Correlation between Epigenetic Markers and Sociodemographic Factors in Autism Spectrum Disorder in Brazil

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Abstract: Autism Spectrum Disorder (ASD) is a multifactorial neurodevelopmental condition whose etiology involves interactions between genetic, environmental, and epigenetic factors. Epigenetics acts as a molecular interface between the environment and gene expression, being sensitive to adverse social conditions. This study analyzed the sociodemographic distribution of ASD in Brazil using data from the 2022 Demographic Census conducted by the Brazilian Institute of Geography and Statistics (IBGE), correlating the observed patterns with findings from the epigenetic literature. The descriptive analysis revealed that, in Brazil, the highest prevalence of diagnoses is in the Southeast region (1,042,066 cases); among males (ratio ~3:1), in the 5-to-9-year age group, and among self-declared white individuals. These patterns are subject to underreporting bias and unequal access to diagnosis. The integration of these sociodemographic data with molecular findings indicates that sex-linked differences in DNA methylation (involving genes such as MECP2), regionally variable environmental exposures (pollutants, psychosocial stress), and food insecurity may modulate the expression of ASD susceptibility genes, such as RELN and SHANK3. Recent data show that chronic stressors alter methylation patterns in neurodevelopmental genes, suggesting that regional and racial disparities do not merely reflect access barriers but also actual differences in the burden of exposure to environmental factors with epigenetic potential. It is concluded that disparities in ASD diagnosis in Brazil reflect structural inequalities in healthcare access, exacerbated by epigenetic mechanisms mediated by socio-environmental conditions in vulnerable populations. Equitable policies and integrative research are essential for early diagnosis and universal care.

Keywords: Autism Spectrum Disorder; epigenetics; social inequalities; Demographic Census; Brazil.

Resumen: El Trastorno del Espectro Autista (TEA) es una condición del neurodesarrollo multifactorial cuya etiología involucra interacciones entre factores genéticos, ambientales y epigenéticos. La epigenética actúa como una interfaz molecular entre el ambiente y la expresión génica, siendo sensible a condiciones sociales adversas. Este estudio analizó la distribución sociodemográfica del TEA en Brasil utilizando datos del Censo Demográfico 2022, realizado por el Instituto Brasileño de Geografía y Estadística (IBGE), correlacionando los patrones observados con hallazgos de la literatura epigenética. El análisis descriptivo reveló que, en Brasil, la mayor prevalencia de diagnósticos se encuentra en la región Sudeste (1.042.066 casos); entre el sexo masculino (proporción ~3:1), en el grupo etario de 5 a 9 años y entre individuos autodeclarados blancos. Estos patrones están sujetos a sesgos de subnotificación y al acceso desigual al diagnóstico. La integración de estos datos sociodemográficos con los hallazgos moleculares indica que las diferencias ligadas al sexo en la metilación del ADN (que involucran genes como MECP2), las exposiciones ambientales con variabilidad regional (contaminantes, estrés psicosocial) y la inseguridad alimentaria pueden modular la expresión de genes de susceptibilidad al TEA, como RELN y SHANK3. Datos recientes muestran que los estresores crónicos alteran los patrones de metilación en genes del neurodesarrollo, lo que sugiere que las disparidades regionales y raciales no reflejan únicamente barreras de acceso, sino también diferencias reales en la carga de exposición a factores ambientales con potencial epigenético. Se concluye que las disparidades en el diagnóstico del TEA en Brasil reflejan desigualdades estructurales en el acceso a la atención sanitaria, exacerbadas por mecanismos epigenéticos mediados por condiciones socioambientales en poblaciones vulnerables. Las políticas equitativas y la investigación integrativa son esenciales para el diagnóstico temprano y la atención universal.

Palabras clave: Trastorno del Espectro Autista; epigenética; desigualdades sociales; Censo Demográfico; Brasil.

Resumo: O Transtorno do Espectro Autista (TEA) é uma condição do neurodesenvolvimento multifatorial cuja etiologia envolve interações entre fatores genéticos, ambientais e epigenéticos. A epigenética atua como uma interface molecular entre o ambiente e a expressão gênica, sendo sensível a condições sociais adversas. Este estudo analisou a distribuição sociodemográfica do TEA no Brasil a partir de dados do Censo Demográfico 2022, realizado pelo Instituto Brasileiro de Geografia e Estatística (IBGE), correlacionando os padrões observados com achados da literatura epigenética. A análise descritiva revelou que, no Brasil, a maior prevalência de diagnósticos encontra-se na região Sudeste (1.042.066 casos); entre o sexo masculino (razão ~3:1), na faixa etária de 5 a 9 anos e entre indivíduos autodeclarados brancos. Esses padrões estão sujeitos a vieses de subnotificação e ao acesso desigual ao diagnóstico. A integração desses dados sociodemográficos com as evidências moleculares indica que diferenças ligadas ao sexo na metilação do DNA (envolvendo genes como MECP2), exposições ambientais com variabilidade regional (poluentes, estresse psicossocial) e insegurança alimentar podem modular a expressão de genes de suscetibilidade ao TEA, como RELN e SHANK3. Dados recentes mostram que estressores crônicos alteram os padrões de metilação em genes do neurodesenvolvimento, sugerindo que as disparidades regionais e raciais não refletem apenas barreiras de acesso, mas também diferenças reais na carga de exposição a fatores ambientais com potencial epigenético. Conclui-se que as disparidades no diagnóstico do TEA no Brasil refletem desigualdades estruturais no acesso aos serviços de saúde, exacerbadas por mecanismos epigenéticos mediados por condições socioambientais em populações vulneráveis. Políticas equitativas e pesquisas integrativas são essenciais para o diagnóstico precoce e o cuidado universal.

Palavras-chave: Transtorno do Espectro Autista; epigenética; desigualdades sociais; Censo Demográfico; Brasil.

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition of multifactorial etiology, characterized by the dynamic interaction between genetic, epigenetic, and environmental components[1]. Contemporary understanding surpasses reductionist views that exclusively privileged hereditary or environmental factors, revealing a complex system in which these elements are articulated through sophisticated epigenetic mechanisms[2].

