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ORIGINAL ARTICLE

Fluid intelligence, traits of personality and personality disorders in a cohort of adult KS patients with the classic 47, XXY karyotype

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Abstract
Purpose Klinefelter's syndrome (KS) is associated with specific neurobehavioral features and personality traits. The aim of our study was to investigate fluid intelligence, personality traits and personality disorders (PD) and possible correlations with testosterone in a cohort of adult KS patients.
Methods We analyzed 58 adult KS patients with the classic 47, XXY karyotype. The Structured Clinical Interview for axis II disorders was used to assess DSM IV personality disorders. Personality traits were assessed using MMPI-2. Fluid intelligence was tested by using Raven's Standard Progressive Matrices (SPM) Test. Testosterone blood concentration was measured by CMIA.
Results PD prevalence was 31%. Four altered MMPI scales (Social Responsibility, Dominance, Ego Strength and Repression) were found in more than 40% of patients. Overcontrolled hostility and MacAndrew Alcoholism Scale-Revised scales were altered in the PD− group only. Biz-Odd Thinking and Post-Traumatic Stress Disorder scale were associated with the presence of personality disorder. The raw SPM score was 44 ± 10.8 without any significant correlation with testosterone. No significant difference in mean age, SPM raw score and MMPI score was observed between eugonadal, hypogonadal and treated patients.
Conclusions Most KS patients had average fluid intelligence. PD prevalence was higher than in the general population. Testosterone was not correlated with fluid intelligence, personality traits or PD, but a reduction in marital distress was observed in treated patients. This could suggest that testosterone therapy can improve physical symptoms and this effect could also improve relationship abilities and wellness awareness.

Keywords Klinefelter syndrome · Personality · Fluid intelligence · Testosterone · Hypogonadism

Introduction

Klinefelter syndrome (KS) is the most common male sex chromosome disorder, occurring in about 1 in 500 men and boys in the general population [1]. It is caused by the presence of one or more supernumerary X chromosomes. The 47, XXY variant is undoubtedly the most widespread (80% of cases), but both mosaicism [2] and higher-grade chromosome aneuploidies are seen in KS patients. The clinical and genetic presentation of the syndrome show extreme heterogeneous [3, 4]. As traditionally described, patients with KS have tall stature, small testes, gynecomastia in late puberty, gynoid aspect of hips, sparse body hair, signs of androgen deficiency and low serum testosterone coupled with elevated gonadotropins, and azoospermia [5]. KS patients also have an increased probability of endocrine and/or metabolic disease, especially obesity, metabolic syndrome and type 2 diabetes mellitus [6]. KS has also been associated with specific neurobehavioral and personality

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features: although KS patients were found to have a generally normal cognitive level, average IQ scores were ten points lower compared with siblings or peers [7–9]. Some studies, based on the administration of Wechsler Adult Intelligence scale, found a difference between scores on performance tasks and those achieved in verbal subtests, with higher scores seen in the former [10, 11]. This pattern is probably linked to the development of fundamental difficulties with language skills and to decreased auditory memory and processing [12, 13]. Fluid intelligence is normal in most cases, although its evaluation through specific psychometric scales has not received much attention in the literature.

Evidence of cognitive improvement induced by early hormonal therapy in pediatric KS patients has been found, but there is little evidence of such improvement in adult patients receiving androgen replacement therapy [14–16].

Personality disorders form a class of mental disorders that are characterized by long-lasting, rigid patterns of thought and behavior and include clusters of characteristics that share common themes or elements. These disorders typically remain undiagnosed until subjects reach adulthood, and often until their 20s or even 30s. Personality disorders are grouped as follows: Cluster A (odd or eccentric disorders), Cluster B (dramatic, emotional or erratic disorders) and Cluster C (anxious or fearful disorders) [17, 18]. Personality studies in the literature have reported conflicting descriptions of patients with KS [12, 19, 20]. Some characterize them as timid, immature, and reserved, with difficulties in relating to their peer group, whereas others describe 47, XXY subjects as friendly, kind, helpful, and able to relate well with other people [21]. Some personality features may favor the onset of anxiety, depression and substance abuse in adolescents with KS [22–24]. Klinefelter patients have a nearly four times higher risk of being diagnosed with schizophrenia and bipolar disorder and an approximately six times higher risk of autism spectrum disorder and ADHD [23, 25, 26]. Although these studies offer detailed descriptions of the personality of patients with KS, there is little literature evidence concerning the incidence and features of personality disorders linked to adult KS subjects. Some studies based on wellbeing scales indicate adverse quality of life, low self-esteem, poor self-concept and higher risk of depression. Testosterone level was not associated with psychosocial health measures [27], and testosterone supplementation was not found to influence cognitive flexibility or autism traits in KS boys [28].

