IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

BONGO PRODUCTIONS, LLC, et al.,	)	
	)	
Plaintiffs,	)	
	)	
v.	)	Civ. Action
	)	No. 3:21-cv-490
	)	Judge Trauger
CARTER LAWRENCE, et al.,	)	
	)	
Defendants.	)	
	)	

DEFENDANTS' RESPONSE TO PLAINTIFFS' STATEMENT OF UNDISPUTED MATERIAL FACTS

Defendants respond as follows to Plaintiffs' statement of material facts as to which there are no genuine issues for trial:

PARTIES

1. Plaintiff Bongo Productions, LLC ("Bongo") owns several restaurants, coffee shops and a coffee roasting company all located in Nashville, Tennessee. Bernstein Decl. ¶ 1, ECF No. 7-1; Bernstein Dep. at 16:14–17:3, Picasso Decl. Ex. 2.

RESPONSE: Undisputed for purposes of summary judgment.

2. Plaintiff Robert M. Bernstein is the founder and chief manager of Bongo. Bernstein Decl. ¶ 2, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment.

3. Mr. Bernstein is responsible for decisions regarding compliance with state and local building codes for Bongo's establishments. Pls.' Resp. to Defs.' Interrogs. at 5–6, Picasso Decl. Ex. 10.

RESPONSE: Undisputed for purposes of summary judgment.

4. Defendant Carter Lawrence is the Commissioner of the Tennessee Department of Commerce and Insurance, and in that capacity, is also the Tennessee Fire Marshal and authorized by statute to enforce the state building code. Defs.' Resp. to Pls.' Interrogs. at 6–7, Picasso Decl. Ex. 9; Tenn. Code Ann. § 68-120-106.

RESPONSE: Undisputed for purposes of summary judgment.

5. Defendant Christopher Bainbridge is the Director of the Codes Enforcement Section of the Tennessee State Fire Marshal's Office and in that capacity has enforcement authority over statewide building codes and standards, including the Act. Defs.' Resp. to Pls.' Interrogs. at 6–7; Tenn. Comp. R. & Regs. 0780-02-16.01.

RESPONSE: Undisputed for purposes of summary judgment.

6. Defendant Glenn R. Funk is the District Attorney General for the 20th Judicial District which covers Metropolitan Davidson County and Nashville, Tennessee, and in that

capacity is responsible for prosecuting all violations of the state criminal statutes occurring in the judicial district. Tenn. Code Ann. §§ 8-7-103, 40-3-104.

RESPONSE: Undisputed for purposes of summary judgment.

7. Defendant Neal Pinkston is the District Attorney General for 11th Judicial District which covers Hamilton County and Chattanooga, Tennessee, and in that capacity is responsible for prosecuting all violations of the state criminal statutes occurring in the judicial district. Tenn. Code Ann. §§ 8-7-103, 40-3-104.

RESPONSE: Undisputed for purposes of summary judgment.

<u>THE ACT</u>

8. On April 29, 2021, the Tennessee General Assembly passed H.B. 1182 ("The Act"). H.B. 1182/S.B. 1224, 112th Gen. Assemb., 1st Reg. Sess. (Tenn. 2021), Picasso Decl. Ex. 1.

RESPONSE: Undisputed for purposes of summary judgment.

9. On May 17, 2021, the Governor of Tennessee signed the Act into law. H.B. 1182.

RESPONSE: Undisputed for purposes of summary judgment.

10. The Act went into effect on July 1, 2021. H.B. 1182.

RESPONSE: Undisputed for purposes of summary judgment.

11. Enforcement of the Act was enjoined by the Court's Order granting Plaintiffs' Motion for a Preliminary Injunction against enforcement of the Act, dated July, 9, 2021. Mem. Op., ECF No. 22.

RESPONSE: Undisputed for purposes of summary judgment.

12. As enacted, the Act requires "[a] public or private entity or business that operates a building or facility open to the general public and that, as a matter of formal or informal policy, allows a member of either biological sex to use any public restroom within the building or facility shall post notice of the policy at the entrance of each public restroom in the building or facility." H.B. 1182 § 1(a).

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

13. The Act's definition of "policy" includes "the internal policy of a public or private entity[.]" H.B. 1182 § 1(d)(1).

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

14. The Act defines "public restroom" to include those with facilities that are designated for "a specific biological sex," and to "exclude" "a unisex, single-occupant restroom or family restroom intended for use by either biological sex." H.B. 1182 § 1(d)(2).

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is disputed for purposes of summary judgment as the Act specifically sets forth a number of criteria in (d)(2)(A) beyond those restated here.

15. The Act further mandates: "Signage of the notice must be posted in a manner that is easily visible to a person entering the public restroom and must meet the following requirements: (1) Be at least eight inches (8") wide and six inches (6") tall; (2) The top one-third (1/3) of the sign must have a background color of red and state "NOTICE" in yellow text, centered in that portion of the sign; (3) The bottom two-thirds (2/3) of the sign must contain in boldface, block letters the following statement centered on that portion of the sign: THIS FACILITY MAINTAINS A POLICY OF ALLOWING THE USE OF RESTROOMS BY EITHER BIOLOGICAL SEX, REGARDLESS OF THE DESIGNATION ON THE RESTROOM; (4) Except as provided in subdivision (b)(2), have a background color of white

with type in black; and (5) Be located on a door to which the sign must be affixed or have its leading edge located not more than one foot (1') from the outside edge of the frame of a door to which the sign must be affixed." H.B. 1182 § 1(b).

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

16. The Act does not define "biological sex." H.B. 1128.

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

17. Tennessee law requires that "[p]ublicly and privately owned facilities where the public congregates shall be equipped with sufficient temporary or permanent restrooms to meet the needs of the public at peak hours." Tenn. Code Ann. § 68-120-503(a); Ferguson Dep. at 15:23–16:14, Picasso Decl. Ex. 8.

RESPONSE: Defendants submit that the quoted language speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

LEGISLATIVE HISTORY

18. During the legislative debates on H.B. 1182, the sole justification offered by its sponsor, Representative Tim Rudd, was that the bill was necessary to "protect[] women and children against" people who could "tak[e] advantage of policies, executive orders, or legislation[] that [] allow the 'opposite biological sex' to enter a [multi-occupancy] restroom, shower, or locker room." Picasso Decl. ¶ 20.

RESPONSE: Defendants submit that the legislative history of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is disputed as it is a modified version. The original version can be found here: https://wapp.capitol.tn.gov/apps/BillInfo/Default.aspx?BillNumber=HB1182. Defendants submit that the separate recitation in the Declaration of Malita Picasso (DE 37-1, ¶ 20) is accurate.

19. He explained with "new [laws] . . . giving transgenders [sic] [more] rights . . . I don't want women . . . or children calling me next year [about] how they have been raped or molested [while using the bathroom facility]." Picasso Decl. ¶ 21.

RESPONSE: Defendants submit that the legislative history of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is disputed as it is a modified version. The original version can be found here: https://wapp.capitol.tn.gov/apps/BillInfo/Default.aspx?BillNumber=HB1182. Defendants submit that the separate recitation in the Declaration of Malita Picasso (DE 37-1, ¶ 21) is accurate.

20. During a subsequent committee meeting, Representative Rudd stated that "a woman has the right to know whether a man is going to be in her bathroom and vice versa for a man." This too was a reference to transgender people using the restrooms that accord with their gender identity. Picasso Decl. ¶ 22.

RESPONSE: Defendants submit that the legislative history of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement in the first sentence is undisputed. But Defendants submit that the editorializing in the second sentence is not supported by the Declaration of Malita Picasso (DE 37-1, ¶ 22), and is therefore disputed.

21. When questioned by other representatives about the need for this bill, Representative Rudd responded that the bill was suggested by a constituent at a fundraiser, and he felt that the bill was needed because of the executive orders regarding rights for transgender people "coming out of Washington." Picasso Decl. ¶¶ 21, 23.

RESPONSE: Defendants submit that the legislative history of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this description of the legislative history is disputed as it is not in its original form. The original version can be found here: https://wapp.capitol.tn.gov/apps/BillInfo/Default.aspx?BillNumber=HB1182. Defendants submit that the separate recitations in the Declaration of Malita Picasso (DE 37-1, ¶¶ 21, 23) are accurate.

22. During House floor debates on March 29, Representative Mike Stewart asked about the public policy underlying H.B. 1182. Representative Rudd once more responded that with the new executive orders and policies from Washington, it would be "good to put on notice." He also stated that it is "shocking and a danger to people that enter a bathroom marked 'men' or 'women' and someone of the opposite sex is standing there, which could scare people and provoke violence." Picasso Decl. ¶¶ 24–25.

RESPONSE: Defendants submit that the legislative history of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is disputed as it is a modified version. The original version can be found here: https://wapp.capitol.tn.gov/apps/BillInfo/Default.aspx?BillNumber=HB1182. Defendants submit that the separate recitations in the Declaration of Malita Picasso (DE 37-1, ¶¶ 24–25) are accurate.

23. In 2021, the Tennessee General Assembly passed, and Governor Lee signed into law, five bills targeting transgender people in Tennessee, two of which specifically use the term "biological sex." Tenn. Code Ann. §§ 49-2-802, 68-120-120.

RESPONSE: Defendants submit that the cited statutes speak for themselves and require no separate acknowledgement. However, Defendants submit that the editorialization of these statutes is unsupported by the citations to this proposed undisputed fact and thus dispute Plaintiffs' depiction of them.

ENFORCEMENT

24. The Office of the State Fire Marshal ("SFMO") is authorized to enforce the provisions of the Tennessee Building Code, which includes the Act. Defs.' Resp. to Pls.' at 6–7; Ferguson Dep. at 14:9–23, 17:14–18:2, 19:10–14.

RESPONSE: Undisputed for purposes of summary judgment.

25. SFMO is authorized to enforce provisions of the Tennessee Building Code, including the Act, by receiving, reviewing, and responding to complaints from the public about violations. Ferguson Dep. at 21:2–25, 24:24–25:25.

RESPONSE: Undisputed for purposes of summary judgment.

26. When SFMO receives a complaint alleging a violation of the Tennessee Building Code, it is authorized to send a building inspector to conduct a safety inspection of the building, and to issue a notice of violation to the building occupant informing them of the violation and directing them to remedy the violation by a set deadline. Ferguson Dep. at 25:17–27:3, 30:12–24.

RESPONSE: Undisputed for purposes of summary judgment.

27. The Tennessee Building Code contemplates and permits the existence of exempt jurisdictions, which are those in which the local governmental body shares authority to enforce the provisions of the code with SFMO. Ferguson Dep. at 21:15–25.

RESPONSE: Undisputed for purposes of summary judgment.

28. The SFMO shares the authority to enforce the provisions of the Tennessee Building Code, which includes the Act, with these local law enforcement agencies because its enabling statute sets forth concurrent jurisdiction. Ferguson Dep. at 21:15–25.

RESPONSE: Undisputed for purposes of summary judgment.

29. Where there is a conflict between SFMO and the local law enforcement agency, SFMO is authorized to resolve the conflict. Ferguson Dep. at 21:15–25.

RESPONSE: Undisputed for purposes of summary judgment.

30. When an exempt jurisdiction refuses or otherwise fails to enforce the provisions of the Tennessee Building Code, SFMO is authorized to notify the exempt jurisdiction of the failure and to take further enforcement action if the local authority persists in its failure to enforce. Ferguson Dep. at 23:5–24:7.

RESPONSE: Undisputed for purposes of summary judgment.

31. If SFMO were to receive a complaint of an alleged violation of the Act, an SFMO inspector would schedule an inspection of the building that is the subject of the complaint. Ferguson Dep. at 51:8–23.

RESPONSE: Undisputed for purposes of summary judgment.

32. Defendants allege that the Act, "puts the burden on the business owner to either post a sign if they have a policy that allows a member of either biological sex to use the public restroom[,]" or not post a sign if they do not have a policy. Ferguson Dep. at 51:24–52:11, 59:1–6; 101:13–102:9.

RESPONSE: Undisputed for purposes of summary judgment.

33. Defendants have not provided any guidance to assist Tennessee business owners with complying with the Act. Ferguson Dep. at 51:24–53:19.

RESPONSE: Undisputed for purposes of summary judgment.

34. Defendants acknowledge that it is a crime to submit false information to a state agency and that they are authorized to verify whether a business owner "submitted false information to a state agency in a regulatory context[,]" if a business owner informed SFMO that his building does not have a restroom policy that would require it to post the sign mandated by the Act. Ferguson Dep. at 55:17–56:13.

RESPONSE: Undisputed for purposes of summary judgment.

35. Defendants' representative testified that an entity that permits transgender people to use the restroom that aligns with their gender identity but refused to post the sign mandated by the Act would be in violation of the Act. Ferguson Dep. at 60:9–65:8.

RESPONSE: Undisputed for purposes of summary judgment.

36. Buildings or entities that violate the Act would be given written notice directing discontinuance of such illegal action and would be required to post the required sign within thirty days of receipt of the notice. Defs.' Resp. to Pls.' at 6–7, 13.

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

37. Failure to post the required signage within the thirty-day period is classified as a Class B misdemeanor. Defs.' Resp. to Pls.' at 6–7, 13.

RESPONSE: Undisputed for purposes of summary judgment.

38. Under Tennessee Law, a Class B misdemeanor is punishable by six (6) months in prison and fines of up to $500.00. Tenn. Code Ann. § 40-35-111(e)(2).

RESPONSE: Defendants submit that the language of the cited statute speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement is undisputed for purposes of summary judgment.

39. Defendants allege that the Act is intended to further the state's interest in "providing people who may be using facilities where there is a reasonable expectation of privacy what they may encounter." Ferguson Dep. at 37:20–38:3.

RESPONSE: Undisputed for purposes of summary judgment.

40. Defendants have not provided any definition of the phrase "biological sex" in the Act, asserting a lack of the requisite scientific and medical expertise to do so. Ferguson Dep. at 41:20–43:1, 91:19–95:6.

RESPONSE: Defendants submit that the language of the Act speaks for itself and requires no separate acknowledgement. However, to the extent a response is required, this restatement of the language of the Act is undisputed for purposes of summary judgment.

41. If a business owner asserted that the phrase "biological sex" as it appears in the Act lacks a clear meaning, that business would be treated as refusing to comply with the Act and SFMO would refer the business owner to the local District Attorney for further enforcement. Ferguson Dep. at 95:7–99:5.

RESPONSE: Undisputed for purposes of summary judgment.

42. Defendants have never received a complaint relating to a transgender person using a restroom at a business open to the public. Ferguson Dep. at 71:1–6.

RESPONSE: Undisputed for purposes of summary judgment.

43. An exempt jurisdiction that persistently fails to enforce the Act could lose its exempt status based on its persistent failure to enforce the Act. Ferguson Dep. at 81:8–82:21.

RESPONSE: Undisputed for purposes of summary judgment

44. SFMO is not prohibited from enforcing the Act in an exempt jurisdiction in which the local authority is refusing or otherwise failing to enforce the Act. Ferguson Dep. at 82:22–84:16.

RESPONSE: Undisputed for purposes of summary judgment.

PLAINTIFFS ARE SUBJECT TO THE ACT

45. Mr. Bernstein opened Fido in 1996. Fido is a restaurant located in the Hillsboro Village neighborhood of Nashville. Bernstein Decl. ¶ 4, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

46. Fido has 25 employees currently on staff and has employed hundreds of people over the years. Bernstein Decl. ¶ 5, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

47. In the past, Bongo has employed transgender people. Bongo's and Fido's patrons include members of the transgender community. Bernstein Decl. ¶ 6, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

48. Bongo and Mr. Bernstein have worked over the years to create a welcoming environment in their business for the LGBTQ community. In reaction to the rash of anti-transgender laws that passed this year and to show their support for transgender people, Fido's staff decorated one of their drink menu signs with transgender and LGBTQ pride flag colors. Bernstein Decl. ¶¶ 7–8, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment except that Defendants dispute the mischaracterization of Tennessee's laws.

49. Fido has three restrooms. One is a single-user unisex restroom, which is not subject to the Act. The other two restrooms have multiple stalls and/or urinals and bear sex-designations. Bernstein Decl. ¶ 9, ECF No. 7-1; Bernstein Dep. at 17:24–18:11.

RESPONSE: Undisputed for purposes of summary judgment

50. Fido's two multi-stall and/or urinals that bear sex-designations are subject to the Act. Bernstein Decl. ¶ 9, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

51. Prior to the passage of the Act, Fido's management and Mr. Bernstein had never thought about a formal policy as to who could use which restroom. Bernstein Decl. ¶ 11, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

52. Plaintiffs' informal policy was to allow people to use the sex-designated restroom that best matches their gender identity. Bernstein Decl. ¶ 11, ECF No. 7-1.

RESPONSE: Undisputed for purposes of summary judgment

53. Plaintiffs allows all women, including transgender women, to use the women's restroom and all men, including transgender men, to use the men's restroom. Bernstein Decl. ¶ 10, ECF No. 7-1.

RESPONSE: Defendants do not dispute that Plaintiffs allow anyone who identifies as a woman to use the women's restroom and anyone who identifies as a man to use the men's restroom, regardless of their biological sex.

54. Plaintiffs have never received any complaints or concerns about their restroom policy or about transgender people using the restrooms consistent with their gender identity. Bernstein Decl. ¶ 12, ECF No. 7-1; Bernstein Dep. at 11:25–13:14, 28:5–29:23.

RESPONSE: Undisputed for purposes of summary judgment

55. Plaintiffs believe that posting the warning notice sign required by the Act will offend Bongo's staff, customers, friends, and family, and that Plaintiffs may lose staff and customers if forced to post the sign. Bernstein Decl. ¶ 14, ECF No. 7-1; Bernstein Dep. at 34:10–16, 35:23–36:22, 50:9–13.

RESPONSE: Undisputed for purposes of summary judgment

56. On or about August 18, a customer dining at Plaintiff Robert Bernstein's restaurant left a note for Mr. Bernstein expressing support of his and Plaintiff Bongo Production, LLC's challenge to the Act. The handwritten note states, "Thank you for suing the Tennessee Gov't on the Anti-Transgender Bathroom Bill. Here is a small contribution towards legal fees or

as you see fit. Thanks!!!" The customer did not disclose their identity and, to date, Mr. Bernstein does not know who left the note. Pls.' Resp. to Defs.' Interrogs. at 6–7.

RESPONSE: Undisputed for purposes of summary judgment

"BIOLOGICAL SEX"

57. The phrase "biological sex" is a relatively recent one without a fixed or uniform definition. Its uses within the fields of science and medicine are uncommon and at best reflect differing and inconsistent interpretations among users, which can only be ascertained by relying on additional information and the context in which it is used. Pls.' Resp. to Defs.' Interrogs. at 8; Taylor Expert Report ¶¶15–16, Picasso Decl. Ex. 7.

RESPONSE: Disputed. The phrase "biological sex" is a common phrase that is also used throughout scientific literature and possesses a fixed and uniform definition. *See* Am. Psychiatric Assoc., *The Diagnostic and Statistical Manual of Mental Disorders*, 15 (5th ed. 2013); Riittakerttu Kaltiala-Heino et al., *Gender dysphoria in adolescence: current perspectives*, ADOLESCENT HEALTH, MEDICINE AND THERAPEUTICS 2018: 9, 21, 21 (2018); L.A. Walter and A.J. McGregor, *Sex- and Gender-specific Observations and Implications for COVID-19*, WEST J EMERG MED. 21(3): 507-509 (2020); E.P. Scully et al., *Considering how biological sex impacts immune responses and COVID-19 outcomes*, NAT REV IMMUNOL 20, 442-447 (2020); S.L. Klein et al., *Biological sex impacts COVID-19 outcomes*, PLOS PATHOG 16:6 (2020). Further, "biological sex" has the same meaning as the longstanding and broadly accepted definition of "sex." *See, e.g.*, *Sex*, New Oxford American Dictionary (3d ed. 2010) ("either of the two main categories (male and female) into which humans and many other living things are divided on the basis of their reproductive functions").

58. Plaintiffs understand the phrase "biological sex" to be frequently used by those who seek to limit or eliminate the legal recognition, protection, and rights of transgender people. Plaintiffs understand the phrase to be used in the Act in order to single out transgender people by attempting to suggest a distinction between gender identity and so-called "biological sex." Used in contexts like the Act, Plaintiffs understand "biological sex" to be a phrase that is stigmatizing to transgender people. Pls.' Resp. to Defs.' Interrogs. at 8; Taylor Expert Report ¶¶ 30–31; Bernstein Decl. ¶¶ 14–16, ECF No. 7-1; Bernstein Dep. at 39:3–8, 41:22–42:5, 44:1–7, 53:7–54:6, 56:14–22.

RESPONSE: Disputed. The term "biological sex" is a neutral term that conveys no stigma or viewpoint. Nor is the term necessarily indicative of attempts to "limit or eliminate the legal recognition, protection, and rights of transgender people." *See* Resp. to Undisputed Material Fact # 57; *Doe 2 v. Shanahan*, 917 F.3d 694, 698 (D.C. Cir. 2019); *Able v. United States*, 88 F.3d 1280, 1286 (2d Cir. 1996); *Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 614 (4th Cir. 2020); *Parents for Priv. v. Barr*, 949 F.3d 1210, 1217 (9th Cir. 2020); *Doe by and through Doe v. Boyertown Area Sch. Dist.*, 897 F.3d 518, 529 (3d Cir. 2018); *Hively v. Ivy Tech Cmty. Coll. of Ind.*, 853 F.3d 339, 347 (7th Cir. 2017); *Cruzan v. Special Sch. Dist, No. 1*, 294 F.3d 981, 983 (8th Cir. 2002); *Jackson v. Valdez*, --- Fed.App'x ---, 2021 WL 1990788, at *5 (5th Cir. 2021); *Etsitty v. Utah Transit Auth.*, 502 F.3d 1215, 1225 (10th Cir. 2007); *E.E.O.C. v. R.G. & G.R. Harris Funeral Homes, Inc.*, 884 F.3d 560, 578 (6th Cir. 2018) (affirmed by *Bostock v. Clayton Cnty., Ga.*, 140 S.Ct. 1731 (2020)); *Doe v. Hamilton Cnty. Bd. of Educ.*, 329 F.Supp.3d 543, 580 (E.D. Tenn. 2018); *Farmer v. Brennan*, 511 U.S. 825, 829 (1994); *Bostock*, 140 S.Ct. at 1752. The challenged Act speaks for itself, and like the cited judicial opinions, uses the term "biological sex" objectively and neutrally. *See also* Taylor Depo. at 79: 17-22 ("I think the intention of both of those terms ["biological sex" and "sex assigned at birth"] is the same".)

59. The sex of a child is most often determined after delivery based on the visual appearance of an infant's external genitals. Taylor Expert Report ¶ 14.

RESPONSE: Undisputed for purposes of summary judgment.

60. Research has identified that determination of sex is far more complex than what is seen on genital exam. Instead, sex is a complex compilation of multiple factors including one's chromosomal make up (XX for those assigned female at birth, XY for those assigned male at birth), gonadal sex (presence of ovaries or testes), fetal hormonal sex (production of sex hormones by the fetus or exogenous exposure of sex hormones to the developing fetus), pubertal hormonal sex (the change in hormonal milieu that results in the development of secondary sexual characteristics- facial hair and deep voice for those assigned male at birth, breasts and menstrual cycles for those assigned female), hypothalamic sex (variations in brain structure and function as a result of embryonal exposure of sex hormones), and gender identity. Taylor Expert Report ¶ 15.

RESPONSE: Disputed. In humans, sex is determined by organization with respect to the reproductive system, which is determined by the sex chromosomes. *See* Bachtrog et al., *Sex Determination, Why So Many Ways of Doing It?* PLoS Biol, 2014 Jul; 12(7). These chromosomes initiate gonadal differentiation and "sex hormones initiate further sexual differentiation in nongonadal tissues and organs." *Id*. Gender identity is irrelevant to the determination of a human's sex. Defendants also dispute that sex is "assigned" at birth; it is recorded.

61. For each of the factors that contribute to the development of sex, there can be variations. Sex related characteristics do not always align as either completely male or completely female. Taylor Expert Report ¶ 16.

RESPONSE: Disputed as the underlying premise is disputed. *See* Resp. to Undisputed Material Fact # 60

62. Many children are born with ambiguous genitalia, and as a result it is difficult to assign these infants as either male or female at birth. These patients are often identified as intersex, which is one of many disorders of sexual development (DSD). These children often see multiple specialists throughout their lifespan. Other examples of DSDs are those of chromosomal differences. The typical human chromosomal make up includes 46XY for males and 46XX for females. However, in male patients with Kleinfelter's syndrome their chromosomal makeup is 47XXY. These chromosomal male individuals have an extra X chromosome. The results include breast development and small testes, in addition to other physical findings. Patients with Turner Syndrome are 45XO. These female individuals are missing an X chromosome, and as such many of them do not develop normal female puberty and are often infertile. These variations are common. The Monroe Carrell Children's Hospital at Vanderbilt has an entire clinic to cater to the medical needs of this patient population. Taylor Expert Report ¶ 16.

RESPONSE: Disputed except for the fifth and last sentences, which are undisputed for the purposes of summary judgment. Most children are not born with ambiguous genitalia. Further, sex is not assigned at birth; it is recorded as male or female. Humans with disorders of sexual development still have a sex. For example, humans with Klinefelter syndrome (47XXY) are still men, and humans with Turner syndrome (45XO) are still women. Despite departures from the normal development expected for humans with 46XY or 46XX chromosomes, those with Klinefelter syndrome still have a male reproductive system while those with Turner system still have a female reproductive system. These two chromosomal disorders occur in a small proportion of the population. *See* NIH, *Klinefelter Syndrome*, Eunice Kennedy Shriver National Institute of Child Health and Human Development - NICHD (nih.gov); NIH, *Turner Syndrome*, Eunice Kennedy Shriver National Institute of Child Health and Human Development - NICHD (nih.gov)

63. Gender identity is a person's inner sense of belonging to a particular gender. Identifying as male or female is a core component of one's overall identity. Every person has a gender identity. Research has shown that children begin to develop and express their gender identity during their toddler years, at around the age of 3 years old. It has a strong biological basis and cannot be changed. Taylor Expert Report ¶ 17.

RESPONSE: Disputed. "Gender identity" is a term popularized by Robert Stoller, a UCLA psychoanalyst. According to Stoller, "sex was biological but gender was social." David Haig, *The Inexorable Rise of Gender and the Decline of Sex: Social Change in Academic Titles, 1945-2001*, Archives of Sexual Behavior, Apr. 2004, at 93. The term "gender"—previously a grammatical term only—was itself introduced into scientific discourse in the 1950s by John Money, a psychologist at Johns Hopkins University. Joanne Meyerowitz, *A History of "Gender,"* 113 The American Historical Review 1346, 1354 (2008). Research has not established "a strong biological basis" connecting transgender individuals' gender identity with the biological reality of how their bodies' reproductive systems are organized. Accordingly, many purported gender identities are unmoored from the male/female binary. *Cf. United States v. Varner*, 948 F.3d 250, 256-57 (5th Cir. 2020). And toddlers' beliefs about reality are not always (1) accurate, or (2) incapable of changing.

64. Scientific research has discovered many biological reasons for how an individual develops a gender identity. Complex interactions between hormones, chromosomes, and the developing embryo in utero are at the center of these theories. Taylor Expert Report ¶ 18.

RESPONSE: Disputed. These novel ideas are merely theories, and a transgender individual's gender identity is not determined by the biological reality of how his or her reproductive system is organized.

65. From a medical perspective, in the event that one's gender identity does not match their sex assigned at birth, i.e. in transgender people, one's gender identity should be the determining factor of their sex. The medical consensus recognizes that when one's sex related-characteristics are not in alignment, a person's gender identity is the determining factor, more important than the presence of their genitals, their chromosomal analysis, or their hormone levels. Taylor Expert Report ¶ 19.

RESPONSE: Disputed. Sex is not "assigned" at birth; it is recorded in recognition of the organization of the baby's reproductive system. The organization of the reproductive system is determined by sex chromosomes. *See* Bachtrog et al., *Sex Determination, Why So Many Ways of Doing It?* PLoS Biol, 2014 Jul; 12(7). These chromosomes initiate gonadal differentiation and "sex hormones initiate further sexual differentiation in nongonadal tissues and organs." *Id*. Gender identity plays no role in determining sex.

66. Transgender people have a gender identity that differs from the sex that was assigned to them at birth. Taylor Expert Report ¶ 20.

RESPONSE: Undisputed for purposes of summary judgment except that Defendants dispute the assertion that sex is "assigned" at birth; it is recorded.

67. This lack of alignment of assigned sex and gender identity can result in severe distress, depression, and anxiety. This constellation of symptoms is termed gender dysphoria. Taylor Expert Report ¶ 21.

RESPONSE: Undisputed for purposes of summary judgment except that Defendants dispute the assertion that sex is "assigned" at birth; it is recorded.

68. Treating gender dysphoria results in significant improvement in the quality of life, mental and physical health of transgender persons. Transgender people undergoing treatment for

their gender dysphoria can live long, happy, productive and meaningful lives. Taylor Expert Report ¶ 22.

RESPONSE: Immaterial for the purposes of summary judgment. This fact is irrelevant to the constitutionality of the Act on First Amendment compelled speech-grounds.

69. Gender transition for those that suffer from Gender Dysphoria is a lengthy process with multiple components. These components may include social transition, medical transition, and surgical transition. Each transgender individual approaches transition differently, as the decision to undergo any aspect of transition is deeply personal and depends on the degree and type of dysphoria the patient is experiencing. Taylor Expert Report ¶ 23.

RESPONSE: Undisputed for purposes of summary judgment.

70. The social transition is a formative aspect of a transgender person's experience. Social transition can include going by a different name, using different pronouns, or changing one's haircut or clothing to match one's gender identity. Taylor Expert Report ¶ 24.

RESPONSE: Immaterial for the purposes of summary judgment. This fact is irrelevant to the constitutionality of the Act on First Amendment compelled speech-grounds.

71. As part of the social transition, a transgender individual will make changes that will allow them to seamlessly incorporate into their communities with a presentation that

matches with their gender identity. This may mean using a restroom facility that matches their gender identity in the same way that a non-transgender person uses the bathroom that matches their gender identity. Taylor Expert Report ¶ 25.

RESPONSE: Disputed. Not all transgender individuals view transition the same way, *see* Taylor Expert Report ¶ 25, and this "social transition" is not necessarily "seamless[]." Additionally, many purported gender identities are unmoored from the male/female binary. *Cf. United States v. Varner*, 948 F.3d 250, 256-57 (5th Cir. 2020). Individuals normally use the bathroom that matches their sex, which is biological.

72. In addition to social transition, some transgender individuals interface with a healthcare setting for medical or surgical intervention. Medical transition often includes the prescription of hormones so that the transgender person can develop secondary sexual characteristics of the sex with which they identify. This may mean that a transgender man (or someone who was assigned female at birth) may grow facial hair and develop a much deeper voice as a result of testosterone treatment. Alternatively, transgender women (assigned male at birth), may develop breast tissue and a more feminine body fat distribution as a result of estrogen that may be prescribed by a clinician. Taylor Expert Report ¶ 26.

RESPONSE: Immaterial for the purposes of summary judgment. This fact is irrelevant to the constitutionality of the Act on First Amendment compelled speech-grounds.

73. Some transgender patients also seek surgical transition. These surgical procedures further change the patient's anatomy so that their outward appearance matches more closely with their gender identity. Taylor Expert Report ¶ 27.

RESPONSE: Immaterial for the purposes of summary judgment. This fact is irrelevant to the constitutionality of the Act on First Amendment compelled speech-grounds.

74. Given the medical and surgical treatments that transgender patients may encounter, they are often no longer presenting as their sex assigned at birth. Taylor Expert Report ¶ 28.

RESPONSE: Disputed. Sex is not "assigned" at birth; it is recorded in recognition of the organization of the baby's reproductive system. As the organization of the reproductive system is determined by sex chromosomes, *see* Bachtrog et al., *Sex Determination, Why So Many Ways of Doing It?* PLoS Biol, 2014 Jul; 12(7), transgender patients still medically present as their immutable biological sex, despite any differentiation in appearance.

75. Forcing transgender people to use the restroom designated for the sex assigned to them at birth will increase rather than reduce stress and anxiety for bathroom users, both transgender and otherwise. Taylor Expert Report ¶ 28.

RESPONSE: Disputed. *See* Taylor Depo. 108; 8-13:

Q: Okay. Now is it possible that someone who has gender dysphoria could see the sign that's proposed by the challenged law and not think—not risk worsening their gender dysphoria or having any—or not thinking that it's dangerous and distressing?
A: Sure. That's certainly possible.

76. There are approximately 1.6 million people in the United States who identify as transgender, of which an estimated 31,000 transgender people (or 0.6% of the state's population) live in the state of Tennessee. Tennessee is ranked 10th in the nation for its percentage of transgender residents. Taylor Expert Report ¶ 29.

RESPONSE: Undisputed for purposes of summary judgment that this reflects the estimates of the 2016 Williams Institute report. *See* Taylor Expert Report ¶ 29. This organization's estimate is based on an optional questionnaire that did not include any responses by Tennesseans. *See* Williams Institute, *How Many Adults Identify as Transgender in the United States?* 7 (June 2016).

77. Experts who study sex and gender understand that the biology and identity of a human being is far more complex than what can be identified on an individual's genital anatomy or chromosomal evaluation. Taylor Expert Report ¶ 30.

RESPONSE: Disputed. While biology is no doubt a "complex" field of scientific inquiry, the phrase "biological sex" is a commonly used phrase that is also used throughout scientific literature and possesses a fixed and uniform definition. *See* Resp. to Undisputed Material Fact #

57. Further, sex is recorded in recognition of the biological organization of the reproductive system. This is not typically a "complex" analysis.

78. A large, posted sign referencing "biological sex" on every business is stigmatizing and isolating for transgender Tennesseans and runs the risk of worsening gender dysphoria for those that suffer from the condition. Taylor Expert Report ¶ 31.

RESPONSE: Disputed. *See* Taylor Depo. 109; 24-25; 110; 1-7:

Q: Okay. Having you had any—without going into patient identity, without broaching any sort of confidentiality, have you had a patient who has—who has had worsening gender dysphoria for seeing the term or having the term said to them "biological sex"?

A: No, not specifically that—

Q: Okay.

A: Nobody has come to my office and said, "I read this term and that made my dysphoria worse."

See also Taylor Depo. 111: 6-12

Q: But in your opinion, in your years of practice, the term "biological sex" isn't one of those common triggers for worsening gender dysphoria?

A: No. That has not been something that somebody has come to my office and complained about specifically.

79. The phrase "BIOLOGICAL SEX" does not have a single, agreed upon definition. Pls.' Resp. to Defs.' Interrogs. at 11; Taylor Expert Report ¶ 15, Katrina Karkazis, *The Misuses*

of 'Biological Sex,' 394 The Lancet 1898 (Nov. 23, 2019), https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)32764-3/fulltext.

RESPONSE: Disputed. *See* Resp. Undisputed Material Fact # 57 and # 58.

80. There have never been any incidents or causes for concern arising from the Plaintiffs' restroom policies. Pls.' Resp. to Defs.' Interrogs. at 12; Bernstein Decl. ¶¶ 14–16, ECF No. 7-1; Bernstein Dep. 11:25–13:14, 28:5–29:23.

RESPONSE: Undisputed for purposes of summary judgment.

Respectfully submitted,

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In The Matter Of:

Bongo Productions, LLC, et al. vs.

Carter Lawrence, et al.

Shayne Taylor, M.D.

December 22, 2021

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IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION

BONGO PRODUCTIONS, LLC, ROBERT BERNSTEIN, SANCTUARY PERFORMING ARTS LLC, and KYE SAYERS,	)
Plaintiffs,	)
	) NO. 3:32-cv-00490
vs.	)
	) JUDGE TRAUGER
CARTER LAWRENCE, Tennessee State Fire Marshal, in his official capacity, CHRISTOPHER BAINBRIDGE, Director of Codes Enforcement, in his official capacity, GLENN R. FUNK, District Attorney General for the 20th Judicial District, in his official capacity, and NEAL PINKSTON, District Attorney General for 11th Judicial District, in his official capacity,	)
Defendants.	)

WEB CONFERENCE/REMOTE DEPOSITION OF

SHAYNE TAYLOR, M.D.

December 22, 2021

LYNETTE L. MUELLER, LCR, RDR, CRR, FAPR
LCR No. 351

The web conference/remote deposition of SHAYNE TAYLOR, M.D. is taken on December 22, 2021, on behalf of the Defendants, pursuant to notice and consent of counsel, beginning at approximately 11:00 a.m.

This web conference/remote deposition is taken pursuant to the terms and provisions of the Federal Rules of Civil Procedure.

The right to read and sign was requested.

A P P E A R A N C E S

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I N D E X

E X H I B I T S

SHAYNE TAYLOR, M.D.,

having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. RIEGER:

Q. Hi, Dr. Taylor. Thanks for -- thanks for sitting down with us to have this deposition right before the holidays. We do appreciate it.

My name is Alex Rieger, and I am with the Attorney General's office. And I am lead counsel for the Defendants in this case.

For the record, could I get you to introduce yourself and spell your last name for the record.

A. Sure. My name is Dr. Shayne Taylor. My last name is Taylor. T, as in Tom, A-Y-L-O-R.

Q. All right. Well, thank you.

So in order to ensure that the deposition goes as smoothly as possible, I like to start with some rules of the road. So I know, from your preliminary statement in your expert report, that you have given a deposition before; is that correct?

A. Just one. Yes.

Q. Okay. And what was the -- what was your role in that case? Were you an expert witness in that case?

Q. Okay. Is there anything else you do to stay current on medical research and literature as described in paragraph 9?
A. That's generally most of what I do.
Q. Okay.
A. The occasional just literature search to make sure I'm not missing anything big.
Q. Okay. All right.
Paragraph No. 14, when you say "sex" in that paragraph, what are you referring to? Are you referring to biological sex?
MS. PICASSO: Object to form.
But go ahead and answer, Dr. Taylor.
A. I'm describing the sex as assigned at birth by the visual appearance of an infant's genitals, external genitals.
Q. Is the concept of sex assigned at birth different from the concept of biological sex?
MS. PICASSO: Object to form.
But go ahead and answer, Dr. Taylor.
A. I think the intention of both of those terms is the same. I think the difference in the language is just a bit more nuanced.
Q. Can you describe the nuance for me.
A. I think "biological sex" can mean any number

just in general.

A. I think -- I think both. I think it's problematic for the person who is faced with the decision to go to the bathroom and being faced with this sign. I think it's also a larger scale as being a member of a community whose state legislature feels that it's appropriate to put up that sign.

Q. Okay. Now, is it possible that someone who has gender dysphoria could see the sign that's proposed by the challenged law and not think -- not risk worsening their gender dysphoria or having any -- or not thinking that it's dangerous and distressing?

A. Sure. That's certainly possible.

Q. So is there any way to know in advance who would have that issue of thinking the sign is dangerous and distressing and -- you know, someone with gender dysphoria, is there any way to tell whether or not, in advance of them seeing the sign, that seeing that sign would worsen their gender dysphoria or be dangerous or distressing to them?

