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Systematic Review and Meta-Analysis of Late Diagnosis of Autism Spectrum Disorder (ASD) in Women

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Abstract

This article investigates the late diagnosis of Autism Spectrum Disorder (ASD) in women, identifies factors contributing to underdiagnosis and estimates the average age of diagnosis for women diagnosed after the age of 15. Following systematic review and meta-analysis guidelines, the study qualitatively analyzed literature from seven databases and assessed the quality of the studies. A random-effects meta-analysis was used to calculate the average age of diagnosis. Out of 102 studies reviewed, 17 involving 472 women were selected for quantitative analysis. The "Extreme Male Brain," "Female Phenotype," and "Protective Female Effect" theories were identified as factors for underdiagnosis, with an average diagnosis age of 28.24 years and high variability ($I^2 = 99\%$). The study highlights the need for improved diagnostic strategies and psychological support for women with late ASD diagnosis.

Keywords: Autism spectrum disorder; Delayed diagnosis; Women; Neurodevelopmental disorders.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by communication and social interaction impairments and repetitive behaviors. Diagnosis relies on neuropsychological tools and screening tests, such as the M-CHAT for children and the AQ for adults (Losapio & Pondé, 2008; Baron-Cohen *et al.*, 2001).

ASD often coexists with psychiatric comorbidities, including anxiety disorders (20%) and depression (11%), as well as mood disorders, personality disorders, attention deficit and hyperactivity disorder, and intellectual disabilities (Fusar-Poli *et al.*, 2022). It also increases the risk of anxiety, depression, post-traumatic stress disorder (PTSD), and suicidal ideation (Gesi *et al.*, 2021), complicating the diagnostic process.

Though ASD is seen as predominantly male, the current ratio is about one woman for every three men (Loomes *et al.*, 2017). Variations in symptom presentation or diagnostic criteria might contribute to this disparity (Driver & Chester, 2021; Gould, 2007). Research shows distinct behavioral patterns between autistic boys and girls, influenced by cultural norms or symptom

presentations (Bitsika & Sharpley, 2019). Additionally, females may mask symptoms more effectively due to better social skills (Lai & Szatmari, 2020; Attwood, 2006; Miller *et al.*, 2021; Dean *et al.*, 2017).

Diagnostic tools and criteria, initially developed with a male-centric perspective, may contribute to lower diagnosis rates in females. This study aims to identify factors contributing to underdiagnosis and estimate the average age of diagnosis for women diagnosed after age 15.

2. Methods

2.3 Instruments

This study used a systematic review and meta-analysis approach, following PRISMA guidelines (Galvão *et al.*, 2015), and was approved by the local Research Committee (Registration 202352698).

2.4 Procedures

Keywords included: 1. Autism Spectrum Disorder, Autism, ASD, Transtorno do Espectro Autista, Autismo, Trastorno del Espectro Autista, TEA; 2. Women, Woman, Girls, Female, Mulheres, Meninas, Feminino, Mujeres, Niñas; 3. Diagnóstico, Subdiagnóstico, Diagnosis, Misdiagnosis, Under-diagnosis, Diagnóstico Erróneo, Infradiagnóstico.

We searched the Brazilian Digital Library of Thesis and Dissertation (BDTD), Cochrane Library, LILACS, PubMed, SciELO, Scopus, and The Lens, using the combinations **1 and 2**, **2 and 3**, and **1 and 2 and 3**, from June to July 2022.

2.5 Eligibility Criteria

For the systematic review, we included: 1. primary studies; 2. studies of any nationality; 3. studies with adult and/or child populations; and 4. studies on the impact of ASD diagnosis on women or the general population.

For the quantitative analysis, we considered publications reporting sample size, percentage of women/girls, and participant age.

2.6 Exclusion Criteria

We excluded: publications before 2000, duplicates, studies in languages other than English, Portuguese, or Spanish, literature reviews, and meta-analyses. For the meta-analysis, we excluded studies involving children under 15 and those without age of ASD diagnosis data for females.

