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A Gender Hypothesis of sex disparities in adverse drug events

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ABSTRACT

Pharmacovigilance databases contain larger numbers of adverse drug events (ADEs) that occurred in women compared to men. The cause of this disparity is frequently attributed to sex-linked biological factors. We offer an alternative Gender Hypothesis, positing that gendered social factors are central to the production of aggregate sex disparities in ADE reports. We describe four pathways through which gender may influence observed sex disparities in pharmacovigilance databases: healthcare utilization; bias and discrimination in the clinic; experience of a drug event as adverse; and pre-existing social and structural determinants of health. We then use data from the U.S. FDA Adverse Event Reporting System (FAERS) to explore how the Gender Hypothesis might generate novel predictions and explanations of sex disparities in ADEs in existing widely referenced datasets. Analyzing more than 37 million records of ADEs between 2014 and 2022, we find that patient-reported ADEs show a larger female skew than healthcare provider-reported ADEs and that the sex disparity is markedly smaller for outcomes involving death or hospitalization. We also find that the sex disparity varies greatly across types of ADEs, for example, cosmetically salient ADEs are skewed heavily female and sexual dysfunction ADEs are skewed male. Together, we interpret these findings as providing evidence of the promise of the Gender Hypothesis for identifying intervenable mechanisms and pathways contributing to sex disparities in ADEs. Rigorous application of the Gender Hypothesis to additional datasets and in future research studies could yield new insights into the causes of sex disparities in ADEs.

1. Introduction

Research on drug safety persistently cites statistics showing higher rates of adverse drug events (ADEs) in women compared to men, with some claiming the rate to be 1.5–1.7 times higher for women (R. M. Martin et al., 1998), and others generalizing this statistic to "nearly twice as often as men" (Tharpe, 2011; Zucker and Prendergast, 2020). These striking statistics, suggesting a large and intransigent sex disparity in ADEs, have made addressing ADEs a health equity priority for health agencies and women's health advocates and have been extensively cited to bolster calls and mandates for additional research into biological sex differences (Clayton and Collins, 2014; Rabin, 2013; Sandberg and Verbalis, 2013).

An alternative, under-explored view is that—after adjustment for sex-specific drugs and conditions such as those related to pregnancy—gendered social, demographic, and other factors (such as body weight, age, polypharmacy, and prescription drug usage rates) largely explain the observed sex disparity in ADEs in pharmacovigilance data. This paper elaborates this view, proposing a *Gender Hypothesis of Sex Disparities in ADE*. According to this hypothesis, gender-related social factors are central to the production of aggregate sex disparities in ADE rates.

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Specifically, the Gender Hypothesis predicts that, due to gendered social factors, one gender/sex-class may be more likely to experience an ADE, have this ADE taken seriously by medical professionals, and/or bring this ADE to the attention of medical professionals and pharmacovigilance databases. The Gender Hypothesis does not rule out a role for biological sex-related factors in interaction with social factors that compound or attenuate a disparity in ADEs. Rather, the Gender Hypothesis engages with the call to recognize the multidimensionality of gender/sex (Bauer, 2023) and makes visible the myriad ways that gender shapes definitions of disease or disorder, how people interact with various forms of healthcare, and how people subjectively experience adverse events.

This paper motivates and develops the Gender Hypothesis of male-female sex disparities in adverse drug events and demonstrates the hypothesis's promise to generate novel explanations and predictions for analyzing and interpreting existing datasets as well as for incorporation in future research designs. First, we articulate four interconnected pathways through which gender-related related factors might influence sex disparities in ADE. Second, we demonstrate how the Gender Hypothesis offers concrete, testable predictions and suggests novel avenues for future research on ADE sex disparities, using data from the FDA Adverse Event Reporting System (FAERS). In the closing discussion, we address potential challenges and limitations and outline a forward-looking agenda for the consideration of gendered factors in ADE research.

Across the social science and biomedical literature, there are a number of terms that are used sometimes interchangeably when discussing sex and gender in the context of health disparities (Rioux et al., 2022). Similar to Danielsen et al. (2022), in the following, we use the terms "male" and "female" to refer to biological sex as well as to the categories labeled as "male" and "female" in existing datasets. ,while we use the terms "man" and "woman" when discussing social categories and gendered experiences. "Gender" refers to individual identity as well as to social structures and power relations that inequitably distribute power and resources across genders/sexes. We use the term "gender/sex" when discussing topics where it is difficult to disentangle the contributions of sex and gender on an outcome (van Anders, 2015), and we use the term "gender" alone when referring to the social and cultural roles, expectations, and interactions within and between people. Finally, we use the commonly used term "sex disparities" as shorthand to refer to male-female comparisons in existing datasets.

2. Gendered pathways in adverse drug event reporting

The existence of an ADE report in a pharmacovigilance database is the endpoint of a multistep process that begins with an individual experiencing a condition that could receive a drug treatment, then proceeding to actually receive the drug treatment, identify an outcome as adverse, and report an ADE to the database. Gendered factors can enter at each of these steps (Fig. 1). The literature on gender and medicine suggests multiple possible pathways by which gender might influence sex disparities in ADE reports.

