Obesity and Metabolic Comorbidity in Bipolar Disorder: Do Patients on Lithium Comprise A Subgroup? A Naturalistic Study.

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Obesity and metabolic comorbidity in bipolar disorder: Do patients on lithium comprise a subgroup? A naturalistic study.

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Running Head: Obesity & Metabolic Comorbidity in Bipolar

ABSTRACT

Background: Bipolar disorders (BD) are associated with increased prevalence of obesity and metabolic syndrome (MetS). Nevertheless, there is a wide range in prevalence estimates, and little is known about the relative contributions of medications, especially lithium. We hypothesized that lithium use is not associated with increased body mass index (BMI), metabolic syndrome, and type II diabetes (DM II), when compared to non-lithium users (those on anticonvulsants (ACs) or second-generation antipsychotics (APs)).

Methods: Cross-sectional study of 129 patients aged 18-85 with bipolar disorder, followed at tertiary care clinics in Montreal. Patients using lithium were compared with those not on lithium, for body mass index and metabolic syndrome.

Results: The prevalence of obesity and MetS in the sample of lithium-using bipolar patients was 42.4% and 34.9%, respectively, with an average BMI of 29.10 (+/-6.70). Lithium and non-lithium groups did not differ in BMI or prevalence of MetS. However, compared to the non-lithium group, lithium users had lower hemoglobin A1C (5.24 +/- 0.53 versus 6.01 +/- 1.83, U=753.5, p=0.006) and lower triglycerides (1.46 +/- 0.88 versus 2.01 +/-1.25, U=947, p=0.020).

Conclusions: There is a high prevalence of obesity and metabolic syndrome among bipolar disorder patients. However, this did not appear to be associated with lithium use,

when compared to those not on lithium. The lithium subgroup was also associated with lower prevalence of type II diabetes. Future prospective and intervention studies with larger sample sizes are necessary to further explore the association between lithium and insulin resistance, as well as its underlying mechanisms.

Key words: obesity; metabolic syndrome; lithium; bipolar disorder; medical comorbidity

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INTRODUCTION

Lithium remains a first-line therapy in bipolar disorder, with indications in acute mania, depression, and maintenance treatment[1]. Additionally, it is associated with unique anti-suicidal properties[2]. Despite this, lithium is often avoided for its adverse physical effects including reduced renal function, hypothyroidism, and hyperparathyroidism[3]. Lithium is also avoided for weight gain, though alternatives (especially SGAs quetiapine and olanzapine) are thought to be more detrimental in this regard[4,5].

Among these adverse physical effects, weight gain is especially concerning, as it can lead to obesity. Obesity is a constituent of metabolic syndrome, a constellation of risk factors notably associated with cardiovascular disease and stroke[6]. Weight gain is further recognized in the literature as contributing to poor physical health and early mortality[7], treatment non-adherence[8], worsening psychiatric outcomes[9], and elevated economic costs[10]. Mitigating obesity is highlighted in numerous consensus guidelines[1,11], which state that body mass index, diabetes, and dyslipidemia be assessed at treatment baseline and then regular intervals thereafter.

While it is known that patients with a bipolar disorder are at an increased risk of obesity[12], prevalence rates remain heterogeneous. Estimates range from 20-65% of patients with a bipolar disorder[13]. The same is true for metabolic syndrome, including waist circumference, diabetes, and dyslipidemia. Further, the relative contributions of the bipolar illness itself, aging, and mood-stabilizing medications (such as lithium) remain to

be clarified. A number of randomized clinical trials (RCTs) and cohort studies suggest that lithium causes less weight gain[4,5,14-16]. However, in these studies, BMI and metabolic effects are not reported as primary outcomes. These trials also include strict 'treatment arms' that do not reflect true clinical prescribing patterns (for example, medication combinations, augmentation, and polypharmacy).

The purpose of this study is to 1) estimate the prevalence of obesity and MetS amongst a cross-sectional sample of bipolar disorder patients. We will also 2) examine the prevalence of constituents of MetS, including BMI, waist circumference, hypertension, lipid profile, and diabetic screening tests. Finally, we will 3) assess whether there are any differences in these measures between lithium and non-lithium BD patients. We hypothesize that lithium users will have less medical comorbidity, including obesity, metabolic syndrome, and diabetes.

MATERIALS and METHODS

We combined data from two studies that examined physical comorbidity in bipolar patients. We have provided individual descriptions of the methods of each study below. Specific inclusion or exclusion criteria of the studies have been previously reported[17,18].

