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Neuropsychological functions, sleep, and mental health in adults with Klinefelter syndrome

Krister W. Fjermestad[1,2] | Rene Huster[1] | Christina Thunberg[1] | Simen Stokke[2] | Claus H. Gravholt[3] | Anne-Kristin Solbakk[1,4,5,6]

[1]Department of Psychology, University of Oslo, Oslo, Norway

[2]Frambu Resource Centre for Rare Disorders, Siggerud, Norway

[3]Department of Clinical Medicine, rhus University, Aarhus, Denmark

[4]Department of Neurosurgery, Oslo University Hospital, Oslo, Norway

[5]Department of Neuropsychology, Helgeland Hospital, Mosjøen, Norway

[6]RITMO Centre for Interdisciplinary Studies in Rhythm, Time and Motion, University of Oslo, Oslo, Norway

Correspondence
Krister W. Fjermestad, Department of Psychology, University of Oslo, Forskningsveien 3a, 0317 Oslo, Norway.
Email: kristefj@uio.no

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Abstract

A few studies have examined neuropsychological functions, sleep, and mental health combined in Klinefelter syndrome (KS; 47,XXY). We investigated neuropsychological functions with standard tests, sleep with actigraphy, and self-reported mental health in 30 men with KS (Mean age = 36.7 years) compared to 21 controls (Mean age = 36.8 years). Men with KS scored significantly lower on mental speed, attention span, working memory, inhibition, and set-shifting tests, as well as overall IQ (mean effect size difference Cohen's d = 0.79). Men with KS had significantly longer night wakes, with no differences in other sleep variables (mean d = 0.34). Men with KS reported poorer mental health than controls (mean d = 1.16). Regression analyses showed neuropsychological functions explained variance in some sleep domains for men with KS but not for controls. Neuropsychological functions explained variance in some mental health domains for controls. For men with KS, however, verbal IQ was the only significant predictor of mental health. Altogether, men with KS display problems in neuropsychological functions and mental health but do not appear different from controls on most sleep parameters. Our findings indicate that relations between neuropsychological functions, sleep, and mental health differ between men with KS and controls.

KEYWORDS

47,XXY, executive functions, Klinefelter syndrome, mental health, sleep

1 | INTRODUCTION

Klinefelter syndrome (KS) is the most prevalent sex-chromosome disorder (i.e., 47,XXY) in humans, with an estimated prevalence of 1:660 (Bojesen, Juul, & Gravholt, 2003). KS is underdiagnosed. Due to a National Health Registry, Danish researchers estimated that around 25% of men with KS are diagnosed in their lifetime, in most cases as adults (Bojesen, Stochholm, Juul, & Gravholt, 2011). Men with KS have increased risk of several physiological, cognitive, psychological, and socioeconomic challenges compared to controls without KS (Giagulli et al., 2019; Gravholt et al., 2018; Leggett, Jacobs, Nation, Scerif, & Bishop, 2010).

In terms of physiology, hypogonadism (e.g., low testosterone levels) is prevalent for conditions with supernumerary X chromosomes, occurring in up to 85% of postpubertal men with KS (Chang et al., 2015; Smyth & Bremner, 1998). Hypogonadism is due to accelerated testicular failure with low testicular volume and high rates of infertility and leads to sparse body hair growth, increased fat mass, and reduced muscle strength (Aksglaede, Molgaard, Skakkebaek, & Juul, 2008; Ross et al., 2008). Additional physiological challenges

facing men with KS include increased risk of developing metabolic syndrome and/or diabetes Type 2 (Bojesen et al., 2006; Ishikawa, Yamaguchi, Kondo, Takenaka, & Fujisawa, 2008).

In terms of cognitive functioning, full-scale IQ scores are generally within the normal range, with considerable individual variation (Leggett et al., 2010). However, the IQ profile is commonly skewed toward significantly lower verbal IQ relative to performance IQ (Gravholt et al., 2018). Compared to controls, specific cognitive challenges that have been identified more frequently among men with KS include receptive and expressive language abilities (Ross et al., 2012; Ross, Zeger, Kushner, Zinn, & Roeltgen, 2009). The increased prevalence of reading and writing difficulties for men with KS is likely associated with the broader language problems (Boone et al., 2001; Rovet, Netley, Keenan, Bailey, & Stewart, 1996; Stewart, Bailey, Netley, Rovet, & Park, 1986). A specific area of concern among men with KS is problems with executive functions, which refers to cognitive control processes necessary for goal-directed behavior and problem solving (e.g., organization, planning, judgment, decision-making; Gravholt et al., 2018). A common division of core executive functions encompasses three theoretically derived components: Inhibitory control, working memory, and mental set shifting, which are all found to play important roles in learning/memory and educational achievements (e.g., Miyake et al., 2000; Miyake & Friedman, 2012). All are viewed as basic and moderately correlated control functions that are critical for higher-order executive functions. The current study utilized the three-component model, as it seems highly relevant for understanding the cognitive difficulties associated with KS. We also included tests of mental efficiency/speed and attention, because studies have reported that men with KS have problems with these cognitive domains as well (Fales et al., 2003; Kompus et al., 2011; Ross et al., 2008; Temple & Sanfilippo, 2003; van Rijn & Swaab, 2015).

With regard to psychological functioning, men with KS have an increased risk of experiencing general psychological distress, as well as higher prevalence rates of depression, anxiety disorders, attention deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia (Giagulli et al., 2019; Skakkebaek, Wallentin, & Gravholt, 2015). The risk of being admitted to a psychiatric ward has been estimated as 3.65 the risk of the general population (Bojesen, Juul, Birkebaek, & Gravholt, 2006). Up to 45% of KS samples have shown psychotic symptoms (Bruining, Swaab, Kas, & van Engeland, 2009). Depression rates among men with KS have ranged from 19 to 69% (Boks et al., 2007; Turriff, Levy, & Biesecker, 2011).

In terms of socioeconomic functioning, Danish Registry data have shown poorer socioeconomic functioning for men with KS compared to other men, among others via low education and low lifetime income (Skakkebæk et al., 2015). In a larger Australian study of 87 adult males with one or more surplus X chromosomes, 22% reported to be unemployed or on benefit pensions (Herlihy et al., 2011). A Danish registry study showed that the mean retirement age among 903 men with KS was 46 years, compared to 60 years in the control group. Over a third of men with KS were retired, compared to 20% of controls (Bojesen et al., 2011).

Despite the growing documentation of challenges in multiple areas of functioning among men with KS, there are considerable knowledge gaps. Sleep is an area with practically no systematic knowledge regarding men with KS. This is surprising, as many of the documented challenges for men with KS, including neuromuscular problems, endocrinological problems, and low socioeconomic status, are all associated with poor sleep in the general population (Joiner, 2016; Walker & Stickgold, 2005; Walker & van der Helm, 2009). A study of 53 adults with KS showed that these men had considerably poorer self-reported sleep compared to normative data (Fjermestad & Stokke, 2018). Although this finding is concerning, it is important to note that there is considerable evidence of limited overlap between subjectively and objectively measured sleep (Mezick, Wing, & McCaffery, 2014). The overlap may be particularly low, or questionable, for informants with language problems and/or mental health problems, which many men with KS experience. The current study includes sleep measured with actigraphy watches, an objective sleep measure, aiming to enhance the knowledge about sleep in men with KS.