2.1. First pathway: healthcare utilization

Acknowledging heterogeneity across social groups defined by race/ethnicity, class, and other minoritized statuses, in the US, women utilize healthcare at far higher rates than men (Manuel, 2018), and may be therefore more likely to be prescribed pharmaceuticals. Higher rates of drug prescription and usage among women increases the risk of experiencing an adverse event (Rushovich et al., 2023). It is well established that women participate in health seeking behavior and interface more frequently with medical professionals (Bertakis et al., 2000; Escoffery, 2018; Rana et al., 2020; Xu and Borders, 2003). Personal healthcare spending is higher in women than men (Lassman et al., 2014) across all age categories (Centers for Medicare & Medicaid Services, 2014), which is not fully explained by the costs of maternity care in some demographic age strata and spending categories. In general, women are more likely

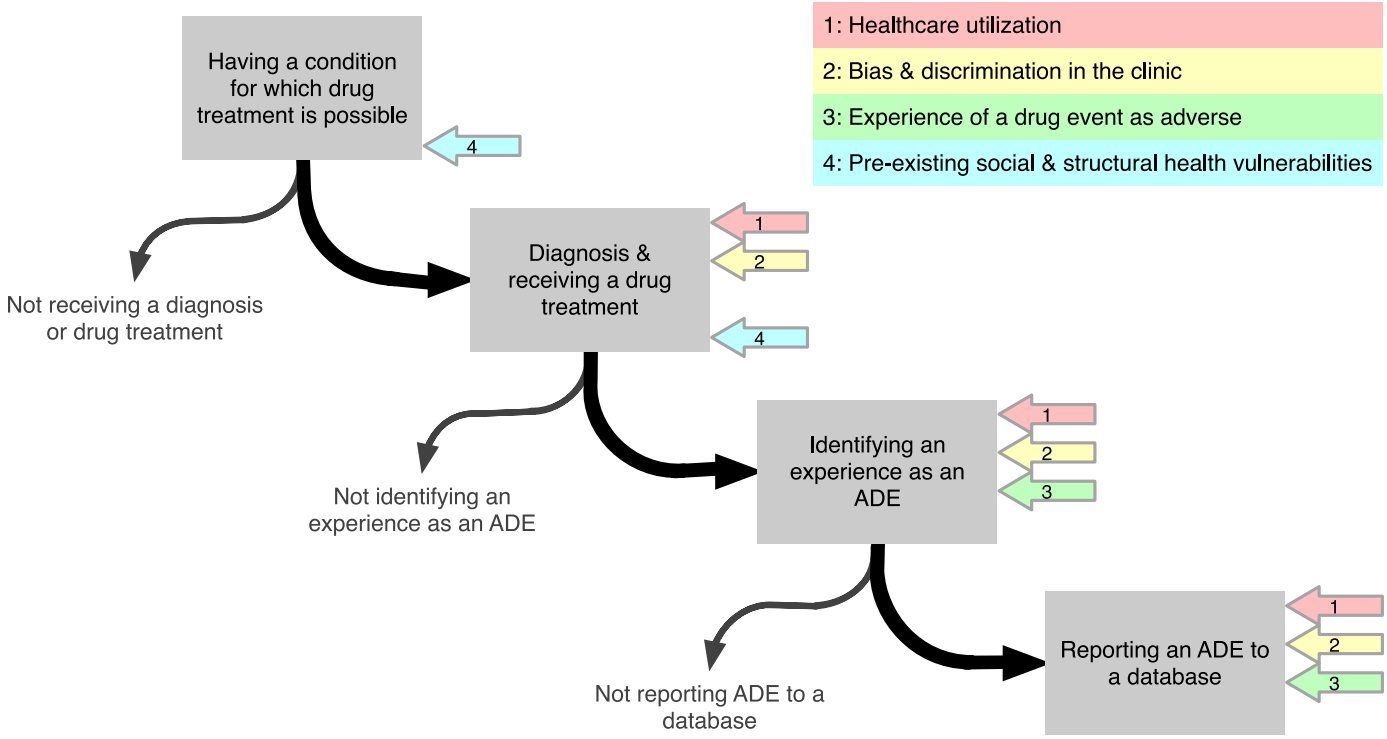

Fig. 1. Title: Hypothesized gendered pathways at each step in the adverse drug event (ADE) reporting process: The gray boxes represent key points in the ADE reporting process from having a treatable condition to reporting an ADE in a pharmacovigilance database. The numbered arrows represent places where gendered pathways may influence the next step in the process.

than men to visit primary care providers and specialists for physical and mental health concerns, and this remains true even after accounting for sex-specific conditions and across a variety of medical care provision contexts (Bertakis et al., 2000; Green and Pope, 1999; Thompson et al., 2016; Vogel et al., 2014). Men's avoidance or underutilization of primary care (or women's over-utilization) has downstream effects, including the likelihood that concerns will be identified and addressed later in the disease process, contributing to poorer outcomes.

Gendered beliefs as well as gendered structural factors likely contribute to different rates of healthcare utilization by men and women. In a U.S. context, masculine norms contribute to men's tendencies to downplay illness, wait for symptoms to resolve without intervention, and delay seeking care (Bertakis et al., 2000; Galdas et al., 2005; Mackenzie et al., 2006; Yousaf et al., 2015). Men report attitudinal and access barriers to seeking care, such as not wanting to be a "bother" or "burden" to others and described "waiting it out" as a strategy (Locke et al., 2022). In contrast, women are often socialized as responsible for advocating for their own and their families' health needs and overall well-being, in part due to the existence of powerful gender norms that feminize care work and prioritize monitoring reproductive health (Collins, 2019; Damaske, 2022; Glabau, 2022; Murphy, 2006, 2012; O'Rourke, 2022; Wilkerson, 2018).

