RESEARCH

The impact of Klinefelter syndrome on socioeconomic status: a multicenter study

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Abstract

Klinefelter syndrome (KS) is associated with an increased risk of neuropsychological morbidity, such as learning disabilities, which may have a significant impact on socioeconomic status (SES). The objective of this study was to investigate the SES in men with KS and to associate this outcome with social participation, age at diagnosis, testosterone therapy and physical and mental health status. Men with KS were recruited in 14 clinical study centers in six European countries which participated in the European dsd-LIFE study. Two hundred five men with KS were eligible for inclusion. Male normative data from the European Social Surveys (ESS) were used for comparison. Data related to education, occupation, satisfaction with income and householding were collected. Compared to the ESS reference population, fewer men with KS achieved a high level of education (13% vs 25%, \(P < 0.001\)). There was a significant difference in having a paid job (55% vs 66%, \(P < 0.001\)), and the percentage of absence by sickness or disability was higher among men with KS (10% vs 3%, \(P < 0.001\)). Furthermore, satisfaction with current household's income was lower (32% vs 42%, \(P < 0.01\)). Lower scores for subjective general health were associated with lower scores for these outcomes. Men with KS achieve on average lower levels of education, occupation and report less satisfaction with income compared to the ESS reference population. The presence of health problems and lower scores of subjective general health was related to lower levels of occupation and lower satisfaction with income in men with KS.
Introduction

Klinefelter syndrome (KS), caused by at least one additional X-chromosome in males (47,XXY), is one of the most common numerical chromosomal anomalies in men, with an estimated prevalence of 1–2 per 1000 men (1). Despite the relatively high prevalence, KS is a highly underdiagnosed syndrome: only about 25% of the affected men are diagnosed, most likely due to a high variation in phenotype (1). One of the most common medical effects of KS is impaired fertility. Nonobstructive azoospermia is found in about 90% of adult men with KS (2). Other frequent clinical symptoms include gynecomastia, a low sexual drive, small testes and hypogonadism due to impaired testosterone production (3, 4). KS is also associated with neuropsychological impairment as well as impaired psychological well-being: affected males often suffer from learning disability and social challenges (5, 6). In a web-based survey study, many participants with a late diagnosis reported to have struggled at school, which has led to feelings of inferiority, low self-esteem and depression (6). Furthermore, men with KS have an increased risk to develop a variety of mental and somatic disorders (7). Mental and somatic challenges, such as learning disabilities and absence at school or work due to illness, can also lead to lower socioeconomic outcomes during life. Previous studies described inferior outcomes in many different socioeconomic parameters for men with KS compared to the general population such as education, satisfaction with income and social activities (8, 9, 10). A recent study reports an overall lower educational level in Danish men with KS compared to a matched control cohort, leading to a lower income during their lifetime. Additionally, they reported that men with KS retire 16 years earlier on average (11). The risk of a hospital admission was reported to be elevated by 70% compared to the general population (8). The life expectancy of men with KS is reduced by 5.6 years compared to the general male population (8).

The objective of this study was to investigate the socioeconomic status (SES), measured by individual education, occupation status and income level, in men with KS and to associate these outcomes with social engagement, age of diagnosis, testosterone therapy and physical and mental health status, and to compare values to a European Social Surveys (ESS) reference population.

Methods

Study population

This study was part of the European dsd-LIFE study, a non-interventional, clinical, cross-sectional study (12). The purpose of the dsd-LIFE study was to investigate and compare the long-term outcomes of surgical and hormonal therapy and psychological and social support in adolescents and adults with different forms of differences/orders of sex development, aiming to provide the basis for improvements in evidence-based recommendations for care. Ethical approval was first sought from the medical ethics committee at the Charité Universitätsmedizin Berlin. The study was further approved by all institutional ethical boards of the participating centers and informed consent was provided by all participants.

The dsd-LIFE consortium consists of 14 European centers in six European countries, that is Germany, France, the Netherlands, Poland, Sweden and the United Kingdom (UK). The 14 centers approached former and current patients by mail, e-mail, phone or direct contact of the physician and promoted participation in patient support groups. Details on the theoretical and methodological framework of the dsd-LIFE study have been published earlier (12).

Men with KS were asked to fill out a digital Patient-Reported Outcome (PRO) form that comprised validated and self-constructed questionnaires on health status, mental health, quality of life, psychological well-being, psychosexual outcome, testosterone treatment, fertility, experiences with care and sexuality (12). To ensure confidentiality, men with KS were asked to fill out the PRO with a secure password either in the clinic or at home. Data were entered anonymously into a database.

