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# Why do we need sex-balanced studies of autism?

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## Abstract

Males are diagnosed with autism much more frequently than females, and most research study samples reflect this male predominance. The result is that autistic females are understudied. There is a critical need to increase our understanding of autistic females, both biologically and clinically. The only way to do this is to recruit sex-balanced cohorts in studies so that similarities and differences between males and females can be evaluated in all autism research studies. The purpose of this commentary is to 1) provide historical context about how females came to be under-represented in all research, not just in the field of autism and 2) learn from other areas of health and medicine about the potentially dire consequences of not studying both sexes, and 3) draw attention to the need to recruit sex-balanced cohorts in autism research, particularly in neuroimaging studies.

**Lay Summary—**Most of what we know about autism comes from studies of males. Because there are so many more males diagnosed with autism than females, most research studies do not include enough autistic females to evaluate how autistic females may be different from autistic males. The purpose of this commentary is to provide some historical background from other areas of health and medicine on how leaving females out of research studies can sometimes lead to harmful outcomes. The hope is that the field of autism will not repeat these mistakes and that more studies will recognize the need to make every effort to include equal numbers of autistic females in research.

### Keywords

female; girl; woman; sex difference; biological sex; autism; brain; MRI

## Introduction

One of the most consistent findings in the field of autism research is that more males are diagnosed with autism than females. The male to female ratio has remained relatively constant at 3–4 males diagnosed with autism for every female even as prevalence rates of autism have climbed over the past two decades. This male preponderance, and relative infrequency of autism in females, has long been used as justification for small and imbalanced numbers of females included in research studies. Many studies have even excluded females from research samples. The reality, however, is that autism in females is not rare. In the most recent 2020 report, the CDC estimates the prevalence of autism at 1 in 88 females[1]. With over 1% of females in the US diagnosed with autism, there is a critical need to increase our understanding of autistic females, both biologically and clinically. The purpose of this commentary is to 1) provide historical context about how females came to

be under-represented in all research studies, 2) learn from other areas of health and medicine of the potentially dire consequences of not studying both sexes, and 3) draw attention to the need recruit sex-balanced cohorts in autism research, particularly in neuroimaging studies.

## A note about sex and gender

In this commentary, and in most research studies, sex is conceptualized as a binary variable and refers to sex assigned at birth, which is based on physical characteristics of genital anatomy. A person's gender identity, which includes the social constructs of masculinity and femininity, does not always align with sex assigned at birth. Current estimates suggest that gender diversity occurs at higher rates in autistic individuals than in non-autistic individuals (4–8% vs ~1%) [2–4]. Moreover, autistic individuals assigned female at birth are more likely to be gender diverse than autistic individuals assigned male at birth [5,6]. The intersection between sex assigned at birth and gender identity, including nonbinary and trans identities, in autism is an important area of study, but remains a nascent area of research, particularly in the realm of neurobiology.

## The relevance of sex in health and medicine – a historical perspective

The field of autism research is not the first, or only scientific area to neglect females. Historically, a lack of female representation in studies ranging from preclinical investigations of basic cellular mechanisms to human clinical trials has led to an incomplete understanding of how biological functioning and physiological mechanisms differs by sex[7]. It is worth taking a step back to consider how and why females were systematically excluded from research and the consequences this has had in the broader arena of biomedical research and on the health and well-being of females.

In 1977, in response to a high rate of birth defects arising from thalidomide taken during pregnancy in Europe and Canada, the FDA recommended systematic exclusion of women of childbearing potential from Phase 1 and early Phase 2 clinical trials [8,9]. This act had far-reaching consequences on biomedical research into women's health. Throughout the 1980s, females were excluded from several large and influential studies, including the Multiple Risk Factor Intervention Trial (MRFIT) on the effects of dietary change and exercise as preventative measures for heart disease (12,866 men, 0 women) and the Physicians Health Study that examined the effects of aspirin on cardiovascular disease (22,071 men, 0 women). Findings from these and many other studies with male-only cohorts were often extrapolated to females, assuming that females were simply smaller versions of males. Females were also systematically excluded from preclinical studies. Most rodent model work included only males because hormone fluctuations related to the estrous cycle in females were considered a complication for the interpretation of results [10].

