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Sleep Problems and Life Satisfaction as Predictors of Health in Men with Sex Chromosome Aneuploidies

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ABSTRACT

More knowledge is needed about men with sex chromosome aneuploidies (SCA). We present self-reported data from 53 men with SCA ($M_{\text{age}} = 36.8$ years, $SD = 12.3$, range 19–67). The Health Survey–Short Form (SF-36) measured eight health domains (physical functioning, role-physical, role-emotional, vitality, emotional health, social functioning, pain, general health). The Pittsburgh Sleep Quality Index measured sleep problems. The Personal Wellbeing Index measured satisfaction with eight life domains. Compared to norms, SCA reported poorer health (mean $d = -0.80$) and more sleep problems (mean $d = -0.85$). Differences between SCA and norms on personal well-being were small, except lower health satisfaction in SCA ($d = -1.06$). Seven of eight regression models predicting the SF-36 domains from life satisfaction and sleep problems were significant (explained variance 12.2% to 46.2%), except physical functioning (*ns*). Clinical assessment/intervention for a broad range of health and sleep problems is indicated for men with SCA.

KEYWORDS

47XXY; 47XYY; Klinefelter syndrome; male health; sex chromosome aneuploidy

Introduction

Sex chromosome aneuploidies (SCA), a term used to describe an atypical number of X and/or Y sex chromosomes, represent the most prevalent chromosome change in humans.^{1,2} Among men, 47XXY (Klinefelter syndrome, KS) is the most prevalent karyotype (1/426 to 1/1000), followed by 47XYY (1/1000) and rarer karyotypes 48XXYY and 48XXXY with prevalence rates from 1/17,000 to 50,000.^{3,4} Men with SCA have increased risk of several physiological, cognitive, psychological, and socioeconomic challenges compared to controls without SCA.^{5,6}

In terms of physiology, hypogonadism (i.e., low testosterone levels) is prevalent for conditions with supernumerary X chromosomes, occurring in up to 85% of postpubertal men with 47,XXY.⁷ Hypogonadism often causes low testicular volume and high rates of infertility as well as sparse body hair growth. In terms of cognitive functioning, full-scale IQ scores are generally within the normal range for karyotypes 47,XXY and 47,XYY with considerable individual variation.⁸ IQ tends to be lower and in the borderline to mild mental retardation range for the tetrasomy conditions.^{9,10} Significantly lower verbal IQ relative to performance IQ has been found across karyotypes.¹⁰ Relative to controls, specific cognitive challenges, which have been identified more frequently among men with SCA, include receptive and expressive

language abilities as well as short-term and verbal memory, attention, and executive functions.^{4,11,12} Increased prevalence of reading and writing difficulties for men with SCA is likely to be a result of the language problems.^{13–15} In terms of psychological functioning, men with SCA have increased risk of experiencing general psychological distress, as well as higher prevalence rates of depression, anxiety, attention deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia.⁶

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.⁶ In a Scottish study of 19 men with 47XYY, most were employed in jobs that required less formal competencies than their fathers.¹⁶ 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.⁵ A Danish registry trial 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.¹⁷

SCA in men is underdiagnosed. Due to a National Health Registry, Danish researchers have estimated around 25% of men with the most prevalent and clinically recognizable SCA, KS, are diagnosed in their lifetime, in most cases as adults.¹⁹ This means there is

limited knowledge of men with SCA as a group. More knowledge is needed about everyday functioning among men with SCA, to increase awareness of the experiences of these men and to further identify their health needs.

The present study seeks to contribute to the increasing knowledge about health and functioning among men with SCA through a broad self-report survey. We had three main aims. First, we examined four background factors relevant to everyday functioning in men with SCA, aiming for thorough descriptive data of this group. The four factors were (a) demographic background; (b) diagnostic information; (c) substance use; and (d) experiences with health services. Second, we examined three health-related factors for which norm data were available for comparison: (a) self-reported health in eight domains including physical and emotional functioning, vitality, and mental health; (b) personal wellbeing in eight life domains including overall life satisfaction; and (c) sleep problems. Third, we examined if overall life satisfaction and sleep problems predicted health. We hypothesized that men with SCA would experience poorer health and wellbeing compared to norms. We had no a priori hypothesis concerning sleep problems due to limited existing data. We hypothesized that sleep problems and quality of life would predict health based on data from other populations.²⁰ The overall purpose of the study is to increase the knowledge of health service needs among men with SCA.