The aim of our study was therefore to investigate fluid intelligence, personality traits and personality disorders in a cohort of adult KS patients with the classic 47, XXY karyotype in order to evaluate possible correlations with other variables, such as blood testosterone levels and testosterone replacement therapy.

Materials and methods

Participants

A cohort of adult KS Caucasian patients with the classic 47, XXY karyotype was recruited from the Center of Rare Diseases, Department of Experimental Medicine, Sapienza University of Rome in the period 2012–2014. The diagnosis was made after birth in all patients and confirmed by karyotype analysis from cultured peripheral lymphocytes. Karyotypes were established on 40 metaphases from each patient.

The initial sample comprised 74 subjects. Eight patients were excluded due to diagnosis in axis 1 of DSM IV-TR, which includes major mental disorders potentially influencing personality assessment. The remainder (66 patients) were invited to complete the self-report psychometric tests. After excluding eight subjects whose tests were considered invalid, we obtained a final sample of 58 patients (age range 18–63 years, mean 34.6, standard deviation 12.3, median 37.5). The educational level of our sample was varied: 4.5% had received tertiary education, 56% had received upper secondary education and 38 and 1.5% of patients lower secondary and primary education, respectively.

The subjects' medical history, including ongoing testosterone replacement therapy, was obtained. Only subjects who had undergone a minimum of 18 months of replacement therapy were included (25 patients). The mean age at the start of testosterone treatment was 32.7 years (SD 10.9, min 16.3, max 52.8, median 33.1), and the mean treatment duration was 7 years (SD 8.5, min 1.5, max 28.7, median 2.83). All treated subjects had reached and maintained physiological testosterone serum levels throughout the study period ($\geq$12 nmol/L).

The remaining non-treated patients (*n* 33) were divided as follows: 12 patients with testosterone <12 nmol/L (hypogonadal) and 21 subjects with naïve physiological testosterone serum levels (eugonadal).

Analysis of endocrine parameters

Blood samples were drawn from the antecubital vein in the early morning (07:30–09:30) in all subjects. Serum testosterone concentration was measured by chemiluminescent microparticle immunoassay (CMIA) (Architect System, Abbott) [29].

Psychometric measures

Structured Clinical Interview for DSM-IV-TR axis II disorders (SCID-II)

The Structured Clinical Interview for axis II disorders (SCID-II) was used to assess the ten DSM IV personality disorders divided into clusters A, B and C [17, 18]. SCID-II includes a 3-point rating with 1 indicating "no", 2 indicating "yes" and 3 indicating "yes, sub-threshold". The results of the interview are based on the underlying SCID algorithm and scoring system.

Multiphasic Personality Inventory-2 (MMPI-2)

Personality traits were assessed using MMPI-2, which is a standardized self-report measure intended for adults (18 years and older). It consists of 567 true–false items and assesses the overall profile configuration of ten clinical scales (Hypochondriasis, Depression, Hysteria, Psychopathic Deviance, Masculinity–Femininity, Paranoia, Psychasthenia, Schizophrenia, Hypomania and Social Introversion) that provide a reliable personality profile. This test also contains several new clinical scales (supplemental, content and validity scales) [30, 31]. A score of $\geq$65 is elevated, and is used as a cut-off indicating distinct psychological problems or disorders. The MMPI-2 validated Italian version was used for this study.