The genetic basis of ASD manifests through over a hundred genes, with particular emphasis on those involved in processes such as neurogenesis, transcriptional regulation, and synaptogenesis. The risk for psychiatric disorders is shaped by a complex interaction of hereditary factors, and in the case of ASD, the genetic burden is especially linked to critical events of early cortical development, such as neurogenesis and neuronal migration[3-6]. Recent studies highlight those genes are involved not only in the differentiation of glutamatergic neurons but also in the development of interneurons and non-neuronal cells[3, 7].

However, the mere presence of genetic variants only partially explains the manifestation of ASD, highlighting the need to consider other levels of biological regulation. Epidemiological studies indicate that environmental factors such as toxic exposures, teratogens, perinatal insults, and prenatal infections also influence cases of ASD[8-11]. In this context, epigenetics emerges as a fundamental paradigm, operating as a molecular interface between the genome and the environment.

1.2. Theoretical Foundation

1.2.1 Epigenetic Influence

Distinct from classical genetics, which studies alterations in the DNA nucleotide sequence, epigenetics investigates reversible functional modifications that modulate gene expression without altering the genetic code[12-13]. This process is particularly relevant in the fine-tuning of the expression of genes involved in brain development, and its dysregulation has been associated with the emergence of several neurodevelopmental disorders, including ASD[14].

1.2.2. DNA Methylation

DNA methylation consists of the covalent addition of a methyl group to the 5-position of cytosine (5mC), which can be subsequently oxidized to 5-hydroxymethylcytosine (5hmC), an epigenetic modification directly associated with ASD[15]. While in somatic cells this phenomenon occurs predominantly at CpG dinucleotides, in neurons methylation at non-CG sites (5mCpH) is equally abundant, conferring a distinct cellular epigenetic profile specific to the central nervous system[16]. Among the approximately 800 regulatory genes potentially related to ASD, MECP2 (methyl-CpG-binding protein 2), located on the X chromosome, stands out, exhibiting distinct methylation patterns between sexes and directly acting on the modulation of critical synaptic and cortical genes, such as GAD1, RELN, SHANK3, and ADAK[17-21].

Being a dynamic modification, DNA methylation is consolidated as the molecular mechanism most susceptible to demographic conditions, family planning, and socioeconomic determinants[13]. In the demographic sphere, advancing parental age, particularly paternal age, is associated with ASD due to male germline cellular aging. Continuous spermatogenesis throughout life favors the progressive accumulation of epigenetic errors and methylation dysregulation, transmitting aberrant de novo methylation profiles to the offspring, which compromises neural progenitor proliferation and synaptogenesis[14].

Molecular evidence indicates that epigenetic alterations in paternal sperm play a critical role in susceptibility to ASD, manifesting consistently in the cerebellum of affected individuals[22]. Additionally, variations in sperm DNA methylation profiles demonstrate clinical potential as specific predictive biomarkers, achieving a diagnostic accuracy of approximately 90%[23]. This germline epigenetic signature has been directly correlated with the development of autistic traits in children at 3 years of age, with mechanisms validated in post-mortem brain tissue analyses, corroborating the transgenerational impact of paternal factors on the disorder's etiology[24].

Furthermore, socioeconomic and regional disparities exert a direct influence on the metabolic machinery of methylation. The synthesis of S-adenosylmethionine (SAM), the universal methyl group donor, strictly depends on the dietary intake of folate, choline, and B-complex vitamins[13]. Pregnant women in contexts of social vulnerability face higher rates of food insecurity and barriers to accessing early prenatal folic acid supplementation. The scarcity of these micronutrients during critical windows of embryonic development restricts the one-carbon pathway, culminating in states of global DNA hypomethylation or site-specific hypermethylation of promoters of vital genes such as MECP2 and

SHANK3, which mimics or potentiates the effect of deleterious genetic mutations linked to ASD[13, 20]. These findings demonstrate that social asymmetries directly impact genomic expression in ASD.

Given the above, it becomes imperative to investigate the correlation between structural determinants and socioeconomic vulnerabilities, whose direct impacts on nutrition and gestational stress, and epigenetic factors of ASD, warrant further investigation. The present study is justified by the analytical interface that articulates demographic and regional indicators with the current biomolecular literature, aiming to elucidate the relationship between social inequalities and epigenetic risk factors associated with neurodevelopment in the Brazilian context.

1.2.3. Histone Modification

At the structural level of chromatin, post-translational modifications of histones control the accessibility of transcription factors to DNA, and their dysregulation directly influences ASD by compromising essential neural processes[25]. Specifically, histone acetylation mediated by HAT and reversed by HDAC alters chromatin conformation to a relaxed state (euchromatin), while trimethylation of histone H3 lysine 4 (H3K4me3) recruits remodeling complexes such as CHD8 and SWI/SNF, both of which are fundamental for neuronal differentiation, cell growth, and hippocampal synaptic plasticity[14, 26, 27].

When epigenetic dysregulations occur in enzymes such as the methyltransferases KMT2C and EHMT1, the demethylase KDM5C, the repressive complex EZH2, regulators such as HDAC4 and the ADNP gene, or mutations in linker histones such as HIST1H1E, the result is a direct contribution to the etiology of ASD and to the associated intellectual impairment[14, 20, 28-31]. These chromatin signatures are vulnerable to chronic psychosocial stressors and environmental pollutants, factors linked to socioeconomic inequalities and spatial segregation[20, 25].

Chronic maternal gestational stress, exacerbated by economic vulnerabilities, activates the HPA axis by elevating glucocorticoids, which alters the acetylation and methylation of histones such as H3K4 and H3K27 at promoters of neurotrophic genes in the fetal brain, impairing the maintenance of neural progenitors and synaptic maturation, two critical processes whose dysregulation leads to ASD[20, 25]. Simultaneously, exposure to pollutants such as pesticides and phthalates in metropolitan areas induces oxidative stress that inhibits HAT enzymes, altering global chromatin remodeling; this epigenetic

blockade represses neurobiological pathways essential for GABAergic signaling and for the arborization and maturation of dendritic spines, directly mimicking the molecular deficits observed in ASD pathogenesis[21, 40].