In the early 1980s, increasing awareness about sex disparities in biomedical research led to protests against the lack of representation of females in clinical trials. By 1987, the NIH had introduced a policy encouraging the inclusion of women and in 1990, the NIH established the Office of Research on Women's Health. Finally, in 1993, Congress passed the NIH Revitalization Act, which required that women and minorities be included in research studies. These days, both basic and clinical researchers who submit grant proposals

to the NIH are required to consider sex as a biological variable (SABV) in their experiments. This stems from a NIH policy instituted in 2014 requiring researchers to include sex as a factor in research design, analyses, and reporting of all vertebrate and human studies[11].

## The effects of under-representation of females in research – a broader view in health and medicine

Generalizing results from male cohorts to females has had serious consequences on the health and well-being of females. Looking to other areas of health and medicine, a lack of understanding about sex differences has been detrimental to females in examples ranging from diagnoses, treatments, and preventative measures. These include:

1. Sex differences in acute symptoms of myocardial infarction (i.e., heart attack) that make diagnosis more challenging in females. While chest pain is the hallmark symptom of a heart attack in men, less than 30% of women report chest discomfort, and many women do not even experience acute chest pain. Instead, the most common acute symptoms of heart attack in women are shortness of breath, weakness, and fatigue[12]. Sex differences in pathophysiological mechanisms, treatments and outcomes in acute myocardial infarction have also been described[13].

2. A higher incidence of driving impairment the morning after ingesting zolpidem (Ambien) and evidence for slower metabolism of zolpidem (Ambien) in females[14] led to the first ever sex-specific dosage recommendations by the FDA in 2013[15]. Sex differences in the absorption and clearance of various medications remains an understudied area, yet these studies are critical for understanding why females experience a higher incidence of adverse drug reactions[16,17].

3. The effects of low dose aspirin as a preventative measure for cardiovascular incidents differ across men and women[18,19]. In the 1980s, the all-male Physicians Health Study found that aspirin reduces the risk of a first heart attack, and thus for decades, men and women were advised to take low dose aspirin to reduce the risk of cardiovascular incidents. However, in 1993 when Congress finally mandated that women be included in clinical trials, the Women's Health Study was launched to specifically investigate the effects of low dose aspirin on cardiovascular disease in women. In 2005, researchers found that while aspirin did lead to a decrease in major cardiovascular events, the effects were different from what had been observed in men. In women under 65, aspirin reduced the risk of stroke, but not myocardial infarction [18]. Sex differences in the preventative effects of aspirin continue to be investigated, and clear understanding has been impeded by under-representation of females, even in more contemporary trials [20].

4. Safety performance of cars may depend on whether crash test dummies are modeled after average male or female body types. Females are at greater risk for injury than males in comparable motor vehicle accidents [21]. Historically, crash test dummies have been modeled after males, and to simulate the effect of impact on females, smaller versions of the male models, scaled down in height and

weight, have been used. Researchers in Sweden have recently developed the first dummy modeled after the average female body that factors in differences in body shape in the torso and pelvic areas, as well as differences in joint stiffness. They found that that safety performance of vehicular seats varied based on whether a male or female dummy was used in impact tests[22] and demonstrate why females may be more prone to whiplash injuries.

These are just a few examples of how under-representation of females in research studies has led to disparities in the understanding of women's health. Females continue to be at risk for missed diagnoses, confusion over preventative measures, non-optimal dosing of pharmaceuticals, and greater risk of injury. Although these examples are obviously not directly applicable to autism research, they serve as a cautionary note about the importance of examining both males and females in any area of research.

## What is the male to female ratio in autism?

Although the ~4 to 1 ratio of males to females with autism is practically dogmatic in most autism literature, even this finding is more complicated than meets the eye. Several recent studies and meta-analyses suggest that the precise male to female ratio is difficult to pinpoint, as estimates vary with several factors, including the age of the cohort being examined. The CDC reports that in 4-year-old children, 4.7 males are diagnosed for every female, but this ratio decreases to 3.4 to 1 in 8-year-olds[23,24]. In Norway, the male to female ratio is 3.7 to 1 in children, but decreases to 2.6 to 1 in adults[25]. Estimates also vary by geographic location [26,27] and whether prevalence estimates are population based or clinically-ascertained cohorts [28]. There is convincing evidence that some females, particularly those without intellectual disability or other psychiatric symptoms, may be under- or misdiagnosed [29]. Even if the precise ratio of autistic males to autistic females remains difficult to nail down, all estimates suggest that there are more autistic males than females, though perhaps the ratio is not as skewed as previously thought. The old argument that autism is so rare in females and therefore it is justifiable to focus only on males is no longer tenable.