A. No, not that I'm aware of.

Q. Okay. Would it just be in -- you know, does it depend on what they think it represents? What someone with gender dysphoria, if they saw the sign, is the harm that you described, that it's dangerous and distressing and runs the risk of worsening gender dysphoria, is that based upon their perception of what the sign and use of the term "biological sex" represents?

A. Again, I think that that's part of it, for sure.

Q. Okay. And the other part being the sort of penumbral societal issue that you've talked about; is that right?

A. Yeah.

Q. Okay. Are there any other -- are there any other facets of harm besides that, you know, person by person, you know, it's dangerous, distressing, worsening gender dysphoria, and the societal aspect, are there any other facets of harm that you think would be caused by the sign referenced in the challenged law?

A. I'm sure --

MS. PICASSO: Object to form.

But go ahead and answer, Dr. Taylor.

A. I'm sure there are plenty. And if -- you know, given time, I could maybe think of others. But those are the overarching ones that I'm seeing right now.

Q. Okay. Have you had any -- without going into patient identity, without broaching any sort of

confidentiality, have you had a patient who has -- who has had worsening gender dysphoria for seeing the term or having the term said to them "biological sex"?
A. No, not specifically that --
Q. Okay.
A. Nobody has come to my office and said, "I read this term and that made my dysphoria worse."
Q. Okay. Are there common -- this is -- I'm not a doctor. I'm a lawyer. So forgive me if this is -- this is imprecise or a problem. Feel free to correct me.
Are there common triggers for worsening gender dysphoria that are common in your practice?
A. Yes.
Q. What are those?
A. There are many upon many upon many. But one of them could be discrimination that patients are facing in their communities or at their schools or in their families. You know, they can be -- I mean, there are countless reasons why people come to me or reasons to tell me that their dysphoria is worsening.
For fear -- like, in my young -- my young patients, fear that they will no longer be able to legally access hormonal treatment; that that could potentially be taken away from them. They lose

insurance. They can potentially lose access to their treatment.

There are many things that -- I mean, hundreds -- of why somebody would come to my office and be feeling more dysphoric than prior.

Q. But in your opinion, in your years of practice, the term "biological sex" isn't one of those common triggers for worsening gender dysphoria?

A. No. That has not been something that somebody has come to my office and complained about specifically.

Q. Okay. Okay.

MR. RIEGER: Well, that will do it for me. I believe that your counsel wants to take a break and then ask you a couple more questions. I can't promise that I'm done. Because, you know, I may, depending on the cross, have one or two.

But I'm ready to take that break, Malita, if you are to go from there.

MS. PICASSO: Yeah. Is there any way I could just have like a ten-minute break? I just have to run to the restroom. Is that all right?

MR. RIEGER: Of course.

MS. PICASSO: All right. Cool.

MR. RIEGER: Thank you, Dr. Taylor, for

AMENDMENT SHEET

I, the undersigned, SHAYNE TAYLOR, M.D., do hereby certify that I have read the foregoing deposition in the case of BONGO PRODUCTIONS vs. CARTER LAWRENCE and that, to the best of my knowledge, said deposition is true and accurate with the exception of the following corrections listed below:

PAGE/LINE/REASON

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______________ ______________________
Date Signature of Witness

Sworn to and Subscribed before me, __________________, this _______ day of _______________, 2022.

______________________ ______________________
Notary Public My Commission Expires

REPORTER'S CERTIFICATE

STATE OF TENNESSEE)

COUNTY OF SHELBY)

I, LYNETTE L. MUELLER, LCR #351, RDR, CRR, FAPR, and Notary Public for the State of Tennessee, do hereby certify that the above transcript of proceedings was reported by me and that the foregoing transcript, consisting of Pages 1-115, at the time and place set forth in the caption thereof, were stenographically reported by me; constitute a true and correct transcript of said proceedings to the best of my knowledge, skills, and ability.

I FURTHER CERTIFY that I am not related to any of the parties named herein, nor their counsel, and have no interest, financial or otherwise, in the outcome or events of this action.

I FURTHER CERTIFY that I am duly licensed by the Tennessee Board of Court Reporting as a Licensed Court Reporter as evidenced by the LCR number and expiration date following my name below.

I FURTHER CERTIFY that the right to read and sign was requested.

IN WITNESS WHEREOF, I have hereunto affixed my official signature and seal of office on 6th of January, 2022.

LYNETTE L. MUELLER, LCR, RDR, CRR, FAPR
LCR NO. 351, Expires June 30, 2022
Tennessee LCR No. 351
Mississippi CSR No. 1794
Arkansas CCR No. 788
Notary Public at Large
For the State of Tennessee
Commission Expires August 17, 2025

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

FIFTH EDITION

DSM-5®

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1844

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These three concepts (for which discussion and examples are provided in Section III and the Appendix) suggest cultural ways of understanding and describing illness experiences that can be elicited in the clinical encounter. They influence symptomatology, help seeking, clinical presentations, expectations of treatment, illness adaptation, and treatment response. The same cultural term often serves more than one of these functions.

Gender Differences

Sex and gender differences as they relate to the causes and expression of medical conditions are established for a number of diseases, including selected mental disorders. Revisions to DSM-5 included review of potential differences between men and women in the expression of mental illness. In terms of nomenclature, *sex differences* are variations attributable to an individual's reproductive organs and XX or XY chromosomal complement. *Gender differences* are variations that result from biological sex as well as an individual's self-representation that includes the psychological, behavioral, and social consequences of one's perceived gender. The term *gender differences* is used in DSM-5 because, more commonly, the differences between men and women are a result of both biological sex and individual self-representation. However, some of the differences are based on only biological sex.

Gender can influence illness in a variety of ways. First, it may exclusively determine whether an individual is at risk for a disorder (e.g., as in premenstrual dysphoric disorder). Second, gender may moderate the overall risk for development of a disorder as shown by marked gender differences in the prevalence and incidence rates for selected mental disorders. Third, gender may influence the likelihood that particular symptoms of a disorder are experienced by an individual. Attention-deficit/hyperactivity disorder is an example of a disorder with differences in presentation that are most commonly experienced by boys or girls. Gender likely has other effects on the experience of a disorder that are indirectly relevant to psychiatric diagnosis. It may be that certain symptoms are more readily endorsed by men or women, and that this contributes to differences in service provision (e.g., women may be more likely to recognize a depressive, bipolar, or anxiety disorder and endorse a more comprehensive list of symptoms than men).

Reproductive life cycle events, including estrogen variations, also contribute to gender differences in risk and expression of illness. Thus, a specifier for postpartum onset of mania or major depressive episode denotes a time frame wherein women may be at increased risk for the onset of an illness episode. In the case of sleep and energy, alterations are often normative postpartum and thus may have lower diagnostic reliability in postpartum women.

The manual is configured to include information on gender at multiple levels. If there are gender-specific symptoms, they have been added to the diagnostic criteria. A gender-related specifier, such as perinatal onset of a mood episode, provides additional information on gender and diagnosis. Finally, other issues that are pertinent to diagnosis and gender considerations can be found in the section "Gender-Related Diagnostic Issues."

Use of Other Specified and Unspecified Disorders

To enhance diagnostic specificity, DSM-5 replaces the previous NOS designation with two options for clinical use: *other specified disorder* and *unspecified disorder.* The other specified disorder category is provided to allow the clinician to communicate the specific reason that the presentation does not meet the criteria for any specific category within a diagnostic class. This is done by recording the name of the category, followed by the specific reason. For example, for an individual with clinically significant depressive symptoms lasting 4 weeks but whose symptomatology falls short of the diagnostic threshold for a major depressive episode, the clinician would record "other specified depressive disorder, depressive episode with insufficient symptoms." If the clinician chooses not to specify the

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REVIEW

Gender dysphoria in adolescence: current perspectives

This article was published in the following Dove Press journal:
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Abstract: Increasing numbers of adolescents are seeking treatment at gender identity services in Western countries. An increasingly accepted treatment model that includes puberty suppression with gonadotropin-releasing hormone analogs starting during the early stages of puberty, cross-sex hormonal treatment starting at ~16 years of age and possibly surgical treatments in legal adulthood, is often indicated for adolescents with childhood gender dysphoria (GD) that intensifies during puberty. However, virtually nothing is known regarding adolescent-onset GD, its progression and factors that influence the completion of the developmental tasks of adolescence among young people with GD and/or transgender identity. Consolidation of identity development is a central developmental goal of adolescence, but we still do not know enough about how gender identity and gender variance actually evolve. Treatment-seeking adolescents with GD present with considerable psychiatric comorbidity. There is little research on how GD and/or transgender identity are associated with completion of developmental tasks of adolescence.
Keywords: gender dysphoria, gender identity, adolescence, developmental tasks

Gender dysphoria and related concepts

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1] defines gender dysphoria (GD) as a condition in which a person has marked incongruence between the expressed or experienced gender and the biological sex at birth. This causes clinically significant distress or impairment in social, occupational or other important areas of functioning. Individuals with GD experience a strong desire to be treated as the other gender (or some alternative gender different from their assigned gender) and/or to be rid of their sex characteristics, and/or the strong conviction of having feelings and reactions typical of the other gender (or some alternative gender). The previous diagnostic term, gender identity disorder, was rejected in the DSM-5 to avoid pathologizing identity.

According to the International Classification of Diseases (ICD)-10,[2] transsexualism is defined as a desire to live and be accepted as a member of the opposite sex, usually accompanied by a sense of discomfort with or the inappropriateness of one's anatomical sex and a wish to undergo surgery and hormonal treatment to make the body as congruent as possible with the individual's preferred sex. The forthcoming ICD-11 will reconceptualize gender identity-related diagnoses using gender incongruence as the main term.[3]

In addition to the DSM-5 diagnostic term, gender dysphoria can also refer to anxiety and distress about gender features at large. Gender nonconformity refers to

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behaviors and an appearance that are considered atypical of an individual's assigned gender. Gender variance refers to a spectrum of gender experience, in contrast to the dichotomized conception of gender. The term "transgender" is used as an umbrella term to refer to wider variation of gender identities. Not all who identify as transgender or display gender nonconformity or gender variance suffer from dysphoria.

In this article, we use the DSM-5 and ICD-10 terms "gender dysphoria (GD)" and "transsexualism/transsexual", respectively, when referring to diagnosed clinical samples, and also when referring to the literature published when earlier versions of the DSM classification were in use. We use "transgender" to refer to self-identified population samples and "gender dysphoria" to refer to those who present clinical symptoms.

How common are GD and transgender identity among adults and adolescents?

The number of people who seek treatment suggest that male-to-female transsexualism has a prevalence of 6.8/100,000 and female-to-male transsexualism has a prevalence of 2.6/100,000 among adults.[4,5] In the Netherlands, 0.6% of men and 0.2% of women (aged 15–70 years) reported incongruent gender identity and a desire to undergo sex reassignment (SR).[6] Population surveys have suggested that about 0.5% of adults in the general population identify as transgender.[5,7]

The number of adolescents contacting specialized gender identity services has risen considerably over the past decade across Europe and North America.[8,9] No conclusions regarding the prevalence of GD in general or of GD/transsexualism specifically can be drawn based on these increases. Studies using short (one to three item) self-reports of gender identity and its variance suggest that 0.17%–1.3% of adolescents and young adults identify as transgender.[5,10] A school-based survey eliciting gender experiences with scales commonly used at gender identity services suggested that 1.3% of 16–19 year olds had potentially clinically significant gender dysphoria.[11]

Gender identity

Identity is the way one understands, describes and expresses oneself and the reflection of those entities to others. Identity consists of many integrated aspects such as gender, nationality, language, academic and occupational endeavors, and religious and political convictions. It is affected by interpersonal relationships, society and different events throughout the life course.[12] Adolescence is an important period of identity formation and integration.[12,13] Adolescents and young adults establish their identity by actively exploring identity-related choices and making identity commitments in their chosen directions.[12,13]

Gender identity concerns the individual's core sense of being "female", "male" or another gender. The development of gender identity is a complex process affected by multiple factors.[14,15] In the research tradition of gender identity, the broad focus has been on the theme "sex differences", and two major topics have received the most attention: the description and measurement of sex differences and the etiology of these differences.[16] Several theories have been proposed. According to early psychodynamic theories, gender variant behavior was hypothesized to derive from parent–infant interpersonal issues or trauma (see Gray et al[15]). However, these theories have not undergone adequate scientific testing. Gender identity development has mostly been described from the viewpoint of cognitive and social learning theories, which argue that human beings are active constructors of cognitive schemas, including gender, in continuous interaction with the environment.[14] Other theories on processes of gender typing have focused on proximal and distal biological influences, genetic and epigenetic or hormonal and neural mechanisms as well as brain anatomy differences in the etiology of gendered behavior and gender variance.[17–19] There are structural and functional sex differences in the brain, some of them observable across the life span and others only during specific developmental phases. Sex differences in the brain are largely determined by steroid hormone exposure during a perinatal sensitive period that alters subsequent hormonal and non-hormonal responses throughout the lifespan, but they also depend on genes on sex chromosomes. Moreover, there is continuous interaction between genes and experiences, "epigenetics", which changes the expression of genes without any change in the underlying DNA sequence. Research suggests that, for example, early social experiences may act as such epigenetic influence that they ultimately shape lasting sex differences in brain and behavior,[20–22] but a lot more research is needed in this field to obtain solid knowledge relevant for understanding GD.

While the theories proposed in the past have generally been either essentialist or social cognitive/constructivist in nature, researchers today are expanding the focus to include the bio-psycho-social processes that probably occur across development.[14,15,23]

Childhood GD and puberty development

GD in childhood (GDC)[1] describes a feeling of incongruence between the experienced (psychological) gender and the sex assigned at birth. A corresponding diagnosis is included in the ICD-10.[2] Healthy children vary considerably in their gendered behaviors.[15] The diagnosis of GD in prepubescent children has been widely discussed throughout the history of gender identity research, mainly in terms of weighing the risk of stigmatization against diagnosis as a means of access to publicly funded or insurance-covered health care.[3,24] The prevalence of GDC is not known.[5]

Adolescence is a crucial time for identity and psychosexual development in young people with gender identity concerns.[25] The outcomes of GDC have been discussed in terms of its persistence and desistence. For most children with GDC, whether GD will persist or desist will probably be determined between the ages of 10 and 13 years,[26] although some may need more time.[27] Evidence from the 10 available prospective follow-up studies from childhood to adolescence (reviewed in the study by Ristori and Steensma[28]) indicates that for ~80% of children who meet the criteria for GDC, the GD recedes with puberty. Instead, many of these adolescents will identify as non-heterosexual.[17,29] Steensma et al[26] interviewed adolescents with different outcomes of GDC (persistence or desistance). The adolescents mentioned social environment, the anticipated results of bodily changes and first romantic and/or sexual experiences as central factors in the desistance or persistence of GD.

Treatment of GD intensifying in puberty: the Dutch model

The most commonly used guidelines for the treatment of GD in children and adolescents are those of The Endocrine Society[30] and the Standard of Care from the World Professional Association for Transgender Health,[31] which are based on the so-called Dutch Model protocols published and practiced at the Amsterdam Gender Clinic in the Netherlands.[32]

The Dutch protocol recommends medical treatment if GD intensifies in puberty, while the care for children with GD and their families consists of providing information, psychological support, parental or/and family counseling. In adolescents, medical treatment is recommended at age 12 years and older for those who are in or beyond the early stages (Tanner II–III) of puberty and are still experiencing persistent GD. Puberty suppression with gonadotropin-releasing hormone analogs is part of the protocol for these patients. The purpose of puberty suppression is to relieve the psychological suffering caused by the development of secondary sex characteristics, to give the adolescent time to make a balanced decision regarding whether to undergo actual medical gender-confirming treatment (with cross-sex hormones and surgery) and to make social "passing" in the experienced gender easier. Cross-sex hormones are used for adolescents aged 16 years and older who continue to experience persistent GD. People aged 18 years and older with a diagnosis of GD may undergo SR surgery.[32]

Outcome of and ethical debates around medical interventions for GD in adolescence

The Dutch protocol is largely used, but it has its critics.[33–35] Controversy regarding the use of drugs for puberty touches on fundamental ethical concepts in pediatrics: the best interests of the minor, autonomy and the role of social context. Professionals recognize the distress of young people with GD and feel an urge to treat them. At the same time, most of these professionals have doubts because of the lack of data regarding long-term physical and psychological outcomes.[36,37]

Reports of the outcomes of puberty suppression treatment in adolescents have shown reasonable safety and good outcomes regarding patient satisfaction and psychosocial functioning, but research is still scarce. Nevertheless, puberty suppression is not indicated in a considerable proportion of gender dysphoric minors because of several reasons, for example, severe psychiatric comorbidity, considerable instability of psychosocial support or onset of GD later during puberty and diagnostic uncertainty;[38–40] nevertheless, more follow-up data even from patients who are fulfilling the criteria for "the Dutch model" are still needed.[37]

Psychiatric disorders among adolescents with GD

Descriptive studies of adolescents referred to specialized gender identity services at different centers in Europe and North America have mainly suggested that ~40%–45% of these young people present with clinically significant psychopathology.[38,39,41–50] The lowest figures for psychiatric comorbidity (one-third of the presenting population) were reported in the Netherlands,[41] and the highest (up to three quarters) was reported in Finland and Canada.[39,50] Gender-referred adolescents actually appear to display clinically significant psychopathology to the same extent as adolescents referred to mental health services due to other reasons.[48,50] The most commonly reported disorders are depression and anxiety disorders. Self-harm and suicidal ideation/behavior are also common, whereas conduct disorder and antisocial development do not appear central in this population.

Likewise, community-level information suggests that transgender-identifying youth present four to six times more often with depression and three to four times more often with self-harm and/or suicidal behavior compared with cisgender adolescents.[10,51] Clinical and population data, though scarce, also suggest an overrepresentation of eating pathology among adolescents with GD or transgender identity.[46,52]

An increased prevalence of autism spectrum disorders (ASDs), varying from ~6% to over 20%, has been reported among samples of adolescents referred to gender identity services.[39,42,46,53] This vastly exceeds the estimated prevalence of 0.6%–0.7%[54] in the general population. In comparison, among children and early adolescents with ASDs, gender variance is >7-fold more common than among non-referred controls.[53,55]

Hypotheses to explain this are manifold. The theory of the extreme male brain suggests that individuals with ASD demonstrate an extreme of the typical male pattern of behaviors and cognitions originating from high levels of fetal testosterone. High fetal levels could likewise contribute to GD in natal girls, explaining their male identity and behavior. However, this theory cannot explain the association between ASD and GD in natal boys. Social factors-related hypotheses propose that the social perception and communication difficulties typical of autism could make a child more likely to miss social cues regarding how to conform to gender norms or to identify with the opposite sex when he/she faces difficulties joining the peer group of her/his own sex. Hypotheses focusing on individual psychological characteristics suggest, firstly, that gender could be among the preoccupations or obsessions often seen in ASDs. On the other hand, the development of atypical gender identity in autism could relate to the developmental rigidity typical of autism. Individuals with ASD might not reach normative flexibility in gender development necessary to deal with gender variant feelings, which might lead to the overrepresentation of ASD in GD.[53,56] The suggested causes, however, remain speculative. In a recent study, both boys and girls with GD displayed elevated levels of autistic symptomatology in all subdomains of autism, which did not exclusively support any of the suggested hypotheses.[56] Nevertheless, ASDs pose particular challenges for the diagnosis and treatment of GD in adolescents.

GD and the developmental tasks of adolescence

"Developmental tasks" refer to the normative developmental milestones that should be reached during a given developmental stage.[57,58] They arise from interactions among physical development, personal attributes and societal expectations. Favorable completion of the developmental tasks of a given stage is a prerequisite for success in the subsequent stages. The developmental tasks of adolescence were first formulated by Havighurst[57] and comprise accepting one's body, adopting a masculine or feminine social role, achieving emotional independence from parents, developing close relationships with peers of the same and opposite genders, preparing for an occupation, preparing for marriage and family life, establishing a personal value or an ethical system and achieving socially responsible behavior. Although puberty now occurs earlier and the transition to adulthood occurs later than they did when these developmental tasks were initially proposed, they remain relevant.[58] The relationship with one's own body and the acquisition of a gendered social role – not necessarily binary – are by definition challenging for adolescents with GD. In the following sections, we discuss the available information on GD/transgender identity and the other developmental tasks of adolescence.

GD in adolescence and relationships with parents

Parents of adolescents with GD and/or transgender identity may face special challenges that are shaped by a variety of factors, such as ethnicity, religious background, social class and the prevailing attitudes in their community and society.[59,60] These challenges likely shape the support that a nonconforming adolescent can receive. Adverse parental reactions toward an adolescent's gender nonconformity have been noted as a special risk,[61] but parents of sexual- and gender-minority offspring have also reported particular positive aspects of being a parent in this situation, such as personal growth, unconditional love, activism, social connection and closer relationships.[62] However, few studies have empirically explored the parental reactions and support among youth with GD and/or transgender identity.

In a Canadian community study of transgender-identifying youth,[63] of those who had disclosed their gender identity to their parents, 34% considered their parents "very" supportive and 25% considered their parents "somewhat" supportive. Forty-two percent reported that their parents were "not very" or "not at all" supportive. However, the study was based on a nonrandom sample and solely adolescent self-reports, so findings need to be interpreted with caution and causalities cannot be concluded. Strong perceived parental support was, nevertheless, associated with many positive mental health outcomes. Lack of parental support was associated with inadequate housing and homelessness in addition to negative psychological outcomes. Better parental support has also been associated with fewer risk-taking sexual behaviors among transgender youth.[64]

In a community study of trans female adolescents and young adults,[65] more than half of the participants reported that their parents supported their gender identity, showed their support in many ways and believed the respondent could have a happy future as a trans adult. However, approximately two in five respondents had not experienced parental acceptance. Parental acceptance was associated with perceiving parents as the primary source of social support.

In a school-based survey[51] transgender-identifying adolescents felt less often (odds Ratio 0.3) than their cis-gender peers that at least one parent cared for them.

Studies of clinically referred gender dysphoric youth have rarely addressed parent-related issues. Simons et al[66] reported that in a clinical sample of adolescents with GD, parental support was significantly associated with higher life satisfaction, lower perceived burden of being transgender and fewer depressive symptoms. In a Finnish study comparing childhood gender identity in community and clinical samples, a smaller proportion of adolescents with GD than of non-referred adolescents in the population agreed with the statement "I always felt that my parents cared fore me."[11] It was also noticed that the clinically referred adolescents with GD less commonly lived with both their parents than the adolescents in the normal population (48% vs. 78%).[67] In British and Spanish samples of gender-referred adolescents, parental divorce was observed in the background of approximately three in five participants, but the authors did not compare this finding with a corresponding rate in the general population.[46,49]

Gender nonconformance and peer relationships in adolescence

During adolescence, peer relationships are critical for psychological well-being.[68,69] Peer relationships also shape development, including aspects of gender identity consolidation.[70] Loneliness and social isolation from peer relationships is associated with developmental difficulties and impaired mental health.[71,72] An important peer network-related risk factor is bullying.[73]

Observations in referred samples of adolescents with GD suggest considerable peer relationship difficulties. In both the UK[46] and in Finland,[39] approximately half of adolescents who presented at a specialized gender identity service reported significant experiences of being bullied. In the Finland study, 45% of the referred adolescents also had a history of marked periods of social isolation in childhood and/or adolescence. In the Netherlands and in Canada, self-, parent and teacher ratings indicated poorer peer relationships among adolescents referred for GD than in the same-aged population[47,48] and poor peer relationships were an important correlate of mental health problems in this group. Similarly, in another Canadian comparison among gender-referred, mental health-referred and general population adolescents bullying was reported by the GD group more commonly than by population controls, and to the same extent as by those referred due to mental health issues. Gender-related bullying was most common among the GD group.[74]

On the population level, Clark et al[51] found that transgender-identifying adolescents had 4.5-fold increased odds of being bullied and were approximately twice as likely to report being afraid for their personal safety, having been in a serious physical fight and having been hit or otherwise harmed by others, compared with their cisgender-identifying peers. They also less commonly felt that their friends cared about them and that school was okay.

Gender-nonconforming behavior is characteristic of both sexual- and gender-minority youth and has been associated with an increased likelihood of experiencing bullying and harassment in peer groups.[75,76] Adolescents with GD likely represent the extreme end of gender nonconformity, and this may strongly contribute to their experiences of being bullied. Bullying and stigmatization have also been suggested to (partially) mediate the association between gender nonconformity and lower mental well-being across adolescence.[74,77–79]

However, not all the difficulties the gender dysphoric adolescents face in peer relationships can be explained by gender expression-related victimization or discrimination. In the Finnish clinical sample, of the gender identity-referred adolescents who had experienced severe bullying at school, three quarters had been bullied before they ever questioned their gender. Likewise, three-quarters of them reported that the bullying had not been related to gender expression or sexual identity, but to other factors such as not being slim, being successful at school or having unfashionable hobbies and interests.[39] Bullying is a severe problem regardless of the reported reasons for it, but it is important to acknowledge that adolescents who develop GD also have unrelated difficulties that may need attention.

GD, transgender identity and sexuality in adolescence

Sexual orientation and gender identity are different entities, and transgender people present with a variety of sexual orientations. Nevertheless, sexual orientation has long been used to subtype GD/transsexualism.[80] During adolescence, the different facets of sexual orientation – attraction, behavior and identity – may still be developing. It may be more important to determine whether adolescents with GD or transgender identity display developmentally appropriate and favorable involvement in romantic and erotic relationships.

In adolescence, sexual development accelerates. Young people's experiences of a maturing and changing body, sexuality and their developing gender identity affect intrapersonal, interpersonal and societal interactions.[81] In Western countries, between one-tenth and one-third of adolescents first experience sexual intercourse by the age of 15, and the vast majority experience it by age 20.[82,83] Various practices of kissing and petting typically precede first sexual intercourse by several years. Early sexual activity has been viewed as a problem behavior associated with risky sexual behaviors, psychosocial difficulties and emotional and behavioral disorders.[82,83] In contrast, in the late stages of adolescent development, a lack of experiences might suggest developmental difficulties.

GD and/or transgender identification could be expected to be associated with delayed sexual development, given that it is the sexual body, in particular, that is the source of distress in GD and that differing from the mainstream may increase the adolescent's risk of problems in social relationships, including dating, and sexual encounters. Sexual- and gender-minority adolescents may also have a reduced availability of potential partners and increased challenges in finding potential partners than their heterosexual peers.[84] However, developmental challenges have also been associated with premature and risky sexual behavior.[82,85] Adolescents with GD and/or transgender identification could engage in risky sexual behaviors due to identity experiments or because associated mental health problems could increase their search for comfort in intimacy or decrease their self-protection skills.

To the best of our knowledge, the only study focusing on the sexual experiences of treatment-seeking adolescents with GD is that of Bungener et al[86] from the Netherlands. They compared the sexual experiences of 137 transsexual adolescents (mean [SD] age 14.69 [2.2] years) with those of a same-aged adolescent population. Transsexual adolescents had fewer sexual experiences than the same-aged population in all areas measured (falling in love, romantic relationships, kissing, petting, intercourse). However, a majority of the transsexual adolescents had fallen in love and approximately half had been involved in romantic relationships. One quarter had experienced petting while undressed, and 5% had experienced sexual intercourse. Fewer transsexual adolescents than the adolescents in the same-aged population (24% vs. 48%) valued sex as important. In a descriptive study of clinically presenting adolescents with GD in the USA,[45] nearly half of the respondents (mean [SD] age 19.2 [2.9] years) reported being sexually active.

Some population studies provide information regarding transgender identity in adolescence and aspects of sexual development. Korchmaros et al[84] compared the romantic relationships of lesbian, gay, bisexual, transgender and questioning (LGBTQ) adolescents and those of adolescents with mainstream sexual and gender identities. Contrary to expectations, the LGBTQ adolescents were more experienced with romantic relationships and more active in initiating relationships both online and offline. Results were not reported separately for the transgender group. Robinson and Espelage[87] reported that LGBTQ adolescents were more likely to display risky sexual behaviors than same-aged non-LGBTQ youth. However, in more detailed analyses, the risk was associated with homosexual/bisexual orientation and not with transgender identity. Veale et al[88] set out to study pregnancy involvement among transgender youth and the health correlates of this involvement. In a large (n=923) sample of transgender-identifying youth, 540 responded to the pregnancy involvement item. Almost 5% of Canadian transgender adolescents had ever been pregnant or impregnated a partner; approximately the same proportion as their same-aged peers. Those with a history of pregnancy involvement were also more likely to have a history of sexually transmitted disease, but they did not differ from the rest of the transgender youth in terms of hormone use, living in the felt gender, self-reported mental health and level of social support.

Sexual harassment is a common problem among adolescent populations.[89] Transgender-identifying adolescents appear to be at the greatest risk of sexual harassment and to experience the greatest distress due to it.[89] Sexual harassment is suggested to function to maintain heteronormativity, which transgender adolescents likely challenge. Their perception of sexual harassment as more distressing compared with other adolescents could be due to harsher harassment, increased vulnerability due to uncertainty about self, or fear.[89]

Similarly, in a large school-based survey study on teen dating violence,[90] the few transgender-identifying youth in the sample reported the highest victimization rates for physical dating violence, psychological dating abuse, cyber dating abuse and sexual coercion. Differences from cisgender adolescents varied from 2- to 7-fold for the different forms of violence. However, the transgender-identifying youth also reported the highest rates of perpetrating dating violence. Minority stress theory[91] posits that the chronic stressors that minorities experience (e.g., gender-based discrimination) shape their coping mechanisms (such as substance use, aggression) and lead to adverse psychosocial and health outcomes. The particular vulnerability to perpetrating dating violence observed among transgender adolescents by Dank et al[90] could be understood through minority stress theory, but more research is needed.

Transgender adolescents and young adults, particularly trans females, are at a disproportionately high risk of contracting human immunodeficiency virus and other sexually transmitted diseases.[79,92] The risk of unprotected sex in this population has been associated with sex work and drug use, which are further associated with rejection, stigma and discrimination.[79,92] Of the studies of referred samples, only one addressed sex work.[45] In that sample, 6% of the referred adolescents reported engaging in the trading of sex.

Sexual education is an important way to promote positive and responsible sexual behaviors in youth. The planned curricula and practical applications likely vary widely across countries and schools. Sexual- and gender-minority youth were found to desire minority-inclusive sexual education in a study by Gowen and Wingez-Yanez.[93] The sexual- and gender-minority youth felt that the sexual education that was offered isolated them by silencing them, adopting a heterocentric perspective and pathologizing minorities. Reflecting on the available sexual education in light of these findings is appropriate for all educators.

Preparing for occupation: academic performance and socioeconomic status

To the best of our knowledge, research has not specifically focused on academic performance and the progression to work life among adolescents with GD, but given the burden of psychiatric comorbidities among gender-referred youth, special needs regarding education are likely to exist.

Aspects of social relationships are relevant to well-being in school, school performance and pathways to occupation. Transgender youth have been reported to experience bullying and discrimination in schools, not only by peers but even by teachers; consequently, they perceive schools as unsafe places, which again increases the risk of non-attendance and poorer results.[75,94] Gender- and sexuality-related victimization may impair academic performance through, for example, decreased motivation, concentration and self-efficacy and the resulting school avoidance and harmful coping strategies.[94,95] Nevertheless, being "out" at school improves self-esteem among gender- and sexual-minority youth and increases their well-being, which can have a positive impact on academic performance.[94]

School dropout is strongly linked to social exclusion. School dropout was associated with high masculinity in girls and low masculinity combined with high femininity in boys in a study of late-adolescent school dropouts and attenders in the Netherlands.[96] The authors suggested that such deviation from gender norms increases the risk of unpopularity among peers, which again predisposes individuals toward school dropout. However, school dropout was also associated with very masculine attitudes and self-evaluations among boys. The role of gendered behaviors, attitudes and experiences in school adjustment and academic performance deserves further research.

In Clark et al's[51] school-based survey, adolescents reporting non-cisgender identity came disproportionately often from families with high socioeconomic deprivation and less often felt that their family got along. Any explanation for this remains unknown; however, young people are likely to stay in the same socioeconomic position as their parents.[97] Jacob and Cox[98] also pinpointed transgender people's greater risk of having a disadvantaged socioeconomic status (in the USA), associating this with increased unemployment, and employment in low-paid jobs, because of stigmatization.

Why the increase in referrals?

Zucker et al[99] observed an increase in the number of adolescents presenting at gender identity services in the early 2000s. Since then, several gender identity services for minors from across Western countries have reported increases.[8,9,42,49] Simultaneously, the earlier overrepresentation of natal boys has equaled or turned to overrepresentation of natal girls.[9] Natal girls now comprise from half[49] to ~90%[39] of clinical adolescent samples. The reasons for these changes are not known. The increase in referrals could be attributable to enhanced provision of services, or the threshold for seeking help may now be lower due to increased knowledge and improved societal acceptance. Aitken et al,[9] however, did not find evidence supporting a lowered threshold to gender identity services. Sociocultural features related to what kind of identities are available for whom, and sex-related differences of pressure to conform may play a role.

Comments

Research regarding the clinical treatment of adolescents with GD has mainly focused on childhood-onset GD that intensifies during puberty, and the Dutch treatment protocol is also tailored for this group. There is little empirical knowledge regarding young people who experience their first signs of GD in adolescence, well after the onset of puberty, especially regarding biological girls.[50,100] Among a treatment-seeking sample in the UK, 18% experienced their first feelings of GD in adolescence[46] compared with approximately two-thirds of the Finnish sample,[39] and for the majority of adolescent-onset cases, GD presented in the context of severe mental disorders and general identity confusion. In such situations, appropriate treatment for psychiatric comorbidities may be warranted before conclusions regarding gender identity can be drawn. Gender-referred adolescents actually display psychopathology to the same extent as mental health–referred youth.[48,50] In a nationwide long-term follow-up study of adult cases, psychiatric morbidity, suicide attempts and suicide mortality persisted as elevated after juridical and medical SR.[101]

Emerging discussions raise concern for post-pubertally abruptly emerging cross-gender identification ("rapid onset"), particularly among biological girls, suggesting a role for intensive media influences and generous group validation as shaping the understanding of, and giving new meanings to, the body discomfort common among female adolescents at large.[100] The persistence of increasing adolescent-onset transgender identification is not known.[5,100]

More empirical research is needed regarding virtually all aspects of GD in adolescence to create treatment approaches that optimize these young people's future psychosocial health and well-being. It seems unlikely that all the psychopathology observed in the referred samples is secondary to gender identity issues and would resolve with hormonal and later surgical treatments. There is still no clear consensus regarding hormonal treatment for adolescents because long-term data are unavailable;[36] actually, only one long-term follow up has been carried out, with a highly selected intervention group and an at baseline non-comparable comparison group.[102]

An affirmative approach[103] is increasingly implemented in the health care of gender nonconforming children. This includes, based on a comprehensive psychological and psychosocial assessment, work with the children and their families and schools to support the gender-nonconforming minors to express themselves in a way that feels most comfortable for them. With the starting point that gender presentations are fluid and changing over time, gender variant children need to be allowed to freely explore a range of gender identities and expressions. A debate concerns whether or not a prepubertal child should be allowed to completely transition to live in other than birth gender. Concerns include that childhood transition may be forcing adolescents to proceed to biomedical interventions, as stepping back may be psychologically troublesome, even though identity development has taken a new direction.[28,104]

The etiology of gender incongruence remains unknown. Gender identity differentiation does not occur in a psychosocial vacuum; instead, research in the field suggests that the developmental course is influenced by numerous psychosocial factors, likely in continuous interaction with biological factors.[23,105] Gray et al[15] noted that the general narrative in the research literature concerning gender variation among children focuses on gender "atypical" behavior and deviation from "normative patterns", thus viewing gender in a binary way instead of as a wider spectrum of (healthy) identities, personalities and behaviors among children. This is surely relevant for adolescents as well. These authors also requested a shift in research paradigms away from the study of outcomes of sexuality and gender identity and the child/adolescent in isolation toward outcomes of adjustment and the child/adolescent in contexts that affect adjustment. Along with further discussions of the best treatment interventions, it is relevant to attempt to contribute to societal attitudes that enable children and adolescents with gender variance to express themselves and successfully complete the developmental tasks common to all, independent of gender.

Disclosure

The authors report no conflicts of interest in this work.

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Sex- and Gender-specific Observations and Implications for COVID-19

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Disclaimer: Due to the rapidly evolving nature of this outbreak, and in the interests of rapid dissemination of reliable, actionable information, this paper went through expedited peer review. Additionally, information should be considered current only at the time of publication and may evolve as the science develops. On February 11, 2020, the World Health Organization renamed the virus COVID-19.

This is a critical time for medicine. As we observe the exponential rise in the number of individuals in the United States (US) who are infected with COVID-19, we try to prepare. Those in the front lines are trying to protect themselves and their patients with the daily ration of personal protective equipment and ventilation assistive equipment. Many individuals are racing against time to develop the needed novel treatments and vaccines. Public health officials work with what little information is known in order to make effective recommendations for prevention. However, at this pivotal time in history where every detail obtained by US health officials could be lifesaving, we are leaving out vital information.

Descriptive and observational data from Wuhan, China, note that the majority (51%-66.7%) of affected patients have been male. In addition, male sex was an independent risk factor associated with refractory disease and death (2.8% death rate for men vs 1.7% for female).[1,2] Currently, men represent 58% of COVID-19 infected patients in Italy and 70% of COVID-related deaths.[3] As coronavirus cases and deaths in the US continue to soar, sex-specific, comprehensive data with regard to US patients is not yet available.

Sex- and gender-based medicine (SGBM) incorporates how biological *sex* and the sociocultural aspects of *gender* affect health and illness. It acknowledges the interrelationship between sex and gender on health outcomes and promotes consideration of this variable in both research and clinical practice. SGBM has demonstrated significant evidence-based impact on cardiovascular disease, stroke, sports medicine, and pain management, just to name a few

Sex and gender differences have been observed in infectious diseases previously. On a broad and critical scale, Nasir et al demonstrated that males with all-cause infectious sepsis have a 70% greater mortality than their female counterparts. Likewise, respiratory infection-specific epidemiological data from recent SARS (2003) and MERS (2012) outbreaks demonstrated a significantly higher case fatality rate in males as compared to females, 21.9% vs 13.2%.[4,5]

Sex-specific Factors

Is the biological male more susceptible to an increased severity of infection? Or does the biological woman have natural protection against these viruses? In a 2017 *BMJ* article, Dr. Kyle Sue demonstrated the effect of sex hormones, estrogen and testosterone, on immune system response and engagement, resulting in a less robust immunologic response in males and subsequent increased morbidity and mortality from viral respiratory illnesses.[6] In addition, the X chromosome carries the largest number of immune-related genes in the human genome, perhaps also contributing to female's superior immune response (as well as a female preponderance in autoimmune diseases).[7]

Angiotensin-converting enzyme 2 (ACE2) and its role in viral transmission and associated morbidity has also been a topic of recent COVID-19 associated discussion. ACE2 receptors on pulmonary endothelium serve as a main entry point for coronavirus. Several previous animal models have demonstrated increased ACE2 activity in the male or ovariectomized model, suggesting a sex hormone influence.[8] The gene for the ACE2 receptor is also, interestingly, on the X chromosome.[9]

Gender-specific Factors

Behavioral and cultural variables have also influenced current COVID-19 epidemiology. Smoking in particular has been implicated as a significant contributor to disease severity, and gender-specific patterns are quite apparent here. The smoking rate in China is much higher in men than in women (288 million men vs 12.6 million women; 2018 data).[10] Likewise, in Italy, men are more likely to smoke than women at any age (1.12x to 1.7x, depending on age cohort; 2018 data).[11] Similar gender-specific trends are also present in the US, where 17.6% of smokers are men as compared to 13.6% of women.[12]

In addition, as the traditional caregivers and coordinators of care for their loved ones, women, particularly working mothers, tend to spend more time than men focused on medical issues related to both their own healthcare and that of their families.[13] In general, men are more likely to engage in health-related risks which, even prior to the COVID-19 pandemic, has been shown to result in higher rates of injury and disease.[14] Suen et al demonstrated in 2019 that being a middle-aged female was a protective factor with regard to hand hygiene knowledge and practice.[15]

Population Health Research Capsule

What do we already know about this issue?
COVID-19 represents an unparalleled public health crisis. Like many other infectious diseases, sex and gender differences in health outcomes have already been globally observed.