1.2.4. MicroRNA Dysregulation

MicroRNAs (miRNAs) are small non-coding RNAs, ranging from 15 to 22 nucleotides in length, that act as post-transcriptional regulators of gene expression, controlling processes such as cell proliferation and differentiation[32, 33]. It is estimated that 50% of human genes are regulated by miRNAs, which coordinate functional pathways essential for development, apoptosis, and cellular homeostasis[32]. A substantial portion of known miRNAs is expressed in the central nervous system, where they control synaptic plasticity, axonal guidance, and neuronal homeostasis through the silencing of target messenger RNAs[14, 34].

In ASD, chronically altered profiles of specific miRNAs impact signaling pathways crucial for neurodevelopment, such as the Wnt, mTOR, and MAPK pathways[14, 20]. This dysregulation is supported by animal models[35-37] and confirmed in humans through post-mortem brain tissue analyses, which have identified at least 28 differentially expressed miRNAs in the cortex of individuals with ASD, with findings replicated in lymphoblastoid cell lines and peripheral blood[38-40].

At the molecular level, Cui and colleagues (2021) found that children diagnosed with ASD exhibit a serum signature characterized by a marked reduction in the levels of hsa-miR-181b-5p and hsa-miR-320a, concomitant with a significant elevation of hsa-miR-19b-3p, suggesting a peripheral epigenetic biomarker profile. Mechanistically, the dysregulation of these specific microRNAs correlates with stressors and insults from the intrauterine and perinatal microenvironment[41].

Aligned with this perspective of environmental vulnerability, the present study identified that the ASD group exhibited a significantly higher prevalence of adverse gestational determinants compared to the control group, notably maternal stress and chronic alcohol consumption, threat of miscarriage, hypertension and gestational diabetes, as well as maternal anemia[41].

Regarding obstetric and neonatal components, complications such as nuchal cord, neonatal jaundice, and birth weight restriction were also found to be strongly associated with the phenotype. These complications act as potential epigenetic triggers or neurodevelopmental disruptors in participation with family psychiatric history[41].

Sociodemographic determinants, such as disadvantaged socioeconomic status and barriers to accessing prenatal care, which may lead to untreated gestational infections, late diagnosis of maternal pathologies, and use of teratogenic substances such as valproic acid influence miRNA dysregulation during corticogenesis[14, 20].

Collectively, these determinants act synergistically with modifications in DNA methylation and histone remodeling, redefining the neurodevelopmental vulnerability threshold toward the autistic phenotype[14, 25].

1.3 Sociodemographic Factors

1.3.1 Global Data

Several studies have demonstrated that financial stress, psychosocial stress, and trauma are associated with epigenetic factors. There are some studies that have investigated the effects of racism on ASD diagnosis. Most studies have evaluated epigenetic or genomic alterations in maternal blood, umbilical cord blood, or the placenta. Several studies included multi-omic assessments in which DNA methylation and/or microRNA expression were associated with gene expression. There is strong evidence for the role of epigenetics in determining the health outcomes considered[42].

The dynamic expression of miRNAs during neurogenesis and neurodevelopment has received increasing attention in the context of ASD development. Furthermore, miRNAs can interact with inflammatory factors modulated by the gut microbiota, which results in altered downstream gene expression in the brain and periphery. In this way, the wide distribution and functional versatility of miRNAs suggest that they may underlie various recurrent biological abnormalities in ASD that would otherwise remain unexplained[43].

Although ASD is predominantly considered a disorder of genetic origin, growing evidence highlights the role of environmental factors, particularly during the prenatal period. The natural immunosuppression of pregnancy increases the vulnerability of the mother and fetus to infectious agents, which may interfere with neurodevelopment[44-45]. Epidemiological studies associate parental viral infections, especially in the first trimester of pregnancy, with an increased risk of ASD in offspring[46-47].

The study by Durkin and colleagues (2017) analyzed the prevalence and characteristics of ASD in 8-year-old children in the U.S. in 2012, using data from the Autism and Developmental Disabilities Monitoring (ADDM) Network. This study

revealed that 1 in 68 8-year-old children had ASD, with variations across states. Boys were diagnosed 4.5 times more often than girls, and White children presented a higher prevalence than Black and Hispanic children. These differences may reflect both biological factors and sociodemographic inequalities in access to diagnosis and treatment[48].

Studies with identical (monozygotic) twins estimate that the heritability of ASD may reach over 90%[49]. However, other research indicates that genetic and environmental factors contribute equally, approximately 50% each[50]. The concordance rate for ASD is much higher in monozygotic twins than in non-identical (dizygotic) twins, and this rate varies according to the level of ASD support needs. Nevertheless, concordance is not complete[51]. The fact that monozygotic twins do not always develop the same disorder confirms that epigenetic factors and environmental stressors influence neurodevelopment[52-53].

The literature presents contradictory findings regarding the association between socioeconomic status and ASD, reflecting both methodological differences and the concentration of research in nations with high gross domestic product per capita. Studies such as those by Yu and colleagues (2021) and Kelly and colleagues (2019) reported a higher prevalence of ASD in socioeconomically privileged classes, possibly due to greater access to diagnostic services and parental awareness[54-55].

In contrast, Silva and colleagues (2022) found a higher prevalence in low-income families and in contexts of social vulnerability, attributable to adverse environmental exposures and psychosocial stress during pregnancy[56]. Larsson and colleagues (2005), on the other hand, did not identify a significant association between socioeconomic status and ASD, suggesting that genetic factors and other unmeasured variables may carry greater weight[57].

These discrepancies highlight the need for standardized and inclusive studies across different economic contexts to elucidate how the social environment interacts with epigenetic mechanisms in modulating the risk for ASD.