## Females are understudied and underserved in most of autism research

Some have argued that because the number of females in research studies matches the prevalence ratio of autism, they are not actually underrepresented. However, there is no question that females are both understudied and underserved by autism researchers. Virtually everything we know about autism comes from studies that reflect the male predominance in prevalence. Most research studies reflect at least a 4 to 1 male to female ratio in sample sizes. The much smaller number of females in these studies leads to a lack of statistical power, and in many cases sex is included in statistical models only as a nuisance covariate to ensure that the small number of autistic females are not influencing diagnostic group differences across the whole (mostly male) sample. The problem is that there are seldom enough females to have sufficient statistical power to analyze sex as a covariate of interest, or in other words, to specifically test for similarities and differences between autistic males and females and their non-autistic counterparts. Under recruitment of autistic female

participants severely limits our ability to draw conclusions about potential sex differences in autism.

In studies that use neuroimaging tools like magnetic resonance imaging (MRI) scans to study brain differences, females are not only understudied, but also underrepresented. In neuroimaging studies, the male to female ratio of most research samples is even more imbalanced at 8 males for every 1 female[30]. Advances have been made in recent years, with larger female sample sizes from multi-site datasets, including ABIDE I & II[31,32], which aggregates imaging data from 17 sites and includes 73 autistic females and the GENDAAR consortium, which includes data from 4 sites and 46 autistic females. The ongoing MIND Institute Autism Phenome Project (APP) and Girls with Autism Imaging of Neurodevelopment (GAIN) studies include over 100 autistic females, enrolled at 2–6 years of age and imaged longitudinally across childhood[33]. While these efforts are a step in the right direction, a greater emphasis on recruiting more autistic females into neuroimaging studies is still needed.

## Why should we care about sex differences in the autistic brain?

In the early days of neuroimaging studies of autism (with predominantly male samples), early brain overgrowth was considered to be a hallmark feature of autism [34] . When we initiated the Autism Phenome Project in 2006, this was the first finding we aimed to replicate in our cohort of 2–4 year old children. Indeed, we identified early brain enlargement in a subset of participants with a regressive onset to autism[35]. However, when we examined males and females separately, we did not see evidence of brain enlargement in autistic females. But with a sample size of 22 autistic females and 92 autistic males, it was unclear whether the lack of brain enlargement in females was due to inadequate statistical power or that females truly did not exhibit this ‘hallmark’ brain difference. Since that time, we have targeted recruitment of additional females, and with a larger sample of 95 autistic females, we still see no evidence of brain enlargement in most autistic females[36,37]. This is an example of a finding that was identified in predominantly male samples and widely considered to be a hallmark feature of brain differences in autism that turned out to not apply to autistic females. What is true for autistic males cannot be assumed to be true for autistic females.

Additionally, there is ample evidence from a growing number of studies with adequately sized samples of autistic females that there ARE many sex differences in the autistic brain[38]. These difference ranges from structural studies of regional brain volumes[39,40] and diffusion properties in white matter tracts[41,42], to functional connectivity studies of the amygdala [43] and canonical resting state networks [44–46]. A series of intriguing studies from the GENDAAR consortium integrate neuroimaging and genetic data to identify sex differences [47–49].

A greater understanding of the neurobiological processes that give rise to the skewed male to female ratio will help to identify sex-specific etiological mechanisms. This, in turn, could be useful in predicting different outcomes, co-occurring conditions, and development of sex-specific supports and interventions for autistic individuals. Current research is focused on identifying factors that contribute to either female resilience (i.e. protection) or male

vulnerability for autism in the brain. In neurotypical development, sex differences have been observed at multiple levels of neurobiological organization, from synaptic function[1,2], microglia and neuroimmune function[51], to brain size[52] and whole brain connectivity[53]. Investigating how these sex differences may contribute to female protection and male vulnerability for autism will be especially informative.