Methods

Sample and procedures

The sample comprised 53 men with SCA (M age = 36.8 years, SD = 12.3, range 19 to 67 years). The participants were recruited from two settings. Thirty-three participants were recruited from the annual meeting of the Norwegian Klinefelter Association in March 2012. Information about the study was presented at the meeting, and men aged 18 years and older were invited to participate. The exact response rate from this meeting is unknown, as we do not know the exact number of meeting attendees with SCA. The remaining sample (20 participants) was recruited through the database of Frambu Resource Centre for Rare Disorders (Frambu). Frambu is part of the Norwegian Competence Centre for Rare Disorders, a national specialist service for patients with rare disorders, offering liaison services and residential courses, but no assessment or treatment. At the time of recruitment (April 2012), 64 men with SCA aged 18 years and older were registered in the database. Registration in the database is voluntary, and usually occurs following patient application for liaison services or residential

courses. Twenty of these 64 men were already recruited at the user group meeting. The remaining 44 were invited to participate via regular mail, and 20 returned forms (45% response rate). One reminder was sent to non-responders after four weeks. In both recruitment settings, participants received a ready stamped return envelope for the questionnaires and consent forms. The study was approved by the Regional Committee for Research Ethics.

Measures and analyses

Participants received a questionnaire developed for this study, covering (a) demographic background including education, vocational functioning, marital and parental status, and sexual orientation; (b) diagnostic information including experiences of testosterone treatment; (c) substance use, including tobacco, alcohol, and illegal drug use; and (d) experiences with health services. In addition, three standardized questionnaires covering health, personal well-being, and sleep were included.

The Short Form Health Scale (SF-36) covers eight health domains and has well-documented psychometric properties.²¹ The subscales, with internal consistency for the current sample are: (1) Physical functioning, 10 items ($\alpha = 0.93$); (2) Role-physical, 4 items ($\alpha = 0.84$); (3) Role-emotional, 3 items ($\alpha = 0.84$); (4) Vitality, 4 items ($\alpha = 0.83$); (5) Emotional health, 5 items ($\alpha = 0.85$); (6) Social functioning, 2 items ($\alpha = 0.85$); (7) Pain, 2 items ($\alpha = 0.88$); and (8) General health, 5 items ($\alpha = 0.88$).

Personal Wellbeing Index (PWI) covers satisfaction in seven life domains as well as overall life satisfaction, rated on a 0 to 10 scale.²² The scale has well-documented psychometric properties.²² In the present sample, internal consistency was $\alpha = 0.90$.

Pittsburgh Sleep Quality Index (PSQI) is a well-validated measure of subjective sleep.²³ We used four components (13 items) of the PSQI; that is, subjective sleep quality, sleep disturbance, daytime functioning, and sleep medication use. Internal consistency was $\alpha = 0.88$.

Data analytic plan

All analyses were conducted with IBM Statistics SPSS version 22.0. When comparing our sample to norms the following equation was used to calculate effect size difference (d): Mean men with SCA—mean norms/pooled standard deviation.²⁴ We applied the following criteria for magnitude of effect sizes (i.e., small = 0.10 to 0.29; medium = 0.30 to 0.49; large > 0.50).²⁵ Linear regression models predicting health from sleep problems and quality of life were conducted using the enter method.²⁶

Results

First, we will present background data specific for this study. Second, we present data on personal well-being, sleep problems, and self-perceived health compared to norms. Finally, we present eight regression models in which overall life satisfaction and sleep problems were entered as predictors of the SF-36 health scales. As preliminary analyses, we compared the participants recruited from the user meeting to those recruited from the resource center on the variables included in regression models (i.e., overall life satisfaction, sleep problems, the SF-36 health scales). There were no significant differences (data not shown).