2.2. Second pathway: bias and discrimination in the clinic

Gender stereotypes at the clinical interface, in interaction with race, class, and other markers of social status, affect the likelihood that an individual will be diagnosed with a condition (Russell et al., 2011), the alacrity with which they are treated for that condition (Liaudat et al., 2018), the likelihood of referral for specialist care (Adamson et al., 2003; Franks and Clancy, 1997), and the likelihood of being prescribed a particular drug for that condition (Morabia et al., 1992). Women with ADHD are more easily overlooked and less likely to be prescribed medication for ADHD (Mowlem et al., 2019), and more likely to be misdiagnosed and receive inappropriate treatments for ADHD (Waite, 2007). A stream of scholarship on gender bias in the diagnosis of heart disease demonstrates that sex-stereotyping of symptoms leads to poorer cardiovascular outcomes for women, including a study demonstrating that women with chest pain are 2.5 times less likely to be referred to a cardiologist than men (Liaudat et al., 2018). Yet another classic example is the well documented role of gender norms and gender role expectations in the management of pain, resulting in the psychologization of women's complaints leading women to receive less adequate pain medication and more antidepressants than men (Racine et al., 2014). Such striking evidence of the health implications of gender bias in the patient encounter and in clinicians' treatment decisions undergirds recent efforts to expose clinicians to anti-bias trainings and other interventions (e.g., Metzl and Hansen, 2014; Hughto et al., 2015). Gender bias and discrimination in the clinic carries potential implications for the reporting of adverse events. Gendered interactional factors such as the perception of an individual as being of a particular gender or as having a particular sex/gender role may affect the likelihood of an adverse event being reported to or taken seriously by a clinician (Anspach, 2010; Hamberg, 2008; McMurray et al., 1991), as well as the hazard of misdiagnosis and/or inappropriate therapies.

2.3. Third pathway: gendered factors in the subjective experience of perception of an event as adverse

A compelling stream of scholarship demonstrates how gendered factors—such as gender stereotypes, stigma, identities and social norms—influence how events are subjectively experienced (see e.g. Eckermann, 2013; Poláčková Šolcová and Lačev, 2017). This research has implications for understanding sex differences in ADEs. The role of such gendered factors is particularly stark when considering appearance-related ADEs. Consider, for example, weight gain, a frequently reported ADE. Studies show that women tend to perceive weight gain more negatively and report experiencing greater stigma from weight gain than do men (Barbui et al., 2005; Haack et al., 2009; Sattler et al., 2018). This suggests that women may be more likely than men to categorize and report a given event of weight gain as adverse. Certain appearance-related gender norms also influence nonbinary and trans individuals, with implications for ADE reporting: one study, for example, suggested that trans women may sustain a greater degree of distress than trans men in response to androgenetic alopecia since "hair loss, particularly with frontal M-shaped hairline recession and vertex thinning, represents a characteristically male phenotype" (Marks and Senna, 2020).

Gendered factors may also influence observed sex differences in ADEs unrelated to appearance. For instance, studies show that individuals who identify more strongly with idealized "masculine" gender norms (e.g. "boys don't cry") show higher pain tolerance than those who don't (Pool et al., 2007), and may thus be less likely to experience and report a given event as adverse. Research also indicates that masculinity norms may make men more likely to report issues related to sexual function – e.g. Hendren et al. (2005) found that men are more likely than women to report that surgery for rectal cancer made their "sexual life worse", though men and women both report concerns about ostomy, bowel function, and body image as specific reasons alongside sex-specific genital-based concerns such as vaginal dryness and erectile dysfunction (Hendren et al., 2005).

2.4. Fourth pathway: upstream genered social and structural determinants of health

We live in a highly gender-stratified world in which men and women experience, on average, different environments and exposures. Gender contributes—in interaction with race, socioeconomic status, sexuality and other social categories—to health status via a multitude of mechanisms (Heise et al., 2019; Homan, 2019; Krieger, 2003). Women are more likely than men to live in poverty (Shrider et al., 2021), experience intimate partner violence (Sumner et al., 2015), and encounter sexual harassment and violence at work (Clancy et al., 2014, 2017; McCall and Horwitz, 2004; Sexual Harassment in Our Nation's Workplaces, 2022), all of which are associated with increased risk of mental and physical health problems. These and other upstream experiences and exposures create preexisting vulnerabilities that structure the likelihood of experiencing debility or disability, and health status is a well-evidenced risk factor for ADEs (Bates et al., 1999).

For example, gender is one of the factors that influences exposure to phthalates, volatile organic compounds (VOCs), and other carcinogenic and endocrine-disrupting chemicals. Gendered (and racialized) beauty standards lead to differential exposures to numerous toxins, such as those found in hair and nail products (Eberle et al., 2020; Ma et al., 2019). Higher exposure to phthalates from personal care products (Duty et al., 2005; Pagoni et al., 2022), diapers, and menstrual hygiene products (Park et al., 2019) partly explains why phthalates tend to be present in higher concentrations in women compared to men (Blount et al., 2000; Silva et al., 2004). Occupational exposure to chemicals such as phthalates is also often highly gendered such as through increased exposure for men working in plastics manufacturing (Petrovičová et al., 2016) and increased exposure for women working in hair and nail salons (Quiros-Alcala et al., 2019).

2.5. Predictions of the gender hypothesis

These pathways, individually and in interaction with one another, give rise to several testable predictions of the Gender Hypothesis. The Gender Hypothesis predicts that an empirically measurable, explanatorily significant portion of the disparity between men and women in rates of ADEs, after adjustment for sex-specific conditions, may be explained by social-contextual factors. Specifically, it predicts that sex

differences in ADE rates, whether reported in clinical studies for particular drug formulations or health conditions, in contexts such as clinics and institutional settings, or in pharmacovigilance surveillance databases, are driven in part by gendered factors in the rate at which conditions are diagnosed, drugs are prescribed, and adverse events (e.g. nausea, headache) are ascertained and affirmed in the population generally. The hypothesis also predicts that gendered factors in the subjective experience of events as adverse contribute to the different kinds of events reported by men, women, and people of non-binary or gender expansive identities and their healthcare providers to these databases.

Empirically exploring the predictions of this hypothesis requires research designs that go beyond raw comparisons of numbers of ADEs by sex to textured qualitative and quantitative analysis of sex disparities in ADEs stratified by age, gender/sex category, and social group, for particular conditions, drugs, and biological mechanisms, in specified settings. However, we posit that the Gender Hypothesis can also motivate new analyses and spotlight under-recognized patterns in existing datasets not designed for testing gender hypotheses.

