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An extra X chromosome among adult women in the Million Veteran Program: A more benign perspective of trisomy X

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Abstract

Despite affecting in 1 in every 1000 females, remarkably little is known about trisomy X syndrome (47,XXX), especially among older adults who are undiagnosed. In this study, we aimed to determine the prevalence of 47,XXX among females enrolled in the Million Veterans Program (MVP; mean age 50.2 ± 13.6 years), and compare broad health outcomes between females with 47,XXX and 46,XX matched controls. We identified 61 females with an additional X chromosome, corresponding to a prevalence of 103 per 100,000 females; 27.9% had been clinically diagnosed. Females with 47,XXX had taller stature (+6.1 cm, $p < 0.001$), greater rate of outpatient encounters ($p = 0.026$), higher odds of kidney disease (odds ratio [OR] = 12.3; 95% confidence interval [CI] 2.9–51.8), glaucoma (OR = 5.1; 95% CI 1.5–13.9), and congestive heart failure (OR = 5.6; 95% CI 1.4–24.2), and were more likely to be unemployed

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($p = 0.008$) with lower annual income ($p = 0.021$) when compared with 46,XX controls of the same age and genetic ancestry. However, there were no differences in the rates of other encounter types, Charlson Comorbidity Index, all other medical and psychological diagnoses, military service history or quality of life metrics. In conclusion, in this aging and predominately undiagnosed sample, 47,XXX conferred few differences when compared with matched controls, offering a more reassuring perspective to the trisomy X literature.

KEYWORDS
healthcare utilization, Million Veteran Program, morbidity, sex chromosome aneuploidy, triple X syndrome

1 | INTRODUCTION

Trisomy X syndrome (47,XXX) is a genetic condition characterized by an additional X chromosome in 1 in 1000 females (Stochholm et al., 2010). Despite this relatively high prevalence, clinical ascertainment of 47,XXX remains limited, with only 10%–15% diagnosed over their lifetimes (Berglund et al., 2019; Nielsen & Wohlert, 1991). With few exceptions, the trisomy X literature is limited to the minority of clinically ascertained individuals, which may or may not be generalizable to all females with an additional X chromosome.

Even among clinically diagnosed individuals, the phenotypic spectrum of trisomy X is broad. Reported physical features include tall stature, hypertelorism, epicanthal folds, clinodactyly, pes planus, and hypotonia (Tartaglia et al., 2010; Wigby et al., 2016). Population-based studies have reported an increased morbidity and mortality in trisomy X (Stochholm et al., 2010), and an increased risk for various comorbidities including diabetes, asthma, respiratory infection, gastroesophageal reflux, dental problems, clotting disorders, and abnormalities of the urogenital systems. Premature ovarian insufficiency has also been reported (Berglund et al., 2022; Davis et al., 2020; Singhal et al., 2021; Villanueva & Rebar, 1983). A complex neuropsychological profile for 47,XXX has been described to include developmental delays, impaired emotional development and social cognition, learning disabilities, and executive dysfunction, while neuroimaging studies have found decreased brain volume and cortical thickness (Lenroot et al., 2014; van Rijn & Swaab, 2015; Wigby et al., 2016). Psychiatric illnesses that can develop in Trisomy X include anxiety disorders, depression, and attention-deficit disorder (Lenroot et al., 2014; Wigby et al., 2016). Little to no data exist on subjective metrics such as sleep health, quality of life (QoL), social support, employment, and adult experiences in females with 47,XXX. Prior descriptions of social impairments (Otter et al., 2021) and lower socioeconomic outcomes (Stochholm et al., 2013) are also limited by ascertainment bias, and racial and ethnic homogeneity.

The Veteran's Health Administration (VA) Million Veteran Program (MVP) is a voluntary population-based study aiming to investigate genetic determinants of medical, neurological, and psychiatric illnesses, and health outcomes for individuals who have served in the US military (Gaziano et al., 2016). In this context, we used the MVP cohort to address existing research limitations pertaining to 47,XXX. The aims of our investigation were to (1) establish the prevalence of females with 47,XXX in the MVP cohort, including both clinically diagnosed and undiagnosed cases, and (2) to compare sociodemographic, military service, medical morbidity, mortality, and participant-reported outcomes between females with 47,XXX and typical 46,XX controls.

2 | METHODS

The MVP biobank enrolls US military veterans and detailed methods are published elsewhere (Gaziano et al., 2016). In this cross-sectional, case–control study, we utilized Single nucelotide polymorphism (SNP)-based genotype, EHR, and survey responses from 73,759 females with both genotype and VA EHR data available. DNA extracted from peripheral blood leukocytes was analyzed on the MVP custom Affymetrix Axiom Biobank 1.0 array consisting of 723,305 unique SNPs. Details on this platform, technical processes, and quality control measures have previously been published (Hunter-Zinck et al., 2020). To identify women with an additional X chromosome, array intensity (median log-R ratios) from more than 20,000 probe sets from the non-pseudoautosomal region of X was used to estimate X chromosome dosage. This yielded two clear clusters corresponding to two versus three copies of the X chromosome.

All genotyped females with available VA EHR data were included in the analysis to determine the prevalence of 47,XXX. We determined the prevalence of sex chromosomal aneuploidy (SCA) based on the number of females with a second X chromosome over the total number of females in MVP expressed as the number per 100,000 females, and then stratified by genetic ancestry. Genetic ancestry was determined using the harmonized ancestry and race/ethnicity (HARE) method (Fang et al., 2019). To determine whether an individual with genetically identified 47,XXX was clinically ascertained to have trisomy X, we queried the EHR for corresponding diagnostic codes (International Classification of Disease Ninth Edition 758.7–81; ICD-10 Q98.0–9). If a diagnostic code consistent with trisomy X was present in the EHR, the youngest age this diagnostic code was documented and used as the estimated age of clinical diagnosis.

Demographic variables, military service metrics, and health outcomes were obtained from a combination of VA records and

self-reported answers on the MVP Baseline Survey and Lifestyle Survey (Harrington et al., 2019). Survey response rates in our cohort were similar to MVP metrics as a whole (Nguyen et al., 2018). We used the Charlson Comorbidity Index (CCI), a validated metric incorporating multiple medical conditions obtained from the EHR, as an estimate of morbidity (Charlson et al., 1987). Healthcare utilization was assessed by the number of outpatient, emergency, and overnight hospital encounters per year followed, with duration of follow-up determined as the difference between the initial and most recent encounter dates. Additional outcomes included height, weight, and body mass index (BMI), self-reported diagnoses, and validated summary scores from the baseline and lifestyle surveys as previously described (Harrington et al., 2019), including the Veterans RAND 12 Item Health Survey (VR-12) (Clark et al., 2023; Kazis et al., 2006) as a measurement of physical and mental health-related QoL, Medical Outcomes Study Cognitive Functioning-Revised Scale (MOS-Cog-R) (Fink et al., 2022; Merritt et al., 2022) as a subjective estimate of cognitive difficulties, and the Patient Health Questionnaire-4 (PHQ-4) (Kroenke et al., 2009), and the Posttraumatic Stress Disorder Checklist (PCL) (Blevins et al., 2015) as estimates of psychological functioning.