2.7 Risk of Bias

Two independent reviewers selected publications, with disagreements resolved by a senior reviewer. Study quality was assessed using the Mixed Methods Assessment Tool (MMAT) (Hong *et al.*, 2018), involving double assessment and scoring.

2.8 Data Analysis

We calculated the mean age at diagnosis with a significance level of $\alpha = 0.05$ using a random effects model (Hedges & Vevea, 1998). Median-to-mean conversion methodology (Hozo *et al.*, 2005) was used for studies providing only median age and range. Heterogeneity was assessed using the Sidik and Jonkman method with Knapp-Hartung adjustments (Sidik & Jonkman, 2005; Knapp & Hartung, 2003).

3. Results

3.3 Overview

We identified 73,316 publications, of which 102 were selected for qualitative analysis. From these, 14 studies with 472 women provided data for quantitative analysis (Figure 1).

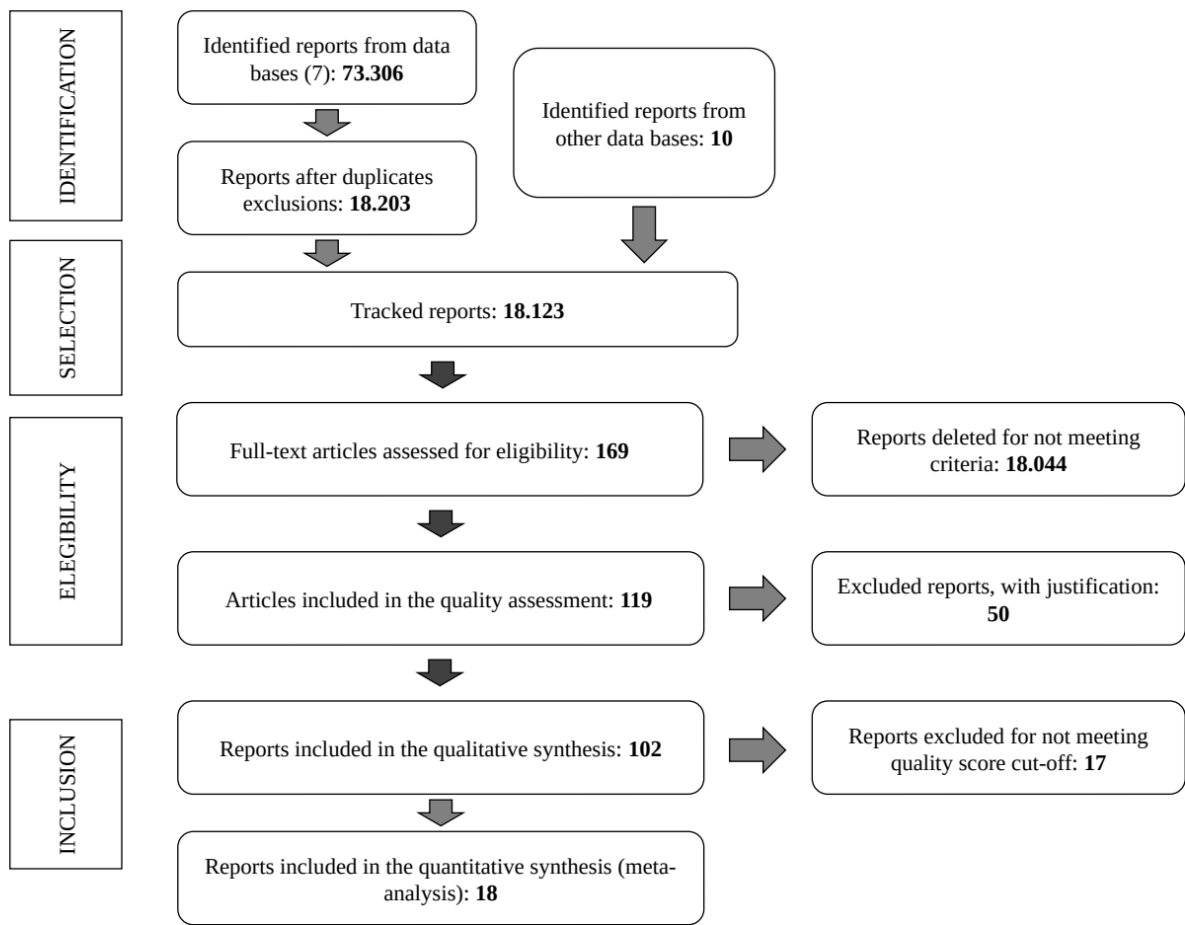


Figure 1. Report on found publications.

3.4 Systematic Review

The qualitative analysis identified three themes: Underdiagnosis/Delayed Diagnosis of ASD, Underdiagnosis/Delayed Diagnosis of ASD in Women, and Impact of ASD on Mental Health.

Underdiagnosis of ASD

Underdiagnosis includes late, erroneous, or missed diagnoses, influenced by:

- **Lack of ASD Knowledge:** Limited awareness among parents, caregivers, and teachers delays diagnosis and worsens outcomes (Giarelli *et al.*, 2010; Punshon *et al.*, 2009; Lewis, 2016a; Aggarwal & Angus, 2015; Happé *et al.*, 2016; Huang *et al.*, 2021).