Reference population

Normative data on sociodemographic and economic factors were retrieved from the European Social Survey (ESS, http://www.europesocialsurvey.org).

For our study, we used ESS data on health and care, SES, family, work and wellbeing and personal and social wellbeing questions from the surveys from 2010 to 2013 including reference data from 1515 participants. We included male participants from the United Kingdom, Poland, the Netherlands, Germany, Sweden and France to match this data with our cohort of men with KS. The distribution of
participants from the ESS reference population was matched to the distribution of countries and age of participants of the study population using SPSS random matching tool. For the evaluation of SES, the same questionnaires as stated below were used for the ESS reference population (http://www.europeansocialsurvey.org).

Description of outcome variables
Standardized validated questions were used in the study- and reference population, as stated in the ESS. For further evaluation of specific aspects of men with KS, self-constructed questions were added to the KS population. The SES consisted of the three following main variables (see Table 1).

- Level of education: The international standard classification of education scale is a standardized scale measuring seven levels of education. For parts of the current study, this scale was recoded into three groups to compare the outcome to the ESS reference population.
- Occupational status: The standardized ESS question was used to assess occupational status. For linear regression analysis, the variable was recoded into two categories. The first category was ‘occupation’, containing ‘in paid work’, ‘in education’ and ‘retired’. The other possible answers were regrouped into ‘no occupation’.
- Satisfaction with household income: For the evaluation of satisfaction with household income, the standardized ESS question was used.

Possible associated factors
A subgroup analysis based on the karyotype of study participants was planned but could not be executed due to low numbers of the karyotype. Descriptive analysis of the karyotype (47,XXY; 47,XXY/46,XY; 47,XXY/46,XX; Other; Unknown) was done (see Table 2). Other possible associated factors that have been investigated are subjective general health, social activity, presence of health status, discrimination, testosterone treatment and age at diagnosis and are described in more detail in Table 1.

Statistical analysis
This study embodied three parts:

1. The SES was analyzed in the study population and the reference population and results were compared to each other, using the following outcome variables:
   - level of education, occupation and satisfaction with household income.
2. Within the study population, effects of possibly with SES associated variables such as age at diagnosis, testosterone treatment, social participation and discrimination were further analyzed using linear regression analysis.
3. Furthermore, an exploratory investigation into the relationships between the various variables in men with KS was conducted, based on structural equation modeling (SEM).

The following statistical analyses were done in the three parts of the study:

1. Characteristics of the men with KS and the ESS reference population were described using means and s.d. or frequencies and percentages. Main outcome variables (i.e. level of education, occupation status and satisfaction with income) were reported as counts and percentage. For group comparisons between men with KS and the ESS reference population, chi-square tests and Mann–Whitney U tests were used for the main outcome variables.
2. Linear regression analysis was done within the KS study population to investigate possible associations between the main outcome variables and variables of possible influence, such as hormone therapy with testosterone, age at diagnosis, and presence of physical or mental morbidities among men with KS. All analyses were adjusted for age and country of residency. There was no adjustment for multiple comparisons because of the exploratory nature of this study and the primary concern about type II error.
3. Furthermore, an exploratory investigation into the relationships between the various variables in men with KS was conducted, based on SEM. SEM is a multivariate technique that requires specification of a model based on theory and research that incorporates both measured variables and latent constructs. The resulting model, based on the best of our knowledge on KS together with model fit criteria, is presented by a path diagram. In addition to the explanatory and dependent variables as mentioned above, a latent variable was included, representing the severity of KS, in an attempt to estimate the (unmeasured) direct impact of the severity of KS. The latent variable, ‘Extent of KS’, is based on the variables ‘gynaecomastia’, ‘small testes’ and ‘physical health problems’. SEM was performed with maximum likelihood estimation in proc Calis, from the SAS/STAT software, version 9.4.
Table 1  Questions used to evaluate socioeconomic status and possible associated factors in men with KS and a European reference population.