Continuous variables are reported as means and standard deviations or medians with interquartile range. Categorical variables are reported as frequency/number and percentage. Because several outcomes of interest vary by age and ancestry, we matched each individual with 47,XXX (cases) to five 46,XX individuals (controls) of the same sex, age at time of enrollment, and HARE ancestry. We conducted outcome comparisons between 47,XXX cases versus their matched controls using chi-squared tests for categorical variables with cell counts >5, and Fisher exact tests for variables with smaller cell counts. *t*-test or Wilcoxon tests were used to for continuous variables depending on distribution. An α of 0.05 without multiplicity adjustment was used given the exploratory nature of the study. Odds ratios and 95% confidence intervals were calculated and forest plots created for visualization. Analyses were conducted using R v4.0.3 and Prism Graphpad v10.0.2.

3 | RESULTS

Of 59,007 genotyped females, we identified 61 with an additional X chromosome (47,XXX), corresponding to a prevalence of 103 per 100,000 (1 in 971) females (Table 1 and Figure 1). The prevalence was quite varied when stratified by genetic ancestry, with 47,XXX more than twice as common in females of European descent compared with other ancestry groups. Age of enrollment and response rate to questionnaires were similar among females with 47,XXX to the overall female MVP population. The majority of participants were receiving medical care at VA facilities. Approximately, 27.9% of females with 47,XXX had a clinical diagnosis of trisomy X documented in their EHR.

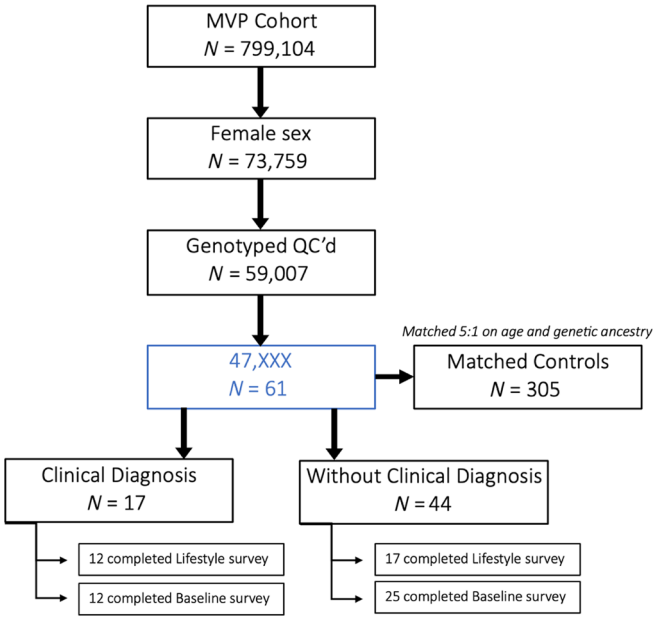

FIGURE 1 Flow diagram of Million Veterans Program (MVP) participants included in the analysis.

TABLE 1 Demographics and prevalence of females with 47,XXX within the MVP population.

	All genotyped females ($N = 59,007$)	Females with 47,XXX ($N = 61$)	Prevalence of 47,XXX per 100,000 females
Age at enrollment (years)	50.2 ± 13.6 51 (18–101)	51.7 ± 13.4 54 (24–80)	
Genetic ancestry[a]			103 (77–129)
African	16,993 (28.8%)	8 (13.1%)	47 (14–80)
European	34,438 (58.4%)	49 (80.3%)	142 (102–182)
All others	7576 (12.8%)	4 (6.6%)	53 (1–105)
Clinical SCA diagnosis	17 (0.03%)	17 (27.9%)	
Age first documented	49 (35–94)	49 (35–94)	

Note: Data are shown as mean ± SD and/or mean (range) for numerical data, *n* (%) for categorical data, and prevalence estimate with 95% confidence interval in parentheses.

Abbreviations: 47,XXX, trisomy X syndrome; MVP, Million Veteran Program; SCA, sex chromosome aneuploidy.

[a]Chi-squared comparison of ancestry categories for 47,XXX versus all genotyped females is $p = 0.0023$.

TABLE 2 Military service, morbidity, and mortality assessed from the VA records in females with 47,XXX.

	47,XXX cases ($n = 61$)	46,XX controls ($n = 305$)	p-value
Period of military service			0.182
Pre-Vietnam era	2 (3.3%)	10 (3.3%)	
Vietnam era	11 (18.0%)	44 (14.4%)	
Post-Vietnam era	15 (25.6%)	79 (25.9%)	
Persian Gulf War era	27 (44.3%)	162 (53.1%)	
Other/missing	6 (9.9%)	10 (3.3%)	
First military service branch			0.282
Air force	6 (9.8%)	40 (13.1%)	
Army	15 (24.6%)	79 (25.9%)	
Navy	12 (19.7%)	31 (10.2%)	
Other	3 (4.9%)	12 (3.9%)	
Unknown/missing	25 (50.0%)	143 (46.9%)	
Combat service	3 (4.9%)	20 (6.6%)	0.630
Military discharge status			0.211
Honorable	33 (54.1%)	156 (51.1%)	
General-honorable conditions	3 (4.9%)	6 (2.0%)	
Other than honorable[a]	0 (0%)	0 (0%)	
Unknown/missing	25 (41.0%)	143 (46.9%)	
Disability service connection of 100%	5 (8.20%)	41 (13.44%)	0.359
Height (cm)	**170.7 ± 7.4**	**164.6 ± 6.9**	**<0.001**
Weight (kg)	**91.1 ± 22.3**	**80.8 ± 19.4**	**0.001**
BMI (kg/m^2)	31.6 ± 7.4	30.4 ± 7.0	0.226
Marital status			0.112
Married	18 (29.5%)	103 (33.8%)	
Separated/divorced	23 (37.7%)	135 (44.3%)	
Widowed	0 (0%)	9 (3.0%)	
Never married	19 (31.3%)	53 (17.4%)	
Unknown/missing	1 (1.6%)	5 (1.6%)	
Charlston Comorbidity Index	2.7 ± 2.2	2.4 ± 2.3	0.410
Calculated 10-year survival (%)	82.3%	85.2%	
Outpatient encounters/year	**23.7 (15.6–35.6)**	**19.0 (10.24–31.9)**	**0.026**
Emergency encounters/year	0.5 (0.3–0.9)	0.4 (0.2–0.8)	0.111
Inpatient encounters/year	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.247
Deceased	3 (4.9%)	13 (4.3%)	1
Age of death (years)	75 (61–83)	60 (50–85)	0.329

Note: Data are shown as mean ± SD and/or median (25th–75th percentile) for numerical data, and n (%) for categorical data, unless otherwise specified. Bolded variables indicate significance at the predetermined α level.

