



Sex differences in the association of overweight with cognitive performance in individuals with first-episode psychosis

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Cognitive deficits and overweight are prominent challenges in the treatment of psychosis, which have a direct impact on patients' quality of life. We aim to determine whether there is an association of overweight with cognitive performance and whether there are sex differences in this association. We included 170 individuals with first-episode psychosis (FEP) (mean age 23.08 years, 32.9% females) attending an early intervention service who underwent clinical, biometric, and cognitive assessments by the MATRICS Consensus Cognitive Battery. A set of two-way analyses of covariance (ANCOVAs) were conducted for each cognitive test. Sex, overweight, and their interaction were included as factors. Nearly 34% of the participants were overweight without differences between males and females. The excess of weight did not exert any main effect on cognition; however, overweight females performed significantly worse than non-overweight females in processing speed, verbal learning and memory, reasoning and problem-solving, and global cognitive function, whereas in males, there were no differences. Our findings highlight that sex matters in the study of metabolic and cognitive factors in FEP to develop targeted interventions based on sex perspectives.

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INTRODUCTION

It is well established that individuals with schizophrenia (SCZ) have increased rates of overweight and other metabolic syndrome components compared to healthy individuals^{1,2}. Despite treatment with antipsychotics (AP) having a direct impact on weight gain^{3,4}, increased cardiovascular risk and metabolic abnormalities have also been observed in individuals at the early stages of psychosis and in AP-naive individuals^{5–8}, which suggests an intrinsic vulnerability even before treatment. A greater prevalence of both overweight and obesity has been observed in females with established SCZ compared with males^{9,10}. In contrast, there is a lack of conclusive research conducted on first-episode psychosis (FEP) patients. Two studies with AP-naive subjects^{7,11}, reported that females were more likely to be overweight than males, whereas other¹² did not find differences.

Cognitive impairment is a core feature of psychosis, and the most commonly affected domains are working memory, processing speed, motor and verbal learning, and perception^{13,14}. Studies aiming to investigate sex differences in cognitive performance in both established SCZ and FEP samples have yielded conflicting results^{15,16}. Some studies have indicated that females perform better than males in terms of verbal and visual memory, processing speed, and social cognition^{17–19}. Conversely, other studies have reported that males perform better than females in terms of attention²⁰, processing speed²¹, and visual memory²². Additionally, others have not identified sex differences^{23–25} in cognitive functioning.

Overweight and obesity have been linked to an increased risk of cognitive impairment and dementia^{26–29}. In addition, an inverse association between BMI and cognitive function has been documented in both obese and community-based samples^{26–29}. Nevertheless, despite the high prevalence of overweight and cognitive dysfunction in patients with SCZ, the association between

these two factors has been understudied. The limited number of studies on patients with established SCZ suggest that overweight is associated with reduced psychomotor abilities, decreased processing speed, and poorer performance in executive function and visual learning and memory^{30,31}. However, less evidence exists for FEP patients. A previous study conducted by our group revealed a significant association between overweight and executive function in FEP patients, especially in inhibitory control³². Furthermore, another study suggested a negative correlation between BMI and intelligence quotient scores³³, without significant associations observed with any other specific cognitive domain. Nevertheless, only two studies have considered sex differences in established SCZ patients, reporting a positive association between BMI and language scores in males but no relationship in females^{10,34}. In addition, a recent study identified sex-specific associations between metabolic risk factors and cognitive impairment in a sample of individuals with SCZ. Specifically, dyslipidemia and hyperlipidemia were inversely correlated with performance on several cognitive domains in females and males, respectively³⁵.

To the best of our knowledge, no other study has investigated the association of overweight and sex with cognition in FEP patients. Given this knowledge gap, we aimed to determine (1) whether there is an association between overweight and cognitive performance, and (2) whether this association is different in females than males.

RESULTS

Sample characteristics

Table 1 shows the sample characteristics. The sample consisted of 170 FEP patients (56 females and 114 males), and the mean age was 23.05 years. The mean BMI of the whole sample was 23.77 kg/m²; 33.53% of the participants were overweight ($n = 57$), 24.6% of

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Table 1. Characteristics of participants stratified by overweight status and sex.