3. Gendered pathways in the FDA Adverse Event Reporting System

To explore the promise of the Gender Hypothesis for generating new predictions and alternative explanations, and for capturing under-analyzed data in existing datasets, we analyzed 33,719,943 million records representing 11,413,854 million people reported between January 1, 2014 and December 31, 2022 in the US FDA Adverse Event Reporting System (FAERS) database. FAERS is a publicly available voluntary reporting system for adverse drug events that is "designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products" (Center for Drug Evaluation and Research, 2019). Reports can be submitted to FAERS by healthcare professionals, patients/consumers, and product manufacturers. While FAERS is widely recognized as an inappropriate source of data for documenting actual population rates of ADEs because it captures a mix of health provider and unverified patient self-reports with widely varying completeness (for instance, 43.1% of reports are missing age), FAERS and other pharmacovigilance databases form the basis for the widely-circulated claim that women experience 1.5-2x the rate of ADEs compared to men (Tharpe, 2011), and empirical findings from large databases such as FAERS and VigiBase form a key element of the empirical literature on adverse drug events (Chandak and Tatonetti, 2020; Watson et al., 2019; Yu et al., 2016; Zucker and Prendergast, 2020), alongside clinical and observational studies of ADEs.

The FAERS database contains data at (1) the individual report level, which we refer to as "person-report," at (2) the ADE level, which we refer to as "ADE" or "event," and at (3) the drug level. A single person may submit multiple person-reports reflecting separate incidents, and each person-report may involve multiple ADEs and multiple drugs. Each person-report is categorized as having an outcome that is "serious" or "non-serious". A characterization as "serious" occurs when an outcome such as death or hospitalization is recorded in FAERS for a particular person-report (Fig. 2). In this analysis, we investigated outcomes at the person-report level and at the ADE-level. The specific variables we investigated are: who submitted the person-report (healthcare provider or consumer); the seriousness of the person-report outcome (serious or not); and the class of ADE (i.e. dermatological, hair-related, weight-related, skin-related, and sexual-function related). We stratify the dataset by the listed variables and calculate the proportion female for each. For all analyses, ADEs that occurred in the database fewer than 50 times were excluded. For analysis of cosmetically salient and sexual

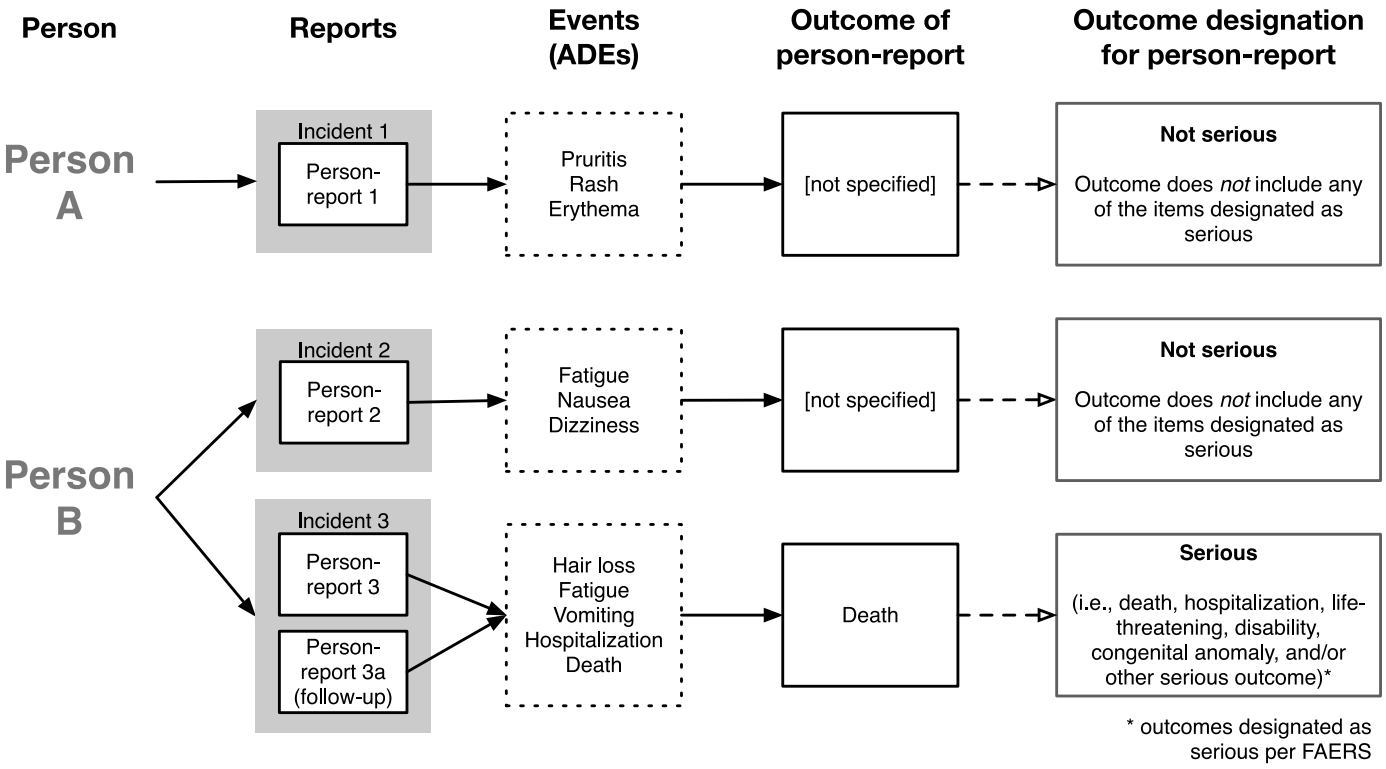

Fig. 2. Title: Structure of ADE data in the FAERS database: Each unique individual can submit a report for a unique incident. If an individual experiences more than one incident (i.e., at different points in time or for different drugs), they can submit additional incident reports. The FAERS database does not include an identifier for the individual, so it is not possible to determine whether one individual submitted multiple reports. Furthermore, an incident could include one or more follow-up reports if, for example, outcome information changes after a long hospital stay. Each incident is associated with one or more ADEs, and assigned a single outcome. The designated outcome is classified as serious or not serious.

