control			Female	Male				
Number	120	60	60	-	-	68	52	-	-	-	-
Age (Years)	25.1 ± 6.60	24.7 ± 6.03	25.4 ± 7.20	F = 0.65 p = 0.42	0.006	24.9 ± 7.40	25.3 ± 5.40	F = 0.14 p = 0.71	0.001	F = 2.98 p = 0.09	0.025
Weight (Kg)	73.8 ± 16.3	74.6 ± 16.1	73.3 ± 16.7	F = 0.13 p = 0.72	0.001	68.8 ± 16.2	80.8 ± 13.9	F = 18.2 *p < 0.001*	0.135	F = 0.87 p = 0.35	0.007
BMI (Kg/m^2)	25.5 ± 5.40	25.8 ± 5.40	25.1 ± 5.40	F = 0.31 p = 0.58	0.003	25.4 ± 6.10	25.5 ± 4.40	F = 0.01 p = 0.91	0.001	F = 1.36 p = 0.25	0.012
Waist (Cm)	87.0 ± 0.14	89.0 ± 0.14	85.0 ± 0.13	F = 2.10 p = 0.15	0.018	82.0 ± 0.13	90.0 ± 0.12	F = 3.33 p = 0.07	0.028	F = 2.95 p = 0.09	0.025
HR (Beats/min)	73.7 ± 12.9	74.5 ± 12.1	72.9 ± 13.8	F = 0.33 p = 0.57	0.003	69.2 ± 12.2	77.2 ± 12.5	F = 12.1 *p = 0.001*	0.095	F = 0.97 p = 0.33	0.008
SBP (mmHg)	119.7 ± 13.9	118.7 ± 12.5	121 ± 15.2	F = 1.28 p = 0.26	0.011	112.2 ± 9.20	129.5 ± 12.9	F = 74.3 *p < 0.001*	0.390	F = 1.95 p = 0.17	0.017
DBP (mmHg)	73.1 ± 8.80	73.9 ± 8.04	72.2 ± 9.58	F = 0.77 p = 0.38	0.007	72.3 ± 8.70	74.1 ± 9.01	F = 1.14 p = 0.29	0.010	F = 1.19 p = 0.28	0.010

MDD: Major Depressive Disorder. BMI: Body Mass Index. HR: Heart Rate. SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. ^Two-Way ANOVA

physiological processes [12]. Notably, prolactin has an underlying role in stress response regulation and stress adaptation [12,53,55]. This is particularly relevant since maladaptation of the stress response is one of the major hypotheses for the development of MDD [23], and stress is also related to an increased risk of health disorders relevant to CMD morbidity [14]. Higher prolactin has also been associated with the risk of developing psychosis [29], and with specific psychological symptoms of anxiety, hostility, somatization [21,44]. These symptoms often occur in MDD [6,16], and are themselves associated with hypertension [38], and increased overall risk of CVD [36,51] and metabolic syndrome [20]. Further, prolactin has a role in energy balance and food intake [12], and consequently weight gain and obesity [48]. This is significant given that appetite and weight changes are a symptom of MDD [2] and a characteristic of CMD [9].

These associations with stress, psychological symptoms, weight gain and obesity implicate prolactin dysregulation both in MDD itself, and in the development of CMD. However, there is very limited research on this, and with inconsistent findings. With respect to whether prolactin dysregulation is a feature of MDD, two studies found an elevated prolactin level among MDD participants compared with healthy controls [23,28], while several studies reported no difference in basal prolactin level when compared between participants with versus without MDD [4,26,35,58]. In terms of the associations of prolactin with obesity, an early study showed that among individuals with a prolactinoma (prolactin-secreting pituitary gland tumor), high plasma prolactin was associated with weight gain, and that this weight gain was reversed when prolactin level was pharmacologically normalized [22]. Prolactin has also been positively correlated with measures of abdominal obesity in women [17], and was shown to enhance the accumulation of visceral adipose tissue in animal models [7]. However, in contrast, two more recent studies found no association between plasma prolactin concentrations and body mass index (BMI) [5,51]. Further, females have been shown to have higher prolactin levels [46], and higher rates of MDD [1] than males. Therefore, it is important to consider prolactin levels with respect to effects of sex as well as MDD status, in addition to associations with psychometric measures and CMD risk indices including weight, BMI, blood pressure and heart rate.