Background data

See Table 1 for karyotype details, marital status, living situation, education, and employment. Body mass index (BMI) was classified as normal (18.5–25.0) for 44% of participants, overweight (25.0–29.9) for 22%, and obese (> 30.0) for 34%. Seven participants reported living with children, and two participants reported care responsibilities for children with whom they did not live. Two participants reported having biological children. Seven participants reported having stepchildren, and five

Table 1. Background information for 53 men with sex chromosome aneuploidies.

Karyotype	Percentage	Highest education	Percentage
47XXY	77.3%	Primary school	3.8%
47XYY	3.8%	Secondary school	22.6%
48XXYY	3.8%	High school	54.7%
Mosaic	3.8%	< 3 year post high school	13.2%
Not reported	11.3%	> 3 year post high school	0.0%
Marital status		Not reported	5.7%
Living alone	56.6%	Work situation	
Cohabiting/married	30.2%	Working	37.7%
Living with parents	13.2%	Disability pensions	35.8%
Housing arrangement		Student	11.3%
Apartment	62.2%	Early retirement	3.8%
House/Terraced house	32.1%	Unemployed	1.9%
Shared housing	1.9%	Other	9.5%
Assisted living	1.9%	Part time work ^a	22.6%
Other	1.9%	NLWA assisted job ^a	17.0%
Age of diagnosis	M (SD) 21 years (10)	Weekly work hours ^a	M (SD) 31.2 (16.0)
Height	186 cm (7)	Years in current job ^a	5.5 (7.4)
Weight	98 kg (26)		
Body mass index	27.9 (6.9)		

Note.

^aAmong those working.

^bNLWA = Norwegian Labour and Welfare Administration.

participants reported having children conceived by donor. None of the participants reported to have adopted or foster children.

Sexuality

In terms of sexual orientation, 81.1% identified as heterosexual. One participant identified as homosexual, and three as bisexual. Three participants rated they were unsure about their sexual orientation, one rated sexual orientation as “other,” and two did not report.

Substance use

The reported frequency of smoking was daily (28.3%), sometimes (17.0%), and never (54.7%). The reported number of weekly alcohol units was zero (47.2%), 1 to 5 units (45.2%), 6 to 10 units (5.7%), and more than 10 units (0.0%), with information missing for one participant (1.9%). Participants rated their alcohol dependency on a scale from 0 (abstinent) to 7 (addicted) with a mean score of 1.7 (*SD* = 1.3; range 0–4). One participant reported occasional use of hash/marijuana, and one occasional use of cocaine.

Diagnostic information

The mean age of SCA diagnosis was 21.0 years (*SD* = 10.4, range 0 to 49), with 42.9% reporting they were diagnosed at or before age 17 years. Two participants reported to have been diagnosed before age one year.

Testosterone treatment

The vast majority (88.7%) reported receiving testosterone treatment, in the form of injections (83.3%), gel (29.2%), and pills (6.3%), or a combination thereof. None of the participants reported using testosterone patches. Positive effects of testosterone treatment were reported by 85.4%. From most to least frequent, the reported positive effects were on mood (67.9%), concentration (56.6%), increased sex drive (50.9%), body hair (45.3%), energy (39.6%), muscle mass (28.3%), and sleep (26.4%). Negative effects of testosterone treatment were reported by 35.8%. The most frequently reported negative effects were on mood (13.2%) and sleep (9.4%).

Health service use and satisfaction

From most to least frequent, health service professionals reported to be involved due to the SCA diagnosis were general practitioner (69.8%), endocrinologist (32.7%), psychologist (5.7%), and habilitation services (3.8%). Eight participants (15.1%) reported no health professionals were involved. Twenty participants (37.7%) reported to have been assessed for infertility, and three of these reported having received fertility treatment. In terms of satisfaction with health services for SCA diagnosis,

Table 2. SF-36 scores in men with sex chromosome aneuploidies compared to norwegian norms.