Study 1 assessed atorvastatin (20mg/day) versus placebo in the treatment of lithium users with nephrogenic diabetes insipidus (DI). It was a double-blind, placebo-

controlled RCT at three tertiary mental health sites in Montreal, Québec: Douglas Mental University Institute (DMHUI), Jewish General Hospital (JGH), and McGill University Health Centre (MUHC). Patients were lithium users aged 18-85, with any psychiatric disorder. At baseline, patients' self reported demographic information, past medical and psychiatric history, and somatic complaints. Current medication was obtained from medical charts and confirmed by the patient. At each visit (baseline, 4-weeks, 12-weeks), psychiatric symptoms were measured using the Montgomery-Asberg Depression Scale (MADRS)[19] and Young Mania Rating Scale (YMRS)[20]. Finally, physical measures (BMI and waist circumference), serum cholesterol levels, serum glucose levels, and thyroid function were also measured at each visit. For this analysis, baseline data from Study 1 was used from patients with bipolar disorder (*n=43*).

Study 2 examined the relationship between mood, sleep, and food intake in bipolar patients. Patients were recruited from those presenting at the Bipolar Disorders clinic at the DMHUI. This is a specialized clinic where the diagnosis of patients has been systematically evaluated and scrutinized before acceptance. Patients were 18 years or older and were receiving care exclusively as outpatients. Medication, demographic, clinical, and laboratory information, including serum cholesterol, serum glucose, and thyroid function, were retrieved for the initial visit. Two in-person visits, two weeks apart, were used to evaluate physical measures and mood. For this analysis, baseline data from Study 2 was used (*n=86*).

***Exposures – Lithium Users and Non-Users*:**

We classified bipolar disorder patients into current lithium users or non-users. This was achieved by a chart review of any prescriptions valid within a 2-week period before or after the initial baseline visit.

Primary Outcome:

Our primary outcome is obesity, measured via BMI. Obesity was chosen as lithium and other mood stabilizers have frequently been associated with weight gain, which may lead to treatment non-adherence and metabolic complications. It is also a value that can be easily measured and trended, no matter the healthcare setting. BMI was calculated using a standard formula: BMI = weight (kg) / height^2 (meters). A BMI $\geq$ 30 was taken to indicate obesity, according to the National Institute of Health (NIH).

Secondary Outcomes:

Our secondary outcomes are average BMI, BMI classes, metabolic syndrome, and hemoglobin A1c. The BMI classes designated by the NIH are: BMI < 19.0 (underweight), BMI 19-24.9 (normal), BMI 25.0 – 29.9 (overweight), BMI 30.0-34.9 (class I obesity), BMI 35.0+ (class II & III obesity).

Metabolic syndrome was diagnosed in patients who fulfilled three or more of the five criteria based on the National Cholesterol Education Program Treatment Panel III (NCEP III) criteria: 1) Abdominal obesity: waist circumference $\geq$ 102cm for men and $\geq$ 88cm for women. Waist circumference was measured in two ways: at the top of the iliac crest as per the National Institutes of Health (NIH), and midway between the last palpable

rib and the top of the iliac crest according to World Health Organization (WHO) standards; 2) Glucose dysmetabolism: impaired fasting plasma glucose (5.5-6.9mmol/L) or diabetes (fasting plasma glucose ≥ 7mmol/L; 3) Dyslipidemia: elevated plasma triglyceride (≥1.7mmol/L); 4) Dyslipidemia (second, separate criteria): decreased high-density lipoprotein (HDL) (<1.03mmol/L for men and <1.30mmol/L for women); and 5) Hypertension. Hypertension was defined as high blood pressure on patients' self-reported medical history or indication of pharmacologic intervention according to a medication report.

Hemoglobin A1c is the most widely used clinical test to diagnose diabetes, indicating the mean glucose concentration over 120 days, although it is not traditionally used in the diagnosis of metabolic syndrome.

Exploratory Outcomes:

Our exploratory outcomes were the constituents of MetS: abdominal obesity, glucose dysmetabolism, dyslipidemia: elevated plasma triglyceride, dyslipidemia: decreased high-density lipoprotein, and hypertension. Additionally, we examined thyroid function, as it is a frequent adverse event during lithium use. Hypothyroidism was characterized as a TSH > 5.0mIU/L or necessitating thyroid hormone replacement.

