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Criminality in males with Klinefelter syndrome and XYY syndrome – a cohort study

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Article focus: To investigate crime rates of persons with an extra sex chromosome (47,XXY and 47,XYY). Based on previous small studies we hypothesized that an increased crime rate would be present males with an extra sex chromosome and investigated this in a nationwide registry study.

Key messages:

1. **Using a nationwide approach we show that persons with KS (47,XXY) og 47,XYY are more frequently convicted for sexual abuse, burglary, arson, and other reasons. Traffic offenses are seen less frequently in both groups.**
2. **Whether early diagnosis and improved clinical care can lead to a decrease in convictions is not clear.**
3. **Socio-economic conditions modify our findings.**

Strengths and limitations:

1. **The study clearly delineates a pattern of increased crime rates among males with an extra sex chromosome. The strength of the present study is the large number of subjects with sex chromosomes and the large control group and the merging of several registries.**
2. **The limitations are that we were not able to control for concomitant medicinal use, especially testosterone use in Klinefelter syndrome, and to include clinical data**

Data sharing statement: There is no additional data available.

Abstract

Objective To investigate the criminal pattern in men between 15 and 70 years of age diagnosed with 47,XXY (Klinefelter syndrome [KS]) or 47,XYY compared to an age-matched cohort of men from the background population.

Design Register-based cohort study comparing the incidence of convictions among men with KS and with 47,XYY with matched samples of the general population. Crime was classified in eight types (sexual abuse, homicide, burglary, violence, traffic, drug-related, arson, and "others").

Setting Denmark 1978-2006.

Participants All men diagnosed with KS (N=934) or 47,XYY (N=161) at risk and their age and calendar time matched controls (N=88,979 and 15,356, respectively).

Results The incidence of convictions was increased in KS persons (omitting traffic offenses) compared to controls with a hazard ratio (HR) of 1.40 (1.23 – 1.59, p<0.001), with significant increases in sexual abuse, burglary, arson, and "others", but with a decreased risk of traffic and drug-related offenses. The incidence of convictions was significantly increased among 47,XYY persons compared to controls with a HR of 1.42 (1.14 to 1.77, p<0.005) in all crime types, except drug-related crimes and traffic. Adjusting for socio-economic variables (education, fatherhood, retirement and cohabitation) reduced the total hazard ratio to levels similar to controls, while some specific crime types remained increased.

Conclusion The overall risk of conviction (excluding traffic offenses) was moderately increased in 47,XYY persons and KS, however it was similar to controls when adjusting for socio-economic parameters. Convictions for sexual abuse, burglary, arson, and "others" were significantly increased. The increased risk of convictions may be partly or fully explained by the poor socio-economic conditions related to the chromosome aberrations.

What is already known on this topic

Increased crime rates of persons with an extra sex chromosome (47,XXY and 47,XYY) have been described in small studies. A study in tall persons and an extra sex chromosome reported crime rates similar to tall controls.

What this study adds

Using a nationwide approach we show that persons with KS (47,XXY) og 47,XYY are more frequently convicted for sexual abuse, burglary, arson, and other reasons. Traffic offenses are seen less frequently in both groups. Whether early diagnosis and improved clinical care can lead to a decrease in convictions is not clear.

Introduction

The sex chromosome trisomies 47,XXY (Klinefelter syndrome [KS]) and 47,XYY are the most common male sex chromosome aneuploidies compatible with live birth. KS affects 167 per 100,000 males [1,2,3], while the prevalence estimates of 47,XYY are highly variable, ranging in live born males from 26 per 100,000 [4] to 375 per 100,000,[5] although many are not diagnosed or diagnosed late[6]. Both KS and 47,XYY are much more frequent when studied in a tall population,[7] which is readily explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature) in males with KS and 47,XYY.[8] As with 47,XYY, many KS are not diagnosed, and a considerable delay in diagnosis exists for those who get a diagnosis.[2]

The 47,XYY sex chromosome abnormality has been described in various settings[9,6] since the first descriptions of a group of 47,XYY persons in 1965 by Jacobs et al[10] who conducted a chromosome survey of male patients at the State Hospital in Carstairs, Scotland, and found that men with the 47,XYY karyotype were particularly frequent among inmates in penal institutions. During the 1960s and 1970s, studies of KS and 47,XYY persons identified an increased frequency in hospitals for mentally handicapped,[11] and 47,XYY males seemed to be overrepresented in prisons.[12] Several of these studies reported a general increased rate of criminal behavior and increased crime rates among both cohorts, especially due to sexual crimes.[13] These studies were associated with selection problems as they investigated institutionalized individuals. Two relatively new studies of criminal behavior among sex chromosome trisomies have been published. Götz et al found an increased rate of criminal behavior among 47,XYY persons, but not among KS persons.[14] Another study from 1989 [15] linked KS with arson. However, both studies include a very limited number of persons. The study by Witkin et al in tall persons concluded that there was no evidence of an increased crime rate among KS and 47,XYY, but again with very few study subjects.[7] Long term follow-up of a cohort of KS (n=19) and 47,XYY (n=19) indicated that 47,XYY persons had a four-fold increase in convictions, mostly due to minor offenses. [16] All investigations conducted so far on this issue are limited by the study of selected groups, either institutionalized or clinic patients, in addition to methodological shortcomings such as self report of crimes, poorly defined definition of crime type and poorly defined controls groups. All studies have also been conducted in very small groups comprising less than 20 persons with a chromosome abnormality. The full spectrum of all types of crime has never been reported. As mentioned, diagnosis of both

syndromes is usually delayed and more than half of the expected individuals are never diagnosed [2,6], and a more thorough knowledge of all aspects these syndromes would most likely facilitate earlier diagnosis and possibly also better clinical care.

In order to examine the crime characteristics of KS and 47,XYY men, we undertook the present nationwide study, focusing not only on the total number of convictions, but also on various crime types. Thus, we investigated the criminal pattern of all diagnosed men with 47,XYY and KS compared with a large age and calendar time matched control group. We compared hazard ratios without and with adjustment for socio-economic variables in order to assess whether any increased risk of conviction could be explained by the poorer socio-economic conditions of KS and 47,XYY men. Further, the criminal pattern before and after the diagnosis of the chromosomal aberration was investigated.

Methods

The present study is a register-based study combining information from the Danish Cytogenetic Central Register, Statistics Denmark and the Danish Central Crime Registry.

Study population

Using the Danish Cytogenetic Central Register, we identified all males diagnosed with a karyotype compatible with KS, 47,XYY or variants thereof in Denmark by January 2009. These males are hereafter referred to as index-persons. The register was founded in 1967, and contains all information regarding cytogenetic analyses undertaken nationwide since 1960 including date of diagnosis. Unique identification numbers (ID-numbers) from the Civil Registration System enabled identification of every single person who is tested with an aberrant chromosomal analysis. ID-numbers are given to all Danish citizens since 1968. The ID-numbers ensured a one-to-one linkage between the registries.

Controls

For each index-person Statistics Denmark identified up to 100 age and calendar-time matched controls (matched on month and year of birth) from the male background population. All

dates of emigration and death were retrieved. All controls were alive and living in Denmark when their index-person was diagnosed. All controls emigrated or deceased before the index-person turned 15 years were excluded.

Convictions

The Danish Central Crime Register has previously been described as possibly the most thorough, comprehensive, and accurate crime register in the western world [17]. Since the register was digitalized on 1 November 1978, all charges and decisions for any reported offense in Denmark have been registered. We had access to annual information, and a person could be registered with multiple convictions the same year. We defined 1 July the relevant year as the date of the conviction. The study period was from 1 November 1978 to 31 December 2006, as 2006 was last year with available information.

In Denmark, the age of criminal responsibility is 15 years. All solved criminal acts committed by individuals born after 1 November 1963 has been registered in the crime register. We considered only persons between 15 and 70 years during the study period to be at risk of an event. We categorized the offenses into 8 groups – i.e. (1) sexual-related convictions including rape, (2) homicides, (3) violent convictions, (4) robbery, burglary and theft, (5) traffic offenses, (6) drug-related convictions not including violence, (7) arson and (8) others.

All convictions of an index-person or a control were retrieved from the crime register. We defined an event as the first conviction in all groups and in each of the 8 groups separately. Thus, only the first event was analyzed, and all succeeding events in the same group were excluded.

We discriminated between events before and after the diagnosis of a chromosome aberration. Also, in order to analyze whether the conviction and the diagnosis could be related, we in a separate analysis excluded all convictions up to two years before and two years after the diagnosis. We also discriminated between persons diagnosed early and late in life, using the median age at diagnosis as cut-point.

Socio-economic outcome parameters

From Statistics Denmark, we retrieved information regarding time of the following events, as previously described [18]: cohabitation with a partner, achievement of an education, fatherhood and retirement.

Cohabitation and marriage: We retrieved all persons' marital and cohabitational status each 1st of January. Data were available from 1980 through 2007. The event was first change from being single to be cohabitating with a partner.

Education: Data were category of education and dates for achieved education. An achieved bachelor degree or higher was considered "an education". The event was first achieved bachelor degree for a person between 18 and 40 years.

Children: All children born or adopted were registered from 1942 until 2007 with a linkage to both of their registered parents. Fatherhood was defined as the event of the first fathering of a child.

Retirement: We defined retirement as due to age, sickness and voluntary choice. A person was considered retired the first year money was received due to retirement, regardless of a later return to the labor market.

Ethics

The study protocol was approved by the Danish Data Protection Agency.

Statistics

Kaplan-Meier estimates were constructed for time of first conviction. Time at risk started at age of 15 years or at start of registration, whichever came last, and ended at the date of first event, at the age of 70 years, at emigration/death or 31 December 2006, whichever came first.

Hazard ratios (HR) were calculated using stratified Cox proportional hazards regression, where each case and his matched controls were one stratum. For the analyses, time at risk started on the 15th birthday or 1 November 1978, whichever came last, and time at risk ended 1 July the year we registered an event for the first time, on the date of emigration, on the 70th birthday, on the date of death, or 31 December 2006, whichever came first. For analyses before the diagnosis, time at risk ended no later than the date of diagnosis. For analyses after the diagnosis, time at risk started no earlier than the date of diagnosis.

For the analyses excluding all convictions two years before and after the diagnosis, all persons who had a first registration of a conviction of the relevant crime type during this period were excluded.

Finally, we analyzed convictions adjusted for cohabitation, education, fatherhood, and retirement.

All results are shown with 95% confidence interval, and $p<0.05$ was considered statistically significant. We made no formal correction for multiple comparisons. We used Stata 10.0 (Stata Corp. College Station,TX, USA) for all calculations.

Results

We identified 1,049 KS persons, whereof 934 were at risk of an event due to age between 15 and 70 during the registration period; similarly, 208 47,XYY persons were identified, and 161 were at risk of an event. For details on both cohorts of index-persons and their controls, see table 1.

KS persons

The risk of any conviction was similar in KS persons and controls with a hazard ratio of 0.95 (95% CI: 0.86 to 1.05, p=0.28), but was increased to 1.40 (95% CI: 1.23-1.59) when excluding traffic offenses (Table 2). Convictions of sexual abuse, burglary, arson, and "other" were moderately increased in KS persons (Figure 1 and 2). Only in the group "other" did the significance level change when excluding convictions two years before or after the diagnosis (Supplemental Figure 1) (from significantly increased to similar to controls). The hazard ratios were significantly increased for convictions of sexual abuse, burglary, and arson both before and after the KS diagnosis (Supplemental Table 1). The hazard ratios were lower in the cohort diagnosed late in life (Supplemental Figure 2). Adjusting for socio-economic parameters reduced the total hazard ratio (excluding traffic offenses) to a hazard ratio of 1.05 (95% CI: 0.90 – 1.23) (Table 2), but it was still significantly increased in the subgroups sexual abuse and arson. The hazard ratio for convictions of traffic offenses was significantly decreased both before and after adjustment for socio-economic parameters.

47,XYY persons

In total, the risk of convictions was moderately increased in 47,XYY persons compared to controls (HR: 1.42 (1.14 to 1.77), p<0.005) and even more pronounced (HR 2.09 (1.61-2.71), p<0.001) when excluding traffic offenses (Figure 3 and Table 2). A significantly increased hazard ratio was identified for convictions of sexual abuse, homicide, violence, burglary, arson, and "others" (Figure 4). In none of the eight conviction groups did the estimate change substantially when excluding convictions two years before or after the diagnosis (Supplemental Figure 3). Before the diagnosis, the hazard ratios were significantly increased for convictions of

sexual abuse only, and there were no events among the 47,XYY persons in homicides, drug-related convictions and the arson group (Supplemental Table 1). After the diagnosis, hazard ratios were significantly increased in all offense groups except for the traffic offenses (data not shown). There were no significant differences between hazard ratios for those diagnosed younger and older than the median age at diagnosis (Supplemental Figure 4). Adjusting for socio-economic parameters reduced the total hazard ratio (excluding traffic offenses) to 1.04 (95% CI: 0.68 – 1.61) (Table 2), and all other subgroup hazard ratios, but sexual abuse, decreased.

Discussion

This large study in KS and 47,XYY persons covering all diagnosed individuals in Denmark demonstrates that 47,XYY and KS persons are convicted of a number of specific offenses more frequently than the background population. The total number of convictions, however, was not increased in KS persons, primarily due to a significantly decreased number of traffic-related convictions. The study also demonstrates that unfavorable socio-economic conditions may be part of the explanation for the increased rate of convictions, since adjustment for socio-economic variables reduced the hazard ratio in both cohorts. We could also demonstrate an association between convictions and age at diagnosis in KS persons, i.e. the earlier the diagnosis had been made, the greater the likelihood of having been convicted of an offense.

Both KS and 47,XYY males are to a large extent diagnosed late or not diagnosed at all [2,6] and we have previously estimated that only 25 % of KS and 15% of 47,XYY get a diagnosis. The same pattern is seen in other countries [19,20]. Thus, the results of the present study apply to the studied cohort – in other words patients with KS and 47,XYY seen in daily clinical practice, and risk estimates may therefore not be applicable to groups of yet un-diagnosed males with sex-chromosome trisomies or even patients from other countries. We are well aware that the results of the present study may stigmatize persons with KS and 47,XYY due to the overrepresentation of convictions of sexual abuse and arson. But instead of suppressing such data we believe that they are pivotal in furthering the understanding of these syndromes.