- **Ethnicity:** Predominantly Caucasian samples may skew diagnosis rates across different ethnic groups (Colbert *et al.*, 2017; Atherton *et al.*, 2022; Bello-Mojed *et al.*, 2017; Huang *et al.*, 2021; Kreiser & White, 2014; Holtmann *et al.*, 2007; Aggarwal & Angus, 2015; Dworzynski *et al.*, 2012; Cariveau *et al.*, 2021; Corden *et al.*, 2021; Garel & Garel, 2019; Gesi *et al.*, 2021; Hull *et al.*, 2017; Lewis, 2017; Lodi-Smith *et al.*, 2021).
- **Symptom Severity and Comorbidities:** Prolonged diagnostic process often involve misdiagnoses and referrals after treatment for other conditions (Fusar-Poli *et al.*, 2022; Garel & Garel, 2019; Punshon *et al.*, 2009; Milner *et al.*, 2019; Lim *et al.*, 2018; Lewis, 2016a, 2016b; Tsirgiotis *et al.*, 2022; Rødgaard *et al.*, 2021; Suckle, 2021; Murray *et al.*, 2019; Takara & Kondo, 2014).

Underdiagnosis of ASD in Women

Women with ASD are often underdiagnosed compared to men (Loomes *et al.*, 2017) and tend to have more severe symptoms when diagnosed (Lai *et al.*, 2011). Four main theories explain this:

- **Extreme Male Brain Theory:** Autism may manifest through traits associated with a male personality (Baron-Cohen *et al.*, 2011; Dean *et al.*, 2017; Sedgewick *et al.*, 2021).
- **Female Phenotype:** Diagnostic tools may be biased toward male presentations, leading to delayed diagnoses in women (Lever & Geurts, 2018; Posserud *et al.*, 2021; Haney, 2016; Lundström *et al.*, 2019). Social stigma and professional expectations also play a role (Bargiela *et al.*, 2016; Elie-Fortier & Braun, 2019).
- **Protective Female Effect:** Girls may require more genetic mutations to exhibit autism symptoms (Zhang *et al.*, 2020; Jack *et al.*, 2021).
- **Camouflage:** Women may mask autism traits more effectively due to social pressures, which can delay diagnosis (Bargiela *et al.*, 2016; Cumin *et al.*, 2022; Milner *et al.*, 2019; Hull *et al.*, 2017).