This study aimed to compare plasma prolactin between untreated participants with MDD versus healthy controls, and determine associations between plasma prolactin concentration and psychometric and biometric measures relevant to MDD and CMD, with examination of between-sex differences. Since antipsychotic and antidepressant treatments themselves also affect plasma prolactin concentration [41], only depressed participants who were not receiving treatment were included in this study. It was hypothesized that plasma prolactin would be: 1) higher in the MDD group than healthy controls and in females than males; 2) associated with biometric measures of BMI, waist circumference, blood pressure and heart rate, and 3) associated with psychometric measures of overall distress, stress, anxiety, hostility and somatization. Examination of associations between prolactin and multiple psychometric and biometric measures relevant to physical and mental health is novel, and will increase our knowledge of the increased risk of CMD among those with MDD.

2. Method

2.1. Participants

Participants with MDD and healthy controls were recruited by media and university advertisements. Across both groups, exclusion criteria included the use of any corticosteroids, pre-existing medical conditions, and substance use disorders. Depressed participants were thoroughly prescreened to confirm that they met DSM-5 criteria for a current major depressive episode, prior to inclusion in the MDD group. In addition, MDD participants were required to be treatment free, and not be taking any antidepressant or antipsychotic medications for at least two months prior to the study. All control participants had no significant history of mental health problems or diagnosed mental disorders.

2.2. Measures and procedure

This was a cross-sectional study. All participants attended the university Clinical Trials Research Unit (Illawarra Health and Medical Research Institute) for data collection. Participants were given information about the study, and all participants provided written informed consent prior to participating. Depressed participants were interviewed using the Mini Neuropsychiatric Interview, version 7.0.2 for DSM-5 (MINI; [49]. Biometric measures (height, weight, waist circumference, blood pressure and heart rate) were recorded for all participants, and BMI (Kg/m^2) was calculated. A phlebotomist then collected a non-fasted sample of blood (10 mL) into an EDTA tube. All blood samples were taken between 9:00–11:00 a.m. to control for diurnal variation in hormone levels. All participants then completed the Brief Symptom Inventory (BSI) and Depression Anxiety Stress Scale 21 (DASS) questionnaires. The BSI consists of 53 items covering nine symptom dimensions: Somatization (e.g. faintness or dizziness), Obsessive-Compulsive (e.g. having to check and double-check what you do), Interpersonal Sensitivity (e.g. feeling inferior to others), Depression (e.g. feeling no interest in things), Anxiety (e.g. feeling tense or keyed up), Hostility (e.g. having urges to break or smash things), Phobic anxiety (e.g. feeling uneasy in crowds), Paranoid ideation (e.g. others not giving you proper credit for your achievements) and Psychoticism (e.g. the idea that something is wrong with your mind); and with the Global Severity Index as a measure of overall symptomatology during the past seven days [13]. Good internal consistency reliability is reported for the nine

dimensions of the BSI, ranging from 0.71 for Psychoticism to 0.85 for Depression [13]. The Depression, Anxiety and Stress Scale (DASS) is a 21 item self-report questionnaire assessing depression, anxiety and stress severity over the past week [31]. The DASS and its three subscales also have demonstrated high internal consistency (Cronbach's $\alpha = 0.96$ for depression, 0.89 for anxiety, 0.93 for stress, 0.94 for total) [8]. Subscale scores were summed and then doubled for comparison with the DASS 42. Severity descriptors were calculated for both groups according to the established cut off scores for each DASS subscale [31].

2.3. Data and statistical analysis

Within 5 min of blood collection, 200 μL of aprotinin was added to each blood sample, which was then immediately centrifuged at 4 °C and 3000 rpm for 10 min. Plasma aliquots were stored at −80 °C and thawed prior to hormone analysis and measurements. Plasma concentration of prolactin was measured using ab226901 Human Prolactin/PRL Simple-Step standard ELISA testing kit (Abcam) with detection at 450 nm (SpectraMax Plus 384 microplate reader). Statistical analyses were conducted using 'Statistical Package for the Social Sciences' (SPSS, Version 23).