We found a significantly increased cause-specific risk of convictions due to sexual abuse, burglary, arson and “others” among 47,XYY and KS men. Furthermore, the cause-specific risk of convictions due to homicide and violence was increased among persons with 47,XYY. We then studied the impact of socio-economic factors by adjusting for level of education, fatherhood, retirement and cohabitation. This adjustment lead to reductions in most HR, and only the risk of convictions for sexual abuse and arson among KS and only sexual abuse among 47,XYY persons remained significantly elevated. Among KS persons we found a significantly decreased risk of traffic-related convictions.

In general, information about sexual function in males with sex chromosome aberrations is sparse. Schiavi et al found that fewer 47,XYY men, but not KS men, were married,

experienced greater sexual dissatisfaction in general, acknowledged unconventional sexual experiences compared to a control group and demonstrated a less masculine gender role[21]. Furthermore 47,XYY men have been described as immature, having interpersonal and sexual difficulties[22]. Thus, men with KS and 47, XYY have been described with increased frequency of different or deviating sexual behavior, although it is important to stress that only few and small studies have investigated this subject. In addition, an increased vulnerability to psychiatric disorders and deviant behavior [23,24,25], psychophysiological dysfunction [26] and increased levels of autism traits in KS [27,28] together with a lower educational level and poor socio-economic status [18] may result in a increased susceptibility to commit a crime. We did not expect the finding of significantly increased risk of convictions for sexual abuse, and we believe this to be of considerable importance. The reason for the increased frequency of sexual abuse convictions is of course speculative, but may be due to the previously described feeling of being sexually different, which may end up in misinterpreting sexual cues, or possibly frustration leading to socially and legally unacceptable ways of achieving sexual satisfaction. Further studies are needed to clarify whether early diagnosis, sex steroids treatment, psychological therapy, or other initiatives may alter this finding.

Our findings of an increased frequency of convictions other than traffic offenses were not corroborated by the long term follow-up study by Ratcliffe, who only found increased criminality among 47,XYY persons (n=19), but not among KS persons (n=19), and that this increase primarily was due to minor offenses.[16]

Previous reports have linked KS persons with arson,[15,29] and a case report identified improvement on treatment for hypergonadotropic hypogonadism.[30] There have only been case reports of arson in 47,XYY males [14,31]. We have no specific explanation as to why this specific tendency is present, but it is possible that some of the psychopathological traits mentioned above, especially for the KS group, may prove explanatory in future studies.

Previously, lower intelligence has been pointed out as a contributing factor to the increased criminal behavior in 47,XYY men [14]. Götz et al investigated criminality and antisocial behavior in unselected KS and 47,XYY men and showed that 47,XYY men were more likely to have a criminal record compared to controls, and found this to be due to lower IQ (n=16) [14]. They found

no increase in the number of criminal records among KS persons compared with controls, possibly due to low power (n=13) [14]. Witkin et al found a significantly increased rate of criminality in 47,XYY (n=12) even after adjusting for social class and intelligence, while the crime rate among KS (n=16) after adjustment was similar to the background population [7].

We did find that the association between the crime rate (excluding traffic offenses) and either KS or 47,XYY was reduced when adjusting for socio-economic variables, such as level of education, retirement, cohabitation and fatherhood. In other words, the increased risk of conviction among the cases may partly or fully be explained by disadvantageous socio-economic conditions. However, although there may be a relationship between increased convictions and poor socio-economic status in persons with sex chromosomal abnormal phenotype, the causal relationship cannot be established.

We matched the current large group of patients with approximately 100 controls for each case. We did not match on other variables, such as socio-economic factors, since these factors could easily be causally involved in how the chromosome abnormality leads to a deviant pattern of criminality. This approach allowed us to use subsequent adjustments to clarify whether socio-economic factors were involved, which they in fact turned out to be. We did correct for level of education, fatherhood, retirement and cohabitation, although it can be problematic to control for social factors, because the chromosome aberrations per se can be the very reason for social problems, while the reverse is not possible. In addition, social problems – marginalization, lack of education, poverty, etc – can affect the risk of criminal behavior and of being detected and convicted. In other words, social problems may be part of a chain of events and adjustment would therefore introduce confounding. However, having controlled for these factors, we found that the hazard ratios for being convicted decreased and were no longer statistically significant for either group. Being well aware of the deviant behavior and learning difficulties present in both cohorts from a very young age, we hypothesize that these difficulties are part of the background for the identified increased number of convictions.

We identified an association between age at diagnosis and convictions in some groups in both cohorts. The findings of a more “normal” number of convictions in KS persons in those diagnosed when older than the median age of diagnosis might be explained by a less typical

phenotype, both physical and, perhaps more importantly, cognitive phenotype. However, this finding was not present in the 47,XYY persons. We find no reason to believe that a late diagnosis per se is positive. Due to the reported increased criminal problems we undertook analyses excluding those convicted in close proximity to the diagnosis. We hereby intended to avoid detection bias by excluding those who were diagnosed due to a conviction, and who may bias the results towards an increased number of convictions in the index-persons. As exclusion of such persons hardly changed the findings we believe that this type of bias can be ignored. The drawback of this study is the lack of clinical information, including IQ level, treatment with sex steroids, number of persons with a driving license and access to a car, and for instance psychiatric diagnoses. The advantages are the nationwide inclusion of all diagnosed men at risk with sex chromosome trisomies, and the close matching of the controls.

We were not able to control for concomitant medicinal use. There are usually no known hormonal deficits among males with 47,XYY, while men with KS often receive testosterone substitution therapy due to hypergonadotrophic hypogonadism. It has been speculated that early testosterone substitution in KS [32,33] would partially attenuate the impact of the syndrome on intellectual functioning and possibly other factors, but this remains to be studied. Others have speculated that testosterone substitution therapy could cause psychological disturbances, such as aggressive behavior and occasionally lead to violent crime, especially at supraphysiological doses [34], although a placebo controlled study of androgen treatment in healthy young males showed no or minimal change in mood or behavior [35,36]. We cannot fully exclude the possibility that the pattern of criminality among KS could be related to testosterone substitution therapy, while it seems unlikely that medicinal use among males with 47,XYY is related to criminality.

In conclusion, this study on all diagnosed men with a sex chromosome trisomy in Denmark identified a significantly increased number of convictions, excluding traffic offenses, both in KS persons and in 47,XYY persons. When adjusting for socio-economic factors, the adjusted risk was similar to controls for both cohorts. We interpret this as indicating that a main explanation of the increased risk of conviction is due to unfavorable living conditions associated with these syndromes. In both cohorts we found a significantly increased number of convictions due to sexual

offense and arson. Further studies are needed to identify whether these findings can be prevented by improved clinical care, including earlier diagnosis.

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Authorship and contributorship

KS, AB, SJ and CHG participated in the conception and design of the study. KS, AB, SJ, ASJ and CHG participated in the analysis and interpretation of data. KS and CHG drafted the article and KS, AB, SJ, ASJ and CHG approved the final version to be published.

Table 1

Karyotype	Number of persons at risk	Number of persons with at least one conviction	Median age at diagnosis	Median year of diagnosis	Median year of birth
47,XXY (KS)	934	385	27.7 (26.6 to 28.3)	1986 (1984 to 1987)	1961 (1959 to 1962)
Controls (KS)	88,829	37,085	-	-	-
47,XYY	161	80	20.6 (17.6 to 23.7)	1985 (1982 to 1989)	1969 (1963 to 1971)
Controls (47,XYY)	15,356	6,284	-	-	-

Basic characteristics of persons with Klinefelter syndrome (KS) or 47,XYY.
In parentheses 95% confidence intervals.

Table 2

Hazard ratios (95% confidence interval) for overall cause-specific convictions without and with adjustment for education, retirement, cohabitation, and fatherhood in KS and 47,XYY males.

	Crude HR	HR with adjustment
Klinefelter syndrome	1.40 (1.23 – 1.59)*	1.05 (0.90 – 1.23)*
Sexual abuse	4.02 (2.71 – 5.95)	2.74 (1.60 - 4.69)
Homicide	1.65 (0.23 – 11.90)	4.49 (0.54 – 37.04)
Violence	1.26 (0.95 – 1.66)	0.88 (0.62 – 1.26)
Burglary	1.59 (1.36 – 1.85)	1.03 (0.86 – 1.29)
Traffic	0.76 (0.57 – 0.86)	0.80 (0.69 – 0.93)
Drug-related	0.78 (0.52 – 1.17)	0.34 (0.20 – 0.60)
Arson	7.35 (4.42 – 12.23)	5.33 (2.67 – 10.63)
Others	1.21 (1.02 – 1.48)	1.01 (0.81 – 1.26)
47,XYY	2.09 (1.61 – 2.71)*	1.04 (0.68 – 1.61)*
Sexual abuse	11.79 (6.46 – 21.52)	3.66 (1.06 – 12.59)
Homicide	10.36 (1.31 – 81.77)	N/A
Violence	2.54 (1.57 – 4.11)	1.16 (0.51 – 2.63)
Burglary	2.07 (1.47 – 2.91)	0.93 (0.52 – 1.65)
Traffic	0.95 (0.72 – 1.26)	0.89 (0.60 – 1.31)
Drug-related	1.74 (0.90 – 3.36)	0.59 (0.19 – 1.85)
Arson	10.57 (3.76 – 29.76)	N/A
Others	1.89 (1.32 – 2.71)	1.39 (0.82 – 2.37)

*total HRs are computed omitting traffic offenses. N/A – a HR could not be computed due to low *n*.

Legends:

Figure 1

Legend: Kaplan-Meier plot of proportion of persons convicted (excluding traffic offenses) for the first time in the background population (thin line) and in males with Klinefelter syndrome (bold line). All were 15-70 years of age. The X-axis indicates age. HR: Hazard ratio.

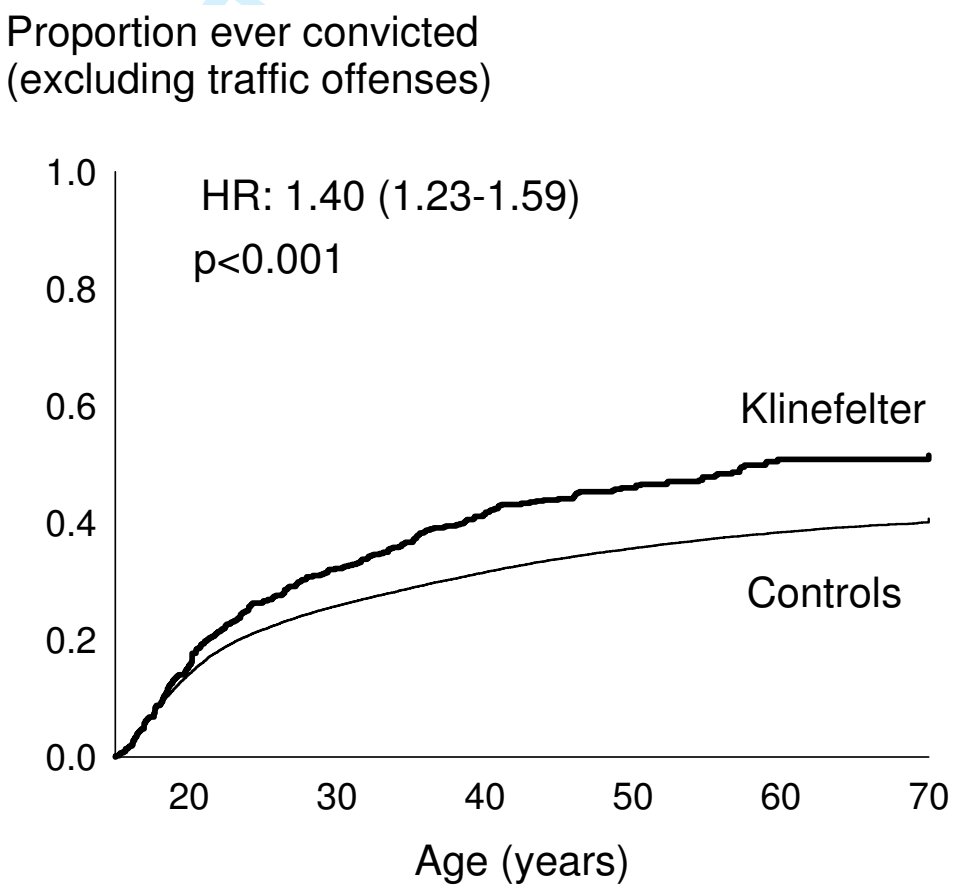


Figure 2

Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males (see Materials and Methods for details). Actual numbers of offenders (KS/controls) are given in parentheses.