| Subject                      | Classification/question                                                                 | Type       | Answering options                                                                                                                                 |
|------------------------------|-----------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Socioeconomic status         | Level of education: ‘What is the highest level of education you have successfully completed?’ → Categorized according to the ES-ISCED: standardized scale that measures education in seven levels. | ESS        | ES-ISCED I – V2 Classification:                                                                                                                    |
|                              |                                                                                         |            | • Low: ES-ISCED I and II                                                                                                                        |
|                              |                                                                                         |            | • Medium: ES-ISCED IIIb, IIIa and IV.                                                                                                            |
|                              | ‘About how many years of education have you completed, whether full-time or part-time?’ | ESS        | • High: ES-ISCED V1 or V2                                                                                                                        |
|                              |                                                                                         |            | Number of years                                                                                                                                  |
| Occupational status          | ‘Which of these descriptions best describes your situation in the last seven days?’     | ESS        | • In paid work (or away temporarily; employee, self-employed, working for your family business)                                                |
|                              |                                                                                         |            | • In education (not paid for by employer), even if on vacation                                                                                |
|                              |                                                                                         |            | • Unemployed and actively looking for a job                                                                                                     |
|                              |                                                                                         |            | • Unemployed, wanting a job but not actively looking for a job                                                                                |
|                              |                                                                                         |            | • Permanently sick or disabled                                                                                                                   |
|                              |                                                                                         |            | • Retired                                                                                                                                       |
|                              |                                                                                         |            | • In community or military service                                                                                                               |
|                              |                                                                                         |            | • Doing housework, looking after children or other persons                                                                                 |
|                              |                                                                                         |            | • Other                                                                                                                                        |
| Satisfaction with income     | ‘Which of the descriptions comes closest to how you feel about your household’s income nowadays?’ | ESS        | • Living very comfortably on present income                                                                                                     |
|                              |                                                                                         |            | • Coping                                                                                                                                      |
|                              |                                                                                         |            | • Finding it difficult on present income                                                                                                       |
|                              |                                                                                         |            | • Finding it very difficult on present income                                                                                                  |
| Possible associated factors  | Subjective general health: ‘How is your health in general?’                             | ESS        |                                                                                                                                                |
| Social activity              | ‘Compared to other people of your age, how often would you say to take part in social activities?’ | ESS        | • Very good                                                                                                                                    |
| Presence of health problems  | ‘Do you have any longstanding illness or health problem? (apart from your condition)’  | SC         | • Good                                                                                                                                         |
| Discrimination               | ‘Have you been discriminated against because of your condition?’                         | SC         | • Fair                                                                                                                                 |
|                              |                                                                                         |            | • Bad                                                                                                                                            |
|                               |                                                                                         |            | • Very bad                                                                                                                                     |
| Testosterone supplement      | ‘Are you on testosterone therapy at present?’                                           | SC         | • Much more than most                                                                                                                           |
| Age at diagnosis             | ‘At what age was your condition diagnosed?’                                             | SC         | • More than most                                                                                                                                |
|                              |                                                                                         |            | • About the same                                                                                                                                |
|                              |                                                                                         |            | • Less than most                                                                                                                                |
|                              |                                                                                         |            | • Much less than most                                                                                                                          |

ESS, European Social Survey question; SC, self-constructed question; ES-ISCED Classification: I, less than lower secondary; II, lower secondary; IIIb, lower tier upper secondary; IIIa, upper tier upper secondary; IV, advanced vocational, sub-degree; V1, lower tertiary education, BA level; V2, higher tertiary education, ≥ MA level.

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of the SAS System for Windows. SAS is a registered trademark of SAS Institute Inc., Cary, NC, USA. For all other analyses, SPSS software version 22.0 was used (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. IBM Corp).

Results

Basic characteristics of the study population

A total of 205 men with KS were included in the study. The baseline characteristics of men with KS and the ESS reference population are listed in Table 2. All 205 included men with KS had a 47,XXY karyotype. Thirteen men with KS had been excluded from analysis due to mosaicism or more than one additional X-chromosome. KS was diagnosed in 63/205 (31%) men during childhood/adolescence and in 120/205 (59%) during adulthood, for the remaining 22/205 (11%) men with KS age at diagnosis was unknown.

Men with KS were significantly taller compared to the ESS reference population: 185.1 (SD 10.0) cm vs 178.8 (SD 7.7) cm; \(P\) < 0.001. The BMI of men with KS was lower compared to the ESS reference population: 24.6 (6.7) vs 26.2 (9.2); \(P\) <0.01. Testosterone replacement therapy was given to 145/205 (70.7%) men with KS, described in detail by Nordenström et al. (13).

Unfortunately, no data was available on the dosage or duration of testosterone treatment.

Socioeconomic status men with KS vs ESS reference population

The distribution of participants from the ESS reference population was matched to the distribution of countries and age of participants of the study population. The SES and possible associated factors of men with KS compared to the ESS reference population are shown in Table 3.

Level of education

Information on education was available for 176 of 205 men with KS. On average, less men with KS achieved a high level of education compared to the ESS reference population (Fig. 1 and Table 3). The mean number of years in education was comparable for men with KS and the ESS reference population. A subgroup analysis in men 25 years and older has shown the same results.