Two-way factorial analysis of variance (ANOVA) was used to compare plasma prolactin level and biometric data between the MDD versus control groups and male versus female participants. Pearson's correlations were performed to determine associations between prolactin and the biometric and psychometric measures across both groups. Due to previously reported differences in prolactin level by sex and MDD diagnosis, correlations were also conducted separately per sex and per group. For all statistical tests, probability $\alpha < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and biometric data

Participant characteristics are shown in Table 1. Data were collected from a total of 60 MDD participants and 60 healthy control participants aged between 18 and 54 years (M = 25.05, SD = 6.61 years). There were 34 females and 26 males in each group, with no significant difference between groups for age or any of the biometric data (Table 1). Weight, systolic blood pressure and heart rate were higher in males than females (Table 1). There were no further sex differences in the rest of the biometric data and there were no significant interactions between group and sex for any of the biometric data (Table 1). Just more than half of all participants (n = 64; 53%) were born in Australia, with the remainder born in various countries across Europe and Asia. Of those born in Australia, 35 were in the control group and 29 were participants with MDD. The mean duration ±standard deviation of the current depressive episode of participants in the MDD group was 3.6 ± 3.1 months, ranging between 2 weeks and 2 years, and with a median of 2 months. The mean duration of lifetime depression among participants with MDD was 2.25 years ± 3.08 years, with a range of 2 weeks–13 years. A minority of female participants were on the contraceptive pill (n = 12 and n = 5 in the MDD and control groups, respectively).

3.2. Psychometric data

The means for the relevant psychometric measures from the BSI and DASS by group (MDD and healthy controls) and sex are presented in Table 2. Scores for all the BSI and DASS measures of psychopathology and distress were significantly higher in the MDD than control group.

Table 2
Psychometric data (mean ± standard deviation) per cohort, group (MDD and control) and sex.

Psychometric measure		Cohort	Group		Between groups comparison ^	Effect size partial η^2	Sex		Between sex comparison ^	Effect size partial η^2	Interaction (Group by Sex)	Effect size partial η^2
			MDD	Control			Female	Male				
BSI	Total	54.8 ± 48.4	95.0 ± 35.6	14.4 ± 12.8	F = 275.1 *p < 0.001*	0.703	59.9 ± 52.7	48.1 ± 41.6	F = 6.030 *p = 0.016*	0.049	F = 3.081 p = 0.082	0.026
	SOM	0.69 ± 0.86	1.24 ± 0.90	0.15 ± 0.25	F = 85.01 *p < 0.001*	0.425	0.86 ± 1.01	0.48 ± 0.53	F = 11.36 *p = 0.001*	0.089	F = 10.86 *p = 0.001*	0.086
	OC	1.50 ± 1.15	2.39 ± 0.84	0.60 ± 0.56	F = 183.9 *p < 0.001*	0.613	1.55 ± 1.19	1.42 ± 1.10	F = 0.950 p = 0.332	0.008	F = 0.060 p = 0.810	0.001
	IS	1.44 ± 1.26	2.41 ± 1.03	0.47 ± 0.49	F = 174.8 *p < 0.001*	0.601	1.60 ± 1.30	1.22 ± 1.20	F = 6.950 *p = 0.010*	0.057	F = 1.971 p = 0.163	0.017
	DEP	1.34 ± 1.25	2.43 ± 0.79	0.24 ± 0.32	F = 386.3 *p < 0.001*	0.769	1.41 ± 1.31	1.24 ± 1.18	F = 2.380 p = 0.125	0.020	F = 0.430 p = 0.512	0.004
	ANX	0.95 ± 0.94	1.67 ± 0.82	0.23 ± 0.25	F = 164.4 p < 0.001	0.586	1.04 ± 0.99	0.82 ± 0.87	F = 3.891 p = 0.051	0.032	F = 2.270 p = 0.134	0.019
	HOS	0.89 ± 0.92	1.52 ± 0.91	0.27 ± 0.27	F = 100.6 *p < 0.001*	0.464	0.99 ± 1.01	0.77 ± 0.78	F = 2.992 p = 0.087	0.025	F = 1.750 p = 0.189	0.015
	PHB	0.68 ± 0.92	1.28 ± 0.98	0.08 ± 0.17	F = 84.18 *p < 0.001*	0.421	0.77 ± 1.01	0.57 ± 0.80	F = 2.470 p = 0.118	0.021	F = 2.201 p = 0.140	0.019
	PAR	0.91 ± 0.92	1.45 ± 0.90	0.36 ± 0.55	F = 60.47 *p < 0.001*	0.343	1.00 ± 1.02	0.78 ± 0.77	F = 2.771 p = 0.101	0.023	F = 1.070 p = 0.304	0.009
	PSY	0.98 ± 1.01	1.80 ± 0.79	0.15 ± 0.27	F = 228.2 *p < 0.001*	0.663	1.04 ± 1.09	0.89 ± 0.91	F = 1.901 p = 0.170	0.016	F = 1.290 p = 0.258	0.011
	GSI	1.04 ± 0.91	1.79 ± 0.67	0.28 ± 0.24	F = 275.1 *p < 0.001*	0.703	1.13 ± 0.99	0.91 ± 0.79	F = 6.020 *p = 0.016*	0.049	F = 3.080 p = 0.082	0.026
DASS	DEP	13.6 ± 12.8	24.5 ± 8.99	2.80 ± 3.46	F = 291.5 *p < 0.001*	0.715	13.7 ± 13.2	13.5 ± 12.5	F = 0.02 p = 0.895	0.000	F = 0.090 p = 0.762	0.001
	ANX	8.60 ± 9.19	14.8 ± 8.85	2.43 ± 3.81	F = 97.38 *p < 0.001*	0.456	9.85 ± 9.50	6.96 ± 8.57	F = 5.520 *p = 0.020*	0.045	F = 1.390 p = 0.242	0.012
	Stress	13.9 ± 11.3	22.4 ± 9.28	5.37 ± 4.86	F = 155.5 *p < 0.001*	0.573	15.0 ± 11.4	12.4 ± 11.0	F = 3.550 p = 0.062	0.030	F = 0.650 p = 0.423	0.060