Many studies of men with KS are focused on a narrow set of function domains, leaving limited knowledge about how different functional domains in men with KS affect each other. This is unfortunate, as there are several unanswered questions about the patterns of influence across domains in men with KS (Turriff et al., 2011). A more coherent picture of the functional dependencies of different domains (e.g., sleep, cognition, and mental health) will inform men with KS and the professionals caring for them about how to design and tailor interventions to aid and improve wellbeing. Another issue is the frequent lack of appropriate control groups that too often are constituent of persons with sex chromosome aneuploidies other than 47,XXY. This lack of contextualization with men without KS makes findings difficult to interpret.

In the current study, we compare clinician-rated neuropsychological functioning, objectively measured sleep, and self-reported mental health in adults with KS and controls. We had two research questions. First, are neuropsychological functions, sleep, and mental health poorer for men with KS than for controls? We hypothesized that all three domains would be poorer for men with KS. Second, what are the relations between neuropsychological functions, sleep, and mental health among men with KS? We hypothesized overlap between domains, but explored directions openly given the novelty of this approach.

2 | METHODS

The study was approved by the Regional committees for medical and health research ethics—South-Eastern Norway. All participants provided written informed consent prior to participation. All participants took part in a draw for a universal gift certificate (≈100 USD), one for men with KS and one for controls. Participants were not compensated in other ways, but travel and accommodation costs were covered and food and snacks were served during test days.

2.1 | Sample and recruitment

The KS sample comprised 30 men with KS aged 18–60 years (*M* [mean] age = 36.7 years, *SD* = 10.6). They were recruited from multiple nonclinical settings, that is, the user registry of Frambu resource center for rare disorders, a national (nonclinical) advisory center for rare disorders, the annual Klinefelter syndrome user association meeting, and an online video ad posted on various websites, including the Klinefelter syndrome user association website, and various rare disorders-oriented online forums.

The control sample comprised 21 men without KS aged 18–65 years (*M* age = 36.8 years, *SD* = 14.4). Controls were recruited from multiple settings, that is, ads in local newspapers; an online video ad posted on various websites, including the Klinefelter syndrome user association website and various rare disorders-oriented online forums; and the social network of male KS participants (note that there was only one family relation, i.e., a cousin). See Table 1 for background information on both samples.

2.2 | Procedures

Neuropsychological testing took place at the Department of Psychology at the University of Oslo, Norway. Test administers were a team of clinical-program psychology students trained by a specialist in clinical neuropsychology with >20 years of clinical neuropsychological experience. Participants completed the mental health questionnaire on site. They were given an actigraphy watch toward the end of the test appointment, along with verbal instructions about how to use it.

TABLE 1 Sample characteristics for men with Klinefelter syndrome and controls

Participant characteristics, *N* (%)	KS (*n* = 30)	Controls (*n* = 21)
Highest completed education*		
Primary school	1 (3.3)	0 (0.0)
Secondary school	3 (10.0)	2 (9.5)
High school	20 (66.7)	7 (33.3)
+2-year higher education (e.g., University)	6 (20.0)	12 (57.2)
Vocational status*		
Student	4 (13.3)	1 (4.7)
Working	15 (50.0)	19 (90.6)
On sickness benefits	8 (26.7)	0 (0.0)
Other (e.g., retired, unemployed)	3 (10.0)	1 (4.7)
Marital status		
Single	16 (53.3)	5 (23.8)
Married/cohabiting	12 (40.0)	15 (71.5)
Divorced/separated	2 (6.7)	1 (4.7)

Note: KS, Klinefelter syndrome. *Frequency distribution difference is significant at the $p < .05$ level (chi-square).

The actigraphy watches were returned by regular mail in envelopes with prepaid postage. All participants received a written report summarizing their neuropsychological profile (percentiles), mental health profile, and sleep data. The reports were followed up with a telephone consultation with the PI, who is a Clinical Psychologist. Men with KS who showed elevated mental health scores were assisted with clinical referrals when needed. The current study is part of a larger trial and the neuropsychological data were gathered after participants had been through resting-state structural MR imaging and performed auditive tasks while undergoing electroencephalogram recordings (data not reported here).

2.3 | Measures

2.3.1 | Neuropsychological tests

The neuropsychological test battery comprised tests from the Delis–Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), the Wechsler Adult Intelligence Scale fourth edition (WAIS-IV; Wechsler, 2008), and the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

2.3.2 | Digit span

We used the Digit Span from WAIS-IV to measure auditory attention span and working memory capacity. The participant listens while the test administrator reads a series of digits aloud; the first set starting with only two digits. Two lists are presented at each set size. If the participant accurately reproduces at least one digit list, then the set size is increased by one digit. Testing terminates when the participant fails to reproduce both digit lists in a set. We ran all three conditions of the Digit Span task, that is, forward span (e.g., 4–2-6 repeated as 4–2-6), backward span (e.g., 4–2-6 repeated as 6–2-4), and sequencing, in which the participant is to repeat the digits in increasing order (e.g., 4–2-6 repeated as 2–4-6). The backward and sequencing conditions place concurrent demands on short-term memory storage and manipulation of information with increasing working memory load. The three tasks are scored separately and combined to a total score.

2.3.3 | Trail making test

We used three conditions of the Trail Making Test (TMT) to measure processing speed and cognitive set-shifting (Delis et al., 2001). The participant is instructed to draw a line between circles containing numbers and letters distributed across an A3-sized sheet of paper, as quickly as possible without lifting the pencil from the paper. In the Number Sequencing condition (TMT-2), the participant is to draw the line from the lowest to the highest number (1–16), ignoring letters. The Letter Sequencing condition (TMT-3) requires the participant to

draw the line from the first to the last letter in alphabetical order (A–P), ignoring numbers. The Number–Letter Switching condition (TMT-4) requires cognitive set shifting in addition to processing speed. It follows the same principles as the Number and Letter Sequencing conditions (TMT-2 and 3), but the participant is now to draw lines to connect the circles in an ascending pattern alternating between the numbers and letters (i.e., 1-A-2-B-3-C and so on). Time in seconds is recorded, but there is no maximum time limit. If the participant makes a mistake, the test administrator points out the mistake and the participant is allowed to correct the mistake and continue without stopping time taking.

2.3.4 | Color–word interference test

The Color–Word Interference Test (CWIT) was employed to measure processing speed, inhibitory control, and set-shifting (Delis et al., 2001). It contains four conditions with different demands on executive control. In the Color Naming condition (CWIT-1) the participant is to name different color patches, whereas the Word Reading condition (CWIT-2) requires reading words in black ink that denote colors. Color Naming and Word Reading (CWIT-1 and 2) are believed to index language-mediated processing speed that is demanded for the following conditions placing additional demands on cognitive control processes. The subsequent Inhibition condition (CWIT-3), which is an extension of the classic Stroop test (Stroop, 1935), measures interference control and response inhibition. Finally, the Inhibition/Switching condition (CWIT-4) has the added requirement of set shifting. As in the Inhibition condition (CWIT-3), color words are printed in an inconsistent color ink, and some of the color words are boxed in. The participant is instructed to name the color of the ink instead of reading the word if the word is not boxed in, but to read the word instead of name the color of the ink if the word is boxed in (i.e., alternating between two task rules). All four task conditions are timed and the participant is instructed to work as fast as possible without making mistakes. Task completion time in seconds, as well as the number of errors, is recorded.