	Whole sample N = 170	Overweight status		p-value	Sex		p-value
		Non-overweight N = 113	Overweight N = 57		Female N = 56	Male N = 114	
Sociodemographic variables							
Sex (n, %)				0.337 ^c			
Female	56 (32.9)	40 (35.4)	16 (28.1)				
Male	114 (67.1)	73 (64.6)	41 (71.9)				
Age, years (m, SD)	23.05 (5.37)	23.03 (5.58)	23.10 (4.98)	0.939 ^a	23.07 (6.25)	23.05 (4.91)	0.985 ^a
Education, years (med, IQR)	10 (9–13)	10 (8.5–13)	10 (9–12.5)	0.353 ^b	10 (8–12)	10 (9–13)	0.718 ^b
Ethnicity (n, %)				0.976 ^c			0.742 ^c
Caucasian	131 (77.1)	87 (77)	44 (77.2)		44 (78.6)	87 (76.3)	
Non-Caucasian	39 (22.9)	26 (23)	13 (22.8)		12 (21.4)	27 (23.7)	
Biometric variables							
BMI (m, SD)	23.77 (3.89)	21.59 (2.25)	28.08 (2.66)	<0.001 ^a	23.41 (3.69)	23.95 (3.99)	0.397 ^a
Overweight (n, %)	57 (33.53)				16 (28.57)	41 (36.00)	0.337 ^c
Obesity, BMI ≥ 30 (n, %)	14 (8.20)	0 (0.00)	14 (24.56)	<0.001 ^c	4 (7.14)	10 (8.77)	0.716 ^c
Treatment variables							
AP intake (n, %)	160 (94.1)	105 (92.9)	55 (96.5)	0.350 ^c	52 (92.9)	108 (94.7)	0.624 ^c
CPZE, mg/day (med, IQR)	300 (200–450)	300 (199.9–400)	300 (200–552.8)	0.093 ^b	300 (162.5–400)	300 (200–450)	0.049 ^b
Treatment length, days (med, IQR)	88 (42–161)	67 (34.5–142)	125 (70–207)	<0.001 ^b	90.5 (47–161)	87 (37–157.5)	0.557 ^b
Clinical variables							
DUP, days (med, IQR)	29.5 (10–60)	30 (10–60)	21 (10–60)	0.557 ^b	26.5 (10–60)	30 (10–60)	0.997 ^b
PANSS+ (med, IQR)	12 (8–18)	13 (8–18)	11 (8–19)	0.548 ^b	13 (8–19)	12 (8–18)	0.601 ^b
PANSS– (med, IQR)	16 (11–24)	15 (10–23)	18 (11.5–27)	0.193 ^b	14 (11–23)	17 (11–24.5)	0.393 ^b
PANSS general (med, IQR)	33 (24–45)	33 (24.5–43)	31 (23–46)	0.903 ^b	31 (25.5–46.5)	33 (24–44.5)	0.909 ^b
PANSS total (med, IQR)	61 (46–82)	61 (47–81)	63 (45.5–91.5)	0.889 ^b	57 (47–90)	64 (46–82)	0.890 ^b
CDS (med, IQR)	2 (0–5.25)	2 (0–5)	2 (0–8)	0.488 ^b	3 (0–8)	1 (0–5)	0.015 ^b
GAF (med, IQR)	60 (52–65)	60 (53–65)	60 (51.5–64.5)	0.669 ^b	58 (52.5–60)	60 (52–65)	0.217 ^b
Frequent substance use (≥1 time/week)							
Tobacco (n, %)	113 (66.50)	75 (66.4)	38 (66.7)	0.969 ^c	33 (58.9)	80 (70.2)	0.144 ^c
Cannabis (n, %)	67(39.40)	43 (38.1)	24 (42.1)	0.610 ^c	17 (30.4)	50 (43.9)	0.090 ^c
Alcohol (n, %)	50 (29.4)	31 (27.4)	19 (33.3)	0.425 ^c	10 (17.9)	40 (35.1)	0.020 ^c

m mean, med median, SD standard deviation, IQR interquartile range, AP antipsychotic, CPZE chlorpromazine equivalent, DUP duration of untreated psychosis, PANSS Positive and Negative Symptom Scale, CDS Calgary Depression Scale, GAF Global Assessment Functioning Scale.