Standard Progressive Matrices Test (SPM)

Fluid intelligence was tested using Raven's Standard Progressive Matrices Test, which is based on items assessing abilities in the fields of non-verbal reasoning [32, 33]. This test was chosen because of its high specificity in investigating problem-solving, pattern-recognition and abstract reasoning abilities, as these features were not investigated in depth in previous studies. Moreover, it does not depend on previously acquired knowledge and is not influenced by educational experience, providing a result that is easy to interpret and compare. The test comprises five sets of 12 items each, with items within a set becoming increasingly difficult. It directly measures two components of fluid cognitive ability defined as: (1) "The ability to draw meaning out of confusion; and (2) the ability to recall and reproduce information that has been made explicit and communicated from one to another" [34]. A score of '1' is assigned for a correct answer and of '0' for an incorrect answer.

Statistical analysis

Data were collected in an Excel database and analyzed using the statistical software program *GraphPad Prism* for Windows. The main descriptive statistical indices were calculated (including mean, median and standard deviation) and a frequency analysis was performed. Mann–Whitney *U* test was performed to evaluate any differences between continuous variables. Categorical variables were compared using the Chi-squared test. The correlation between the examined variables was investigated by Spearman's rank correlation coefficient. All figures were created using *GraphPad Prism* and *Microsoft Excel for Windows*.

Results

The first aim was to identify the prevalence of personality disorders in our KS population. Table 1 shows their prevalence in comparison with community samples as reported in a large number of published studies [35–39]. The Structured Clinical Interview for DSM IV axis II disorders (SCID II) detected personality disorders in 31% of our sample, versus a mean of 10.7% obtained from different community samples.

We divided the whole KS population into two subgroups: 18 patients diagnosed with personality disorders (PD+) and 40 who were not (PD−). There was no statistically significant difference in mean age and mean serum testosterone levels between these sub-populations, as seen in Table 2.

Personality traits were evaluated using the MMPI II test. Figure 1a shows the percentage of pathological scores for each scale. We found four altered scales, corresponding to Social Responsibility, Dominance, Ego Strength and Repression, in more than 40% of patients. All their scores were under the minimum cut-off. Twenty-four of 34 MMPI scales were pathological (over the maximum cut-off) in at least 10% of patients. Two scales (overcontrolled hostility and MacAndrew Alcoholism Scale-Revised) were altered in the PD group only. We performed the same analysis on the whole KS population divided into the subgroups PD+ and PD−, as shown in Fig. 1b. There was a significant association with the presence of personality disorder for two MMPI scales only (Biz-Odd Thinking and PS-Post-Traumatic Stress Disorder scale) (OR 5.4, $p = 0.0451$, 95% CI, respectively, 1.29–27.74 and 1.29–23.74).

The second aim was to measure fluid intelligence using Raven's Standard Progressive Matrices (SPM). The mean raw score was 44 $\pm$ 10.8 (10–58), with a maximum score of 60. This result is similar to the mean value associated with upper secondary education in the general population [32]. There was no significant correlation between testosterone serum level and SPM score in the KS population.

There was no difference when comparing PD+ and PD− SPM raw scores, with mean values of 42 $\pm$ 12.48 and 45.5 $\pm$ 9.98, respectively (p = n.s.). The number of

Table 1 Comparison of prevalence of personality disorders in KS and community samples

	Our KS sample (%)	Community samples				
		Coid et al. [35][b] (%)	Crawford et al. [36][b] (%)	Samuels et al. [37][a] (%)	Torgersen et al. [38][a] (%)	Lenzenweger et al. [39][a] (%)
Personality disorder	31	5.7	15.7	9	13.4	11.02
Paranoid	3.4	0.7	5.1	0.7	2.4	1
Schizoid	3.4	0.8	1.7	0.9	1.7	1
Schizotypal	3.4	0.06	1.1	0.6	0.6	1.6
Narcissistic	3.4	0	2.2	0	0.8	2.7
Antisocial	–	0.6	1.2	4.1	0.7	0.6
Histrionic	–	0	0.9	0.2	2	2.9
Borderline	5.2	0.7	3.9	0.5	0.7	1.3
Obsessive compulsive	6.9	1.9	4.7	–	2	1.3
Passive-aggressive	5.2	0	0	–	1.7	1.6
Dependent	–	0.1	0.8	–	1.5	0.6
Avoidant	–	0.8	6.4	1.8	5	1

KS Klinefelter syndrome

[a] IPDE (International Personality Disorder Examination) was administered to detect Personality Disorders

[b] SCID II was administered to detect Personality Disorders

Table 2 Variables of the KS population divided by presence/absence of personality disorder

	PD+	PD−	*p*
n	18	40	
Age (years)	34.5 ± 11.6	36.6 ± 14.2	n.s.
Testosterone (nmol/mL)	22.19 ± 10.43	17.11 ± 8.5	n.s.