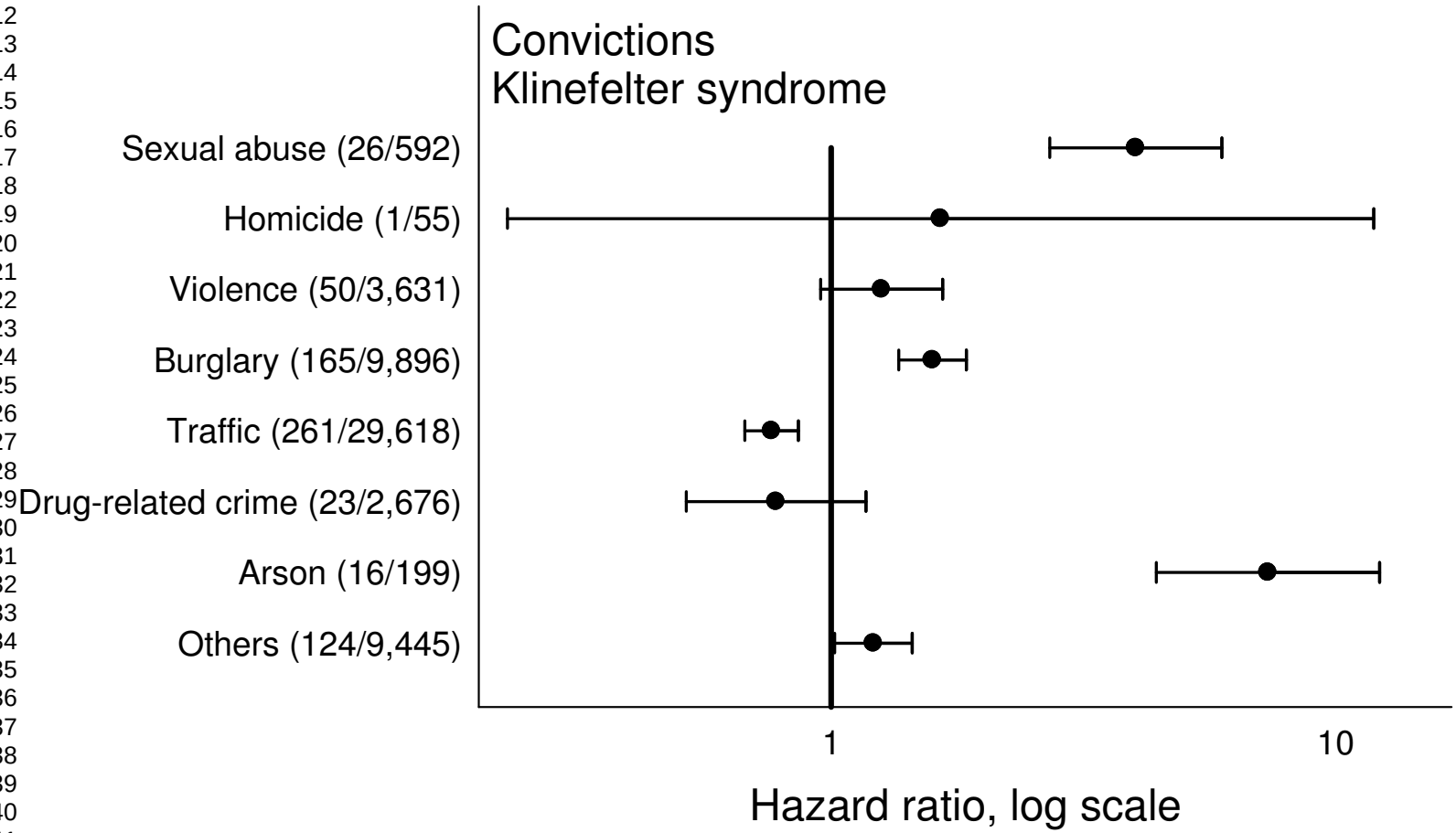


Figure 3

Legend: Kaplan-Meier plot of proportion of persons convicted (excluding traffic offenses) for the first time in the background population (thin line) and in males with 47,XYY (bold line). All were 15-70 years of age. The X-axis indicates age. HR: Hazard ratio.

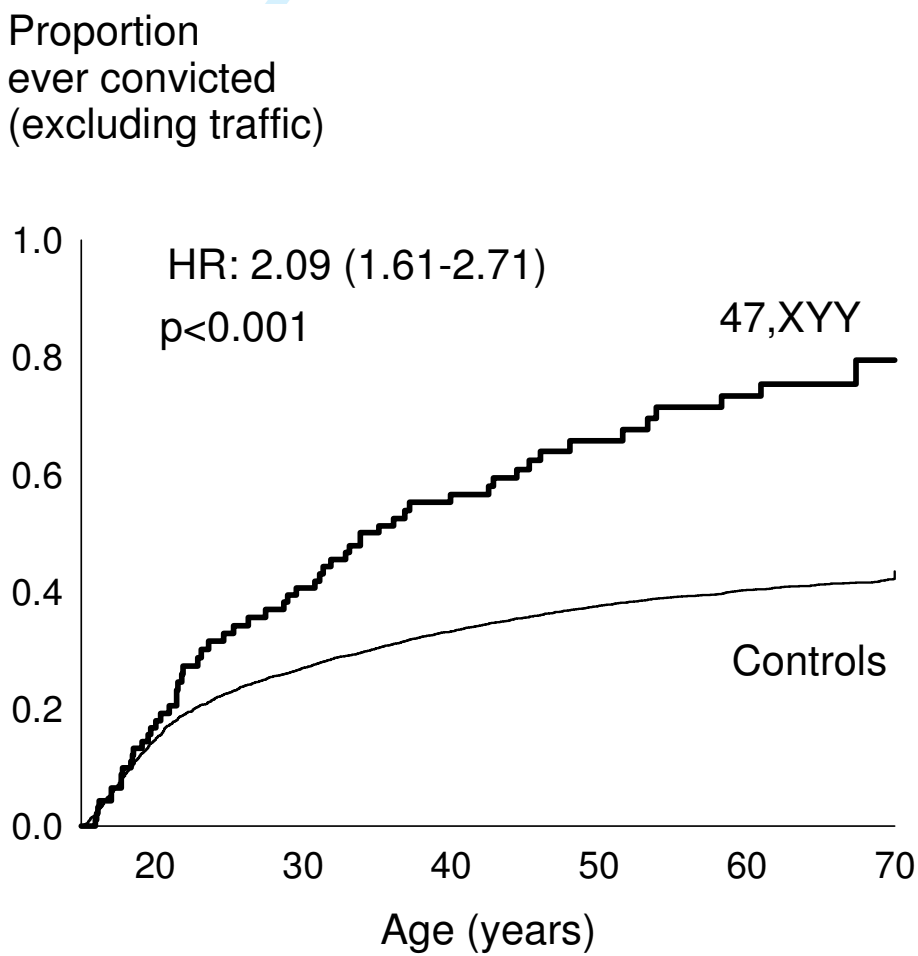
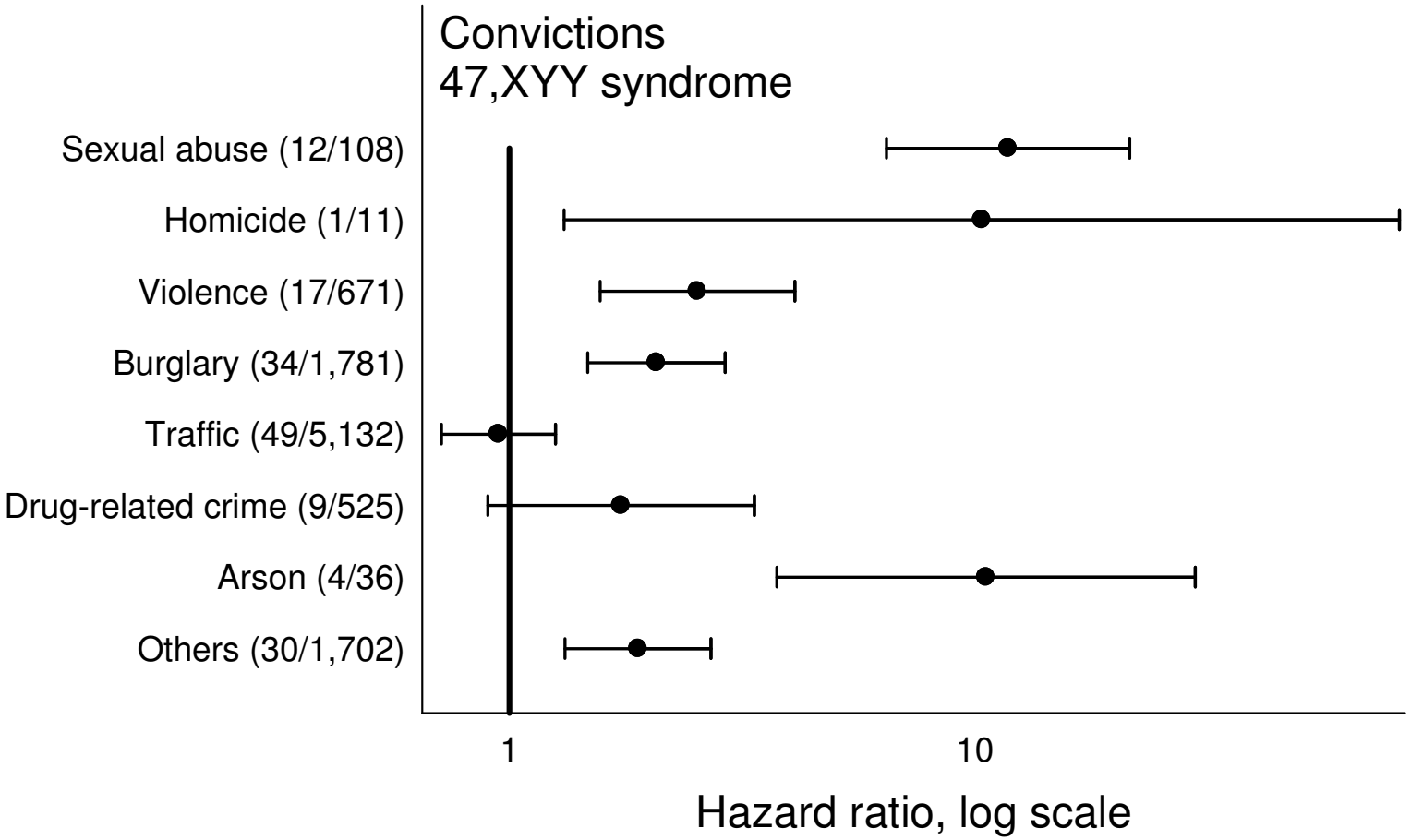


Figure 4

Legend: Hazard ratios of convictions due to cause in 47,XYY syndrome compared to age-matched males (see Materials and Methods for details). Actual numbers of offenders (KS/controls) is given in parentheses.



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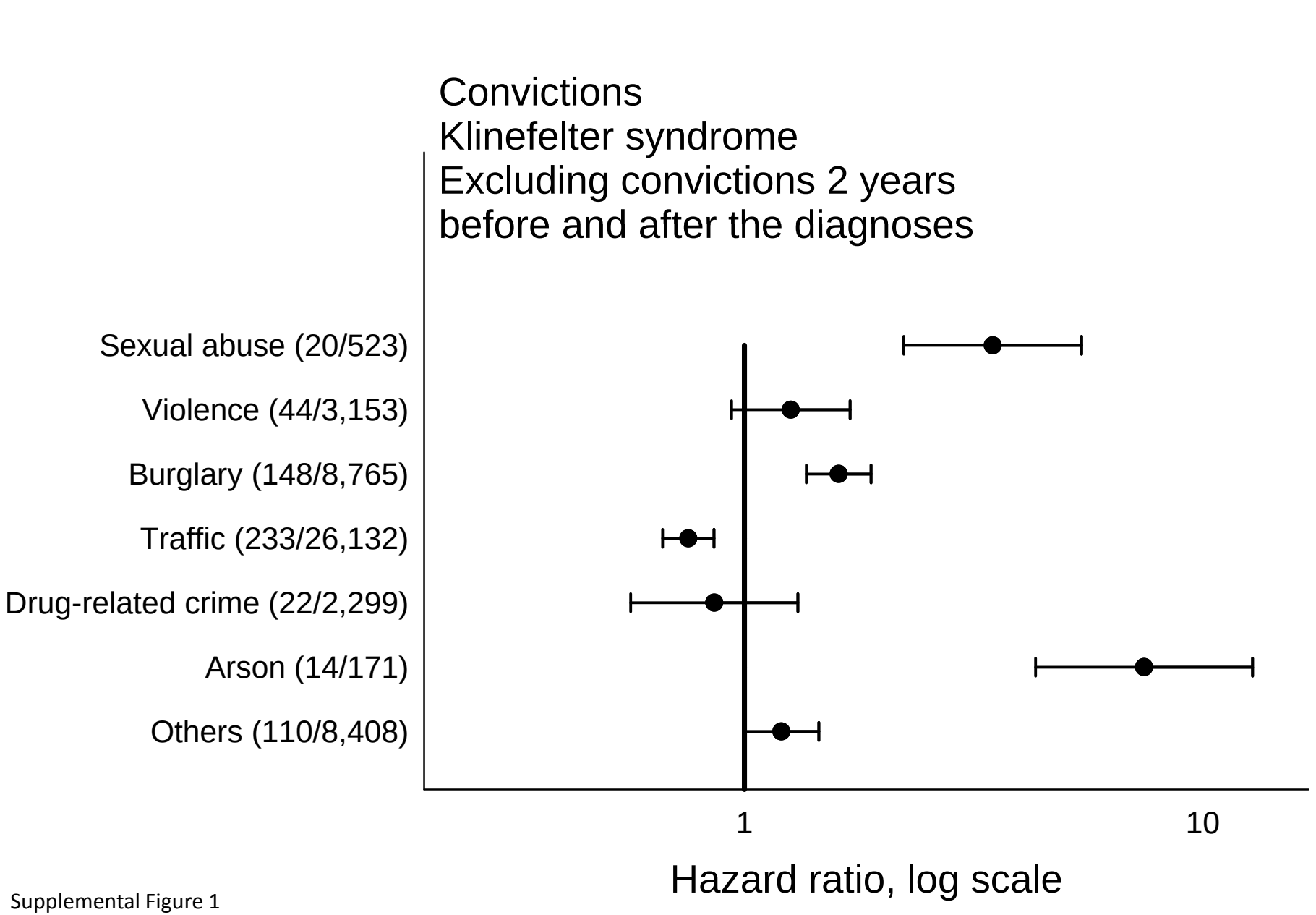
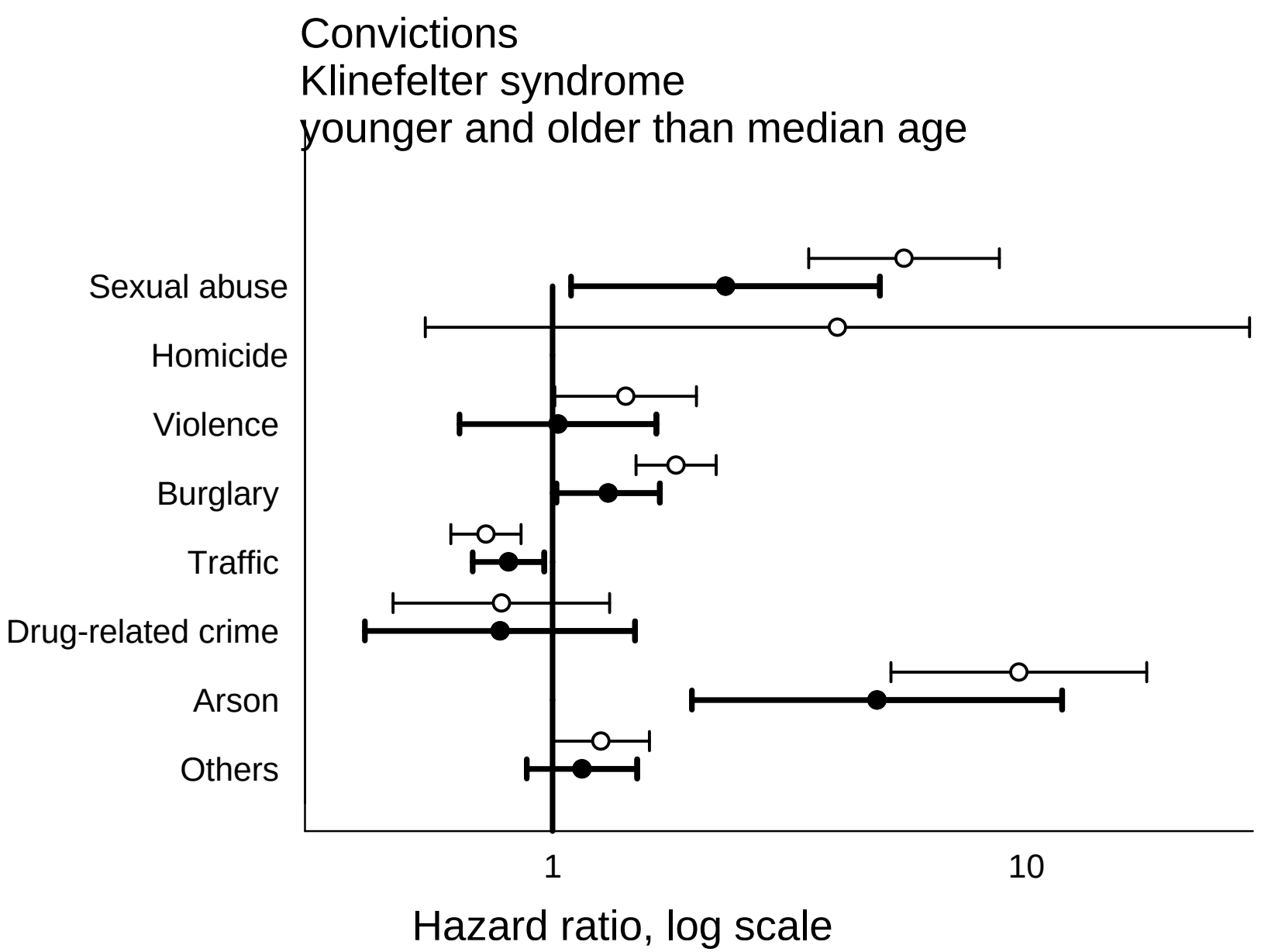