^aTwo-sided Student's t-test.
^bMann-Whitney U-test.
^cPearson's Chi-squared test.

whom were obese ($n = 14$). Almost the whole sample was receiving AP treatment (94.1%), and the median treatment duration was 88 days. No differences were found in the prevalence of overweight between males and females (Table 1). When groups were compared by weight status, the only significant difference was that overweight participants had a median AP treatment duration of 125 days, whereas non-overweight participants had a median treatment duration of 67 days ($U = 4272.50$, $p < 0.0005$). When groups were compared by sex, females had greater CDS scores than males ($U = 3898.5$, $p = 0.0149$), whereas males were treated with a significantly greater AP dose than females ($U = 2600.50$, $p = 0.0489$).

Associations between sex and overweight status, and cognitive performance

There were no significant differences between groups regarding weight status in any of the cognitive test scores (Fig. 1 and Supplementary Table 2). However, when comparing cognitive scores between females and males, females exhibited significantly

higher scores in BACS-SC [$t = -2.656$ (95% CI -0.736 to -0.108), $p = 0.0087$], HVLT-R [$t = -3.551$ (95% CI -0.863 to -0.246), $p = 0.0005$] and MSCEIT-ME [$t = -2.807$ (95% CI -0.758 to -0.132), $p = 0.0056$] subtests than males (Fig. 2 and Supplementary Table 2).

Two-way ANCOVAs were performed for each cognitive test, adjusting for the following variables showing a $p < 0.1$ in the univariate analysis: educational level (years), CDS score, AP CPZE, treatment duration, and frequency of cannabis and alcohol use. The analyses (Table 2) revealed a significant main effect of overweight status on HVLT-R, and a significant main effect of sex on BACS-SC, HVLT-R, and MSCEIT-ME scores. There was a significant interaction effect between overweight status and sex on the BACS-SC ($F = 5.672$, $p = 0.018$), HVLT-R ($F = 12.471$, $p < 0.001$), and NABMazes ($F = 8.751$, $p = 0.004$). Additionally, a significant interaction effect was found for the global cognition z-score ($F = 8.555$, $p = 0.004$). Figure 3 shows the marginal mean analyses from the ANCOVAs revealing the direction of the interaction effects across the statistically significant tests. In all

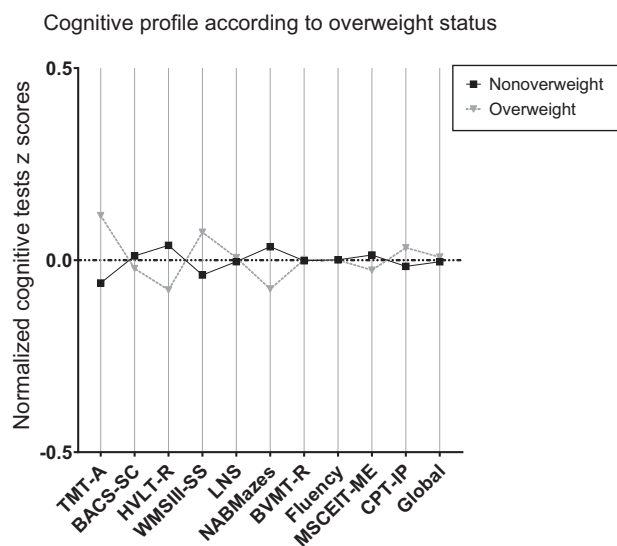


Fig. 1 Comparison of normalized cognitive tests z-scores according to overweight status. TMT-A Trail-Making Test Part A, BACS-SC Brief Assessment of Cognition in Schizophrenia-Symbol Coding, HVLT-R Hopkins Verbal Learning Test-Revised, WMSIII-SS Weschler Memory Scale III-Spatial Span, LNS Letter-Number Sequencing, NAB-Mazes Neuropsychological Assessment Battery-Mazes, BVMT-R Brief Visual Memory Test-Revised, Fluency Verbal Fluency Test, MSCEIT-ME Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions, CPT-IP Continuous Performance Test-Identical Pairs.