2.3.5 | General intellectual function

We employed the WASI (Wechsler, 1999) to estimate general intellectual function (McCrimmon & Smith, 2012). Two tests are used to calculate verbal IQ. The Vocabulary test is an index of word knowledge and concept formation. The participant is instructed to explain the meaning of words, and the responses are scored 0, 1, or 2, based on their accuracy. Testing is discontinued after five consecutive 0-point answers. The Similarities test measures verbal reasoning and concept formation. The participant is asked to explain how two words representing common objects or concepts are similar. The words are presented orally. The responses are scored 0, 1, or 2, based on accuracy. The test administrator stops after four consecutive 0-point answers.

Scores on two tests are used to calculate Performance IQ. Block design measures the ability to analyze and organize abstract visual stimuli as well as nonverbal concept formation. It comprises 13 subtasks in which the participant is to recreate two-dimensional designs from a stimulus booklet using the top of 4–9 cubes with red and white patterns. Each attempt is scored based on completion time and accuracy. Test administration stops after three consecutive failures.

Matrix Reasoning measures perceptual analysis/organization and abstract reasoning skills for visual stimuli. The task comprises 30 visually depicted incomplete matrices in a stimulus booklet. The participant is to choose from one of five options at the bottom of the stimulus booklet that in his/her opinion best completes the matrix. Responses are scored 0 and 1, and test administration stops after four consecutive errors or four 0-point answers among five consecutive subtasks.

2.3.6 | Sleep assessment

We assessed sleep and circadian rhythm with an actigraph, a device used to measure and record motion over a period of time. The actigraph (Actiwatch Spectrum Plus, Phillips, the Netherlands) is integrated into a small wristwatch. The actigraphy raw data are reviewed and predefined algorithms are used to analyze the recorded data. Actigraphy is commonly used to predict sleep/wake patterns and circadian rhythms based on periods of activity versus inactivity, and light measurements. Compared to polysomnography, actigraphy can measure sleep over an extended period of time in the persons's normal environment. Participants wore the actigraphy watch for 7 consecutive days and nights following the neuropsychological testing day. All took part on a Saturday or Sunday, so the 7-day/night sleep registration was either Sun–Sat or Mon–Sun. In the current study, we used actigraphy-generated data for the mean over those 7 days and nights on eight sleep domains: (a) time getting out of bed, measured as the time (hh:mm) the person rises from the bed in the morning; (b) time going to bed, measured as the time (hh:mm) the person tucks into bed at night; (c) time in bed, measured as the number of hours the person spent in bed each night; (d) wait time before sleep, measured as the number of minutes the person lay in bed awake between going to bed and falling asleep; (e) sleep duration, measured as the number of hours spent in bed sleeping; (f) number of night wakes, measured as the number of the times the person woke during the night; (g) duration of night wakes, measured as the combined duration of the wakes after sleep onset in minutes; and (i) sleep efficiency, measured as the percentage of time spent in bed used for sleep (sleep duration/time in bed).

2.3.7 | Mental health

We used the Hopkins Symptom Checklist-90-Revised (SCL-90-R; Derogatis, 1994) as a screening measure of mental health. The SCL-90-R is a 90-item self-report questionnaire where items describing

various mental health symptoms experienced during the last 7 days are rated 0 (not at all) to 4 (very much). The SCL-90-R comprises a global severity index as well as nine subscale scores (i.e., somatization; obsessive–compulsive symptoms; interpersonal sensitivity, depression, anxiety; hostility; phobic anxiety; paranoid ideation; and psychoticism). The SCL-90-R has documented psychometric properties and is widely used in adult mental health services (Siqveland & Leiknes, 2016). In the current sample, internal consistency (Cronbach's α) was excellent for men with KS (α = .97) and controls (α = .92).

2.4 | Data analytic plan

In addition to descriptive analyses, we ran independent samples *t*-tests to examine if variables related to cognitive functions, sleep, and mental health were different between men with KS and controls. We investigated potential differences in subdomains of IQ in men with KS with paired samples *t*-tests Effect size differences were calculated as Cohen's *d* using the formula $(M_{Group1} - M_{Group2})/SD_{pooled}$ (Cohen, 1992). We interpreted effect sizes using the following criteria: Small effect $0.2 \leq d < 0.5$, medium: $0.5 \leq d < 0.8$, large: $d \geq 0.8$ (Cohen, 1988). To examine how much variance cognitive functions explained in sleep and mental health, we ran separate multiple regression models using the enter method (Jaccard, Guliamo-Ramos, Johanson, & Bouris, 2006). One model was run for each of the main neuropsychological function domains (i.e., mental efficiency/speed, attention/working memory, inhibition/set-shifting), all controlled for verbal and performance IQ. Across variables, the average amount of missing data were 3.7%. Little's MCAR test showed data were missing completely at random (Little, 1988). Most missing data were due to participants who could not complete the CWIT due to being colorblind (*n* = 3, 5.6%). Missing data were deleted listwise. Variables were mostly normally distributed (i.e., no skewness values >1.841; no kurtosis values >2.899). The SCL-90 scale psychotic ideation was not normally distributed (skewness = 2.340; kurtosis = 6.381). Four of the men with KS had total IQ scores <70 (of which one had performance IQ > 70). These were included in analyses to give the most representative picture of intellectual functioning in men with KS. However, all regression and comparison analyses were repeated excluding these four men, and these results are specified below. We did all analyses with IBM Statistics SPSS 26.0.

3 | RESULTS

3.1 | Baseline characteristics

See Table 1 for baseline characteristics for the men with KS and controls, including differences between the samples. Controls had significantly higher education, and more were working, compared to men with KS. Among men with KS, the mean age of being diagnosed was 29.5 years (*SD* = 11.8, range 4–52 years). All participants with KS except two (93.3%) reported current testosterone treatment, with the average age of testosterone treatment onset reported being 27.6 years (*SD* = 12.6, range 11–56 years). The late-onset probably reflects the age of KS diagnosis. About half the KS sample self-reported reading and/or writing difficulties (46.7%).

3.2 | Group differences in cognitive functions

In terms of information processing speed, men with KS scored significantly lower than controls on all measures, and irrespective of oral (CWIT) or manual (TMT) output (Figure 1 for an overview of cognitive function *T*-scores for men with KS and controls). With regard to attention span and working memory, they had significantly poorer performance on both Digit Span forward and backward but not on the Sequencing condition. The total Digit Span score differed significantly between the groups. Moreover, men with KS scored significantly inferior to controls on the Inhibition condition (both completion time and errors), as well as the Inhibition/Switching condition (completion time only) of the CWIT. The second measure of set-shifting, that is, Number/Letter Switching (TMT-4), also significantly distinguished the groups. Notably, the mean scores of the group with KS fell, with few exceptions, within 1 *SD* from the means of the control group. In terms of group means on the neuropsychological tests (disregarding overall IQ), all were below the normative means (*T* = 50) but well within the normal variation (all test *T*-scores were between 41 and 48).