Occupational status

Information on current occupation was available for 185 of 205 men with KS. On average, less men with KS had paid work compared to the ESS reference population. The percentage of men being permanently sick or disabled was higher among men with KS compared to the ESS reference population. There were no differences for unemployment, retirement and housework (see Fig. 1 and Table 3). A subgroup analysis in men aged 25 years and older has shown the same results.

Satisfaction with household income

When comparing the overall satisfaction with current household’s income, significantly less men with KS reported to live comfortably on their present income compared to the ESS reference population (Fig. 1 and Table 3). A subgroup analysis in men aged 25 years and older has shown the same results.

Socioeconomic status associated factors within the study population

Table 4 shows the univariate analysis of the association between SES and possible associated factors within men with KS.

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Table 2  Baseline characteristics of men with Klinefelter syndrome and the ESS reference population.

|                        | Klinefelter Syndrome \((n = 205)\) | ESS reference population \((n = 1515)\) | \(P\)-value |
|------------------------|-----------------------------------|--------------------------------------|-------------|
| Age in years, mean (s.d.), range | 39.9 (15.0), 15–75                | 40.7 (15.7), 14–75                  | 0.31        |
| Height in cm, mean (s.d.)       | 184.0 (12.5)                      | 179.6 (7.7)                          | <0.01       |
| Weight in kg, mean (s.d.)       | 82.6 (27.6)                       | 82.7 (14.4)                          | 0.95        |
| BMI in kg/m\(^2\), mean (s.d.)  | 24.6 (6.7)                        | 26.2 (9.2)                           | <0.01       |
| Country of residence (n/%)       |                                  |                                      |             |
| Germany                  | 36 (17.6%)                        | 251 (16.6%)                          |             |
| France                   | 23 (11.2%)                        | 184 (12.1%)                          |             |
| Netherlands              | 83 (40.5%)                        | 606 (40.0%)                          |             |
| Poland                   | 23 (11.2%)                        | 167 (11.0%)                          |             |
| Sweden                   | 32 (15.6%)                        | 268 (17.7%)                          |             |
| United Kingdom           | 8 (3.9%)                          | 39 (2.6%)                            |             |
### Table 3 Socioeconomic status of men with Klinefelter syndrome vs a European reference population.

|                          | Participants with Klinefelter syndrome (n = 205) | ESS reference population (n = 1515) | P-value |
|--------------------------|--------------------------------------------------|-------------------------------------|---------|
| **Level of education (n/%)** |                                                 |                                     |         |
| High                     | 21 (11.9%)                                       | 378 (24.4%)                         | <0.01   |
| Medium                   | 95 (54.0%)                                       | 743 (49.3%)                         | 0.06    |
| Low                      | 60 (34.1%)                                       | 394 (26.3%)                         |         |
| Missing                  | 29                                               | 3                                   |         |
| **Educational years**    |                                                 |                                     |         |
| Median (Q1–Q3)           | 13.1 (11.0–15.0)                                 | 13.5 (11.0–16.0)                    |         |
| **Occupational status (n/%)** |                                         |                                     |         |
| Paid work                | 103 (55.7%)                                      | 1006 (66.5%)                        | <0.01   |
| Education                | 13 (7.0%)                                        | 157 (10.4%)                         |         |
| Unemployed               | 18 (9.8%)                                        | 102 (6.8%)                          |         |
| Permanently sick or disabled | 19 (10.3%)                                      | 50 (3.3%)                           |         |
| Retired                  | 13 (7.0%)                                        | 160 (10.6%)                         |         |
| Housework/looking after children | 1 (0.5%)                                    | 24 (1.6%)                           |         |
| Other                    | 18 (9.7%)                                        | 14 (0.9%)                           |         |
| Missing                  | 19                                               | 2                                   |         |
| **Satisfaction with income (n/%)** |                                         |                                     |         |
| Living comfortably       | 53 (30.8%)                                       | 625 (41.9%)                         | 0.01    |
| Coping                   | 86 (50.0%)                                       | 645 (43.2%)                         |         |
| Difficult                | 26 (15.1%)                                       | 170 (11.4%)                         |         |
| Very difficult           | 7 (4.1%)                                         | 52 (3.5%)                           |         |
| Missing                  | 28                                               | 0                                   |         |
| **Subjective general health (n/%)** |                                         |                                     |         |
| (very) good              | 104 (50.9%)                                      | 1155 (76.6%)                        | <0.01   |
| Fair                     | 57 (27.7%)                                       | 293 (19.4%)                         |         |
| (very) bad               | 44 (21.3%)                                       | 66 (4.4%)                           |         |
| Missing                  | 0                                                | 1                                   |         |
| **Social activities (n/%)** |                                              |                                     |         |
| (much) more than others  | 88 (48.1%)                                       | 492 (32.7%)                         | <0.01   |
| The same as others       | 74 (40.4)                                        | 730 (48.5%)                         |         |
| (much) less than others  | 21 (11.4%)                                       | 282 (18.8%)                         |         |
| Missing                  | 22                                               | 11                                  |         |
| **Presence of health problems** |                                          |                                     |         |
| Yes                      | 109 (53.2%)                                      | N/A                                 |         |
| No                       | 69 (33.7%)                                       |                                     |         |
| Unknown                  | 27 (13.2%)                                       |                                     |         |
| **Discrimination based on condition** |                                          |                                     |         |
| Yes                      | 42 (20.5%)                                       | N/A                                 |         |
| No                       | 139 (67.8%)                                      |                                     |         |
| Unknown                  | 24 (11.7%)                                       |                                     |         |
| **Testosterone supplement at present** |                                      |                                     |         |
| Yes                      | 145 (70.7)                                       | N/A                                 |         |
| No                       | 9 (4.4%)                                         |                                     |         |
| Unknown                  | 51 (24.9%)                                       |                                     |         |
| **Age at diagnosis**     |                                                 |                                     |         |
| Prenatal                 | 11 (5.4%)                                        | N/A                                 |         |
| Childhood                | 52 (25.4%)                                       |                                     |         |
| Adulthood                | 120 (58.5%)                                      |                                     |         |
| Unknown                  | 22 (10.8%)                                       |                                     |         |