What was the research question?
We sought to summarize and explain known COVID-19-related sex and gender differences.

What was the major finding of the study?
Sex and gender differences are having significant impacts on current COVID-19 health outcomes.

How does this improve population health?
This perspective brings attention to the importance of sex and gender, specifically as they impact current clinical management and research during the COVID-19 pandemic.

Implications for COVID-19 Management

As clinical researchers and pharmaceutical companies race to find an effective treatment strategy or vaccine for COVID-19, no sex- or gender-specific recommendations have been released with regard to the care and management of individuals affected by the novel coronavirus. Appreciating the weight of known sex- and gender-specific epidemiologic observations thus far, however, will be an important highlight of the information gathered to date. This, combined with what is already known about sex- and gender-based pulmonary and infectious disease pathology, may lead to important treatment breakthroughs that consider the sex and/or gender of patient in the comprehensive management plan.

In addition, the current pandemic weighs heavily on emotional wellness along with physical health. COVID-19 has also released a contagion of fear, anxiety, and stigma that will have implications for downstream mental health effects including post-traumatic stress disorder (PTSD). In general, the prevalence of PTSD has been shown to be substantially higher in women.[16] This has been re-substantiated in the setting of the COVID-19 outbreak in Wuhan, China, where women scored significantly higher on the PCL-5 (DSM-5 self-report measure for PTSD) than men, including higher rates of re-experiencing and negative alterations in cognition or mood.[17] Early recognition and effective treatment can ameliorate the burden of PTSD on both the individual and society, particularly for women who have been shown to have a modest advantage with regard to treatment response.[18]

Future Considerations

Since 2016, the NIH has required inclusion of sex as a biological variable (SABV) in the study design for funded research.[19] Recognizing the weight these variables play in disease outcome should result in universal adoption of SABV as scientists develop and engage in COVID-19 research. While men appear to be disproportionately affected and at risk for COVID-19 infection and associated morbidity, researchers should avoid the slippery slope of the traditional male-dominant test and analysis approach.

When considering pharmaceutical therapy advances, several previous studies have established that women are much more likely to experience adverse drug reactions (ADR) than men.[20] In fact, historically the majority of drugs recalled from the market were done so due to serious ADRs reported by women, quite often because they were never tested on women during clinical trials. Several sex-specific pharmacokinetic and pharmacodynamic differences have been well documented.[21]

Yes, time is of the essence right now; however, COVID-19 does not get a "pass" in considering sex and gender when gathering data or testing treatments. Sex and gender have already proven to be crucial variables in the short history of COVID-19; they will continue to be factors of marked importance. Making healthcare providers and researchers aware of their impact in real time will be crucial to the integration of susceptibility profiles and improving outcomes during an active public health crisis.

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Considering how biological sex impacts immune responses and COVID-19 outcomes

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Abstract | A male bias in mortality has emerged in the COVID-19 pandemic, which is consistent with the pathogenesis of other viral infections. Biological sex differences may manifest themselves in susceptibility to infection, early pathogenesis, innate viral control, adaptive immune responses or the balance of inflammation and tissue repair in the resolution of infection. We discuss available sex-disaggregated epidemiological data from the COVID-19 pandemic, introduce sex-differential features of immunity and highlight potential sex differences underlying COVID-19 severity. We propose that sex differences in immunopathogenesis will inform mechanisms of COVID-19, identify points for therapeutic intervention and improve vaccine design and increase vaccine efficacy.

The COVID-19 pandemic, caused by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of infections and hundreds of thousands of deaths worldwide. Human biological sex plays a fundamental role in heterogeneous COVID-19 outcomes. Sex, defined as male, female or intersex on the basis of sex chromosome complement, reproductive tissues (ovaries or testes) and sex steroid hormone (oestrogen, progesterone and testosterone) concentrations, is a multidimensional biological characteristic that shapes infectious disease pathogenesis. We discuss how sex differences in basic molecular and cellular mechanisms can be leveraged to define the immune response to infection with SARS-CoV-2.

Sex differences in COVID-19 severity

The precise drivers of death, regardless of sex, in COVID-19 remain unknown. There appears to be a subset of patients in whom high levels of dysregulated inflammation lead to severe multisystem organ pathology[1,2]. A postviral inflammatory syndrome has also emerged in children with COVID-19 (REFS[3,4]). As a result, research on therapeutics has focused on both antiviral and immunomodulatory pathways[2,5] with the goal of achieving an optimized balance in immune response induction and resolution. Unfortunately, most studies fail to consider the sex of the patients, which may mask therapeutic targets.

Evidence of sex differences in COVID-19 severity emerged in China, where hospital admissions and mortality were higher among males than females[6–8]. In South Korea, where community testing was widespread, females represented ~60% of those testing positive for SARS-CoV-2, suggesting that females acquire infection, despite having a lower case fatality rate (CFR)[9,10]. In the United States, where testing was prioritized for people with symptomatic disease, the diagnosis rates were similar in males and females, but males had 1.5 times higher mortality[11].

A male bias in COVID-19 mortality is currently reported in 37 of the 38 countries that have provided sex-disaggregated data (FIG. 1a). Our analyses show that the average male CFR across 38 countries is 1.7 times higher than the average female CFR ($P < 0.0001$) (male CFR 7.3 (95% CI 5.4–9.2); female CFR 4.4 (95% CI 3.4–5.5)), which is consistent with other reports[12,13]. There is increased risk of death for both sexes with advancing age, but at all ages above 30 years males have a significantly higher risk of death than females ($P < 0.05$) (FIG. 1b). A male predominance of deaths from COVID-19 is consistent with what was observed in the prior SARS[14,15] and Middle East respiratory syndrome (MERS)[16] epidemics (caused by SARS-CoV and MERS-CoV, respectively). Although gender-related social factors, including smoking, health care-seeking behaviours and some co-morbid conditions, may impact the outcomes of COVID-19 (REFS[6,17]) and contribute to male–female differences in disease severity, the cross-cultural emergence of increased risk of death for males points to biological risk determinants. In animal models of SARS-CoV infection, differences in mortality between male and female mice were observed and were attributed to steroid hormones[18]. Multiple dimensions of biological sex, including sex steroids, sex chromosomes and genomic and epigenetic differences between males and females, impact immune responses[19–26] and may affect responses to SARS-CoV-2 infection[27].

Ageing, sex and COVID-19

Although advancing age is associated with greater risk of death in both sexes, the male bias remains evident (FIG. 1b). An analysis of COVID-19 data from Italy, Spain, Germany, Switzerland, Belgium and Norway reveals that among all age groups older than 20 years, fatality rates are greater for males than females[28]. By contrast, male–female differences in the rate of confirmed SARS-CoV-2 infections are age dependent in all countries, being greater among females aged between 10 and 50 years and greater among males before the age of 10 years and after the age of 50 years[28]. The age-related male–female differences in confirmed cases of SARS-CoV-2 infections are consistent with reported confirmed cases of seasonal and pandemic influenza A virus infections in Australia and Japan[29,30]. We interpret these data to suggest that biological sex differences contribute to male-biased death, but gender-associated risk of exposure may affect rates of infection differently for males and females.

With a focus on biology, the impact of age on susceptibility to severe COVID-19 needs to be parsed, with both immunosenescence and dysregulation of innate immune responses as potential

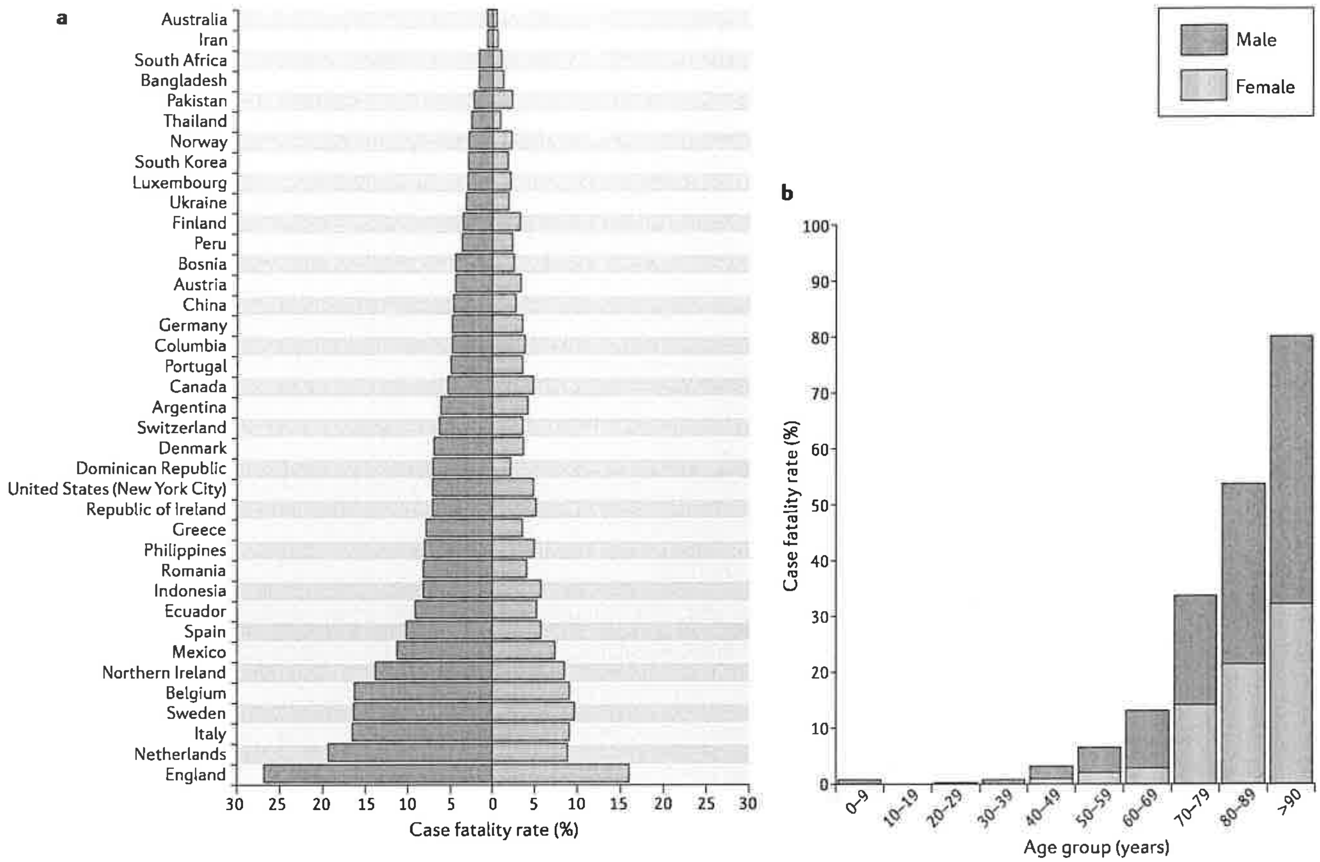

Fig. 1 | **Comparative analyses of COVID-19 case fatality rates by country, sex and age. a** | COVID-19 case fatality rates (CFRs) for males and females across 38 countries or regions reporting sex-disaggregated data on COVID-19 cases and deaths. CFR was calculated as the total number of deaths divided by the total number of cases for each sex multiplied by 100. The male CFR is higher than the female CFR in 37 of the 38 regions, with an average male CFR 1.7 times greater than the average female CFR ($P < 0.0001$, Wilcoxon signed rank test). **b** | Average COVID-19 CFRs for males and females stratified by age. The data represent 12 countries currently reporting sex- and age-disaggregated data on COVID-19 cases and deaths (Australia, Columbia, Denmark, Italy, Mexico, Norway, Pakistan, Philippines, Portugal, Spain, Switzerland and England). The COVID-19 CFR increases for both sexes with advancing age, but males have a significantly higher CFR than females at all ages from 30 years ($P < 0.05$, Wilcoxon signed rank test). The data were obtained from Global Health 50/50 and official government websites of each respective country on 7 May and 8 May 2020. For more information on the data source for a specific country, please contact the corresponding author.

mechanisms[31,32]. Biological sex differentially affects ageing of the immune system[33], in part through changing concentrations of sex steroids[34]. In addition to reduced concentrations of sex steroids, an age-related mosaic loss of chromosome Y in leukocytes can alter transcriptional regulation of immunoregulatory genes[35]. Whether sex differences in the genomic signatures of aged immune cells translate to functional differences in the response to SARS-CoV-2 infection requires attention.

Sex differences in immune responses

Biological sex affects innate and adaptive immune responses to self and foreign antigens, resulting in sex differences in autoimmunity as well as in responses to infections and vaccines[36,37]. Immune cell subsets have sex-specific patterns of gene expression, with most differentially expressed genes found on autosomes, demonstrating sex-specific regulation of shared genetic material[26]. The sex chromosomes also directly contribute. Males are at higher risk of diseases caused by deleterious X-linked alleles. Incomplete inactivation of immunoregulatory genes on the X chromosome can also occur in females, which results in a gene dosage imbalance between sexes[38,39]. Incomplete X chromosome inactivation has been implicated in female-biased autoimmune diseases[40] and in vaccine efficacy[41]. The Y chromosome has immunoregulatory function, broadly impacting immune transcriptional profiles linked to autoimmune disease[42] and impacting outcomes of influenza virus and coxsackie virus infection in animals[43,44]. Sex-specific features of epigenomic organization also dictate differential availability of transcriptional targets[21,45]. Superimposed on these genomic elements is the direct effect of sex steroid exposure. Oestrogens[46,47], progesterone[48–52] and testosterone[53] have direct effects on immune cell function that are driven by the signalling of these hormones through their respective cellular receptors. The variation in sex steroid concentrations that occurs over the life course contributes to differences in immune profiles and disease susceptibility patterns at different ages[20,52]. Consistent with this variation, both sex and age contribute to unique transcriptional signatures of immune cells both at the baseline and after exposure to immunostimulants[19,21,22]. The summative effect is a sex-specific transcriptional regulatory network of genetic variants, epigenetic modifications, transcription factors and sex steroids that leads to a functional difference in the immune response[25,54]. FIGURE 2 highlights intersections between SARS-CoV-2 infection and sources of sex bias in pathophysiology that warrant further investigation.

Sex bias in SARS-CoV-2 infection

Virus entry receptors. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as an entry receptor, with virus entry enhanced by cellular transmembrane serine protease 2 (TMPRSS2), which primes the spike protein of the virus[55,56]. *ACE2* is an X chromosome-encoded gene that is downregulated by oestrogens[57] and exhibits tissue-specific expression patterns[59]. Differences in *ACE2* expression may be driven by sex-differential expression of *ACE2* variants[58–60]. ACE2 is associated with interferon gene expression[61,62], which in turn shows sex-specific regulation. The cell-intrinsic regulation of ACE2 expression may change with age, in response to changing levels of sex steroids, or following viral challenge. TMPRSS2 is regulated by androgen receptor signalling in prostate cells[63]. Initial investigations have not demonstrated a significant difference in *TMPRSS2* mRNA expression in lung tissue from males and females, but it is unknown whether androgens may impact expression in the setting of infection with SARS-CoV-2 (REFS[63,64]) or whether the level of expression has an impact on SARS-CoV-2 burden. Further research is needed to determine whether sex-biased expression of *ACE2*, coupled with the regulation of *TMPRSS2* by androgens, increases SARS-CoV-2 susceptibility of males compared with females.

Interferons. Innate sensing of viruses, production of interferons and activation of the inflammasome are the first line of defence against viruses[65]. In the case of SARS-CoV-2, where there is no pre-existing adaptive immune memory, the success of this early antiviral response may be a determinant of disease outcome. Innate sensing of viral RNA by the pattern-recognition receptor Toll-like receptor 7 (TLR7) is sex biased, as *TLR7* escapes X chromosome inactivation, resulting in greater expression in female immune cells; this has also been linked to sex differences in autoimmunity[40,66] and vaccine efficacy[41]. There is greater production of interferon-α (IFNα) from plasmacytoid dendritic cells from adult females than from adult males[67,68], an effect modulated by sex steroids[69–71]. In animal models of SARS-CoV infection, pretreatment with pegylated IFNα was associated with protection of lung tissue[72] but without consideration of biological sex. In SARS-CoV-2, emerging data suggest that there is aberrant activation of interferon responses but preserved chemokine signalling, which has been postulated to contribute to immunopathology[73]. Studies are needed

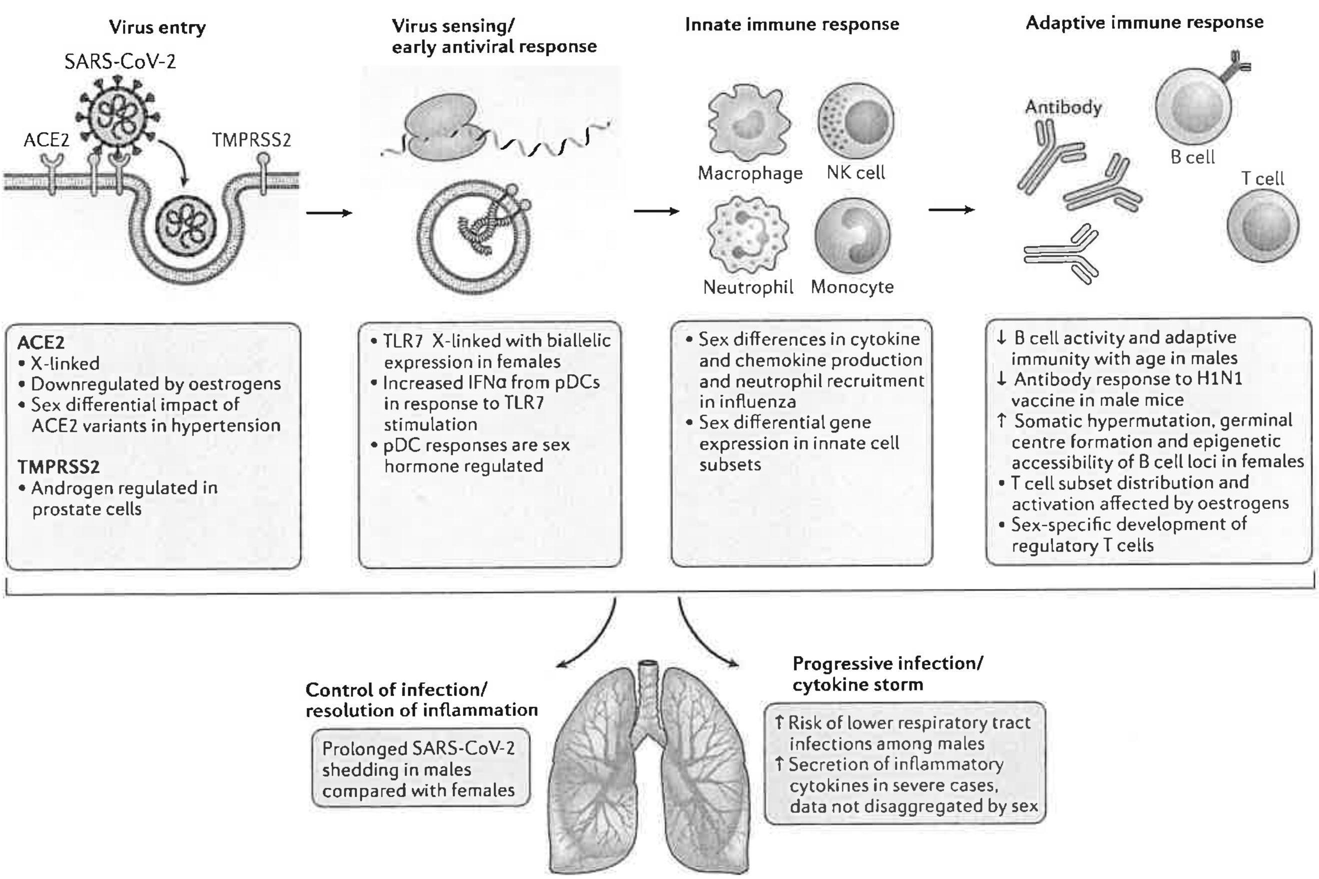

Fig. 2 | **Known sex differences that may impact immune responses to SARS-CoV-2 and COVID-19 progression.** An illustrative summary of the sequence of events in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the associated immune responses. Broadly speaking (from left to right), there are the initial steps of virus entry, innate recognition of the virus with activation of antiviral programmes, the recruitment of innate immune cells and induction of an adaptive immune response. These major steps culminate either in successful control of infection and pathogen elimination or in a pathological inflammatory state. Sex differences that may be operative at multiple points along these pathways are indicated in the blue boxes. ACE2, angiotensin-converting enzyme 2; H1N1, H1N1 influenza virus; IFNα, interferon-α; NK, natural killer; pDC, plasmacytoid dendritic cell; TLR7, Toll-like receptor 7; TMPRSS2, transmembrane protease serine 2.

to determine whether differences in the magnitude or kinetics of the interferon response may contribute to a sex bias in the early control or severity of SARS-CoV-2 infection and may inform considerations of interferons as therapies for COVID-19 (REF.[74]). Early data suggest that male sex may be associated with a longer duration of viral detection, even within families[75,76], raising the question of whether females have more efficient clearance of the virus. The rate of virus clearance will need to be assessed in evaluating the efficacy of innate and adaptive immune responses.

Adaptive immunity. Females generally mount greater antibody responses to viral infection and vaccination, albeit with higher levels of autoreactivity[77]. The mechanisms for sex differences in antibody production include oestrogenic enhancement of somatic hypermutation[78], less stringent selection against autoreactive B cells[77,79–82] and sex differences in germinal centre formation[83] and in the epigenetic accessibility of B cell loci[21]. It is still unknown whether sex has an impact on antibody generation in SARS-CoV-2 infection. Early studies suggest that titres of antibodies to some viral epitopes are higher in patients with severe COVID-19 and that seroconversion may not be tightly linked to declining virus titres[84,85]. Ongoing studies evaluating the infusion of convalescent serum may provide answers as to the protective capacity of these antibodies[86], but these studies are currently not considering biological sex. Generation of protective, neutralizing antibodies is a goal of vaccine development, with the cautionary note that in models of SARS-CoV vaccination some antibody responses induced potent inflammatory responses[57]. Persistence of antibodies, epitope targeting and non-neutralizing Fc-mediated antibody characteristics should be assessed with sex-stratified analyses. As vaccines are developed, the female bias towards both potent responses and adverse effects should be considered and sex-specific dosing should be tested, where appropriate[87].

Sex impacts the development of regulatory T cells[88–91], the distribution of lymphocyte subsets[92] and the overall quality of T cell responses[93,94]. In T cells, overexpression of X-encoded immune genes, including *CD40LG* and *CXCR3*, has been linked to incomplete X chromosome inactivation and T cell-specific epigenetic modifications of the X chromosome[95,96]. It is unknown whether T cell phenotypes contribute to COVID-19; data from the prior SARS outbreak did not link T cell responses to outcomes in humans[97], but mouse models suggest a role for CD4+ T cells[98]. In patients with MERS, T cell responses were dysregulated[99], but sex differences were not analysed. In the current pandemic, lymphopenia is associated with severe disease[100,101], and early evidence suggests that the clinical markers of lymphocyte count may be lower in males and neutrophil–lymphocyte ratios may be higher[17]. Further work is needed to define the sex-differential role of T cells in acute infection, in acute lung injury phenotypes[102] and as potential vaccine targets.

Severe infection and acute respiratory distress syndrome. Severe cases of COVID-19 are typically marked by acute respiratory distress syndrome (ARDS), with respiratory failure requiring oxygen support and mechanical ventilation. The infection is primarily characterized by diffuse alveolar damage without a consistent pattern of cell infiltration[75,103–105]. The pathogenesis of ARDS involves the disruption of normal barrier function, inflammation and subsequent tissue repair. Whether there are sex-specific risks for ARDS and death from other causes, such as trauma, remains unknown[106,107], although there is a suggestion of a higher risk of lower respiratory tract infections among males[108] and that steroid hormones modulate the immune response to respiratory viral pathogens[109]. In one cohort of patients with COVID-19, severe respiratory failure was associated with a pattern of inflammation, macrophage activation and depletion of lymphocytes that was distinct from bacterial infection[110]. There was a sex bias for severe COVID-19 not observed in the comparator group with bacterial infections[110]. Sex-differential production of IL-6 (REF.[111]), monocyte transcriptional patterns and inflammatory set point[19,21,22] could contribute to an enhanced risk of death in males and highlight the importance of sex-stratified analyses to guide deployment of safe and effective immunomodulatory therapeutics for males and females[112].

Conclusions

Emerging data demonstrating more favourable outcomes for community-dwelling adult females across age strata offer an immediate opportunity for comparative biology experiments to define features of COVID-19 pathogenesis and the associated immune response. The research pipeline should integrate sex as a biological variable in all stages, from fundamental research to preclinical drug development, clinical trials and epidemiological analyses[113]. Considering the role of intersecting factors — including, but not limited to, gender, age, race and other identifying characteristics — is critical to understanding the biological and sociocultural factors contributing to heterogeneous COVID-19 outcomes. Sex is a driver of discovery and innovation[114], and taking a sex-informed approach to COVID-19 research[115] and medicine[116] will uncover novel features of the host immune response to SARS-CoV-2 and ultimately result in more equitable health outcomes.

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PLOS PATHOGENS

OPINION

Biological sex impacts COVID-19 outcomes

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Abstract

The current novel coronavirus disease 2019 (COVID-19) pandemic is revealing profound differences between men and women in disease outcomes worldwide. In the United States, there has been inconsistent reporting and analyses of male–female differences in COVID-19 cases, hospitalizations, and deaths. We seek to raise awareness about the male-biased severe outcomes from COVID-19, highlighting the mechanistic differences including in the expression and activity of angiotensin-converting enzyme 2 (ACE2) as well as in antiviral immunity. We also highlight how sex differences in comorbidities, which can be associated with both age and race, impact male-biased outcomes from COVID-19.

We are in the midst of a pandemic. Many of us predicted that the next "100 year pandemic" would be caused by an influenza A virus, like the H1N1 virus that caused the 1918 influenza pandemic. Instead, the current pandemic is caused by a novel β-coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Currently, there are almost 2 million cases and over 100,000 deaths worldwide from the disease caused by this virus, called the novel coronavirus disease 2019 (COVID-19). Like the 1918 influenza pandemic [1], men are at greater risk of more severe COVID-19 outcomes than women, with both sex (i.e., biological differences) and gender (i.e., sociocultural and behavioral differences) playing fundamental roles.

The initial reports from China, followed by data from several countries in Europe, have highlighted that there are roughly similar numbers of confirmed SARS-CoV2 cases between men and women. The severity of COVID-19, as measured by hospitalization, admission to intensive care units, and rates of fatality, however, has consistently been 2-fold greater for men than women [2], with the Global Health 50/50 research initiative providing real-time sex-disaggregated data from most countries worldwide [3]. Unfortunately, despite the United States currently having the most COVID-19 cases in the world, considerably less attention has been paid to sex-disaggregation of data than in Europe and China.

We took this opportunity to evaluate the current situation in the US to both determine if similar patterns of male–female differences are observed and to document which states are or are not disaggregating and analyzing data by sex. As of this writing, 26 states have more than 2,000 confirmed cases (https://www.worldometers.info) and from these states, only three (Louisiana, New Jersey, and Pennsylvania) have not sex-disaggregated cases of COVID-19. New York has the greatest number of COVID-19 cases in the US and is an epicenter of this pandemic. Of the data from the remaining 23 states, 7 states replicate the epidemiological pattern seen in New York City (NYC) (**Fig 1**) and elsewhere in the world [3], in which numbers of COVID-19 cases are similar between men and women. The other 16 states, however, suggest a female-bias exists in COVID-19 cases (i.e., 1 to 0.9/0.8 male to female ratio). This includes Washington state, which is another epicenter of the COVID-19 pandemic in the US. Of 167 COVID-19 cases from a Washington state long-term care facility, a majority of cases were women (68% of residents and 76% of healthcare workers) [4]. The total number of men and women among facility residents and healthcare workers was not provided and with women living longer than men and being more likely to work as healthcare providers [5], gender-associated factors may be involved [5].

Of the 26 states analyzed, only two counties within two different states (i.e., NYC and Bucks County, Pennsylvania) have reported rates of hospitalization broken down by sex, and both report greater rates of hospitalization from COVID-19 among men than women (**Fig 1**). Lastly, of the 26 states with more than 2,000 confirmed COVID-19 cases, only 13 (New York, Michigan, California, Illinois, Texas, Washington, Connecticut, Indiana, Colorado, Ohio, North Carolina, Wisconsin, and Alabama) have disaggregated fatalities from COVID-19 by sex and consistently show that fatality rates are 2-fold greater for men than women (**Fig 1**). Gender-associated factors have been reviewed elsewhere [2, 5]; thus, we seek to focus on biological mechanisms that could impact male–female differences in severe COVID-19 outcomes to call attention to sex-associated factors that could potentially provide novel insights into therapeutic interventions.

Angiotensin-converting enzyme 2 (ACE2) is a monocarboxpeptidase that counteracts the vasoconstrictor effects of angiotensin (Ang)-(1–8) by converting this octapeptide hormone to the vasodilator heptapeptide Ang-(1–7) [6]. In 2003, ACE2 was found to be the SARS-CoV (i.e., the virus that caused the 2002 to 2003 SARS outbreak) receptor [7, 8], with SARS-CoV2

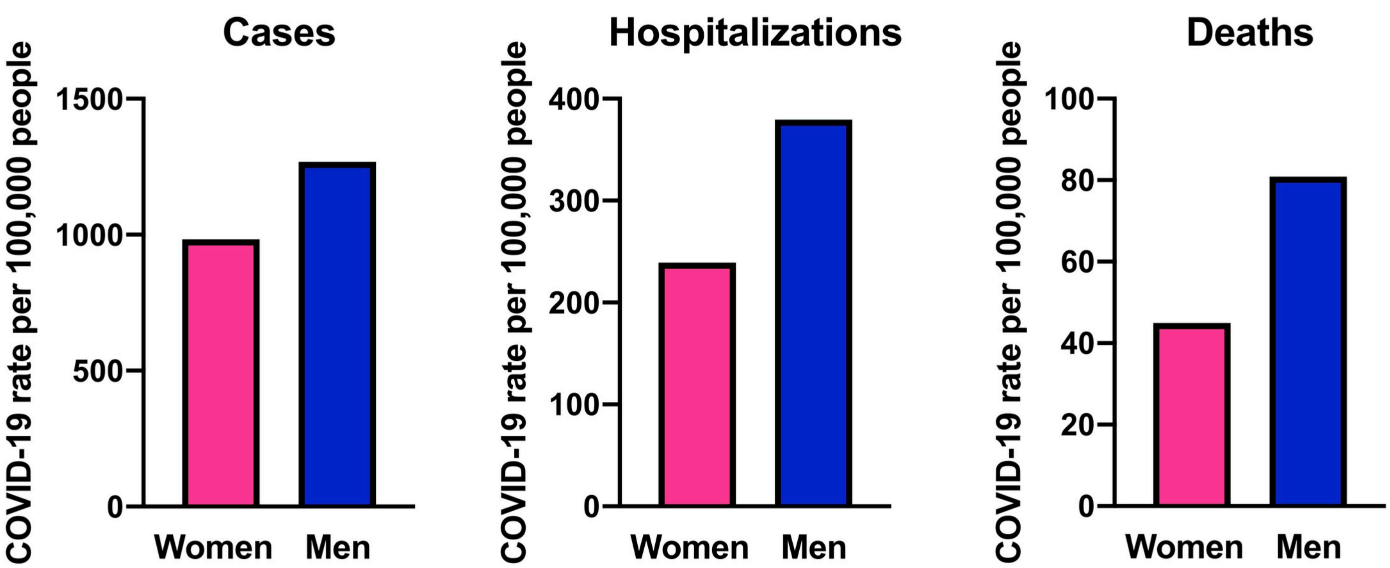

Fig 1. Sex-disaggregated numbers of COVID-19 cases, hospitalizations, and deaths per 100,000 people in NYC. Data were accessed from https://www1.nyc.gov/site/doh/covid/covid-19-data.page on April 11, 2020. COVID-19, novel coronavirus disease 2019; NYC, New York City.

https://doi.org/10.1371/journal.ppat.1008570.g001 binding ACE2 with even higher affinity [9]. ACE2 is expressed primarily in the kidney, heart, and testes, with the highest expression occurring in the kidney; it is, however, also expressed in the lungs at much lower levels [10]. The SARS-CoV2 virus S1 spike protein binds to the ACE2 receptor in alveolar epithelial cells of the lungs. ACE2 protein is expressed in a sex-specific manner in the mouse kidney; male mice have nearly 2-fold higher levels of renal ACE2 protein than female mice [11]. Furthermore, using the four core genotype mouse model in which gonadal sex (ovaries versus testes) is separated from the sex chromosome complement (XX versus XY) [12], we found renal ACE2 activity was greater in the male kidney regardless of the sex chromosome complement [11]. This sex difference in renal ACE2 activity was driven by estradiol reducing ACE2 activity regardless of the sex chromosome complement. These findings have implications for the observed sex differences in COVID-19 outcomes. It will be important to study the sex-specific regulation of ACE2 in the lung and other tissues involved in COVID-19 pathogenesis including the heart and brain [6] and also to investigate whether estrogens protects women from COVID-19 by reducing the expression levels of the receptor for the SARS-CoV2 virus.

The innate recognition and response to viruses as well as downstream adaptive immune responses during viral infections also differ between females and males [13]. We and others have illustrated that females generally mount greater inflammatory, antiviral, and humoral immune responses than males during viral infections [14], which contributes to better clearance of viruses, including SARS-CoV [15]. Enhanced immunity in females can, however, also result in greater immunopathology and tissue damage at later stages of viral disease, such as during influenza A virus infection [16]. To date, we have only identified two COVID-19 studies that have disaggregated and analyzed immunological outcome data by sex. In a published study of 168 patients with severe COVID-19 in Wuhan, China, it was reported that men were significantly more likely to remain hospitalized and die and less likely to be discharged from the hospital during the study period than women [17]. The male–female difference was most pronounced among individuals 60 years of age and older. In this study, the neutrophil to lymphocyte ratio and serum C-reactive protein concentrations were twice as high in male as in female COVID-19 patients, as well as in patients who died compared with patients who were discharged from the hospital (not disaggregated by sex) [17]. These data suggest that inflammatory immune responses and cell counts might be more elevated in men and associated with worse outcomes from COVID-19 than in women.

Mounting evidence suggests that humoral immune responses can be measured not only to confirm exposure to SARS-CoV2 but also to assess adaptive immune responses necessary for clearance of SARS-CoV2. As a result, convalescent plasma transfer studies are underway for compassionate care of severe COVID-19 patients [18], without, however, consideration of the sex of the donor. In a not yet peer-reviewed study of 331 patients with confirmed SARS-CoV2 infections in Wuhan, China, anti–SARS-CoV2 immunoglobulin G (IgG) responses were measured and compared among patients with either clinically diagnosed mild or severe disease. The sex distribution of recovering cases was 36% and 65% for men and women, respectively [19]. Among patients with mild COVID-19, anti–SARS-CoV2 IgG titers were similar between the sexes. In contrast, among patients with severe disease, women exhibited greater antibody responses than men, with production of antibodies at earlier phases of disease suggesting one possible immunological mechanism mediating better recovery from COVID-19 in women than men [19].

Development of mouse models for SARS-CoV2 will be instrumental for mechanistically assessing the causes of sex differences in the pathogenesis of COVID-19. In a mouse model of SARS-CoV infection, female mice had lower virus titers and less severe pulmonary damage from monocyte–macrophage infiltration and cytokine production, resulting in lower mortality in female (20%) compared with male (80%) mice [15]; a sex distribution similar to that observed in human SARS [20]. Notably, the endogenous production of estradiol in female mice was important for this protection.

Comorbidities that are associated with more severe outcomes from COVID-19 in the US, include diabetes, obesity, hypertension, heart disease, chronic kidney disease, and chronic pulmonary disease. Notably, diabetes, obesity, and hypertension are the top three conditions associated with fatal COVID-19 cases in China and Italy [4, 21–23]. As of April 14, 2020, in New York, hypertension accounted for 56.8% and diabetes 42.4% of fatal cases [24]. In Louisiana, where New Orleans is the epicenter by death rate per capita, hypertension accounted for 59.8%, diabetes 38.1% and obesity 22.3% of fatal cases [25]. To date, no study has reported whether these comorbidities are influenced by sex or gender in COVID-19 patients. Biological (sex) as well as behavioral (gender) factors contribute to differences between men and women in these comorbidities [26]; the sex and gender-associated factors that underlie these comorbidities, however, have not been evaluated in context of COVID-19. There also has been no consideration about how sex intersects with age and race to further increase risk of severe COVID-19 outcomes in men, despite observations illustrating that older aged individuals [27] and African Americans [28] are also at risk for severe COVID-19 outcomes. For these reasons, we call on clinicians and epidemiologists to report data pertaining to comorbidities associated with COVID-19 disaggregated by sex, age, and race. We also emphasize the importance of considering the biological variable of sex when conducting basic science studies of COVID-19.

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Essay

Sex Determination: Why So Many Ways of Doing It?

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Abstract: Sexual reproduction is an ancient feature of life on earth, and the familiar X and Y chromosomes in humans and other model species have led to the impression that sex determination mechanisms are old and conserved. In fact, males and females are determined by diverse mechanisms that evolve rapidly in many taxa. Yet this diversity in primary sex-determining signals is coupled with conserved molecular pathways that trigger male or female development. Conflicting selection on different parts of the genome and on the two sexes may drive many of these transitions, but few systems with rapid turnover of sex determination mechanisms have been rigorously studied. Here we survey our current understanding of how and why sex determination evolves in animals and plants and identify important gaps in our knowledge that present exciting research opportunities to characterize the evolutionary forces and molecular pathways underlying the evolution of sex determination.