Abbreviations: 47,XXX, trisomy X syndrome; BMI, body mass index; VA, Veteran's Health Administration.

[a]Dishonorable discharge was combined with other than honorable discharge due to low numbers.

EHR data found females with 47,XXX to be 6.1 cm taller ($p < 0.001$) and 10.3 kg heavier ($p = 0.001$) than controls, but BMI was not different (Table 2). Although of borderline statistical significance, there was an emergence of a greater number of outpatient encounters per year for 47,XXX females when compared with controls ($p = 0.026$), but there were no differences in the CCI, rates of emergency encounters, inpatient hospitalizations, number of prescription medications, or mortality. Period of service, military service branch, service era, and discharge status obtained from military records were similar between cases and controls.

Survey demographics revealed no between-group differences in age, self-ascribed racial and ethnic background, education level, or marital status (Table 3). However, the 47,XXX group were less likely to be currently employed ($p = 0.008$) and reported a lower annual

TABLE 3 Self-reported metrics baseline MVP survey.

Baseline survey	47,XXX cases $N = 37$	Controls $N = 194$	*p*-value
Age at time of survey (years)[a]	55.2 ± 11.6	53.2 ± 13.6	0.353
Maternal age at birth (years)	27.1 ± 7.1	26.0 ± 6.0	0.424
Paternal age at birth (years)	29.7 ± 7.9	29.3 ± 6.6	0.755
Self-reported race			0.115
White	30 (81.1%)	170 (87.6%)	
Black/African American	5 (13.5%)	16 (8.2%)	
American Indian/Alaskan Native	1 (2.7%)	11 (5.7%)	
Asian	1 (2.7%)	7 (3.6%)	
Other/prefer not to say	2 (5.4%)	1 (0.5%)	
Highest education level			0.233
High-school diploma/GED	6 (43.2%)	64 (32.8%)	
Associate degree	5 (13.5%)	38 (19.6%)	
Bachelor's degree	12 (32.4%)	50 (25.8%)	
Master's/professional/doctorate degree	4 (10.8%)	41 (21.1%)	
Annual household income[b]			**0.021**
<$30,000	20 (54.1%)	67 (34.5%)	
$30,000–$59,999	10 (27.0%)	59 (30.3%)	
>$60,000	3 (8.1%)	51 (26.2%)	
Military service branch(es)[c]			0.127
Army	21 (56.8%)	91 (56.9%)	
Navy	10 (27.0%)	44 (22.7%)	
Air force	3 (8.1%)	53 (27.3%)	
Other[d]	5 (13.5%)	26 (13.3%)	
Deployed outside the USA	15 (40.5%)	107 (55.2%)	0.110
Exposure to biochemical warfare	6 (16.2%)	7 (3.6%)	**0.020**
Healthcare from VA facilities			0.670
<50% of care	7 (18.9%)	43 (22.2%)	
51%–75% of care	3 (8.1%)	8 (4.1%)	
76%–99% of care	7 (18.9%)	45 (23.2%)	
100% of care	20 (54.1%)	96 (49.5%)	
Hospitalizations in the past year			
One or more at VA facility	9 (24.3%)	35 (18.0%)	0.173
One or more at non-VA facility	4 (10.8%)	24 (12.3%)	0.351
Number of prescription meds from a VA pharmacy			0.117
0–3	11 (31.4%)	86 (47.3%)	
4–9	18 (51.4%)	61 (33.5%)	
>10	6 (17.1%)	35 (19.2%)	
Tobacco use lifetime total > 100[b]	17 (45.9%)	116 (59.8%)	0.147
Daily for >1 year[b]	24 (64.9%)	92 (47.4%)	0.072
Current use[b]	7 (18.9%)	39 (20.1%)	0.810
Alcohol use frequency			0.195
Never	21 (56.8%)	79 (40.7%)	
Weekly or less	11 (29.7%)	74 (38.2%)	
More than weekly	4 (10.8%)	34 (17.5%)	

(Continues)

TABLE 3 (Continued)

Baseline survey	47,XXX cases $N = 37$	Controls $N = 194$	*p*-value
Moderate to vigorous exercise			0.324
Regularly (more than weekly)	10 (27.0%)	77 (39.6%)	
Infrequent (less than weekly)	14 (37.8%)	59 (30.4%)	
Rarely/never	13 (35.1%)	56 (28.9%)	
Handedness			0.107
Right-handed	26 (70.3%)	165 (85.1%)	
Left-handed	4 (10.8%)	12 (6.2%)	
Both	6 (16.2%)	16 (8.2%)	
Health-related QoL (VR-12)			
Physical functioning summary	37.5 ± 12.0	39.7 ± 13.0	0.329
Mental health summary	41.5 ± 12.3	44.5 ± 13.5	0.185

Note: Data are shown as mean ± SD and/or median (range) for continuous data, and *n* (%) for categorical data, unless otherwise specified. Bolded *p*-values indicate significance at the predetermined α level.

Abbreviations: 47,XXX, trisomy X syndrome; MVP, Million Veterans Program; QoL, quality of life; VA, Veteran's Health Administration; VR-12 = Veterans RAND 12 Item Health Survey (higher values indicate better QoL).

[a]Participants were matched on age at time of study enrollment, which does not necessarily indicate balanced age at time of survey completion.

[b]Eight percent or more of respondents did not answer these questions; however, the proportion of non-responders was similar between all groups and results did not change if missing was included as a separate category.

[c]More than one selection was allowed; therefore, percentages add up to more than 100%.

[d]Other military branches include coast guard, marine corps, national guard, merchant marines.

income ($p = 0.023$). Of the participants that were employed or retired but once employed, females with 47,XXX were more likely to work in production ($p = 0.023$) or food preparation/serving-related occupations ($p = 0.019$) than in controls (Figure 2). Alcohol and tobacco use and exercise frequency were similar. There were not differences in the summary QoL variables between groups; however, females with 47,XXX reported to be more often limited in the type of work or activity because of their health ($p = 0.034$). Females with 47,XXX also reported their cognitive health to have improved during the last year more than the control females ($p = 0.016$).

The majority of self-reported medical diagnoses were similar between groups, although chronic kidney disease, glaucoma, and congestive heart failure were reported in significantly more females with 47,XXX (Figure 3). In addition, the 47,XXX sample reported more difficulties falling asleep, wakefulness during the night, and excessive daytime sleepiness (Table 4); however, none of these reached statistical significance. There were trends toward higher self-reported fertility problems but no differences in numbers of pregnancies, menarchal age, or menopausal age. Scores from standardized questionnaires revealed similar subjectivity of cognitive difficulties, social support, and personality traits between groups.

