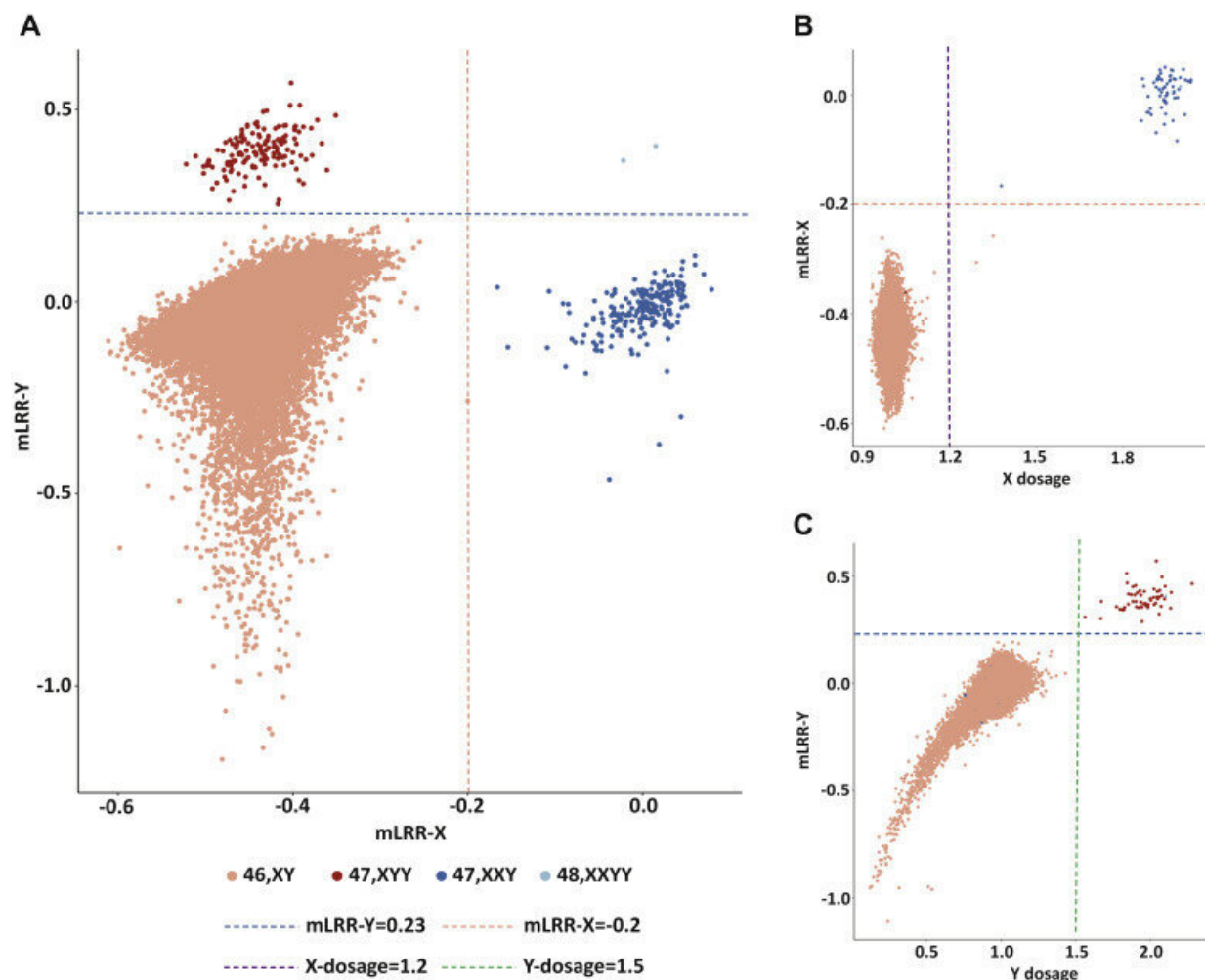


One in 500 men carry extra sex chromosome, putting them at higher risk of several common diseases