Supplemental Figure 1

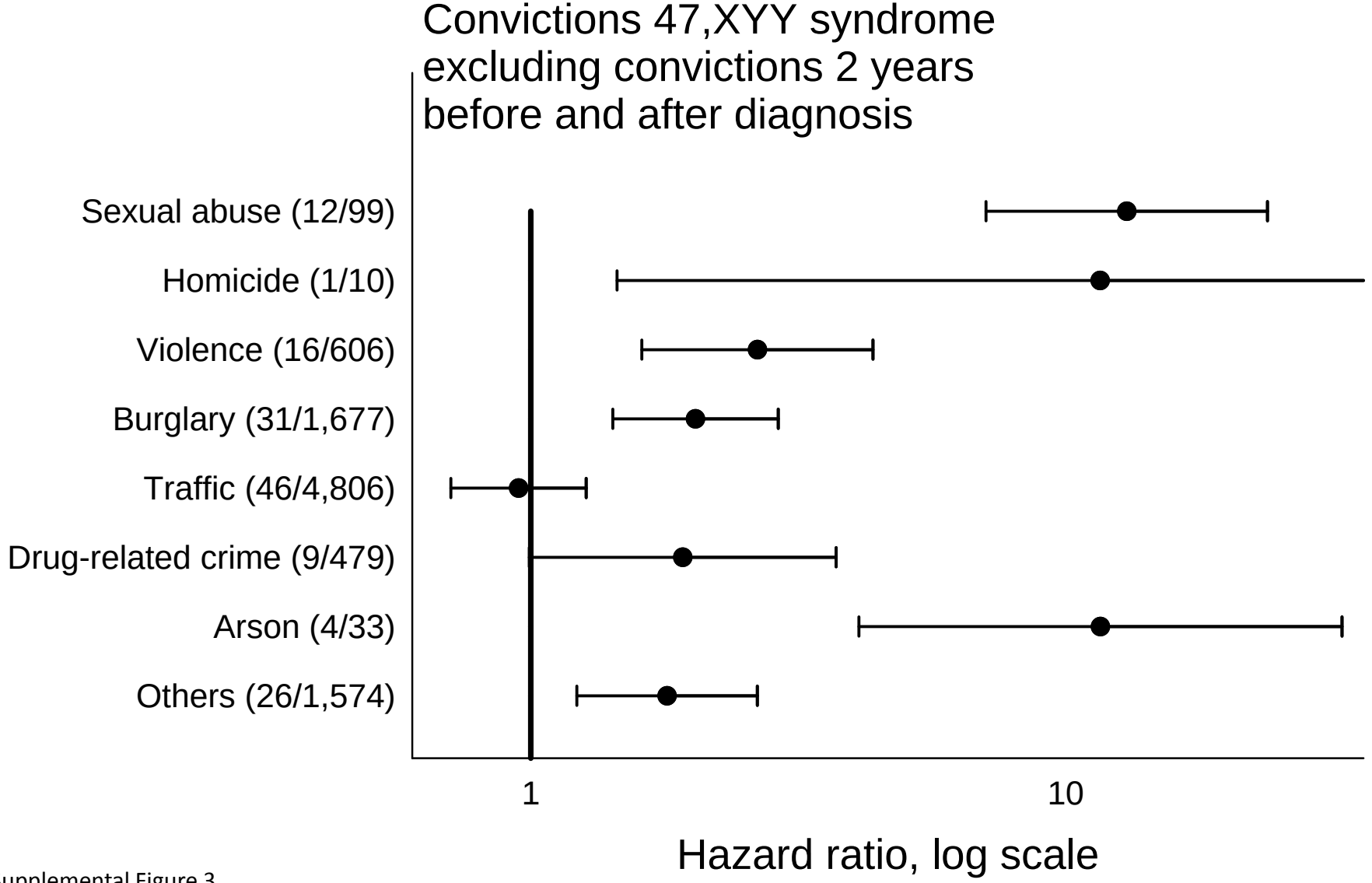
Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males (see Materials and Methods for details) after having excluded cases (and their controls) diagnosed 2 years before or after a conviction.

Actual numbers of offenders (KS/controls) are given in parentheses.



Supplemental Figure 2

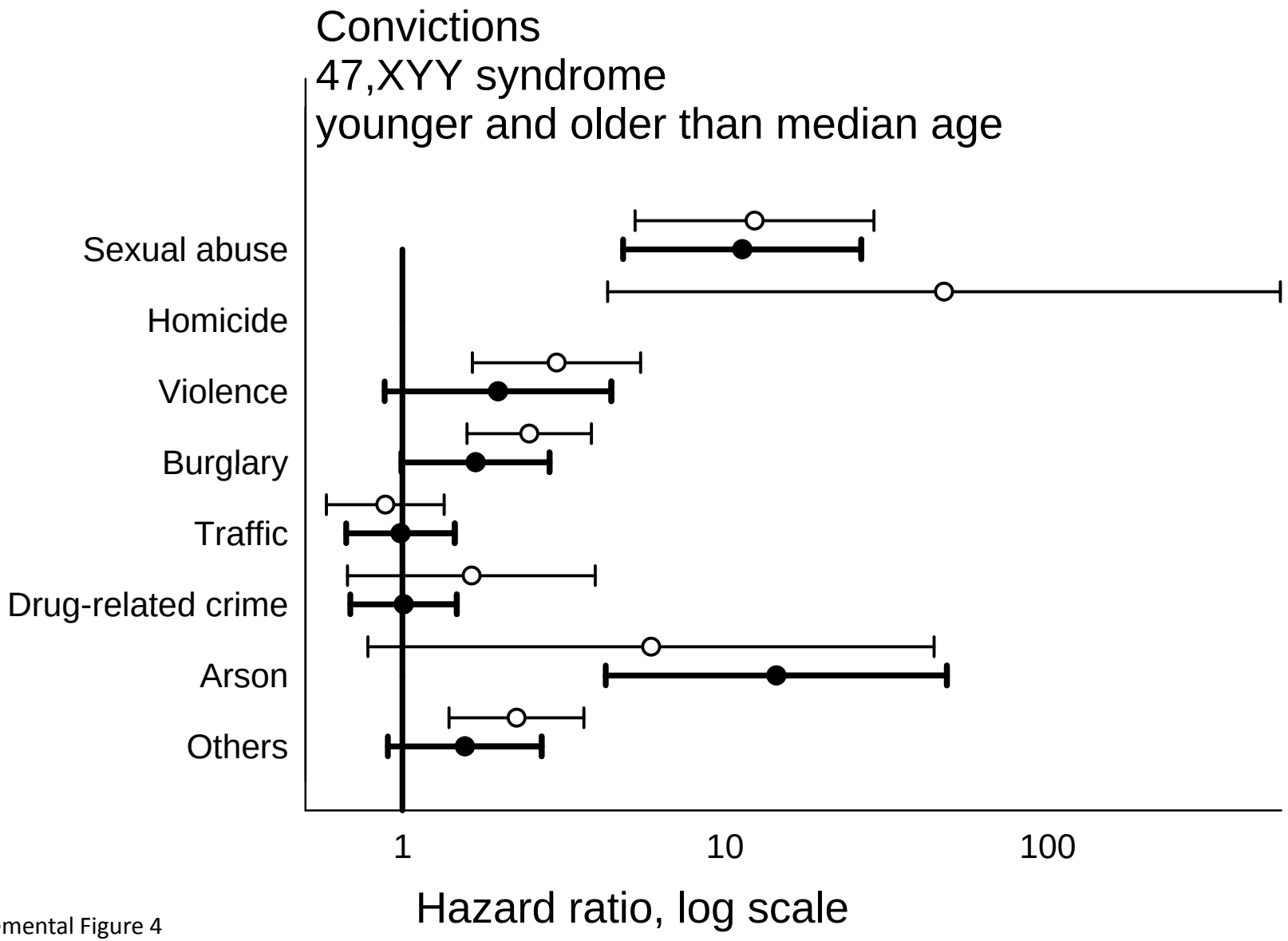
Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males after having divided cases (and their controls) in two depending on the median age at diagnosis into those diagnosed at a younger age (open circles) and those diagnosed at an older age (filled circles).



Supplemental Figure 3

Legend: Hazard ratios of convictions due to cause in 47,XYY syndrome compared to age-matched males (see Materials and Methods for details) after having excluded cases (and their controls) diagnosed 2 years before or after a conviction.

Actual numbers of offenders (47,XYY/controls) are given in parentheses.



Supplemental Figure 4

Legend: Hazard ratios of convictions due to cause in 47,XYY sndrome compared to age-matched males after having divided cases (and their controls) in two depending on the median age at diagnosis into those diagnosed at a younger age (open circles) and those diagnosed at an older age (filled circles).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Criminality in males with Klinefelter syndrome and XYY syndrome - a cohort study

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Criminality in males with Klinefelter syndrome and XYY syndrome – a cohort study

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Article focus: To investigate crime rates of men with an extra sex chromosome (47,XXY and 47,XYY). Based on previous small studies we hypothesized that an increased crime rate would be present in males with an extra sex chromosome and investigated this in a nationwide registry study.

Key messages:

1. **Using a nationwide approach we show that diagnosed men with Klinefelter syndrome (47,XXY) and 47,XYY are more frequently convicted for sexual abuse, burglary, arson, and other reasons. Traffic offenses are seen less frequently in both groups.**
2. **Whether early diagnosis and improved clinical care can lead to a decrease in convictions is not clear.**
3. **The increased crime rate may be partly or fully mediated by poor socio-economic conditions.**

Strengths and limitations:

1. **The study clearly delineates a pattern of increased crime rates among diagnosed males with an extra sex chromosome. The strength of the present study is the large number of males with sex chromosomes and the large control group and the merging of several registries.**
2. **The limitations are that we were not able to control for concomitant medicinal use, especially testosterone use in Klinefelter syndrome, nor to include clinical data**

Data sharing statement: There is no additional data available.

Abstract

Objective To investigate the criminal pattern in men between 15 and 70 years of age diagnosed with 47,XXY (Klinefelter syndrome [KS]) or 47,XYY compared to the general population.

Design Register-based cohort study comparing the incidence of convictions among men with KS and with 47,XYY with age and calendar matched samples of the general population. Crime was classified in eight types (sexual abuse, homicide, burglary, violence, traffic, drug-related, arson, and "others").

Setting Denmark 1978-2006.

Participants All men diagnosed with KS (N=934) or 47,XYY (N=161) at risk and their age and calendar time matched controls (N=88,979 and 15,356, respectively).

Results The incidence of convictions was increased in men with KS (omitting traffic offenses) compared to controls with a hazard ratio (HR) of 1.40 (1.23 – 1.59, p<0.001), with significant increases in sexual abuse, burglary, arson, and "others", but with a decreased risk of traffic and drug-related offenses. The incidence of convictions was significantly increased among men with 47,XYY compared to controls with a HR of 1.42 (1.14 to 1.77, p<0.005) in all crime types, except drug-related crimes and traffic. Adjusting for socio-economic variables (education, fatherhood, retirement and cohabitation) reduced the total hazard ratio for both KS and 47,XYY to levels similar to controls, while some specific crime types (sexual abuse, arson, etc.) remained increased.

Conclusion The overall risk of conviction (excluding traffic offenses) was moderately increased in men with 47,XYY or KS, however it was similar to controls when adjusting for socio-economic parameters. Convictions for sexual abuse, burglary, arson, and "others" were significantly increased. The increased risk of convictions may be partly or fully explained by the poor socio-economic conditions related to the chromosome aberrations.