Statistical Analysis:

Data was initially assessed for normality using the Shapiro-Wilk test. We compared the exposure groups for demographic values, as well as for primary, secondary,

and exploratory outcomes. We used Mann-Whitney U tests to examine continuous variables for non-normal distributions. Chi-squared tests were employed for dichotomous variables (eg. Diabetes Yes/No). A two-tailed alpha of 0.05 was used to determine statistical significance and all analyses were performed using IBM SPSS 26.0 (IBM SPSS Inc, Chicago, IL, USA).

RESULTS

In total, 129 bipolar disorder patients were included in the analysis of this study. Of these, 66 were lithium users and 63 were non-users. The lithium group was 43.9% male, and the mean age was 49.1 (±11.78). The majority (n=50, 79.4%) of lithium users had an age of onset of psychiatric symptoms < 30 years of age, with an average of more than four mood episodes in the course of their illness.

Table 1 summarizes the study participants' baseline demographic and clinical characteristics. The lithium and non-lithium groups differed significantly in their age of onset ($p=0.017$, $x^2=13.8$) number of mood episodes ($p=0.001$, $x^2=15.9$), and their baseline MADRS (4.30 ± 4.62 versus 6.81±6.93 respectively) and YMRS scores (4.42 ± 8.03 versus 15.90 ± 12.80 respectively). There were higher standardized scores for depression and mania in the non-lithium group. Additionally, there were significant differences in the patients' medication profiles. Intuitively, a higher proportion of non-lithium users were on antipsychotic medications and anticonvulsants, as well as antidepressants. More specifically, 76.2% of non-lithium users were on antipsychotics,

compared to only 58.7% of lithium users (p=0.036, $x^2 = 4.375$). This pattern continued for anticonvulsants (82.5% of non-lithium users, versus 36.5%) and antidepressants (57.1% for non-lithium users, versus 38.1%). In terms of somatic medications, patients in the non-lithium group were also on more medications for diabetes and dyslipidemia.

Table 2 summarizes obesity, BMI and other physical health outcome data. With respect to the primary outcome, 43.94% of lithium using and 34.92% of non-lithium bipolar patients had obesity. There was no statistically significant difference in rate of obesity between these groups (p=0.384, x^2=0.758).

For secondary outcomes, mean BMIs were on the cusp of overweight and class I obesity; average BMI of the lithium-using patients was 29.10 (± 6.70) kg/$m^{2,}$ and non-lithium users 30.20 (+/-8.57) kg/m^2. There was no statistically significant difference in BMI between the two groups. The vast majority of the 66 lithium-using patients were outside of the normal BMI range: 27.3% were overweight, 25.8% had class I obesity, and 16.7% class II & III obesity. The prevalence of metabolic syndrome in lithium users was 35.7%. There was no significant difference between lithium users and non-lithium users in BMI classes or prevalence of metabolic syndrome. However, there was a statistically significant difference in glucose metabolism as measured by HbA1C. Lithium use was associated with lower HbA1c overall (p=0.006, U=753.5).

Lastly, for exploratory outcomes, lithium use was associated with abnormal levels of triglycerides, with lower levels than non-lithium users (p=0.020, U=947). There was

no difference in the remaining constituents of metabolic syndrome, including waist circumference, fasting plasma glucose or diabetes, cholesterol profile or dyslipidemia, or hypertension. There was also no difference in thyroid function, despite lithium's well-established association with hypothyroidism.

DISCUSSION

We present a sample of patients with a bipolar disorder in a tertiary care, naturalistic setting, where polypharmacy is common. Overall, the prevalence of obesity and metabolic syndrome in this sample of 129 bipolar patients is 44% and 35% respectively. There was no statistically significant difference in prevalence of obesity in lithium and non-lithium BD patients. This was also true for secondary outcomes, including average BMI, BMI classes, and metabolic syndrome, as well as exploratory outcomes, such as waist circumference, fasting glucose and diabetes, impaired lipids and dyslipidemia, hypertension, and hypothyroidism. However, the most interesting finding is that the groups differed in the markers of insulin resistance, HbA1C and triglycerides. Despite polypharmacy, patients on lithium had a lower level of insulin resistance.