Introduction

Sex—the mixing of genomes via meiosis and fusion of gametes—is nearly universal to eukaryotic life and encompasses a diverse array of systems and mechanisms [1]. One major role of sex is to bring together alleles carried by different individuals, revealing beneficial genetic variance that is otherwise hidden [2]. While many unicellular organisms produce gametes of equal size (isogamy, see Box 1), sexual reproduction in most multicellular organisms has led to the evolution of female and male gametes differing in size (anisogamy), and often to the evolution of two separate sexes. Even though the outcome of sex determination—whether an individual produces relatively few large ova or many small sperm—is strongly conserved, a bewildering number of underlying mechanisms can trigger development as either a male or female [3,4].

In humans, sex is determined by sex chromosomes (XX females, XY males). The X and Y chromosomes harbor dramatically different numbers and sets of genes (about 1,000 genes on the X and only a few dozen genes on the Y), yet they originated from ordinary autosomes during the early evolution of mammals (Figure 1). Restriction of recombination followed by gene loss on the Y has resulted in the morphological differentiation of sex chromosomes (for a review of the molecular and evolutionary processes involved in Y degeneration, see [4,5]). The vast majority of genes on the sex chromosomes are not directly involved in sex determination, and development as a male or female depends on the presence of a single master sex-determining locus, the *Sry* gene, on the male-limited Y chromosome. Expression of *Sry* early in embryonic development initiates testis differentiation by activating male-specific developmental networks, while in its absence, ovaries develop. The first visible signs of sexual differentiation of the ovary and testis occur by the sixth week of gestation in humans [6], and sex hormones initiate further sexual differentiation in nongonadal tissues and organs [7]. When this developmental process goes awry, the effects can be catastrophic, causing everything from ambiguous external genitalia (which occurs in up to one in 4,500 infants) to sterility (which is more cryptic and difficult to diagnose but may be far more common).

Like humans and most mammals, other genetic model systems, such as *Drosophila melanogaster* flies and *Caenorhabditis elegans* nematodes, harbor sex chromosomes, and their commonalities have led to general assumptions about the conservation of sex determination mechanisms. However, these model organisms present a false impression of stability in how sex is determined, and their commonalities mask the diversity and turnover in sex determination mechanisms that is readily

Essays articulate a specific perspective on a topic of broad interest to scientists.

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apparent when taking a broader taxonomic view. In this article, we address three common myths about sex determination and then deconstruct them based on a broad taxonomic survey of animals and plants.

Myths of Sex Determination

Myth 1: Sex is typically determined by X and Y chromosomes

Many biologists are habituated to thinking about sex determination through the familiar examples of mammals and *D. melanogaster*, and assume that sex determination by sex chromosomes is the norm, that males are XY and females are XX, and that sex chromosomes are a stable component of the genome. While biologists are generally aware of other modes of sex determination (such as female heterogamety in birds, temperature-dependent sex determination in reptiles, or development of males from unfertilized eggs in bees), these alternatives are often viewed as strange and aberrant [8].

Myth 2: Sex is controlled by one master-switch gene

Sex determination in model species suggests that a master-switch gene (e.g. *Sry* in mammals, *Sxl* in *D. melanogaster*, and *xol-1* in *C. elegans*) acts as the main control element to trigger either male or female sexual development. Changes in the sex determination pathways across taxa are assumed to involve adding a new master-switch gene to this molecular pathway (as in some fly taxa; [9]), with little change to downstream elements of the sex determination pathway [10]. A few genes are thought to have the capacity to take on the role of sex determination genes, and these have been co-opted as master-switch genes independently in different lineages (for example, *dmrt1* in several vertebrates [11–14] and *tra* in insects [15–17]).

Myth 3: Sex chromosome differentiation and degeneration is inevitable

Sex chromosomes originate from identical autosomes by acquiring a sex determination gene (for example, the origin of the *Sry* gene in mammals approximately 180 million years ago or *Sxl* in the *Drosophila* genus >60 million years ago). They are then thought to differentiate through an inevitable and irreversible process in which recombination between X and Y chromosomes is shut down and the Y degenerates (see Figure 1). Ultimately, Y chromosomes are fated to disappear entirely ("born to be destroyed," [18]). Thus, sex chromosomes that are morphologically similar (homomorphic) must be evolutionarily young, and in time they too will degenerate.

The Myths Deconstructed

These myths do not survive a survey of sex determination systems across the tree of life. To deconstruct these myths, we first provide background on the evolution of separate sexes. We then summarize the diversity of sex-determining mechanisms found among animals and plants and discuss the evolutionary forces that drive transitions among systems (Myth 1 revisited). This is followed by a summary of more recent findings on the underlying molecular genetics of sex determination (Myth 2 revisited) and a deconstruction of common misconceptions of sex chromosome evolution in humans and other species (Myth 3 revisited). We conclude with an outlook for future research that might improve our understanding of how and why sex determination evolves so rapidly in many animals and plants.

The Evolution of Separate Sexes

While the evolution of anisogamy led to the evolution of male and female functions, the evolution of separate sexes is not inevitable across lineages. Indeed, most flowering plants (94%, [19]) have both male and female sex organs within a single individual and often within the same flower. By contrast, hermaphroditism is rare among animals considered as a whole (about 5% of all species), which is largely due to the absence of hermaphrodites in the species-rich insects, but it is common in many other animal taxa, including fish and many invertebrates (most snails, corals, trematodes, barnacles, and many echinoderms) [20]. Hermaphrodites can mate with each other and benefit from the advantages of sex by mixing their genomes, but when mates are difficult to find, hermaphrodites can also escape the need for a reproductive partner by self-fertilization (which, however, may produce low-fitness offspring due to "inbreeding depression;" see below). This advantage of reproductive assurance is particularly pronounced in sessile animals—like corals—and plants, which cannot move to find a mate [21,22]. Thus there is a clear advantage to combining both male and female functions within an individual, especially in taxa with low mobility.

However, in some plants and most animals, species are driven to separate the sexes. This can be achieved in several ways. One partial solution is the spatial separation of male and female gonads in the same individual, as in monoecious plants with separate male and female flowers (e.g., maize) and in most hermaphroditic animals. Alternatively, male and female function can be separated in time within an individual, as found in many plants ("dichogamy," [23]) and some animals ("sequential hermaphroditism," [24]); slipper shells, for example, are born male and become female later in life. Finally, male and female reproductive organs can be segregated into different individuals, as in some plants (such as papaya and cannabis) and most animals.

Separate sexes have evolved independently many times among plants and animals, which suggests that there must be an evolutionary cost to hermaphroditism, at least in some groups. Two major hypotheses have been proposed to explain the evolution of separate sexes. The first hypothesis is that there are trade-offs between male and female function, such as when mating displays enhance male fitness but decrease female fitness. In this case, individuals can gain reproductive advantages by specializing as a male or female [25]. Direct evidence for the trade-off hypothesis is sparse [26], and observations consistent with it come from hermaphroditic great pond snails, which reallocate resources to female function when sperm production is experimentally abolished [27], and from strawberries, in which increased pollen production comes at the cost of reduced seed set [28]. Indirect evidence of a trade-off comes from the fact that many asexual animals [29] and plants [30] that still have residual sperm/pollen production evolve reduced investment in male gametes over time, suggesting that doing so increases female function. The second major hypothesis is that separate sexes evolve as a means to avoid self-fertilization, which can produce low-fitness offspring because of the exposure of recessive deleterious alleles ("inbreeding depression") [31]. Empirical evidence for inbreeding depression is widespread in animals and plants [32,33]; for instance, in the Hawaiian endemic plant genus *Scheidia*, high inbreeding depression promotes the evolution of dioecy [34].

When separate sexes are favored, the transition can occur via several evolutionary pathways. Separate sexes may evolve from hermaphrodites either by gradual increases in sex-specific investment or rapidly by the appearance of male- or female-sterility mutations (Figure 2). The latter occurs regularly in plants, often generating mixed sexual systems, such as

Box 1. From Mating Types to Sexes

Meiotic sex likely has a single origin, which dates back to the origin of eukaryotes [144,145]). While most eukaryotes display some form of meiotic sex, many lack differentiated male and female gametes—a situation referred to as isogamy. Even with isogamy, however, mating is often not random but requires that joining cells differ at a mating type (MAT) locus. Mating types might have evolved to orchestrate the developmental transition from the haploid to the diploid phase of the life cycle [146,147]: *plus* and *minus* gametes express complementary transcription factors, encoded by different alleles at the MAT locus; these combine in the zygote into heterodimers that silence the genes expressed in the haploid phase and switch on the diploid program.

Isogamy permits a theoretically unlimited number of mating types; high numbers increase the probability that randomly mating partners display complementarity. Most basidiomycete fungi, for instance, present two independent MAT loci (and are therefore said to be tetrapolar, because a single meiosis can produce cells of four distinct mating types); each locus can be multiallelic, resulting in up to thousands of different mating types. Alternatively, a low probability of encountering complementary partners might have driven a transition to homothallism observed in many ascomycete fungi, which refers to a mating compatibility between genetically identical individuals. Homothallism evolved via genic capture: a single genome harbors complementary mating-type alleles, which are differentially expressed in *plus* and *minus* gametes. Mating-type switching in yeasts allows different cells from the same clone to express complementary mating types, and thus enter the diploid phase of their life cycle.

Anisogamy (small male and large female gametes) evolved independently in many eukaryotic lineages, including several different groups of protists (such as red algae, brown algae, apicomplexa, dinoflagellates, and ciliates; [148]), as well as most plants and animals. The transition towards anisogamy is thought to result from disruptive selection [1,149,150]: given opposing pressures to simultaneously maximize the number of gametes, their encounter rate, as well as the mass and ensuing survival of resulting zygotes, the fitness of both partners is often maximized when one interacting gamete is small and mobile, while its large and sessile partner provides the resources required for zygote development. Intermediate gametes do worse than small ones in terms of mobility and numbers, and worse than large ones in terms of provisioning. Such constraints largely explain why sexes (at the gametic level) are two and only two, and why anisogamy independently evolved in many lineages. At the molecular level, one route to anisogamy is by the incorporation of genes controlling gamete size into the MAT region [151]. Further extensions of the MAT region, possibly involving additional sex-antagonistic genes, led to the U and V chromosomes characterizing male and female gametophytes, as found, e.g., in mosses and liverworts [152].

Importantly, the evolution of anisogamy does not require the evolution of separate sexes, because hermaphrodites can produce both sperm and eggs. Similarly, several unicellular organisms that are anisogamous, such as apixomplexa and dinoflagellates, can make cells that produce sperm as well as cells that produce eggs. The evolution of completely separate sexes, where individuals cannot give rise to both sperm and egg descendants, is thought to be fairly derived and is found primarily among multicellular organisms with rare unicellular exceptions (e.g., the ciliate *Vorticella* [153] and several dioecious diatoms [154]).

gynodioecy (mixtures of females and hermaphrodites) and androdioecy (mixtures of males and hermaphrodites). Figure 2 highlights the possible pathways for the evolution of separate sexes from a hermaphrodite ancestor and illustrates their relation to sex chromosome evolution. While we have emphasized the evolutionary transition from hermaphroditism to separate sexes, several examples are known where the opposite transitions occur (e.g., [35,36]), indicating that the conditions favoring the separation of male and female function are not always present.

Myth 1 Revisited—Sex-Determining Mechanisms Are Diverse and Can Evolve Rapidly

In animals and plants that have evolved separate sexes, accurate differentiation into fertile males and females is a fundamental developmental process. Contrary to Myth 1, however, diverse mechanisms are used to determine sex [3,4] (Figure 3, Figure 4; Box 2). All crocodiles, most turtles, and some fish exhibit temperature-dependent sex determination; *Wolbachia* infections override existing sex determination systems in many arthropod species and either kill/sterilize males or transform them into phenotypic females; male scale insects eliminate their father's genome after fertilization; marine worm Bonellidae larvae develop as males only if they encounter a female; and many plants and animals—including some snails and fish—change sex during their lifetime in response to environmental or social cues [3,37].

In fact, sex determination is a rapidly evolving trait in many lineages (Figure 3), and sometimes closely related species, or populations of the same species, have different modes of sex determination [3,4,38]. Houseflies, for example, normally have XY sex chromosomes, but dominant masculinizing and feminizing alleles on other chromosomes exist in some populations that override sex determination by the XY chromosomes [39]. This variety has stimulated investigation into what evolutionary forces drive the turnover of sex determination mechanisms, what molecular mechanisms underlie the different modes of sex determination, and why sex determination is labile in some taxa and not in others.

Genotypic versus environmental sex determination

With *genotypic sex determination* (GSD), which occurs in the majority of species with known sex-determining mechanisms, genetic elements specify whether individuals are female or male. In many animals and some plants, however, the switch to develop into a female or male does not lie in the genes. With *environmental sex determination* (ESD), external stimuli control sex determination, such as temperature in reptiles [40], photoperiod in marine amphipods and some barnacles [41,42], and social factors in many coral-reef-dwelling fish and limpets [43,44]. Exactly how the environment triggers sex development has remained an open question, although a recent study found that methylation provided the link in European sea bass [45]. In many species, the line between GSD and ESD is blurred, with certain environments altering the (otherwise genetically determined) sex of developing offspring [46]. For example, tongue sole have differentiated ZW sex chromosomes, but

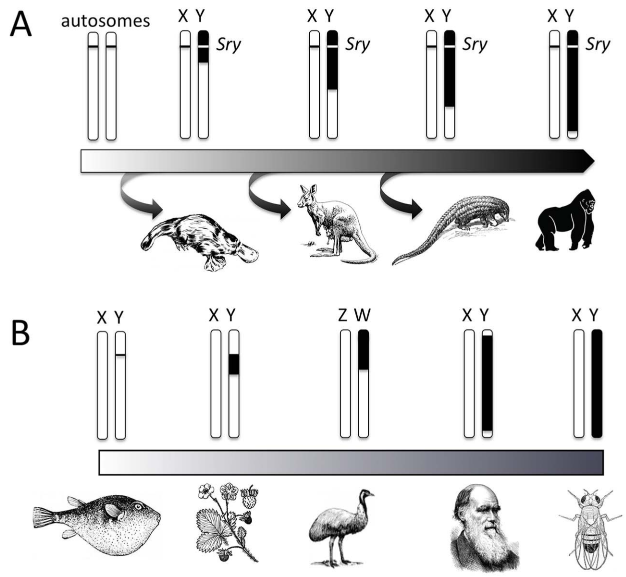

Figure 1. Sex chromosome differentiation. A. Reconstructed evolutionary path of sex chromosome differentiation in humans. Sex chromosomes originate from autosomes that acquired a sex-determining function (the *Sry* gene) after their split from monotremes. Suppression of recombination between the sex chromosomes, associated with degeneration of the non-recombining region of the Y chromosome, results in the morphological and genetic differentiation of sex chromosomes. Recombination suppression occurred in multiple episodes along the human X and Y chromosome, forming so-called evolutionary strata. The oldest stratum is shared between eutherian mammals and marsupials, while the youngest stratum of humans is primate-specific. **B.** The degree of sex chromosome differentiation ranges widely across species, spanning the entire spectrum of homomorphic to heteromorphic sex chromosomes, from a single sex-determining locus, as seen in pufferfish, a small differentiated region (strawberry and emu), most of the sex chromosomes apart from short recombining regions (humans), to the entire sex chromosome pair, as seen in *Drosophila*. Note that the sex chromosomes are not drawn to scale.
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ZW embryos develop into males when incubated at high temperatures, and sex reversal is accompanied with substantial methylation modification of genes in the sex determination pathway [47].

ESD is favored over GSD when specific environments are more beneficial to one sex [3], selecting for sex-determining mechanisms that match each sex to its best environment. For example, in some gobies and wrasses, nest sites are limited, and a male's ability to defend his nest depends on body size; individuals tend to start life as females, and only become males once they are sufficiently large to successfully defend a nesting site [48]. The reverse transition, from ESD to GSD, is thought to be favored when the environment is unpredictable or not variable enough, in which case ESD could produce strongly skewed sex ratios or intersex individuals [3]. Indeed, snow skinks, which are small, live-bearing lizards, have different sex-determining mechanisms in different environments. ESD occurs at low altitudes where early birth is advantageous for females and the variance in temperature between years is low. GSD predominates at high altitudes where there is no advantage for early-born females and between-year variance in temperature is high [49]. In this situation, ESD produces optimal sex ratios at low elevations, while GSD prevents extreme sex ratios at high altitudes. Importantly, global climate change poses a threat to species with temperature-dependent sex determination if they cannot adapt rapidly enough to avoid biased sex ratios [50]. Another threat to ESD systems comes from within: they may be prone to invasion by genetic elements that favor biased sex ratios (see below).

Genomic conflict and transitions in sex determination

More generally, selection on the sex ratio can trigger transitions between and among different ESD and GSD systems [3]. Sex-biased inheritance patterns of different genetic elements—such as sex chromosomes, organelles, or endosymbionts—create a conflict over which sex is preferred, and can drive the evolution of male- or female-biased sex ratios. In populations with a skewed sex ratio, selection on autosomal genes typically favors equal investment in males and females [51,52], and a new GSD or ESD system can become established if it restores a more even sex ratio. An equal number of males and females is, however, not always favored, even among autosomal genes (e.g., with local mate competition, [53]). In this case, selection for biased sex ratios can favor the establishment of a new sex-determining system [54].

Many examples are known of sex chromosomes, organelles, and endosymbionts that bias the primary sex ratio. Meiotic drive, where genetic elements bias the proportion of gametes that carry them, can create male-biased sex ratios if they are located on the Y or Z chromosomes (as seen in many *Drosophila* species [55]), whereas driving X or W chromosomes create female-biased sex ratios (found in *D. simulans* [56], stalk-eyed flies [57], and rodents [58]); autosomal genes that restore unbiased sex ratios are known in many systems. Cyto-nuclear conflict arises because cytoplasmic factors such as mitochondria or chloroplast are often inherited only through the mother, and they favor production of females, while autosomal genes are inherited through both sexes and favor more equal sex ratios. Cytoplasmic male sterility encoded by mitochondria has been widely reported in plants, including maize, petunia, rice, common bean, and sunflower [59], as have nuclear-encoded male fertility restorer genes [60]. Likewise, cellular endosymbionts are only transmitted through the mother and can create maternally inherited female-biased sex ratios; examples include male-killing bacteria in butterflies and *Drosophila* [61,62]. Recurrent invasions of sex ratio distorters and their suppressors can result in rapid transitions among sex determination mechanisms between species, and may be a major force contributing to the diversity of sex-determining mechanisms observed across the tree of life.

Turnover of sex chromosomes

In species with genotypic sex determination, the chromosome pair that determines sex can change rapidly over time. Transitions are particularly likely when the ancestral sex chromosome exhibits little genetic differentiation, since WW or YY combinations are then less likely to be lethal (Figure 5). New sex-determining genes (or copies of the original gene in a new location) can lead to transitions within and between different XY and ZW systems (Figure 5). Invasions of sex-deter-

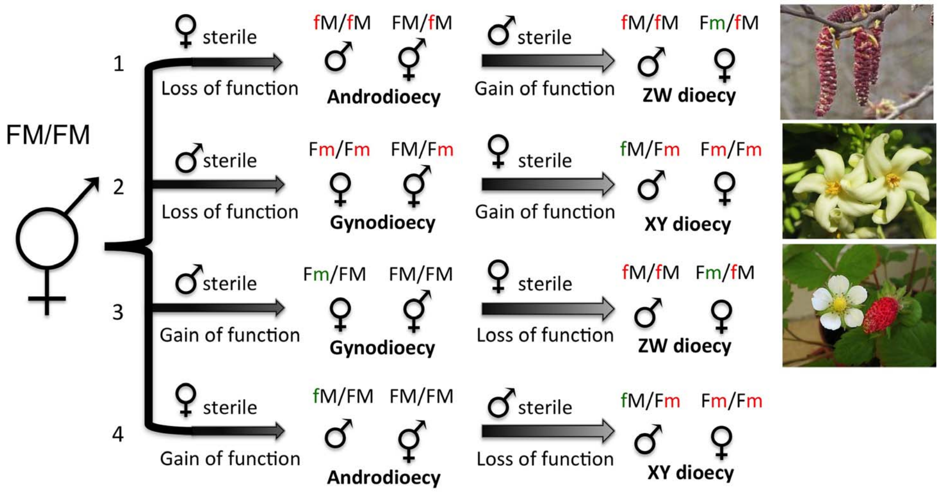

Figure 2. Evolutionary pathways from hermaphroditism to separate sexes. Shown are two-step pathways involving intermediate male- and female-sterile individuals. Loss-of-function mutations (red) are assumed to be recessive, while gain-of-function mutations (green) are assumed to be dominant. Ancestral alleles are in black. M, male fertility allele; m, male sterility mutation; F, female fertility allele; f, female sterility mutation. Because loss of function mutations (red) are almost 50 times more frequent than gain of function mutations (green) in flowering plants, we would expect pathways 1 (e.g., some poplar species) or 2 (e.g., papaya) to arise earlier. Furthermore, transitions through gynodioecy, pathways 2 and 3 (e.g., strawberry) allow females to completely avoid inbreeding depression, while transitions through androdioecy are more costly because males must compete with hermaphrodites for fertilization and do not have any of their own ovules to fertilize. These theoretical arguments help to account for the prevalence of gynodioecy and the XY chromosome system (via pathway 2) observed in plants; nevertheless, all four pathways may be biologically relevant, although no known examples for pathway 4 currently exist.
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mining genes are facilitated when the new sex-determining gene (or a gene closely linked to it) has beneficial effects on fitness [63].

Sexually antagonistic selection, which occurs when a mutation is beneficial to one sex but detrimental to the other, can also drive transitions between sex determination by different pairs of chromosomes [64,65]. For example, if an allele of an autosomal gene is beneficial to males but harmful to females and becomes linked to a dominant masculinizing mutation, then chromosomes that carry both the male-beneficial and male-dominant alleles create a novel Y that can replace the ancestral mechanisms. Conversely, alleles that benefit females and harm males can create novel W chromosomes when linked to feminizing mutations. Turnover of sex chromosomes can also be triggered by the degeneration of the Y and W chromosome, which commonly follows the cessation of recombination [66,67], and will result in the replacement of a low-fitness Y or W chromosome with a nondegenerate one [68].

Sex determination by the whole genome

In many animals, sex determination involves the entire genome. With haplodiploidy (found in about 12% of animal species, including all ants, wasps, and bees) and paternal genome elimination (found in scale insects), males only transmit their maternal set of genes (see Figure 4; Box 2: Glossary). The loss of the paternal genome in sons benefits mothers but not fathers because these uniparental sons transmit more of a mother's genome to grandchildren than do biparental sons [3]. Females also experience a selective advantage from haplodiploidy (but not paternal genome elimination) because unfertilized eggs can develop and contribute to fitness when mating opportunities are rare.

Despite numerous theoretical predictions for how and why sex determination mechanisms change, many hypotheses remain untested. Only a small proportion of taxa have actually been characterized for their sex determination mechanisms, hindering the use of comparative methods to assess the factors associated with transitions between them. However, because sex determination changes so rapidly in many clades, we can catch these transitions *in action* to test theoretical predictions in a direct, experimental way.

Myth 2 Revisited—Multiple and Various Genes Can Determine Sex

The pathways that control sexual development have been well characterized at the molecular level in *D. melanogaster*, *C. elegans*, and mammals. All three involve a master-switch sex-determining gene, which led to the birth of Myth 2. Although the simplicity of a single master-switch is alluring, this archetype of sex determination is clearly not universal. Below we discuss systems where sex is determined by multiple genes, recent molecular data on the nature and evolution of sex-determining genes, and how sex determination can vary in different parts of the body.

Polygenic sex determination

In some species, sex determination is polygenic. For example, in zebrafish (*Danio rerio*), a key developmental model organism, sex is not controlled by a single master regulator but is instead a quantitative threshold trait with either a male or female outcome, which is determined by multiple regions in the genome [69–71]. While some of those regions contain genes known to play a role in sex determination in other organisms [70], there is an enduring mystery as to how these multiple loci and the environment interact to control downstream sexual differentiation in zebrafish. Zebrafish gonads develop as testes in the absence of signals from germ line cells, suggesting that the factors determining sex may regulate germ cell proliferation [72]. Sex as a threshold trait has been inferred in several other fish [73–75]

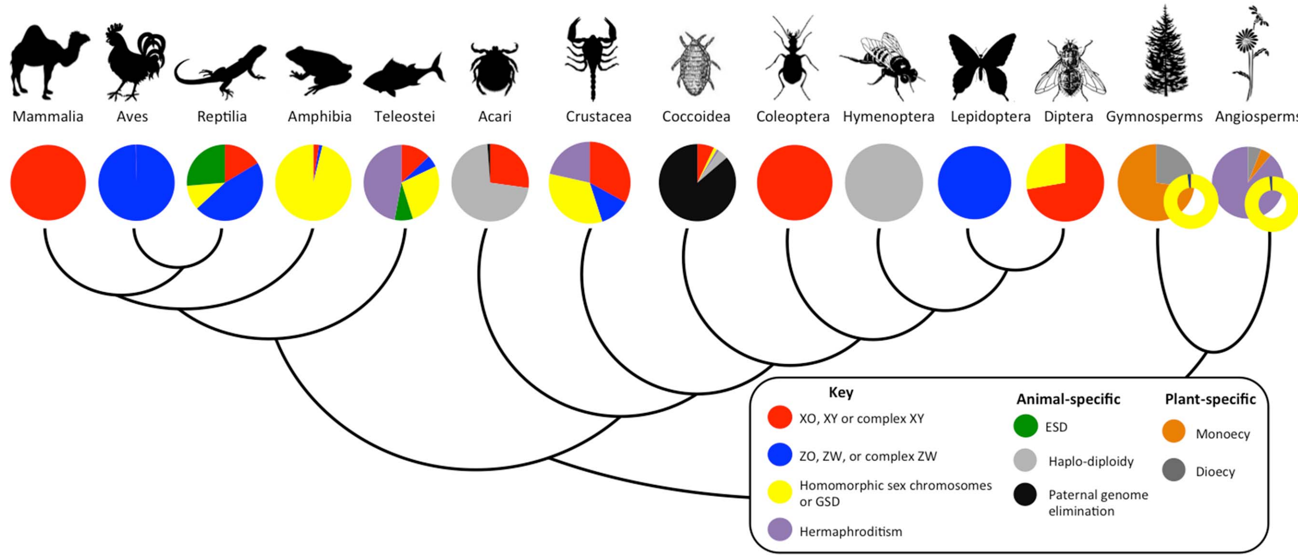

Figure 3. Diversity of sex determination systems for representative plant and animal clades. The bubble insert graph for the plant clades represents the relative proportion of species with documented sex chromosomes within plants with separate sexes. Vertebrates: Mammalia (placental, marsupial, and monotreme mammals), Aves (birds), Reptilia (turtles, snakes, crocodiles, lizards), Amphibia (frogs, toads, salamanders), and Teleostei (bony fishes). Invertebrates: Acari (mites and ticks), Crustacea (shrimps, barnacles, crabs), and Insects, which include Coccoidea (scale insects), Coleoptera (beetles), Hymenoptera (ants, bees, and wasps), Lepidoptera (butterflies), and Diptera (flies). Plants: Gymnosperms (non-flowering plants) and Angiosperms (flowering plants).
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and invertebrates [76], and further examples of multiple interacting loci controlling sex determination are no doubt waiting to be described. Indeed, in taxa where separate sexes evolved recently from a hermaphrodite ancestor, as is common in plants, multiple sex-determining loci are in fact expected, since at least two independent mutations—one suppressing male function, one suppressing female function—are necessary to produce separate sexes from a hermaphrodite (Figure 2). If separate sexes evolve by gradual increase in sexual investment from a hermaphrodite, sex determination may also be due to polygenic inheritance.

The nature and evolution of sex-determining genes and pathways

Some taxa have master-switch sex-determining genes that are highly conserved, such as the *Sry* gene in nearly all mammals [77]. In other lineages, such as fish from the genus *Oryzias* [78–80], the master-switch gene differs among closely-related species (Table 1). There is some empirical evidence for the repeated use of the same master sex determination switch genes in animals. For example, in vertebrates other than mammals, *dmrt1* (a DM family gene) and its paralogs act as the primary sex determination signal in African clawed frog (*Xenopus laevis*) [13], chicken (*Gallus gallus*) [12], medaka fish (*Oryzias latipes*) [78,79], and possibly the smooth tongue sole (*Cynoglossus semilaevis*) [14]. In insects, paralogs of *transformer* (*tra*), a key gene in the sex determination cascade of *Drosophila*, have evolved as the primary switch in houseflies *Musca domestica* [17], as well as the haplodiploid wasp *Nasonia vitripennis* [15] and the honeybee *Apis mellifera* [16].

These data suggest that there are constraints on the types of genes that can be co-opted as master sex determination genes [81]. Nevertheless, there are several cases of switch genes with no homologs in closely related taxa. These include an immunity-related gene in rainbow trout (*Oncorhynchus mykiss*) [82] and *Sxl* in *Drosophila* [83], whose ortholog has a non-sex-related function in mRNA splicing in other flies [84]. The primary master sex-determining gene in the silkworm *Bombyx mori* is a W-derived female-specific piRNA (produced from a piRNA precursor termed *Fem*) that targets a Z-linked gene (named *Masc*), and silencing of *Masc* mRNA by *Fem* piRNA is required for female development [85]. Undoubtedly, many other sex determination genes remain to be found, making it unclear at present whether there truly are constraints on the types of genes that could evolve to be master control switches.

No master sex determination gene has been identified in dioecious plants, but genes that affect flower sex determination have been found [86,87]. Indeed, many genes may serve as potential targets for sex determination in plants, given that male or female sterility can evolve in various ways [86]. For example, 227 male-sterility genes have been identified in rice, with at least one male-sterility gene found on each of rice's 12 chromosomes—hence each autosome could, in principle, evolve a sex-determining function [88]. This abundance and diversity within a single species indicates that the initial evolution of separate sexes is unlikely to be limited to a scant handful of master genes.

In sharp contrast with the diversity of primary sex-determining signals, some key regulatory genes play conserved roles in the molecular pathways leading to male or female gonad development across invertebrates and vertebrates, such as the *doublesex-mab3* (DM) family genes [89,90]. Despite profound differences in the mode of sex determination and the identity of the master-switch genes, DM genes are specifically expressed in the developing gonads of almost all animals, including vertebrates (mammals [91], birds [92], turtles and alligators [93–95], amphibians [96], and fish [97]) and invertebrates (*Drosophila* [98], hymenoptera [99], crustaceans

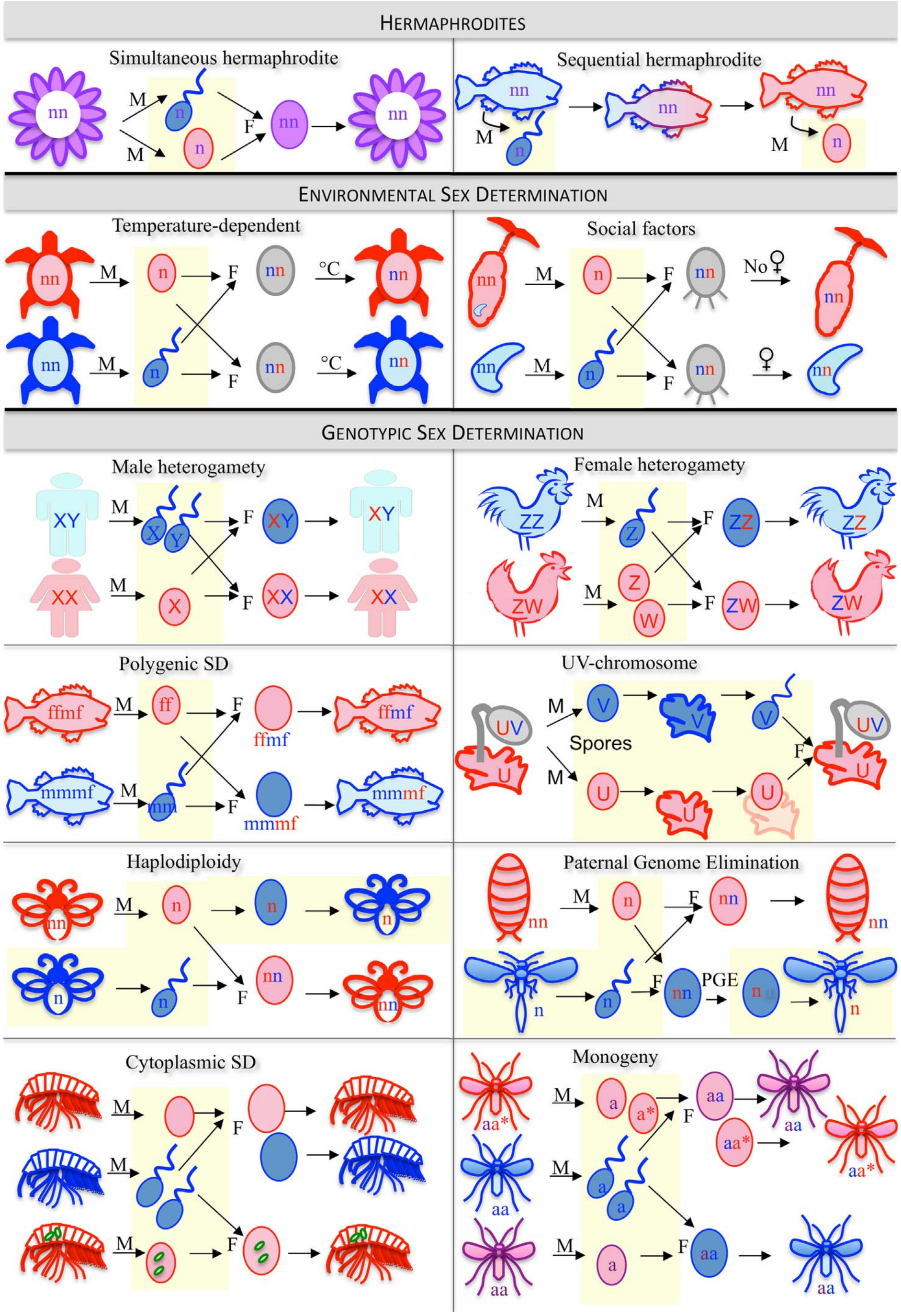

Figure 4. Schematic overview of some sex determination (SD) mechanisms. M refers to meiosis, F to fertilization. Haploid stages (n) are indicated as shaded areas and diploid stages (nn) are unshaded. **Hermaphrodites:** Most flowering plants (and gastropods and earthworms) simultaneously contain both male and female sexual organs (*simultaneous hermaphrodites*). Many fish and some gastropods and plants are *sequential hermaphrodites*; clownfish, for example, are born males and change into females, while many wrasses or gobies begin life as females and then change to males. **Environmental Sex Determination:** In turtles and some other reptiles, sex is determined by incubation temperature of the eggs (*temperature-dependent sex determination*). *Social factors* can act as primary sex-determining cues: sexually undifferentiated larvae of the marine green spoonworm that land on unoccupied sea floor develop into females (and grow up to 15 cm long), while larvae that come into contact with females develop into tiny males (1–3 mm long) that live inside the female. **Genotypic Sex Determination:** Almost all mammals and beetles, many flies and some fish have *male heterogamety* (XY sex chromosomes), while *female heterogamety* (ZW sex chromosomes) occurs in birds, snakes, butterflies, and some fish. In mosses or liverworts, separate sexes are only found in the haploid phase of the life cycle of an individual (*UV sex chromosomes*). In some flowering plants and fish, such as zebrafish, sex is determined by multiple genes (*polygenic sex determination*). In bees, ants, and wasps, males develop from unfertilized haploid eggs, and females from fertilized diploid eggs (*haplodiploidy*), while males of many scale insects inactivate or lose their paternal chromosomes (*paternal genome elimination*). In some species, sex is under the control of cytoplasmic elements, such as intracellular parasites (e.g., *Wolbachia*) in many insects or mitochondria in many flowering plants (*cytoplasmic sex determination*). In some flies and crustaceans, all offspring of a particular individual female are either exclusively male or exclusively female (*monogeny*).
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[100,101], and mollusks [102,103]). Thus, the evolution of sex-determining pathways, at least in animals, appears to occur by the recruitment of new master-switches controlling sexual fate, while the downstream developmental pathways that regulate gonadal differentiation are retained [10,81,104], although the function of some of these downstream elements appears to diverge among lineages [105]. Characterization of polygenic sex determination systems and identification of master sex determination genes across kingdoms will provide insight into the mechanistic constraints limiting the evolution of sex determination pathways.

Sex determination: soma vs. germ line

Sex determination can also differ with respect to where in the body sex is determined. In humans, sex is determined in the developing gonad, and gonadal sex hormones in turn trigger sex determination and differentiation in nongonadal tissues. By contrast, in birds, *Drosophila*, and nematodes [106–109], sexual differentiation is a cell-autonomous process, although secreted signaling molecules can play a role in generating sexual dimorphism in somatic tissues. Studies in *Drosophila* have shown that only a subset of cells express the genes of the sex determination cascade and have a sexual identity [106]. Cell-autonomous sex determination can result in the formation of gynandromorphs—individuals that contain both male and female characteristics, found in birds and many insects, including butterflies and beetles. Sex determination can also be regulated differently in the soma versus the germ line of the same species [110,111]. In houseflies [112] and some frogs [113] and fish [114–116], transplantation experiments indicate that the sex of germ cells depends on the surrounding soma, i.e., XX germ cells transplanted into male soma form sperm, and XY germ cells transplanted in a female soma form oocytes. In contrast, germ cells in *Drosophila* [117] and mammals [118] receive signals from the surrounding somatic gonad, but they also make an autonomous decision during germ line sexual development; this may also be true for chickens [107]. In these animals, the "sex" of the soma must match the "sex" of the germ cells for proper gametogenesis to occur. If XX germ cells are transplanted into male soma they do not form sperm, and XY germ cells transplanted into female soma fail to form oocytes.