## Who should we be comparing autistic females to?

Because of well-established sex differences in body and brain size, it is standard practice in neuroimaging studies of autism to compare autistic females to a sex-matched non-autistic comparison group of neurotypical or typically developing individuals. Autistic females are almost never compared directly to autistic males in terms of brain differences because it is critical to tease apart sex differences due simply to being male or female from sex differences specifically related to autism. What we are really interested in is whether autistic females differ from non-autistic females in ways that are similar or different to how autistic males differ from non-autistic males. To statistically test for these interactions between sex and autism, 2×2 factorial designs that include balanced numbers of autistic and non-autistic males and females are required.

This approach of comparing autistic females to non-autistic females and autistic males to non-autistic males is not utilized as often in studies examining behavioral sex differences. It is more common to compare autistic males and females directly. However, there are well-documented sex and gender differences in behavioral development of typically developing males and females[54]. In a meta-analysis of 13 behavioral and cognitive studies that included both autistic and non-autistic males and females, there were several measures (e.g. executive function, internalizing and externalizing problems) in which sex/gender differences in autistic individuals were not the same as sex/gender differences observed in typically developing groups [55] . Additional studies should focus on identifying behavioral, cognitive, and physiological differences between autistic and non-autistic females and comparing the magnitude of these differences to those between autistic and non-autistic males.

## Where should we go from here?

Although it is easy to say that we need to over-recruit females in order to have more sex-balanced autism research studies, there are several challenges that we must acknowledge. We know from multiple studies that the average age of diagnosis in females is about 1.5 years later than boys[56,57], which makes recruiting very young females more difficult. Females without co-occurring intellectual disability or other behavioral challenges may go undiagnosed[29], and females may be misdiagnosed with other mental health conditions such as anxiety, obsessive-compulsive disorder, or ADHD prior to receiving an autism diagnosis[58].

Another challenge is the reliance on diagnostic tools that were designed utilizing predominantly male samples[59]. The Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R) are standardized instruments widely used by researchers and clinicians to diagnose autism [60,61]. Although a recent large scale, multi-site study found negligible sex differences in scores on the ADOS and ADI-R, a major

limitation was that all of the participants in the study already had a diagnosis of autism[62]. Thus, the study could not address potential sex differences in the sensitivity of the ADOS and ADI-R in identifying autism in individuals in the first place. Indeed, another recent study found that reliance on the ADOS as a confirmatory diagnostic measure for study inclusion resulted in excluding females at a rate 2.5 times higher than males [63]. We have had a similar experience in recruiting 2–4 year old females into the GAIN Study, which feeds into the larger Autism Phenome Project. In our initial phase of recruitment from 2014–2019, females had a much higher rate of study exclusion than males due to having subthreshold scores on either the ADOS or ADI-R. Almost 10% of females interested in enrolling (compared to <1% of males during the same time frame) had a community diagnosis of autism but did not meet ADOS or ADI-R score cutoffs and were thus excluded from further participation. Increasing the numbers of females in research studies will require careful consideration of study inclusion criteria and the diagnostic processes of autism[64]. For our current enrollment into the GAIN study, we have expanded the age range to include the average age of diagnosis in females and we have dropped the requirement of having a prior community diagnosis. For our initial screening measures (MCHAT and SCQ), we have lowered the scoring thresholds to ensure that females are not being excluded at the earliest stages of the study. We still utilize ADOS and ADI-R score thresholds to maintain consistency of inclusion criteria with prior phases of the study, but we are casting a broader net in order to enroll more females.

Despite these challenges in identifying autistic females, more girls than ever are being diagnosed with autism. The CDC now estimates that over 1% of 8-year-old females in the US (1 in 88) are diagnosed with autism, so it should be possible to recruit more even numbers of autistic males and females into research studies. It is time to stop leaving autistic girls behind. In recent years, there have been great strides made in studying sex differences in autism both in terms of behavioral presentation as well as in the brain. There is a need for sex-balanced studies in all areas of autism research, including preclinical, biological, behavioral and physiological research. As our field moves towards discovery of biomarkers for autism[65,66], development of targeted interventions and supports[67], or outcome prediction[36] it is increasingly important to ensure that findings are generalizable to both sexes.

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## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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