BSI: Brief Symptom Inventory. SOM: Somatization. OC: Obsessive-Compulsive. IS: Interpersonal Sensitivity. DEP: Depression. ANX: anxiety. HOS: Hostility. PHB: Phobic Anxiety. PAR: Paranoid Ideation. PSY: Psychoticism. GSI: Global Severity Index. DASS: Depression Anxiety Stress Scale. ^Two-Way ANOVA.

Table 3
Raw and log-transformed plasma prolactin concentrations (mean ± standard deviation) by group and sex. MDD group: 34 females; 26 males. Controls: 34 females; 26 males.

	Overall Cohort	Group						Sex	
		MDD	MDD	MDD	Control	Control	Control	Female	Male
		Total	Female	Male	Total	Female	Male		
Prolactin (ng/mL)	7.91 ± 5.03	8.79 ± 5.16	10.64 ± 6.37	6.37 ± 2.92	7.03 ± 4.78	7.64 ± 5.03	6.24 ± 4.40	9.14 ± 5.57	6.31 ± 3.70
Log Prolactin (ng/mL)	0.82 ± 0.27	0.87 ± 0.26	0.96 ± 0.26	0.76 ± 0.20	0.76 ± 0.27	0.80 ± 0.27	0.71 ± 0.26	0.88 ± 0.27	0.74 ± 0.23

MDD: Major Depressive Disorder.

Table 4
Pearson's Correlation of prolactin with biometrics and psychometric measures per cohort, group (MDD and control), and sex.