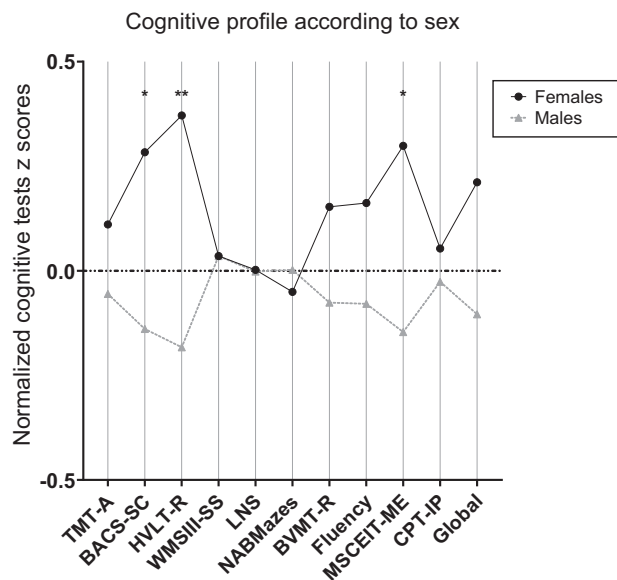


Fig. 2 Comparison of normalized cognitive tests z-scores according to sex. * p -value < 0.05, ** p -value < 0.001. TMT-A Trail-Making Test Part A, BACS-SC Brief Assessment of Cognition in Schizophrenia-symbol Coding, HVLT-R Hopkins Verbal Learning Test-revised, WMSIII-SS Weschler Memory Scale III-Spatial Span, LNS Letter-number Sequencing, NAB-Mazes Neuropsychological Assessment Battery-mazes, BVMT-R Brief Visual Memory Test-revised, fluency Verbal Fluency Test, MSCEIT-ME Mayer-salovey-caruso Emotional Intelligence Test-managing Emotions, CPT-IP Continuous Performance Test-identical Pairs.

cases, being overweight was associated with lower scores than being non-overweight in females. However, no differences in cognitive scores were found between overweight and non-overweight males.

Partial correlations were conducted using BMI as a continuous variable controlled by education level, CDS score, AP CPZE, treatment duration, and frequency of cannabis and alcohol use in the whole sample and stratifying by sex groups. Results show a negative correlation between BMI and HVLT-R z-score ($\rho = -0.390$, $p = 0.006$) only in females, with no other significant correlations. Further correlation results are shown in the Supplementary Table 3.

DISCUSSION

To our knowledge, this is the first study to report sex differences in the association of overweight and cognitive performance in a sample of FEP patients. Our main finding is that non-overweight females significantly outperformed overweight females in terms of processing speed, verbal learning and memory, reasoning and problem-solving, and global cognitive function, whereas these differences were not found in males. Given the lack of previous studies, our findings should be considered preliminary and need replication.

The prevalence of overweight within our sample (33.53%) aligns with findings from previous studies with FEP patient samples³⁶⁻³⁸. The median AP treatment duration of the sample was less than 90 days; however, overweight participants had received AP treatment for approximately 4 months, and non-overweight participants had received AP treatment for approximately 2 months, reflecting the rapid weight gain associated with AP use at the beginning of treatment^{3,4}. In line with the findings of Correll et al.¹², we did not find differences in the rate of overweight between males and females, and similar to previous studies^{39,40}, we found more severe symptoms of depression in females and a higher AP dosage in males^{15,41}.