In terms of general intellectual functioning, total, verbal, and performance IQ scores for men with KS were significantly below those of controls. Mean total IQ was 98.0 for men with KS (*SD* = 14.6) and 115.8 for controls (*SD* = 11.8). Mean verbal IQ was 92.2 for men with KS (*SD* = 15.9) and 114.0 for controls (*SD* = 11.6), whereas mean performance IQ was 104.9 for men with KS (*SD* = 14.6) and 114.3 for controls (*SD* = 12.7) (Table 2). Within the KS sample, verbal IQ was significantly lower than performance IQ (effect size difference *d* = 0.83).

3.3 | Group differences in sleep domains

Men with KS had significantly longer night wakes than controls (Tables 2 and 3). There were no other significant differences in any of the other sleep variables. The pattern was the same when we excluded males with KS with IQ scores <70.

3.4 | Group differences in mental health domains

Men with KS reported significantly higher levels of mental health problems on the SCL-90 Global Severity Index and all SCL-90-R subscales compared to controls (Figure 2; Table 2). The pattern was the same when we excluded participants with IQ scores <70. The highest scores for men with KS were on the domains somatization, obsessive–compulsive symptoms, and anxiety, which also

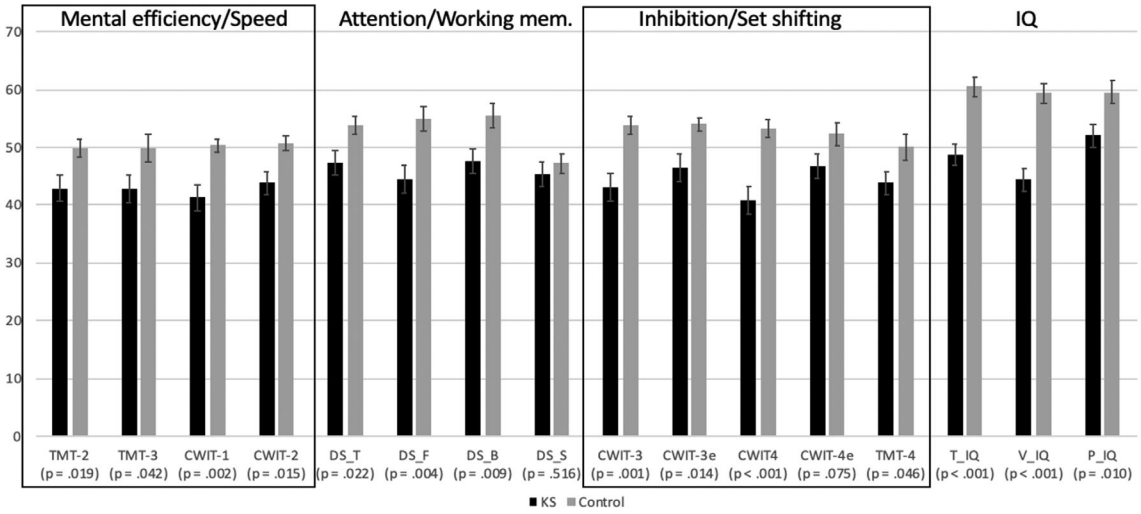

FIGURE 1 Neuropsychological functions in 30 men with Klinefelter syndrome (KS) compared to 21 controls. Age-corrected *T*-scores are reported. Abbreviations: Mem, memory; TMT, trail making test; CWIT, color–word interference test; DS, digit span; T, total; F, forwards; B, backwards; S, sequencing; e, mistakes; V, verbal; P, performance; IQ, intelligence quotient

represent the areas with the largest difference compared to controls.

3.5 | Executive functions and sleep

We ran a series of multiple regression models to examine if the neuropsychological function domains (i.e., mental efficiency/speed, attention/working memory, inhibition/set-shifting, verbal/performance IQ) explained variance in any of the eight actigraphy-measured sleep domains. For the complete group of men with KS, neuropsychological functions significantly predicted two sleep domains. First, the model for working memory significantly explained 24.7% of the variance in time getting to bed (F = 3.053, p = .039). Second, the model for inhibition/set-shifting significantly explained variance in wait before sleep (min). This model explained 26.7% of the variance (F = 2.820, p = .044), with Inhibition (CWIT-3) and Number/Letter Switching (TMT-4) as significant predictors. See Tables S1 and S2 in for the regression models predicting time getting to bed and wait time before sleep for the complete KS group.

For males with KS who had IQ scores >70, neuropsychological functions significantly explained variance in two sleep domains. As for the complete KS group, the model for inhibition/set-shifting significantly explained variance in wait before sleep (min). This model explained 33.6% of the variance (F = 3.225, p = .031), with Inhibition (CWIT-3) and Number/Letter Switching (TMT-4) as significant predictors. The model for inhibition/set-shifting also significantly explained variance in the duration of the night wakes (min). This model explained 30.0% of the variance (F = 2.882, p = .046), with Inhibition (CWIT-3) mistakes as a significant predictor. See Tables S3 and S4 in for the regression models predicting wait time before sleep and duration of the night wakes for the men with KS who had IQ > 70.

For controls, none of the neuropsychological functioning domains explained variance in any of the sleep domains (data not shown).

3.6 | Executive functions and mental health

We ran a series of multiple regression models to examine if the neuropsychological function domains (i.e., mental efficiency/speed, attention/working memory, inhibition/set-shifting, verbal/performance IQ) explained variance in self-reported mental health. For the complete KS group, the only significant model predicting the mental health global severity index was for IQ. The total IQ model explained 22.8% (adj. r^2) of the variance in mental health global severity index (F = 4.839, p = .017), with verbal IQ as the only significant predictor (p = .005). The pattern was the same when we ran the models for mental health global severity index for men with KS who had IQ scores >70 only (i.e., the IQ model was the only significant model with verbal IQ as the only significant predictor). In terms of the mental health subscales, the same pattern (i.e., verbal IQ significantly explaining variance) held for phobic anxiety, hostility, interpersonal sensitivity, depression, and anxiety (all p < .045). See Table S5 for the regression model predicting mental health global severity index for the complete KS group.

For controls, the model for mental efficiency/speed explained 36.3% of the variance in mental health global severity index (F = 3.560, p = .033), with Number Sequencing (TMT-2) and Inhibition (CWIT-3) as significant predictors (p = .017 and .019, respectively). The models for the three remaining neuropsychological functioning domains were non-significant. In terms of mental health subscales, the same pattern (i.e., mental efficiency/speed significantly explaining variance) held for depression, paranoid thinking, interpersonal sensitivity, and obsessive–compulsive symptoms (all p < .049). See Table S6 for the regression model predicting mental health global severity index for controls.