1.3.1 Data from Brazil

The Mapa Autismo Brasil (MAB), conducted by the Instituto Autismos (2026), reveals a strong dependence on the private healthcare network for access to healthcare in the country. This study, which collected 23,632 online interviews in 2025, indicates that only 20.4% of respondents obtained an ASD diagnosis through the Unified Health System

(SUS), while the vast majority (78.4%) had to resort to the private network or health insurance plans to obtain a medical report[58].

Diagnosis and follow-up in Brazil are, therefore, highly marked by socioeconomic and regional inequalities: diagnosis occurs in 55.3% through the private network, 23.1% via health insurance plans, and only 20.4% through the SUS[58]. Access to therapies follows the same pattern, with over 60% of respondents depending on health insurance or private resources, while only 15.5% undergo therapies in the public network[58]. The study also reveals a massive burden on women, with 92.4% of caregivers being female, and approximately 30.5% of caregivers reported being unemployed or without their own income, evidencing the impact of caregiving demands on professional trajectories[58].

To understand and advance in this discussion, it is important to observe the regional differences pointed out by the research, such as the greater dependence on the SUS in the North (33.48%) and Northeast (24.11%) for diagnostic confirmation, contrasting with the reality in the Southeast and South[58]. Access to health and education services for individuals with ASD presents a heterogeneous scenario, where geographic, economic, and ethnic-cultural factors determine radically different care trajectories. Inequalities in access to diagnoses and specialized treatments constitute one of the main challenges of the Brazilian healthcare system. Socioeconomic variations impose additional barriers[59-60].

Families with higher household income (approximately 20 times the minimum wage), predominantly residing in urban areas of large centers, have greater access to early ASD assessments in private clinics. In contrast, economically vulnerable individuals, dependent exclusively on the Unified Health System (SUS), face long waiting periods and limited availability of specialized services. This inequality results in late ASD diagnoses and interventions among children from less favored social classes[61-62].

The ethnic-racial dimension adds another layer of complexity. Black, Indigenous, and Quilombola populations face additional barriers in ASD recognition, ranging from cultural unawareness to structural racism within healthcare services. Studies indicate that Black children with ASD receive diagnoses later than White children, often being initially referred to mental health services[63-64].

Given the scarcity of data in Latin America and the significant socio-familial impact of ASD[65], the present study sought to investigate the relationship between socioeconomic markers (education, occupation, income, family composition) and demographic markers (ethnicity, gender, age) with ASD. This study aims to analyze the

sociodemographic disparities associated with ASD diagnosis in Brazil, based on data from the 2022 Census, and to discuss how these inequalities may influence epigenetic mechanisms linked to neurodevelopment.

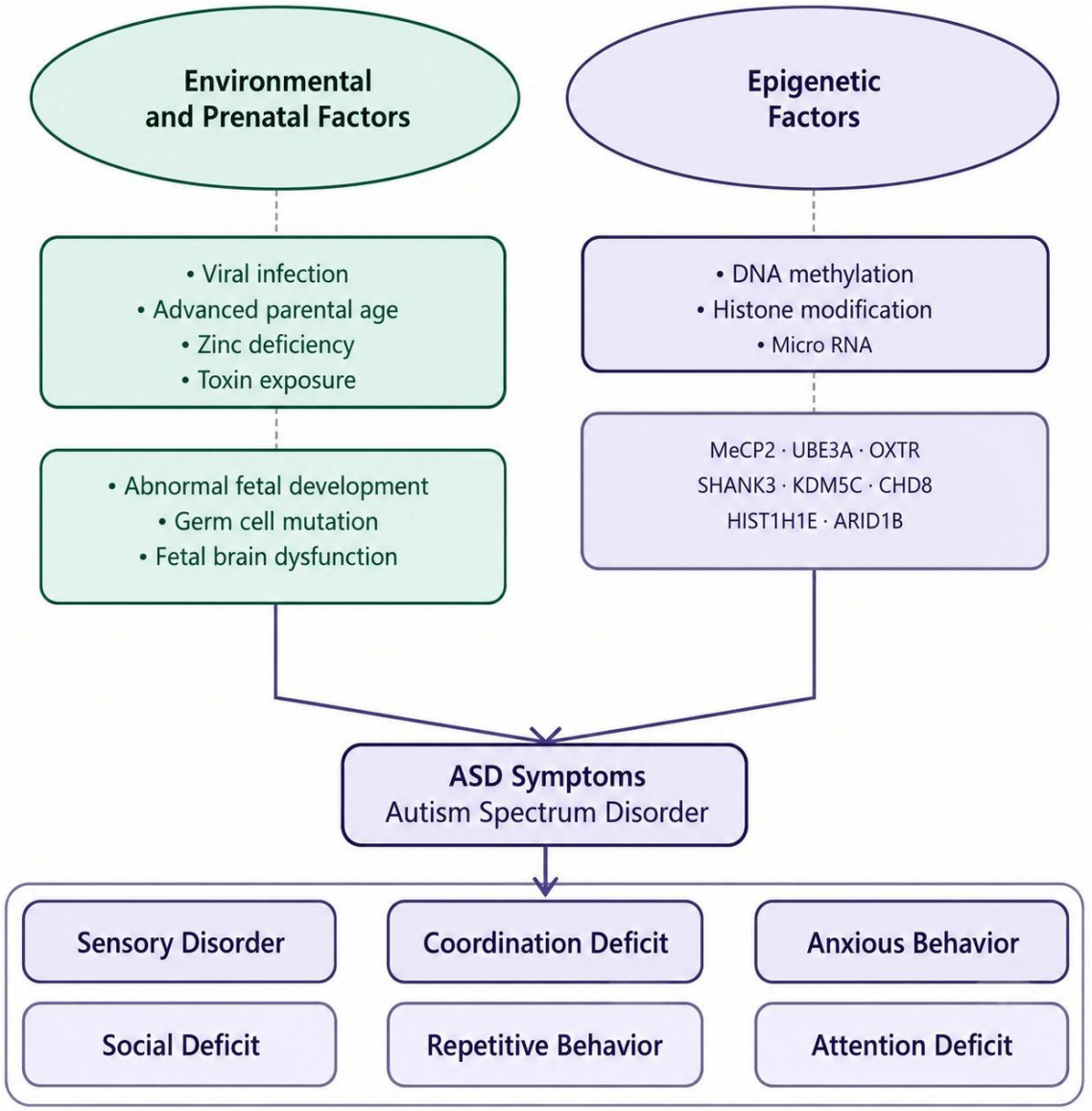

Figure 1. Diverse etiology of autism spectrum disorder (ASD). Accumulated evidence points to environmental and epigenetic risk factors. Figure prepared by the author, with modifications adapted from Yoon et al. (2020).