function ADEs, we focused on those ADEs occurring at least 10,000 times in FAERS. Data management and analysis were conducted in Python (3.10.9) and R (4.2.3). These data do not enable inferences about ADEs in transgender individuals or those who identify outside of the gender/sex binary. When describing FAERS data, we refer to reports and ADEs occurring among "females" and "males" because these are the primary labels assigned in the dataset. Incorporating an understanding of gender positionality as influencing the reporting of ADEs in FAERS, as posited by the Gender Hypothesis, we refer to "women" and "men" in our discussion and interpretation of findings.

When viewed through the lens of the Gender Hypothesis, FAERS data make available a range of socially salient and gender-rich variables, including: healthcare provider vs. consumer-reported events, rare vs. common events, severe vs. mild events, and specific classes of events, such as cosmetically-salient symptoms related to skin, hair, and weight, or symptoms related to sexual function. We used these variables to test a series of predictions. Given the gendered structure of healthcare norms and utilization, we predicted a greater capture of healthcare provider and serious ADE reports in men compared to women. This would be reflected in reduced sex disparities in these categories of reports than in the database as a whole. Given the role of gender norms, biases, and stigma in the subjective experience of adversity and in the clinical encounter, we predicted gendered patterns of reporting for particular classes of ADEs. Specifically, we expected cosmetically-salient symptoms to be overrepresented among women, and symptoms related to sexual function to be overrepresented among men.

3.1. First prediction: reports made by healthcare providers will show less female skew than patient reports

The Gender Hypothesis predicts that higher utilization of health and medical resources among women as well as women's higher likelihood of interpreting the subjective experience of an event as adverse will make women more likely to report ADEs either directly (patient reported to FAERS) or indirectly (reporting to healthcare providers). Without implying that healthcare provider reports are more valid or accurate than patient reports, the gendered interactional context of clinician provider reports compared to direct patient reports is a site where gender plausibly influences the likelihood of an ADE report entering an ADE surveillance database. A reduced skew in the sex disparity among provider-reported ADEs compared to patient-reported ADEs may be explained in part by bias and discrimination in the clinic, if healthcare providers take women's complaints less seriously and are therefore less likely to report all their symptoms or events to FAERS. A higher number of patient-reported ADEs by women may capture more common and mild ADEs, reflecting heightened familiarity with reporting options and experience with self advocacy in healthcare.

Results: In the FAERS data overall, 63% of ADEs were experienced by females, and 60% of person-reports in FAERS referred to incidents occurring in females. Just over 4% of all person-reports in FAERS were made by healthcare providers, however, among reports from healthcare providers, 56% of ADEs occurred in females and 57% of person-reports represented incidents experienced by females. Additionally, among person-reports made by healthcare providers, similar numbers of ADEs were reported per person-report for males and females (1.83 and 1.81, respectively) (Table 1). This is in contrast to patient-reported person-reports, where females included more ADEs per report (1.92 ADEs per person-report in males vs. 2.09 in females) (Table 1).

3.2. Second prediction: ADEs associated with 'serious' outcomes will show a smaller sex disparity and be overrepresented among healthcare provider-reported events

ADEs reported to FAERS and similar databases vary across the spectrum from trivial and mild to serious and severe. There is known variation in the sex disparity across these event types. A prior (Yu et al., 2016) analysis of sex disparities in the FAERS system, for instance, found that while there were overall similar rates of adverse events for Heparin for men and women, among the most common ADEs for women was "Feeling Hot," while one of the most common for men was "Death." A recent review on sex and gender differences in ADEs noted that women report more ADEs overall, but men report more "serious" ADEs than women (Brabete et al., 2022). Thus, analyzing sex disparities in the severity of events, in interaction with data on healthcare provider vs. patient-reported events, presents potentially valuable information for probing how gendered pathways interact with ADE event reporting.

Results: The FDA identifies a serious outcome in FAERS as a person-report that resulted in one of the following: "death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome" (Center for Drug Evaluation and Research, 2019).

Among the 20 most frequently reported ADEs, the proportion of females reporting each ADE was higher for 19. The single exception was "death," which was reported more often for males in FAERS (53% of deaths were males) (Table 2).

The proportion of ADEs associated with a serious outcome was higher in males than females (71% vs. 63% respectively); among health

Table 1
Adverse drug events in FAERS by sex.

	All reports in FAERS			Healthcare provider reports in FAERS			Non-healthcare provider reports in FAERS		
Variable	Female	Male	Prop. Female	Female	Male	Prop. Female	Female	Male	Prop. Female
Full FAERS dataset									
Number of ADEs	21,154,750	1,256,5193	0.63	673,333	524,540	0.56	20,481,417	12,040,653	0.63
Number of person-reports[a]	6,893,008	4,520,846	0.60	269,430	202,443	0.57	6,623,578	4,318,403	0.61
Average[a] number of ADEs per person-report	2.08	1.92	–	1.81	1.83	–	2.09	1.92	–
Proportion of ADEs that are associated with a serious outcome[c]	0.63	0.71	–	0.62	0.73	–	0.63	0.71	–
Subset of FAERS person-reports with serious outcomes									
Number of ADEs associated with a serious outcome	13,246,539	897,1491	0.60	414,502	382,126	0.52	12,832,037	8,589,365	0.60
Number of person-reports associated with a serious outcome	3,543,456	2,870,339	0.55	137,420	128,149	0.52	3,406,036	2,742,190	0.55
Average[b] number of ADEs per person-report with serious outcome	2.46	2.11	–	2.15	2.12	–	2.47	2.11	–

[a] See Supplemental Fig. 1 for details on the data structure.
[b] 20% trimmed mean.
[c] The FDA identifies a serious ADE in FAERS as an event that results in one of the following outcomes: "death, hospitalization, life-threatening, disability, congenital anomaly, and/or other serious outcome." (Center for Drug Evaluation and Research, 2019).