TABLE 2 Effect size (*d*) differences in neuropsychological functions, sleep, and self-reported psychological health between 30 men with Klinefelter syndrome and 21 controls

Domain	*d*
Neuropsychological functions	0.79
Mental efficiency/speed	0.84
Number sequencing	0.73
Letter sequencing	0.81
Color naming	1.04
Word reading	0.79
Attention/working memory	0.66
Digit span total	0.70
Digit span forward	0.92
Digit span backward	0.80
Digit span sequencing	0.20
Inhibition/set-shifting	0.87
Inhibition	1.08
Inhibition mistakes	0.81
Inhibition/switching	1.29
Inhibition/switching mistakes	0.56
Number/letter switching	0.60
Total IQ	1.35
Verbal IQ	1.62
Performance IQ	0.80
Sleep	0.34
Time getting out of bed	0.33
Time going to sleep	0.00
Time in bed	0.36
Wait time before sleep	0.11
Sleep duration	0.25
Number of night wakes	0.56
Duration of night wakes	0.78
Sleep efficiency	0.34
Mental health	1.16
Global severity index	1.44
Somatization	1.69
Obsessive–compulsive	1.58
Interpersonal sensitivity	0.89
Depression	0.96
Anxiety	1.47
Hostility	1.04
Phobic anxiety	1.17
Paranoid ideation	0.72
Psychoticism	0.68

TABLE 3 Mean scores of actigraphy-measured sleep domains in 30 men with Klinefelter syndrome (KS) compared to 21 controls

Sleep domain	KS	Controls	*p*-value
Time getting out of bed	08:30 a.m.	08:00 a.m.	.298
Time going to sleep	00:00 a.m.	00:00 a.m.	.965
Time in bed (hr)	8.7 (1.2)	8.3 (1.0)	.177
Wait time before sleep (min)	34.5 (30.7)	31.7 (20.4)	.735
Sleep duration (hr)	6.9 (0.9)	6.7 (0.7)	.429
Number of night wakes	41.0 (10.8)	35.4 (9.0)	.073
Duration of night wakes	50.1 (18.2)	37.4 (14.3)	.015
Sleep efficiency (%)	79.3 (8.3)	81.2 (6.3)	.278

4 | DISCUSSION

We examined neuropsychological function, sleep, and mental health, as well as the relations between these domains, in men with KS compared to controls. Men with KS had lower scores on tests of general intellectual function, mental speed, and executive functions. They also reported poorer mental health than controls, but there were no differences between the groups on seven out of eight sleep domains measured with actigraphy. We found significant associations between neuropsychological functions and sleep for men with KS, however, no such associations were observed for controls. Conversely, there were significant associations between neuropsychological functions and mental health for controls. However, verbal IQ was the only neuropsychological predictor of mental health for men with KS. Altogether, the associations between neuropsychological functions, sleep, and mental health appear to differ between men with KS and controls.

Men with KS scored poorer than controls across several of the tested neuropsychological domains, including information processing speed, auditory attention span, and the key executive functions working memory (one out of two tests), interference control/inhibition, and set-shifting. The mean scores were, with a few exceptions, not larger than 1 *SD* from the normative mean. The findings are in line with previous studies (e.g., Kompus et al., 2011; Ross et al., 2008; van Rijn & Swaab, 2015). The overall effect size differences were borderline medium to large. In terms of overall IQ, the effect size difference between the samples was large, however, with a particularly large discrepancy for verbal IQ. This finding concurs with previous studies, but the 17-point difference in mean total IQ points between men with KS and controls in our sample is more pronounced than the average finding of a 10-point difference across studies (Gravholt et al., 2018). It is important to note that the men with KS in our sample had a total IQ close to the population average of 100, and performance IQ slightly above average. The latter finding indicates that nonverbal analysis and reasoning abilities are not impacted in our KS sample. Taken together, our results align with existing evidence demonstrating that adult men with KS have lower results than controls in several neuropsychological domains, including verbal IQ, despite close to average total and performance IQ. It is important to note, however, that the controls in the current study were in the upper range on many domains, and that men with KS, although they scored lower than controls, were within the normal range on many tests. The large difference between verbal and performance IQ for the KS group is also important to note. There is accumulating evidence that the typical gap between verbal and

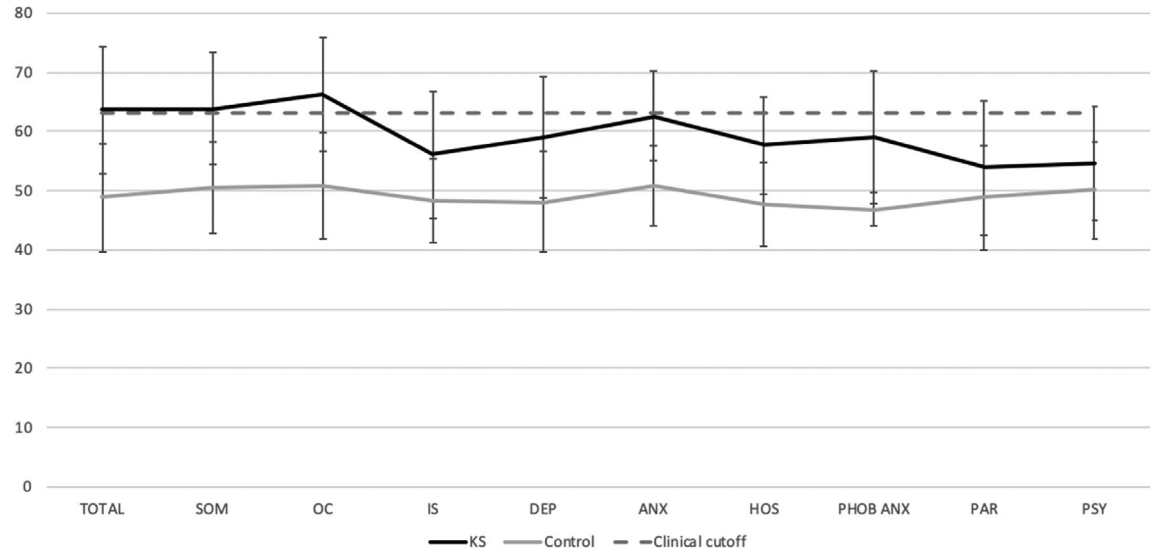

FIGURE 2 Mental health scores in 30 men with Klinefelter Syndrome (KS) compared to 21 controls. Age- and sex-corrected *T*-scores are reported. Clinical cut-off is $T \geq 63$. Abbreviations: SOM, somatization; OC, obsessive–compulsive; I-S, interpersonal sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHOB ANX, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism

performance IQ observed in the KS population emerges in childhood, and that the difference sometimes disappears in adulthood (Gravholt et al., 2018). In our sample, there was a significant difference in adults with KS, indicating specific language problems.