In other words, our findings largely indicate similar physical and metabolic comorbidity between lithium-using and non-lithium bipolar patients. This offers important insight into the adverse effects of 'real-life' bipolar pharmacotherapy treatment. In this analysis, the majority of patients were treated with conventional mood stabilizers, lithium or valproate, combined with various antidepressants and second-

generation antipsychotics. These medications have been studied and compared more extensively as monotherapy; for example, lithium has previously been reported to cause more clinically significant weight gain than valproate, but less than quetiapine[14,16]. However, the research is largely mixed regarding weight gain and other side effects (ie. metabolic syndrome and its constituents) of pharmacotherapy combinations. Previous studies are limited by their focus on individual antipsychotics or mood stabilizers and modest sample sizes[21]. Overall, the present study seems to suggest that lithium and non-lithium combinations emerge as comparable.

Interestingly, we found lithium use to be associated with lower markers of insulin resistance, as measured by HbA1c and triglycerides respectively. This fits into a larger discussion in the literature that conceptualizes bipolar disorder as being comprised of multiple subgroups, such as lithium-responders. One interpretation of this finding is that lithium-responders, even prior to lithium exposure, represent a subgroup that is naturally less predisposed to insulin resistance. However, a recent retrospective study has found the inverse to be true: comorbid bipolar disorder and insulin resistance appears to be associated with more severe clinical features and poor response to lithium[22,23]. This association can potentially be explained by shared pathophysiological mechanisms between bipolar disorder and glucose dysregulation, including genetic and epigenetic links, mitochondrial dysfunction, and hypothalamic-pituitary-adrenal axis alterations[24]. In particular, glycogen synthase kinase-3 beta (GSK-3b), an essential kinase involved in cell metabolism and survival, has been identified as having significant effects on neuronal plasticity in bipolar disorder patients. It may also suppress two important targets of

208 insulin action, glycogen synthase and insulin receptor substrate-1[25]. Lithium, moreso than
209 other mood stabilizers such valproate, appears to act as an inhibitor of the GSK-3b
210 enzyme. Therefore, a second and competing hypothesis that lithium itself modulates both
211 affective and dysmetabolic disorders[26]. Sleep deprivation can rapidly result in insulin
212 resistance, and while in general patients with a bipolar disorder have disrupted circadian
213 rhythms, lithium seems to be more likely to regulate the rhythms[27]. In sum, these
214 pathophysiological explanations are consistent with our results in lithium-responsive
215 bipolar patients, who experienced lower levels of glycosylated hemoglobin and
216 triglycerides.
217
218 From a population health perspective, our findings contribute to a growing
219 understanding about metabolic comorbidities in severe mental illness. The prevalence of
220 obesity in this bipolar study group was almost double that of the general Canadian adult
221 population (42.3% versus 24.1%)[28], and almost triple that of the general Québecois adult
222 population (42.3% versus 16.4%)[29]. The same can be said about metabolic syndrome
223 (35.7% versus 19.1%)[30]. This confirms previous findings that obesity is startlingly
224 common in bipolar patients and necessitates urgent attention. Prevention and early
225 intervention with lifestyle interventions and pharmacological options is recommended[31].
226 Further, the high concurrence between psychiatric and medical comorbidity argues for
227 primary care models that allow an integrated treatment approach to optimize outcomes.
228
229 ***Strengths and limitations:***

This study has several strengths. To begin, the study design is representative of the "real-world": it had the enrolment of both bipolar I and II patients, enrolment of patients of all ages, and the inclusion of patients with concomitant psychiatric diagnoses (eg. personality disorder, substance use). The findings can be generalized to tertiary care bipolar outpatients. The grand majority of patients were based at the same hospital and so their lab tests were processed by the same laboratory. Additionally, the sample size was comparable or larger than many existing studies.

We recognize some limitations of our study. The largest limitation is that the study design was cross-sectional, which makes causation difficult to infer. Furthermore, body mass index, the basis of the primary outcome, is frequently criticized in the literature for its true clinical relevance as it has arbitrarily defined categories, does not differentiate between fat and muscle mass[32], and has been paradoxically associated with lower mortality[33], although the inclusion as waist circumference as a surrogate for obesity helps to mitigate this. Further, there was an important reliance on self-reported data for hypertension. Future studies could (a) incorporate a larger number of patients in a prospective study design to improve statistical power and better quantify effects of lithium (and other mood stabilizers) on metabolic outcome, (b) examine combination treatments more exhaustively, and (c) explore the postulated pathophysiological mechanisms linking bipolar disorders and metabolic dysregulation.