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Estimates of sex chromosome intensity and dosage by array genotyping or exome sequencing in UK Biobank men. A. Median array genotype intensity on the X chromosome (mLRR-X) and Y chromosome (mLRR-Y) for each of $n = 207,067$

men, including 213 with 47,XXY (Klinefelter syndrome), 143 with 47,XYY, and 2 with 48,XXYY. B. X dosage estimated from exome sequencing plotted against mLRR-X (n = 83,104). C. Y dosage estimated from exome sequencing plotted against mLRR-Y (n = 83,104). Credit: *Genetics in Medicine* (2022). DOI: 10.1016/j.gim.2022.05.011

Around one in 500 men could be carrying an extra X or Y chromosome—most of them unaware—putting them at increased risk of diseases such as type 2 diabetes, atherosclerosis and thrombosis, say researchers at the universities of Cambridge and Exeter.

In a study published in *Genetics in Medicine*, researchers analyzed [genetic data](#) collected from more than 200,000 U.K. men aged 40–70 from U.K. Biobank, a biomedical database and research resource containing anonymized genetic, lifestyle and [health information](#) from half a million U.K. participants. They found 356 men who carried either an extra X chromosome or an extra Y chromosome.

Sex chromosomes determine our biological sex. Men typically have one X and one Y chromosome, while women have two Xs. However, some men also have an extra X or Y chromosome—XXY or XYY.

Without a genetic test, it may not be immediately obvious. Men with extra X chromosomes are sometimes identified during investigations of delayed puberty and infertility; however, most are unaware that they have this condition. Men with an extra Y chromosome tend to be taller as boys and adults, but otherwise they have no distinctive physical features.

In their study, the researchers identified 213 men with an extra X chromosome and 143 men with an extra Y chromosome. As the

participants in U.K. Biobank tend to be "healthier" than the [general population](#), this suggests that around one in 500 men may carry an extra X or Y chromosome.

Only a small minority of these men had a diagnosis of sex chromosome abnormality on their [medical records](#) or by self-report: fewer than one in four (23%) men with XXY and only one of the 143 XYY men (0.7%) had a known diagnosis.

By linking genetic data to routine health records, the team found that men with XXY have much higher chances of reproductive problems, including a three-fold higher risk of delayed puberty and a four-fold higher risk of being childless. These men also had significantly lower blood concentrations of testosterone, the natural male hormone. Men with XYY appeared to have a normal reproductive function.

Men with either XXY or XYY had higher risks of several other health conditions. They were three times more likely to have type 2 diabetes, six times more likely to develop [venous thrombosis](#), three times as likely to experience [pulmonary embolism](#), and four times more likely to suffer from chronic obstructive pulmonary disease (COPD).

The researchers say that it isn't clear why an extra chromosome should increase the risk or why the risks were so similar irrespective of which sex chromosome was duplicated.

Yajie Zhao, a Ph.D. student at the Medical Research Council (MRC) Epidemiology Unit at the University of Cambridge, the study's first author, said: "Even though a significant number of men carry an extra sex chromosome, very few of them are likely to be aware of this. This extra chromosome means that they have substantially higher risks of a number of common metabolic, vascular, and respiratory diseases—diseases that may be preventable."

Professor Ken Ong, also from the MRC Epidemiology Unit at Cambridge and joint senior author, added: "Genetic testing can detect chromosomal abnormalities fairly easily, so it might be helpful if XXY and XYY were more widely tested for in men who present to their doctor with a relevant health concern.

"We'd need more research to assess whether there is additional value in wider screening for unusual chromosomes in the general population, but this could potentially lead to early interventions to help them avoid the related diseases."

Professor Anna Murray, at the University of Exeter, said: "Our study is important because it starts from the genetics and tells us about the potential health impacts of having an extra sex chromosome in an older population, without being biased by only testing men with certain features as has often been done in the past."

Previous studies have found that around one in 1,000 females have an additional X chromosome, which can result in delayed language development and accelerated growth until puberty, as well as lower IQ levels compared to their peers.

More information: Yajie Zhao et al, Detection and characterization of male sex chromosome abnormalities in the UK Biobank study, *Genetics in Medicine* (2022). [DOI: 10.1016/j.gim.2022.05.011](https://doi.org/10.1016/j.gim.2022.05.011)

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