3. Methodology:

3.1 Analysis of Sociodemographic Data on ASD

To evaluate the distribution of ASD in Brazil, microdata from the 2022 Demographic Census, made available by the Brazilian Institute of Geography and Statistics (IBGE), were used. The primary cut considered the ASD diagnosis variable (affirmative response to the question regarding autistic condition in the questionnaire). Descriptive analyses were performed on the following sociodemographic variables: geographic region (North, Northeast, Southeast, South, Central-West), sex (male or female), age group, and self-reported color/race (White, Black, Mixed-race/Brown, Yellow/Asian, Indigenous) with ASD.

3.2. Graph Elaboration and Data Visualization

The graphs were generated from the SIDRA/IBGE platform: https://sidra.ibge.gov.br/pesquisa/censo-demografico/demografico-2022/amostra-pessoas-com-deficiencia-e-espectro-autista. The visualizations included: distribution of ASD cases by geographic region, prevalence by sex, color/race, age group, educational attainment, and basic sanitation, using vertical and horizontal bar charts, pie charts, and thematic maps.

3.3. Literature Review on Epigenetics and ASD

In order to correlate the sociodemographic data with the epigenetic mechanisms involved in ASD, a narrative review of the scientific literature was conducted. The search was carried out in the main databases, including PubMed, SciELO, Google Scholar, and ScienceDirect, using specific search strategies. Articles published between 2015 and 2025, in English, addressing the relationship between epigenetics and ASD were included. The keywords used in the search included combinations such as "Autism Spectrum Disorder" OR "ASD" AND "Epigenetics", "Socioeconomic Factors" AND "Neurodevelopment"*, and "DNA methylation" AND "Autism". As exclusion criteria, studies without peer review and research conducted exclusively in animal models, without human data, were eliminated.

3.4. Integrative Analysis

To articulate the Census data with the epigenetic literature, a two-step approach was adopted, beginning with the identification of patterns in the IBGE data, such as the higher prevalence of diagnoses in light of epigenetics, examining how adverse socioeconomic conditions may influence epigenetic marks associated with ASD.

4. Results and Discussion:

4.1 Region

The regional distribution of diagnoses reveals a significant concentration in the Southeast region (1,042,066 cases), contrasting with the lower records in the North (~200,000) and Central-West (~180,000) regions.

Such disparity should not be interpreted as indicative of a higher biological prevalence of ASD in these regions, but rather as a reflection of the profound asymmetries in access to specialized diagnosis and healthcare services, corroborating previous findings that point to socioeconomic status and regional infrastructure as central determinants of diagnostic trajectories[59, 62].

From an epigenetic perspective, regions marked by greater socioeconomic vulnerability tend to expose their populations to chronic environmental stressors, such as malnutrition, air pollution, and psychosocial stress, conditions widely recognized as capable of inducing lasting epigenetic modifications, including alterations in DNA methylation patterns and post-translational histone modifications, which impair the expression of genes critical for neurodevelopment[13-14].

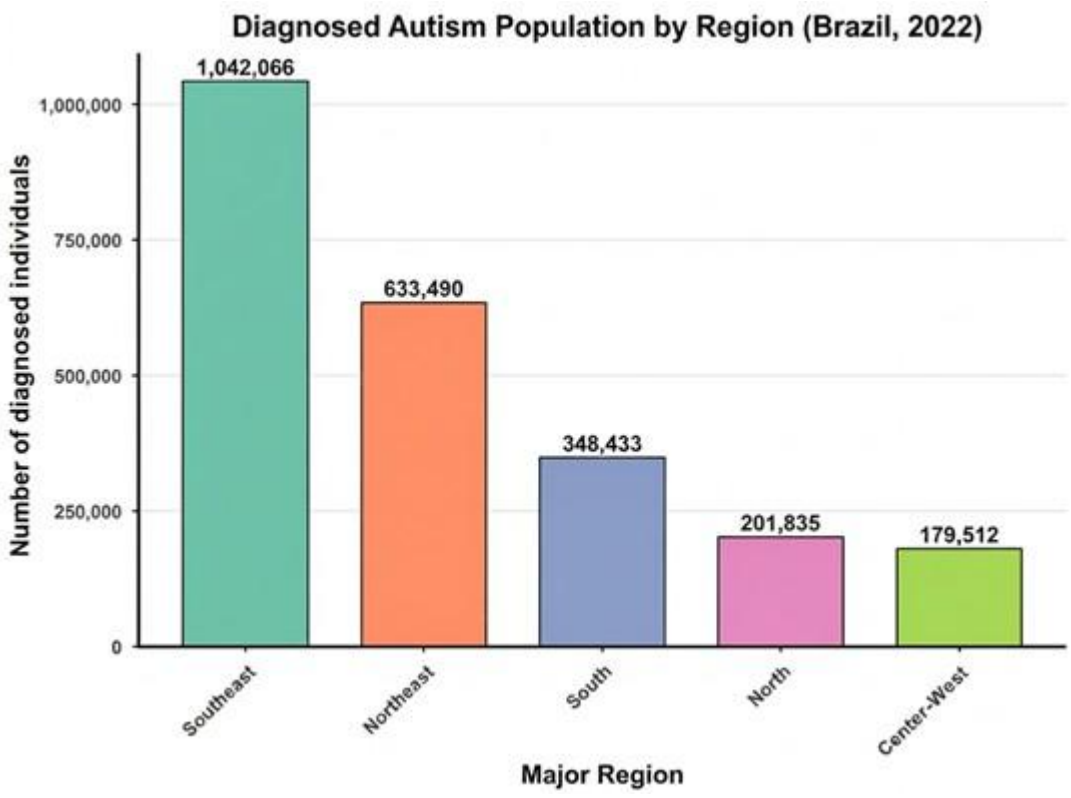

Figure 2. Distribution of the resident population diagnosed with Autism Spectrum Disorder (ASD) by region of Brazil. Source: IBGE - Demographic Census.