### Level of education

We found a positive association between scores for subjective general health and level of education. There was no association between age at diagnosis, presence of health problems, experienced discrimination, testosterone substitution or social activity and level of education.

### Occupational status

A positive association was found between subjective general health and occupation. Men with KS with a (very) bad subjective general health were significantly more often without occupation, compared to men with (very) good subjective general health. We found negative...
associations for the presence of health problems and occupation, and for experienced discrimination and occupation. But a positive association between age of diagnosis and occupation. Men with KS who received their diagnosis in adulthood had significantly higher levels in occupation. There was no association found for testosterone substitution, social activity or occupation.

**Satisfaction with income**

A positive association was found for subjective general health and satisfaction with household income. Men who got their diagnosis at adulthood were significantly more satisfied with their household income compared to men who got their diagnosis of KS at childhood or adolescence. Furthermore, a positive association was
found for subjective general health and satisfaction with household income. Men with a better subjective general health were more satisfied with their household income compared to those with a worse subjective general health. Finally, a negative association was found for experienced discrimination and satisfaction with household income. Men with KS who had experienced discrimination were significantly less satisfied with their household income compared to those who did not experience discrimination. There were no other significant associations for presence of health problems, testosterone substitution or social activity and satisfaction with household income.

**Latent structure analysis**

Based on the subgroup of men with KS of 25 years and older, a SEM was built to explore the relationships between all variables mentioned above, except for testosterone substitution, experienced discrimination, and age of KS diagnosis. Testosterone substitution was removed from the model as it was frequently missing (51/205 missing) and almost always positive if non-missing (145/154). The role of ‘experienced discrimination’ in the SEM was unclear, for example, it was unclear whether it was a cause or an effect in the relation with occupation. Therefore, it was not included in the model. Inclusion of age of diagnosis resulted in worse model fit and it was not included in the final model. Possibly this variable was too much affected by the current age of the participants and country to result in clear patterns. Due to missing data, data of 137/164 men with KS ≥ 25 years were included in the final SEM.

The resulting exploratory model (see Fig. 2 and Table 5) shows the relationships between all other variables mentioned above. Overall, it indicates a strong impact of the severity of KS and the presence of health problems on the social economic status outcomes of occupation and satisfaction with income. Lower levels of education were associated with a worse subjective general health. Better general health was associated with higher levels of occupation. Having an occupation was related to higher levels of satisfaction with income (see Table 5).

**Discussion**

This is the first European multicenter study comparing education and socioeconomic outcomes of 218 men with KS with data from a European reference population of more than 1500 men. Our study shows that men with KS achieve lower levels of education and occupation and report less satisfaction with income compared to the ESS reference population.