Measure		Total cohort		MDD		Control		Females		Males	
		r	p	*r*	p	*r*	p	*r*	p	*r*	p
Biometrics	BMI (kg/m^2)	0.036	0.694	0.061	0.644	−0.013	0.920	0.124	0.314	−0.140	0.321
	Waist (cm)	−0.028	0.764	−0.023	0.860	−0.102	0.440	0.059	0.630	−0.069	0.628
	Systolic blood pressure (mmHg)	−0.149	0.105	−0.306	*0.017*	−0.006	0.965	−0.044	0.721	0.096	0.500
	Diastolic blood pressure (mmHg)	0.126	0.169	0.035	0.791	0.171	0.192	0.098	0.425	0.252	0.072
	Heart rate (beats/min)	0.254	*0.005*	0.339	*0.008*	0.170	0.193	0.268	*0.027*	0.063	0.656
BSI	Total	0.226	*0.013*	0.135	0.305	0.057	0.664	0.256	*0.035*	0.097	0.493
	Somatization	0.232	*0.011*	0.220	0.090	−0.064	0.624	0.232	0.057	0.059	0.677
	Obsessive Compulsive	0.173	0.059	−0.029	0.829	0.090	0.494	0.227	0.063	0.059	0.680
	Interpersonal Sensitivity	0.201	*0.028*	0.103	0.434	0.017	0.898	0.229	0.061	0.069	0.628
	Depression	0.173	0.060	−0.088	0.505	0.151	0.251	0.203	0.097	0.088	0.537
	Anxiety	0.221	*0.015*	0.163	0.213	−0.025	0.847	0.263	*0.030*	0.086	0.543
	Hostility	0.195	*0.033*	0.145	0.270	−0.094	0.475	0.251	*0.039*	0.011	0.938
	Phobic Anxiety	0.184	*0.045*	0.102	0.437	−0.018	0.890	0.204	0.096	0.080	0.575
	Paranoid Ideation	0.268	*0.003*	0.243	0.061	0.112	0.394	0.289	*0.017*	0.158	0.263
	Psychoticism	0.226	*0.013*	0.172	0.188	−0.038	0.771	0.269	*0.027*	0.114	0.419
	Global Severity Index	0.226	*0.013*	0.135	0.305	0.057	0.664	0.256	*0.035*	0.097	0.493
DASS	Depression	0.155	0.213	−0.152	0.246	−0.061	0.643	0.145	0.238	0.072	0.614
	Anxiety	0.243	*0.008*	0.145	0.268	0.185	0.158	0.273	*0.024*	0.105	0.457
	Stress	0.160	0.082	−0.024	0.858	0.065	0.624	0.201	0.100	0.030	0.835

BSI: Brief Symptom Inventory. DASS: Depression Anxiety Stress Scale.

Mean DASS scores for both Depression and Anxiety were in the Severe range for the MDD group and Normal range for the controls; mean Stress scores were in the Moderate range for the MDD group and in the Normal range for the controls. Additionally, females scored significantly higher than males for Somatization, Interpersonal Sensitivity, and the Global Severity Index of the BSI, and the Anxiety subscale of the DASS.

3.3. Plasma prolactin concentration

The prolactin data showed a positively skewed distribution (skewness = 0.844). Shapiro-Wilk tests for all the prolactin data were significant ($p < 0.001$) indicating that these did not follow a normal distribution; therefore all prolactin values were logarithmic-transformed for analyses. No outliers were detected in the prolactin values. The mean raw values of plasma prolactin concentration in the MDD and control groups, and for females and males were all within the normal range (Table 3) [11]. When prolactin was compared between MDD and control groups, by sex, with age as a covariate, there was a significant effect of group and sex ($F_{1, 115} = 4.528$, $p = 0.035$ and $F_{1, 115} = 9.157$, $p = 0.003$, respectively), but no interaction between group and sex ($F_{1, 115} = 1.514$, $p = 0.221$) and no effect of age ($F_{1, 115} = 0.224$, $p = 0.637$).

3.4. Associations between prolactin with biometric and psychometric measures

Correlations between prolactin and biometric and psychometric measures are included in Table 4. For the total cohort, plasma prolactin was significantly correlated with heart rate, but no other biometric measure. When correlations were conducted per group and per sex, the only significant associations were that prolactin correlated with heart rate and negatively with systolic blood pressure in the MDD group, and with heart rate in females. In terms of the psychometric measures, in the total cohort, prolactin was significantly correlated with all BSI measures except the Obsessive Compulsive and Depression scales, and with Anxiety but not with Stress or Depression of the DASS (Table 4). When correlations were conducted separately for group and sex sub-groups, the only significant correlations that remained where that among females, prolactin was significantly correlated with Anxiety, Hostility, Paranoid Ideation, Psychoticism and Global Severity Index. Though prolactin was correlated with heart rate and with several psychometric measures, there were no significant correlations between heart rate itself and any of the psychometric measures.

4. Discussion

The current study examined plasma prolactin concentration and the associations between prolactin, with biometric and psychological distress measures, among individuals with MDD in comparison to healthy controls. The results confirmed Hypothesis 1, but only parts of Hypotheses 2 and 3. Plasma prolactin was significantly higher in the MDD versus the healthy control group, and in females versus males, as hypothesized. Prolactin was significantly correlated with heart rate and a wide range of self-reported measures of distress and psychopathology, including anxiety, hostility and somatization, as hypothesized. But contrary to the hypotheses, prolactin was not correlated with waist circumference, BMI or blood pressure and nor was it associated with stress. Overall these results add important information with respect to prolactin dysregulation in MDD with sex-differences, and associations of prolactin with psychological distress, and heart rate.