We did not find an independent effect of overweight on cognitive performance, thus contrasting with prior studies of individuals with established SCZ^{30,31}, but our results are in agreement with the scarce previous research on FEP patients³². Notably, research to date has also reported inconsistent results regarding the direction of the association between overweight/obesity and cognitive performance in the general population⁴²⁻⁴⁴, as well as in established SCZ populations⁴⁵⁻⁴⁸. In fact, the diversity in methodological approaches, sample features, and cognitive tests limits the comparability of these studies³⁰. As mentioned earlier, the most consistent finding within obese individuals and the general population is that deficits in executive functioning may affect the regulation of eating behavior^{28,49}. Thus, the extent to which excess weight influences cognitive performance and whether specific cognitive domains, such as executive dysfunction, play a role in weight gain in individuals with psychosis spectrum disorders must still be determined.

Concerning sex differences in cognitive performance, we observed that females outperformed males in terms of processing speed, verbal learning and memory, and social cognition. These findings are in line with an earlier study on an FEP sample by Ferrer-Quintero et al.^{17,19}, who highlighted enhanced verbal abilities and social cognition in females, especially in emotional regulation⁵⁰ (assessed by the MSCEIT-ME). As discussed in the aforementioned study, the objective measurements of social cognition are not always accurate, as it is difficult to assess the behavioral or emotional response in a fictional social situation. Meaning that many factors could mediate this association (e.g., verbal abilities to comprehend the social task). However, the observed differences in processing speed require further investigation, as the results remain inconclusive, with previous research showing opposite or incongruent results in FEP and established SCZ patients^{16,22}. Notably, in the general population, there seems to be a consensus that females score better than males in verbal learning tasks, and males outperform females in spatial memory tasks⁵¹. Researchers have attempted to explain sex differences in

Table 2. Two-way ANCOVA results for each of the MCCB tests.

MCCB tests	Two-way ANCOVA ^a								
	Overweight effect size (η^2_{partial})	Overweight effect <i>F</i>	<i>p</i> -value	Sex effect size (η^2_{partial})	Sex effect <i>F</i>	<i>p</i> -value	Sex × overweight effect size (η^2_{partial})	Sex × overweight effect <i>F</i>	<i>p</i> -value
TMT-A	0.002	0.314	0.576	0.002	0.319	0.573	0.018	2.922	0.089
BACS-SC	0.006	0.974	0.325	0.024	3.978	0.048	0.034	5.672	0.018
HVLT-R	0.026	4.221	0.042	0.026	4.246	0.041	0.072	12.471	<0.001
WMSIII-SS	0.001	0.104	0.748	0.005	0.772	0.381	0.015	2.458	0.119
LNS	0.004	0.684	0.409	0.002	0.337	0.562	0.012	2.021	0.157
NABMazes	0.019	3.096	0.080	0.002	0.340	0.561	0.052	8.751	0.004
BVMT-R	0.002	0.276	0.600	0.011	1.763	0.186	0.001	0.190	0.664
Fluency	0.002	0.325	0.569	0.004	0.628	0.429	0.023	3.705	0.056
MSCEIT-ME	<0.001	<0.001	0.991	0.035	5.718	0.018	0.001	0.092	0.762
CPT-IP	<0.001	0.092	0.762	<0.001	0.025	0.874	0.011	1.813	0.180
Global	0.005	0.769	0.382	0.010	1.588	0.210	0.051	8.555	0.004

η^2_{partial} Partial Eta Squared, *TMT-A* Trail-making Test Part A, *BACS-SC* Brief Assessment of Cognition in Schizophrenia-Symbol Coding, *HVLT-R* Hopkins Verbal Learning Test-Revised, *WMSIII-SS* Wechsler Memory Scale III-Spatial Span, *LNS* Letter-number Sequencing, *NABMazes* Neuropsychological Assessment Battery-Mazes, *BVMT-R* Brief Visual Memory Test-Revised, *Fluency* Verbal Fluency Test, *MSCEIT-ME* Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions, *CPT-IP* Continuous Performance Test-Identical Pairs, *Global* Global z-score Mean.