CONCLUSION

There is a higher prevalence of obesity and metabolic syndrome in this sample of bipolar disorder patients, when compared to the general population. However, prevalence of obesity and metabolic syndrome within bipolar disorder patients did not appear to be associated with lithium use, when compared to non-lithium users (e.g. those on anticonvulsants, second-generation antipsychotics). Constituents of metabolic syndrome also did not significantly differ between lithium users vs. non-users. An important exception was insulin resistance as reflected in HbA1c and triglycerides, with healthier levels in lithium users compared to non-lithium users. Future prospective studies with larger sample sizes will be necessary to confirm whether the association between lithium use and insulin resistance is due to a causal effect of lithium or other factors. A proactive approach to care focused on prevention, early intervention, and consistent monitoring may help prevent long-term health consequences of obesity.

DECLARATIONS

Ethics approval and consent to participate

The two studies from which data was used for this study were performed in accordance with the Declaration of Helsinki. They received ethics approval by the institutional review boards at the Douglas Mental Health University Institute (Study 1 and 2), McGill University Health Centre (Study 1), and Jewish General Hospital (Study 1).

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

S.R. receives investigator-initiated grant funding from Satellite Healthcare for an unrelated project. S.B. has received peer-reviewed research funding from Canadian Institutes of Health Research, Pfizer Research Award, National Alliance for Research on Schizophrenia and Depression (NARSAD), and support for knowledge translation and research contracts from Astra-Zeneca, Bristol-Myers-Squibb, Lundbeck, Otsuka, Sunovion; has been a consultant or part of an advisory board for Allergan, Astra Zeneca, Bristol-Myers Squibb (BMS), Forest Laboratories, Janssen-Ortho, Lundbeck, Merck, Otsuka, Pfizer, Sunovion; and part of the speaker bureau for Allergan, Astra Zeneca, BMS, Janssen-Ortho, Lundbeck, Otsuka, Pfizer, Purdue, Sunovion.

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299

300 ***Author's contributions***

301 S.R., O.L., J.F.S., and J.P. designed the study; S.R., O.L., J.F.S., H.P. and J.P. analyzed
302 and interpreted the data; S.R.., O.L., J.F.S., H.P. and J.P. drafted and revised the paper;
303 all authors approved the final version of the manuscript and have agreed both to be
304 personally accountable for the author's own contributions and to ensure that questions
305 related to the accuracy or integrity of any part of the work, even ones in which the author
306 was not personally involved, are appropriately investigated, resolved, at the resolution
307 documented in the literature.

308

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310 Not applicable.

Table 1: Demographics & Clinical Characteristics in Lithium Users and Non-Users with Bipolar Disorder (BD), *n*= 129

Variable	Li Users (*n*=66)	Non-Li Users (*n*=63)	Stats
Age (years), [mean (±SD)]	49.05 (11.78)	46.71 (11.20)	U=1850.5, p=0.281, z=-1.077
% Male, [% (*n*=)]	43.94% (*n*=29)	53.96% (*n*=34)	p=0.043, x^2=0.169
Age of onset of any psychiatric symptoms, [% (*n*=)]			p=0.017, x^2=13.8
o Age < 18	33.84% (*n*=22)	59.68% (*n*=37)	
o Age 18-30	43.08% (*n*=28)	24.19% (*n*=15)	
o Age 30-50	18.46% (*n*=12)	12.90% (*n*=8)	
o Age > 50	4.62% (*n*=3)	0.0% (*n*=0)	
o Not known	0.0% (*n*=0)	3.23% (*n*=2)	
Total number of previous mood episodes, [% (n=)]			p=0.001, x^2=15.9
o 1 episode	11.67% (*n*=7)	0% (*n*=0)	
o 2 episodes	10% (*n*=6)	0% (*n*=0)	
o 3 episodes	8.33% (*n*=5)	3.33% (*n*=2)	
o > 4 episodes	70% (*n*=45)	91.67% (*n*=55)	
MADRS score, [mean (±SD)]	4.30 (4.62)	6.81 (6.93)	U=4922.5, p=0.045 z=-2.01
YMRS score, [mean (±SD)]	4.42 (8.03)	15.90 (12.80)	U=719, p=1.57^-12, z=-7.07
Number of psychotropic medications, *n*=126**,** [mean (±SD)]	3.13 (1.72)	3.40 (1.40)	U=1738, p=0.280, z=-1.080
o On anticonvulsants, [n (%)]	36.5% (*n*=23)	82.5% (*n*=52)	p=1.414x 10-7, x^2=27.70
o On antidepressants, [n (%)]	38.1% (*n*=24)	57.1% (*n*=36)	p=0.032, x^2=4.582
o On antipsychotics, [n (%)]	58.7% (*n*=37)	76.2% (*n*=48)	p=0.036, x^2=4.375