4 | DISCUSSION

In this large, ethnically diverse cohort of female US military veterans participating in the MVP, an additional X chromosome was common and was associated with minimal health and psychosocial concerns, with the notable exception of current income and employment status. Although this is a unique subpopulation of females with 47,XXX as they have elected to enroll in military service and subsequently in MVP research, trisomy X likely has a much broader phenotype than previously described from clinical ascertained cohorts (Berglund et al., 2022; Davis et al., 2020; Stochholm et al., 2010, 2013; Sugawara et al., 2013; Wallerstein et al., 2004; Wigby et al., 2016). These results impartially inform the impact of the aneuploidy on aging as the majority of the cohort were unaware of their karyotype variation at >50 years of age. Finally, several novel hypotheses have come out of this work, including the potential influence of ancestry on aneuploidy risk and the association of 47,XXX to several chronic medical conditions, demonstrating the power of population-based biobanks in the study of genetic variations across the lifespan.

Pooled data from international birth cohort studies in the 1960s and 1970s found 62 females with 47,XXX of 73,990 live female births, corresponding to a prevalence of 84 per 100,000 or 1 in 1190 newborn females (Berglund et al., 2020). This is at the lower end of our calculated 95% confidence interval (77–129 per 100,000 females in the MVP). The only other population genetic database to publish the prevalence of 47,XXX to our knowledge is the UK Biobank, which reported 45 per 100,000 females—half as many as found in our study or predicted from the newborn studies (Tuke et al., 2019). This result has been hypothesized to be due to the "healthy volunteer bias." Our prevalence data indicate that females with an additional X chromosome join the military at similar rates to females in the general

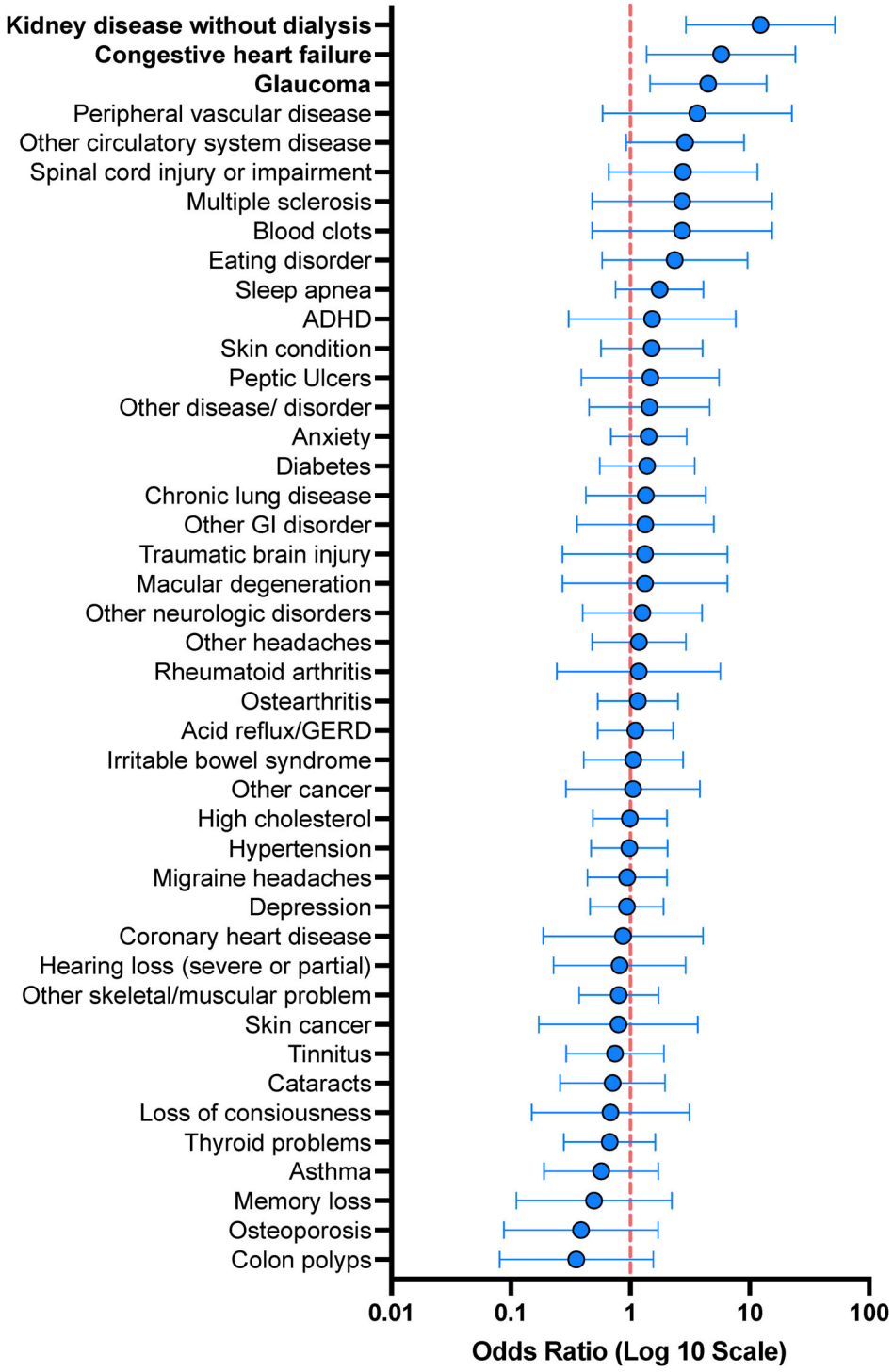

FIGURE 2 Forest plot of the odds ratios (point estimate) and 95% confidence intervals (error bars) for all self-reported medical and mental health conditions having at least one individual in both trisomy X syndrome (47,XXX) case ($n = 37$) and control ($n = 194$) groups. Three conditions had a significantly higher odds ratio in females with 47,XXX: kidney disease (16.2% of cases vs. 1.5% of controls), congestive heart failure (10.8% of cases vs. 2.1% of controls), and glaucoma (16.2% of cases vs. 4.1% of controls). ADHD, attention-deficit hyperactivity disorder; GERD, gastroesophageal reflux disease; GI, gastrointestinal.

population. Furthermore, metrics obtained both from military records and self-report support a similar military service history to their 46,XX counterparts.