PD+ KS patients with diagnosis of personality disorder, *PD−* KS patients without diagnosis of personality disorder, *n.s.* not significant

pathological MMPI scales (MMPI score) was then correlated to the SPM raw scores. This revealed an inverse relationship, as indicated by the linear regression shown in Fig. 2 ($p = 0.0078$; $r^2 = 0.1603$). The same evaluation performed on the different MMPI scales revealed that only 12 of them significantly correlated with SPM raw scores. The p values and r^2 of the obtained linear regressions are shown in Table 3: two MMPI scales (Dominance and Ego Strength) were directly correlated with SPM raw scores.

We evaluated the possible differences in personality and cognitive abilities in the eugonadal, hypogonadal and treated subgroups. The prevalence of personality disorders was 33.3% in eugonadal, 16.6% in hypogonadal and 36% in treated KS patients. No statistically significant difference was observed for mean age, SPM raw score and MMPI score, as shown in Table 4.

Two statistically significant correlations were found between testosterone serum level and the MMPI scales Re and MDS, but only in the treated group, as shown in Fig. 3.

Discussion

The prevalence of personality disorders in our KS group was higher than in the general population. Although a larger sample is required for more accurate results, this is the first study investigating the prevalence of such disorders in KS subjects.

A study by Skakkebaek et al. in 2013 [40], using the Revised NEO Personality Inventory (NEO PI-R) in a Danish population, found more symptoms of psychological distress, a different personality profile, a significantly higher level of neuroticism and a significantly lower level of extraversion, agreeableness and conscientiousness in 47, XXY subjects. However, this study did not calculate the prevalence of personality disorders.

Four MMPI scales—social responsibility, dominance, Ego Strength and Repression—were altered in more than 40% of our sample. This personality pattern characterizes subjects as undependable, unlikely to take on positions of leadership or responsibility within a group, pessimistic, and rigid in their problem-solving approaches. This kind of patient is more likely to feel helpless, chronic fatigue, withdrawn, confused, impulsive, and aggressive [41].