4.2 Sex

Regarding the distribution by sex, the data confirm the male predominance among those diagnosed with ASD. The data indicate 1,441,208 men and 964,129 women diagnosed. This asymmetry is consistent with the international scientific literature, which describes diagnostic ratios ranging from 3:1 to 4:1 between males and females[48].

From an epigenetic perspective, such a difference may be related to gene regulation mechanisms associated with the X chromosome, which confer upon females a possible epigenetic protection against the expression of ASD, a hypothesis reinforced by the role of the MeCP2 gene, located on the X chromosome, and its distinct methylation patterns between sexes[17, 21]. Additionally, the phenomenon of camouflage, by which women tend to mask symptoms with greater adaptive efficacy, contributes to the underdiagnosis in females, suggesting that the actual prevalence of ASD among women may be substantially higher than official records indicate.

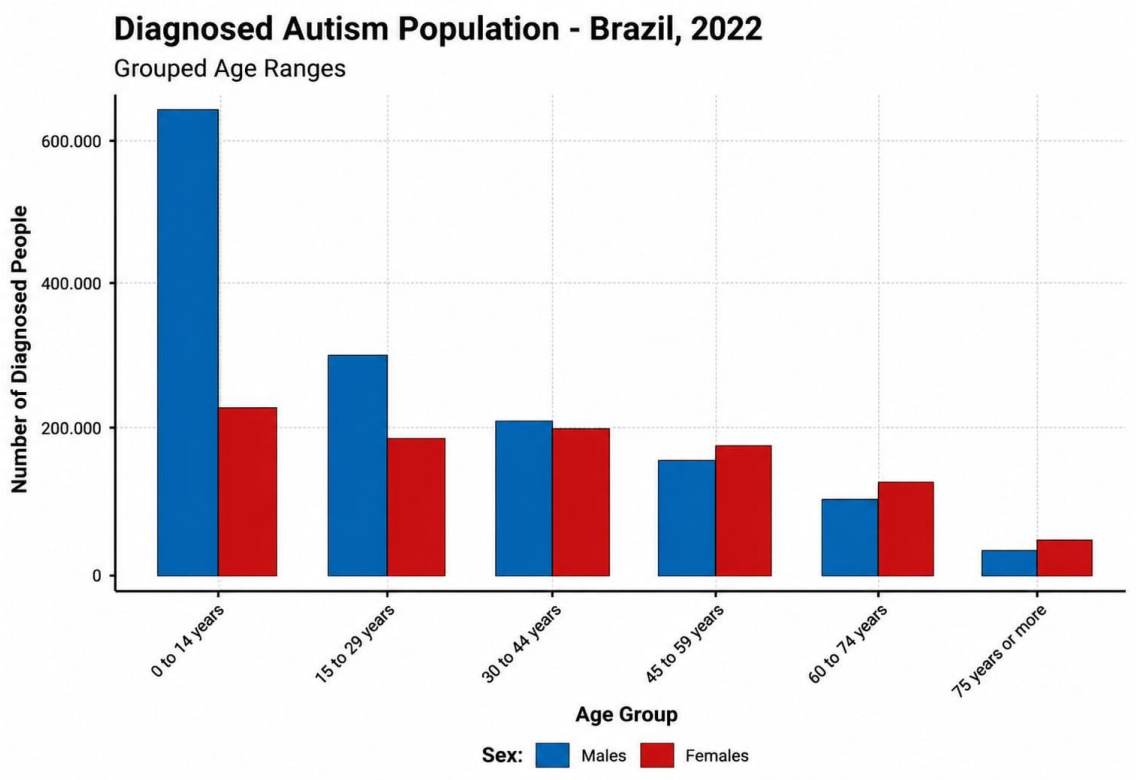

Figure 3. Resident population diagnosed with Autism Spectrum Disorder (ASD) in Brazil, by sex and age group.

4.3 Age Group

The analysis of age distribution revealed a significant concentration of diagnoses in the 5-to-9-year age group (350,942 cases), followed by the 0-to-4 and 10-to-14-year groups, with a progressive decline in adult age groups. This pattern reflects, in part, the advances in early screening programs implemented in recent decades, but also highlights the historical underdiagnosis in adults, a generation that grew up without contemporary diagnostic criteria and without access to specialized services[66].

4.4 Color/Race

The analysis by color or race demonstrated that, in absolute terms, the White population concentrates the highest number of diagnoses (1,103,580), followed by the Mixed-race/Brown population (1,057,955) and, to a lesser extent, the Black population (221,667), with significantly lower values among Yellow/Asian and Indigenous individuals. These data, however, must be interpreted with strict critical scrutiny, as they do not necessarily reflect differences in the biological prevalence of ASD across racial groups, but rather reveal historically unequal access to specialized healthcare services in Brazil[63-64].

Mixed-race, Black, and Indigenous populations are often more exposed to adverse social determinants, such as food insecurity, precarious housing conditions, and chronic stress arising from structural racism. These factors act through the epigenetic pathway and may increase susceptibility to ASD while simultaneously broadening barriers to diagnosis, configuring a cycle of invisibility that compromises both care and the production of scientific knowledge representative of Brazil's population diversity[67].

Altogether, the analyzed data reinforce that ASD cannot be understood exclusively from the perspective of classical genetics. Environmental, social, and economic factors interact with the genome through epigenetic pathways, modulating the expression of the disorder in distinct ways according to the geographic region, age group, sex, and race of individuals. The Brazilian scenario, marked by wide population diversity and profound structural inequalities, constitutes a privileged field for investigations that integrate population data and epigenetic biomarkers, contributing to a more comprehensive and equitable understanding of ASD and to the formulation of truly inclusive public policies.