Table 2
Top 20 ADEs in FAERS by sex.

All FAERS data				Subset of FAERS person-reports with serious outcomes				Subset of FAERS person-reports with non-serious outcomes			
ADE	Count Female	Count Male	Prop. Female	ADE	Count Female	Count Male	Prop. Female	ADE	Count Female	Count Male	Prop. Female
Drug ineffective	480,307	267,680	0.64	Death	219,104	250,098	0.47	Drug ineffective	326,929	171,782	0.66
Nausea	315,356	119,808	0.72	Drug ineffective	153,378	95,898	0.62	Nausea	164,192	56,902	0.74
Fatigue	298,261	158,325	0.65	Pain	151,554	86,295	0.64	Fatigue	148,465	78,792	0.65
Off label use	269,800	172,435	0.61	Nausea	151,164	62,906	0.71	Headache	146,803	53,189	0.73
Headache	266,683	99,241	0.73	Fatigue	149,796	79,533	0.65	Off label use	146,210	71,744	0.67
Pain	256,389	124,161	0.67	Dyspnoea	141,323	87,116	0.62	Diarrhea	112,210	57,962	0.66
Death	219,598	250,518	0.47	Off label use	123,590	100,691	0.55	Pain	104,835	37,866	0.73
Diarrhea	234,962	132,643	0.64	Diarrhea	122,752	74,681	0.62	Injection site pain	99,794	37,453	0.73
Dyspnoea	203,779	119,156	0.63	Headache	119,880	46,052	0.72	Rash	90,956	45,237	0.67
Malaise	192,382	83,864	0.70	Vomiting	108,159	52,187	0.67	Malaise	89,484	31,853	0.74
Dizziness	185,707	91,835	0.67	Malaise	102,898	52,011	0.66	Dizziness	89,377	40,558	0.69
Vomiting	172,298	76,068	0.69	Fall	101,533	55,999	0.64	Pruritus	79,083	32,574	0.71
Arthralgia	166,357	68,560	0.71	Pneumonia	97,190	76,541	0.56	Arthralgia	78,648	31,794	0.71
Rash	154,618	83,242	0.65	Dizziness	96,330	51,277	0.65	Drug hypersensitivity	70,354	19,513	0.78
Pruritus	133,012	59,427	0.69	Arthralgia	87,709	36,766	0.70	Wrong technique in product usage process	68,086	38,285	0.64
Pain in extremity	129,989	50,989	0.72	Asthenia	85,565	57,958	0.60	Drug dose omission	65,967	36,636	0.64
Asthenia	129,369	83,104	0.61	Pyrexia	81,260	64,453	0.56	Vomiting	64,139	23,881	0.73
Fall	128,269	66,019	0.66	Drug dependence	53,626	77,052	0.41	Pain in extremity	62,771	22,083	0.74
Injection site pain	119,767	44,601	0.73	Pain in extremity	67,218	28,906	0.70	Dyspnoea	62,456	32,040	0.66
Pyrexia	108,892	79,171	0.58	Anxiety	66,746	35,316	0.65	Feeling abnormal	58,576	23,852	0.71

provider reports, this disparity was slightly greater (73% vs. 62%, respectively) (Table 1).

When patients reported ADEs associated with a serious outcome, 60% of these originated from females. By contrast, when healthcare providers reported ADEs associated with a serious outcome, 52% were experienced by females. Consistent with the full dataset, among reports originating from healthcare providers and associated with a serious outcome, similar numbers of ADEs were reported per person-report (2.12 in males vs. 2.15 in females).

3.3. Third prediction: excess female bias in cosmetically salient ADEs

Though gendered body ideals exist for both men and women, a greater societal emphasis is placed on women's appearance. In a recent poll of Americans, "physical attractiveness" was the top trait that respondents believed society values in women, while in men, the top traits were "honesty/morality" and "professional/financial success" (Parker et al., 2017). Gender socialization of the body starts at a young age; not only do girls/women experience more scrutiny of their bodies, the message is qualitatively different than the expectations communicated to boys/men, with the former centering on appearance and the latter emphasizing functionality and ability. Moreover, constant sexual objectification of women's bodies often results in women's self-objectification and acceptance that their bodies exist to be looked at and evaluated. Women's self-worth is tightly linked to appearance, and as such women experience higher rates of body dissatisfaction (Calogero and Thompson, 2010; Murnen, 2011). Due to these greater expectations and internalized pressure regarding women's appearances, we predicted that women may experience more distress due to outwardly visible drug effects than men, and would consequently be more likely to report such ADEs.

We examined hair-related and weight-related categories of ADEs in particular. The extent to which a drug causes a person to deviate from the social construction of the normative body influences whether an event is experienced as adverse and thus reported. Using this model, disparities in hair loss can be understood through the gendered expectations for women to have hair and particularly to have long hair as "an essential element of femininity" (Marks and Senna, 2020). For men, balding is considered a normal part of aging and hair loss is less stigmatized than in women (Cartwright et al., 2009; Gonul et al., 2018; Hoffer et al., 2021). In the US and Western societies, women are more likely to overestimate their body size and men are more likely to underestimate their body size. From a young age, parents, peers, and the media enforce cultural expectations of thinness in women and muscularity in men, ultimately leading to the internalization of these ideals and the shaping of highly gendered perceptions, feelings, cognitions, and behaviors about the body (Calogero and Thompson, 2010). As such, women may be more likely to perceive weight gain and then report it as an adverse event.