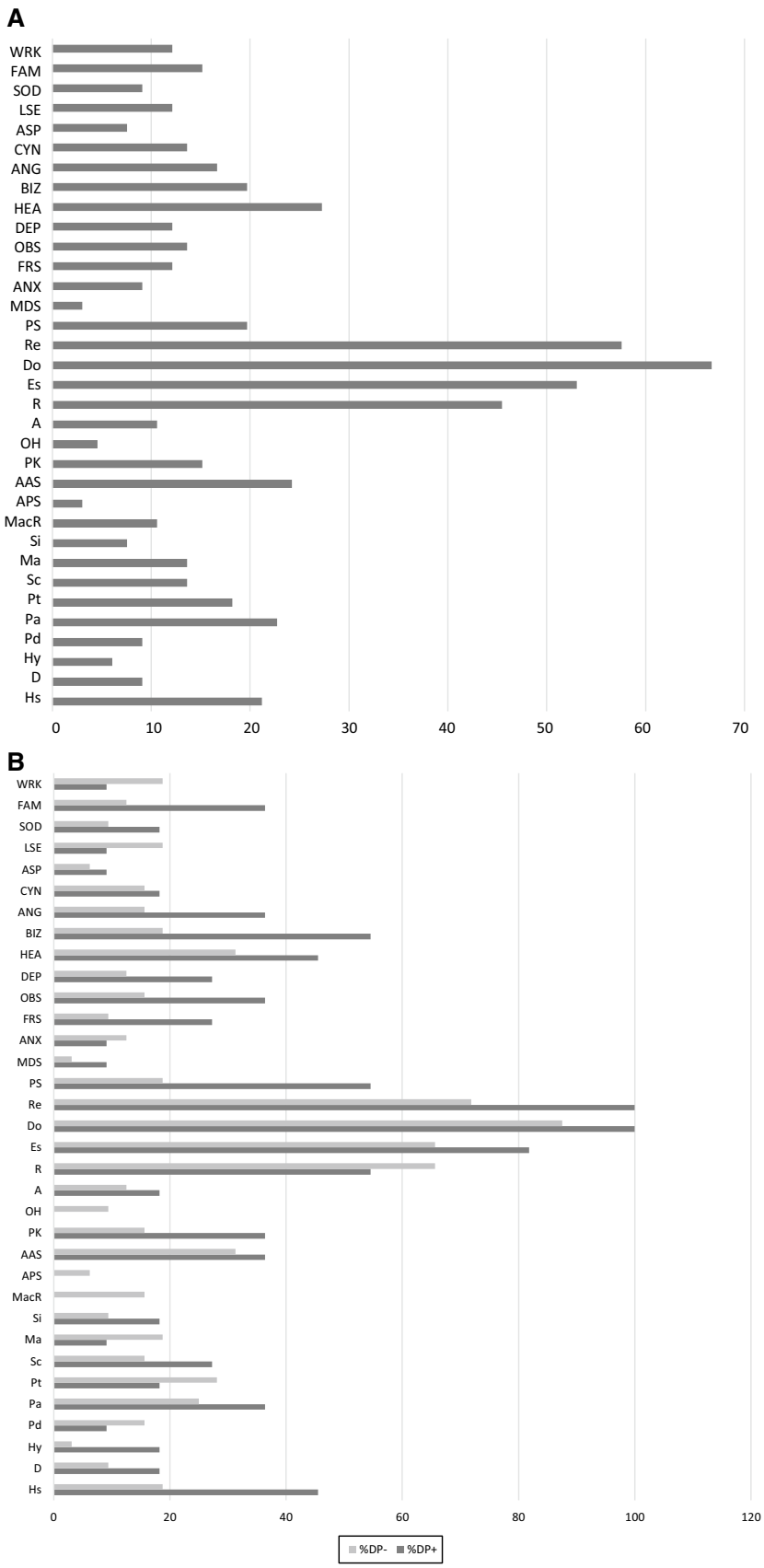

Fig. 1 **a** Percentages of patients with pathological MMPI scores. *Each bar* corresponds to a personality trait detected by MMPI. **b** Percentages of patients with pathological MMPI scores. KS subjects were divided according to the presence or absence of personality disorders, as detected with Structured Clinical Interview for DSM IV axis II disorders (SCID II). Each pair of bars corresponds to a personality trait detected by MMPI. The MMPI handbook sets the modal values as between 41 and 55. Values below 41 and above 55 were therefore considered pathological. *WRT* Work Interference, *FAM* Family Problems, *SOD* Social Discomfort, *LSE* Low Self-Esteems, *ASP* Antisocial Practices, *CYN* Cynicism, *ANG* Anger, *BIZ* Bizarre Meditation, *HEA* Health Concerns, *DEP* Depression, *OBS* Obsessiveness, *FRS* Fears, *ANX* Anxiety, *MDS* Marital Distress scale, *PK/PS* Post-Traumatic Stress Disorder scales, *Re* Social Responsibility, *Do* Dominance, *Es* Ego Strength, *R* Repression, *A* Anxiety, *OH* overcontrolled hostility, *AAS* Addiction Admission scale, *APS* Addiction Potential scale, *MACR* MacAndrew Alcoholism Scale-Revised, *Si* Social Introversion, *Ma* Hypomania, *Sc* Schizophrenia, *PT* Psychasthenia, *Pa* Paranoia, *Pd* Psychopathic Deviate, *Hy* Conversion Hysteria, *D* Depression, *Hs* Hypochondriasis