	Men with SCA (N = 53) M (SD)	Norms (N = 1138) M (SD)	<i>d</i>
General health	51.4 (29.5)	77.4 (21.3)	-1.01
Physical functioning	72.5 (28.5)	89.8 (15.5)	-0.75
Role – physical	46.2 (40.8)	80.5 (33.6)	-0.92
Role – emotional	62.2 (42.3)	84.5 (29.7)	-0.61
Vitality	45.6 (23.7)	63.2 (19.9)	-0.80
Mental health	67.4 (21.9)	80.0 (15.8)	-0.66
Social functioning	65.0 (30.4)	87.6 (20.9)	-0.87
Pain	53.7 (32.8)	77.2 (25.0)	-0.81

Note. SF-36: Short Form Health Survey. *d* = effect size difference (> 0.50 = large). Higher scores indicate better health. Norms based on data from Norwegian males aged 19 to 80 years, M age = 44.9 years.²⁶

15.1% of participants rated satisfied or very satisfied, whereas 58.8% rated dissatisfied or very dissatisfied. The remaining respondents rated neither satisfied nor dissatisfied (24.5%) or did not respond (3.8%).

Health compared to norms

Men with SCA had lower scores on all SF-36 scales, indicating more health problems, compared to norm data for 1138 Norwegian males aged 19 to 80 years.²⁶ All effect size differences were large, and the mean effect size difference between the SCA sample and norms for the 8 SF-36 scales was $d = -0.80$. (See Table 2.)

Personal well-being compared to norms

See Table 3 for overall life satisfaction and personal well-being in seven life domains compared to a norm sample of 593 adults aged 18 to 65 years (46.9% men) from Canada and Australia.²⁷ There was a large effect size difference for satisfaction with personal health ($d = -1.06$) with the SCA sample rating lower. On the other PWI domains, there were small to negligible effect size differences (d range (except health) -0.22 to 0.12). (See Table 3.)

Table 3. Personal well-being in 53 men with sex chromosome aneuploidies compared to norms.

Well-being domain	SCA (N = 53) M (SD)	Norms (N = 593) M(SD)	<i>d</i>
Overall life satisfaction	6.8 (2.4)	7.2 (1.5)	-0.20
Standard of living	7.2 (2.3)	7.1 (2.1)	0.05
Personal health	5.2 (2.7)	7.6 (1.7)	-1.06
Achieving in life	6.7 (2.4)	6.9 (2.1)	-0.09
Personal relationships	7.6 (2.5)	7.5 (2.2)	0.04
Personal safety	7.6 (2.3)	7.8 (1.9)	-0.09
Community connectedness	6.5 (2.5)	7.0 (2.0)	-0.22
Future security	6.9 (2.8)	6.6 (2.3)	0.12

Note. Scale range 0–10 for all variables (possible and within-sample). *d* = effect size difference (small = 0.10 to 0.29; medium = 0.30 to 0.49; large > 0.50²⁵). Norms based on data from Canadian and Australian adults aged 18 to 65 years (46.9% males) with no gender differences.²⁷

Correlations between all life domains and overall life satisfaction were significant (mean $r = 0.56$).

Sleep compared to norms

The mean subjective sleep quality score was 1.25 (SD = 1.08). This represents poorer sleep quality compared with norms for 318 Norwegian students with a mean age of 21.7 years,²⁸ a medium effect with $d = -0.21$. The mean sleep disturbance score was 1.70 (SD = 0.72), representing more sleep disturbance compared to norms,²⁸ a large effect with $d = -1.24$. The mean daytime functioning score was 1.31 (SD = 0.92), representing higher impact on daily functioning from drowsiness compared to norms,²⁸ a large effect with $d = -0.51$. Finally, use of sleep medication was much higher than norms²⁸ with a mean score of 0.43 (SD = 0.92), a large effect with $d = -1.42$.

Personal well-being and sleep problems as predictors of health

We calculated regression models predicting the eight SF-36 scales from overall life satisfaction and sleep problems. To ease interpretability of these regression models, we added the four sleep components into a combined sleep problems variable (summed means of the four components/4) with a mean score of 1.18 (SD = 0.65, range 0.25 to 2.75) and used this variable as a predictor in the models. Seven of the eight regression models were significant, with explained variance (*adjusted R*²) ranging from 19.4% to 46.2%. The model predicting physical functioning was not significant. Life satisfaction was a significant predictor for general health and social functioning. Sleep problems was a significant predictor for all health variables except physical functioning. (See Table 4.)