Myth 3 Revisited—Sex Chromosomes' Eternal Youth

Heteromorphic sex chromosomes evolve from autosomes that are initially identical but then stop recombining and differentiate. Recombination suppression is favored when it links together sexually antagonistic alleles and sex-determining loci (i.e., a male-beneficial allele and a male-determining gene on a Y chromosome, or a female-beneficial allele and a female-determining gene on a W chromosome). A side effect of repressed recombination on Y and W chromosomes is that natural selection is inefficient (reviewed in [4,5]), which can result in the loss of most of their genes. Y or W degeneration has occurred in many animal taxa with heteromorphic sex chromosomes, including mammals [119], many birds [120], snakes [121], and many insects [122,123], along with some plants, including *Rumex* [124]. In the most extreme cases, the Y or W is entirely lost, resulting in so-called X0 and Z0 systems. According to Myth 3, differentiation of sex chromosomes is evolutionarily inevitable, and the degree of heteromorphism reflects their age (Figure 5). However, as we explain below, evidence from a broad array of organisms indicates that the link between sex chro-

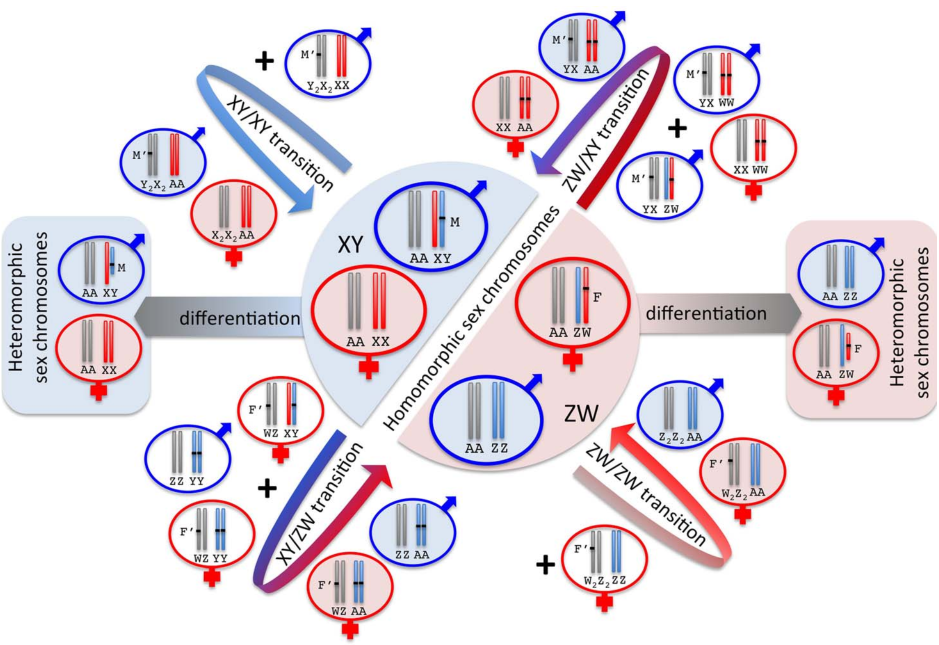

Figure 5. Transitions versus differentiation of sex chromosomes. Transitions between homomorphic sex chromosomes result from new masculinizing (M′) or feminizing (F′) mutations that invade an existing XY or ZW system to create a new chromosome pair (in grey) that harbors the sex-determining gene (additional transitional karyotypes are indicated by unshaded circles). XY→XY transitions result in the loss of the ancestral Y (and ZW→ZW transitions cause loss of the ancestral W). Transitions between XY and ZW systems result in some offspring that are homozygous for the Y (blue) or W (red) chromosome and are thus more likely if the chromosomes have similar gene content but become increasingly difficult if these chromosomes have degenerated (side boxes on left and right), causing YY and WW individuals to be less fit.
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Box 2. Glossary of Sex-Determining Mechanisms

- Hermaphrodites: individuals that contain both male and female sex organs.
- Simultaneous hermaphroditism: male and female sexual organs coexist in one individual (e.g., most flowering plants and earthworms, many terrestrial gastropods).
- Sequential hermaphroditism: individuals change sex at some point during their life (e.g., many fish, snails, and some plants).
- Dioecy (plants) or gonochorism (animals): individuals are either male or female throughout their life.
- Environmental sex determination: sex is triggered by environmental cues, such as temperature, pH, social interactions, and seasonality (e.g., many reptiles and some fish).
- Genotypic sex determination: an individual's sex is established by its genotype (e.g., mammals, birds, amphibians, most insects, some reptiles and fish, and some plants).
- Male heterogamety: type of genotypic sex determination in which males are heterozygous for the sex-determining locus (termed X and Y, as seen in therian mammals and *Drosophila*).
- Female heterogamety: type of genotypic sex determination in which females are heterozygous for the sex-determining locus (termed Z and W, as seen in birds, snakes, butterflies, and gingko trees).
- UV sex determination: separate sexes are only found in the haploid phase of the life cycle of an individual (e.g., mosses or liverworts).
- Polygenic sex determination: sex is determined by multiple genes (e.g., some fish and flowering plants).
- Haplodiploidy: males develop from unfertilized, haploid eggs, and females from fertilized, diploid eggs (e.g., bees, ants, and wasps).
- Paternal genome elimination: paternal chromosomes in males are inactivated or lost after fertilization, leaving males functionally haploid (e.g., many scale insects).
- Cytoplasmic sex determination: sex is under the control of cytoplasmic elements, such as intracellular parasites (e.g., *Wolbachia* in many insects) or mitochondria (e.g., cytoplasmic male sterility in flowering plants).
- Monogeny: all offspring of a particular individual female are either exclusively male or exclusively female (e.g., some flies and crustaceans).
- Sexual reproduction: the mixing of genomes via meiosis and fusion of gametes.
- Sex: the sexual phenotype of an individual.
- Sex determination: the mechanism by which the sexual phenotype of an individual is established in a given species.
- Sex chromosome: a chromosome involved with determining the sex of an individual.
- Autosome: a chromosome not involved with determining the sex of an individual (i.e. any chromosome that is not a sex chromosome).
- Y degeneration: the loss of genetic information on the non-recombining Y chromosome.
- Homomorphic sex chromosomes: sex chromosomes that are morphologically indistinguishable.
- Heteromorphic sex chromosomes: sex chromosomes that are morphologically distinct.
- Sexually antagonistic selection: selection for a trait that benefits one sex to the detriment of the other sex.
- Gynodioecy: a breeding system that consists of a mixture of females and hermaphrodites.
- Androdioecy: a breeding system that consists of a mixture of males and hermaphrodites.
- Meiotic drive (also called segregation distortion): a system in which genetic elements termed segregation distorters bias the proportion of gametes that carry them, resulting in over- or under-representation of one gametic type (i.e. non-mendelian segregation).
- Nucleo-cytoplasmic conflict: conflict in inheritance patterns between the nuclear genome and organelle genomes that are transmitted only maternally.
- Gynandromorphs: individuals that contain both male and female characteristics.

mosome heteromorphism and age is often far from direct.

Not all sex chromosomes become differentiated

Differentiation is often seen as the default path of sex chromosome evolution, but contrary to Myth 3, some ancient sex chromosomes recombine and are undifferentiated over most of their length. Examples are found in python snakes and ratite birds, whose homomorphic sex chromosomes are about 140 and 120 million years old, respectively [121,125,126], i.e. almost as old as the heteromorphic sex chromosomes of therian mammals (about 180 million years old).

How do some ancient sex chromosomes avoid differentiation? One hypothesis is that occasional X-Y recombination purges deleterious alleles on the Y. A mechanism proposed for tree frogs is that XY embryos are occasionally sex-reversed, and so the X and Y recombine when these embryos develop into females [127,128]. Second, some taxa may have few genes under sexually antagonistic selection on their sex chromosomes and thus avoid selection to suppress recombination between the X and Y [129]. Third, sexually antagonistic selection can be resolved by other means, such as the evolution of sex-specific expression [130]. Sexually antagonistic alleles can accumulate along the sex chromosomes, and sex-specific expression will confine the product of such alleles to the sex they benefit, thereby eliminating the selective pressure for recombination suppression. Consistent with this last

Table 1. Known master sex-determining genes in vertebrates and insects, and their paralogs.

Species	Master sex determining gene	Sex-determining mechanisms	Gene paralog	Paralog function	Reference
mammals	*Sry*	sex-determining Y	*Sox3*	HMG-box transcription factor	[77]
chicken (*Gallus gallus*)	*dmrt1*	dose-dependent Z	-	SD pathway transcription factor	[12]
African clawed frog (*Xenopus laevis*)	*dmW*	sex-determining W	*dmrt1*	SD pathway transcription factor	[13]
medaka (*Oryzias latipes*)	*dmrt1Y*	sex-determining Y	*dmrt1*	SD pathway transcription factor	[78,79]
(*Oryzias luzonensis*)	*gsdfY*	sex-determining Y	*gsdf*	secretory protein in SD pathway	[80]
Patagonian pejerrey (*Odontesthes hatcheri*)	*amhY*	sex-determining Y	*amh*	anti-Mullerian hormone	[155]
rainbow trout (*Oncorhynchus mykiss*)	*sdY*	sex-determining Y	*Irf9*	interferon regulatory factor	[82]
tiger pufferfish (*Takifugu rubripes*)	*amhr2*	dose-dependent X	*amhr*	anti-Mullerian hormone receptor	[156]
smooth tongue sole (*Cynoglossus semilaevis*)	*dmrt1*	dose-dependent Z	-	SD pathway	[14]
fruit flies (*Drosophila*)	*Sxl*	dose-dependent X	*CG3056*	mRNA splicing, non-sex specific	[83,84]
housefly (*Musca domestica*)	*F*	sex-determining W	*tra*	SD pathway switch splice factor	[17]
silkworm (*Bombyx mori*)	*Fem*	sex-determining W	-	piRNA	[85]
honeybee (*Apis mellifera*)	*csd*	haplodiploid	*tra*	SD pathway switch splice factor	[16]
wasp (*Nasonia vitripennis*)	*Nvtra*	haplodiploid	*tra*	SD pathway switch splice factor	[15]

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possibility, the recombining, non-differentiated region along the sex chromosomes of the emu (a ratite bird) contains an excess of genes whose expression is sex-biased, relative to autosomes [126].

Y chromosomes are not doomed

Y chromosome degeneration has prompted the suggestion that the human Y will eventually disappear [131–133], a claim based on the naïve assumption of a constant rate of gene loss from the Y over time. However, theory predicts that the rate of gene decay on the Y decreases over evolutionary time and should halt on an old, gene-poor Y chromosome [67,134]. Recent comparative genomic studies support this hypothesis as the gene content of the primate Y chromosome has been stable over the last 25 million years, suggesting that an equilibrium gene content has been reached in humans [135]. Moreover, old gene-poor Y chromosomes that are tens of millions of years old, such as the *Drosophila* Y [136], actually show a net rate of gene gain rather than gene loss [137]. Thus, the Y chromosome can be a stable and important component of the genome in many species, and may even prevent turnover of sex-determining mechanisms (see below).

Evolutionary traps and conserved sex-determining systems

In contrast to the lability of sex determination mechanisms in some groups, eutherian mammals, birds and many insects exhibit virtually no variation in how sex is determined (Figure 3). This stability could be due to an absence of genetic variation, particularly when multiple genetic steps are required for a transition to a new sex-determining system (Figure 2). Mutations are known, however, that override sex determination (Table 1) [138], suggesting that the conservation is not due to a lack of genetic variation. Instead, evolutionary traps may stabilize sex-determining systems for long spans of evolutionary time.

Heteromorphic sex chromosomes may act as just such a trap. Transitions between XY and ZW systems that create YY or WW individuals are prevented when Y or W chromosomes lack essential genes (Figure 5). Also, if the Y (or W) chromosome has evolved sex-essential genes, such as spermatogenesis genes located on the human and *Drosophila* Y, sex chromosome transitions are only possible if these genes are moved to another chromosome, since the old Y, along with its genes, is lost during the transition (Figure 5). Overall, phylogenetic patterns in vertebrates or insects [3,139] are consistent with the notion that heteromorphic sex chromosomes constrain shifts in sex determination mechanism, but several notable exceptions exist in both groups. In rodents, for example, many species with unusual sex-determining systems can be found: XY females in some lemming species, X0 females or XX males in vole species, and X0 females and males in some Japanese spiny rats and mole voles [140]. Likewise, some insect groups are known that harbor variation in sex chromosome karyotype among species; in grasshoppers, fusions between sex-chromosomes and autosomes combined with Y-degeneration and/or Y-loss have created much variation in sex chromosome karyotype, including species with multiple X or Y chromosomes [141]; true fruit flies (Tephritidae) that contain both XY and ZW species [142]; or blowfly species that have secondarily lost their heteromorphic sex chromosomes [143].

How much sex chromosome heteromorphism is required to create a trap, and how strong this trap is, remains unknown. To date, only one example of the reversal of an ancient sex chromosome back to an autosome has been characterized. Specifically, all *Drosophila* species contain an autosome that was formerly an X chromosome: the dot chromosome. This chromosome still has a minor feminizing role during sex determination, is targeted by a chromosome-specific regulatory mechanism similar to dosage compensation of the X, and its patterns of biased gene expression during early embryogenesis, oogenesis, and spermatogenesis resemble that of the current X in *Drosophila* [136]. The retention of the specialized genomic architecture of highly differentiated sex chromosomes on the dot chromosome illustrates the numerous barriers to sex chromosome turnover that exist in highly heteromorphic systems, even though there are some cases where these are overcome.

Haplodiploidy also appears to be an evolutionary trap. While it has arisen a few dozen times, the reverse transition has not been reported [3]. Transitions from or to haplodiploidy require changes in genetic architecture and meiotic mechanisms, which are likely more complex than a simple change in a master-switch sex-determining gene. Furthermore, females switching from haplodiploidy would lose the fitness benefit associated with producing uniparental sons.

Systems that involve interacting somatic and germ line sex determination mechanisms may also limit transitions of sex-determining mechanisms, since changes in either germ line sex or somatic sex alone may produce infertile individuals [111]. Thus, while sex determination is generally characterized by diversity and turnover, some sex-determining systems appear to be more evolutionarily stable than others [3].

Outlook

Studying the forces that drive the evolution of sex determination has mainly come from theoretical works, with little empirical data. However, the genomic revolution has allowed researchers to address scientific questions and tackle novel biological systems at the molecular level. As new genomic approaches increase the pace of discovery and characterization of sex determination innon-model organisms, we anticipate that comparative phylogenetic methods will be key to examining the roles of various ecological and genetic factors that drive changes in sex determination mechanisms. Additionally, genomic data make it increasingly possible to map sex-determining loci from closely related species and to identify the evolutionary mechanisms hypothesized to cause transitions among sex-determining systems. Finally, comparative and functional genomic data will allow researchers to address how new master sex determination genes are incorporated into existing genetic networks controlling sexual development. A full understanding of the diversity of sex determination mechanisms will require that we expand the taxonomic breadth of study systems well beyond classic model organisms. Promising models include dipteran insects, such as houseflies or chironomids; teleost fish; and reptilian clades, including turtles and lizards; as well as plant genera, such as strawberries, that show variation within and between species in how sex (or gender in plants) is determined. Integrative and interdisciplinary approaches across the tree of life will illuminate the diversity of sex determination and yield exciting new insights of how and why sex determination evolves in animals and plants.

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Klinefelter Syndrome (KS)

KS describes a set of physical, language, and social development symptoms in males who have an extra X chromosome. Its main feature is infertility. Outward signs of KS can be subtle, so symptoms often are not recognized, and may not be treated in a timely manner. The NICHD is one of many federal agencies and NIH Institutes working to understand KS, discover why it occurs, and identify and treat its symptoms.

Common Name

- Klinefelter syndrome

Medical or Scientific Names

- Klinefelter syndrome
- 47,XXY
- XXY syndrome or condition
- XXY trisomy
- 47,XXY/46,XY or mosaic syndrome (rare variation)
- Poly-X Klinefelter syndrome, including the following rare variations:
  - 48,XXYY (or tetrasomy)
  - 48,XXXY (or tetrasomy)
  - 49,XXXXY (or pentasomy)

Klinefelter Syndrome (KS): Condition Information

What is KS?

The term "Klinefelter (pronounced *KLAHYN-fel-ter*) syndrome," or KS, describes a set of features that can occur in a male who is born with an extra X chromosome (pronounced *KROH-muh-sohm*) in his cells. It is named after Dr. Henry Klinefelter, who identified the condition in the 1940s.[1 (/health/topics/klinefelter/conditioninfo/Pages/Default.aspx#f1)]

Usually, every cell in a male's body, except sperm and red blood cells, contains 46 chromosomes. The 45th and 46th chromosomes—the X and Y chromosomes—are sometimes called "sex chromosomes" because they determine a person's sex. Normally, males have one X and one Y chromosome, making them XY. Males with KS have an extra X chromosome, making them XXY.

KS is sometimes called "47,XXY" (47 refers to total chromosomes) or the "XXY condition." Those with KS are sometimes called "XXY males."

Some males with KS may have both XY cells and XXY cells in their bodies. This is called "mosaic" (*mo-ZAY-ik*). Mosaic males may have fewer symptoms of KS depending on the number of XY cells they have in their bodies and where these cells are located. For example, males who have normal XY cells in their testes may be fertile. [2] (/health/topics/klinefelter/conditioninfo/Pages/Default.aspx#f2)

In very rare cases, males might have two or more extra X chromosomes in their cells, for instance XXXY or XXXXY, or an extra Y, such as XXYY. This is called poly-X Klinefelter syndrome, and it causes more severe symptoms.[1] (/health/topics/klinefelter/conditioninfo/Pages/Default.aspx#f1)

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What causes it? (/health/topics/klinefelter/conditioninfo/Pages/causes.aspx) »

What causes Klinefelter syndrome (KS)?

The extra chromosome results from a random error that occurs when a sperm or egg is formed; this error causes an extra X cell to be included each time the cell divides to form new cells. In very rare cases, more than one extra X or an extra Y is included.

« Condition Information (/health/topics/klinefelter/conditioninfo/Pages/Default.aspx)
How many people are affected/at risk?
(/health/topics/klinefelter/conditioninfo/Pages/risk.aspx) »

How many people are affected by or at risk for Klinefelter syndrome (KS)?

Researchers estimate that 1 male in about 500 newborn males has an extra X chromosome, making KS among the most common chromosomal disorders seen in all newborns.[1] (/health/topics/klinefelter/conditioninfo/Pages/risk.aspx#f1) The likelihood of a third or fourth X is much rarer: 2 (/health/topics/klinefelter/conditioninfo/Pages/risk.aspx#f2)

Prevalence of Klinefelter syndrome variants

Number of extra X chromosomes	One (XXY)	Two (XXXY)	Three (XXXXY)
Number of newborn males with the condition	1 in 500	1 in 50,000	1 in 85,000 to 100,000

Scientists are not sure what factors increase the risk of KS. The error that produces the extra chromosome occurs at random, meaning the error is not hereditary (pronounced *huh-RED-i-ter-ee*) or passed down from parent to child. Research suggests that older mothers might be slightly more likely to have a son with KS. However, the extra X chromosome in KS comes from the father about one-half of the time.[3] (/health/topics/klinefelter/conditioninfo/Pages/risk.aspx#f3)

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« What causes it? (/health/topics/klinefelter/conditioninfo/Pages/causes.aspx)
What are common symptoms? (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx) »

What are common symptoms of Klinefelter syndrome (KS)?

Because XXY males do not really appear different from other males and because they may not have any or have mild symptoms, XXY males often don't know they have KS.[1 (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f1), 2 (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f2)]

In other cases, males with KS may have mild or severe symptoms. Whether or not a male with KS has visible symptoms depends on many factors, including how much testosterone his body makes, if he is mosaic (with both XY and XXY cells), and his age when the condition is diagnosed and treated.

KS symptoms fall into these main categories:

- Physical Symptoms (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#physical)
- Language and Learning Symptoms (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#language)
- Social and Behavioral Symptoms (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#social)
- Symptoms of Poly-X KS (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#polyx)

Physical Symptoms

Many physical symptoms of KS result from low testosterone levels in the body. The degree of symptoms differs based on the amount of testosterone needed for a specific age or developmental stage and the amount of testosterone the body makes or has available.

During the first few years of life, when the need for testosterone is low, most XXY males do not show any obvious differences from typical male infants and young boys. Some may have slightly weaker muscles, meaning they might sit up, crawl, and walk slightly later than average. For example, on average, baby boys with KS do not start walking until age 18 months.[3 (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f3)]

After age 5 years, when compared to typically developing boys, boys with KS may be slightly:

- Taller
- Fatter around the belly
- Clumsier
- Slower in developing motor skills, coordination, speed, and muscle strength

Puberty for boys with KS usually starts normally. But because their bodies make less testosterone than non-KS boys, their pubertal development may be disrupted or slow. In addition to being tall, KS boys may have:

- Smaller testes and penis
- Breast growth (about one-third of teens with KS have breast growth)
- Less facial and body hair
- Reduced muscle tone
- Narrower shoulders and wider hips
- Weaker bones, greater risk for bone fractures
- Decreased sexual interest
- Lower energy
- Reduced sperm production

An adult male with KS may have these features:

- Infertility: Nearly all men with KS are unable to father a biologically-related child without help from a fertility specialist.[4] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f4)
- Small testes, with the possibility of testes shrinking slightly after the teen years[5] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f5)
- Lower testosterone levels, which lead to less muscle, hair, and sexual interest and function
- Breasts or breast growth (called gynecomastia, pronounced *GUY-nuh-kow-mast-ee-uh*).

In some cases, breast growth can be permanent, and about 10% of XXY males need breast-reduction surgery.[6] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f6)

Language and Learning Symptoms

Most males with KS have normal intelligence quotients (IQs)[7] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f7),[8] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f8) and successfully complete education at all levels. (IQ is a frequently used intelligence measure, but does not include emotional, creative, or other types of intelligence.) Between 25% and 85% of all males with KS have some kind of learning or language-related problem, which makes it more likely that they will need some extra help in school. Without this help or intervention, KS males might fall behind their classmates as schoolwork becomes harder.

KS males may experience some of the following learning and language-related challenges:[9] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f9)

- **A delay in learning to talk**. Infants with KS tend to make only a few different vocal sounds. As they grow older, they may have difficulty saying words clearly. It might be hard for

them to distinguish differences between similar sounds.
- **Trouble using language to express their thoughts and needs.** Boys with KS might have problems putting their thoughts, ideas, and emotions into words. Some may find it hard to learn and remember some words, such as the names of common objects.
- **Trouble processing what they hear**. Although most boys with KS can understand what is being said to them, they might take longer to process multiple or complex sentences. In some cases, they might fidget or "tune out" because they take longer to process the information. It might also be difficult for KS males to concentrate in noisy settings. They might also be less able to understand a speaker's feelings from just speech alone.
- **Reading difficulties.** Many boys with KS have difficulty understanding what they read (called poor reading comprehension). They might also read more slowly than other boys.

By adulthood, most males with KS learn to speak and converse normally, although they may have a harder time doing work that involves extensive reading and writing.

Social and Behavioral Symptoms

Many of the social and behavioral symptoms in KS may result from the language and learning difficulties. For instance, boys with KS who have language difficulties might hold back socially and could use help building social relationships.

Boys with KS, compared to typically developing boys, tend to be:

- Quieter
- Less assertive or self-confident
- More anxious or restless
- Less physically active
- More helpful and eager to please
- More obedient or more ready to follow directions

In the teenage years, boys with KS may feel their differences more strongly. As a result, these teen boys are at higher risk of depression, substance abuse, and behavioral disorders. Some teens might withdraw, feel sad, or act out their frustration and anger.

As adults, most men with KS have lives similar to those of men without KS. They successfully complete high school, college, and other levels of education. They have successful and meaningful careers and professions. They have friends and families.

Contrary to research findings published several decades ago, males with KS are no more likely to have serious psychiatric disorders or to get into trouble with the law.[10] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f10)

Symptoms of Poly-X KS[11] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f11)

Males with poly-X Klinefelter syndrome have more than one extra X chromosome, so their symptoms might be more pronounced than in males with KS. In childhood, they may also have seizures, crossed eyes, constipation, and recurrent ear infections. Poly-KS males might also show slight differences in other physical features.

Some common additional symptoms for several poly-X Klinefelter syndromes are listed below.

48,XXYY

- Long legs
- Little body hair
- Lower IQ, average of 60 to 80 (normal IQ is 90 to 110)
- Leg ulcers and other vascular disease symptoms
- Extreme shyness, but also sometimes aggression and impulsiveness

48,XXXY (or tetrasomy)

- Eyes set further apart
- Flat nose bridge
- Arm bones connected to each other in an unusual way
- Short
- Fifth (smallest) fingers curve inward (clinodactyly, pronounced *KLAHY-noh-dak-tl-ee*)
- Lower IQ, average 40 to 60
- Immature behavior

49,XXXXY (or pentasomy)

- Low IQ, usually between 20 and 60
- Small head
- Short
- Upward-slanted eyes
- Heart defects, such as when the chambers do not form properly[12] (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx#f12)
- High feet arches
- Shy, but friendly
- Difficulty with changing routines

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« How many people are affected/at risk? (/health/topics/klinefelter/conditioninfo/Pages/risk.aspx)
What are the treatments? (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx) »

What are the treatments for symptoms in Klinefelter syndrome (KS)?

It's important to remember that because symptoms can be mild, many males with KS are never diagnosed ore treated.[1] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f1)

The earlier in life that KS symptoms are recognized and treated, the more likely it is that the symptoms can be reduced or eliminated.[2] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f2) It is especially helpful to begin treatment by early puberty. Puberty is a time of rapid physical and psychological change, and treatment can successfully limit symptoms. However, treatment can bring benefits at any age.

The type of treatment needed depends on the type of symptoms being treated.

Treating Physical Symptoms (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#physical)
Treating Language and Learning Symptoms (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#language)
Treating Social and Behavioral Symptoms (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#social)

Treating Physical Symptoms

Treatment for Low Testosterone[3] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f3)

About one-half of XXY males' chromosomes have low testosterone levels.[4] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f4) These levels can be raised by taking supplemental testosterone. Testosterone treatment can:

- Improve muscle mass
- Deepen the voice
- Promote growth of facial and body hair
- Help the reproductive organs to mature
- Build and maintain bone strength and help prevent osteoporosis in later years
- Produce a more masculine appearance, which can also help relieve anxiety and depression
- Increase focus and attention

  There are various ways to take testosterone:

- Injections or shots, every 2 to 3 weeks

- Pills
- Through the skin, also called transdermal (pronounced *tranz-DERM-ul*); current methods include wearing a testosterone patch or rubbing testosterone gel on the skin

Males taking testosterone treatment should work closely with an endocrinologist (pronounced *en-doe-kren-AWL-oh-jist*), a doctor who specializes in hormones and their functions, to ensure the best outcome from testosterone therapy. For information on how to find an endocrinologist, see the Resources and Publications section (/health/topics/klinefelter/resources/Pages/patients.aspx).

Is testosterone therapy right for every XXY male?

Not all males with XXY condition benefit from testosterone therapy.

For males whose testosterone level is low to normal, the benefits of taking testosterone are less clear than for when testosterone is very low. Side effects, although generally mild, can include acne, skin rashes from patches or gels, breathing problems (especially during sleep), and higher risk of an enlarged prostate gland or prostate cancer in older age. In addition, testosterone supplementation will not increase testicular size, decrease breast growth, or correct infertility.

Although the majority of boys with KS grow up to live as males, some develop atypical gender identities. For these males, supplemental testosterone may not be suitable. Gender identity should be discussed with health care specialists before starting treatment.[5] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f5)

Treatment for Enlarged Breasts

No approved drug treatment exists for this condition of over-developed breast tissue, termed gynecomastia. Some health care providers recommend surgery—called mastectomy (pronounced *ma-STEK-tuh-mee*)—to remove or reduce the breasts of XXY males.

When adult men have breasts, they are at higher risk for breast cancer than other men and need to be checked for this condition regularly. The mastectomy lowers the risk of cancer and can reduce the social stress associated with XXY males having enlarged breasts.

Because it is a surgical procedure, mastectomy carries a variety of risks. XXY males who are thinking about mastectomy should discuss all the risks and benefits with their health care provider.

Treatment for Infertility

Between 95% and 99% of XXY men are infertile because they do not produce enough sperm to fertilize an egg naturally. But, sperm are found in more than 50% of men with KS.[6] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f6)

Advances in assistive reproductive technology (ART) have made it possible for some men with KS to conceive. One type of ART, called testicular sperm extraction with intracytoplasmic (pronounced *in-trah-sigh-toe-PLAZ-mick*) sperm injection (TESE-ICSI), has shown success for XXY males. For this procedure, a surgeon removes sperm from the testes and places one sperm into an egg.

Like all ART, TESE-ICSI carries both risks and benefits. For instance, it is possible that the resulting child might have the XXY condition. In addition, the procedure is expensive and is often is not covered by health insurance plans. Importantly, there is no guarantee the procedure will work.

Recent studies suggest that collecting sperm from adolescent XXY males and freezing the sperm until later might result in more pregnancies during subsequent fertility treatments.[7] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f7),[8] (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f8) This is because although XXY males may make some healthy sperm during puberty, this becomes more difficult as they leave adolescence and enter adulthood.

Treating Language and Learning Symptoms

Some, but not all, children with KS have language development and learning delays. They might be slow to learn to talk, read, and write, and they might have difficulty processing what they hear. But various interventions, such as speech therapy and educational assistance, can help to reduce and even eliminate these difficulties. The earlier treatment begins, the better the outcomes.

Parents might need to bring these types of problems to the teacher's attention. Because these boys can be quiet and cooperative in the classroom, teachers may not notice the need for help.

Boys and men with KS can benefit by visiting therapists who are experts in areas such as coordination, social skills, and coping. XXY males might benefit from any or all of the following:

- **Physical therapists** design activities and exercises to build motor skills and strength and to improve muscle control, posture, and balance.
- **Occupational therapists** help build skills needed for daily functioning, such as social and play skills, interaction and conversation skills, and job or career skills that match

interests and abilities.

- **Behavioral therapists** help with specific social skills, such as asking other kids to play and starting conversations. They can also teach productive ways of handling frustration, shyness, anger, and other emotions that can arise from feeling "different."
- **Mental health therapists or counselors** help males with KS find ways to cope with feelings of sadness, depression, self-doubt, and low self-esteem. They can also help with substance abuse problems. These professionals can also help families deal with the emotions of having a son with KS.
- **Family therapists** provide counseling to a man with KS, his spouse, partner, or family. They can help identify relationship problems and help patients develop communication skills and understand other people's needs.

Parents of XXY males have also mentioned that taking part in **physical activities at low-key levels**, such as karate, swimming, tennis, and golf, were helpful in improving motor skills, coordination, and confidence.

With regard to education, some boys with KS will qualify to receive state-sponsored special needs services to address their developmental and learning symptoms. But, because these symptoms may be mild, many XXY males will not be eligible for these services. Families can contact a local school district official or special education coordinator to learn more about whether XXY males can receive the following free services:

- The Early Intervention Program for Infants and Toddlers with Disabilities (https://www2.ed.gov/programs/osepeip/legislation.html) is required by two national laws, the Individuals with Disabilities and Education Improvement Act (IDEIA) and the Individuals with Disabilities Education Act (IDEA). Every state operates special programs for children from birth to age 3, helping them develop in areas such as behavior, development, communication, and social play.
- An Individualized Education Plan (IEP (https://www2.ed.gov/parents/needs/speced/iepguide/index.html)) for school is created and administered by a team of people, starting with parents and including teachers and school psychologists. The team works together to design an IEP with specific academic, communication, motor, learning, functional, and socialization goals, based on the child's educational needs and specific symptoms.

Treating Social and Behavioral Symptoms

Many of the professionals and methods for treating learning and language symptoms of the XXY condition are similar to or the same as the ones used to address social and behavioral symptoms.

For instance, boys with KS may need help with social skills and interacting in groups. Occupational or behavioral therapists might be able to assist with these skills. Some school districts and health centers might also offer these types of skill-building programs or classes.

In adolescence, symptoms such as lack of body hair could make XXY males uncomfortable in school or other social settings, and this discomfort can lead to depression, substance abuse, and behavioral problems or "acting out." They might also have questions about their masculinity or gender identity.[9 (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f9)] In these instances, consulting a psychologist, counselor, or psychiatrist may be helpful.

Contrary to research results released decades ago, current research shows that XXY males are no more likely than other males to have serious psychiatric disorders or to get into trouble with the law.[10 (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx#f10)]

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« What are common symptoms? (/health/topics/klinefelter/conditioninfo/Pages/symptoms.aspx)

How is it diagnosed? (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx) »

How do health care providers diagnose Klinefelter syndrome (KS)?

The only way to confirm the presence of an extra chromosome is by a karyotype (pronounced *care-EE-oh-type*) test. A health care provider will take a small blood or skin sample and send it to a laboratory, where a technician inspects the cells under a microscope to find the extra chromosome. A karyotype test shows the same results at any time in a person's life.

Tests for chromosome disorders, including KS, may be done before birth. To obtain tissue or liquid for this test, a pregnant woman undergoes chorionic villus (pronounced *KAWR-ee-on-ik vil-uhs*) sampling or amniocentesis (*am-nee-oh-sen-TEE-sis*).[1] (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx#f1) These types of prenatal testing carry a small risk for miscarriage and are not routinely conducted unless the woman has a family history of chromosomal disorders, has other medical problems, or is above 35 years of age.

Factors that Influence when KS is Diagnosed

Because symptoms can be mild, some males with KS are never diagnosed.[2] (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx#f2)

Several factors affect whether and when a diagnosis occurs:

- Few newborns and boys are tested for or diagnosed with KS.
  - Although newborns in the United States are screened for some conditions, they are not screened for XXY or other sex-chromosome differences.
  - In childhood, symptoms can be subtle and overlooked easily. Only about 1 in 10 males with KS is diagnosed before puberty.[1] (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx#f1)
  - Sometimes, visiting a health care provider will not produce a diagnosis. Some symptoms, such as delayed early speech, might be treated successfully without further testing for KS.
- Most XXY diagnoses occur at puberty or in adulthood.
  - Puberty brings a surge in diagnoses as some males (or their parents) become concerned about slow testes growth or breast development and consult a health care provider.
  - Many men are diagnosed for the first time in fertility clinics.[3] (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx#f3) Among men seeking help for infertility, about 15% have KS;[4] (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx#f4)

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« What are the treatments? (/health/topics/klinefelter/conditioninfo/Pages/treatments.aspx)
Is there a cure? (/health/topics/klinefelter/conditioninfo/Pages/cure.aspx) »

Is there a cure for Klinefelter syndrome (KS)?

Currently, there is no way to remove chromosomes from cells to "cure" the XXY condition.

But many symptoms can be successfully treated, minimizing the impact the condition has on length and quality of life. Most adult XXY men have full independence and have friends, families, and normal social relationships.[1 (/health/topics/klinefelter/conditioninfo/Pages/cure.aspx#f1)] They live about as long as other men, on average.[2 (/health/topics/klinefelter/conditioninfo/Pages/cure.aspx#f2)]

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« How is it diagnosed? (/health/topics/klinefelter/conditioninfo/Pages/diagnosed.aspx)

Other FAQs (/health/topics/klinefelter/conditioninfo/Pages/faqs.aspx) »

Klinefelter Syndrome (KS): NICHD Research Goals

The NICHD has a long history of supporting research to learn more about Klinefelter syndrome. Early research included a study that examined the cells of more than 40,000 infants for extra X chromosomes. NICHD-supported research has also explored topics including the roles of sex chromosomes in development; symptoms that arise in KS such as infertility, low testosterone, and problems with language, learning, and behavior; and how best to treat males with these symptoms. Among the areas of research that hold hope for more successful intervention and prevention in Klinefelter syndrome are studies in the following areas:

- **Genetics of Klinefelter syndrome.** The full extent of the role of the X chromosome in development is not well understood. NICHD research into disorders of the X chromosome, such as Klinefelter, Turner, and Fragile X syndromes, will reveal more about how this chromosome functions and, ultimately, how to prevent or treat symptoms in individuals with an atypical number of X chromosomes. NICHD research also aims to improve understanding of processes that can go wrong in male germ cells before fertilization or right after it, when chromosomes conjugate and divide and can leave the resulting gamete with an unusual number of sex chromosomes.
- **Pathophysiological mechanisms of KS.** KS alters hormonal balance, especially reducing testosterone levels, and exactly how this leads to infertility is unclear. Researchers are studying the mechanisms behind sperm creation and how Leydig cells function, which could identify interventions that may help preserve or restore fertility in males with KS. Investigations also include those on gonadotropin-regulated genes involved in the progression of testicular gametogenesis, Leydig cell function, and other endocrine processes.
- **Treatment strategies for KS.** Research on early interventions has successfully limited the development and severity of symptoms in KS. The NICHD is gathering evidence to identify the best interventions for learning disabilities, osteoporosis (later in life), and infertility—all symptoms of KS.

Klinefelter Syndrome (KS): Research Activities and Scientific Advances

Institute Activities and Advances

KS can influence many aspects of a person's entire life, starting very soon after conception. Therefore, many branches, sections, and laboratories at NICHD conduct research that is relevant to males with XXY or poly-KS variations.

Investigating Sex Chromosomes

KS arises from an unusual number of sex chromosomes, so research into these is important to finding ways to prevent or one day cure KS. Several components of the Division of Intramural Research (/about/org/dir/Pages/index.aspx) are studying these types of problems. The Section on Epigenetics and Development is studying how X chromosome genes influence brain, reproductive, metabolic, and immune system development. The Section on Gamete Development is studying the fruit fly for insight into early gamete cell division and how an additional X chromosome can become included. Other scientists are examining the formation of male germ cells, which are present before and after fertilization and can contain an extra X. In the Section on Clinical Genomics, scientists apply information gained from biochemical and genomic studies to clinical investigations, while also studying the biomechanical mechanisms that may contribute to genetic disorders.

Understanding KS Symptoms and Preventing or Treating Them

Infertility is a key symptom in KS and many researchers at NICHD are involved in improving understanding of how sperm production fails, starting from early in development. In the Section on Clinical Genomics, scientists developed mouse models to analyze proteins that may be key in sperm production. Other research aims to explain the network of genes involved in the renewal and differentiation of spermatogonial stem cells, meiosis, and the post-meiotic differentiation of germ cells. Researchers are also exploring mechanisms behind sperm creation and the function of Leydig cells, which produce testosterone in the presence of luteinizing hormone, and searching for new gonadotropin-regulated genes involved in testicular gametogenesis, Leydig cell function, and other endocrine processes that are disrupted in KS.

Aside from infertility, scientists are working to find ways to treat other symptoms associated with KS. The Child Development and Behavior Branch (CDBB) (/about/org/der/branches/cdbb/Pages/overview.aspx) is examining the behavioral, neurobiological, and genetic aspects of typical development and is focusing on factors that can threaten normal development. CDBB researchers are also studying prevention steps and, where intervention is needed, the most effective conditions and timing. Their findings will have implications for boys with KS, who can have some learning difficulties, such as in processing language.

Researchers in the Pediatric Growth and Nutrition Branch (/about/org/der/branches/pgnb/Pages/overview.aspx) focus on nutritional science, childhood antecedents of adult disease, developmental endocrinology, developmental neuroendocrinology, and physical growth and body composition. Topics relevant to KS males include bone weakness and gender identity issues.

Other Activities and Advances

The projects below also study aspects of health and infertility that might be related to KS.

- The Reproductive Medicine Network (RMN) (/research/supported/Pages/rmn.aspx), founded in 1990, carries out large, multicenter clinical trials of diagnostic and therapeutic interventions for male and female infertility and reproductive diseases and disorders. The network is funded through the NICHD's Fertility and Infertility (FI) Branch (/about/org/der/branches/fi/Pages/overview.aspx) and comprises seven research sites as well as a data coordinating center. The RMN currently has several ongoing clinical studies, including a clinical trial to determine a level of oxygen in culture media that improves live birth rates in couples undergoing *in vitro* fertilization.
- The National Centers for Translational Research in Reproduction and Infertility (NCTRI) (/research/supported/Pages/NCTRI.aspx) (Formerly the Specialized Cooperative Centers Program in Reproduction and Infertility Research [SCCPIR]) is a national network of research-based centers, supported by the FI Branch, that aims to promote interactions between basic and clinical scientists with the goal of improving reproductive health.
- The Learning Disabilities Research Centers Consortium (/research/supported/Pages/ldrc.aspx) includes four centers in Boulder, Houston, Tallahassee, and Seattle that conduct research on the causes and treatment of learning disabilities. Supported by the NICHD's CDBB, the centers emphasize, among other things, reading comprehension—how children understand what they read—which is difficult for some children with KS.
- The Biological Testing Facility, funded under contract with the Contraceptive Discovery and Development Branch (/about/org/der/branches/crb/Pages/overview.aspx), has developed radioimmunoassay tests to accurately measure the impact of hormone

treatment given orally, subcutaneously, or transdermally. In individuals with KS taking testosterone, accurate testing helps determine the appropriate dose.