^aANCOVAs adjusted for years of education, Calgary Depression Scale (CDS) score, antipsychotic dosage (CPZE), treatment duration, weekly cannabis use, and weekly alcohol use.

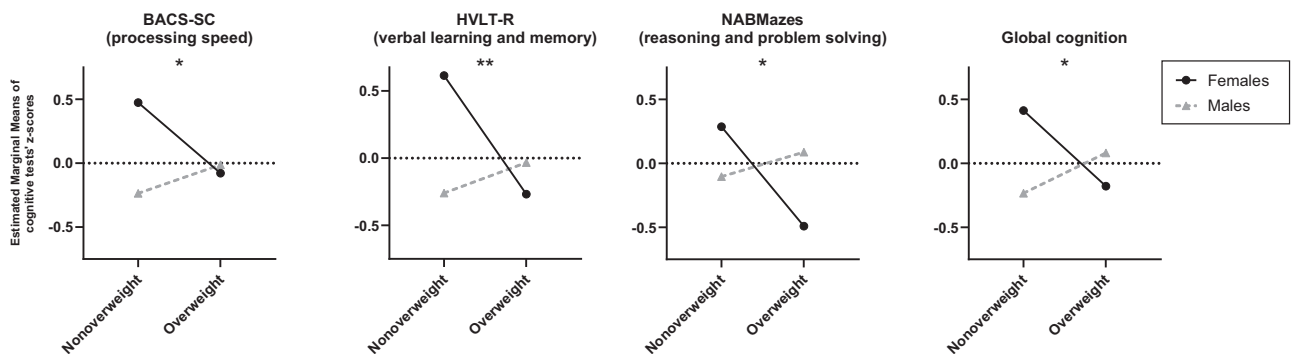


Fig. 3 Comparison of estimated marginal means from cognitive test z-scores by overweight status and sex, obtained by the individual ANCOVAs for each cognitive test. **p*-value < 0.05, ***p*-value < 0.001. BACS-SC Brief Assessment of Cognition in Schizophrenia-symbol Coding, HVLT-R Hopkins Verbal Learning Test-revised, NABMazes Neuropsychological Assessment Battery-Mazes.

cognitive performance, and one of the most accepted theories is that males and females use different brain networks in cognitive processing pathways. Moreover, these pathways are influenced by the effects of sex hormones, which can lead to differences in cognitive performance⁵². Similarly, the role of the hippocampus in cognitive processes, together with the prefrontal cortex⁵³, and its sensitivity to sex hormones could contribute to these changes and differences^{51,52}. Researchers have attempted to explain sex differences in cognitive performance, and one of the most accepted theories is that males and females use different brain networks in cognitive processing pathways. Moreover, these pathways are influenced by the effects of sex hormones, which can lead to differences in cognitive performance⁵². Similarly, the role of the hippocampus in cognitive processes, together with the prefrontal cortex⁵³, and its sensitivity to sex hormones could contribute to these changes and differences^{51,52}.

In addition, males and females also show different mechanisms for metabolic and endocrine regulation^{54,55}. Leptin, for instance, is a hormone known to be involved in eating behavior and metabolism regulation and provides feedback between the central nervous system and fat cells. Leptin's role is linked to metabolic syndrome, as increased blood leptin levels have been

associated with the development of certain conditions associated with metabolic syndrome⁵⁶. In fact, a previous study by our group⁵⁷ revealed an association between increased blood leptin levels and a higher BMI. Interestingly, a correlation between blood leptin levels and food-craving behavior was found only in females. Notably, food-craving behavior is linked to cognitive performance through inhibitory control and prefrontal cognitive processes such as executive functioning^{49,58}. Furthermore, a meta-analysis suggested that blood leptin levels are inversely correlated with the activation of the prefrontal cortex⁵⁹, and a reduction in the activity of the prefrontal cortex could lead to a lack of cognitive control and executive function impairment⁶⁰. In the case of prolactin levels, which are also upregulated in AP-naive early-stage psychosis patients⁶¹, a previous study on the part of our sample showed a direct association between prolactin levels and cognitive performance only in male participants⁶². However, research has revealed no associations between prolactin levels and BMI or overweight in early-stage psychosis patients^{63,64}; therefore, even though associations among prolactin levels, overweight status, sex, and cognition have not yet been identified, there is more than sufficient evidence of a link between hormone levels and cognitive performance.