Discussion

This broad self-report survey is the first survey of Norwegian men with SCA. The study provides insights into several demographic and health-related factors that can be used to further understand functioning and service needs for men with SCA. In terms of education and work, 13.2% of the sample reported education beyond high school, compared to 27.0% of the general Norwegian male population.²⁹ Around a third of our sample (35.8%) reported to be on disability pensions, compared to 7.8% of the general Norwegian male population.³⁰ A Danish registry study showed 7.0% of men with SCA had obtained education beyond high school by the age of 30 years, and that 11.8% of men with SCA were on disability pensions at age 30 years compared to 1.3% of the

Table 4. Regression models predicting health from life satisfaction and sleep problems among 53 men with sex chromosome aneuploidies.

KEY WORDS:	General Health	Physical Functioning	Role—Physical	Role—Emotional	Vitality	Mental Health	Social Functioning	Pain
Model significance (<i>p</i>)	0.000	0.148	0.006	0.001	0.000	0.001	0.000	0.026
Constant (<i>p</i>)	0.018	0.001	0.012	0.000	0.000	0.000	0.001	0.007
Life satisfaction (β)	0.414*	0.177	0.138	0.048	0.198	0.208	0.434**	0.166
Sleep problems (β)	-0.366*	-0.191	-0.415*	-0.511**	-0.600**	-0.424**	-0.383**	-0.316*
Explained variance (%)	38.0	4.7	19.4	24.5	46.2	24.9	42.4	12.2

Note. *predictor is significant at the $p < 0.05$ level. **predictor is significant at the $p < 0.001$ level.

general Danish population.¹⁷ Based on our findings and previous studies^{6,17} men with SCA seem to be at risk of poorer socioeconomic status.

In terms of marital and parental status, 30.9% of participants reported to be married or cohabiting, compared to 64.7% of the general Norwegian male population.²⁹ The low number of fathers in the sample is likely to be due to the fact that men with KS (47,XXY), the largest group in our sample, most often are infertile.⁷ Thus, living alone and without children seems more common for men with SCA relative to the general population.

In terms of BMI, the fact that one third of participants could be classified as obese is concerning. Due to the risk of metabolic syndrome (a cluster of hyperglycemia, dyslipidemia, and hypertension) and mortality due to diabetes found among men with KS,³¹ developing interventions to reduce obesity rates among men with SCA are essential.

In terms of sexuality, 17% reported other categories than heterosexual. This is comparable to numbers from an Australian study of men with SCA in which 16% reported their sexuality as bisexual, homosexual, or "other."⁵ In the latest Norwegian population survey including sexuality, less than 1% of men identified as homo- or bisexual.³² These findings indicate that sexual orientation may be an important issue to address in consultation with men with SCA.

In terms of substance use, nearly a third reported to be daily smokers compared to 13% of the general male population in Norway.²⁹ The general alcohol consumption in our sample was considerably lower compared to Norwegian population data. Nearly half our sample reported to not drink at all, compared to an estimated 10% of the Norwegian population.³³ A review study identified that moderate alcohol consumption is likely to be associated with increased social networks³⁴ and a study found male students experienced particular social benefits with drinking compared to female students.³⁵ Thus, we may speculate that participants with minimal alcohol consumption could have restricted social relations. The low rates of alcohol consumption and substance abuse reported by our sample also represent a positive finding, particularly since many of the risk

factors associated with SCA (i.e., being men with low socio-economic status,⁶ poor emotional health,^{6,12} and low impulse control^{4,11}) are associated with increased risk of substance abuse in the general population.^{36,37}

It is noteworthy that more than half the sample had been diagnosed after the age of 17 years. Earlier diagnosis should be an important aim for health providers. Overall, experiences of testosterone treatment were positive, as close to 90% reported positive effects compared to one third who reported negative effects. The negative effects on mood and sleep are important to note, and testosterone treatment providers should inform patients of these possible negative effects. The majority (58.8%) reported to be dissatisfied or very dissatisfied with health services, and this should be a concern for health providers. Future studies should further examine health service experiences of men with SCA.