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Turner Syndrome

Turner syndrome is a condition in which a girl or woman is partially or completely missing an X chromosome. It can cause infertility and heart problems and alter a female's appearance. NICHD plays a leading role in advancing research on Turner syndrome by supporting the investigation of its physical and emotional effects as well as potential therapies.

About Turner Syndrome

Turner syndrome is a disorder caused by a partially or completely missing X chromosome. This condition affects only females.

Most people have 46 chromosomes in each cell—23 from their mother and 23 from their father. The 23rd pair of chromosomes are called the sex chromosomes—X and Y—because they determine whether a person is male or female. Females have two X chromosomes (XX) in most of their cells, and males have one X chromosome and one Y chromosome (XY) in most of their cells. A female with all of her chromosomes is referred to as 46,XX. A male is 46,XY.

Turner syndrome most often occurs when a female has one normal X chromosome, but the other X chromosome is missing (45,X). Other forms of Turner syndrome result when one of the two chromosomes is partially missing or altered in some way.[1]

Citations

1. Turner Syndrome Society. (n.d.). About Turner Syndrome. https://www.turnersyndrome.org/about-turnersyndrome

What are the symptoms of Turner syndrome?

Turner syndrome causes a variety of symptoms in girls and women. For some people, symptoms are mild, but for others, Turner syndrome can cause serious health problems. In general, women with Turner syndrome have female sex characteristics, but these characteristics are underdeveloped compared to the typical female. Turner syndrome can affect:[1]

- **Appearance.** Features of Turner syndrome may include a short neck with a webbed appearance, low hairline at the back of the neck, low-set ears, hands and feet that are swollen or puffy at birth, and soft nails that turn upward.
- **Stature.** Girls with Turner syndrome grow more slowly than other children. Without treatment, they tend to have short stature (around 4 feet, 8 inches) as adults.
- **Puberty.** Most girls with Turner syndrome do not start puberty naturally.
- **Reproduction.** In most girls with Turner syndrome, the ovaries are missing or do not function properly. Without the estrogen made by their ovaries, girls with Turner syndrome will not develop breasts. Most women with Turner syndrome cannot become pregnant without assistive technology.[2]
- **Cardiovascular.** Turner syndrome can cause problems with the heart or major blood vessels. In addition, some women and girls with Turner syndrome have high blood pressure.
- **Kidney.** Kidney function is usually normal in Turner syndrome, but some people with this condition have kidneys that look abnormal.
- **Osteoporosis.** Women with Turner syndrome often have low levels of the hormone estrogen, which can put them at risk for osteoporosis. Osteoporosis can cause height loss and bone fractures.
- **Diabetes.** People with Turner syndrome are at higher risk for type 2 diabetes.
- **Thyroid.** Many people with Turner syndrome have thyroid issues. The most common one is hypothyroidism, or an underactive thyroid gland.
- **Cognitive.** People with Turner syndrome have normal intelligence. Some, however, have challenges learning mathematics or with visual-spatial coordination (such as determining the relative positions of objects in space).

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How many people are affected or at risk of Turner syndrome?

Turner syndrome affects about 1 of every 2,500 female live births worldwide.[1]

This disorder affects all races and regions of the world equally. There are no known environmental risks for Turner syndrome. Parents who have had many unaffected children can still have a child with Turner syndrome later on.

Generally, Turner syndrome is not passed on from mother to child. In most cases, women with Turner syndrome are infertile.

Citations

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What causes Turner syndrome?

Turner syndrome occurs when part or all of an X chromosome is missing from most or all of the cells in a girl's body. A girl normally receives one X chromosome from each parent. The error that leads to the missing chromosome appears to happen during the formation of the egg or sperm.

Most commonly, a girl with Turner syndrome has only one X chromosome. Occasionally, she may have a partial second X chromosome. Because she is missing part or all of a chromosome, certain genes are missing. The loss of these genes leads to the symptoms of Turner syndrome.[1]

Sometimes, girls with Turner syndrome have some cells that are missing one X chromosome (45,X) and some that are normal. This is because not every cell in the body is exactly the same, so some cells might have the chromosome, while others might not. This condition is called mosaicism (pronounced *moh-ZEY-uh-siz-uhm*). If the second sex chromosome is lost from most of a girl's cells, then it's likely that she will have symptoms of Turner syndrome. If the chromosome is missing from only some of her cells, she may have no symptoms or only mild symptoms.

Citations

1. National Human Genome Research Institute. (2011). *Learning about Turner syndrome*. Retrieved June 14, 2012, from https://www.genome.gov/Genetic-Disorders/Turner-Syndrome

How do healthcare providers diagnose Turner syndrome?

Healthcare providers use a combination of physical symptoms and the results of a genetic blood test, called a karyotype, to determine the chromosomal characteristics of the cells in a female's body. The test will show if one of the X chromosomes is partially or completely missing.

Turner syndrome also can be diagnosed during pregnancy by testing the cells in the amniotic fluid. Newborns may be diagnosed after heart problems are detected or after certain physical features, such as swollen hands and feet or webbed skin on the neck, are noticed. Other characteristics, like widely spaced nipples or low-set ears, also may lead to a suspicion of Turner syndrome. Some girls may be diagnosed as teenagers because of a slow growth rate or a lack of puberty-related changes. Still others may be diagnosed as adults when they have difficulty becoming pregnant.[1]

Citations

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What are common treatments for Turner syndrome?

Although there is no cure for Turner syndrome, some treatments can help minimize its symptoms. These include[1]:

- **Human growth hormone.** If given in early childhood, hormone injections can often increase adult height by a few inches.
- **Estrogen replacement therapy (ERT).** ERT can help start the secondary sexual development that normally begins at puberty (around age 12). This includes breast development and the development of wider hips. Healthcare providers may prescribe a combination of estrogen and progesterone to girls who haven't started menstruating by age 15. ERT also provides protection against bone loss.

Regular health checks and access to a wide variety of specialists are important to care for the various health problems that can result from Turner syndrome.[2] These include ear infections, high blood pressure, and thyroid problems.

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The Inexorable Rise of Gender and the Decline of Sex: Social Change in Academic Titles, 1945–2001

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More than 30 million titles of "academic" articles, from the years 1945–2001, were surveyed for occurrences of the words *sex* and *gender*. At the beginning of this period, uses of *gender* were much rarer than uses of *sex*, and often used in the sense of a grammatical category. By the end of this period, uses of *gender* outnumbered uses of *sex* in the social sciences, arts, and humanities. Within the natural sciences, there was now more than 1 use of *gender* for every 2 uses of *sex*. The beginnings of this change in usage can be traced to Money's introduction of the concept of "gender role" in 1955 (J. Money, 1955). However, the major expansion in the use of gender followed its adoption by feminists to distinguish the social and cultural aspects of differences between men and women (gender) from biological differences (sex). Since then, the use of gender has tended to expand to encompass the biological, and a sex/gender distinction is now only fitfully observed.

KEY WORDS: sex; gender; gender role; feminism.

INTRODUCTION

In *The Mill on the Floss*, the novelist George Eliot (Mary Ann Evans) (1860) wrote "Public opinion, in these cases, is always of the feminine gender—not the world, but the world's wife . . ." As this literary example shows, the use of gender as a synonym for sex has a long pedigree and is not a recent aberration as is sometimes claimed. The *Oxford English Dictionary* quotes uses of gender for sex from the fifteenth century, although in the first edition of the Dictionary in 1899 this usage was described as jocular. From the 1950s, however, a trickle of nonjocular uses of gender began to appear in the academic literature and, by the 1980s, this trickle had become a flood.

The most important factor was the adoption of gender in the 1970s by feminist scholars as a way of distinguishing "socially constructed" aspects of male–female differences (gender) from "biologically determined" aspects (sex). This distinction is now only fitfully respected, and gender is often used as a simple synonym of sex. The rise of gender has been accompanied by complaints that the word should refer only to grammatical categories (Fletcher, 1991; Goodhart, 1992; Smyth, 1968) or to socially but not biologically determined differences (Fishman, Wick, & Koenig, 1999; Kim & Nafziger, 2000; Lewine, 1994; Pearson, 1996; Walker & Cook, 1998; Wilson, 2000).

In an attempt to document these changes in usage, I surveyed the titles of over 30 million academic articles, from the years 1945–2001, for occurrences of the words *sex* and *gender*. This work extends a similar analysis by Haig (2000) for the period 1988–1999. The quantitative analysis is followed by a discussion of the shifts in meaning of gender over this period.

METHOD

The ISI Web of Science® is formed from the amalgamation of three databases: the Science Citation Index—Expanded (SCI) contains titles from 1945 until the present; the Social Sciences Citation Index (SSCI) contains titles from 1956 until the present; and the Arts & Humanities Citation Index (AHCI) contains titles from 1975 until the present. The contents of the three databases have considerable overlap. Thus, an article may be indexed in more

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than one database. The combined database contains over 30 million titles for the years 1945–2001.

The titles of all English-language articles in the Web of Science for the years 1945–2001 were searched for occurrences of "sex" and "gender." Such searches retrieved titles that contain hyphenated constructs such as "sex-specific" or "gender-significant" but did not retrieve titles in which sex and gender appear as derived forms, such as "sexual" or "gendered." In total, the searches found 59,262 sex-containing titles and 29,941 gender-containing titles (with some titles belonging to both categories).

The titles of articles in non-English languages often appear in the Web of Science as English translations. These articles were excluded from searches for "sex" and "gender," but I was unable to exclude them from counts of the number of titles being searched. Therefore, whenever I calculated proportions of titles containing "sex" or "gender," the numerator contained English language articles only, but the denominator contained articles in all languages. Most articles in the database are in English, but I do not have a measure of how the proportion of non-English articles has changed over time. This is a potentially confounding factor in the interpretation of Figs. 2–4. However, overall trends were little affected by including or excluding non-English language articles from searches.

Both sex and gender have uses for which the other would rarely, if ever, be substituted. Since the late 1970s, gender in its grammatical sense has contributed a small minority of all gender-containing titles. Of somewhat greater significance are biological uses of sex for which gender is not used (e.g., sex, in the sense of genetic recombination; sex chromosomes; sex hormones). But probably the most important uses of "sex" for which "gender" is not a synonym relate to copulation and other sexual activities (e.g., sex, in the sense of sexual intercourse; anal sex; safe sex; sex worker; sex slave). Such uses contribute a relatively small proportion of sex-containing titles in SCI, but a much greater proportion in SSCI and AHCI. (Analysis of a small sample suggests that about half of all sex-containing titles in SSCI and AHCI for the year 2001 belong in this category. I suspect that the advent of AIDS has increased the frequency of titles in this category, especially in SSCI, but I did not undertake a formal analysis.)

My analysis focused on usage in titles, but fashions in titles may not entirely reflect the content of articles. Articles may use gender in the text without it appearing in the title, or vice versa. In some cases, titles appeared to reflect editorial rather than authorial choices. For example, articles by Rothman and Liess (1976) and Harlap (1979) contained the first nongrammatical uses of gender in titles from the *New England Journal of Medicine* (with the ensuing correspondence, Harlap [1979] contributed six of 33 gender-containing titles in SCI for 1979). In both articles, however, gender appeared in the title but not in the text, where sex was used. Occasionally, tensions came to the surface. Ounsted and Taylor (1972) wrote in their edited volume, "As between the words 'sex' and 'gender' even, while preferring the scope of the latter term, we have accepted our authors' preference for the former where they wish it" (p. vi). Despite this ecumenical principle, "gender" was used in the title of two chapters that used "sex" throughout the text, and the title of a third chapter contained "gender" in the Table of Contents but "sex" at the head of the chapter.

The journals indexed in the databases varied from year to year. Therefore, changes in the number of titles containing a particular word will depend only partly on changes in usage, but will also be influenced by what was and was not included in the database for a particular year. For example, several psychology journals that were covered by both SCI and SSCI in 1977 were no longer covered by SCI in 1978 (e.g., *Child Development*, *Journal of Personality and Social Psychology*). As a result, 28 SCI titles contained gender in 1977 but only nine contained gender in 1978. The latter figure would have been increased to 25 if titles, now included only in SSCI, had still been included in SCI. Thus, a corporate decision at the Institute for Scientific Information® accounted for most of the seemingly anomalous increase in the sex-to-gender ratio of SCI titles in 1978 (Fig. 1), although this factor does not explain the rebound to 33 SCI titles containing gender in 1979.

As another example of changes in coverage, the number of articles included in SSCI increased by 13% between 1994 and 1995. This increase appears to be due to the inclusion of additional journals not previously covered by SSCI. It is possible that the substantial increase in the proportion of titles containing gender that occurred in 1995 (Fig. 3), and the subsequent plateau in this measure, reflected a change in the composition of SSCI rather than any change of usage in the academic community; however, a 25% increase in the number of articles covered by SSCI between 1975 and 1976 does not appear to have affected the relative occurrence of sex and gender. An ideal analysis would separate effects of changes in usage from changes in coverage, but I doubt that such an analysis would change the gross trends detected by the present much simpler, and more easily replicable, analysis.

The databases did not contain book titles, except in book reviews, nor the texts of articles and books. Moreover, it is probable that use of gender in the titles of articles in indexed journals, at first, lagged behind conversational use. My quantitative analysis is restricted to indexed titles. The narrative that follows the quantitative analysis makes use of other published sources that came to light in my readings.

RESULTS

Prior to the late 1960s, nongrammatical uses of gender were exceedingly rare. For the years 1945–1959, 1,685 (.14%) SCI titles out of 1,162,909 contained sex but only five (.0004%) contained gender. Of these, three used gender in a grammatical sense and two were sexological articles, both by Money (Money, 1955; Money, Hampson, & Hampson, 1957).

For the years 1960–1966, 2,094 (.17%) out of 1,253,631 titles in SCI contained sex and eight (.0006%) contained gender, of which three were grammatical uses and five were sexological (including three articles by Money and coauthors). For these same years, 819 (.24%) out of 353,069 titles in SSCI contained sex and 12 (.004%) contained gender (including four articles by Money and coauthors). Four gender-containing titles appeared in both SCI and SSCI.

Figure 1 presents changes in the ratio of sex-containing and gender-containing titles for the years 1966–2001 (from 1975 for AHCI). The ratio is expressed on a logarithmic scale because this is unbiased with respect to whether sex or gender appears in the denominator (i.e., 1:2 and 2:1 ratios are represented as equidistant from 1:1). There was substantial noise in the signal for the early years of this series because of the small number of gender-containing titles.

Some general observations can be made. The sex-to-gender ratio has always been lower in SSCI than in SCI, but this became more pronounced after 1973 when the SSCI initiated a sustained decline in the sex-to-gender ratio, which then leveled off in the 1990s (by which time gender-containing titles outnumbered sex-containing titles). A similar decline in the sex-to-gender ratio for SCI titles did not start until about 1980 and is still continuing. The ratio for AHCI followed closely that of SSCI, but with a slightly stronger preference for gender over sex. The first year for which gender-containing titles exceeded sex-containing titles was 1987 for AHCI and 1990 for SSCI. Sex-containing titles have always outnumbered gender-containing titles in SCI.

In 1993, the United States Food and Drug Administration (FDA) issued a Guideline requiring studies of "gender differences" in all new drug applications (Kessler,

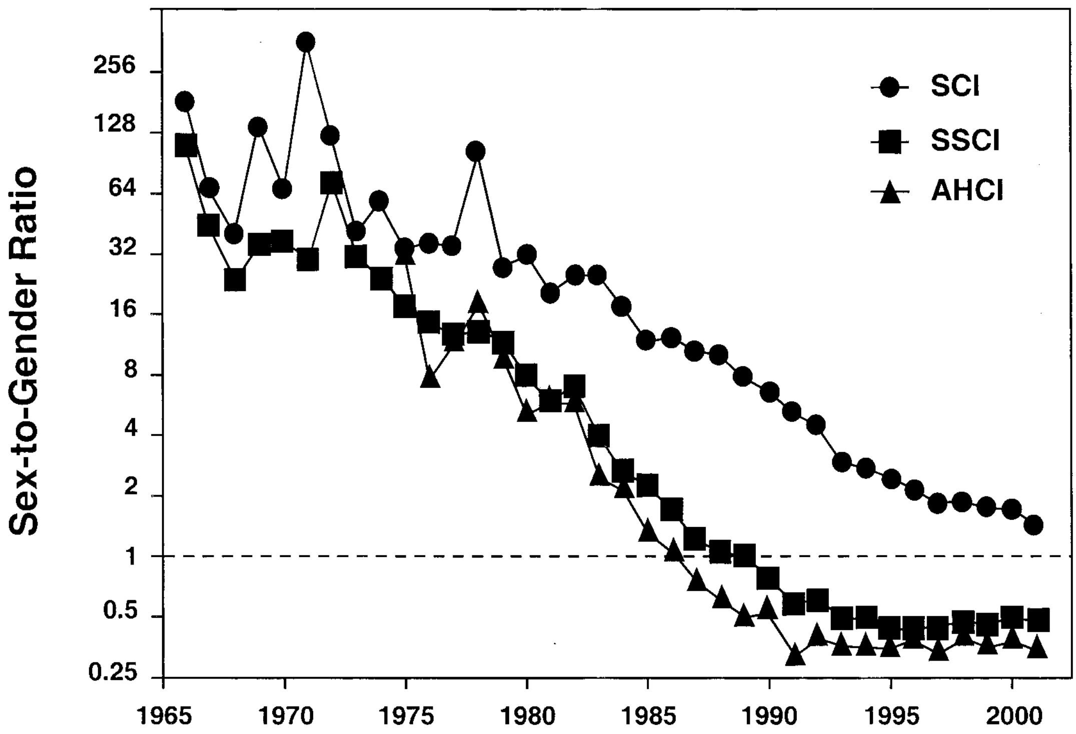

Fig. 1. The ratio of titles containing sex to titles containing gender for all articles in the Science Citation Index (SCI), Social Sciences Citation Index (SSCI), and Arts & Humanities Citation Index (AHCI).

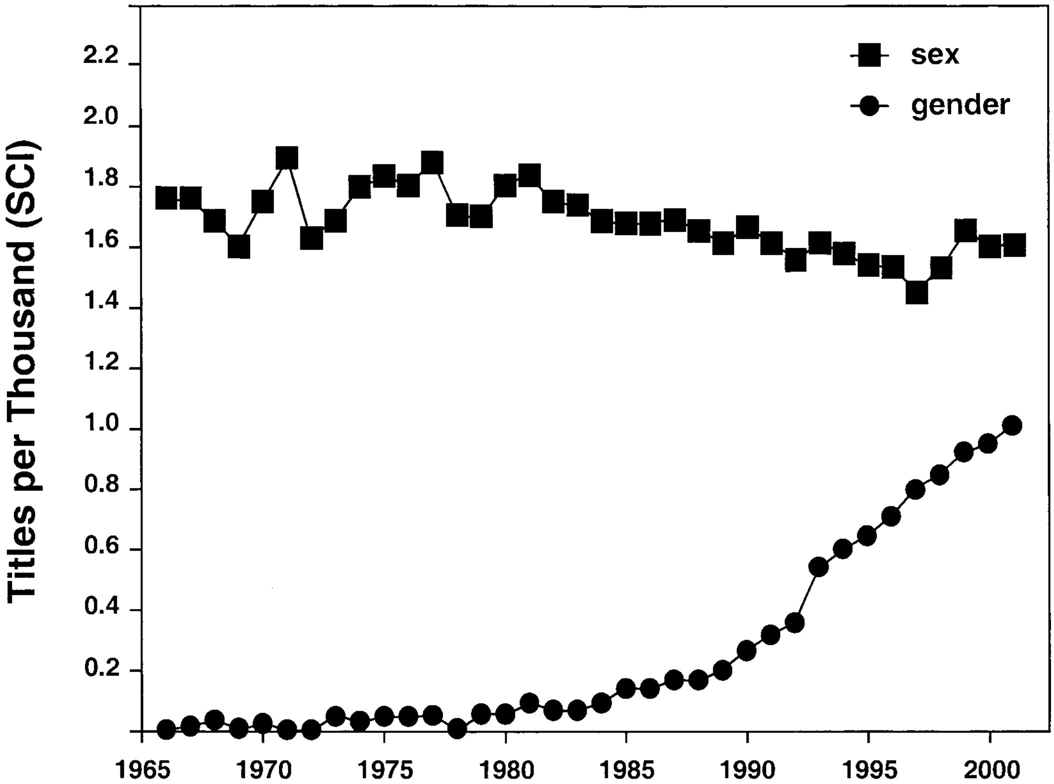

Fig. 2. Proportion of titles in the Science Citation Index containing the word *sex* and proportion containing the word *gender*.

1993). The decline in the sex-to-gender ratio in SCI began years before this Guideline and was not markedly affected by it, although there was a small acceleration in the decline in 1993. If the ratio of titles in SCI containing "sex differences" to titles containing "gender differences" is considered, this subsidiary ratio had been declining more rapidly than the overall sex-to-gender ratio since about 1985 (data not shown). Titles containing "gender differences" first outnumbered titles containing "sex differences" in 1994 (i.e., in the year following the Guideline) and have done so in every year since (except 1995).

Figures 2–4 present changes in the proportion of articles containing sex and gender (expressed as occurrences per thousand titles) for each of the three databases for the same years as covered in Fig. 1. Note that the vertical scales have been adjusted to reflect the fact that the proportion of titles containing sex and/or gender was far higher in SSCI than SCI, with AHCI intermediate. For SCI (Fig. 2), there was a small increase in the proportion of titles containing sex and/or gender over this period, from 1.8 per 1,000 in 1966 to 2.7 per 1,000 in 2001. From about 1980, gender began a steady increase in frequency, partly at the expense of sex. The FDA Guideline on the evaluation of gender differences was possibly responsible for the extra large jump in the frequency of gender in 1993.

For SSCI (Fig. 3), there was a dramatic increase in the proportion of titles containing sex and/or gender from 3.4 per 1,000 in 1966 to 16.3 per 1,000 in 2001. Up until 1980, both gender and sex increased in tandem. During the 1980s, gender began a rapid rise in frequency at the expense of sex. From 1990, the frequency of sex has been roughly constant (as has the frequency of gender from 1995). Thus, there is a hint that the relative interest in sex-related subjects has reached a plateau in the social sciences.

The AHCI database contains data from 1975 until present. Figure 4 shows a dramatic increase over this period in the proportion of titles containing sex and/or gender, from .6 per 1,000 in 1975 to 7.1 per 1,000 in 2001, with a slight lag relative to the corresponding increase in SSCI (on the other hand, the fall in the sex-to-gender ratio in AHCI was slightly ahead of the decline in SSCI). The rapid rise in the frequency of gender began in about 1982, with a slower rise of sex from the late 1980s. Unlike SCI

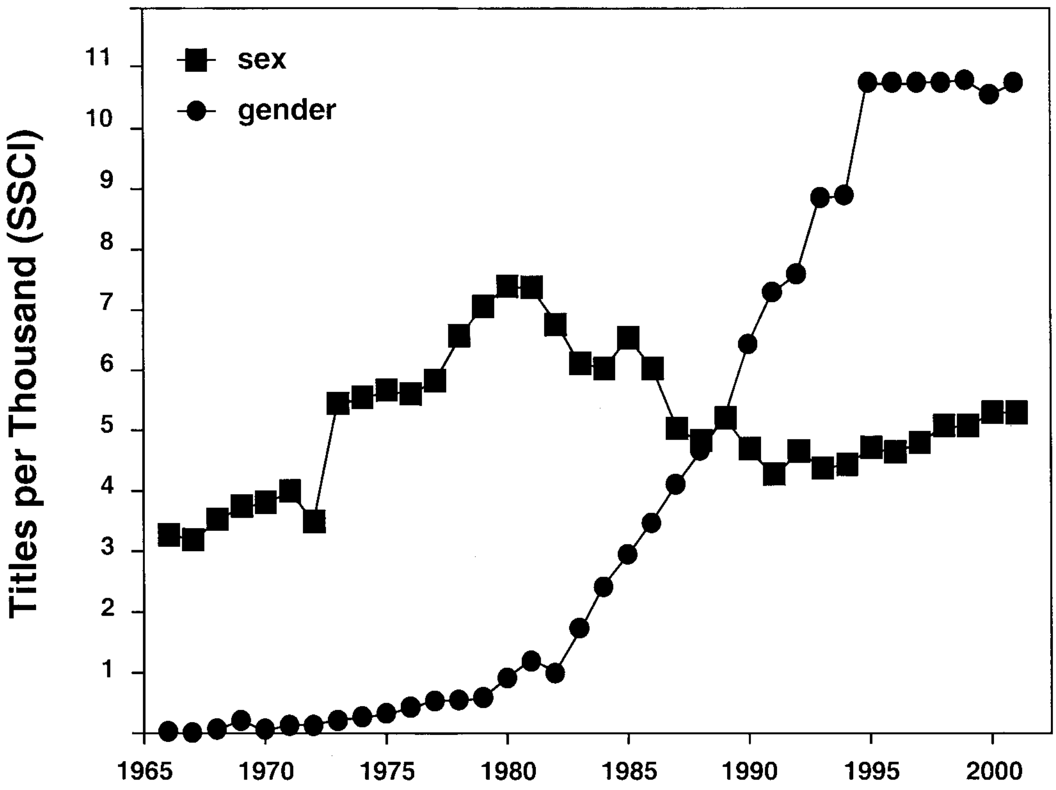

Fig. 3. Proportion of titles in the Social Sciences Citation Index containing the word *sex* and proportion containing the word *gender*.

and SSCI, the rapid rise of gender was not associated with a decline in the frequency of sex.

DISCUSSION

Sexological Origins

The first title in SCI to use gender in a nongrammatical sense was *Hermaphroditism, gender and precocity in hyperadrenocorticism: Psychologic findings* (Money, 1955). This article introduced the concept of a gender role: "The term *gender role* is used to signify all those things that a person says or does to disclose himself or herself as having the status of boy or man, girl or woman, respectively. It includes, but is not restricted to, sexuality in the sense of eroticism." This was one of a series of papers by Money and his collaborators that appeared in the *Bulletin of the Johns Hopkins Hospital* during that year. Other papers in the series employed the concept of gender role (Money, Hampson, & Hampson, 1955a, 1955b), without gender appearing in their titles.

The juxtaposition of *role* and *status* in the above definition suggests that Money was influenced by Parson's concept of *sex roles*. Money received his PhD in 1952 from the Department of Social Relations at Harvard University and listed Parsons among his teachers (Money, 1986, p. 5). For Parsons (1949), a status was "any patterned definition of who and what a person is" whereas a role was "the dynamic aspect of status, the behavior counterpart of the ideal or expected position defined by a status" (p. 43). Uses of *sex role* from the 1940s can be found in Parsons (1940, 1942), Cottrell (1942), and Mead (1949, p. 73). One of the many ironies to emerge from my analysis is that discussion of *sex roles* is now a staple of socio*bio*logy (e.g., Vincent, 1994) without awareness of the term's origin in sociology.

Money (1996) later wrote that he imported the term gender into sexological science "to make it possible to write about people who came into one's office as either male or female, but of whom it could not be said that their sex role in the specific genital sense was either male or female insofar as they had a history of birth defect of the sex organs." He then continued grandiloquently, "The

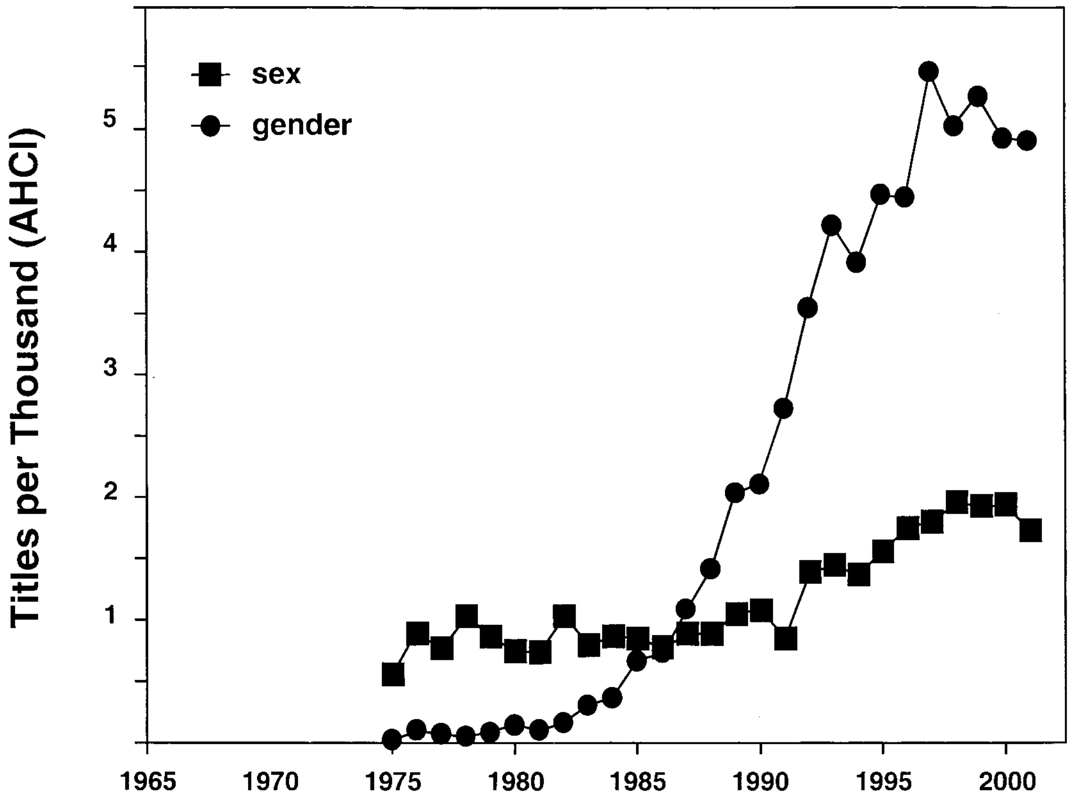

Fig. 4. Proportion of titles in the Arts & Humanities Citation Index containing the word *sex* and proportion containing the word *gender*.

majority of people who contributed to this new meaning of gender were hermaphrodites or intersexes. To them social science and social history overall owe a debt of gratitude. It is impossible to write about the political history of the second half of the twentieth century without reference to the concept of gender. This is particularly true with respect to the women's movement in politics" (p. xii). For similar reminiscences, and claims of priority, see Money (1973, 1985, 1995, p. 17ff.).

Excluding grammatical uses, most, if not all, of the gender-containing titles in SCI and SSCI from the 1960s appear to have derived the term from Money. These papers were mostly published in psychological journals and, at first, were concerned with individuals who did not conform to sexual stereotypes (hermaphrodites, transsexuals, transvestites, homosexuals, feminine boys, and masculine girls). However, in the late 1960s and early 1970s, gender began to appear in the titles of articles that addressed the behaviors and choices of individuals who conformed to gender stereotypes, with an emphasis on the extent to which the stereotypes were mutable or immutable, biological or social.

At this stage, it is worth discussing the causal connotations that had built up around *gender*. Money (1955) concluded that "Gender role and outlook as boy or man, girl or woman, was found to be in agreement with sex of rearing, except in three cases, and not to be automatically or instinctively determined by chromosomes, gonads or hormones." Similarly, Money et al. (1957) observed that "the sex of assignment and rearing is consistently and conspicuously a more reliable prognosticator of a hermaphrodite's gender role and orientation than is the chromosomal sex, the gonadal sex, the hormonal sex, the accessory internal reproductive morphology, or the ambiguous morphology of the external genitalia." They emphasized that "our findings indicate that neither a purely hereditary nor a purely environmental doctrine of the origins of gender role and orientation—of psychologic sex—is adequate."

Money and his co-workers offered two revealing analogies for the acquisition of a gender role: the first was the child's acquisition of a natural language (Money, 1955; Money et al., 1957); the second was the imprinting of a duckling on Konrad Lorenz when he imitated the quacking of a mother duck (Money et al., 1957). In both these examples, the individual was seen as biologically primed to acquire a language or mother figure, but which language was acquired, or what individual was identified as mother, was determined by the environment. Consistent with these analogies, Money et al. (1957) believed that gender role was acquired very early in a child's development and once acquired was resistant to change: "Though the sex of rearing could transcend external genital morphology in psychologic importance, absence or correction of ambiguous genital appearance was psychologically beneficial. Reassignment of the sex of rearing after the early months of life was, without doubt, psychologically injurious." Although Money explicitly adopted an interactionist position as regards nature versus nurture, his work was implicitly read as lying at the nurture-end of the spectrum. Because a person's sex could differ from their gender role, gender became associated with a blurring of the male/female dichotomy, and the claim that upbringing trumped anatomy provided a powerful argument against the essential nature of sex differences.

An early person to employ the terminology of gender was the psychoanalyst Stoller (1964a, 1964b). For Stoller (1965), sex was biological but gender was social. The latter connoted "behavior learned from a tremendous pool of cues present in every culture and from a massive, intricate, though usually subtle, system of rewards and punishments in which every person lives from birth on" (p. 197). Although he did not deny some role for biology, Stoller (1968) wrote that "those aspects of sexuality that are called gender are primarily culturally determined" (p. xiii) and that "*gender* is a term that has psychological or cultural rather than biological connotations" (p. 9). Other psychoanalysts adopted a similar distinction between biological sex and social gender (e.g., Gershman, 1967; Ovesey & Person, 1973).

Stoller (1964b) and Greenson (1964) together introduced the term *gender identity* at the 23rd International Psycho-Analytical Congress in Stockholm (July–August 1963). The latter defined this to be "one's sense of being a member of a particular sex; it is expressed clinically in the awareness of being a man or male in distinction to being a woman or female." For Stoller (1968), "*gender identity* starts with the knowledge and awareness, whether conscious or unconscious, that one belongs to one sex and not the other . . . *gender role* is the overt behavior one displays in society, the role which he plays, especially with other people" (pp. 9–10). For Money and Ehrhardt (1972), "gender role is the public expression of gender identity, and gender identity is the private expression of gender role" (p. 4).

Feminist Adoption

The origins of the use of gender among feminist scholars has been variously dated to the late 1960s (Nicholson, 1994) or the mid-1970s (Unger & Crawford, 1993). My own analysis suggests that its widespread adoption in feminist circles was delayed until the late 1970s or early 1980s. The first gender-containing title in the Web of Science that had an explicitly feminist context was *Some evolutionary aspects of human gender* (Tobach, 1971), in an issue of the *American Journal of Orthopsychiatry* devoted to *The Women's Movement: Social and Psychological Perspectives*. In this article, Tobach differentiated "biological sex" from "societally assigned gender" and warned against using "concepts from evolutionary biology to justify either retaining old traditions or changing them." Her article cited neither Money nor Stoller.

Other early feminist uses of gender occurred in books (not indexed in the Web of Science). Holter (1970) used sex and gender as interchangeable synonyms, seemingly for variety, whereas Millett (1970, p. 29) makes only passing reference to a sex/gender distinction, which she illustrates with a quote from Stoller (1968). Likewise, Bernard (1971, p. 16) derived her definitions of sex and gender directly from Stoller (1968). Oakley (1972) defined sex as biological and gender as psychological and cultural (pp. 16, 158). After a discussion of the work of Money and Stoller, she posed the rhetorical question "Does biology play any role at all in determining the development of gender identity in normal individuals?" and answered:

> The consensus of opinion seems to be that its role is a minimal one, in that the biological predisposition to a male or female gender identity (if such a condition exists) may be decisively and ineradicably overridden by cultural learning. Those who have worked in the field of hermaphroditic disorders and problems of gender identity seem very impressed by the power of culture to ignore biology altogether, (p. 170).

Differences between successive editions of *Masculine/Feminine or Human?* (Chafetz, 1974, 1978) are particularly illuminating. In the first edition, Chafetz (1974) contrasted *innate* gender with *learned* sex roles. This edition contained no citations to Money. However, by the second edition (Chafetz, 1978), the terms had been swapped—innate sex was contrasted with learned gender roles—and references were added to Money and Ehrhardt (1972). Allowing for the time lags associated with publication, this suggests an absence of feminist consensus on the meaning of gender in the early 1970s with an emerging consensus by the late 1970s (see Gould & Kern-Daniels, 1977). This timing is supported by Unger (1979) who was able to write in the *American Psychologist*, "The term gender is *introduced* for those characteristics and traits socioculturally considered appropriate to males and females" (my emphasis).

The only use of gender that I can find in *Women, Culture, and Society* (Rosaldo & Lamphere, 1974) is in the psychoanalytic chapter by Chodorow. Significantly, Ortner did not use gender in her influential chapter—*Is Female to Male as Nature is to Culture?* (an ammended version of Ortner, 1972)—but 7 years later she was an editor of *Sexual Meanings: The Cultural Construction of Gender and Sexuality* (Ortner & Whitehead, 1981). In *Gender and Sex in Society*, Duberman (1975) defined sex as "an ascribed social status referring to the biological differences between people" whereas gender role referred to "the socially learned patterns of behavior that differentiate men from women in a given society" (p. 26). In *Toward an Anthropology of Women*, Rubin (1975) discussed the sex/gender system, which she defined as "the set of arrangements by which a society transforms biological sexuality into products of human activity, and in which these transformed sexual needs are satisfied" (p. 159).

Trends in feminist use of gender were assessed by scanning the contents of early issues of *Feminist Studies* (first issue in 1972) and *Signs: Journal of Women in Culture and Society* (first issue in 1975). The first gender-containing titles in *Feminist Studies* did not appear until Volume 5 (Davidoff, 1979) and Volume 6 (Vance, 1980). These authors derived their uses of gender from Oakley (1972) and Rubin (1975), respectively. Yudkin (1978) had earlier used gender in a philosophical discussion of transsexualism, but without the term appearing in the title. She constructed a trichotomy between biological *sex*, psychological *gender*, and social *sex role*. Her use of gender derived from Money and Stoller. The first issue of *Signs* defined the journal's scope as including both sex and gender (Stimpson, Burstyn, Stanton, & Whisler, 1975), but use of gender was sparse in early issues (and predominantly by male authors). The first gender-containing title in *Signs* did not appear until the sixth volume (Baker, 1980), in a review of the biological literature on sex differences that contained numerous references to Money and coworkers. Gender-containing titles first exceeded sex-containing titles in Volume 11 of *Signs* (1986–1987).

Gender did not achieve uncontested acceptance by all feminists. In *Transsexual Empire*, Raymond (1979) treated *gender* as a technical or therapeutic term associated with the work of Money and Stoller. She found the term to have "certain problems for a feminist critic" as it gives "the impression that there is a fixed set of psychosocial conditions that determines gender identity and role." Nevertheless, there were times that she found the word unavoidable despite her "dissatisfaction," and in these places she "used it with reservation" (pp. 8–10).