**Level of education**

Our observation that fewer men with KS achieve a high level of education compared to the ESS reference population is in accordance with an earlier Danish registry study (8). They compared socioeconomic parameters in 1049 men with KS

**Table 4**  Linear regression analysis of the main outcomes and possibly associated factors in our study population of men with Klinefelter syndrome.

| Independent variable | Regression coefficient (B) | 95% CI          | P-value |
|----------------------|-----------------------------|-----------------|---------|
| Level of education (scale: 1–3) | Age at diagnosis | 0.120 | −0.133; 0.372 | 0.350 |
| | Subjective general health | 0.204 | 0.098; 0.310 | <0.001 |
| | Presence of health problems | −1.106 | −0.321; 0.110 | 0.334 |
| | Experienced discrimination | −0.013 | −0.242; 0.216 | 0.908 |
| | Social activity | 0.019 | −0.084; 0.121 | 0.721 |
| | Testosterone substitution | 0.209 | −0.312; 0.729 | 0.429 |
| Current occupation (scale: 1–2) | Age at diagnosis | 0.183 | 0.007; 0.359 | 0.041 |
| | Subjective general health | 0.155 | 0.081; 0.229 | <0.001 |
| | Presence of health problems | 0.218 | 0.372; 0.065 | 0.006 |
| | Experienced discrimination | −0.307 | −0.471; −0.144 | <0.001 |
| | Social activity | 0.027 | −0.048; 0.102 | 0.476 |
| | Testosterone substitution | 0.120 | −0.230; 0.470 | 0.499 |
| Satisfaction with income (scale: 1–4) | Age at diagnosis | −0.277 | −0.585; 0.031 | 0.077 |
| | Subjective general health | −0.199 | −0.334; −0.065 | 0.004 |
| | Presence of health problems | 0.209 | −0.068; 0.486 | 0.139 |
| | Experienced discrimination | 0.435 | 0.138; 0.731 | 0.004 |
| | Social activity | 0.077 | −0.053; 0.207 | 0.242 |
| | Testosterone substitution | 0.209 | −0.496; 0.913 | 0.559 |

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with 100,824 men of the general Danish population (8). Possible contributing factors to lower levels of education in men with KS may be a delay in neurocognitive development and a higher presence of both mental and somatic comorbidity (7, 14). This is supported by the results of our univariate analysis, showing an association between lower scores for general health and lower levels of education. Numerous studies report on learning problems, especially related to language (11, 15, 16) and difficulties in executive function in KS (17). Males with KS who are diagnosed during childhood have been reported to have a more severe phenotype, compared to men diagnosed at adulthood mainly due to fertility problems (18).

It can be speculated that early diagnosis and subsequent individualized interventions may have a positive effect on level of education, counteracting the effect of a more severe phenotype, especially on learning difficulties (19). We did not find an association between testosterone therapy and the level of education. This could be due to the fact that almost all men with KS in our study have been treated with testosterone. However, earlier studies reported no improvement of cognitive performance in patients with KS after testosterone supplementation (20, 21). In contrast, one study suggested that insufficient hormonal substitution may contribute to an increase in psychosocial morbidity, defined as an impaired ability to function based on the combined influence of psychological factors and the surrounding social environment (22). Furthermore, a prospective study by Samango-Sprouse et al. has found that early testosterone supplementation for 29 children with KS compared to no testosterone supplementation (57 children in the control group) had a significant benefit for social communication and social cognition (23). For clarification, a large randomized controlled study with long-term follow-up would be useful to investigate potential benefits or harms of testosterone therapy on SES in adolescents with KS.

### Occupational status

In our study, the risk of having no occupation was increased for men with KS compared to the ESS reference population. Men with KS were at a higher risk for being unemployed, actively looking for a new job; being permanently sick or disabled; or being in retirement. Our findings are supported by a Danish registry study investigating men...
with KS, reporting a hazard ratio (HR) of 2.4 (2.1–2.4) for early retirement, compared to a matched control group without KS (8). Accordingly, another study found the median age of retirement to be significantly lower for men with KS compared to a matched control group (43 years vs 60 years) (24). Skakkebaek et al. found a higher incidence of absence from work due to illness among men with KS (51%) compared to a matched control group (32%). Furthermore, they also reported a significantly higher percentage of men with KS to be retired compared to the age-matched control group (25). A possible explanation for higher levels of having no occupation of men with KS was given by our latent structure analysis. A higher severity of KS and a worse general health status led to a lower occupational status of men with KS. Therefore, more emphasis should be given to establish and evaluate individualized support programs to increase general health of men with KS.