Intriguingly, 1 in 700 females of European ancestry had 47,XXX, which is almost three times higher than the prevalence observed in other ancestral groups. We also observed this phenomenon among males with 47,XXY and 47,XYY in the MVP (Davis et al., 2023). While unexpected, we initially assumed this finding was secondary to differences in parental age, as the risk of chromosomal aneuploidy increases with maternal and potentially paternal age (Ferguson-Smith & Yates, 1984; Kim et al., 2013) and individuals of European ancestry tend to be older parents due to social influences. However, both maternal and paternal age were nearly identical between the 47,XXX and 46,XX groups, bringing our assumption into question. Approximately 74% of trisomy X aneuploidies occur as a result of maternal nondisjunction errors attributed to a number of genetic and epigenetic factors (Cechova & Miga, 2022; Hall et al., 2006; Tartaglia et al., 2010), and it is plausible these factors affecting chromosome

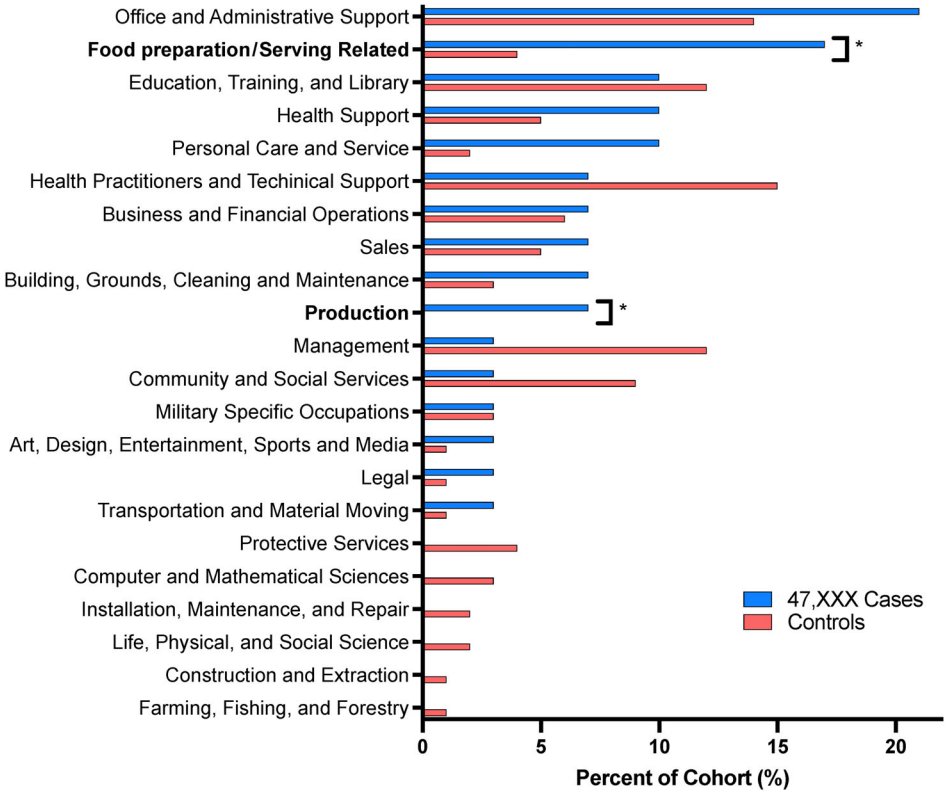

FIGURE 3 Occupational categories in 29 women with trisomy X syndrome (47,XXX) who completed the lifestyle follow-up survey compared with matched controls. Brackets and asterisks are shown when statistical differences were present between 47,XXX and controls. The occupational category "other" was omitted.

stability differ between ancestral groups. Alternatively, women with trisomy X with European ancestry may be more likely to electively join the military compared with those from other genetic ancestry groups. Other ethnically diverse population-based genetic databases are needed to help interpret these data.

Based on the existing literature, we hypothesized females with 47,XXX would have higher rates of multiple medical diagnoses (Berglund et al., 2019; Nielsen & Wohlert, 1991; Tartaglia et al., 2010). However, we found very minimal differences in self-reported comorbidities between females 47,XXX and 46,XX. Predictably, females with 47,XXX were taller and weighed more without differences in BMI when compared with controls. Increased stature can be attributed to an additional copy of the *SHOX* gene, which is located on a portion of the X chromosome which escapes inactivation (Kanaka-Gantenbein et al., 2004; Ogata et al., 2001; Ottesen et al., 2010). Unexpectedly, chronic kidney disease was strongly associated with 47,XXX. Congenital renal and genitourinary anomalies, including renal dysplasia and agenesis, have been reported in 10%–15% of females with trisomy X (Wigby et al., 2016); however, this is the first study to suggest that renal function may be impaired. Similarly, congenital heart disease—primarily septal defects—are estimated to occur in ~10% of females with trisomy X (Wigby et al., 2016), but congestive heart failure has not previously been reported. Defining the underlying etiology will require future investigations. Another novel finding was a higher prevalence of glaucoma in our sample of 47,XXX females. Glaucoma is associated with autosomal trisomies (Wiggs, 2007), and a recent study found an association with three loci on the X chromosome (Simcoe et al., 2020). A population-based registry in Denmark identified females with 47,XXX had a significantly higher incidence rate ratio of non-specific vision-related diagnoses (ICD-10 codes H53–H54) but does not mention glaucoma (H40–H42) (Berglund et al., 2022). Our results indicate a need for further investigation of renal, cardiac, and ophthalmologic disease in 47,XXX.

Contrary to our hypothesis, 47,XXX was not clearly associated with a higher risk of mental health conditions. Notably, the prevalence of anxiety and depression were quite high in both cases and controls, possibly due to military service, and this measure does not address the severity or impact of mood dysregulation. Mental health-related QoL was 10% lower in 47,XXX, and a small but significant difference did emerge on the PCL. Similarly and potentially related, impaired ovarian function has been reported in 47,XXX (Davis et al., 2020; Singhal et al., 2021; Villanueva & Rebar, 1983). While outcomes related to ovarian function in our analysis were not statistically significant, menarche was 2 years later, menopause 2 years earlier, and more than a quarter of women with 47,XXX self-reported fertility problems. Furthermore, menopausal age in women with 47,XXX in our study was nearly identical to the age reported in the UK Biobank. Emerging research suggests that high psychological stress, trauma, and potentially post-traumatic stress disorder (PTSD) may accelerate ovarian aging (Mínguez-Alarcón et al., 2023). In addition, premature ovarian failure is itself associated with increased risk of shyness, social anxiety, and impaired self-esteem (Schmidt et al., 2006). Psychological, mood, and ovarian health, and the potential relationship of these outcomes, warrant further exploration, and trisomy X may be a unique model to study.

TABLE 4 Self-reported metrics from lifestyle MVP survey.