The finding that plasma prolactin was higher in the MDD group than the healthy control group agrees with two previous human studies that compared serum prolactin concentration, also in cohorts of age and sex

matched MDD and healthy control participants. These included 101 participants with MDD and 106 healthy controls [23], and 50 MDD and 50 control participants [28]. While other studies found no differences in prolactin between depressed versus non-depressed participants [4]; Duval et al., 1999; [26,35], there are several methodological constraints that limit the broader interpretation of these results. All of these studies had fewer participants than the current study, including three with less than 50 total participants [4,26,35]; the latter study was further limited because only female participants were included [35]; three studies had unequal numbers of depressed versus non-depressed participants [4]; Duval et al., 1999 [35]; and only two studies had sex-matched participants between groups (Duval., 1999; [26]. The higher plasma prolactin in MDD compared to controls in the current study could be indicative of reduced inhibition by central dopamine. This links to the monoamine theory of depression which suggests an underlying pathophysiology of diminished neurotransmission of serotonin, dopamine and norepinephrine (Duval et al., 2000; [23]. Interestingly, even though plasma prolactin concentration was higher in the MDD group in the current study, it did not significantly correlate with the BSI depression scale ($p = 0.052$). The results of the current study add to the small body of research that suggests prolactin may play a role in the pathophysiology of MDD, and could be used as a potential biomarker in clinical contexts [23,28].

The sex difference in plasma prolactin in the current study, whereby females had greater plasma prolactin concentration than males, agrees with previous reports [45,46]. It is interesting to note that as it was females and those with MDD who had higher prolactin, this could be linked to the higher rate of MDD in females in comparison to males [1]. However, there is a lack of literature that has examined the effect of sex on plasma prolactin specifically in a MDD cohort. Since in the current study, females and those with MDD had higher plasma prolactin than males and healthy controls, respectively, and there is higher prevalence of depression among females [1] it would be interesting to investigate this further in longitudinal studies.

A novel component of the current study was the examination of associations between prolactin and the severity of stress and psychological symptoms, in addition to biometric data. Among the cohort, there were positive correlations between prolactin and overall distress as well as a wide range of psychological symptoms including somatization, anxiety, hostility, paranoid ideation and psychoticism. These associations between prolactin and somatization, anxiety and hostility are particularly important findings due to these being linked with increased CMD risk [20,36]. Previous studies also showed that among females, high plasma prolactin was associated with more symptoms of anxiety [21,44] and with hostility and somatization [15,44]. With respect to the associations between prolactin and paranoid Ideation and psychoticism, although paranoia is a feature of psychosis [42], there are mixed results with respect to prolactin and psychotic disorders. Drug naïve patients diagnosed with schizophrenia and other psychotic disorders had higher levels of serum prolactin compared to healthy controls, but no associations between prolactin and psychopathology symptoms were found [41]. In contrast, other research found significantly lower serum prolactin among paranoid versus non-paranoid schizophrenia patients [47], which was attributed to increased dopaminergic tone seen in patients with paranoid symptoms of schizophrenia [43]. Overall, the results suggest that prolactin is associated with specific psychological symptoms including somatization, anxiety, hostility, paranoid ideation and psychoticism, especially in females, rather than a general indication of depressive symptom severity, and may represent a transdiagnostic hormonal phenotype.

Although it was hypothesized in the current study that prolactin would be associated with stress due to its role in stress coping and adaptation, prolactin was not significantly correlated with self-reported stress over the previous week. Two previous animal studies did report an association between prolactin and stress [54]; however, these used behavioural measurements rather than self-reported stress. An earlier human study also demonstrated an association between prolactin and acute stress induced using the Trier stress test [55]. It may be that prolactin is more closely related to an acute stress situation rather than stress levels over the past week as measured by the DASS, and may also be affected by MDD history in terms of recurrence and duration of depressive episodes. More research is needed to determine the associations between prolactin and stress, including stress response and adaptation.