While discussing our results, we must acknowledge several limitations of our study. On the one hand, stratification by sex and BMI limited subgroup size. Second, our sample was not AP-naive, and we could not assess the effect of each AP due to the sample size; however, we minimized its impact by controlling for AP dosage and treatment duration. We used BMI as an indicator of overweight. However, there are other biometric variables that we did not include to define metabolic conditions^{65,66}. The absence of a healthy control group did not allow us to determine whether the observed cognitive differences were not due to sex-related biological variations. Finally, the cross-sectional nature of the study did not allow us to infer causality.

Despite these limitations, our results suggest the presence of an interaction effect between sex and overweight on cognitive performance in FEP patients, in which the presence of overweight is associated with a worse performance in several domains in females; conversely, these effects were not observed in males. Given the lack of previous studies, our findings should be considered preliminary and need replication. We can speculate that metabolic alterations, together with the action of hormones, may exert differential effects on cognitive processes in males and females. However, as previously mentioned, the inverse association cannot be excluded. Biology of males and females differ due to genetic, neurochemical, hormonal, metabolic, and anatomic factors that are present since conception and evolve throughout neurodevelopment: childhood, adolescence, and adulthood⁶⁷. Considering this complex picture, it is still unknown the mechanism underlying the present findings. However, our findings highlight that sex matters and that differences cannot be ignored in the study of metabolic and cognitive factors in the psychosis field. These findings, therefore, require replication in other samples, and further research on metabolic issues is needed to contribute to the development of specific clinical strategies to improve patients' quality of life.

METHODS

Participants

For the present study, we selected 170 FEP attending the Early Psychosis Intervention Program (EIP) at the Hospital Universitari Institut Pere Mata (Reus, Catalonia, Spain) with complete neuropsychological, clinical, and biometric data. First episode of psychoses (FEP) was defined as the onset of a full psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)⁶⁸ confirmed by the Spanish version of the Structural Clinical Interview for DSM-IV (SCID-I). The exclusion criteria were as follows: more than 12 months of illness duration, more than 12 months of AP treatment, psychosis induced by substances or other medical conditions, intellectual disability, severe head injury, and the inability to understand or speak Spanish or Catalan fluently.

Ethical approval was obtained from the Ethics Committee of the Pere Virgili Research Institute (IISPV). After a complete description of the study was given to the participants, written informed consent was obtained.

Procedure

All participants were assessed when they were clinically stable enough to understand and sign the informed consent and to undergo the cognitive assessment. At study entry, participants underwent biometric, clinical, and cognitive assessments.

Biometric assessments. The biometric weight and height examinations were performed by trained nurses. According to general and World Health Organization criteria, a BMI ≥ 25 kg/m² was considered overweight, and a BMI < 25 kg/m² was considered non-overweight⁶⁵.

Clinical assessments. Sociodemographic, clinical, and treatment-related information was obtained through direct interviews by trained psychiatrists. Sociodemographic data included sex, age, educational level, and ethnicity. The clinical assessments included the Spanish versions of the Positive and Negative Symptoms Scale (PANSS)⁶⁹ to assess the severity of psychotic symptoms (higher scores indicating greater severity), the Calgary Depression Scale (CDS)⁷⁰ to assess the severity of depressive symptoms (higher scores reflecting more severity) and the Global Assessment of Functioning (GAF)⁶⁸ to evaluate general functioning (higher scores meaning better functioning). Information on the duration of untreated psychosis (DUP), variables regarding AP treatment (main AP, treatment length, and AP dosage), and substance use was collected through direct interviews. Each AP dosage was transformed into chlorpromazine equivalents (CPZE) in mg/day⁷¹, and substance use was categorized as frequent use (≥ 1 time/week) or nonfrequent use (< 1 time/week).