Lifestyle survey	47,XXX cases $N = 29$	Controls $N = 148$	*p*-value
Age at survey (years)	55.8 ± 12.5	54.8 ± 13.3	0.713
Current employment			
Employed	**6 (20.7%)**	**70 (47.3%)**	**0.008**
Unemployed	4 (13.8%)	14 (9.5%)	0.302
Disabled	8 (27.6%)	23 (15.5%)	0.178
Retired	10 (34.5%)	54 (36.5%)	1
Age of retirement (years)	57.5 ± 11.8	56.2 ± 9.4	0.771
Other work status[a]	6 (20.7%)	19 (12.8%)	0.256
Sleep health			
Trouble falling asleep	16 (55.2%)	72 (48.6%)	0.549
Waking up at night	21 (72.4%)	82 (55.4%)	0.102
Waking up too early in AM	13 (44.8%)	70 (47.3%)	0.841
Feeling not rested in AM	18 (62.1%)	91 (61.5%)	1
Excessive daytime sleepiness	14 (48.3%)	54 (36.5%)	0.297
Women's reproductive health			
Menarche age (years)	12.8 ± 2.3	12.6 ± 1.6	0.609
Sexual problems (e.g., pain)	11 (37.9%)	47 (31.8%)	0.523
Fertility problems	8 (27.6%)	21 (14.2%)	0.098
Pregnancy (any)	20 (69.0%)	112 (75.7%)	0.486
1	7 (24.1%)	25 (16.9%)	
2	5 (17.2%)	36 (24.3%)	
≥3	8 (27.6%)	50 (33.8%)	
Menopause age	43.1 ± 6.8	45.0 ± 8.9	0.293
Neuropsychological health			
MOS-Cog-R	13.3 ± 7.1	12.0 ± 6.4	0.340
PHQ4 total	3.6 ± 2.4	3.0 ± 2.3	0.481
Anxiety subscale	1.7 ± 1.3	1.5 ± 1.8	0.522
Depression subscale	1.6 ± 1.6	1.5 ± 1.8	0.591
PCL	37.7 ± 14.1	34.2 ± 17.1	0.242
Social support (MOS-SSSI)			
Total score	61.12 ± 30.36	60.71 ± 30.46	0.948
Emotional/informational	62.18 ± 31.2	58.78 ± 32.19	0.595
Tangible support	59.58 ± 34.69	60.56 ± 34.77	0.888
Affectionate support	65.0 ± 37.61	65.82 ± 36.17	0.913
Positive social interaction	60.83 ± 37.47	61.97 ± 34.81	0.878
Personality traits (BFI-10)			
Openness to experience	6.31 ± 1.56	6.73 ± 2.03	0.216
Conscientiousness	7.93 ± 1.53	8.15 ± 1.53	0.481
Extraversion	5.53 ± 2.26	6.27 ± 2.31	0.112
Agreeableness	7.86 ± 1.57	7.46 ± 1.8	0.226
Neuroticism/anxiousness	6.07 ± 2.3	5.56 ± 2.36	0.276

Note: Data are shown as mean ± SD for continuous data, and *n* (%) for categorical data, unless otherwise specified. Bolded *p*-values indicate significance at the predetermined α level.

Abbreviations: 47,XXX, trisomy X syndrome; BFI-10, Big Five Inventory Short Version; MOS-Cog-R, Medical Outcomes Survey Cognitive Functioning Revised Scale (higher values indicate more problems); MOS-SSSI, Medical Outcomes Study Social Support Survey Instrument; MVP, Million Veterans Program; PHQ-4, Patient Health Questionnaire-4 (higher values indicate more concern); PCL, Posttraumatic Stress Disorder Checklist (higher values indicate more concern).

[a]Student, volunteer/unpaid work, homemaker, other.

Finally, our findings of lower income and rate of current employment in 47,XXX are congruent with existing literature (Otter et al., 2021; Wigby et al., 2016). It is not clear that this observation is related to educational achievement, chosen occupation, physical health, cognitive ability, psychological factors, or social function as these measures were similar between groups. Other data suggest that relative neurocognitive or psychosocial deficits in trisomy X may negatively influence societal function (Nguyen et al., 2018; Otter et al., 2021). Population-based biobanks with longitudinal records may be able to explore early predictors of poor socioeconomic outcomes in 47,XXX.

While this study is novel in that it is one of the only studies to include undiagnosed aging individuals with trisomy X, the small sample size greatly limits our ability to detect differences that may be clinically important. For example, our sample size for the Baseline Survey allows us to detect only ORs of >1.5 and <0.7 for common outcomes and >2.2 and <0.5 for rare outcomes, and an effect size of 0.5 for continuous variables with 80% power. Therefore, failure to find a statistical difference in this dataset does not rule out that a true difference may indeed exist, and our statistically significant results should be considered exploratory as we did not adjust for multiple comparisons. In addition, our sample size was too small to examine outcome differences between those with and without a prior clinical diagnosis of trisomy X. Finally, females with or without 47,XXX who electively enroll in the military are distinct from the civilian population, and we cannot generalize these findings to all women with trisomy X.

In conclusion, this study of predominately undiagnosed and aging women with 47,XXX in the MVP found differences in prevalence by genetic ancestry but few differences in sociodemographic, health, and wellbeing outcomes when compared with sex-, age-, and ancestry-matched controls. While existing trisomy X literature emphasizes an increased risk for multiple malformations and disorders among various organ systems, these studies have been conducted in clinically ascertained individuals. Overall, our results provide a more reassuring outlook for females with 47,XXX while also highlighting additional research needs.

AUTHOR CONTRIBUTIONS

Study conception and design: Shanlee M. Davis, Bryan R. Gorman, Judith L. Ross, Richard L. Hauger, Giulio Genovese, and Matthew Panizzon. *Data collection*: Julie A. Lynch, Craig C. Teerlink, Bryan R. Gorman, Meghana S. Pagadala, and Richard L. Hauger. *Designed and performed clinical phenotyping*: Julie A. Lynch and Craig C. Teerlink. *Designed and performed the genetics experiments*: Craig C. Teerlink, Bryan R. Gorman, and Meghana S. Pagadala. *Primary data analysis*: Craig C. Teerlink. *Interpretation of results*: All authors. *Draft manuscript preparation*: Shanlee M. Davis, Judith L. Ross, and Richard L. Hauger. *Critically revised and approved the final version of the manuscript*: All authors. *Administrative, technical, and other support*: Julie A. Lynch. *Funding*: Richard L. Hauger, Julie A. Lynch and Matthew Panizzon. *Supervision*: Shanlee M. Davis and Richard L. Hauger.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Million Veteran Program. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of Million Veteran Program.