Satisfaction with income

The present study showed a lower satisfaction rate with current household’s income among men with KS when compared to the ESS reference population, confirming the results of a national Danish cohort study (8, 24) and a more recent study about SES in men with KS (25). We were able to show in our latent structure analysis that a higher severity of KS and lower levels of education led to lower levels of subjective general health. Lower levels of general health led to lower levels of occupation and subsequently to lower levels of satisfaction with income. The treatment of men with KS may be improved by addressing KS-related physical and mental health problems (25).

Limitations

A main limitation of this study is the possibility of selection bias, as men with KS were mostly recruited from participating outpatient clinics and from patient support groups (for more information see Röhle et al. (12)). Unfortunately, it is unknown how many possible participants have been contacted at the different recruiting clinics and patient support groups. Furthermore, the questionnaire used in this study was rather long, taking about 3 hours to fill in, which might have led to a selection bias in favor of the comparatively better functioning men with KS. However, there was less than 10% missing data for all questions, except for the question about satisfaction with income, which 15% of men with KS did not answer. Additionally, the long questionnaire might have led to a relatively low number of included men with KS. Another limitation of this study is its retrospective, explorative design and that parts of the questionnaire contained self-constructed questions which contained subjective outcomes and were not validated. In the linear regression analysis, there was no adjustment for multiple comparisons because of the exploratory nature of this study and the primary concern about type II error. The results of the latent structure analysis should ideally have been based on more participants, and therefore the results should be considered exploratory.

Conclusion

Men with KS achieve on average lower levels of education, occupation and report less satisfaction with income compared to the ESS reference population. The presence of health problems and lower scores of general health were associated with lower levels of occupation and lower satisfaction with income in men with KS. Further studies are necessary to evaluate the effect of an earlier diagnosis and individualized support programs.

Declaration of interest

All authors declare no support from any organization for the submitted work; no relationship with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. Therefore, the authors declare that they have no competing interests.

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Availability of data and materials

The data sets analyzed during the current study are not publicly available as long as primary analyses for other outcomes of dsd-LIFE are not completed. Afterwards scientific public use files are planned. The data will be made available by the principal investigator upon request to researchers after publication of the primary outcomes described in the grant by the consortium.