Introduction

The sex chromosome trisomies 47,XXY (Klinefelter syndrome [KS]) and 47,XYY are the most common male sex chromosome aneuploidies compatible with live birth. KS affects 167 per 100,000 males [1,2,3], while the prevalence estimates of 47,XYY are highly variable, ranging in live born males from 26 per 100,000 [4] to 375 per 100,000,[5] although many are not diagnosed or diagnosed late[6]. Both KS and 47,XYY are much more frequent when studied in a tall population,[7] which is readily explained by the presence of additional copies of the SHOX gene (and possibly also other genes related to stature) in males with KS and 47,XYY.[8] As with 47,XYY, many KS are not diagnosed, and a considerable delay in diagnosis exists for those who get a diagnosis.[2]

The 47,XYY sex chromosome abnormality has been described in various settings[9,6] since the first descriptions of a group of 47,XYY males in 1965 by Jacobs et al[10] who conducted a chromosome survey of male patients at the State Hospital in Carstairs, Scotland, and found that men with the 47,XYY karyotype were particularly frequent among inmates in penal institutions. During the 1960s and 1970s, studies of KS and 47,XYY persons identified an increased frequency in hospitals for mentally handicapped,[11] and 47,XYY males seemed to be overrepresented in prisons.[12] Several of these studies reported a general increased rate of criminal behavior and increased crime rates among both cohorts, especially due to sexual crimes.[13] These studies were associated with selection problems as they investigated institutionalized individuals. Two relatively new studies of criminal behavior among sex chromosome trisomies have been published. Götz et al found an increased rate of criminal behavior among 47,XYY persons, but not among KS persons.[14] Another study from 1989 [15] linked KS with arson. However, both studies include a very limited number of persons. The study by Witkin et al in tall persons concluded that there was no evidence of an increased crime rate among KS and 47,XYY, but again with very few study subjects.[7] Long term follow-up of a cohort of KS (n=19) and 47,XYY (n=19) indicated that 47,XYY persons had a four-fold increase in convictions, mostly due to minor offenses. [16] All investigations conducted so far on this issue are limited by the study of selected groups, either institutionalized or clinic patients, in addition to methodological shortcomings such as self report of crimes, poorly defined definition of crime type and poorly defined controls groups. All studies have also been conducted in very small groups comprising less than 20 persons with a chromosome abnormality. The full spectrum of all types of crime has never been reported. As mentioned, diagnosis of both

syndromes is usually delayed and more than half of the expected individuals are never diagnosed [2,6], and a more thorough knowledge of all aspects these syndromes would most likely facilitate earlier diagnosis and possibly better clinical care.

In order to examine the crime characteristics of men with KS and 47,XYY, we undertook the present nationwide study, focusing not only on the total number of convictions, but also on various crime types. Thus, we investigated the criminal pattern of all men diagnosed with 47,XYY and KS compared with a large age and calendar time matched control group. We compared hazard ratios without and with adjustment for socio-economic variables in order to assess whether any increased risk of conviction could be explained by the poorer socio-economic conditions of KS and 47,XYY men. Further, the criminal pattern before and after the diagnosis of the chromosomal aberration was investigated.

Methods

The present study is a register-based study combining information from the Danish Cytogenetic Central Register, Statistics Denmark and the Danish Central Crime Registry.

Study population

Using the Danish Cytogenetic Central Register, we identified all males diagnosed with a karyotype compatible with KS, 47,XYY or variants thereof in Denmark by January 2009. These males are hereafter referred to as index-persons. The register was founded in 1967, and contains information regarding all cytogenetic analyses performed in Denmark since 1960 including date of diagnosis. Unique identification numbers (ID-numbers) from the Civil Registration System enabled identification of every single person diagnosed with an aberrant chromosomal analysis. ID-numbers are given to all Danish citizens since 1968. The ID-numbers ensured a one-to-one linkage between the registries.

Controls

For each index-person Statistics Denmark identified up to 100 age and calendar-time matched controls (matched on month and year of birth) from the male background population. All

dates of emigration and death were retrieved. All controls were alive and living in Denmark when their index-person was diagnosed. All controls emigrated or deceased before the index-person turned 15 years were excluded.

Convictions

The Danish Central Crime Register has previously been described as possibly the most thorough, comprehensive, and accurate crime register in the western world [17]. Since the register was digitalized on 1 November 1978, all charges and decisions for any reported offense in Denmark have been registered. We had access to annual information, and a person could be registered with multiple convictions the same year. We defined 1 July the relevant year as the date of the conviction. The study period was from 1 November 1978 to 31 December 2006, as 2006 was last year with available information.

In Denmark, the age of criminal responsibility is 15 years. All solved criminal acts committed by individuals born after 1 November 1963 has been registered in the crime register. We considered only persons between 15 and 70 years during the study period to be at risk of an event. We categorized the offenses into 8 groups – i.e. (1) sexual-related convictions including rape, (2) homicides, (3) violent convictions, (4) robbery, burglary and theft, (5) traffic offenses, (6) drug-related convictions not including violence, (7) arson and (8) others.

All convictions of an index-person or a control were retrieved from the crime register. We defined an event as the first conviction in any group and in each of the 8 groups separately. Thus, only the first event was analyzed, and all succeeding events in the same group were excluded.

We discriminated between events before and after the diagnosis of a chromosome aberration. Also, in order to analyze whether the conviction and the diagnosis could be related, we excluded all convictions up to two years before and two years after the diagnosis in a separate analysis. We also discriminated between persons diagnosed early and late in life, using the median age at diagnosis as cut-point.

Socio-economic outcome parameters

From Statistics Denmark, we retrieved information regarding time of the following events, as previously described [18]: cohabitation with a partner, achievement of an education, fatherhood and retirement.

Cohabitation and marriage: We retrieved all persons' marital and cohabitational status each 1st of January. Data were available from 1980 through 2007. The event was first change from being single to be cohabitating with a partner.

Education: Data were category of education and dates for achieved education. An achieved bachelor degree or higher was considered "an education". The event was first achieved bachelor degree for a person between 18 and 40 years.

Children: All children born or adopted were registered from 1942 until 2007 with a linkage to both of their registered parents. Fatherhood was defined as the event of the first fathering of a child.

Retirement: We defined retirement as due to age, sickness or voluntary choice. A person was considered retired the first year payment was received due to retirement, regardless of a later return to the labor market.

Ethics

The study protocol was approved by the Danish Data Protection Agency.

Statistics

Kaplan-Meier estimates were constructed for time of first conviction. Time at risk started at age of 15 years or at start of registration, whichever came last, and ended at the date of first event, at the age of 70 years, at emigration/death or 31 December 2006, whichever came first.

Hazard ratios (HR) were calculated using stratified Cox proportional hazards regression, where each case and his matched controls were one stratum. For the analyses, time at risk started on the 15th birthday or 1 November 1978, whichever came last, and time at risk ended 1 July the year we registered an event for the first time, on the date of emigration, on the 70th birthday, on the date of death, or 31 December 2006, whichever came first. For analyses before the diagnosis, time at risk ended no later than the date of diagnosis. For analyses after the diagnosis, time at risk started no earlier than the date of diagnosis.

For the analyses excluding all convictions two years before and after the diagnosis, all persons who had a first registration of a conviction of the relevant crime type during this period were excluded. We analyzed convictions adjusted for cohabitation, education, fatherhood, and retirement.

To examine a potential bias associated with undiagnosed KS and 47,XYY cases we performed a sensitivity analysis, assuming that the risk of conviction among undiagnosed cases is smaller than the risk observed among diagnosed cases, and we applied the statistical uncertainty from the observed data expressed by the standard error of the ln(HR) estimate.

All results are shown with 95% confidence interval, and $p<0.05$ was considered statistically significant. We made no formal correction for multiple comparisons. We used Stata 10.0 (Stata Corp. College Station,TX, USA) for all calculations.

Results

We identified 1,049 KS persons, whereof 934 were at risk of an event due to age between 15 and 70 during the registration period; similarly, 208 47,XYY persons were identified, and 161 were at risk of an event. For details on both cohorts of index-persons and their controls, see table 1.

KS persons

The risk of any conviction was similar in KS persons and controls with a hazard ratio of 0.95 (95% CI: 0.86 to 1.05, p=0.28), but was increased to 1.40 (95% CI: 1.23-1.59) when excluding traffic offenses (Table 2). Convictions of sexual abuse, burglary, arson, and "other" were moderately increased in KS persons (Figure 1 and 2). When excluding convictions within two years before and after the diagnosis the hazard ratios did not change substantially (Supplemental Figure 1). The hazard ratios were significantly increased for convictions of sexual abuse, burglary, and arson both before and after the KS diagnosis (Supplemental Table 1). The hazard ratios were lower in the cohort diagnosed late in life (Supplemental Figure 2). Adjusting for socio-economic parameters reduced the total hazard ratio (excluding traffic offenses) to a hazard ratio of 1.05 (95% CI: 0.90 – 1.23) (Table 2), but it was still significantly increased in the subgroups sexual abuse and arson. The hazard ratio for convictions of traffic offenses was significantly decreased both before and after adjustment for socio-economic parameters.

47,XYY persons

In total, the risk of convictions was moderately increased in 47,XYY persons compared to controls (HR: 1.42 (1.14 to 1.77), p<0.005) and even more pronounced (HR 2.09 (1.61-2.71), p<0.001) when excluding traffic offenses (Figure 3 and Table 2). A significantly increased hazard ratio was identified for convictions of sexual abuse, homicide, violence, burglary, arson, and "others" (Figure 4). In none of the eight conviction groups did the estimate change substantially when excluding convictions two years before or after the diagnosis (Supplemental Figure 3). Before the diagnosis, the hazard ratios were significantly increased for convictions of sexual abuse only, and there were no events among the 47,XYY persons in homicides, drug-related

convictions and the arson group (Supplemental Table 1). After the diagnosis, hazard ratios were significantly increased in all offense groups except for the traffic offenses (data not shown). There were no significant differences between hazard ratios for those diagnosed younger and older than the median age at diagnosis (Supplemental Figure 4). Adjusting for socio-economic parameters reduced the total hazard ratio (excluding traffic offenses) to 1.04 (95% CI: 0.68 – 1.61) (Table 2), and all other subgroup hazard ratios but sexual abuse decreased.

Discussion

This large study in KS and 47,XYY persons covering all diagnosed individuals in Denmark demonstrates that 47,XYY and KS persons are convicted of a number of specific offenses more frequently than the background population. The total number of convictions, however, was not increased in KS persons, primarily due to a significantly decreased number of traffic-related convictions. The study also demonstrates that unfavorable socio-economic conditions may be part of the explanation for the increased rate of convictions, since adjustment for socio-economic variables reduced the hazard ratio in both cohorts. We could also demonstrate an association between convictions and age at diagnosis in KS persons, i.e. the earlier the diagnosis had been made, the greater the likelihood of having been convicted of an offense.

Both KS and 47,XYY males are to a large extent diagnosed late or not diagnosed at all [2,6] and we have previously estimated that only 25 % of KS and 15% of 47,XYY get a diagnosis. The same pattern is seen in other countries [19,20]. Thus, the results of the present study apply to the studied cohort – in other words patients with KS and 47,XYY seen in daily clinical practice, and risk estimates may therefore not be applicable to groups of yet un-diagnosed males with sex-chromosome trisomies or even patients from other countries. We are well aware that the results of the present study may stigmatize persons with KS and 47,XYY due to the overrepresentation of convictions of sexual abuse and arson. But instead of suppressing such data we believe that they are pivotal in furthering the understanding of these syndromes.

We found a significantly increased cause-specific risk of convictions due to sexual abuse, burglary, arson and “others” among 47,XYY and KS men. Furthermore, the cause-specific risk of convictions due to homicide and violence was increased among persons with 47,XYY. We then studied the impact of socio-economic factors by adjusting for level of education, fatherhood, retirement and cohabitation. This adjustment lead to reductions in most HR, and only the risk of convictions for sexual abuse and arson among KS and only sexual abuse among 47,XYY persons remained significantly elevated. Among KS persons we found a significantly decreased risk of traffic-related convictions.

In general, information about sexual function in males with sex chromosome aberrations is sparse. Schiavi et al found that fewer 47,XYY men, but not KS men, were married,

experienced greater sexual dissatisfaction in general, acknowledged unconventional sexual experiences compared to a control group and demonstrated a less masculine gender role[21]. Furthermore 47,XYY men have been described as immature, having interpersonal and sexual difficulties[22]. Thus, men with KS and 47,XYY have been described with increased frequency of different or deviating sexual behavior, although it is important to stress that only few and small studies have investigated this subject. In addition, an increased vulnerability to psychiatric disorders and deviant behavior [23,24,25], psychophysiological dysfunction [26] and increased levels of autism traits in KS [27,28] together with a lower educational level and poor socio-economic status [18] may result in a increased susceptibility to commit a crime. We did not expect the finding of significantly increased risk of convictions for sexual abuse, and we believe this to be of considerable importance. The reason for the increased frequency of sexual abuse convictions is of course speculative, but may be due to the previously described feeling of being sexually different, which may end up in misinterpreting sexual cues, or possibly frustration leading to socially and legally unacceptable ways of achieving sexual satisfaction. Further studies are needed to clarify whether early diagnosis, sex steroids treatment, psychological therapy, or other initiatives may alter this finding.

Our findings of an increased frequency of convictions other than traffic offenses were not corroborated by the long term follow-up study by Ratcliffe, who only found increased criminality among 47,XYY persons (n=19), but not among KS persons (n=19), and that this increase primarily was due to minor offenses.[16]

Previous reports have linked KS persons with arson,[15,29] and a case report identified improvement on treatment for hypergonadotropic hypogonadism.[30] There have only been case reports of arson in 47,XYY males [14,31]. We have no specific explanation as to why this specific tendency is present, but it is possible that some of the psychopathological traits mentioned above, especially for the KS group, may prove explanatory in future studies.

Previously, lower intelligence has been pointed out as a contributing factor to the increased criminal behavior in 47,XYY men [14]. Götz et al investigated criminality and antisocial behavior in unselected KS and 47,XYY men and showed that 47,XYY men were more likely to have a criminal record compared to controls, and found this to be due to lower IQ (n=16) [14]. They found

no increase in the number of criminal records among KS persons compared with controls, possibly due to low power (n=13) [14]. Witkin et al found a significantly increased rate of criminality in 47,XYY (n=12) even after adjusting for social class and intelligence, while the crime rate among KS (n=16) after adjustment was similar to the background population [7].