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REFERENCES

Berglund, A., Stochholm, K., & Gravholt, C. H. (2020). The epidemiology of sex chromosome abnormalities. *American Journal Medical Genetics Part C: Seminars Medical Genetics*, *184*(2), 202–215. https://doi.org/10.1002/ajmg.c.31805

Berglund, A., Stochholm, K., & Gravholt, C. H. (2022). The comorbidity landscape of 47,XXX syndrome: A nationwide epidemiologic study. *Genetics in Medicine*, *24*(2), 475–487. https://doi.org/10.1016/j.gim.2021.10.012

Berglund, A., Viuff, M. H., Skakkebæk, A., Chang, S., Stochholm, K., & Gravholt, C. H. (2019). Changes in the cohort composition of turner syndrome and severe non-diagnosis of Klinefelter, 47,XXX and 47,XYY syndrome: A nationwide cohort study. *Orphanet Journal of Rare Diseases*, *14*(1), 16. https://doi.org/10.1186/s13023-018-0976-2

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *Journal of Traumatic Stress*, *28*(6), 489–498. https://doi.org/10.1002/jts.22059

Cechova, M., & Miga, K. H. (2022). Satellite DNAs and human sex chromosome variation. *Seminars in Cell & Developmental Biology*, *128*, 15–25. https://doi.org/10.1016/j.semcdb.2022.04.022

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Clark, A. L., McGill, M. B., Ozturk, E. D., Schnyer, D. M., Chanfreau-Coffinier, C., & Merritt, V. C. (2023). Self-reported physical functioning, cardiometabolic health conditions, and health care utilization patterns in million veteran program enrollees with traumatic brain injury screening and evaluation program data. *Military Medical Research*, *10*(1), 2. https://doi.org/10.1186/s40779-022-00435-7

Davis, S. M., Soares, K., Howell, S., Cree-Green, M., Buyers, E., Johnson, J., & Tartaglia, N. R. (2020). Diminished ovarian reserve in girls and adolescents with trisomy X syndrome. *Reproductive Sciences*, *27*(11), 1985–1991. https://doi.org/10.1007/s43032-020-00216-4

Davis, S. M., Teerlink, C., Lynch, J. A., Gorman, B. R., Pagadala, M., Liu, A., Panizzon, M. S., Merritt, V. C., Genovese, G., Pyarajan, S., Ross, J. L., & Hauger, R. L. (2023). Prevalence, morbidity, and mortality of 1,609 men with sex chromosome aneuploidy: Results from the diverse million veteran program cohort. *medRxiv Preprint Server of Health Sciences*. https://doi.org/10.1101/2023.07.15.23292710

Fang, H., Hui, Q., Lynch, J., Honerlaw, J., Assimes, T. L., Huang, J., Vujkovic, M., Damrauer, S. M., Pyarajan, S., Gaziano, J. M., DuVall, S. L., O'Donnell, C. J., Cho, K., Chang, K. M., Wilson, P. W. F., Tsao, P. S., Sun, Y. V., Tang, H., Gaziano, J. M., … Striker, R. (2019). Harmonizing genetic ancestry and self-identified race/ethnicity in genome-wide association studies. *American Journal of Human Genetics*, *105*(4), 763–772. https://doi.org/10.1016/j.ajhg.2019.08.012

Ferguson-Smith, M. A., & Yates, J. R. W. (1984). Maternal age specific rates for chromosome aberrations and factors influencing them: Report of a collaborative European study on 52 965 amniocenteses. *Prenatal Diagnosis*, *4*(7), 5–44. https://doi.org/10.1002/pd.1970040704

Fink, S. J., Davey, D. K., Sakamoto, M. S., Chanfreau-Coffinier, C., Clark, A. L., Delano-Wood, L., Merritt, V. C., & VA Million veteran program. (2022). subjective cognitive and psychiatric well-being in U.S. military veterans screened for deployment-related traumatic brain injury: A million veteran program study. *Journal of Psychiatric Research*, *151*, 144–149. https://doi.org/10.1016/j.jpsychires.2022.04.019

Gaziano, J. M., Concato, J., Brophy, M., Fiore, L., Pyarajan, S., Breeling, J., Whitbourne, S., Deen, J., Shannon, C., Humphries, D., Guarino, P., Aslan, M., Anderson, D., LaFleur, R., Hammond, T., Schaa, K., Moser, J., Huang, G., Muralidhar, S., … O'Leary, T. J. (2016). Million Veteran Program: A mega-biobank to study genetic influences on health and disease. *Journal of Clinical Epidemiology*, *70*, 214–223. https://doi.org/10.1016/j.jclinepi.2015.09.016

Hall, H., Hunt, P., & Hassold, T. (2006). Meiosis and sex chromosome aneuploidy: How meiotic errors cause aneuploidy; how aneuploidy causes meiotic errors. *Current Opinion in Genetics & Development*, *16*(3), 323–329. https://doi.org/10.1016/j.gde.2006.04.011

Harrington, K. M., Nguyen, X. M. T., Song, R. J., Hannagan, K., Quaden, R., Gagnon, D. R., Cho, K., Deen, J. E., Muralidhar, S., O'Leary, T. J., Gaziano, J. M., Whitbourne, S. B., Gaziano, J. M., Ramoni, R., Breeling, J., Chang, K. M., Huang, G., Muralidhar, S., O'Donnell, C. J., … Striker, R. (2019). Gender differences in demographic and health characteristics of the Million Veteran Program cohort. *Women's Health Issues*, *29*, S56–S66. https://doi.org/10.1016/j.whi.2019.04.012

Hunter-Zinck, H., Shi, Y., Li, M., Gorman, B. R., Ji, S. G., Sun, N., Webster, T., Liem, A., Hsieh, P., Devineni, P., Karnam, P., Gong, X., Radhakrishnan, L., Schmidt, J., Assimes, T. L., Huang, J., Pan, C., Humphries, D., Brophy, M., … Pyarajan, S. (2020). Genotyping array design and data quality control in the million veteran program. *American Journal of Human Genetics*, *106*(4), 535–548. https://doi.org/10.1016/j.ajhg.2020.03.004

Kanaka-Gantenbein, C., Kitsiou, S., Mavrou, A., Stamoyannou, L., Kolialexi, A., Kekou, K., Liakopoulou, M., & Chrousos, G. (2004). Tall stature, insulin resistance, and disturbed behavior in a girl with the triple X syndrome harboring three SHOX genes: Offspring of a father with mosaic Klinefelter syndrome but with two maternal X chromosomes. *Hormone Research in Paediatrics*, *61*(5), 205–210. https://doi.org/10.1159/000076532

Kazis, L. E., Miller, D. R., Skinner, K. M., Lee, A., Ren, X. S., Clark, J. A., Rogers, W. H., Spiro, A., III, Selim, A., Linzer, M., Payne, S. M. C., Mansell, D., & Fincke, B. G. (2006). Applications of methodologies of the veterans health study in the VA healthcare system: Conclusions and summary. *The Journal of Ambulatory Care Management*, *29*(2), 182–188. https://doi.org/10.1097/00004479-200604000-00011

Kim, Y. J., Lee, J. E., Kim, S. H., Shim, S. S., & Cha, D. H. (2013). Maternal age-specific rates of fetal chromosomal abnormalities in Korean pregnant women of advanced maternal age. *Obstetrics Gynecology Science*, *56*(3), 160–166. https://doi.org/10.5468/ogs.2013.56.3.160

Kroenke, K., Spitzer, R. L., Williams, J. B. W., & Löwe, B. (2009). An ultra-brief screening scale for anxiety and depression: The PHQ-4. *Psychosomatics*, *50*(6), 613–621. https://doi.org/10.1016/S0033-3182(09)70864-3