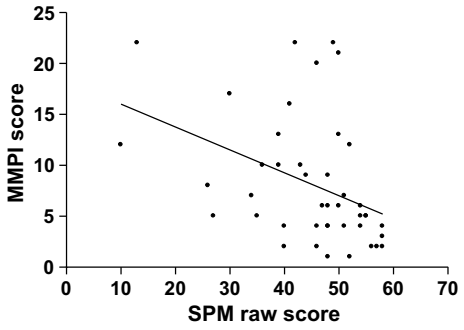

Fig. 2 The figure shows the linear regression between MMPI score and SPM raw score in the whole KS population. $p = 0.0078$; $r^2 = 0.1603$. *MMPI score* number of pathological MMPI scales in each subject, *SPM raw score* Raven's Standard Progressive Matrices raw score in each subject

Table 3 MMPI scales with a statistically significant correlation with SPM raw scores

	r^2	Pearson *r*	*p* value
Hs	0.21	−0.46	0.0017
D	0.14	−0.38	0.0115
Pd	0.18	−0.42	0.0042
Pt	0.25	−0.5	0.0005
Sc	0.16	−0.4	0.0065
MacR	0.15	−0.39	0.0085
Es	0.19	0.44	0.0031
Do	0.13	0.36	0.018
MDS	0.25	−0.5	0.0073
FRS	0.2	−0.45	0.0021
HEA	0.26	−0.51	0.0005
LSE	0.098	−0.31	0.039

Hs Hypochondriasis, *D* Depression, *Pd* Psychopathic Deviate, *Pt* Psychasthenia, *Sc* Schizophrenia, *MacR* MacAndrew Alcoholism Scale-Revised, *Es* Ego Strength, *Do* Dominance, *MDS* Marital Distress scale, *FRS* Fears, *HEA* Health Concerns, *LSE* Low Self-Esteem

A study by Otonicar et al. in 2001 administered MMPI to KS subjects, finding that they had a reduced quality of social life and more schizoid traits.

The descriptions of KS patients suggested by our MMPI results are similar to those in other studies that did not use MMPI to study personality traits. For example, Close [27] affirmed that psychosocial health scores in KS patients indicate adverse quality of life (67%), low self-esteem (38%), poor self-concept (26%), and risk for depression (16%). As expected, our MMPI scales were more often altered in PD+ than in PD− patients.

The association between the presence of personality disorders and both Biz-Odd Thinking and Post-Traumatic Stress Disorder scales suggests that a high score on one of these scales may be a risk factor for the development of personality disorders in KS subjects. This could help detect and prevent any emerging personality disorder prior to its full manifestation.

An overall addiction-prone personality, indicated by high scores in MAC-R Alcoholism—MacAndrew scale, was found only in patients without personality disorders (18%). It is well known that an addiction-prone attitude is more associated with other psychiatric disorders (including personality disorders, especially clusters A and B), but in our sample this trend was not confirmed, probably due to the small sample size.

Our data showed that the majority of KS subjects have a fluid intelligence comparable with that of the general population and that it is possible for them to reach the same educational goals as 46, XY males. Moreover, testosterone is not likely to influence cognitive performances in KS adults.

Although it is evident that intelligence can influence the development of psychopathological traits, there is no evidence that lower intelligence is correlated with the onset of a personality disorder. In 2011, Van Rijn et al. [42] found increased levels of autistic and schizotypal traits in individuals with KS, with schizotypal traits increasing with age.

Table 4 KS population variables by subgroup

	Eugonadal (*n* 21)		Treated (*n* 25)		Hypogonadal (*n* 12)		*p*
	Min–max	Mean ± SD	Min–max	Mean ± SD	Min–max	Mean ± SD	
Testosterone (nmol/mL)	12.3–25.1	17.2 ± 3.5	13.8–47.3	25 ± 10.2	1.2–11.7	7.9 ± 3.8	<0.0001
Replacement therapy (years)	–	–	1.5–28.7	7.8 ± 8.8	–	–	–
Age (years)	18–55.4	28.7 ± 12.3	21.8–63.3	38.9 ± 11.1	19.4–54.9	37 ± 10.7	n.s.
SPM raw score	13–58	45 ± 12	10–58	44 ± 11.4	10–58	44.4 ± 10.4	n.s.
MMPI score	1–25	10 ± 8	1–22	9 ± 6	1–25	8.4 ± 6.4	n.s.
PD prevalence	33.3%		36%		16.7%		n.s.