We did find that the association between the crime rate (excluding traffic offenses) and either KS or 47,XYY was reduced when adjusting for socio-economic variables, such as level of education, retirement, cohabitation and fatherhood. In other words, the increased risk of conviction among the cases may partly or fully be explained by disadvantageous socio-economic conditions. However, although there may be a relationship between increased convictions and poor socio-economic status in persons with sex chromosomal abnormal phenotype, the causal relationship cannot be established.

We matched the current large group of patients with approximately 100 controls for each case. We did not match on other variables, such as socio-economic factors, since these factors could easily be causally involved in how the chromosome abnormality leads to a deviant pattern of criminality. Indeed, matching on socio-economic factors would likely lead to overmatching – which "is potentially capable of biasing study results beyond any hope of repair" [32]. The current approach allowed us to use subsequent adjustments to clarify whether socio-economic factors were involved, which they in fact turned out to be. We did correct for level of education, fatherhood, retirement and cohabitation, although it can be problematic to control for social factors, because the chromosome aberrations per se can be the very reason for social problems, while the reverse is not possible. In addition, social problems – marginalization, lack of education, poverty, etc – can affect the risk of criminal behavior and of being detected and convicted. In other words, social problems may be part of a chain of events and adjustment would

therefore introduce confounding. However, having controlled for these factors, we found that the total hazard ratios for being convicted decreased and were no longer statistically significant for either group. Being well aware of the deviant behavior and learning difficulties present in both cohorts from a very young age, we hypothesize that these difficulties are part of the background for the identified increased number of convictions. We then performed a sensitivity analysis to examine a potential bias arising if the severity of the syndrome affects both the risk of conviction and the probability of being diagnosed [33]. In one analysis we assumed that the excess hazard among undiagnosed cases was half the excess hazard seen among diagnosed cases, and we applied the statistical uncertainty from the observed data. In another similar analysis we assumed that the excess hazard among undiagnosed cases was similar to that in the background population. For KS we assumed that 25% of all cases had been diagnosed. In the sensitivity analyses the hazard ratios were reduced, but still significantly elevated for all convictions (excluding traffic offenses), and for sexual abuse, burglary, and arson (Supplementary Table 2). For 47,XYY we observed a similar pattern. Here we assumed that 15% of all cases had been diagnosed. In the sensitivity analysis the hazard ratios were reduced, but still significantly elevated for all convictions (excluding traffic offenses), and for sexual abuse, violence, burglary, and arson (Supplementary Table 2). In other words, it is highly likely that the crime rate would remain significantly increased in an entirely unbiased population of both KS and 47,XYY with complete diagnosis of all cases.

We identified an association between age at diagnosis and convictions in some groups in both cohorts. The findings of a more “normal” number of convictions in KS persons in those diagnosed when older than the median age of diagnosis might be explained by a less typical phenotype, both physical and, perhaps more importantly, cognitive phenotype. However, this

finding was not present in the 47,XYY persons. We find no reason to believe that a late diagnosis per se is positive. Due to the reported increased criminal problems we undertook analyses excluding those convicted in close proximity to the diagnosis. We hereby intended to avoid detection bias by excluding those who were diagnosed due to a conviction, and who may bias the results towards an increased number of convictions in the index-persons. As exclusion of such persons hardly changed the findings we believe that this type of bias can be ignored. The drawback of this study is the lack of clinical information, including IQ level, treatment with sex steroids, number of persons with a driving license and access to a car, and for instance psychiatric diagnoses. The advantages are the nationwide inclusion of all diagnosed men at risk with sex chromosome trisomies, and the close matching of the controls.

We were not able to control for concomitant medicinal use. There are usually no known hormonal deficits among males with 47,XYY, while men with KS often receive testosterone substitution therapy due to hypergonadotrophic hypogonadism. It has been speculated that early testosterone substitution in KS [34,35] would partially attenuate the impact of the syndrome on intellectual functioning and possibly other factors, but this remains to be studied. Others have speculated that testosterone substitution therapy could cause psychological disturbances, such as aggressive behavior and occasionally lead to violent crime, especially at supraphysiological doses [36], although a placebo controlled study of androgen treatment in healthy young males showed no or minimal change in mood or behavior [37,38]. We cannot fully exclude the possibility that the pattern of criminality among KS could be related to testosterone substitution therapy, while it seems unlikely that medicinal use among males with 47,XYY is related to criminality. We note that the pattern of criminality in 47,XYY, who have a normal testosterone production, was equal or higher than among KS, and furthermore that criminality among KS was elevated even before

diagnosis and thus before commencement of supplementation with testosterone, making it unlikely that testosterone supplementation is causally involved in the excess criminality in KS. In addition in many KS males conventional testosterone supplementation is often not sufficient and many KS males are also not compliant, at least not all the time, resulting in hypotestosteronemia, elevated LH and diseases, symptoms and signs related to hypogonadism [39,40,41].

In conclusion, this study on all diagnosed men with a sex chromosome trisomy in Denmark identified a significantly increased number of convictions, excluding traffic offenses, both in KS persons and in 47,XYY persons. When adjusting for socio-economic factors, the adjusted risk was similar to controls for both cohorts. We interpret this as indicating that a main explanation of the increased risk of conviction is due to unfavorable living conditions associated with these syndromes. In both cohorts we found a significantly increased number of convictions due to sexual offense and arson. Further studies are needed to identify whether these findings can be prevented by improved clinical care, including earlier diagnosis.

Acknowledgements

The authors have no potential conflicts of interest. KS had full access to all of the data in the study and KS and CHG takes responsibility for the integrity of the data, the accuracy of the data analysis and the decision to publish.

Authorship and contributorship

KS, AB, SJ and CHG participated in the conception and design of the study. KS, AB, SJ, ASJ and CHG participated in the analysis and interpretation of data. KS and CHG drafted the article and KS, AB, SJ, ASJ and CHG approved the final version to be published.

Table 1

Karyotype	Number of persons at risk	Number of persons with at least one conviction	Median age at diagnosis	Median year of diagnosis	Median year of birth
47,XXY (KS)	934	385	27.7 (26.6 to 28.3)	1986 (1984 to 1987)	1961 (1959 to 1962)
Controls (KS)	88,829	37,085	-	-	-
47,XYY	161	80	20.6 (17.6 to 23.7)	1985 (1982 to 1989)	1969 (1963 to 1971)
Controls (47,XYY)	15,356	6,284	-	-	-

Basic characteristics of persons with Klinefelter syndrome (KS) or 47,XYY.
In parentheses 95% confidence intervals.

Table 2

Hazard ratios (95% confidence interval) for overall cause-specific convictions without and with adjustment for education, retirement, cohabitation, and fatherhood in KS and 47,XYY males.

	Crude HR	HR with adjustment
Klinefelter syndrome	1.40 (1.23 – 1.59)*	1.05 (0.90 – 1.23)*
Sexual abuse	4.02 (2.71 – 5.95)	2.74 (1.60 - 4.69)
Homicide	1.65 (0.23 – 11.90)	4.49 (0.54 – 37.04)
Violence	1.26 (0.95 – 1.66)	0.88 (0.62 – 1.26)
Burglary	1.59 (1.36 – 1.85)	1.03 (0.86 – 1.29)
Traffic	0.76 (0.57 – 0.86)	0.80 (0.69 – 0.93)
Drug-related	0.78 (0.52 – 1.17)	0.34 (0.20 – 0.60)
Arson	7.35 (4.42 – 12.23)	5.33 (2.67 – 10.63)
Others	1.21 (1.02 – 1.48)	1.01 (0.81 – 1.26)
47,XYY	2.09 (1.61 – 2.71)*	1.04 (0.68 – 1.61)*
Sexual abuse	11.79 (6.46 – 21.52)	3.66 (1.06 – 12.59)
Homicide	10.36 (1.31 – 81.77)	N/A
Violence	2.54 (1.57 – 4.11)	1.16 (0.51 – 2.63)
Burglary	2.07 (1.47 – 2.91)	0.93 (0.52 – 1.65)
Traffic	0.95 (0.72 – 1.26)	0.89 (0.60 – 1.31)
Drug-related	1.74 (0.90 – 3.36)	0.59 (0.19 – 1.85)
Arson	10.57 (3.76 – 29.76)	N/A
Others	1.89 (1.32 – 2.71)	1.39 (0.82 – 2.37)

*total HRs are computed omitting traffic offenses. N/A – a HR could not be computed due to low *n*.

Legends:

Figure 1

Legend: Kaplan-Meier plot of proportion of persons convicted (excluding traffic offenses) for the first time in the background population (thin line) and in males with Klinefelter syndrome (bold line). All were 15-70 years of age. HR: Hazard ratio.

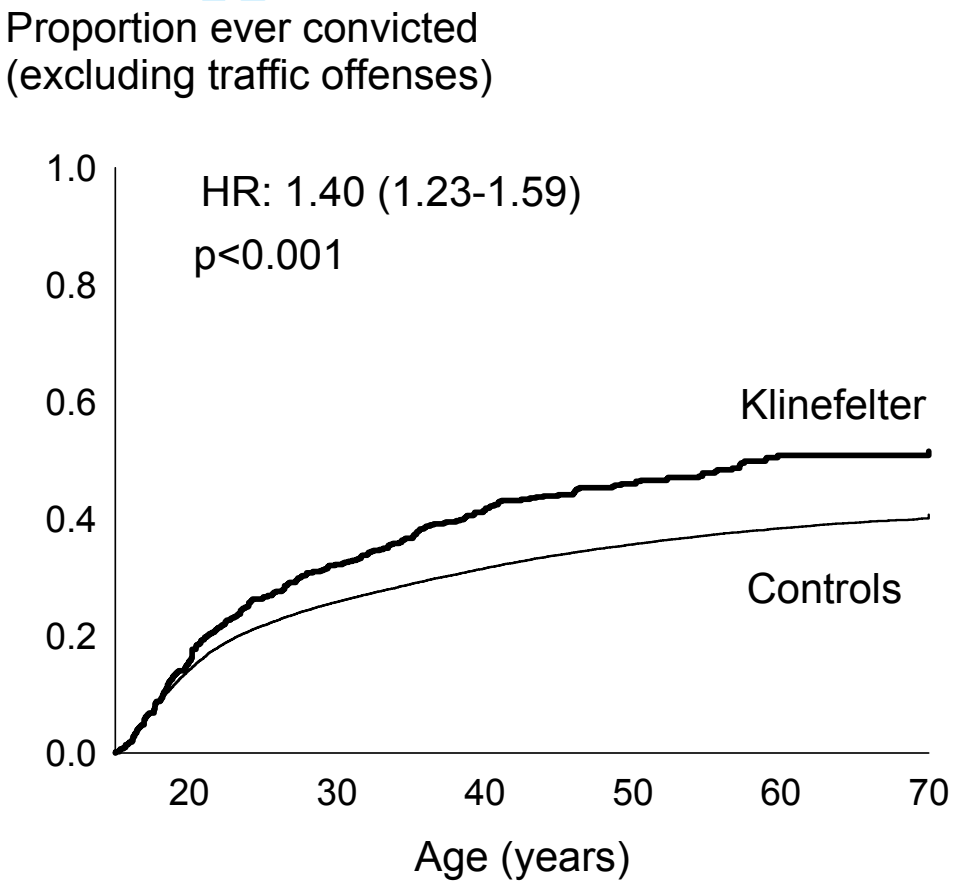


Figure 2

Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males (see Materials and Methods for details). Actual numbers of offenders (KS/controls) are given in parentheses.

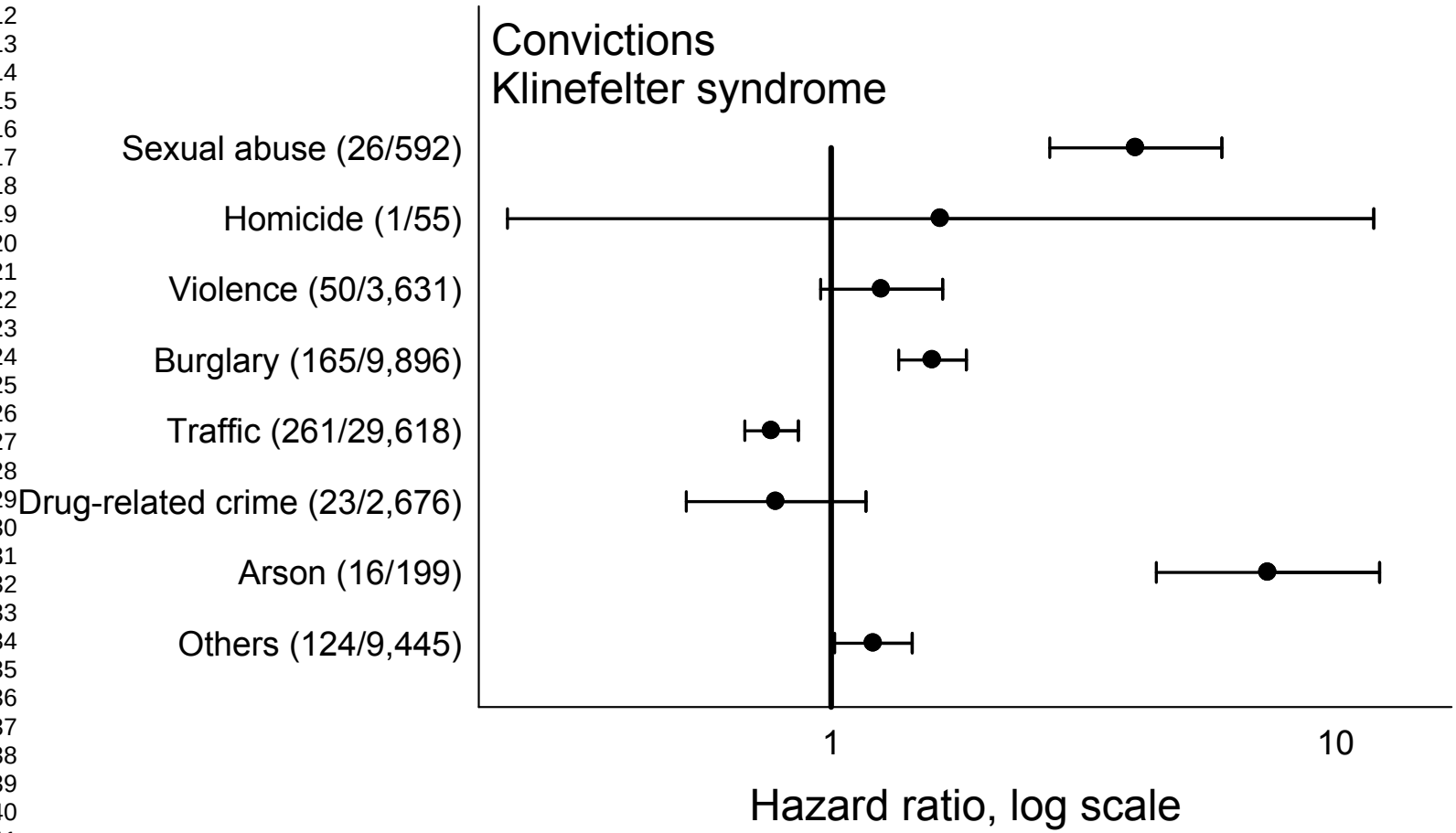


Figure 3

Legend: Kaplan-Meier plot of proportion of persons convicted (excluding traffic offenses) for the first time in the background population (thin line) and in males with 47,XYY (bold line). All were 15-70 years of age. HR: Hazard ratio.