We defined ADEs as "cosmetically salient" by categorizing ADEs into the following categories: those relating to a person's weight (e.g. "weight increased"), hair (e.g. "hair texture abnormal"), or skin (e.g. "rash"), or otherwise outwardly visible (e.g. "tooth loss," "lip swelling"). Because an individual may submit multiple symptoms for a single event, we did not include symptoms that typically accompany an outwardly visible symptom. For example "skin burning sensation" was not categorized as cosmetically salient, because those individuals concerned with the visible appearance would report a rash (see Supplementary Table 1 for categorization of symptoms considered cosmetically salient).

Results: Among ADEs appearing at least 10,000 times in FAERS and categorized as cosmetically salient, 68% were reported among females, while 63% of ADEs overall in the FAERS database occurred among females. This includes dermatological (69% F), hair-related (89% F), weight-related (60%) and other cosmetically related ADEs (63% F) (Table 3).

Hair-related ADEs: The most commonly reported hair-related ADE in FAERS was alopecia (89% F), but abnormal hair texture (94% F) and hair color changes (83% F) were also reported. We further investigated the hair-related ADEs of "hair growth abnormal" and "hirsutism", both of which were reported fewer times than our pre-specified cutoff of 10,000. There were under 1000 instances of "hirsutism" (excess body hair) and just over 4000 instances of "hair growth abnormal" in the data. These were also female-biased (89% and 79% respectively).

Weight-related ADES: In FAERS, 59% of weight-related ADEs were

Table 3
Cosmetically salient ADEs occurring at least 10,000 times in FAERS by sex.

	Count Female	Count Male	Proportion Female
Dermatologic-related ADEs	1,224,641	543,759	0.69
Hair-related ADEs	124,670	15,093	0.89
Weight-related ADEs	267,884	180,483	0.60
Weight increased	81,727	38,102	0.68
Eating disorder	8410	4230	0.67
Hypophagia	8805	6162	0.59
Decreased appetite	77,489	56,165	0.58
Weight decreased	90,009	65,888	0.58
Abnormal weight gain	1444	9936	0.13
All cosmetically-salient ADES	1,955,740	937,096	0.68
See appendix for list of cosmetically salient ADE categories.			

among females, which included "weight increased" (68% F), as well as "abnormal weight gain" (13% F), though "weight increased" appeared 10.5 times more often than "abnormal weight gain" (Table 3).

3.4. Fourth prediction: male bias in ADEs related to sexual function

Gendered cultural expectations around sexual function and desire place greater value and importance on men's sexual agency and performance than on women's (Spurgas, 2020). From adolescence, boys and girls are socialized to have radically different expectations for sexual performance. For boys, predominant discourse holds sexuality to be pleasurable, empowering, and the gateway to masculinity, while for girls sexual pleasure is narrated as painful, shameful, and stigmatized (Martin, 1996), leading to what has been termed a "sexual double standard", where men and women are held to different criteria for what constitutes normative or ideal sexual behavior (Crawford and Popp, 2003; Reid et al., 2011; Bordini and Sperb, 2013; Soller and Haynie, 2017). A consistent finding in sexuality studies is the higher rate of orgasm among men compared to women in heterosexual encounters (Armstrong et al., 2012), attributed to the higher priority placed by both men and women on men's sexual desire and achievement of sexual pleasure through orgasm (Chadwick et al., 2019). Research suggests that, in some contexts, men can experience greater pressure to be sexual due to "gendered heterosexual scripts that associate hegemonic masculinity with sexual virility" (Gupta, 2019), while research on sexual fluidity and rates of bisexual behavior and identity indicate that women are on average comfortable with a wider and less fixed range of sexual desire than men (Diamond, 2003; Mishel et al., 2020), although these gendered norms differ significantly across race, socioeconomic status, sexuality and other social categories. This differential socialization shapes people's desires, expectations, and experiences. Moreover, women's sexual desire has long been systematically understudied and undervalued in the medical and psychological establishment (Spurgas, 2020; Tuana, 2004). Thus, we expected that changes in women's sexual function would be less likely to be taken seriously or reported, and that we would see a preponderance of sexual function from men in the FAERS database.

Results: Among ADEs reported more than 10,000 times in FAERS, the only sexual function-related ADE was erectile dysfunction, 99.6% of which were in males. ADEs that may be related to sexual dysfunction of the female anatomy did appear, but less often: the most common of these events were vaginal discharge (6096 events), vulvovaginal burning sensation (3,787), vulvovaginal pruritus (3,127), and vulvovaginal pain (3,067). These female ADEs are perhaps best classified as urogenital symptoms which may influence sexual function but are often experienced outside of intimate sexual situations.

We further investigated ADEs that are explicitly about sexual function and sexual desire among ADEs reported *fewer* than 10,000 times. "Sexual dysfunction" occurred 4890 times for males and 1441 times for females (22.8% F). "Libido decreased" appeared 4523 times for males and 2361 for females (34.3% F) and "loss of libido" appeared 2686 times for males and 2404 for females (47.2% F). "Libido increased" was far less likely to occur as an ADE, occurring 566 times for males and 427 times for females (43% F).