Number of non-psychotropic medications, [mean (±SD)]	0.67 (1.004)	2.37 (2.951)	U=674, p=0.001, z=-3.371
○ For hypertension, n=117, [n (%)]	13.0% (*n*=7)	19% (*n*=12)	p=0.791, x^2=0.374
○ For diabetes, n=117, [n (%)]	7.4% (*n*=4)	22.2% (*n*=14)	p=0.027, x^2=4.902
○ For dyslipidemia, n=117, [n (%)]	3.7% (*n*=2)	22.2% (*n*=14)	p=0.004, x^2=8.447
○ For thyroid, n= 105, [n (%)]	18.4% (*n*=9)	23.2% (*n*=13)	p=0.543, x^2=0.371

Table 2: Body Mass Index (BMI) and other Physical Health Outcomes in Lithium Users and Non-Users with Bipolar Disorder (BD) (*n*= 129)

Variable	**Li Users** *(n=66)*	**Non-Li Users** *(n=63)*	**Stats**
Obesity, [n (%)]	42.42% (*n*=28)	34.92% (*n*=22)	p=0.384, x^2=0.758
Mean BMI, (kg/m^2) [mean (±SD)]	29.10 (+/-6.70)	30.20 (+/-8.57)	U= 2051, p=0.895, z=-0.132
BMI stratification, [n (%)]			
○ Underweight, <19	0% (*n*=0)	0, 0	p=0.184, x^2=4.85
○ Normal, 19-25	30.30% (*n*=20)	33.33%, (*n*=21)	
○ Overweight, 25-30	27.27% (*n*=18)	31.75%, (*n*=20)	
○ Class I Obesity, 30-35	25.76%, (*n*=17)	11.11%, (*n*=7)	
○ Class II & III Obesity, > 35	16.67%, (*n*=11)	23.81%, (*n*=15)	
Metabolic Syndrome [n (%)]	35.71% (*n*=15)	44.18% (*n*=19)	p=0.623, x^2=0.24
Waist circumference, NIH			U=1906.5, p=0.416, z=-0.813
○ Male, [mean (±SD)]	107.91 (20.51)	107.77 (16.79)	
○ Female, [mean (±SD)]	98.85 (16.28)	105.97 (19.03)	
Glucose Metabolism			U=1344.5, p=0.712, z=-0.369
○ Fasting Blood Glucose (mmol/L), *n=107* [mean (±SD)]	5.52 (1.03)	6.10 (2.90)	
○ HbA1C (mmol/L), *n=95* [mean (±SD)]	5.24 (0.53)	6.01 (1.83)	U=753.5, **p=0.006*,** z=-2.76
○ Diabetes, *n*= 87, [n (%)]	16.67% (*n*=7)	33.33% (*n*=15)	p=0.088, x^2=3.19
Lipid Profile			U=1233, p=0.582, z=-0.55
○ Total Cholesterol (mmol/L), *n=103* [mean (±SD)]	4.72 (1.02)	4.92 (1.10)	
○ HDL (mmol/L), *n=102*, [mean (±SD)]	1.30 (0.33)	1.24 (0.37)	U=1084.5, p=0.162, z=-1.40
○ LDL (mmol/L), *n=100*, [mean (±SD)]	2.79 (0.87)	2.75 (0.89)	U=1110, p=0.377, z=-0.883
○ Triglycerides	1.46 (0.88)	2.01 (1.25)	U=947,

(mmol/L), *n=102*, [mean (±SD)]			**p=0.020***, z=-2.32
○ Dyslipidemia, n=96, [n (%)]	50%, (*n*=23)	70%, (*n*=35)	p=0.06, x^2=4.007
Hypertension			
○ Hypertension, *n*=117, [n (%)]	12.96%, (*n*=7)	19.05%, (*n*=12)	p=0.455, x^2=0.791
Thyroid Function			
○ TSH, *n=103*, [mean (±SD)]	2.39 (1.26)	2.60 (1.43)	U=1187, p=0.411, z=-0.823
○ Hypothyroidism, n=102, [n (%)]	41.81%, (*n*=23)	59.57%, (*n*=28)	p=0.112, x^2=3.196

Complete information was available on all participants for BMI and waist circumference. For other domains, the number of patients available is indicated next to the name of each variable (n=).

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