A novel aspect of the current study was the inclusion of objectively measured sleep over 7 consecutive days. We found no difference between men with KS and controls on any sleep domain, except the duration of the night wakes. This is in contrast to a previous study showing that men with KS self-reported poorer sleep than male controls (Fjermestad & Stokke, 2018). Generally, studies tend to find limited overlap between subjectively and objectively measured sleep (Mezick et al., 2014). Our findings may reflect that although men with KS *think* they sleep poorer than other men, whereas objective data does not corroborate their subjective experience. However, it may also be that the subjective experience of sleep is different for men with KS. It is also important to note that all males with KS, except two, in the current study received testosterone supplementation, which positively impacts sleep, reducing sleep length and improving quality of sleep (Shigehara et al., 2018). Note, however, that a recent review found little evidence that testosterone positively impacts cognitive functions in men (Buskbjerg, Gravholt, Dalby, Amidi, & Zachariae, 2019). Previous studies have demonstrated increased negative effect and neuroticism traits among men with KS (Skakkebæk et al., 2017, 2018a, 2018b). Thus, their subjective experience of sleep may be negatively biased due to their general outlook on life. It may also be the case that KS-related issues like pain and aches, as well as work and finance-related worries, influence the subjective experience of sleep, while we could not demonstrate this through objective sleep measures. The discrepancy between subjective and objective findings regarding sleep among men with KS, as well as the finding of objectively longer nightly wakes for men with KS, warrant further study of both objectively and subjectively measured sleep for this group.

In terms of self-reported mental health, men with KS had significantly elevated scores on all domains compared to controls, with large effect sizes in all domains except the two most severe (paranoid ideation and psychoticism), on which effect size differences were low. Previous research has demonstrated an increased prevalence of also the most severe mental health problems, for example, psychosis (Bojesen, Kristensen, et al., 2006; Bruining et al., 2009). Although the symptom levels on these severe mental health problems were higher than controls also for the current sample, it is important to note that the largest effect size differences were identified for somatization, obsessive–compulsive symptoms, and anxiety. The mental health global severity index, as well as subscales somatization, and obsessive–compulsive symptoms were above clinical cutoff. This provides direction for health professionals in which mental health problems are most essential to target. It is important to note that the SCL-90-R obsessive–compulsive subscale indicates concentration and memory problems along with compensatory behavioral strategies (e.g., controlling own work/doing things slowly to ensure correctness) more than typical obsessive–compulsive traits, and that it has been found to reflect subjectively experienced cognitive difficulties (Siqveland & Leiknes, 2016). The SCL-90 obsessive compulsive scale has been found to poorly predict obsessive–compulsive behaviors and to overlap more with general anxiety (Woody, Steketee, & Chambless, 1995). It is also important to note that the high scores on the somatization scale may reflect KS-related physical issues and not psychosomatic difficulties. Our findings regarding mental health largely align with previous studies (Skakkebæk et al., 2015), and it seems clear that mental health problems in men with KS is an area in urgent need of tailored intervention. Currently, no such intervention programs have been published, but future intervention schemes should focus on this and other related issues.

An important feature of the current study was that we examined several domains of functioning within the same sample of men with KS. Interestingly, the patterns of how neuropsychological functions explained variance in sleep and mental health were different between men with KS and controls. Whereas there were several significant links between neuropsychological functions and sleep domains for men with KS, no such associations were found among controls. In contrast, there were associations between neuropsychological functions and mental health for controls, whereas verbal IQ was the only significant predictor of mental health for men with KS. A previous study that examined relations between neuropsychological function and other domains in men with KS (self-reported), social skills were found to be associated with executive functions (Skakkebæk et al., 2017). Another study of the same KS sample found that the personality trait neuroticism, which is typically inter-related with depression and anxiety, was associated with attention switching, which is an important aspect of executive function (Skakkebæk, Moore, Pedersen, et al., 2018). However, that study used self-reported attention switching and personality measures, so common-rater variance would be likely to enhance the overlap (Shirk, Reyes, & Cristotomo, 2013). It is nevertheless puzzling that we found so few associations between neuropsychological functions and mental health among men with KS. Although the small sample size of 30 men with KS may have left us underpowered to detect effects, the fact that there were significant associations between neuropsychological functions and mental health domains in our even smaller control group of 21 men leaves an open remaining question about why these associations are different between the groups.

The current study has limitations. The sample size is small, which is a common problem for rarely diagnosed disorders such as KS. A major limitation is that the control sample had higher education and a larger percentage was working. Although this does limit the validity of our comparison, it does also reflect the reality of the difference between men with KS and their same-age peers (Skakkebaek et al., 2015). An additional limitation concerns recruitment. Although recruitment from nonclinical settings has potential advantages in terms of representativeness of less severe cases, being the member of a patient advocacy user group and/or being registered at a specialist resource center for rare disorders may represent other forms of ascertainment bias. Another limitation is that we only used a self-reported measure of mental health. A previous study found that the personality trait neuroticism was the main predictor of depression and anxiety in men with KS, and that this pattern was not evident for controls (Skakkebæk et al., 2018). Therefore, negative personality bias may have influenced our mental health results. The inclusion of personality variables may have added to the interpretability of our results. We also lack information concerning the use of medications for mental health and/or sleep problems among our participants. In addition to potentially influencing results, medication use may also have been different between the groups, and such information should be included in future studies.

The use of actigraphy measures provided novel information about sleep domains for men with KS. In particular, the objectivity of this sleep measure represents an important advantage given the potential self-report problems for men with KS due to language problems. However, there are also limitations with the use of actigraphy, compared to even more advanced objective sleep measures such as polysomnography. For instance, actigraphy cannot be used to measure sleep stages, which would provide important information regarding sleep disturbance (Smith et al., 2018). That being said, the use of actigraphy provides insights into "everyday life" sleep patterns while being cost-effective. There is no need for participants to travel, and the only costs involved are personnel costs in calibrating the watches and extracting data. The current study shows using actigraphy is feasible when studying men with KS. Future studies should consider longer registration periods (e.g., 14 days) to obtain an even broader assessment.

The main practice implications from the current article are: (a) Health professionals should assess neuropsychological functioning and mental health in men with KS, or refer men with KS to such services. A thorough case-based neuropsychiatric profile is essential to tailor current and future care plans, given the multiple challenges experienced by men with KS (Gravholt et al., 2018). (b) When assessing sleep in men with KS, which should be done due to previous evidence of poor subjective sleep (Fjermestad & Stokke, 2018), and general documentation of the importance of sleep quality for other areas of functioning (Joiner, 2016), it seems important that professionals add an objective sleep measure if possible. There are several sleep registration apps available that will provide some frame of reference for objective sleep, if actigraphy equipment is not an option. Objectively measuring sleep is important because men with KS may subjectively report poorer sleep than what is evident from the objective measures. Thus, a (potential) discrepancy can be used in clinical consultations to address sleep expectations, beliefs, and habits. (c) As there may be associations between neuropsychological functions, sleep, and mental health for men with KS at the group level, and of course for the individual with KS, it is extremely important that health services are not compartmentalized but coordinated as well as target the many domains that add up to determine overall functioning and quality of life functioning for men with KS.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Krister W. Fjermestad https://orcid.org/0000-0001-7501-0033