The Impact of ASD on the Individual's Mental Health

Male-centric view of ASD and its under-researched manifestation in women increases their risk of underdiagnosis and mental health issues (Haney, 2016).

- **Impact of Underdiagnosis:** Underdiagnosed individuals may experience worsened mental health due to better camouflage skills, social anxiety, and traumatic experiences, leading to a loss of trust in professionals and difficulties in expressing symptoms (Giarelli *et al.*, 2010; Huang *et al.*, 2021; Davidson, 2007; Hickey *et al.*, 2018; Garel & Garel, 2019; Lewis, 2017).
- **Impact of Diagnosis:** Reactions to ASD diagnosis vary, with some hiding their diagnosis due to fear or perceived irrelevance, while others may have positive or negative responses from close ones (Baker & Box, 2015; Fadda, 2019; Lewis, 2016a; Gaffney, 2020).
- **Comorbidities:** ASD is often diagnosed after identifying other conditions, such as depression and suicidal ideation, which can stem from social isolation and emotional vulnerability. Confusion with PTSD can also occur due to symptom overlap and traumatic experiences (Sturrock *et al.*, 2020;

- **Self-Diagnosis:** Attention to self-diagnosed individuals during the diagnostic process is crucial (Lewis, 2017).

3.5 Meta-analysis

We analyzed 14 studies to determine the average age of ASD diagnosis for women who were undiagnosed by age 15. For studies providing only median age and range (Atherton *et al.*, 2022; Fusar-Poli *et al.*, 2022), we converted these to means and standard deviations (Table 1).

Table 1. Transformations of the variable “age at diagnosis”

Study	n (female)	Median	Interval	Average	Standard Deviation
Atherton2022	107	21	[3 - 63]	26.75	14.75
Fusar-Poli2022	47	26	[19 - 51]	30.50	8.00

The weighted average age of ASD diagnosis for these women was 28.24 years (95% CI: 23.16-34.44) using a random effects model. Variance was significant ($\tau^2 = 0.1674$, $p = 0.0001$), with high heterogeneity ($I^2 = 99\%$) (Figure 2).