4. Discussion

Analyzing more than 37 million records of adverse drug events in the FDA Adverse Events Reporting System between 2014 and 2022, we find evidence of a relationship between gender/sex of the patient, whether an ADE is considered serious, and likelihood that the event is reported to the FAERS database by a healthcare provider rather than the patient. We also find evidence that cosmetically salient and sexual dysfunction categories of ADEs are gender-skewed. While these and additional results reported above at best represent exploratory probes of a complex dataset with known limitations, the patterns observed in FAERS point to the need to explore the role of gendered pathways producing sex disparities in ADEs and the possibility that these pathways may offer points of intervention for promoting health equity.

The results of our probe of the FAERS database guided by the Gender Hypothesis raise several questions for future research. Do our findings of higher rates of serious events reported for men result from men underutilizing healthcare resources for less severe ADEs? By contrast, are women more likely to utilize healthcare for certain events not categorized as "serious" by FAERS, or are women more likely to experience such events as distressing? Does bias in the clinic lead to dismissal of women's reports of serious ADEs? In the case of weight, we find that men rarely report weight gain, but are vastly overrepresented in the category of "abnormal" weight gain. Among men, must weight gain pass into "abnormal" or pathological in order for it to be reported as an ADE? How do gendered determinants of and interpretations of health shape what is considered a normative compared to an impaired state and influence the likelihood of ADEs being recorded for individuals of particular genders/sexes?

The Gender Hypothesis conceptualizes ADE sex disparities as in part resulting from the cumulative effects of social, political, and interpersonal experiences of wellness, illness, care-seeking, access, and legibility (of the condition/of the person's perspective when interacting with biomedical infrastructures), rendering experiences of ADEs not only biomedical in nature, but also what Kafer (2013), drawing on disabilities studies, describes as political/relational (Kafer, 2013). Consider the example of "fatigue," the most commonly reported ADE after "drug ineffective" and death (Table 2). In FAERS, there were 342,096 female reports and 185,660 male reports of fatigue as an ADE (65% F). Fatigue is a common experience, regardless of whether one has taken a drug or not. Prevalence of fatigue in the general population is as high as 45%, and tends to be higher among women than men (Lewis and Wessely, 1992). When the background frequency of the symptom is common, causal attribution is distinctly challenging (Aronson and Ferner, 2005). If one experiences fatigue after taking a drug, the individual must decide whether to attribute the fatigue to the drug as opposed to any one of a myriad of other explanations, including that fatigue may be a result of the condition being treated, due to other health issues, or a condition of economic and social stress in a low-safety-net neoliberal society. After a person decides whether fatigue "counts" as an ADE, they must decide whether or not to *report* the ADE. At this point, increased familiarity with healthcare processes may allow an individual to report the ADE themselves, while bias and discrimination in the clinic may influence whether a person brings the symptom to attention, and the provider affirms the patient's concern and identifies fatigue as an ADE. If the provider attributes the fatigue to an ADE, they must also designate the outcome as serious or not.

According to the Gender Hypothesis, the cumulative and interacting effects of gendered social, political, and interpersonal experiences of wellness and illness, and of gendered interactions with medical systems, contribute to and help to explain observed sex disparities in ADEs. Even if we cannot predict and measure the outcome of these interacting and

overlapping pathways and processes with precision, well-grounded and rigorously articulated theory can guide us to remain attentive to gendered processes in the development of research questions, choice of methods and study populations, and the interpretation of data in ADE research.

5. Conclusion

The Gender Hypothesis aligns a range of empirical literatures and observations to advance research on the role that gendered social factors may play in the embodied experience, reporting, interpretation, and categorization of ADEs. In interaction with other markers of social status including race/ethnicity/nationality, SES, and disability, gendered healthcare utilization, gender bias and discrimination in the clinic, upstream gendered contributors to health status, and gendered contributors to the subjective experience or perception of an adverse health event structure peoples' experiences of health and illness and their interaction with healthcare systems. But to date these gendered social factors have been systematically overlooked in the literature on sex disparities in adverse drug events. The Gender Hypothesis of sex disparities in ADEs theory fills an analytic vacuum that will help address gaps in causal accounts of sex disparities in ADEs that focus on sex-related biological variables such as steroidal hormones and sex-related biological states such as pregnancy (Franconi and Campesi, 2014; Rademaker, 2001; Zucker and Prendergast, 2020).

The NIH and other health agencies highlight sex disparities in ADEs as a touchstone example for motivating the prioritization of gender health equity policies and programs (Clayton and Collins, 2014; Heidari et al., 2016; Rabin, 2013; Sandberg and Verbalis, 2013). The Gender Hypothesis argues that consideration of gendered factors is critical for building empirically testable hypotheses necessary for understanding the causes of–and identifying interventions for addressing–sex disparities in ADEs. In this paper, we demonstrated the explanatory potential of the Gender Hypothesis by testing a range of theory-driven predictions using FAERS data. Despite the fact that health datasets and surveillance systems for ADEs, including FAERS, were not constructed to include gender-related variables—such as gender beliefs and identities, care work, sexual violence, measures of political empowerment, reproductive healthcare access, occupation, education, primary household income earner status, and other variables that have been shown to influence health/healthcare access in gendered ways (Read and Gorman 2011; Verbrugge 1985)—when viewed through a Gender Hypothesis lens, analysis of FAERS data reveals patterns of sex disparities that are likely better explained by social, gendered pathways than by biological ones. The ability to use FAERS data to do so would be enhanced in the future by improving its capture of more precise gender/sex categories and identities; however, we also note that inclusion of these categories alone is insufficient for elucidating the gendered social and structural pathways that contribute to sex disparities (Westbrook and Saperstein, 2015). Creative application of the Gender Hypothesis to additional datasets and in future research designs may yield new predictions and insights into the causes of sex disparities in ADEs, addressing gaps in causal accounts of sex disparities in ADEs that focus solely on sex-related biological variables.

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Data availability

Data used in these analyses are publicly available.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2023.116385.

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