REFERENCES

Aksglaede, L., Molgaard, C., Skakkebaek, N. E., & Juul, A. (2008). Normal bone mineral content but unfavourable muscle/fat ratio in Klinefelter syndrome. *Archives of Disease in Childhood*, *93*(1), 30–34. https://doi.org/10.1136/adc.2007.120675

Bojesen, A., Juul, S., Birkebaek, N. H., & Gravholt, C. H. (2006). Morbidity in Klinefelter syndrome: A Danish register study based on hospital discharge diagnoses. *The Journal of Clinical Endocrinology and Metabolism*, *91*(4), 1254–1260. https://doi.org/10.1210/jc.2005-069

Bojesen, A., Juul, S., & Gravholt, C. H. (2003). Prenatal and postnatal prevalence of Klinefelter syndrome: A national registry study. *The Journal of Clinical Endocrinology and Metabolism*, *88*(2), 622–626. https://doi.org/10.1210/jc.2002-021491

Bojesen, A., Kristensen, K., Birkebaek, N. H., Fedder, J., Mosekilde, L., Bennett, P., … Gravholt, C. H. (2006). The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care*, *29*(7), 1591–1598. https://doi.org/10.2337/dc06-0145

Bojesen, A., Stochholm, K., Juul, S., & Gravholt, C. H. (2011). Socioeconomic trajectories affect mortality in Klinefelter syndrome. *The Journal of Clinical Endocrinology and Metabolism*, *96*(7), 2098–2104. https://doi.org/10.1210/jc.2011-0367

Boks, M. P., de Vette, M. H., Sommer, I. E., van Rijn, S., Giltay, J. C., Swaab, H., & Kahn, R. S. (2007). Psychiatric morbidity and X-chromosomal origin in a Klinefelter sample. *Schizophrenia Research*, *93*(1–3), 399–402. https://doi.org/10.1016/j.schres.2007.03.015

Boone, K. B., Swerdloff, R. S., Miller, B. L., Geschwind, D. H., Razani, J., Lee, A., … Paul, L. (2001). Neuropsychological profiles of adults with Klinefelter syndrome. *Journal of the International Neuropsychological Society*, *7*(4), 446–456. https://doi.org/10.1017/s1355617701744013

Bruining, H., Swaab, H., Kas, M., & van Engeland, H. (2009). Psychiatric characteristics in a self-selected sample of boys with Klinefelter syndrome. *Pediatrics*, *123*(5), e865–e870. https://doi.org/10.1542/peds.2008-1954

Buskbjerg, C. R., Gravholt, C. H., Dalby, H. R., Amidi, A., & Zachariae, R. (2019). Testosterone supplementation and cognitive functioning in men—A systematic review and meta-analysis. *Journal of the Endocrine Society*, *3*(8), 1465–1484. https://doi.org/10.1210/js.2019-00119

Chang, S., Skakkebæk, A., Trolle, C., Bojesen, A., Hertz, J. M., Cohen, A., … Gravholt, C. H. (2015). Anthropometry in Klinefelter syndrome—multifactorial influences due to CAG length, testosterone treatment and possibly intrauterine hypogonadism. *The Journal of Clinical Endocrinology and Metabolism*, *100*(3), E508–E517. https://doi.org/10.1210/jc.2014-2834

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, New Jersey: Erlbaum.

Cohen, J. (1992). A power primer. *Psychological Bulletin*, *112*(1), 155–159. https://doi.org/10.1037//0033-2909.112.1.155

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). Delis-Kaplan executive function system (D–KEFS) [Database record]. APA PsycTests. Retrieved from https://doi.org/10.1037/t15082-000

Derogatis, L. (1994). *Symptom checklist 90-R: administration, scoring and procedures manual*. Minneapolis, MN: National Computer Systems.

Fales, C. L., Knowlton, B. J., Holyoak, K. J., Geschwind, D. H., Swerdloff, R. S., & Gonzalo, I. G. (2003). Working memory and relational reasoning in Klinefelter syndrome. *Journal of the International Neuropsychological Society*, *9*(6), 839–846. https://doi.org/10.1017/S1355617703960036

Fjermestad, K. W., & Stokke, S. (2018). Sleep problems and life satisfaction as predictors of health in men with sex chromosome aneuploidies. *Behavioral Medicine*, *44*(2), 116–122. https://doi.org/10.1080/08964289.2017.1282852

Giagulli, V. A., Campone, B., Castellana, M., Salzano, C., Fisher, A. D., de Angelis, C., … Klinefelter Italian Group King. (2019). Neuropsychiatric aspects in men with Klinefelter syndrome. *Endocrine, Metabolic & Immune Disorders Drug Targets*, *19*(2), 109–115. https://doi.org/10.2174/1871530318666180703160250

Gravholt, C. H., Chang, S., Wallentin, M., Fedder, J., Moore, P., & Skakkebæk, A. (2018). Klinefelter syndrome: Integrating genetics, neuropsychology, and endocrinology. *Endocrine Reviews*, *39*(4), 389–423. https://doi.org/10.1210/er.2017-00212

Herlihy, A. S., McLachlan, R. I., Gillam, L., Cock, M. L., Collins, V., & Halliday, J. L. (2011). The psychosocial impact of Klinefelter syndrome and factors influencing quality of life. *Genetics in Medicine*, *13*(7), 632–642. https://doi.org/10.1097/GIM.0b013e3182136d19

Ishikawa, T., Yamaguchi, K., Kondo, Y., Takenaka, A., & Fujisawa, M. (2008). Metabolic syndrome in men with Klinefelter's syndrome. *Urology*, *71*(6), 1109–1113. https://doi.org/10.1016/j.urology.2008.01.051

Jaccard, J., Guliamo-Ramos, V., Johanson, M., & Bouris, A. (2006). Multiple regression analyses in clinical child and adolescent psychology. *Journal of Clinical Child and Adolescent Psychology*, *35*, 456–479. https://doi.org/10.1207/s15374424jccp3503_11

Joiner, W. J. (2016). Unraveling the evolutionary determinants of sleep. *Current Biology*, *26*(20), R1073–R1087. https://doi.org/10.1016/j.cub.2016.08.068

Kompus, K., Westerhausen, R., Nilsson, L. G., Hugdahl, K., Jongstra, S., Berglund, A., … Savic, I. (2011). Deficits in inhibitory executive functions in Klinefelter (47, XXY) syndrome. *Psychiatry Research*, *189*(1), 135–140. https://doi.org/10.1016/j.psychres.2011.02.028

Leggett, V., Jacobs, P., Nation, K., Scerif, G., & Bishop, D. V. (2010). Neurocognitive outcomes of individuals with a sex chromosome trisomy: XXX, XYY, or XXY: A systematic review. *Developmental Medicine and Child Neurology*, *52*(2), 119–129. https://doi.org/10.1111/j.1469-8749.2009.03545.x

Little, R. J. A. (1988). A test of missing completely at random for multivariate data with missing values. *Journal of the American Statistical Association*, *83*(404), 1198–1202. https://doi.org/10.1080/01621459.1988.10478722