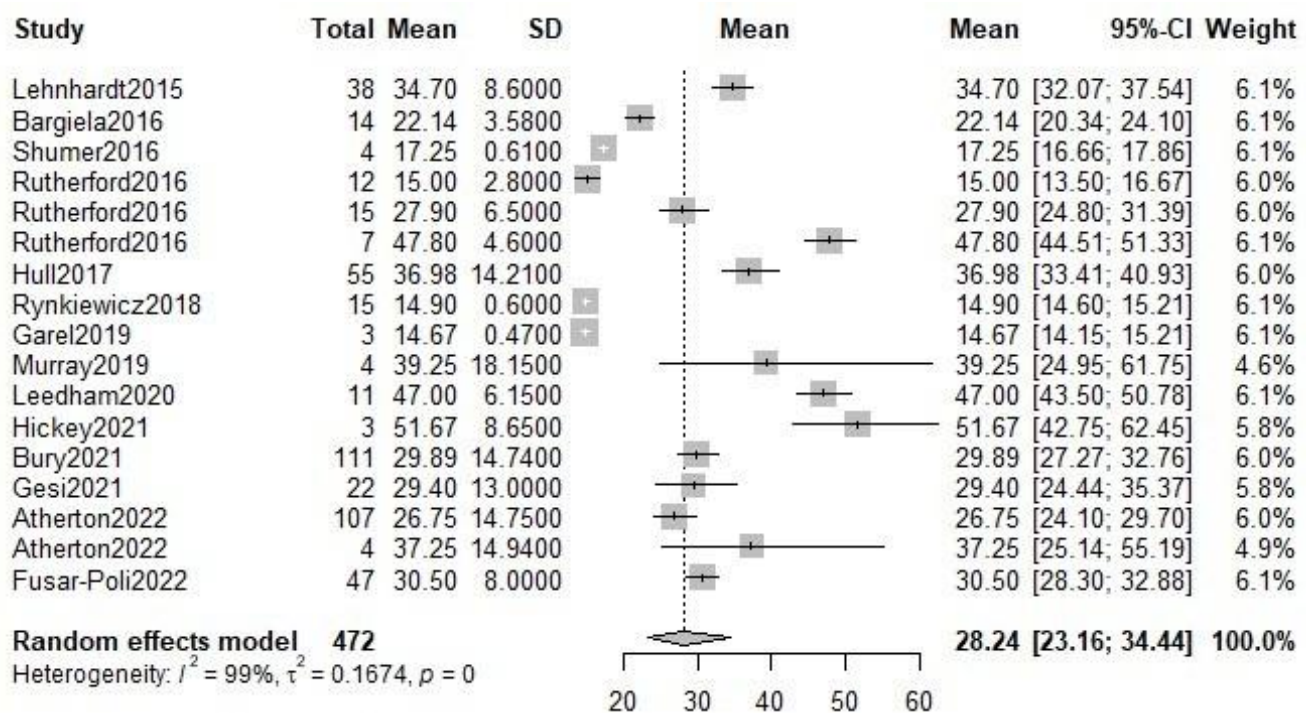


Figure 2. Forest plot: age of diagnosis.

The funnel plot revealed significant publication bias, with studies dispersed around the average (Figure 3). Despite high variability, the results suggest that values might converge with a larger sample.