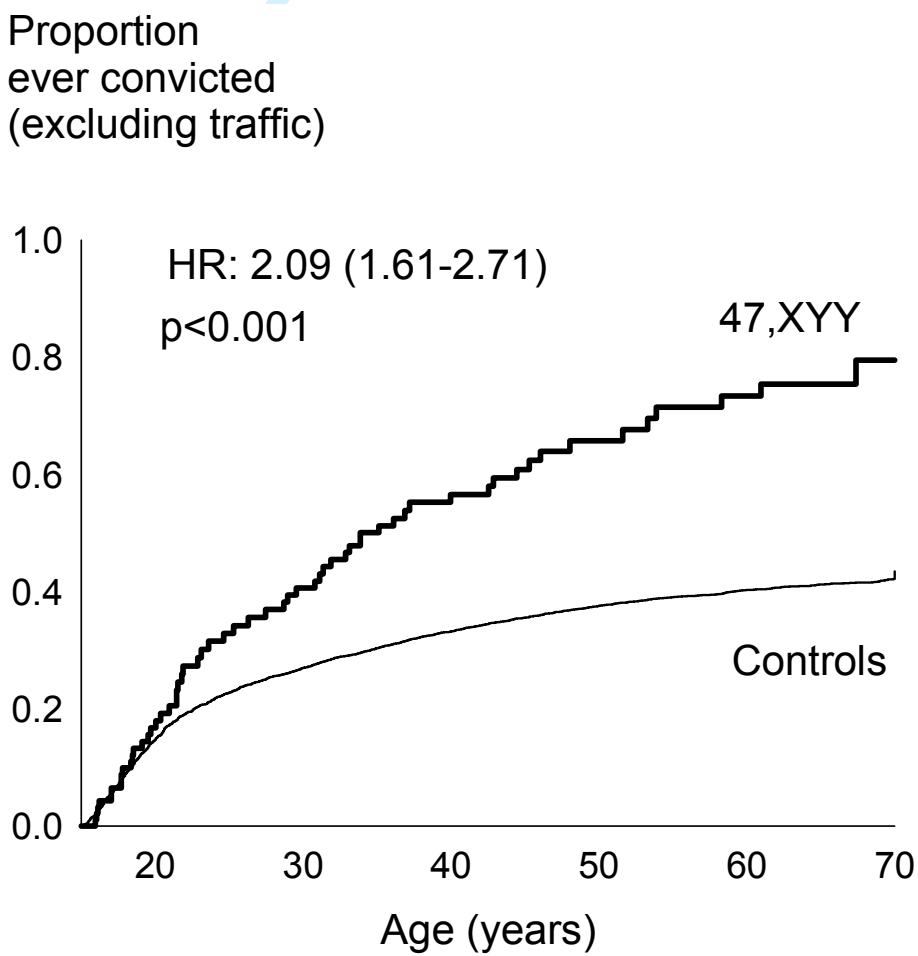
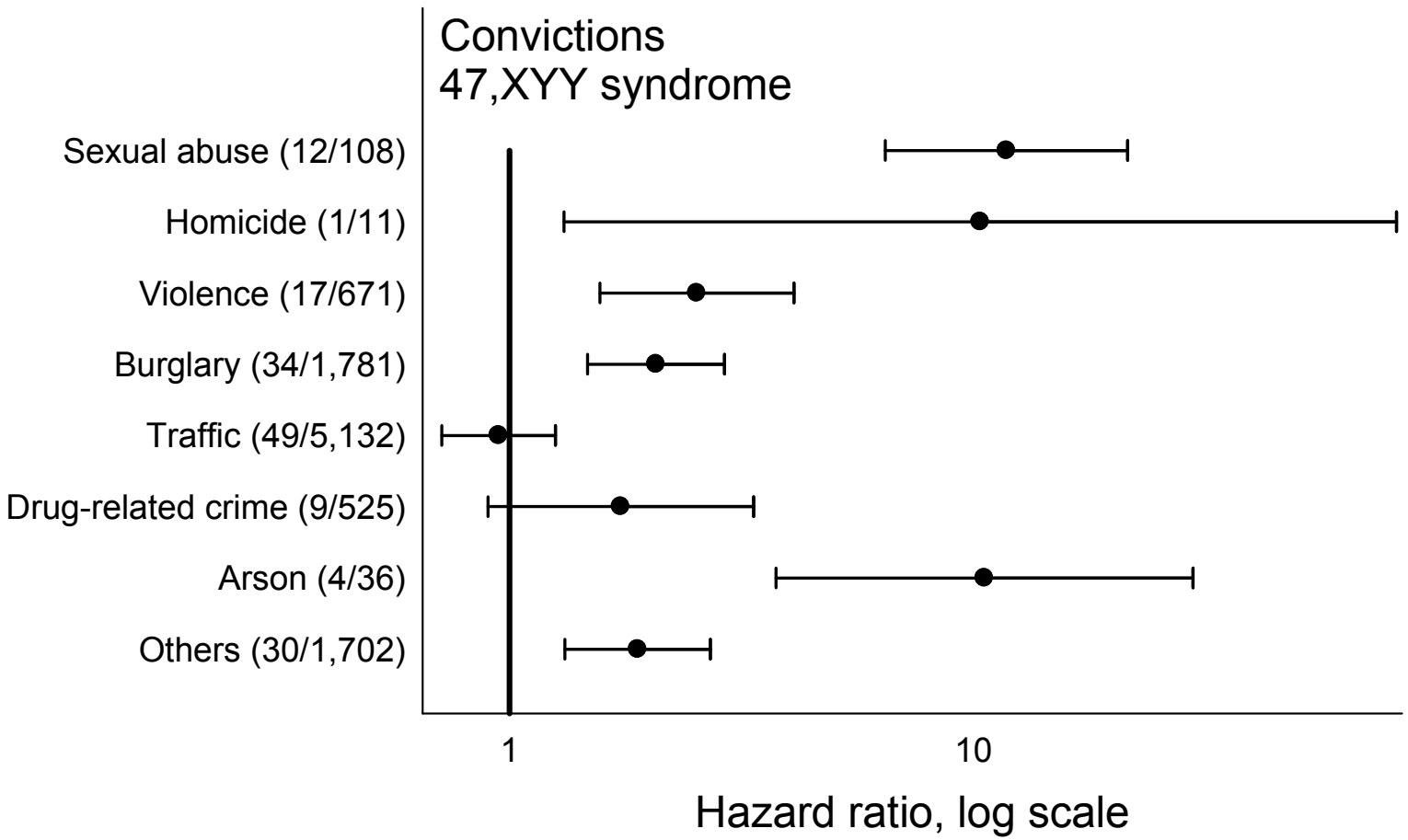


Figure 4

Legend: Hazard ratios of convictions due to cause in 47,XYY syndrome compared to age-matched males (see Materials and Methods for details). Actual numbers of offenders (KS/controls) is given in parentheses.



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Supplemental Table 1

Hazard ratios (95% confidence interval) for convictions before and after a diagnosis of either KS or 47.XYY.

	HR before diagnosis	HR after diagnosis
Klinefelter syndrome		
Sexual abuse	3.2 (1.4 – 7.2)	4.4 (2.8 – 6.8)
Violence	1.1 (0.7 – 1.8)	1.4 (1.0 – 1.9)
Homicide	-	2.7 (0.4 – 20.0)
Burglary	1.3 (1.1 – 1.7)	1.8 (1.5 – 2.2)
Traffic	0.8 (0.7 – 1.0)	0.7 (0.6 – 0.8)
Drug-related crime	0.5 (0.3 – 1.1)	1.0 (0.6 – 1.6)
Arson	5.4 (2.2 – 13.3)	8.8 (4.7 – 16.3)
Others	1.4 (1.1 – 1.8)	1.1 (0.9 – 1.4)
47.XYY		
Sexual abuse	13.7 (4.1 – 46.2)	11.3 (5.6 – 22.5)
Violence	0.5 (0.1 – 3.6)	3.4 (2.1 – 5.6)
Homicide	-	11.7 (1.5 – 93.6)
Burglary	0.5 (0.2 – 1.5)	3.0 (2.1 – 4.3)
Traffic	0.9 (0.5 – 1.5)	1.0 (0.7 – 1.4)
Drug-related crime	-	2.6 (1.3 – 5.0)
Arson	-	14.3 (5.0 – 41.1)
Others	1.5 (0.7 -3.2)	2.0 (1.3 – 3.1)

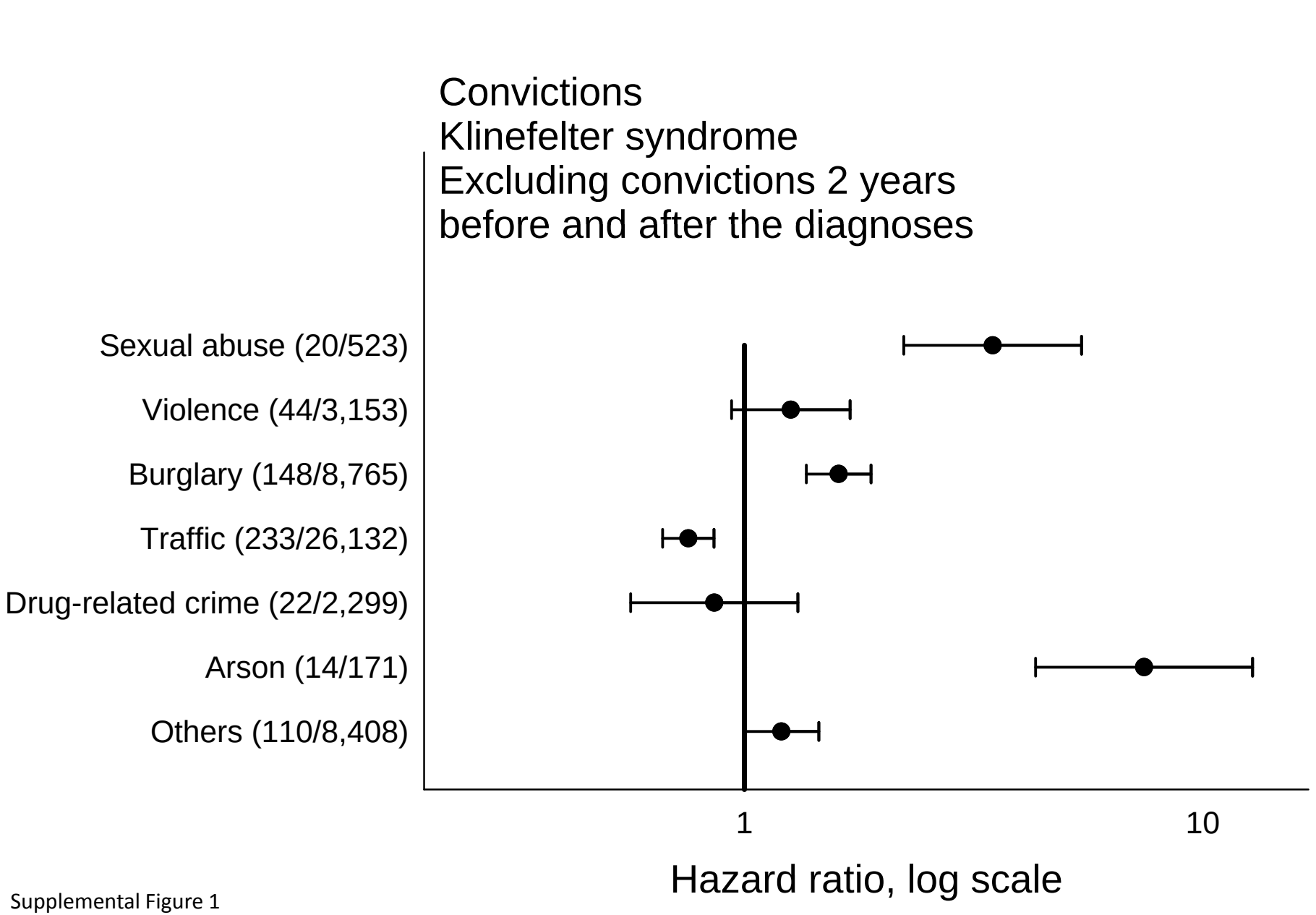
"-" indicates that there was no event in a given class of convictions.

Supplemental Table 1

Hazard ratios (95% confidence interval) for convictions after sensitivity analysis (see Statistics section for details).