Eugonadal KS patients with testosterone ≥12 nmol/mL without testosterone treatment, *Treated* KS patients undergoing testosterone replacement therapy, *Hypogonadal* KS patients with testosterone <12 nmol/mL who have never received replacement therapy, *MMPI score* number of pathological MMPI scales in individual subjects, *SPM raw score* Raven's Standard Progressive Matrices raw score in each subject, *MMPI T* mean raw score of individual patients for all scales

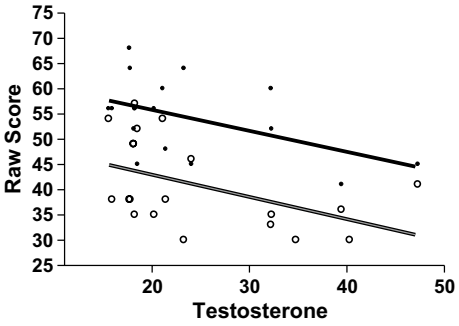

Fig. 3 Re and MDS MMPI scales show a significant inverse correlation with serum testosterone levels in treated KS ($p = 0.0347$ and 0.0468, respectively). *Black points* MDS scores, *empty points* Re scores, *MDS* Marital Distress scale, *Re* Social Responsibility

According to their results, relative deficits in verbal abilities seem more strongly associated with increased autistic traits, whereas relative deficits in visuospatial abilities seem more strongly associated with increased schizotypal traits. Similarly, we found that KS subjects with higher fluid intelligence were more likely to be spontaneous, alert, persistent, self-confident, intelligent and resourceful [41]. These subjects had lower raw scores in five basic MMPI-2 scales (Hypochondriasis, Depression, Psychopathic Deviate, Psychasthenia, Schizophrenia), suggesting that they usually feel healthy, insightful, cheerful and well-identified with social standards and have better impulse control, fewer obsessive–compulsive and schizoid symptoms and a wide range of interests. They also had lower scores in five content and supplementary scales (fear, health concerns, low self-esteem, MacAndrew Alcoholism scale and Marital Distress scale), confirming their more functional and well-developed personality pattern, characterized by fewer phobic and physical symptoms, lower risk for substance addiction and a better relationship with their partner [41]. The correlation between Dominance and Ego Strength scales and SPM raw scores demonstrated that a greater fluid intelligence could improve self-confidence, general adjustment and coping abilities.

Is endogenous testosterone or androgen replacement therapy linked to personality traits and fluid intelligence? The limitation of this study is that a greater sample or a longitudinal perspective is undoubtedly needed to answer this question; however, our data provide an interesting starting point. Even if testosterone does not influence the main variables studied, it is likely to condition some non-secondary life aspects. Like Anne Skakkebæk et al. in 2016, we did not find any statistically significant difference in PD prevalence and cognitive abilities in treated and untreated patients [43]. However, reduced marital distress was observed in KS males under testosterone replacement therapy. This could suggest that testosterone treatment improves physical symptoms and that this effect might also improve relationship abilities and awareness of wellness. According to Kebers [44]: "Testosterone also improves social drive, mood, concentration and ability at work. If KS diagnosis is made at adult age, androgen therapy has also shown some efficacy, though less than if started earlier". Our findings agree with the results obtained by Raboch [45] in 2003. He found that couple sexual activity in KS patients was not related to testosterone serum levels. The improvement in marital life is probably due not just to the increasing frequency/quality of sexual activity, but also to the improvement in wellbeing and relational abilities. However, further studies should be performed to understand this phenomenon.

The strong point of our study is that it provides the first data about the prevalence of personality disorders in a sample of KS subjects. The fluid intelligence of KS subjects was no lower than that of a community sample. This is undoubtedly a starting point to fight against the stigma that continues to consider KS subjects as incapable of achieving high levels of education and individual and social development. Particular attention should be paid to cognitive enhancement during the preschool and school age to support the development of a healthy and well-structured personality.

Clinicians should suggest psychiatric evaluation to KS patients that exhibit Biz-Odd Thinking and Post-Traumatic Stress Disorder symptoms to evaluate the existence of personality disorders. The inclination to alcohol/substance abuse should also be investigated in KS subjects who do not show any personality disorder.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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