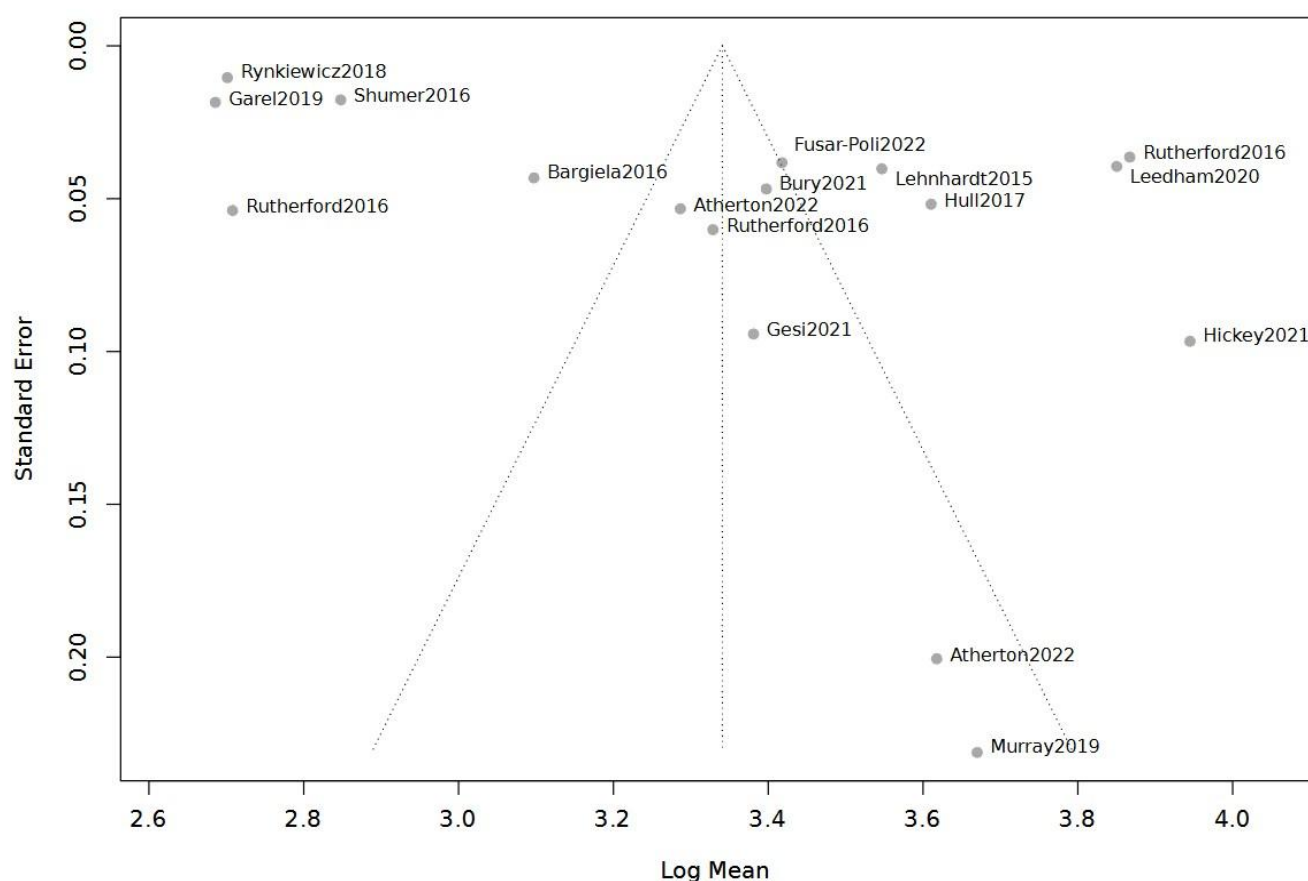


Figure 3. Funnel plot: age of diagnosis.

4. Conclusions

This study examines the underdiagnosis of ASD in women, highlighting how social expectations and diagnostic biases, influenced by the predominance of male-focused research, contribute to this issue. Misdiagnosis in non-white individuals often results from limited healthcare access (Roy & Balaratnasingam, 2010).

Theories such as the Extreme Male Brain Theory, Female Phenotype Theory, and Protective Female Effect provide insights into gender differences in autism. While this study supports the Protective Female Effect, it acknowledges that no single theory fully explains these differences. Factors like camouflage, gender-biased diagnostic tools, and varying genetic presentations all contribute to the underdiagnosis of women.

Underdiagnosis impacts mental health, with early diagnosis potentially reducing comorbidities (Happé *et al.*, 2016; Aggarwal & Angus, 2015). Autism is often identified only after other conditions are diagnosed (Carmassi *et al.*, 2019). Social isolation and difficulties in adaptation exacerbate mental health issues, leading to increased vulnerabilities and trauma (Hickey *et al.*, 2018; Davidson, 2007; Lodi-Smith *et al.*, 2021; Lewis, 2016a; Hartman, 2020; Kreiser & White, 2015; McGillivray & Evert, 2018; Sturrock *et al.*, 2020; Cumin *et al.*, 2022; Gesi *et al.*, 2021; Leedham *et al.*, 2020).

Self-diagnosis often emerges from these challenges, emphasizing the need for sensitivity and empathy from professionals (Lever & Geurts, 2018; Cumin *et al.*, 2022). Diagnostic confusion with similar psychiatric conditions, especially schizophrenia, further complicates the process (Crivelli &

Rocca, 2013; Harvey *et al.*, 2019; Roy & Balaratnasingam, 2010). Secondary disorders, like gender dysphoria, may also occur (Kraemer *et al.*, 2005).

Quantitative analysis shows significant variability in the average age of ASD diagnosis for women, with a mean age of 28.24 years (95% CI 23.16-34.44). This suggests that women are often underdiagnosed or diagnosed later in life. Limitations include the exclusion of treatment-related studies due to specific selection criteria. Future research should include both genders and examine how camouflage ability impacts diagnostic delays.

Overall, this study aimed to identify factors related to underdiagnosis or late diagnosis of ASD in women and estimate their average age of diagnosis. The findings support existing literature on gender differences in ASD prevalence (Loomes *et al.*, 2017) and indicate that women are often diagnosed in their mid-30s, reflecting the ongoing challenges in recognizing and diagnosing ASD in females.

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Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

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