Lenroot, R. K., Blumenthal, J. D., Wallace, G. L., Clasen, L. S., Lee, N. R., & Giedd, J. N. (2014). A case–control study of brain structure and behavioral characteristics in 47,XXX syndrome. *Genes Brain Behaviour*, *13*(8), 841–849. https://doi.org/10.1111/gbb.12180

Merritt, V. C., Crocker, L. D., Sakamoto, M. S., Chanfreau-Coffinier, C., & Delano-Wood, L. (2022). Psychiatric symptoms influence social support in VA Million Veteran Program enrollees screening positive for traumatic brain injury. *Social Science & Medicine*, *312*, 115372. https://doi.org/10.1016/j.socscimed.2022.115372

Mínguez-Alarcón, L., Williams, P. L., Souter, I., Ford, J. B., Hauser, R., & Chavarro, J. E. (2023). Perceived stress and markers of ovarian reserve among subfertile women. *Reproductive Biomedicine Online*, *46*(6), 956–964. https://doi.org/10.1016/j.rbmo.2023.01.024

Nguyen, X. M. T., Quaden, R. M., Song, R. J., Ho, Y. L., Honerlaw, J., Whitbourne, S., DuVall, S. L., Deen, J., Pyarajan, S., Moser, J., Huang, G. D., Muralidhar, S., Concato, J., Tsao, P. S., O'Donnell, C. J., Wilson, P. W. F., Djousse, L., Gagnon, D. R., Gaziano, J. M., … VA Million Veteran Program. (2018). Baseline characterization and annual trends of body mass index for a mega-biobank cohort of US veterans 2011–2017. *Journal of Health Research Review Development Countries*, *5*(2), 98–107. http://www.ncbi.nlm.nih.gov/pubmed/33117892

Nielsen, J., & Wohlert, M. (1991). Chromosome abnormalities found among 34,910 newborn children: Results from a 13-year incidence study in Arhus, Denmark. *Human Genetics*, *87*(1), 81–83. https://doi.org/10.1007/BF01213097

Ogata, T., Matsuo, N., & Nishimura, G. (2001). SHOX haploinsufficiency and overdosage: Impact of gonadal function status. *Journal of Medical Genetics*, *38*(1), 1–6. https://doi.org/10.1136/jmg.38.1.1

Otter, M., Crins, P. M. L., Campforts, B. C. M., Stumpel, C. T. R. M., van Amelsvoort, T. A. M. J., & Vingerhoets, C. (2021). Social functioning and emotion recognition in adults with triple X syndrome. *BJPsych Open.*, *7*(2), e51. https://doi.org/10.1192/bjo.2021.8

Ottesen, A. M., Aksglaede, L., Garn, I., Tartaglia, N., Tassone, F., Gravholt, C. H., Bojesen, A., Sørensen, K., Jørgensen, N., Rajpert-de Meyts, E., Gerdes, T., Lind, A. M., Kjaergaard, S., & Juul, A. (2010). Increased number of sex chromosomes affects height in a nonlinear fashion: A study of 305 patients with sex chromosome aneuploidy. *American Journal of Medical Genetics Part A*, *152A*(5), 1206–1212. https://doi.org/10.1002/ajmg.a.33334

Schmidt, P. J., Cardoso, G. M. P., Ross, J. L., Haq, N., Rubinow, D. R., & Bondy, C. A. (2006). Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. *Journal of the American Medical Association*, *295*(12), 1374–1376. https://doi.org/10.1001/jama.295.12.1374

Simcoe, M. J., Khawaja, A. P., Mahroo, O. A., Hammond, C. J., & Hysi, P. G. (2020). The role of chromosome X in intraocular pressure variation and sex-specific effects. *Investigative Ophthalmology & Visual Science*, *61*(11), 20. https://doi.org/10.1167/iovs.61.11.20

Singhal, P., Singh, S., Kumar, P., & Naredi, N. (2021). Premature ovarian failure related to trisomy X: Two case reports with an aberrant 47,XXX karyotype. *Journal of Human Reproductive Science*, *14*(1), 87–90. https://doi.org/10.4103/jhrs.JHRS_59_20

Stochholm, K., Juul, S., & Gravholt, C. H. (2010). Mortality and incidence in women with 47,XXX and variants. *American Journal of Medical Genetics Part A*, *152A*(2), 367–372. https://doi.org/10.1002/ajmg.a.33214

Stochholm, K., Juul, S., & Gravholt, C. H. (2013). Poor socio-economic status in 47,XXX—An unexpected effect of an extra X chromosome. *European Journal of Medical Genetics*, *56*(6), 286–291. https://doi.org/10.1016/j.ejmg.2013.03.008

Sugawara, N., Maeda, M., Manome, T., Nagai, R., & Araki, Y. (2013). Patients with 47, XXX karyotype who experienced premature ovarian failure (POF): Two case reports. *Reproductive Medicine and Biology*, *12*(4), 193–195. https://doi.org/10.1007/s12522-013-0158-9

Tartaglia, N. R., Howell, S., Sutherland, A., Wilson, R., & Wilson, L. (2010). A review of trisomy X (47,XXX). *Orphanet Journal of Rare Diseases*, *5*(1), 8. https://doi.org/10.1186/1750-1172-5-8

Tuke, M. A., Ruth, K. S., Wood, A. R., Beaumont, R. N., Tyrrell, J., Jones, S. E., Yaghootkar, H., Turner, C. L. S., Donohoe, M. E., Brooke, A. M., Collinson, M. N., Freathy, R. M., Weedon, M. N., Frayling, T. M., & Murray, A. (2019). Mosaic Turner syndrome shows reduced penetrance in an adult population study. *Genetics in Medicine*, *21*(4), 877–886. https://doi.org/10.1038/s41436-018-0271-6

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

Villanueva, A. L., & Rebar, R. W. (1983). Triple-X syndrome and premature ovarian failure. *Obstetrics and Gynecology*, *62*(3 Suppl), 70s–73s.

Wallerstein, R., Musen, E., McCarrier, J., et al. (2004). Turner syndrome phenotype with 47,XXX karyotype: Further investigation warranted? *American Journal of Medical Genetics. Part A*, *125A*(1), 106–107. https://doi.org/10.1002/ajmg.a.20362

Wigby, K., D'Epagnier, C., Howell, S., Reicks, A., Wilson, R., Cordeiro, L., & Tartaglia, N. (2016). Expanding the phenotype of triple X syndrome: A comparison of prenatal versus postnatal diagnosis. *American Journal of Medical Genetics Part A*, *170*(11), 2870–2881. https://doi.org/10.1002/ajmg.a.37688

Wiggs, J. L. (2007). Genetic etiologies of glaucoma. *Archives of Ophthalmology*, *125*(1), 30. https://doi.org/10.1001/archopht.125.1.30

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