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References

1. Bojesen A, Juul S & Gravholt CH. Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. Journal of Clinical Endocrinology and Metabolism 2003 88 622–626. (https://doi.org/10.1210/jc.2002-021491)
2. Forti G, Corona G, Vignozzi L, Krausz C & Maggi M. Klinefelter’s syndrome: a clinical and therapeutic update. Sexual Development 2010 4 249–258. (https://doi.org/10.1159/000360404)
3. Paulsen CA, Gordon DL, Carpenter RW, Gandy HM & Drucker WD. Klinefelter syndrome. Archives of Internal Medicine 1998 158 1309–1314. (https://doi.org/10.1001/archinte.158.12.1309)
4. Van Rijn S, Aleman A, Swaab H, van der Gracht WH, and Bremner WJ. Klinefelter syndrome. Archives of Sexual Behavior 2006 35 261–274. (https://doi.org/10.1007/s10550-005-9046-x)
5. Van Rijn S, Aleman A, Swaab H, Vink M, Sommer I & Kahn RS. Social behaviour and autism traits in a sex chromosomal disorder: Klinefelter (47,XXY) syndrome. Journal of Autism and Developmental Disorders 2008 38 1634–1641. (https://doi.org/10.1007/s10803-008-0542-1)
6. Turriff A, Macnamara E, Levy HP & Biesecker L. The impact of living in Klinefelter syndrome: a qualitative exploration of adolescents and adults. Journal of Genetic Counseling 2017 26 728–737. (https://doi.org/10.1007/s10897-016-0401-z)
7. Van Rijn S, Aleman A, Swaab H, Klein RS & Kahn RS. Social behaviour and autism traits in a sex chromosomal disorder: Klinefelter (47,XXY) syndrome. Journal of Autism and Developmental Disorders 2008 38 1634–1641. (https://doi.org/10.1007/s10803-008-0542-1)
8. Ratcliffe S. Long-term outcome in children of sex chromosome abnormalities. Archives of Disease in Childhood 1999 80 192–195. (https://doi.org/10.1136/adc.80.2.192)
9. Nielsen L. Klinefelter syndrome: the commonest form of hypogonadism, but often overlooked or untreated. Deutsches Ärzteblatt International 2013 110 347–353. (https://doi.org/10.3238/ arztebl.2013.0347)
10. Skakkebaek A, Wallentin M & Gravholt CH. Neuropsychology and socioeconomic aspects of Klinefelter syndrome: new developments. Current Opinion in Endocrinology, Diabetes, and Obesity 2015 22 209–216. (https://doi.org/10.1097/MED.0000000000000157)
11. Roehle R, Gehrmann K, Sasas-Zapnik M, Claahsen van der Grinten H, Pienkowski C, Bovatier C, Cohen-Kettenis P, Nordenström A, Thyen U, et al. Participation of adults with disorders/differences of sex development (DSD) in the clinical study dsd-LIFE: design, methodology, recruitment, data quality and study population. BMC Endocrine Disorders 2017 17 17–52. (https://doi.org/10.1186/s12902-017-0398-y)
12. Nordenström A, Röhle R, Thyen U, Bouvattier C, Slowikowska-Hilczer J, Reisch N, Claahsen van der Grinten H, Brác de la Perriere A, Cohen-Kettenis PT, Köhler B, et al. Hormone therapy and patient satisfaction with treatment, in a large cohort of diverse disorders of sex development. Clinical Endocrinology 2018 88 397–408. (https://doi.org/10.1111/cen.13518)
13. Ross JL, Zeger MP, Kushner H, Zinn AR & Roeltgen DP. An extra X or Y chromosome: contrasting the cognitive and motor phenotypes in childhood in boys with 47,XXX syndrome or 47,XXY Klinefelter syndrome. Developmental Disabilities Research Reviews 2009 15 309–317. (https://doi.org/10.1002/ddr.8)
14. Verri A, Cremante A, Cerici F, Destefani V & Radicioni A. Klinefelter’s syndrome and psychoneurologic function. Molecular Human Reproduction 2010 16 425–433. (https://doi.org/10.1093/molehr/gap018)
15. Van Rijn S, Aleman A, Swaab H, Vink M, Sommer I & Kahn RS. Effects of an extra X chromosome on language lateralization: an fMRI study with Klinefelter men (45,XXXY). Schizophrenia Research 2008 101 17–25. (https://doi.org/10.1016/j.schres.2008.02.001)
16. Tartaglia N, Cordeiro L, Howell S, Wilson R & Janusz J. The spectrum of the behavioral phenotype in boys and adolescents 47,XXY (Klinefelter syndrome). Pediatric Endocrinology Reviews 2010 8 (Supplement 1) 151–159.
17. Van Rijn S & Swaab H. Executive dysfunction and the relation with behavioral problems in children with 47,XXX and 47,XXX. Genes, Brain, and Behavior 2015 14 200–208. (https://doi.org/10.1111/gbb.12203)
18. Davis S, Howell S, Wilson R, Tanda T, Ross J, Zeitler P & Tartaglia N. Advances in the interdisciplinary care of children with Klinefelter syndrome. Advances in Pediatrics 2016 63 15–46. (https://doi.org/10.1016/j.yapd.2016.04.020)
19. Ross JL, Roeltgen DP, Stefanatos G, Benecke R, Zeger MP, Kushner H, Ramos P, Elder FF & Zinn AR. Cognitive and motor development during childhood in boys with Klinefelter syndrome. American Journal of Medical Genetics: Part A 2008 146A 708–719. (https://doi.org/10.1002/ajmg.a.32232)
20. Skakkebaek A, Moore PJ, Pedersen AD, Bojesen A, Kristensen MK, Fedder J, Laurberg P, Hertz JM, Ostergaard JR, Wallentin M, et al. The role of genes, intelligence, personality, and social engagement in cognitive performance in Klinefelter syndrome. Brain and Behavior 2017 7 e00645. (https://doi.org/10.1002/brb3.1220)
21. Simm PJ & Zacharin MR. The psychosocial impact of Klinefelter syndrome – a 10 year review. Journal of Pediatric Endocrinology and Metabolism 2006 19 499–505.
22. Samango-Sprouse C, Stapletoy E, Lawson P, Mitchell E, Sadeghin T, Powell S & Gropman AL. Positive effects of early androgen therapy on the behavioral phenotype of boys with 47,XXY. American Journal of Medical Genetics: Part C, Seminars in Medical Genetics 2015 169 150–157. (https://doi.org/10.1002/ajmg.c.31437)
23. Skakkebaek A, Moore PJ, Chang S, Fedder J & Gravholt CH. Quality of life in men with Klinefelter syndrome: the impact of genotype, health, socioeconomic, and sexual function. Genetics in Medicine 2018 20 214–222. (https://doi.org/10.1038/gim.2017.110)

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