Cognitive assessments. Cognitive tests were administered by experienced psychologists, and all participants completed the tests in a fixed order. The MATRICS Consensus Cognitive Battery (MCCB)^{72,73} was administered to the participants. The MCCB is a neuropsychological battery comprising ten tests that measure seven cognitive domains, including the Trail-Making Test Part A (TMT-A), the Brief Assessment of Cognition in Schizophrenia-Symbol Coding (BACS-SC) subtest, and the Category Fluency Test-Animal Naming (Fluency) to measure processing speed; the Hopkins Verbal Learning Test-Revised (HVLT-R) to measure verbal learning and memory; the Weschler Memory Scale III-Spatial Span (WMSIII-SS) and the Letter-Number Span (LNS) subtests to measure working memory; the Neuropsychological Assessment Battery-Mazes (NAB-Mazes) subtest to measure reasoning and problem-solving; the Brief Visuospatial Memory Test-Revised (BVMTR) to measure visual learning and memory; the Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions (MSCEIT-ME) subtest to measure social cognition (specifically emotional regulation); and the Continuous Performance Test-Identical Pairs (CPT-IP) to measure attention and vigilance.

The z-scores of the MCCB subtests were determined by obtaining the direct score mean and standard deviation from a database with results from a sample of 58 healthy controls who had participated in previous studies^{74,75}. Higher z-scores represented better performance; thus, the z-score for the TMT-A subtest needed to be inverted. A global cognition z-score was derived from the means of all the cognitive tests.

The control sample comprised both friends and relatives who were not genetically related to the patients. To determine their status as healthy controls, we conducted screenings for previous and current psychiatric disorders through the General Health Questionnaire⁷⁶. Sociodemographic characteristics of the HC compared with the FEP sample are presented in Supplementary Table 1.

Statistical analysis

Differences in demographic, biometric, and cognitive data were first compared separately regarding sex (female vs. male) or weight status (overweight vs. non-overweight). The normality of the distribution of variables was checked by the Kolmogorov-Smirnov test. The dependent variables were normalized through the rank-based inverse normal transformation (RankNorm function from the RNOmni R package, version 1.0.1.2) in RStudio (version 2023.5.0) to ensure the ANCOVA assumptions were met by all the variables. Two-sided Student's *t*-tests and Mann-Whitney *U*-tests were used to compare parametric and nonparametric continuous variables, respectively, and the Chi-squared test was used to compare categorical variables.

A two-way univariate analysis of covariance (ANCOVA) was conducted for each cognitive test. Sex (female and male), overweight status (overweight and non-overweight), and their interaction were included as factors. Each analysis was adjusted for variables displaying intergroup differences at a level of significance $p < 0.1$. Multiple testing correction was applied through the Bonferroni method. Given that 11 ANCOVAs were performed, only models with $p < 0.0045$ were considered to be statistically significant ($0.05/11 = 0.0045$).

Additionally, partial correlations using BMI as a continuous variable were carried out for exploratory purposes.

All the analyses were performed using IBM SPSS Statistics, version 25.

DATA AVAILABILITY

The dataset for this manuscript is not publicly available due to issues of data ownership and participant consent.

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Martí Llaurador-Coll: conceptualization, methodology, data curation, software, formal analysis, writing—original draft, writing—review & editing, visualization. Àngel Cabezas: investigation, data curation. M. José Algora: investigation, data curation. Montse Solé: investigation, data curation. Elisabet Vilella: writing—review & editing, supervision, project administration, funding acquisition. Vanessa Sánchez-Gistau: conceptualization, methodology, investigation, data curation, writing—review & editing, visualization, supervision, project administration, funding acquisition.

COMPETING INTERESTS

The authors declare no competing interests.

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