From these small beginnings, use of gender became widely adopted by feminists during the 1980s. It is this adoption that I believe is principally responsible for the explosive growth in gender-containing titles that is observed in SSCI and AHCI during that decade (see Figs. 3 and 4). Feminists were able to embrace the concept of gender as their own contribution to discourse as the term's earlier association with sexological science shifted into the background.

Feminist usage converged on a contrast between socially constructed gender and biologically determined sex. However, it proved difficult to maintain such a distinction. One problem with the simple dichotomization of biological sex and social gender was that no term remained to refer to situations in which causation was unknown, disputed, or involved an interaction between biology and culture. Thus, the choice of term for this middle ground became a simple matter of preference, blurring the conceptual distinction between terms. Moreover, among feminists, the domain of gender had a tendency to expand to subsume the category of sex, because the way that people talk about "male" and "female" bodies was also seen as socially constructed (discussed by Nicholson, 1994). Kessler and McKenna (1978) provided an uncompromising example of this position. They saw the element of social construction as primary in all aspects of maleness and femaleness: even to invoke two categories was a social construct. To emphasize their contention, they wrote of gender chromosomes and gender hormones. In a retrospective, McKenna and Kessler (2000) returned to this theme: "Retaining a separation between sex and gender, even if it is proposed that both are socially constructed, raises the question of why biology is so important that it merits a special category."

Given the expansion in the domain of gender, and a certain indeterminacy in its meaning, it is hardly surprising that some authors who were unfamiliar with the subtleties of feminist debate interpreted gender as a simple synonym for sex and adopted it as such in their own writings. This is unambiguously demonstrated when gender is used in relation to the physiology of nonhuman animals, without any implication of a determining role of culture in the causation of observed differences. Such titles first appear in the 1970s (e.g., Hahn, Norton, & Fishman, 1977) and are now common in SCI.

The appearance of gender in a title from the natural sciences now communicates little if anything about causation or the ideology of the author. Among the reasons that working scientists have given me for choosing gender rather than sex in biological contexts are desires to signal sympathy with feminist goals, to use a more academic term, or to avoid the connotation of copulation.

Conclusion

This article addressed the history of terminology. During the first half of the twentieth century, gender appears to have been used predominantly in its grammatical sense, but its existing (albeit rare) use as a synonym of sex was readily available for anyone who wished to emphasize a dichotomy between different sources of sex-associated differences or to establish a separate domain for territory that had previously been considered part of the realm of sex. The expansion of the use of gender in the second half of the century appears to have derived from Money's concept of a gender role, introduced in the 1950s to refer to the self-identification of individuals whose genital sex was ambiguous. Significantly, in Money's usage, an individual's gender role could differ from various biological definitions of an individual's sex. From this beginning, there was a slow but gradual increase in the use of gender through the 1960s by writers, especially in the social sciences and among psychoanalysts, who wished to emphasize the environmental, social, or psychologic determinants of psychologic/behavioral differences between men and women. Some of these writers would have considered themselves feminists or at least sympathetic to the goals of the women's movement. Debates about nature versus nurture, the biological versus the social, and the autonomy of the social from the natural sciences, were of course much older than their association with a terminological sex vs. gender distinction.

Prior to the early 1980s, the rise in the use of gender in academic titles was not associated with an appreciable decline in the use of sex. The major increase in the use of gender, and the associated decline of sex, occured in the 1980s after the adoption of *gender* as a technical term in feminist discourse. The available evidence strongly suggests that this usage was derived by descent with modification from Money. As the sex-to-gender ratio has declined, gender has come to be adopted as a simple synonym, perhaps a euphemism, for sex by many writers who are unfamiliar with the term's recent history.

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AHR Forum
A History of "Gender"

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SCHOLARLY ARTICLES TEND TO HAVE LIMITED SHELF LIVES, but twenty years on, Joan Scott's "Gender: A Useful Category of Historical Analysis" has no discernible date of expiration. A cursory Google search leads to dozens of syllabi that feature it as required reading, and the figures from JSTOR attest to its durable popularity. Of all the *American Historical Review* articles on JSTOR, Scott's has had by far the most traffic. Since JSTOR first began posting scholarly articles online in 1997, users have accessed "Gender" more than 38,000 times and printed more than 25,000 copies. For the past five years, it has consistently ranked in the top spot as the most frequently viewed and most frequently printed of JSTOR's *AHR* articles.[1]

What elevates one article above the rest? What creates the reputation that makes an article required reading for more than twenty years? In part, it may be a matter of architecture. Scott built "Gender" with an artful use of argument. In one brief essay, she managed to summarize the advent of gender history, provide critiques of earlier theories of women's subordination, introduce historians to deconstructionist methods, and lay out an agenda for future historical studies. But as we all know, academic reputation rests on more than compellingly structured argument, even when the argument is displayed well in a top-tier scholarly journal.[2] For historians, the surest way to explain a text is to place it in historical context. Thus, a short history of "Gender" the article might help us assess its rise to prominence and its influence within the field of U.S. history. And an even shorter history of "gender" the concept might suggest the article's longer-lasting contribution to American social thought.

AS SCOTT NOTED, BY 1986, feminists had already adopted the term "gender" to refer to the social construction of sex differences, and theorists had already posed "gen-

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[1] Joan W. Scott, "Gender: A Useful Category of Historical Analysis," *American Historical Review* 91, no. 5 (December 1986): 1053–1075. Thanks to Robert B. Townsend, Assistant Director for Research and Publications of the American Historical Association, for supplying these figures, which were compiled on December 27, 2007. The exact figures are 38,093 viewings and 25,180 printings. The closest competitors (based on total viewings plus total printings) were Robert Finlay, "The Refashioning of Martin Guerre," *American Historical Review* 93, no. 3 (June 1988): 553–571, with 21,558 viewings and 11,183 printings, and Melvyn P. Leffler, "The Cold War: What Do 'We Now Know'?" *American Historical Review* 104, no. 2 (April 1999): 501–571, with 22,075 viewings and 9,495 printings.

[2] For an attempt to theorize the sources of scholarly reputations, see, for example, Michèle Lamont, "How to Become a Dominant French Philosopher: The Case of Jacques Derrida," *American Journal of Sociology* 93, no. 3 (1987): 584–622.

der" as an analytic category, akin to class and race. A few historians had begun to use the term "gender history" in addition to "women's history," and a handful had looked at men and masculinity as part of a gender history that did not focus solely on women. Scott intervened in this historiographic process at a critical moment. For some historians of women, the shift toward gender history was mostly unwelcome. To replace "women's history" with "gender history" and to include men and masculinity seemed to some at the time like a conservative retrenchment, a quest for respectability, or an abandonment of the study of marginalized and oppressed groups. Scott recognized the pitfalls and offered reassurance. She directly repudiated the use of "gender" as a de-politicized, social-scientized synonym for women or sex, and she promised to reinvigorate feminist history by expanding its realm of influence. In this way, she helped historians of women to approve (and other historians to discern) an emerging shift in historiography.

Scott outlined a problem faced by women's historians and proffered a solution. Two decades after the launching of the field, women's history was, she implied, stuck in a descriptive rut, relegated to the limited byways of social history inquiry. It had failed in its earlier claims to rewrite the master narrative of history, and it had not yet adequately explained the "persistent inequalities between women and men." Existing theories, Scott said, were ahistorical and reductionist. She offered a different approach for rethinking and rewriting history. Influenced by Derrida's deconstructionism and Foucault's formulation of dispersed power, she asked historians to analyze the language of gender, to observe how perceived sex differences had appeared historically as a natural and fundamental opposition. These perceived differences, she wrote, had often subordinated and constrained women, yes, but they had also provided a "primary way of signifying" other hierarchical relationships. This was the heart of her contribution: she invited us to look at how "the so-called natural relationship between male and female" structured, naturalized, and legitimated relationships of power, say, between ruler and ruled or between empire and colony. The history of gender could, it seems, inhabit more of the historical turf than could the history of women. It could even enter and remap the most resistant domains, such as the history of war, politics, and foreign relations.[3]

Although she promised to expand the realm of feminist influence, Scott could not deflect the critics from within her own fractious camp. Her embrace of poststructuralism and her consequent emphasis on the language of sex difference provoked a number of pointed rejoinders from prominent women's historians. Judith Bennett, for example, worried that "the Scottian study of gender ignore[d] women *qua* women," avoided reckoning with "material reality," and "intellectualize[d] and abstract[ed] the inequality of the sexes." Likewise, Linda Gordon suspected that a "focus on gender as difference in itself" as "a kind of paradigm for all other divides" had replaced "gender as a system of domination" and thereby substituted a pluralist vision of "multiple differences" for the study of "power differentials." Joan Hoff went further, even overboard. She accused poststructuralist gender historians, and Scott in particular, of nihilism, presentism, ahistoricism, obfuscation, elitism, obeisance to patriarchy, ethnocentrism, irrelevance, and possibly racism. Poststructur-

[3] Scott, "Gender," 1066, 1067, 1073.

alism, she found, "erased woman as a category of analysis," undermined the "traditional stage of historical fact-finding" for those groups of women whose history had not yet been written, and damaged political activism for women's rights. She titled her essay "Gender as a Postmodern Category of Paralysis."[4]

The critical commentary also came from historians who did not write women's history, especially those who questioned the linguistic turn. Critiques of Scott's work came from both the left and the right. Bryan Palmer, for example, decried her repudiation of historical materialism, and Gertrude Himmelfarb complained about the undermining of fact, reality, and objectivity.[5] In the United States, as others have suggested, "feminist historians" were "in the vanguard" of poststructuralist historical practice, especially in its manifestations outside of intellectual history, and Scott stood out at the front. In this sense, "Gender" came to represent something larger than itself. Scott served as the whipping girl not only for gender history but also for the challenges of poststructuralism, the revisionism of the latest new history, and the vogue—the "intellectual *haute couture*"—of imported French theory.[6] She may not have enjoyed the public flagellation, but it no doubt played a part in attracting readers to her essay.

DESPITE THE MISGIVINGS OF SOME HISTORIANS, gender soon took on a life of its own. Within the field of U.S. history, much of the new work on gender had little direct connection with Scott's essay. Case studies of the intersections of race, class, and gender, for example, and accounts of how various groups of women and men participated differently in politics, labor, and consumption did not necessarily draw on Scott's Derridean, Foucauldian model. Some new histories of gender in public cited Jürgen Habermas and Nancy Fraser more often than they cited Derrida and Scott.[7] But Scott's article did have unquestionable influence, even among those authors who did not adopt the deconstructionist method wholesale. In the 1990s, it inspired a cohort of scholars who wrote gender history in a range of forms and fields. Within this cohort, a number of authors followed Scott's proposal to foreground the dis-

[4] Judith M. Bennett, "Feminism and History," *Gender and History* 1, no. 3 (1989): 258; Linda Gordon, review of Joan Wallach Scott, *Gender and the Politics of History*, *Signs* 15, no. 4 (1990): 858; Joan Hoff, "Gender as a Postmodern Category of Paralysis," *Women's History Review* 3, no. 2 (1994): 149, 162. For additional critical commentaries, see, for example, Sonya O. Rose et al., "Gender History/ Women's History: Is Feminist Scholarship Losing Its Critical Edge?" *Journal of Women's History* 5, no. 1 (1990): 89–128. Some of these authors addressed Scott's essays more generally, not just the article "Gender."

[5] Bryan D. Palmer, *Descent into Discourse: The Reification of Language and the Writing of Social History* (Philadelphia, 1990), esp. chap. 5; Gertrude Himmelfarb, "Some Reflections on the New History," *American Historical Review* 94, no. 3 (June 1989): 661–670.

[6] Joyce Appleby, Lynn Hunt, and Margaret Jacob, *Telling the Truth about History* (New York, 1994), 226; Sandra M. Gilbert and Susan Gubar, "Sexual Linguistics: Gender, Language, Sexuality," *New Literary History* 16, no. 3 (1985): 521. On the "linguistic turn" in history, see, for example, John E. Toews, "Intellectual History after the Linguistic Turn: The Autonomy of Meaning and the Irreducibility of Experience," *American Historical Review* 92, no. 4 (October 1987): 879–907; Kathleen Canning, "Feminist History after the Linguistic Turn: Historicizing Discourse and Experience," *Signs* 19, no. 2 (1994): 368–404.

[7] See, for example, Mary Ryan, *Women in Public: Between Banners and Ballots, 1825–1880* (Baltimore, 1990), and Glenda Elizabeth Gilmore, *Gender and Jim Crow: Women and the Politics of White Supremacy in North Carolina, 1896–1920* (Chapel Hill, N.C., 1996).

cursive use of perceived sex differences and track how they constituted relationships of power. In U.S. history, the case studies of "women's worlds" and "female cultures" that had proliferated in the 1980s dwindled as accounts rose of the ways in which the language of gender had shored up hierarchies of race, class, region, politics, nation, and empire.

A quick (and, forgive me, incomplete) survey of just a few subfields of U.S. history establishes the point. In southern history, Jacquelyn Dowd Hall endorsed the gender project early on. "The South," she wrote in 1989, "provides a prime example of how gender signifies relations of power in hierarchical regimes." Other historians took up the task. Stephanie McCurry found that proslavery ministers and politicians repeatedly drew analogies between "the subordination of women" and "that of slaves," and thereby "endow[ed] slavery with the legitimacy of the family and especially marriage." They used the language of gender "to naturalize other social relations—class and race, for example." Laura Edwards reported similar analogies—between women and other "dependent" groups—in the Reconstruction-era writings of elite white southern men, who used the language of gender to legitimate their bid to monopolize political power. Historians also noted how the southern states themselves were coded as feminine within the United States. Nina Silber, for example, pointed to a postbellum northern language of gender that portrayed the South as a "submissive" wife and helped to enable the "romance" of sectional reunion.[8]

In other areas, historians also attended to the ways that political theorists, government officials, and other writers used the language of sex difference to construct and sustain political and social hierarchies. In early American history, Mary Beth Norton described how seventeenth-century British male colonists established governments based on a gendered, hierarchical model of the family, and Kathleen Brown suggested that gender discourse shaped the emerging political order in Virginia from the first conflicts with the Indians through the course of Bacon's Rebellion. Jennifer Morgan illustrated how early European narratives of the New World "relied on gender," especially on accounts of monstrous Indian and African women, "to convey an emergent notion of racialized difference," and Toby Ditz delineated how eighteenth-century Philadelphia merchants stabilized their own fragile masculine status by feminizing and thereby stigmatizing their failed and dishonest colleagues as "weeping victims and harpies."[9] At the other end of the chronological span, historians of twentieth-century U.S. politics examined how male politicians

[8] Jacquelyn Dowd Hall, "Partial Truths," *Signs* 14, no. 4 (1989): 910; Stephanie McCurry, *Masters of Small Worlds: Yeoman Households, Gender Relations, and the Political Culture of the Antebellum South Carolina Low Country* (New York, 1995), 214, 224; Laura Edwards, *Gendered Strife and Confusion: The Political Culture of Reconstruction* (Urbana, Ill., 1997), esp. chap. 6; Nina Silber, *The Romance of Reunion: Northerners and the South, 1865–1900* (Chapel Hill, N.C., 1993), 10.

[9] Mary Beth Norton, *Founding Mothers and Fathers: Gendered Power and the Forming of American Society* (New York, 1996); Kathleen M. Brown, *Good Wives, Nasty Wenches, and Anxious Patriarchs: Gender, Race, and Power in Colonial Virginia* (Chapel Hill, N.C., 1996); Jennifer L. Morgan, " 'Some Could Suckle over Their Shoulder': Male Travelers, Female Bodies, and the Gendering of Racial Ideology, 1500–1770," *William and Mary Quarterly* 54, no. 1 (1997): 168; Toby L. Ditz, "Shipwrecked; or, Masculinity Imperiled: Mercantile Representations of Failure and the Gendered Self in Eighteenth-Century Philadelphia," *Journal of American History* 81, no. 1 (1994): 54. On gender more generally in early American history, see Toby L. Ditz, "The New Men's History and the Peculiar Absence of Gendered Power: Some Remedies from Early American Gender History," *Gender and History* 16, no. 1 (2004): 1–35.

used the language of gender to create a hierarchy in which they stood above their male opponents. In the early twentieth century, they cast male reformers as feminine and therefore lacking, and in the late twentieth century, they attacked male liberals in somewhat similar form. Gail Bederman and Arnaldo Testi showed how Theodore Roosevelt shook off the gendered smear by combining his reform agenda with an imperialist, racist hypermasculinity, and Robert Dean and K. A. Cuordileone elucidated how John F. Kennedy attempted to repel the aspersion with an aggressive expression of liberalism.[10]

Perhaps most surprising, gender history also made significant forays into the history of foreign policy, the field of U.S. history that had seemed most immune to the women's history enterprise. Scott had specifically called for such an intervention; in 1990, Emily Rosenberg responded and made the case for the potential benefits of gender analysis. Gendered imagery, she said, pervaded accounts of international affairs, legitimating foreign relations of domination and dependence. Andrew Rotter pursued the lead and showed how mid-twentieth-century U.S. policymakers had imagined India as feminine and India's male leaders as passive, emotional, and lacking in virility. In this case, the "feminization" undermined the opportunity for alliance between the U.S. and India. In other cases, though, the "masculinization" of nations and their leaders damaged international relations, while "feminization" eased them. Frank Costigliola, for example, investigated the writings of Cold War architect George Kennan, who shifted from feminizing a beloved Russia in the 1930s to portraying Soviet leaders as "monstrously masculine" and rapacious in the post–World War II years. Petra Goedde traced the inverse shift with regard to Germany. During World War II, American soldiers vilified the Nazi leaders, whom they understood as brutally masculine, but after the war they "developed a feminized image" of Germans as a population in need of protection, and thus, Goedde claimed, "paved the way toward reconciliation."[11]

Historians also began to suggest that discourses of gender had promoted and sustained American military interventions. In *Fighting for American Manhood*, Kristin Hoganson explored "how gender politics provoked the Spanish-American and Philippine-American wars," as the subtitle of her book stated plainly. As they advocated war, jingoes and imperialists expressed heightened concern with masculinity and looked to the military to build and prove American manhood. They posed the

[10] Gail Bederman, *Manliness and Civilization: A Cultural History of Gender and Race in the United States, 1880–1917* (Chicago, 1995), chap. 5; Arnaldo Testi, "The Gender of Reform Politics: Theodore Roosevelt and the Culture of Masculinity," *Journal of American History* 81, no. 4 (1995): 1509–1533; Robert D. Dean, *Imperial Brotherhood: Gender and the Making of Cold War Foreign Policy* (Amherst, Mass., 2001); K. A. Cuordileone, *Manhood and American Political Culture in the Cold War* (New York, 2005).

[11] Emily S. Rosenberg, "Gender," *Journal of American History* 77, no. 1 (1990): 116–124; Andrew J. Rotter, "Gender Relations, Foreign Relations: The United States and South Asia, 1947–1964," *Journal of American History* 81, no. 2 (1994): 518–542; Frank Costigliola, " 'Unceasing Pressure for Penetration': Gender, Pathology, and Emotion in George Kennan's Formation of the Cold War," *Journal of American History* 83, no. 2 (1997): 1333; Petra Goedde, "From Villains to Victims: Fraternization and the Feminization of Germany, 1945–1947," *Diplomatic History* 23, no. 1 (1999): 2, 20. See also the essays on gender in the Winter 1994 issue of *Diplomatic History*, especially Geoffrey S. Smith, "Commentary: Security, Gender, and the Historical Process," *Diplomatic History* 18, no. 1 (1994): 79–90; Petra Goedde, *GIs and Germans: Culture, Gender, and Foreign Relations, 1945–1949* (New Haven, Conn., 2003). For a useful review essay, see Kristin Hoganson, "What's Gender Got to Do with It? Women and Foreign Relations History," *OAH Magazine of History* 19, no. 2 (2005): 14–18.

Spanish soon-to-be enemies as both distastefully feminine and repulsively masculine—"effeminate aristocrats" and "savage rapists"—and sometimes also feminized the Cubans and Filipinos as well as their own domestic opponents. Mary Renda outlined a somewhat different masculine discourse of "interventionist paternalism" that underwrote the American occupation of Haiti. The gendered language of fatherhood helped U.S. policymakers and marines to justify imperialist violence as a manly attempt to protect, educate, and discipline the allegedly childlike Haitians. And Robert Dean wrote of the threats to the "imperial masculinity" of the mid-twentieth-century U.S. foreign policy elite. Politicians and policymakers used the language of gender to defend their own manhood and diminish that of their rivals, and thereby engaged, Dean suggested, in a "politics of manhood" that "crucially shaped the tragedy of the Vietnam War." Hoganson, Renda, and Dean (and the other authors mentioned above) did not confine their analyses to the deconstruction of binary oppositions, but they provided evidence of how the language of gender constructed and legitimated American imperialism and its violent manifestations.[12]

Taken together, these various works point, as Scott predicted, to the multiplicity of meanings that gendered language conveyed. In different historical contexts, masculinity represented strength, protection, independence, camaraderie, discipline, rivalry, militarism, aggression, savagery, and brutality, and femininity represented weakness, fragility, helplessness, emotionality, passivity, domestication, nurturance, attractiveness, partnership, excess, and temptation. The so-called natural differences between the sexes had no fixed and unchangeable meaning, and in their variety they provided potential meaning for a range of other relationships. As other historians have protested, though, the ultimate impact of the language of gender remained hard to discern.[13] When (and how), as Scott asked, did the language of gender crucially structure experience and actually influence behavior and decision-making, and when did it simply add a convenient rhetorical flourish or embellish with a hollow cliché? When (and how), as Scott asked, did the language of gender constitute other relations of power, and when was it just a minor paragraph or a supplemental example within the narratives of social and political order? Even without all the answers, the growing number of studies of gender discourse pushed historians to recognize its pervasiveness, the diverse domains in which perceived sex differences appeared as model, analogy, and metaphor for hierarchical relationships, and the wide-ranging and changing meanings of masculinity and femininity in the modern era.

The studies also enhanced the reputation of Scott's essay and injected its message into traditional subfields of historical study. Almost all of the works cited above (and many other books and articles as well) mentioned "Gender," in the footnotes if not in the text. Some of them quoted it directly. It became a validating authority behind the monographic works that moved gender to the center of specialized subfields in which it had earlier stood at the margins.[14] By the end of the 1990s, through a process

[12] Kristin L. Hoganson, *Fighting for American Manhood: How Gender Politics Provoked the Spanish-American and Philippine-American Wars* (New Haven, Conn., 1998), 11; Mary A. Renda, *Taking Haiti: Military Occupation and the Culture of U.S. Imperialism, 1915–1940* (Chapel Hill, N.C., 2001); Dean, *Imperial Brotherhood*, 243.

[13] See, for example, Melvyn P. Leffler, "New Approaches, Old Interpretations, and Prospective Reconfigurations," *Diplomatic History* 19, no. 2 (1995): 195.

[14] Scott's article also had a significant impact on U.S. labor history. See especially Ava Baron, ed.,

of repetition, "Gender" had reshaped the commonplace wisdom of the discipline. As a measure of its success, Scott's essay increasingly served as a voice from the recent past stating eloquently what everybody, it seems, already knew.

Meanwhile, Scott herself moved in new directions. In 1999, she questioned the ongoing vitality of the term "gender." In the 1980s, she wrote, gender had "seemed a useful category of analysis precisely because it had an unfamiliar, destabilizing effect." Now, however, it had "lost its ability to startle and provoke." In everyday usage, gender had become "a synonym for women, for the differences between the sexes, for sex." The word "gender" had crept into women's history without necessarily transforming the field. It appeared often in "predictable studies of women, or . . . of differences in the status, experience, and possibilities open to women and men." Many accounts failed to "examine how the meanings of 'women' and 'men'" were "discursively established" or to address the "variations of subjectively experienced 'womanhood.'" They thereby imposed a false solidity on the unstable and variable categories of "women" and "men." Scott now avoided the word "gender" and wrote instead about "differences between the sexes and about sex as a historically variable concept." She turned more concertedly to psychoanalysis, to the fantasies that enable identities, including the "phantasmatic projections that mobilize individual desires into collective identifications." In her 2005 book, *Parité! Sexual Equality and the Crisis of French Universalism*, and her 2007 book, *The Politics of the Veil*, she entered into current debates in French politics. She focused less on the language of sex difference and more on the language of universalism in contemporary France. In these books, she did not renounce the study of "gender," but she positioned French gender relations within a discursive analysis of "the abstract individualism" that animates French republican traditions.[15]

As one would expect, other historians also ventured into new territory. In U.S. women's—and now gender—history, they brought in race, sexuality, and nationality as equally useful categories of historical analysis, and they borrowed from postcolonial, critical race, queer, and political theory. Other forms of perceived difference seem to have constituted gender as much as gender constituted them. In particular, the call to address race had at least as much impact on U.S. women's history as the call to attend to gender. Historians of women and gender also turned to the policy history of welfare and wages, the legal history of marriage, and the social history of those who questioned and transgressed gender norms. Historians of women shifted away from the local community studies that had characterized social history and focused more on individual or collective biography, questions of law and citizenship, and transnational circulations of women and ideas about womanhood. They rewrote the history of women's movements with a closer eye to differences among women and conflicts among competing schools of feminists. At the same time, historians of manhood produced a series of studies of shifting conceptions, multiple variants, and

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Work Engendered: Toward a New History of American Labor (Ithaca, N.Y., 1991). The article also had influence outside U.S. history, of course, but I will leave that to the other participants in this forum.

[15] Joan Wallach Scott, *Gender and the Politics of History*, rev. ed. (New York, 1999), xi–xii, 204; Scott, *Parité! Sexual Equality and the Crisis of French Universalism* (Chicago, 2005); Scott, *The Politics of the Veil* (Princeton, N.J., 2007), 154. See also Scott, "Fantasy Echo: History and the Construction of Identity," *Critical Inquiry* 27, no. 2 (2001): 284–304.

repeated crises of masculinity. Gender history, then, continued (and continues) to thrive in several incarnations, and despite the fears of early (and later) critics, it coexists and overlaps with, instead of supplanting or displacing, the history of women.[16] Amid the profusion, Scott's article has taken on the emblematic role of a foundational text.

SCOTT'S ESSAY HAD ITS MOST OBVIOUS INFLUENCE in the fields of women's and gender history, but it also played a significant part in the broader shift from social to cultural history, from the study of the demography, experiences, and social movements of oppressed and stigmatized groups to the study of representations, language, perception, and discourse. In U.S. history, the rise of gender history was similar to and roughly simultaneous with changes in other identity-based fields of history, including African American, Latino/a, Asian American, immigrant, gay and lesbian, and working-class history. Gender history and the historical construction of masculinity had their counterparts in the history of race and the construction of whiteness, the history of ethnicity and the construction of national identity, the history of sexuality and the construction of heterosexuality, and the history of class and the construction of middle-classness. To a certain extent, the same left-leaning political energies that had informed much of the new social history informed the new cultural history as well. The irony is that social history, the alleged source of centrifugal fragmentation, had spun out into a cultural history that seems to have gravitated back—in the histories of masculinity, whiteness, national identity, heterosexuality, and middle-classness—to return, with a new and critical torque, to the pre-social-history center of historical inquiry.[17] "Gender," and Scott's other writings as well, provided a key piece of the theoretical grounding for this historiographic trend.

Like all historiographic moments, this one, too, will no doubt pass. And when it does, what will we remember? We might consider another context for understanding the significance of Scott's essay and its larger contribution beyond historiography. We have only begun to historicize "gender"—that is, to write the history of the concept of gender itself. Scott's essay belongs in that history; it represents a turning point when U.S. feminist scholars pulled "gender" away from its scientific and social scientific origins, reworked its meaning, and suggested its broader social, cultural, and historical impact.

Scott dated the term "gender," in its contemporary usage, to the 1970s feminist movement, but the word has a longer history, even as a reference to the non-biological components of sex. Before the 1950s, linguists used "gender," as Scott acknowledged, to refer to a form of grammatical classification. The concept of socially constructed sex differences did not yet have a word to connote it. Nonetheless, theories of the social construction of sex differences emerged in tandem with theories of the social construction of other forms of group difference. From the early twen-

[16] For more recent concerns that gender history will supplant women's history, see Alice Kessler-Harris, "Do We Still Need Women's History?" *Chronicle of Higher Education* 54, no. 15 (December 7, 2007): B6.

[17] For a recent account of this trend, see Daniel Wickberg, "Heterosexual White Male: Some Recent Inversions in American Cultural History," *Journal of American History* 92, no. 1 (2005): 136–157.

tieth century on, social scientists engaged in a profound questioning of biological determinism and the categories on which it relied, not only with regard to sex but also with regard to race, ethnicity, national character, sexuality, criminality, and mental illness. By the mid-twentieth century, anthropologists and sociologists wrote of "sex roles" to refer to the culturally determined expected behavior of women and men and "sexual status" to acknowledge that different cultures accorded different social rankings to women and men. Psychologists used the phrases "psychological sex" and "sex-role identification" to point to a person's acquired sense of self as female or male.[18]

In the mid- to late 1950s, John Money, Joan Hampson, and John Hampson, all then at Johns Hopkins University, introduced the term "gender" into this scientific literature. In a series of articles on intersexuality, they argued for the environmental determinants of "gender," "gender role," and "gender role and orientation," just as others had earlier argued for the environmental determinants of "sex roles" and "psychological sex." Children learned "gender" in early childhood, they argued, in the same way they learned a language. Biological sex, however it was defined, did not determine one's "gender role and orientation."[19] Other scientists and social scientists picked up the new terminology. In 1962, psychoanalyst Robert Stoller and his colleagues at the University of California in Los Angeles opened the first Gender Identity Research Clinic (GIRC), and in 1968, Stoller published the book *Sex and Gender*, which seems to have been the first American book with the word "gender," in its current non-linguistic form, in the title. For Stoller, gender referred to the particular balance of masculinity and femininity found in each person. It had "psychological or cultural rather than biological connotations." Stoller was not a feminist. In fact, he worried about the erosion of gender roles and the developmental disturbance of "gender identity," the new term he coined for "psychological sex." He and his colleagues at the GIRC worked to instill masculinity in feminine boys and femininity in masculine girls. If gender was mostly socially constructed, then someone, they reasoned, had to repair it when it was improperly built. Stoller and his colleagues signed up for the job.[20]

Influenced by the women's movement, American feminists appropriated the word "gender" in the 1970s and transformed its meaning. Like others before them, feminist social scientists used "gender" to reject the notion that the perceived sex

[18] On American social scientists and the social construction of sex differences, see, for example, Rosalind Rosenberg, *Beyond Separate Spheres: Intellectual Roots of Modern Feminism* (New Haven, Conn., 1982); Carl Degler, *In Search of Human Nature: The Decline and Revival of Darwinism in American Social Thought* (New York, 1991); Mari Jo Buhle, *Feminism and Its Discontents: A Century of Struggle with Psychoanalysis* (Cambridge, Mass., 1998).

[19] For uses of the new terms, see John Money, "Hermaphroditism, Gender, and Precocity in Hyperadrenocorticism: Psychologic Findings," *Bulletin of the Johns Hopkins Hospital* 96 (1955): 253–264; John Money, Joan G. Hampson, and John L. Hampson, "Imprinting and the Establishment of Gender Role," *American Medical Association Archives of Neurology and Psychiatry* 77 (1957): 333–336. Money later retreated from his early environmentalism; by the end of the 1960s, he speculated that early exposure to sex hormones and the neurophysiology of the brain (as well as environment) shaped gender identity. On Money, the Hampsons, and "gender," see Bernice Hausman, *Changing Sex: Transsexualism, Technology, and the Idea of Gender* (Durham, N.C., 1995), chap. 3; Joanne Meyerowitz, *How Sex Changed: A History of Transsexuality in the United States* (Cambridge, Mass., 2002), chap. 3.

[20] Robert J. Stoller, *Sex and Gender: On the Development of Masculinity and Femininity* (New York, 1968), 9. On Stoller and the GIRC, see Meyerowitz, *How Sex Changed*, chap. 3; Phyllis Burke, *Gender Shock: Exploding the Myths of Male and Female* (New York, 1996).

differences in behavior, temperament, and intellect were simply natural or innate, but unlike their predecessors, they rejected functionalism and questioned whether gender and gender roles were necessary or good. If gender was artifice, then many 1970s feminists saw little reason to maintain it, especially when it played a part in subordinating women. But gender, in its multiple variations, was not so easily willed away. It was built into the structure and practice of families, education, labor markets, and government policies, and it had deep roots in the everyday behaviors and fantasies of individual women and men. Some academic feminists, especially in the humanities, turned away from the study of gender roles, gender systems, and gender segregation, and focused instead on the reconstruction and revaluation of femininities, women's writings, women's ethics, and women's worlds.[21]

Others searched for theoretical approaches that could explicate how perceptions of sex difference operated in language, psyche, and symbolic order. In the late 1970s and early 1980s, some American feminist literary critics turned to French poststructuralist theory. They drew on the works of Jacques Lacan, Roland Barthes, and Jacques Derrida, and they translated the writings of Hélène Cixous, Luce Irigary, and Julia Kristeva. They expanded their purview from "the woman reader, women's culture, and the woman's text" to "the whole of literature and culture." Cixous wrote: "Every theory of culture, every theory of society, the whole conglomeration of symbolic systems . . . it is all ordered around hierarchical oppositions that come back to the man/woman opposition." By the early 1980s, male literary critics recognized the feminist affinity to poststructuralism. In 1983, in *Literary Theory*, Terry Eagleton suggested that "the movement from structuralism to post-structuralism was in part a response" to the demands of the women's movement. In this rendition, feminism stood front and center on the poststructuralist stage.[22]

In 1986, with the article "Gender," Joan Scott helped to bridge the gap between the feminist social scientists who critiqued "gender" and "gender roles" and the feminist literary critics who deconstructed textual representations of sex difference.[23] She wrote in a moment, as she noted, "of great epistemological turmoil," when social scientists were shifting "from scientific to literary paradigms," and when feminists were finding "scholarly and political allies" among poststructuralists. For Scott, gender was "a constitutive element of social relationships based on perceived differences between the sexes," and also "a primary way of signifying relationships of power." Scott's dual definition allowed her to bring together the social scientists who rejected biological determinism and questioned the allegedly natural differ-

[21] On 1970s feminists and "gender," see, for example, Suzanne J. Kessler and Wendy McKenna, *Gender: An Ethnomethodological Approach* (Chicago, 1978); see also Rosalind Rosenberg, "Gender," in Theodore M. Porter and Dorothy Ross, eds., *The Modern Social Sciences* (Cambridge, 2003), 678–692.

[22] Elaine Showalter, "Women's Time, Women's Space: Writing the History of Feminist Criticism," *Tulsa Studies in Women's Literature* 3, no. 1/2 (1984): 35; Hélène Cixous, "Castration or Decapitation?" *Signs* 7, no. 1 (1981): 44; Terry Eagleton, *Literary Theory: An Introduction* (Minneapolis, 1983), 149. For American feminist adaptations of French theory, see, for example, Elaine Marks and Isabelle de Courtivron, eds., *New French Feminisms: An Anthology* (Amherst, Mass., 1980); *Writing and Sexual Difference*, Special Issue, *Critical Inquiry* 8, no. 2 (1981); *Feminist Readings: French Texts/American Contexts*, Special Issue, *Yale French Studies* 62 (1981). For critical commentaries by historians, see Buhle, *Feminism and Its Discontents*, chap. 9; Claire Goldberg Moses, "Made in America: 'French Feminism' in Academia," *Feminist Studies* 24, no. 2 (1998): 241–274.

[23] Scott was soon joined in this endeavor by Judith Butler; see Butler, *Gender Trouble: Feminism and the Subversion of Identity* (New York, 1990).

ences on which it was based and the philosophers, psychoanalysts, and literary critics who suggested that the language of difference sustained Western social and political order. She was not alone in this kind of endeavor. A year earlier, for example, Henry Louis Gates, Jr. (and others) had posited race as a "trope of ultimate, irreducible difference" that naturalized distinctions between "cultures, linguistic groups, or adherents of specific belief systems."[24] Within the United States, the scholarly study of difference and inequality, once firmly grounded in social science, had migrated to the humanities and taken root in the study of language. It soon spread beyond the analysis of literature and into the reading of multifarious texts, including the kinds of texts that historians typically use as evidence.

This abbreviated genealogy of gender might help to place Scott's contribution in a broader context. For historians, Scott summarized explanations of gender inequality, captured an emerging historiographic trend, and imported theory to a discipline of committed empiricists. She promised both to expand the terrain of the new social and cultural history and to return to and revivify the traditional fields of historical study. In the 1980s and 1990s, her readers sustained her argument first by publicly debating its merits and then by applying its theory and its method of reading. Beyond the historical discipline, though, Scott's essay entered into decades-long conversations on the social and symbolic constructions of sex difference. She helped to move the American concept of gender beyond its scientific and social scientific origins and nudged the American adaptations of poststructuralism beyond their recognized place in literary criticism. She suggested how the language of sex difference had historically provided a means to articulate relationships of power. In this way, she tied gender back to other forms of difference and pushed us to ponder the metanarratives that mutually constituted various social and political hierarchies. And ponder we should. This may, in the end, prove to be the enduring legacy of "Gender."

[24] Scott, "Gender," 1066, 1067; Henry Louis Gates, Jr., "Writing 'Race' and the Difference It Makes," *"Race," Writing, and Difference*, Special Issue, *Critical Inquiry* 12, no. 1 (1985): 5. Gates's essay is the editor's introduction to the issue; some of the other essays in the issue also address the language of race difference. See also Evelyn Brooks Higginbotham, "African American Women's History and the Metalanguage of Race," *Signs* 17, no. 2 (1992): 251–274.

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HOW MANY ADULTS IDENTIFY AS TRANSGENDER IN THE UNITED STATES?

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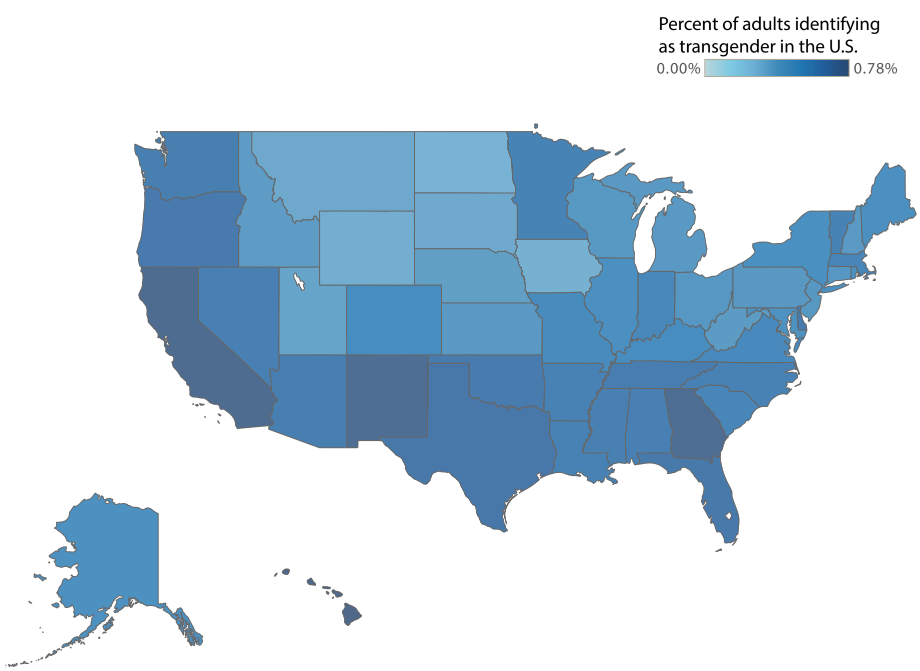
INTRODUCTION AND SUMMARY

Population-based surveys, meaning those that are designed to allow researchers to generalize findings to the population, rarely ask questions to identify transgender people and, therefore, cannot be used to provide estimates of the size and characteristics of the transgender population. The federal government administers several large, national population-based surveys like the American Community Survey and the National Health Interview Survey that track the demographics, health and well-being of U.S. residents. Unfortunately, these surveys do not currently measure gender identity.[1] However, there are several state-level population-based surveys that identify transgender respondents and can be used to estimate the size and characteristics of the transgender population.