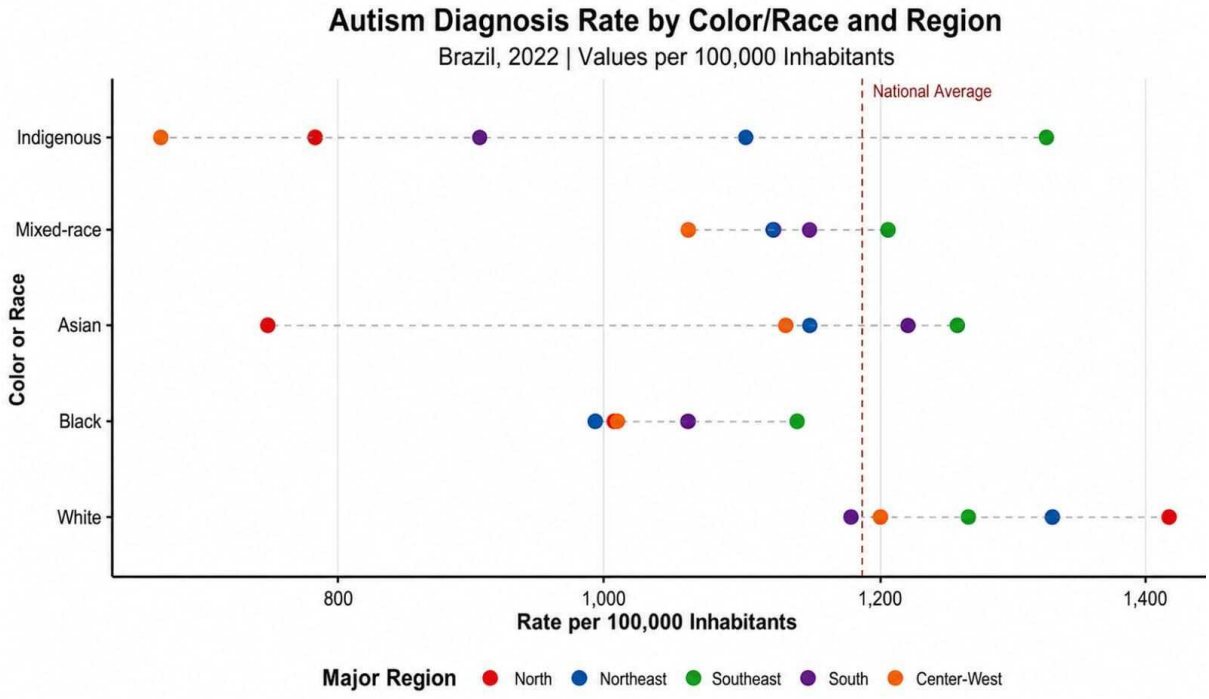

Figure 4. Resident population diagnosed with Autism Spectrum Disorder (ASD) in Brazil, by color/race and by region.

4.5 Integrative Analysis

The articulation between the data from the Demographic Census (IBGE, 2022) and the epigenetic literature reveals convergences and divergences that reinforce the hypothesis that ASD results from the interaction between genetic susceptibility and environmental exposures mediated by epigenetic mechanisms, rather than from isolated genetic determinism.

The concentration of diagnoses in the Southeast region, in contrast to the lower records in the North and Central-West, was primarily interpreted as a reflection of unequal access to specialized diagnosis. However, this regional inequality is also compatible with differences in exposure to environmental factors capable of altering differentially methylated regions (DMRs). In animal models, prenatal exposure to polychlorinated biphenyls, which are persistent environmental contaminants, generates thousands of DMRs similar to those found in human neurodevelopmental disorders[68].

Parental exposures to substances such as nicotine and tetrahydrocannabinol (THC) alter sperm DNA methylation precisely in genes linked to ASD[69]. These findings suggest that the regional distribution observed in the Census may reflect not only unequal access to services but also actual differences in the burden of environmental and

behavioral exposure across regions, with the potential to epigenetically modulate ASD risk.

This hypothesis gains additional support from studies in post-mortem brain tissue. The identification of differentially methylated regions in cortical neurons of individuals with ASD, including loci associated with GABAergic system genes such as ABAT and GABBR1[70], as well as the promoter hypermethylation of the RELN gene in cortical samples from individuals with ASD compared to controls[71], demonstrates that measurable epigenetic alterations accompany the disorder's phenotype.

Adding to this discussion is the hypothesis of an epigenetic delay in the DNA methylation trajectory during brain development in individuals with ASD, whose patterns resemble earlier stages of typical fetal development, reinforcing the prenatal origin of the disorder and its sensitivity to early environmental insults, precisely the period in which adverse maternal socioeconomic conditions exert their greatest impact.