Klinefelter	Proportion detected in study:	25%			If non-detected KS have same rate as background population			If non-detected KS have an excess rate half the observed		
	HR	95% CI		SE(ln HR)	HR	95% CI		HR	95% CI	
All	1.40	1.23	1.59	0.0655	1.10	0.97	1.25	1.25	1.10	1.42
Sexual abuse	4.02	2.71	5.95	0.2006	1.76	1.18	2.60	2.89	1.95	4.28
Homicide	1.65	0.23	11.90	1.0067	1.16	0.16	8.36	1.41	0.20	10.12
Violence	1.26	0.95	1.66	0.1424	1.07	0.81	1.41	1.16	0.88	1.54
Burglary	1.59	1.36	1.85	0.0785	1.15	0.98	1.34	1.37	1.17	1.60
Drug	0.78	0.52	1.17	0.2069	0.95	0.63	1.42	0.86	0.58	1.29
Arson	7.35	4.42	12.23	0.2596	2.59	1.56	4.30	4.97	2.99	8.27
Other	1.21	1.02	1.48	0.0950	1.05	0.87	1.27	1.13	0.94	1.36

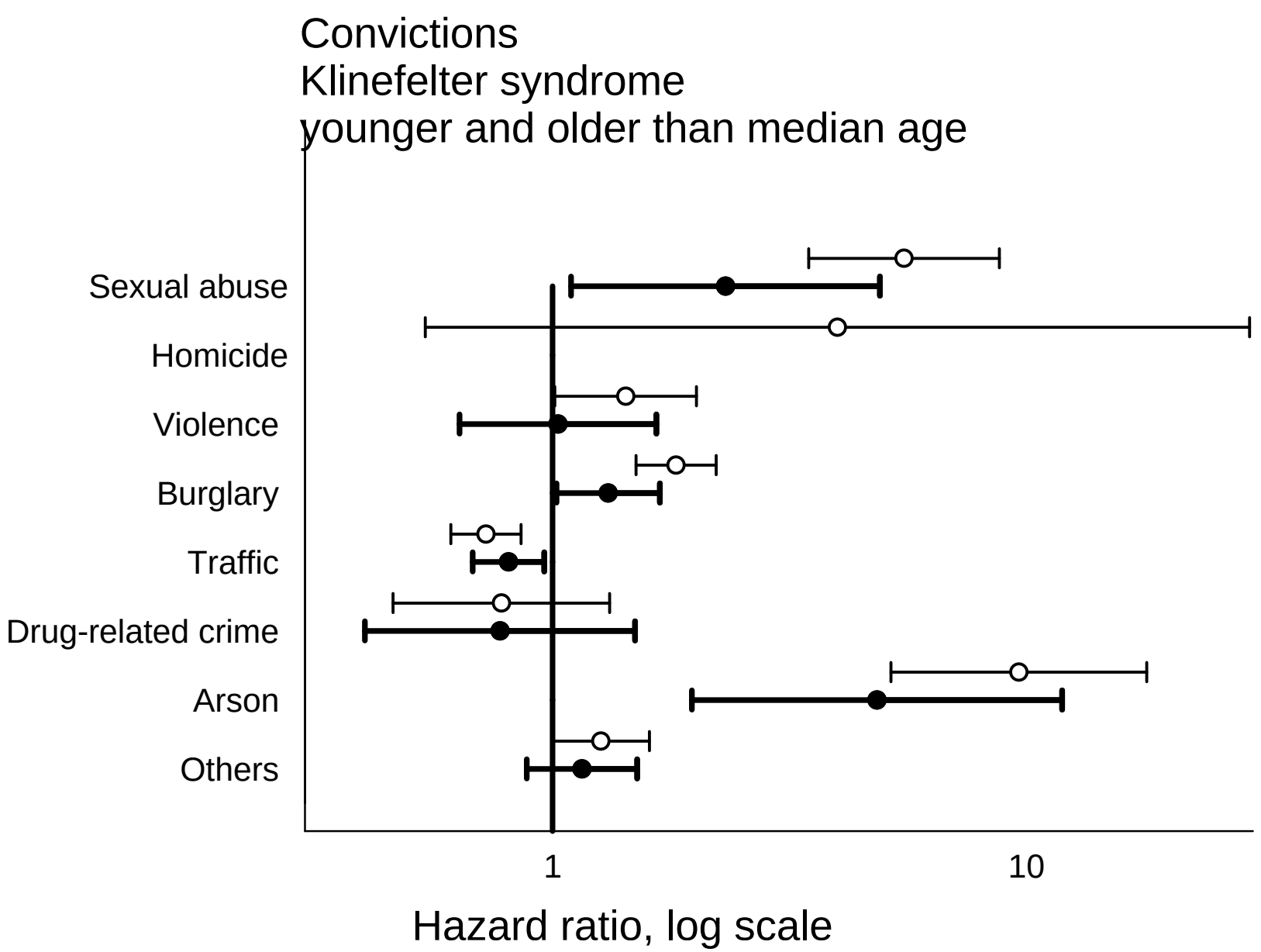
47.XYY	Proportion detected in study:	15%			If non-detected 47,XYY have same rate as background population			If non-detected 47,XYY have an excess rate half the observed		
	HR	95% CI		SE(ln HR)	HR	95% CI		HR	95% CI	
All	2.09	1.61	2.71	0.1328	1.16	0.90	1.51	1.68	1.30	2.18
Sexual abuse	11.79	6.46	21.52	0.3070	2.62	1.43	4.78	7.74	4.24	14.13
Homicide	10.36	1.31	81.77	1.0546	2.40	0.30	18.99	6.85	0.87	54.12
Violence	2.54	1.57	4.11	0.2455	1.23	0.76	1.99	1.96	1.21	3.18
Burglary	2.07	1.47	2.91	0.1742	1.16	0.82	1.63	1.67	1.19	2.35
Drug	1.74	0.90	3.36	0.3360	1.11	0.57	2.15	1.46	0.76	2.83
Arson	10.57	3.76	29.76	0.5277	2.44	0.87	6.85	6.98	2.48	19.64
Other	1.89	1.32	2.71	0.1835	1.13	0.79	1.62	1.56	1.09	2.23



Supplemental Figure 1

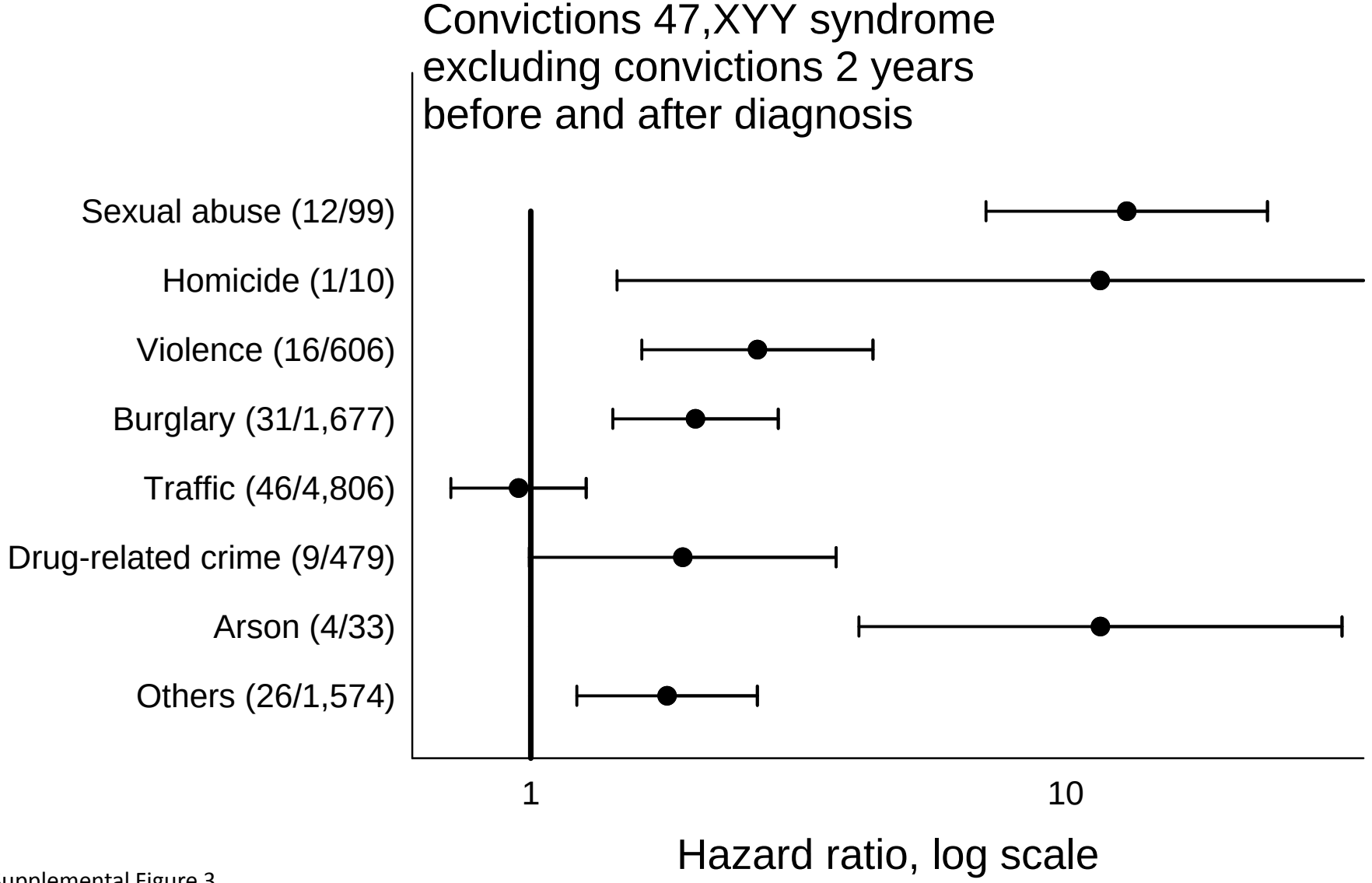
Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males (see Materials and Methods for details) after having excluded cases (and their controls) diagnosed 2 years before or after a conviction.

Actual numbers of offenders (KS/controls) are given in parentheses.



Supplemental Figure 2

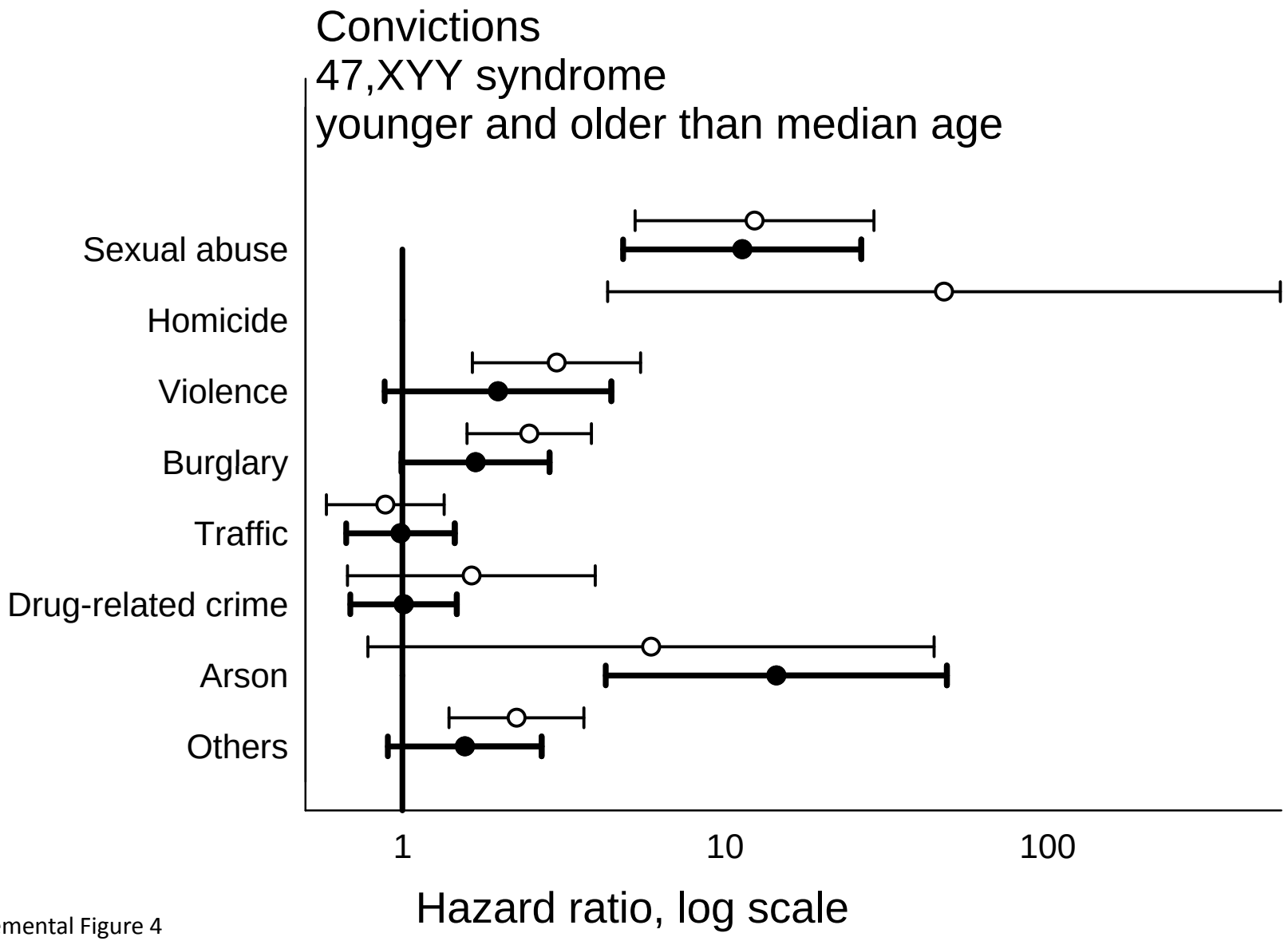
Legend: Hazard ratios of convictions due to cause in Klinefelter syndrome compared to age-matched males after having divided cases (and their controls) in two depending on the median age at diagnosis into those diagnosed at a younger age (open circles) and those diagnosed at an older age (filled circles).



Supplemental Figure 3

Legend: Hazard ratios of convictions due to cause in 47,XYY syndrome compared to age-matched males (see Materials and Methods for details) after having excluded cases (and their controls) diagnosed 2 years before or after a conviction.

Actual numbers of offenders (47,XYY/controls) are given in parentheses.



Supplemental Figure 4

Legend: Hazard ratios of convictions due to cause in 47,XYY sndrome compared to age-matched males after having divided cases (and their controls) in two depending on the median age at diagnosis into those diagnosed at a younger age (open circles) and those diagnosed at an older age (filled circles).

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6-8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	9
		(*e*) Describe any sensitivity analyses	9
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	10-11
		(c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-11
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.