For the total cohort, prolactin was positively correlated with heart rate, which is an interesting finding. An early study found that heart rate was increased in animal models after they were given a prolactin infusion, with proposed mechanism that prolactin affects ion movements and potassium metabolism [37]. Considering that increased heart rate is associated with anxiety and hostility, and a higher risk of all-cause mortality and cardiovascular events [39,40], further examination of the relation between prolactin and heart rate is warranted. The lack of any association between prolactin and blood pressure in the current study likely reflects the participants being normotensive rather than hypertensive. Though research has established that prolactin exerts positive vasoconstrictive effects and is implicated in the development of hypertension [10], the only human study to have examined and confirmed this relation included only males who were older (40.7 ± 8.6 years) than participants in the current study, and 21.5% were diagnosed with hypertension [51].

Contrary to the hypothesis of the current study, prolactin was not correlated with BMI or waist circumference. Nevertheless, with respect to BMI this does agree with two previous studies that also found no association between prolactin and BMI [5,51]. The mean BMI of the participants of both these previous studies and the current study were within the overweight range. In terms of abdominal adiposity, another study found an association between prolactin and visceral fat when it was measured more accurately using magnetic reasoning imaging [27]. Considering the negative health effects of excess visceral fat and its role in inflammation, it would be worthwhile investigating the association between prolactin and central adiposity further.

Interestingly, when correlations were performed separately per sex, the positive correlations of prolactin with the psychological symptoms that were significant in the total cohort remained only for females. Of note is that among females but not males, prolactin was correlated with anxiety and hostility levels. This result is consistent with the literature reviewed [44], including a meta-analysis, which revealed that female patients with high plasma prolactin level expressed more symptoms of anxiety and hostility than females who had a normal prolactin level [3]. Consequently, females could be at risk of developing cardiac events such as coronary heart disease because of their anxiety symptoms [36]. Further, prolactin was only significantly correlated with heart rate in those with MDD and in females. Though this is proposed to be due to the associations of heart rate with psychological symptoms such as anxiety, hostility and somatization [56] there were no significant correlations between heart rate and any of the psychometric measures in the current study. Associations between prolactin, psychometric measures and heart rate, and the influence of sex is worth further consideration in studies examining broader health markers in MDD. The sex effects for plasma prolactin concentration and associations between prolactin and psychometric measures could also help to explain some of the heterogeneity in MDD, and the difference in presentation of the different subtypes of MDD between females and males [1].

Overall, the current results highlight that plasma prolactin concentration is associated with a current diagnosis of MDD and specific psychological symptoms including anxiety, hostility and paranoid ideation. The sex differences in psychometric and biometric data and plasma prolactin suggest that prolactin may contribute to the higher prevalence of MDD in females than males, and suggests a specific role of prolactin among those with MDD who are more anxious, hostile and paranoid. Thus, the current findings provide further support for the implication of prolactin in the overlapping relationships between MDD and CMD, potentially more so in females.

There are several limitations to the current study, which can be improved for future research. Plasma lipids, blood glucose, insulin resistance and visceral fat quantity were not measured, which precluded analysis of any associations between prolactin and these CMD risk factors. Participants did not have particularly high risk factors for CMD, since they were normotensive and with mean BMI in the overweight, rather than obese range. The study was also limited by collection of a single blood sample, which does not account for the ultradian and circadian rhythms of prolactin secretion, and data on menstrual cycle was also not collected. There is a lack of research on prolactin in relation to menstrual cycle in MDD and further research is needed in this area. Finally, being cross-sectional in nature and only including univariate analyses are limitations of the current study. Future longitudinal research will enable the examination of the associations between prolactin and the later development of depression and the associations between prolactin and psychometric and cardiometabolic data among individuals with MDD who are being treated with antipsychotic or antidepressant medication. In addition, given the physiological increase in prolactin during breastfeeding [25], investigation of associations between plasma prolactin and mental health indices during the postpartum period is also warranted.

5. Conclusion

Plasma prolactin was higher in individuals with MDD in comparison to healthy controls, and among females than males. Prolactin was correlated with heart rate and psychometric measures associated with an increased risk of CMD including anxiety and hostility, particularly in females. Overall, the results here indicate that prolactin dysregulation could be a feature of MDD, and specifically associated with a subset of related psychometric and cardiovascular measures. There is a paucity of studies in this area, and the results here suggest that further research into the role of prolactin in MDD is warranted.

Contributors

TL, ST and JK contributed to the design of the study. AE completed sample, data and statistical analyses, interpreted the results, and drafted the article. TL and ST revised the article. JM completed the data collection. All authors approved the final version.

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Declaration of competing interest

None.

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