In 2011, Gary J. Gates utilized two state-level population-based surveys that collected data from 2003 in California and from 2007 and 2009 in Massachusetts to estimate that 0.3% of the U.S. adult population, roughly 700,000 adults, identified as transgender.[2] Since then, more state-level data sources have emerged that allow us to utilize an estimation procedure that would not have been possible with the limited data available in 2011. Compared to the data used in Gates' study, these new data sources provide more recent data (2014), larger sample sizes, and more detailed information about respondents. This allows for the development of more recent, detailed, and statistically robust estimates of the percentage and number of adults in the United States who identify as transgender.

This report utilizes data from the CDC's Behavioral Risk Factor Surveillance System (BRFSS) to estimate the percentage and number of adults who identify as transgender nationally and in all 50 states.[3] We find that 0.6% of U.S. adults identify as transgender. This figure is double the estimate that utilized data from roughly a decade ago and implies that an estimated 1.4 million adults in the U.S. identify as transgender.[4] State-level estimates of adults who identify as transgender range from 0.3% in North Dakota to 0.8% in Hawaii.[5] In addition, due to current state-level policy debates that specifically target and affect transgender students, we provide estimates of the number of adults who identify as transgender by age. The youngest age group, 18 to 24 year olds, is more likely than older age groups to identify as transgender.

Figure 1. Percent of Adults Who Identify as Transgender in the United States



National and State-level Estimates of Transgender-Identified Adults

An estimated 0.6% of adults, about 1.4 million, identify as transgender in the United States. States vary in the percentage of residents who identify as transgender (See Table 1). Hawaii has the highest percentage of adults who identify as transgender, approximately 0.8% of adults, and North Dakota has the lowest percentage, at 0.3%. The District of Columbia is notable for its relatively high percentage of transgender-identified adults (2.8%).[6] Twenty states and the District of Columbia are estimated to have a higher percentage of transgender-identified adults than the national average.

Table 1. Estimated Population of Adults Who Identify as Transgender by State of Residence

STATE	POPULATION	PERCENT	RANK
United States of America	1,397,150	0.58%	-
Alabama	22,500	0.61%	15
Alaska	2,700	0.49%	33
Arizona	30,550	0.62%	12
Arkansas	13,400	0.60%	18
California	218,400	0.76%	2
Colorado	20,850	0.53%	27
Connecticut	12,400	0.44%	37
Delaware	4,550	0.64%	9
District of Columbia[7]	14,550	2.77%	-
Florida	100,300	0.66%	6
Georgia	55,650	0.75%	4
Hawaii	8,450	0.78%	1
Idaho	4,750	0.41%	43
Illinois	49,750	0.51%	30
Indiana	27,600	0.56%	23
Iowa	7,400	0.31%	49
Kansas	9,300	0.43%	41
Kentucky	17,700	0.53%	26
Louisiana	20,900	0.60%	17
Maine	5,350	0.50%	31
Maryland	22,300	0.49%	32
Massachusetts	29,900	0.57%	22
Michigan	32,900	0.43%	40
Minnesota	24,250	0.59%	20
Mississippi	13,650	0.61%	14
Missouri	25,050	0.54%	25
Montana	2,700	0.34%	47
Nebraska	5,400	0.39%	44
Nevada	12,700	0.61%	13

STATE	POPULATION	PERCENT	RANK
New Hampshire	4,500	0.43%	39
New Jersey	30,100	0.44%	36
New Mexico	11,750	0.75%	3
New York	78,600	0.51%	29
North Carolina	44,750	0.60%	16
North Dakota	1,650	0.30%	50
Ohio	39,950	0.45%	34
Oklahoma	18,350	0.64%	8
Oregon	19,750	0.65%	7
Pennsylvania	43,800	0.44%	35
Rhode Island	4,250	0.51%	28
South Carolina	21,000	0.58%	21
South Dakota	2,150	0.34%	46
Tennessee	31,200	0.63%	10
Texas	125,350	0.66%	5
Utah	7,200	0.36%	45
Vermont	3,000	0.59%	19
Virginia	34,500	0.55%	24
Washington	32,850	0.62%	11
West Virginia	6,100	0.42%	42
Wisconsin	19,150	0.43%	38
Wyoming	1,400	0.32%	48

Estimates of Transgender-Identified Adults by Age

Prior research suggests that individuals who identify as transgender are younger, on average, than non-transgender individuals.[8] As expected, we find that younger adults are more likely than older adults to identify as transgender. An estimated 0.7% of adults between the ages of 18 and 24 identify as transgender. Lower percentages of older adults identify as transgender, with 0.6% of adults age 25 to 64 and 0.5% of adults age 65 or older identifying as transgender.

Table 2. Estimated Population of Adults Who Identify as Transgender by Age and State of Residence

STATE	AGE					
	18-24		25-64		65 AND OLDER	
	POPULATION	PERCENTAGE	POPULATION	PERCENTAGE	POPULATION	PERCENTAGE
United States of America	205,850	0.66%	967,100	0.58%	217,050	0.50%
Alabama	3,250	0.67%	15,450	0.61%	3,700	0.53%
Alaska	500	0.60%	1,950	0.48%	250	0.42%
Arizona	4,700	0.72%	20,800	0.63%	4,850	0.50%
Arkansas	1,850	0.65%	9,150	0.61%	2,300	0.52%
California	33,450	0.84%	154,750	0.77%	29,050	0.63%
Colorado	3,200	0.63%	14,900	0.53%	2,750	0.45%
Connecticut	1,750	0.52%	8,450	0.44%	2,100	0.40%
Delaware	700	0.73%	3,050	0.64%	800	0.55%
District of Columbia	2,600	3.14%	9,900	2.66%	1,950	2.72%
Florida	13,450	0.75%	66,750	0.67%	19,350	0.55%
Georgia	8,700	0.86%	39,500	0.75%	7,450	0.66%
Hawaii	1,200	0.89%	5,700	0.77%	1,550	0.72%
Idaho	750	0.47%	3,250	0.41%	750	0.35%
Illinois	7,150	0.57%	34,500	0.50%	7,750	0.46%
Indiana	4,100	0.62%	18,950	0.56%	4,450	0.50%
Iowa	1,100	0.35%	4,900	0.31%	1,350	0.29%
Kansas	1,500	0.49%	6,300	0.43%	1,500	0.38%
Kentucky	2,400	0.57%	12,200	0.52%	3,000	0.49%
Louisiana	3,150	0.66%	14,550	0.60%	3,100	0.52%
Maine	650	0.56%	3,650	0.50%	1,050	0.45%
Maryland	3,200	0.57%	15,650	0.49%	3,300	0.43%
Massachusetts	4,550	0.66%	20,150	0.56%	5,050	0.53%
Michigan	4,800	0.48%	22,400	0.43%	5,600	0.39%
Minnesota	3,450	0.69%	16,750	0.58%	3,950	0.54%
Mississippi	2,100	0.66%	9,400	0.62%	2,150	0.53%
Missouri	3,600	0.60%	17,000	0.54%	4,400	0.50%
Montana	400	0.40%	1,800	0.34%	450	0.30%

STATE	AGE					
	18-24		25-64		65 AND OLDER	
	POPULATION	PERCENTAGE	POPULATION	PERCENTAGE	POPULATION	PERCENTAGE
Nebraska	800	0.44%	3,650	0.39%	900	0.35%
Nevada	1,750	0.70%	9,100	0.61%	1,750	0.49%
New Hampshire	650	0.50%	3,100	0.43%	750	0.39%
New Jersey	3,950	0.51%	21,050	0.44%	5,050	0.41%
New Mexico	1,800	0.85%	8,000	0.75%	1,850	0.62%
New York	11,150	0.56%	54,150	0.51%	12,850	0.47%
North Carolina	6,600	0.68%	31,050	0.60%	7,150	0.53%
North Dakota	300	0.34%	1,050	0.30%	300	0.29%
Ohio	5,550	0.50%	27,150	0.45%	7,000	0.41%
Oklahoma	2,800	0.72%	12,600	0.64%	2,900	0.55%
Oregon	2,800	0.76%	13,700	0.65%	3,150	0.55%
Pennsylvania	6,100	0.48%	29,250	0.44%	8,250	0.40%
Rhode Island	650	0.56%	2,800	0.51%	750	0.46%
South Carolina	3,150	0.64%	14,250	0.58%	3,450	0.50%
South Dakota	350	0.39%	1,400	0.34%	350	0.30%
Tennessee	4,250	0.68%	21,550	0.63%	5,150	0.56%
Texas	19,600	0.73%	88,950	0.66%	15,700	0.55%
Utah	1,350	0.42%	4,950	0.36%	800	0.30%
Vermont	450	0.67%	2,000	0.59%	550	0.53%
Virginia	5,150	0.62%	24,000	0.54%	5,200	0.49%
Washington	4,850	0.73%	23,150	0.62%	4,700	0.52%
West Virginia	750	0.44%	4,150	0.42%	1,200	0.38%
Wisconsin	2,700	0.49%	13,150	0.43%	3,250	0.39%
Wyoming	200	0.37%	1,000	0.32%	200	0.29%

Discussion

Our current best estimate of the percentage of adults who identify as transgender in the United States is double that of the estimate produced by Gary J. Gates in 2011. Several reasons may account for this difference. A perceived increase in visibility and social acceptance of transgender people may increase the number of individuals willing to identify as transgender on a government-administered survey. The Gates estimate was based on data from only two states with very small samples. The current study analyzes population-based data from 19 states that identify transgender individuals. This provides larger samples and a wealth of information about transgender-identified adults not previously available. As a result, more sophisticated estimation procedures are now possible that produce more detailed and robust estimates than were possible in 2011. As new data collection efforts emerge at the state and national levels, estimates can continue to be refined to improve our understanding of the size and characteristics of the transgender population.

Appendix: Methodology and Credible Intervals of Population Estimates

Methodology

The Behavioral Risk Factor Surveillance System (BRFSS) collects state-specific data on health-related factors across the 50 states, the District of Columbia, and the territories of the United States. The survey is designed to be representative within each state. The survey is conducted by an interviewer via landline and cellular telephone. The national response rate for the 2014 BRFSS was 48.7% for landline telephones and 40.5% for cellular telephones (American Association of Public Opinion Research, Response Rate calculation 4).

The BRFSS contains optional module questionnaires in addition to its standard questionnaire for each state.[9] The 2014 BRFSS had 19 optional modules that states were able to opt-into. One of the modules contained the following question:

> Do you consider yourself to be transgender?
>
> Yes
>
> No
>
> [If Yes] Do you consider yourself to be male-to-female, female-to-male, or gender non-conforming?
>
> If the interviewer is asked for a definition of transgender, they respond:
> Some people describe themselves as transgender when they experience a different gender identity from their sex at birth. For example, a person born into a male body, but who feels female or lives as a woman would be transgender. Some transgender people change their physical appearance so that it matches their internal gender identity. Some transgender people take hormones and some have surgery. A transgender person may be of any sexual orientation – straight, gay, lesbian, or bisexual.

Since this question is included in an optional module, some states did not ask this question while others did. The 19 states that did ask this question include: Delaware, Hawaii, Idaho, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maryland, Minnesota, Montana, Nevada, New York, Ohio, Pennsylvania, Vermont, Virginia, Wisconsin, and Wyoming. In total, 0.52% of BRFSS respondents in these states identified as transgender, and 151,456 respondents answered this question.

To estimate the population by state, we relied on multilevel regression and post-stratification.[10] The method fits multilevel logistic regression to the data to predict the likelihood that an individual identifies as transgender relying on demographic attributes about the respondents (e.g., race and ethnicity; age cohorts; and educational attainment). State and regional characteristics were accounted for and state-level characteristics were included to add information about how states differ from one another (e.g., racial composition, median income, percentage of households that are of same-sex couples, and percentage of the population that identifies as Evangelical). This method has been applied to measure statewide political attitudes[11] and to measure Jewish populations.[12] Further, the estimation strategy has undergone rigorous evaluation by other scholars, and these evaluations often show the method produces reliable and valid estimates.[13] While the estimation approach is not without its criticisms,[14] the method remains the best available approach to perform this estimation procedure. A recent research grant was awarded by the National Science Foundation to further refine and build upon the method.[15]

We extend the application of the estimation technique by incorporating all of the states in the BRFSS, even though respondents in only 19 states received the gender identity question. By doing so, we impute the states that did not ask the gender identity question by modeling the probability that a respondent identifies as transgender. The hierarchical model still incorporates the statewide covariates to increase precision in the estimation.[16] All models were estimated using a Hamiltonian Monte Carlo as implemented by the Stan probabilistic programming language.[17] The model was evaluated for appropriate diagnostics before results were presented. In the tables below, 95% credible intervals are provided for both the population estimates and the population estimates by age. A credible interval is a Bayesian equivalent of a confidence interval. A 95% credible interval represents the upper and lower bounds where there is a 0.95 probability an estimate falls between them.

Table A1. Estimated Population of Adults Who Identify as Transgender by State of Residence, 95% Credible Intervals

STATE	POPULATION		PERCENT	
	LOWER BOUND	UPPER BOUND	LOWER BOUND	UPPER BOUND
United States of America	854,066	2,293,511	0.36%	0.95%
Alabama	11,487	46,858	0.31%	1.27%
Alaska	1,634	4,323	0.30%	0.80%
Arizona	17,137	53,889	0.35%	1.09%
Arkansas	6,898	25,072	0.31%	1.12%
California	120,074	378,513	0.42%	1.31%
Colorado	12,094	35,295	0.31%	0.89%
Connecticut	7,454	19,824	0.27%	0.71%
Delaware	3,195	6,176	0.45%	0.87%
District of Columbia	2,608	66,391	0.50%	12.63%
Florida	58,364	163,960	0.38%	1.07%
Georgia	31,243	97,981	0.42%	1.32%
Hawaii	6,310	11,215	0.58%	1.03%
Idaho	3,403	6,800	0.29%	0.58%
Illinois	30,519	77,228	0.31%	0.79%
Indiana	21,867	35,060	0.44%	0.71%
Iowa	4,558	10,398	0.19%	0.44%
Kansas	7,183	11,706	0.33%	0.54%
Kentucky	13,092	23,060	0.39%	0.69%
Louisiana	15,582	27,230	0.45%	0.78%
Maine	3,202	8,895	0.30%	0.84%
Maryland	17,177	28,088	0.38%	0.62%
Massachusetts	17,251	49,307	0.33%	0.94%
Michigan	19,132	52,059	0.25%	0.68%
Minnesota	19,368	30,211	0.47%	0.74%
Mississippi	6,731	27,122	0.30%	1.21%
Missouri	13,512	43,611	0.29%	0.94%
Montana	1,880	3,669	0.24%	0.47%
Nebraska	3,247	8,207	0.23%	0.59%
Nevada	8,570	18,018	0.41%	0.86%
New Hampshire	2,693	7,362	0.26%	0.70%
New Jersey	17,981	49,987	0.26%	0.73%
New Mexico	6,613	19,959	0.42%	1.27%
New York	57,043	103,813	0.37%	0.68%

STATE	POPULATION		PERCENT	
	LOWER BOUND	UPPER BOUND	LOWER BOUND	UPPER BOUND
North Carolina	26,299	76,786	0.35%	1.03%
North Dakota	961	2,785	0.18%	0.51%
Ohio	30,705	50,183	0.35%	0.56%
Oklahoma	9,049	37,798	0.31%	1.31%
Oregon	10,774	36,440	0.35%	1.20%
Pennsylvania	33,506	56,799	0.33%	0.57%
Rhode Island	2,493	6,979	0.30%	0.84%
South Carolina	12,139	38,343	0.33%	1.05%
South Dakota	1,279	3,592	0.20%	0.57%
Tennessee	16,601	60,319	0.33%	1.22%
Texas	71,791	212,200	0.38%	1.11%
Utah	3,338	16,157	0.17%	0.82%
Vermont	2,126	4,034	0.42%	0.80%
Virginia	26,945	44,697	0.43%	0.71%
Washington	18,574	57,196	0.35%	1.08%
West Virginia	3,518	10,477	0.24%	0.71%
Wisconsin	13,920	25,364	0.32%	0.58%
Wyoming	945	2,073	0.22%	0.47%

Table A2. Estimated Population of Adults Who Identify as Transgender by Age and State of Residence, 95% Credible Intervals

STATE	AGE					
	18-24		25-64		65 AND OLDER	
	POPULATION [LB, UB]	PERCENTAGE [LB, UB]	POPULATION [LB, UB]	PERCENTAGE [LB, UB]	POPULATION [LB, UB]	PERCENTAGE [LB, UB]
United States of America	[121,074, 354,454]	[0.39%, 1.13%]	[569,753, 1,649,712]	[0.34%, 1.00%]	[132,175, 360,271]	[0.31%, 0.84%]
Alabama	[1,624, 7,089]	[0.33%, 1.46%]	[7,630, 32,564]	[0.30%, 1.29%]	[1,868, 7,887]	[0.27%, 1.13%]
Alaska	[282, 806]	[0.35%, 0.99%]	[1,132, 3,210]	[0.28%, 0.81%]	[157, 434]	[0.25%, 0.69%]
Arizona	[2,562, 8,556]	[0.39%, 1.31%]	[11,120, 37,886]	[0.34%, 1.14%]	[2,708, 8,560]	[0.28%, 0.88%]
Arkansas	[966, 3,550]	[0.34%, 1.23%]	[4,614, 17,456]	[0.31%, 1.16%]	[1,185, 4,384]	[0.27%, 0.99%]
California	[18,464, 60,029]	[0.46%, 1.50%]	[83,407, 274,478]	[0.41%, 1.36%]	[15,871, 51,075]	[0.35%, 1.11%]
Colorado	[1,796, 5,616]	[0.35%, 1.10%]	[8,404, 25,994]	[0.30%, 0.92%]	[1,595, 4,612]	[0.26%, 0.76%]
Connecticut	[1,024, 2,942]	[0.30%, 0.86%]	[4,988, 14,281]	[0.26%, 0.74%]	[1,253, 3,458]	[0.24%, 0.65%]
Delaware	[451, 974]	[0.49%, 1.05%]	[2,061, 4,417]	[0.43%, 0.92%]	[541, 1,074]	[0.38%, 0.76%]
District of Columbia	[470, 11,880]	[0.57%, 14.48%]	[1,786, 47,078]	[0.48%, 12.65%]	[361, 9,351]	[0.51%, 13.10%]
Florida	[7,554, 23,144]	[0.42%, 1.29%]	[37,404, 114,026]	[0.37%, 1.14%]	[11,453, 32,341]	[0.33%, 0.92%]
Georgia	[4,847, 16,177]	[0.48%, 1.59%]	[21,496, 71,304]	[0.41%, 1.35%]	[4,147, 13,309]	[0.37%, 1.17%]
Hawaii	[845, 1,662]	[0.62%, 1.23%]	[4,005, 7,975]	[0.54%, 1.08%]	[1,088, 2,098]	[0.51%, 0.99%]
Idaho	[500, 1,087]	[0.32%, 0.69%]	[2,224, 4,882]	[0.28%, 0.61%]	[525, 1,068]	[0.25%, 0.50%]
Illinois	[4,255, 11,778]	[0.34%, 0.94%]	[20,559, 55,749]	[0.30%, 0.81%]	[4,668, 12,533]	[0.28%, 0.74%]
Indiana	[3,045, 5,579]	[0.46%, 0.84%]	[14,012, 25,792]	[0.41%, 0.76%]	[3,457, 5,802]	[0.39%, 0.65%]
Iowa	[656, 1,617]	[0.21%, 0.52%]	[2,963, 7,376]	[0.19%, 0.47%]	[841, 1,939]	[0.18%, 0.41%]
Kansas	[1,065, 1,978]	[0.36%, 0.66%]	[4,565, 8,465]	[0.31%, 0.58%]	[1,130, 1,919]	[0.29%, 0.49%]
Kentucky	[1,665, 3,374]	[0.39%, 0.80%]	[8,649, 16,904]	[0.37%, 0.73%]	[2,190, 3,949]	[0.36%, 0.64%]
Louisiana	[2,204, 4,371]	[0.46%, 0.92%]	[10,310, 20,236]	[0.43%, 0.84%]	[2,260, 4,181]	[0.38%, 0.71%]
Maine	[378, 1,146]	[0.32%, 0.98%]	[2,120, 6,268]	[0.29%, 0.87%]	[607, 1,739]	[0.27%, 0.77%]
Maryland	[2,303, 4,398]	[0.41%, 0.78%]	[11,347, 21,316]	[0.35%, 0.66%]	[2,461, 4,307]	[0.32%, 0.57%]
Massachusetts	[2,568, 7,807]	[0.37%, 1.13%]	[11,326, 34,087]	[0.31%, 0.95%]	[2,832, 8,391]	[0.30%, 0.88%]
Michigan	[2,655, 7,870]	[0.27%, 0.79%]	[12,593, 37,168]	[0.24%, 0.72%]	[3,240, 8,999]	[0.23%, 0.63%]
Minnesota	[2,541, 4,552]	[0.51%, 0.91%]	[12,539, 22,498]	[0.44%, 0.78%]	[3,043, 5,080]	[0.42%, 0.70%]

STATE	AGE					
	18-24		25-64		65 AND OLDER	
	POPULATION [LB, UB]	PERCENTAGE [LB, UB]	POPULATION [LB, UB]	PERCENTAGE [LB, UB]	POPULATION [LB, UB]	PERCENTAGE [LB, UB]
Mississippi	[1,009, 4,310]	[0.32%, 1.37%]	[4,490, 19,158]	[0.29%, 1.26%]	[1,036, 4,327]	[0.26%, 1.08%]
Missouri	[1,876, 6,423]	[0.32%, 1.08%]	[8,975, 30,421]	[0.29%, 0.97%]	[2,324, 7,535]	[0.26%, 0.85%]
Montana	[266, 572]	[0.27%, 0.58%]	[1,222, 2,592]	[0.23%, 0.49%]	[323, 650]	[0.21%, 0.41%]
Nebraska	[473, 1,264]	[0.25%, 0.68%]	[2,143, 5,820]	[0.23%, 0.61%]	[551, 1,389]	[0.21%, 0.54%]
Nevada	[1,135, 2,646]	[0.45%, 1.04%]	[5,889, 13,545]	[0.40%, 0.92%]	[1,150, 2,547]	[0.32%, 0.71%]
New Hampshire	[356, 1,067]	[0.28%, 0.85%]	[1,798, 5,237]	[0.25%, 0.72%]	[450, 1,244]	[0.23%, 0.64%]
New Jersey	[2,265, 6,732]	[0.29%, 0.86%]	[12,204, 36,508]	[0.25%, 0.76%]	[3,013, 8,517]	[0.24%, 0.68%]
New Mexico	[988, 3,255]	[0.46%, 1.53%]	[4,389, 14,044]	[0.41%, 1.32%]	[1,011, 3,160]	[0.34%, 1.07%]
New York	[7,732, 15,788]	[0.39%, 0.79%]	[37,363, 76,111]	[0.35%, 0.72%]	[9,137, 17,614]	[0.33%, 0.64%]
North Carolina	[3,765, 11,609]	[0.39%, 1.19%]	[17,757, 54,557]	[0.34%, 1.06%]	[4,194, 12,219]	[0.31%, 0.91%]
North Dakota	[170, 531]	[0.19%, 0.59%]	[593, 1,834]	[0.17%, 0.51%]	[170, 498]	[0.17%, 0.50%]
Ohio	[4,001, 7,561]	[0.36%, 0.68%]	[19,701, 36,836]	[0.32%, 0.61%]	[5,251, 9,125]	[0.31%, 0.54%]
Oklahoma	[1,351, 6,063]	[0.35%, 1.56%]	[6,026, 26,649]	[0.31%, 1.36%]	[1,438, 6,011]	[0.27%, 1.13%]
Oregon	[1,512, 5,190]	[0.41%, 1.42%]	[7,380, 25,644]	[0.35%, 1.22%]	[1,714, 5,934]	[0.30%, 1.02%]
Pennsylvania	[4,284, 8,404]	[0.34%, 0.67%]	[21,090, 40,686]	[0.31%, 0.60%]	[6,172, 10,959]	[0.30%, 0.54%]
Rhode Island	[389, 1,143]	[0.32%, 0.95%]	[1,608, 4,817]	[0.29%, 0.87%]	[424, 1,219]	[0.27%, 0.77%]
South Carolina	[1,784, 5,944]	[0.36%, 1.21%]	[7,977, 26,549]	[0.32%, 1.08%]	[1,963, 6,533]	[0.28%, 0.94%]
South Dakota	[188, 577]	[0.22%, 0.69%]	[827, 2,452]	[0.20%, 0.58%]	[217, 631]	[0.18%, 0.52%]
Tennessee	[2,220, 8,664]	[0.36%, 1.39%]	[11,036, 42,384]	[0.32%, 1.24%]	[2,740, 9,962]	[0.30%, 1.09%]
Texas	[10,763, 33,983]	[0.40%, 1.27%]	[49,965, 156,972]	[0.37%, 1.16%]	[8,906, 27,059]	[0.31%, 0.95%]
Utah	[617, 3,133]	[0.19%, 0.96%]	[2,244, 11,329]	[0.16%, 0.83%]	[385, 1,804]	[0.14%, 0.67%]
Vermont	[299, 629]	[0.46%, 0.96%]	[1,364, 2,844]	[0.40%, 0.84%]	[372, 745]	[0.38%, 0.75%]
Virginia	[3,798, 6,980]	[0.46%, 0.85%]	[17,590, 33,074]	[0.40%, 0.75%]	[3,987, 7,026]	[0.38%, 0.66%]
Washington	[2,662, 8,550]	[0.40%, 1.29%]	[12,748, 41,018]	[0.34%, 1.10%]	[2,655, 8,291]	[0.29%, 0.91%]
West Virginia	[427, 1,325]	[0.25%, 0.76%]	[2,347, 7,299]	[0.24%, 0.74%]	[687, 2,040]	[0.22%, 0.66%]
Wisconsin	[1,883, 3,799]	[0.34%, 0.69%]	[9,141, 18,414]	[0.30%, 0.61%]	[2,287, 4,434]	[0.28%, 0.54%]
Wyoming	[135, 328]	[0.23%, 0.57%]	[634, 1,509]	[0.21%, 0.49%]	[141, 308]	[0.19%, 0.41%]

*Note: LB=95% Lower bound; UB=95% Upper bound

ENDNOTES

[1] For a discussion of gender identity data collection in federal population-based surveys and recommended measures, see The GenIUSS Group. (2014). *Best Practices for Asking Questions to Identify Transgender and Other Gender Minority Respondents on Population-Based Surveys*. J.L. Herman (Ed.). Los Angeles, CA: The Williams Institute, available at http://williamsinstitute.law.ucla.edu/wp-content/uploads/geniuss-report-sep-2014.pdf.

[2] Gates, G.J. (2011). *How many people are lesbian, gay, bisexual, and transgender?* Los Angeles, CA: The Williams Institute, available at http://williamsinstitute.law.ucla.edu/wp-content/uploads/Gates-How-Many-People-LGBT-Apr-2011.pdf. A more recent report that was released in March 2016 provided estimates of the transgender population ages 13 and above in 15 states ("Estimates of Transgender Populations in States with Legislation Impacting Transgender People, available at http://williamsinstitute.law.ucla.edu/research/census-lgbt-demographics-studies/estimates-of-transgender-populations-in-states-with-legislation-impacting-transgender-people/). These estimates were based on Gates' 2011 study and other estimates of the transgender youth population. We believe the current study provides more robust estimates of the percentage of transgender-identified adults in those 15 states.

[3] A detailed description of the methodology for this study is included in the Appendix and further details will be included in a separate document published alongside this report.

[4] For national and state estimates provided in this report, adult general population figures from the U.S. Census Bureau's American Community Survey, 2011-2013 3-year PUMS, were multiplied by the estimated percentage of transgender-identified adults to yield the estimated number of transgender-identified adults.

[5] The District of Columbia is not included in this range for states. DC had a notably high percentage of transgender-identified adults (2.8%) and is considered an outlier due to its unique geographic (urban) and demographic profile.

[6] See note #5.

[7] See note #5.

[8] See, for instance, Conron, K.J., Scott, G., Stowell, G.S., and Landers, S. J. (2012). Transgender Health in Massachusetts: Results from a Household Probability Sample of Adults. *American Journal of Public Health, 102*(1), 118-122.

[9] For more detailed information on gender identity data collection in the BRFSS, see Baker, K.E. & Hughes, M. (2016). *Sexual Orientation and Gender Identity Data Collection in the Behavioral Risk Factor Surveillance System*. Washington, DC: The Center for American Progress, available at https://cdn.americanprogress.org/wp-content/uploads/2016/03/29090401/BRFSSdatacollect-brief-03.31.16.pdf.

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[15] NSF-1424962. (2014-2017). Using multilevel regress and post-stratification to measure and study dynamic public opinion.

[16] See Flores, A.R. (2016). *Estimating the adult population that identifies as transgender in the BRFSS.* Los Angeles, CA: The Williams Institute, UCLA.

[17] Stan Development Team. (2016) RStan: The R interface to Stan, version 2.9.0. http://mc-stan.org.

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The art of medicine

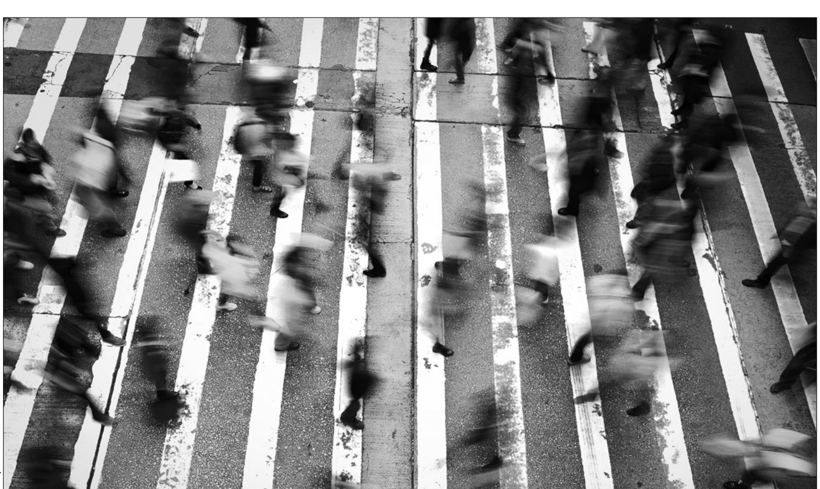
The misuses of "biological sex"

Whether one is entering into military service, seeking identity documents, or participating in sports, the categorisation of bodies according to "sex" is central to the organisation of society. Who is categorised as a woman and who is categorised as a man may seem like simple questions, but making a determination of sex has long been understood as far from straightforward.

For a century, scientists studied an array of human characteristics that inform our ideas of what makes someone a woman or a man, seeking to pin down a single, definitive biological indicator of sex. Bodies troubled these schemes and socially untenable categorisations ensued. If gonads were understood as the essence of sex, women who were phenotypically female but who had testes were men. This seemed illogical, so scientists proposed yet other traits. Even as they debated which biological trait or combination of traits signalled its essence, scientists understood sex as biological and involving multiple, if contested, factors.

Contemporary scientific understanding of sex and its relation to gender was greatly influenced by the work of psychologist John Money, at Johns Hopkins University, USA, beginning in the 1950s. With colleagues, Money further complicated approaches to sex by identifying a range of biological and social factors. Chromosomes, gonads, hormones, and internal and external genital morphology were considered alongside social factors such as assigned sex and rearing, and gender role and sexual orientation. His ideas gained traction, and scientists and medical professionals came to accept sex as inherently knotty: that its "variables" are multiple, come in far more than two versions, and that no single biological factor is determinative.

Research since has expanded the range of variables that produce sex. As one example, the Y chromosome was once said to trigger testes development in fetuses. Later research showed a gene called *SRY*, located on the Y chromosome, "pushed" primordial germ cells in the embryo to become testes. We now know there are active genes involved in both ovary and testis determination across the genome, and not restricted to the X and Y chromosomes. As biologist Anne Fausto-Sterling has observed, "[T]hose looking to biology for an easy-to-administer definition of sex and gender can derive little comfort from the most important of these [research] findings."



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If what we know of sex is its multiplicity, this introduces a conundrum: which factors to use in categorising and defining sex? Policy makers who formulate sex categorisations and definitions overwhelmingly rely on biological features to ground membership. Biological factors hold appeal and power since reference to "biology" and "science" lends any suggested trait or combination of traits the appearance of neutrality and thus objectivity. But biological definitions of sex are at odds with the understanding that sex involves multiple biological and social factors. They are also at odds with social scientific work that complicates the idea that sex is biological whereas gender is cultural; sex, as much as gender, is culturally contingent and produced. As J R Latham notes, "sex" is not a static, discrete, or even strictly biological characteristic that exists prior to the relations and practices that produce it. Historian of science Sarah Richardson, for example, has shown how scientists "sexed" the X and Y chromosomes by glossing over inconsistencies and ambiguities between the two in their research to elevate findings that align with gendered ideas about biological sex differences.

Decisions about which traits or sets of traits are used, in what combination, and for what purpose are inextricably tied to why sex categorisation exists and whom or what it serves. Far from neutral or objective, sex classification and definition rely on cultural norms about the "appropriate" relationships between sex, gender, and sexuality, and work in tandem with power to support social norms and goals as well as sociopolitical hierarchies that determine opportunities, rights, and privileges.

Not surprisingly, there is a long history of using—and misusing—discrete biological criteria to determine sex and thereby include or exclude certain people from categories. Just this year, the administration of US President Donald Trump began requiring military personnel to serve "in their biological sex", which they define as "a person's biological status as male or female based on chromosomes, gonads, hormones, and genitals" (treating these as congruent). Meanwhile, in a leaked memo, the US Department of Health and Human Services (HHS) proposed establishing a federal legal definition of sex "on a biological basis that is clear, grounded in science, objective and administrable". Using early 20th-century criteria, HHS suggested defining individuals as "either male or female, unchangeable, and determined by the genitals that a person is born with", and in yet another definition, "male or female based on immutable biological traits identifiable by or before birth".

For many, these proposed methods for categorisation suggest a commonsense and clear-cut assessment. The US military definition of sex relies on the sex designation on a birth certificate, which is likely based on a glance at the genitals at birth. But its definition of biological sex includes "chromosomes, gonads, hormones, and genitals"—that is, all four characteristics. Someone with what are understood as female-typical genitals and 46,XY chromosomes would be classified as female if genitals are used as the indicator but male if chromosomes are used. The HHS-suggested definition appears to directly prioritise genitals yet gives chromosomes a role too.

Science does not drive these policies; the desire to exclude does. This intentional gerrymandering of sex opportunistically uses the idea of "biological sex"—which lends a veneer of science and thus rationality to any definition—to remove certain individuals from a category based on intolerance. One result is the nullification of the Title IX protections that were expanded under the Obama administration—laws applicable to transgender individuals and people with certain differences of sex development who serve in the military or otherwise seek to be safeguarded from discrimination.

The Trump administration's appeal to "biological sex" has parallels in international elite sport. "The biological sex... must prevail", thundered an official for the International Association of Athletics Federations (IAAF), in the context of a rancorous decades-long battle over sex-testing policies used to determine which women are allowed to compete in the female category. The IAAF's appeal to biological sex is an example of how power, not science, comes to shape sex categorisation. In the 1960s, athletes were sex tested using physical examinations; in the 1970s, chromosomal testing was used. By 2011, sex testing regulations focused exclusively on testosterone (T), and any woman with higher than typical levels of naturally occurring T could not compete in the female category. The rationale for this hinged on T's purported role in athletic performance: high levels of T were said to give some women an unfair "masculine" advantage over their competitors. Their solution: women can lower their T levels or forego sport competition. However, the data didn't support the claim underpinning the regulations: that higher T necessarily improves athletic performance. The IAAF scrambled for a new biological indicator, seizing on a combination of chromosomes and internal reproductive organs, and announced a new, special type of categorisation that was designated "sport sex". This is a category of sex relevant to one unique context: elite sport. Women with high endogenous T could now compete—if they had a specific combination of chromosomes and reproductive organs. Exclusion is based on a woman's primary source of endogenous T, rather than her T level per se.

The newest T regulations were designed by policy makers as an end-run around strict and deterministic criteria for inclusion in the female category—that is, sex testing. But once T couldn't be shown to have the role in athleticism they claimed, they turned to their own idiosyncratic definition of biological sex to keep women with atypical sex traits out of the female category. While the IAAF's focus on women's chromosomes and gonads was a method of calling out certain women as not "really" women, they attempted to cement this notion by then also inaccurately deeming them "biological males".

Debates about sex are often framed falsely as scientific versus cultural arguments, whereby the former by virtue of being grounded in biology are seen as tied to nature and thus truth, whereas the latter are seen as hectoring from a postmodern gender La La Land. T regulation supporters, for example, have argued that critics of the policy misunderstand, or worse, obscure the scientific facts of sex. Yet this profoundly misconstrues who is hewing to science. Those questioning simplistic understandings of sex—scientists among them—are hardly unscientific, but rather keen observers of the science of sex biology and the peculiar categorical gatekeeping of, say, soldiers and elite women athletes. This is not a case of science versus social constructionism as some argue; it's about the calculated use of "biological sex" to buttress obsolete thinking about sex.

Years ago I wondered, "if one postulates bodies (including genitals, gonads, chromosomes, and hormones), what more does the word sex buy us?...The body as a material fact is given, but sex is not." It is long overdue that we understand sex not as an essential property of individuals but as a set of biological traits and social factors that become important only in specific contexts, such as medicine, and even then complexity persists. If we are concerned with certain cancers, for example, knowing whether someone has a prostate or ovaries is what's important, not their "sex" per se. If reproduction is the interest, what matters is whether one produces sperm or eggs, whether one has a uterus, a vaginal opening, and so on. For those arenas where it's not clear what purpose sex designation serves, we might question whether we need it at all. Doing so could lead to better science and health care, and, crucially, less harm.

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I am co-author, with Rebecca M Jordan-Young, of *Testosterone: an Unauthorized Biography* (Harvard University Press, 2019).

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