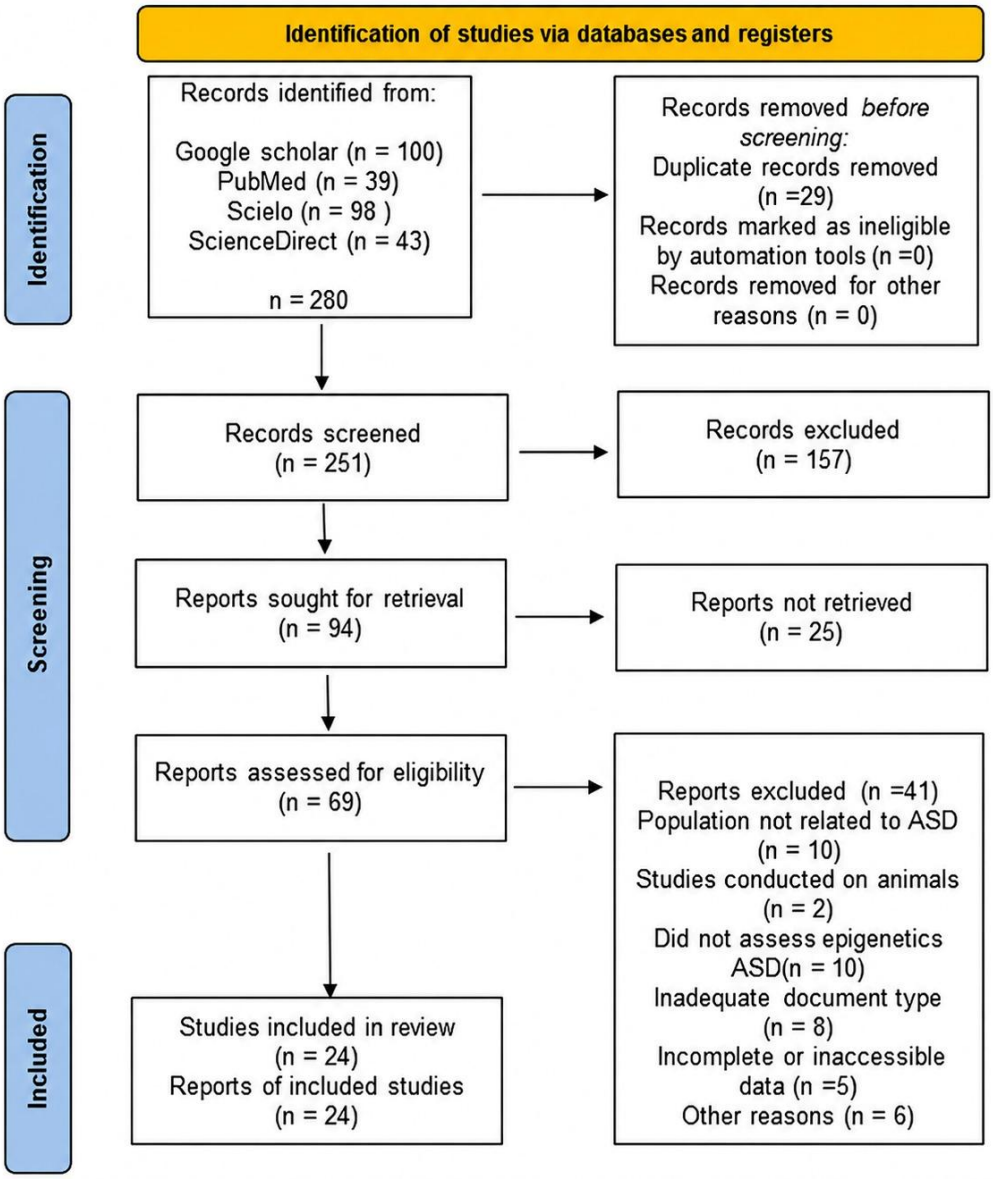

Figure 5. PRISMA 2020 flow diagram for the study selection and inclusion process.

The same reasoning extends to the analysis by color/race. The greater exposure of Black, Mixed-race, and Indigenous populations to adverse social determinants, such as food insecurity and chronic stress associated with structural racism, is compatible with the epigenetic induction mechanisms described in the literature, in which chronic environmental stressors alter patterns of genes relevant to neurodevelopment[13-14]. This suggests that the lower relative proportion of diagnoses among Black and Indigenous populations recorded in the Census likely underestimates the true prevalence of ASD in these groups, since greater environmental exposure does not translate into greater diagnostic identification, but rather into greater access barriers.

Sex distribution, in turn, constitutes the point of greatest direct convergence between the Census and the molecular literature. The 3:1 to 4:1 ratio between males and females observed in the IBGE data is consistent with epigenetic mechanisms linked to the X chromosome and the MeCP2 gene[17, 21]. This finding corroborated by more recent and direct evidence in a whole-genome bisulfite sequencing study of newborn blood, which identified DNA methylation signatures specifically associated with sex in individuals later diagnosed with ASD, suggesting that the diagnostic disparity between sexes has, at least in part, a measurable epigenetic basis already at birth, and not merely an underdiagnosis bias in females due to behavioral camouflage.

The integrative analysis indicates that the sociodemographic patterns revealed by the Census, such as regional concentration, racial disparity, and sex asymmetry, should not be read in isolation as a reflection of unequal access to diagnosis, nor in isolation as evidence of direct biological causality. Rather, they configure a scenario in which social inequality and epigenetic vulnerability feed back into each other: populations more exposed to chronic environmental stressors tend simultaneously to present a higher epigenetic risk for ASD and lower access to specialized diagnosis, resulting in systematic underreporting precisely among the most vulnerable groups.

This correlation, although not proven in terms of direct causality by the Census data, which do not include individual biomarkers, is consistent with the reviewed body of molecular evidence[68-73] and reinforces the need for Brazilian longitudinal studies that integrate population data and individual epigenetic analyses.

5. Conclusion

It is concluded that disparities in ASD diagnosis in Brazil reflect structural inequalities in healthcare access, exacerbated by epigenetic mechanisms mediated by socio-environmental conditions in vulnerable populations. Equitable policies and integrative research are essential for early diagnosis and universal care.

6. Author Contributions Statement (CRediT Taxonomy)

- Júlia Cunha Gonzales: Conceptualization, Methodology, Formal analysis, Data curation, Investigation, Writing – original draft, Writing – review & editing, Visualization.

- Willy Rilston Souza de Jesus: Data curation, Formal analysis, Investigation, Writing – original draft.
- Romulo Diniz de Arruda: Data curation, Investigation, Writing – original draft.
- Alinne Pereira de Castro: Conceptualization, Supervision, Methodology, Writing – review & editing, Funding acquisition.

All authors reviewed and approved the final version of the manuscript and agree with its submission.

7. Data Availability Statement

The data supporting the findings of this study are publicly available and can be accessed from the 2022 Demographic Census of the Brazilian Institute of Geography and Statistics (IBGE), through the SIDRA platform at the following address: https://sidra.ibge.gov.br/pesquisa/censo-demografico/demografico-2022/amostra-pessoas-com-deficiencia-e-espectro-autista. The processed data and descriptive statistical analyses generated during this research are available upon reasonable request to the corresponding author.

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