Turning now to the variables for which norm data were available as comparison, we will first consider health. Self-reported health was poorer than norms for Norwegian males in all domains, including both physical and mental health and functioning, with large effect size differences. Our results indicate a need for assessment and intervention for men with SCA across several areas of health functioning.

In terms of personal wellbeing, the largest difference between the SCA sample and norms was on satisfaction with personal health—a large effect size difference with the SCA sample scoring lower. This is in line with the finding of poorer self-perceived health in this sample. On all other domains—overall life satisfaction, sense of community connectedness, standard of living, achieving in life, personal relationships, personal safety, and future security—there were small to negligible differences between the SCA sample and norms. On the one hand, these results give rise to optimism in that men with SCA, despite their health concerns, are as satisfied as others in several domains of life. The fact that men with SCA consider their sense of achieving in life similar to data from the general population, despite obtaining lower education and having a higher frequency of disability pension retirement at the group level, may mean many men consider their achievements on other domains than

education and work. The fact that satisfaction with personal relationships is at the same level as norm data, despite considerably fewer men with SCA live in partnerships, may indicate many men find satisfying personal relations outside an intimate partner relationship. Other studies have also found lower quality of life among men with SCA.⁵ Our results indicate that overall quality of life may not be the most applicable variable to assess, as a more balanced picture emerges when examining satisfaction in multiple life domains, which should be done in clinical assessment of men with SCA.

In terms of sleep, all problem domains were lower than for Norwegian norms. There were large effect size differences for sleep disturbance, daytime functioning, and sleep medication use. There was a small difference for overall sleep quality. The norm group comprises both males and females, and we have not been able to obtain norm data for males only. Given that in the general population, women report more sleep problems than men,³⁸ we do not believe we overestimate sleep problems among men with SCA using this norm group. We are not aware of studies that have examined sleep in adults with SCA. However, a recent study identified sleep problems for 36% of 25 boys with SCA aged younger than 17 years.³⁹ Our results indicate further need for research on sleep problems in men with SCA. Importantly, since there was only a small difference for overall sleep quality, while the differences for other sleep problem domains were large, sleep assessment in men with SCA should include more details than an overall question of sleep quality.

Finally, we examined if overall life satisfaction and sleep problems predicted the eight SF-36 health variables. All models except the model predicting physical functioning were significant. Life satisfaction was a significant predictor for general health and social functioning. This is in line with general health policies describing overlap between these factors.⁴⁰ However, it is noteworthy that overall life satisfaction did not predict other domains of self-perceived health. Limited overlap between physical ability and perceived quality of life has also been found in studies with other populations.⁴¹ A striking finding is the consistent predictive value of sleep quality for health problems among men with SCA. The clear clinical implication is that sleep assessment, and possibly treatment for sleep problems, should be part of health interventions for men with SCA.

The main limitation of the present study is the lack of a control group or norm data for variables beyond the SF-36, the PWI, and the PSQI. Separate norm data for Norwegian men are not available for the PWI. There were no significant gender differences on the PWI in the norm study, thus the norm data were judged to be representative for both men and women. Further, our data are

cross-sectional and all are self-reported. This means some of the associations are likely to be inflated by within-informant rating effects. We did not obtain diagnostic confirmation for all participants, but have no reason to believe that participants without SCA would attend a KS user group. We included various SCA karyotypes, but the low number of participants with other karyotypes than 47XXY prevented us for examining potential differences due to karyotype. In terms of generalizability, informants were recruited via a resource center and a user group, so results may not be generalizable to men with SCA who for various reasons choose not to be involved with such organizations. Further, participants received the SCA diagnosis late in life, with a mean age of 21 years and older half the sample being diagnosed after the age of 17 years. Results may not be generalizable to men with SCA diagnosed earlier in life, particularly in the first few years of life, as is becoming more common⁵.

Conclusions

The main clinical implication of the present study is that multiple health variables should be assessed in services for men with SCA, including physical and emotional health, pain, vitality, communication problems, and sleep problems. Future studies should examine the development of these variables over time and aim to identify interventions to improve health status in men with SCA.

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