McCrimmon, A., & Smith, A. (2012). Review of the Wechsler abbreviated scale of intelligence, second edition (WASI-II). *Journal of Psychoeducational Assessment*, *31*, 337–341. https://doi.org/10.1177/0734282912467756

Mezick, E. J., Wing, R. R., & McCaffery, J. M. (2014). Associations of self-reported and actigraphy-assessed sleep characteristics with body mass index and waist circumference in adults: Moderation by gender. *Sleep Medicine*, *15*(1), 64–70. https://doi.org/10.1016/j.sleep.2013.08.784

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science*, *21*(1), 8–14. https://doi.org/10.1177/0963721411429458

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: A latent variable analysis. *Cognitive Psychology*, *41*(1), 49–100. https://doi.org/10.1006/cogp.1999.0734

Ross, J. L., Roeltgen, D. P., Kushner, H., Zinn, A. R., Reiss, A., Bardsley, M. Z., … Tartaglia, N. (2012). Behavioral and social phenotypes in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. *Pediatrics*, *129*(4), 769–778. https://doi.org/10.1542/peds.2011-0719

Ross, J. L., Roeltgen, D. P., Stefanatos, G., Benecke, R., Zeger, M. P., Kushner, H., … Zinn, A. R. (2008). Cognitive and motor development during childhood in boys with Klinefelter syndrome. *American Journal of Medical Genetics Part A*, *146A*(6), 708–719. https://doi.org/10.1002/ajmg.a.32232

Ross, J. L., Zeger, M. P., Kushner, H., Zinn, A. R., & Roeltgen, D. P. (2009). An extra X or Y chromosome: Contrasting the cognitive and motor

phenotypes in childhood in boys with 47,XYY syndrome or 47,XXY Klinefelter syndrome. *Developmental Disabilities Research Reviews*, *15*(4), 309–317. https://doi.org/10.1002/ddrr.85

Rovet, J., Netley, C., Keenan, M., Bailey, J., & Stewart, D. (1996). The psychoeducational profile of boys with Klinefelter syndrome. *Journal of Learning Disabilities*, *29*(2), 180–196. https://doi.org/10.1177/002221949602900208

Shigehara, K., Konaka, H., Sugimoto, K., Nohara, T., Izumi, K., Kadono, Y., … Mizokami, A. (2018). Sleep disturbance as a clinical sign for severe hypogonadism: Efficacy of testosterone replacement therapy on sleep disturbance among hypogonadal men without obstructive sleep apnea. *The Aging Male*, *21*(2), 99–105. https://doi.org/10.1080/13685538.2017.1378320

Shirk, S. R., Reyes, J. P. M., & Cristotomo, P. S. (2013). Assessment of therapy processes. In B. D. McLeod, A. Jensen-Doss, & T. H. Ollendick (Eds.), *Diagnostic and behavioral assessment in children and adolescents – A clinical guide*. New York: The Guildford Press.

Siqveland, J., & Leiknes, K. A. (2016). *Måleegenskaper ved den norske versjonen av Symptom Checklist 90 Revidert (SCL-90-R). [Assessment of psychometric properties of the Norwegian version of the Symptom Checklist 90 Revised (SCL-90-R)]*.

Skakkebæk, A., Moore, P. J., Chang, S., Fedder, J., & Gravholt, C. H. (2018). Quality of life in men with Klinefelter syndrome: The impact of genotype, health, socioeconomics, and sexual function. *Genetics in Medicine*, *20*(2), 214–222. https://doi.org/10.1038/gim.2017.110

Skakkebæk, A., Moore, P. J., Pedersen, A. D., Bojesen, A., Kristensen, M. K., Fedder, J., … Gravholt, C. H. (2017). The role of genes, intelligence, personality, and social engagement in cognitive performance in Klinefelter syndrome. *Brain and Behavior*, *7*(3), e00645. https://doi.org/10.1002/brb3.645

Skakkebæk, A., Moore, P. J., Pedersen, A. D., Bojesen, A., Kristensen, M. K., Fedder, J., … Gravholt, C. H. (2018). Anxiety and depression in Klinefelter syndrome: The impact of personality and social engagement. *PLoS One*, *13*(11), e0206932. https://doi.org/10.1371/journal.pone.0206932

Skakkebæk, A., Wallentin, M., & Gravholt, C. H. (2015). Neuropsychology and socioeconomic aspects of Klinefelter syndrome: New developments. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *22*(3), 209–216. https://doi.org/10.1097/MED.0000000000000157

Smith, M. T., McCrae, C. S., Cheung, J., Martin, J. L., Harrod, C. G., Heald, J. L., & Carden, K. A. (2018). Use of actigraphy for the evaluation of sleep disorders and circadian rhythm sleep-wake disorders: An american academy of sleep medicine systematic review, meta-analysis, and grade assessment. *Journal of Clinical Sleep Medicine*, *14*(7), 1209–1230. https://doi.org/10.5664/jcsm.7228

Smyth, C. M., & Bremner, W. J. (1998). Klinefelter syndrome. *Archives of Internal Medicine*, *158*(12), 1309–1314. https://doi.org/10.1001/archinte.158.12.1309

Stewart, D. A., Bailey, J. D., Netley, C. T., Rovet, J., & Park, E. (1986). Growth and development from early to midadolescence of children with X and Y chromosome aneuploidy: The Toronto study. *Birth Defects Original Article Series*, *22*(3), 119–182.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Temple, C. M., & Sanfilippo, P. M. (2003). Executive skills in Klinefelter's syndrome. *Neuropsychologia*, *41*(11), 1547–1559. https://doi.org/10.1016/s0028-3932(03)00061-7

Turriff, A., Levy, H. P., & Biesecker, B. (2011). Prevalence and psychosocial correlates of depressive symptoms among adolescents and adults with Klinefelter syndrome. *Genetics in Medicine*, *13*(11), 966–972. https://doi.org/10.1097/GIM.0b013e3182227576

van Rijn, S., & Swaab, H. (2015). Executive dysfunction and the relation with behavioral problems in children with 47,XXY and 47,XXX. *Genes, Brain, and Behavior*, *14*(2), 200–208. https://doi.org/10.1111/gbb.12203

Walker, M. P., & Stickgold, R. (2005). It's practice, with sleep, that makes perfect: Implications of sleep-dependent learning and plasticity for skill performance. *Clinics in Sports Medicine*, *24*(2), 301. https://doi.org/10.1016/j.csm.2004.11.002

Walker, M. P., & van der Helm, E. (2009). Overnight therapy? The role of sleep in emotional brain processing. *Psychological Bulletin*, *135*(5), 731–748. https://doi.org/10.1037/a0016570

Wechsler, D. (1999). *Wechsler abbreviated scale of intelligence (WASI)*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2008). *WAIS-IV: Wechsler Adult Intelligence Scale*. San Antonio, TX: Psychological Corporation & Pearson Education Inc.

Woody, S. R., Steketee, G., & Chambless, D. L. (1995). The usefulness of the obsessive compulsive scale of the symptom Checklist-90-revised. *Behaviour Research and Therapy*, *33*(5), 607–611. https://doi.org/10.1016/0005-7967(94)00090-7

SUPPORTING INFORMATION

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