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Universidade Federal do Pará
Campus Universitário de Altamira
PROGRAMA DE PÓS-GRADUAÇÃO EM BIODIVERSIDADE E CONSERVAÇÃO

ENZO KAIQUE DA SILVA LOPES

POLIMORFISMOS GENÉTICOS RELACIONADOS AO RISCO DE CONTAMINAÇÃO POR MERCÚRIO EM POPULAÇÕES NATIVAS DA AMAZÔNIA:

UMA REVISÃO SISTEMÁTICA, METANÁLISE E ABORDAGEM FUNCIONAL

ALTAMIRA-PA
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Dissertação apresentada à Universidade Federal do Pará, como parte das exigências do Programa de Pós-graduação em Biodiversidade e Conservação para obtenção do título de Mestre em Biodiversidade e Conservação.

Orientador: Dr. Adenilson Leão Pereira
Coorientador: Dr. Felipe Rodolfo Pereira da Silva

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RESUMO

A contaminação por mercúrio constitui um importante problema de saúde pública na Amazônia, especialmente em populações tradicionais expostas cronicamente ao metal por meio do consumo de peixes contaminados. Evidências recentes indicam que a variabilidade genética pode modular a toxicocinética e a toxicodinâmica do mercúrio, influenciando a retenção corporal do metal e a ocorrência de manifestações clínicas. Nesse contexto, o presente estudo teve como objetivo investigar a relação entre polimorfismos genéticos associados ao metabolismo do mercúrio e os níveis corporais desse metal em populações amazônicas. Trata-se de uma revisão sistemática combinada com metanálise e análise funcional de genes. A busca foi realizada nas bases Google Scholar, PubMed, ScienceDirect e Web of Science, incluindo estudos publicados até dezembro de 2025. Foram incluídos estudos observacionais conduzidos em populações humanas da Amazônia com dados genotípicos e biomarcadores de exposição ao mercúrio. A qualidade metodológica foi avaliada pela escala Newcastle-Ottawa, e as análises estatísticas foram conduzidas no software Review Manager 5.4. Ao todo, 15 estudos preencheram os critérios de elegibilidade, totalizando 3.507 participantes de populações urbanas, ribeirinhas e indígenas. Quinze genes apresentaram associação significativa com os níveis corporais de mercúrio. Na metanálise, os polimorfismos *GSTP1* (rs1965), *GSTT1* (-/-) e *GSTM1* (-/-) mostraram tendência de associação com maiores níveis de mercúrio, porém sem significância estatística. A análise funcional revelou que os genes identificados estão principalmente envolvidos em vias relacionadas ao metabolismo de metais, detoxificação celular, estresse oxidativo, transporte de xenobióticos e modulação da excreção urinária. Os achados indicam que variantes genéticas podem influenciar a suscetibilidade à contaminação por mercúrio em populações amazônicas, embora limitações como heterogeneidade entre estudos e tamanho amostral reduzido ainda restrinjam conclusões definitivas. Conclui-se que os polimorfismos avaliados apresentam potencial como biomarcadores de vulnerabilidade ao mercúrio, podendo subsidiar estratégias de vigilância em saúde e políticas públicas voltadas a populações tradicionais expostas na Amazônia.

Palavras-chave: Metabolismo do mercúrio. Variante genética. Suscetibilidade genética. População ribeirinha. População tradicional da Amazônia.

ABSTRACT

Mercury contamination constitutes an important public health problem in the Amazon, especially among traditional populations chronically exposed to the metal through the consumption of contaminated fish. Recent evidence indicates that genetic variability can modulate the toxicokinetics and toxicodynamics of mercury, influencing body retention of the metal and the occurrence of clinical manifestations. In this context, the present study aimed to investigate the relationship between genetic polymorphisms associated with mercury metabolism and the body levels of this metal in Amazonian populations. This is a systematic review combined with meta-analysis and functional gene analysis. The search was conducted in the Google Scholar, PubMed, ScienceDirect, and Web of Science databases, including studies published up to December 2025. Observational studies conducted in human populations from the Amazon with genotypic data and biomarkers of mercury exposure were included. Methodological quality was assessed using the Newcastle-Ottawa Scale, and statistical analyses were performed using Review Manager 5.4 software. A total of 15 studies met the eligibility criteria, comprising 3,507 participants from urban, riverside, and indigenous populations. Fifteen genes showed significant association with body mercury levels. In the meta-analysis, the polymorphisms *GSTP1* (rs1965), *GSTT1* (-/-), and *GSTM1* (-/-) showed a trend toward association with higher mercury levels, but without statistical significance. Functional analysis revealed that the identified genes are mainly involved in pathways related to metal metabolism, cellular detoxification, oxidative stress, xenobiotic transport, and modulation of urinary excretion. The findings indicate that genetic variants may influence susceptibility to mercury contamination in Amazonian populations, although limitations such as heterogeneity among studies and reduced sample size still restrict definitive conclusions. It is concluded that the evaluated polymorphisms have potential as biomarkers of vulnerability to mercury, and may support health surveillance strategies and public policies aimed at traditional populations exposed in the Amazon.

Keywords: Mercury metabolism. Genetic variant. Genetic susceptibility. Riverside population. Traditional Amazonian population.

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1 INTRODUÇÃO GERAL

A região Amazônica tem sido historicamente marcada por intensas pressões econômicas e estratégicas associadas à exploração de seus recursos naturais, o que gera impactos ambientais e sociais relevantes para os povos que ali vivem (Filho *et al.*, 2025). Esse cenário de uso intensivo do território coloca em risco não apenas a integridade dos ecossistemas, mas também a manutenção dos modos de vida das populações tradicionais amazônicas, que dependem diretamente dos recursos naturais para sua subsistência (Flores *et al.*, 2024; Barreto *et al.*, 2025).

Nas últimas décadas, observa-se uma expansão acelerada da mineração aurífera, especialmente do garimpo ilegal, que se concentra majoritariamente na Amazônia brasileira e incide de forma significativa sobre territórios indígenas (Neto *et al.*, 2024). Entre os Estados mais impactados destacam-se Amazonas, Mato Grosso, Pará e Rondônia, regiões onde a pressão sobre os recursos naturais tem sido particularmente intensa (Neto *et al.*, 2024).

Nesse contexto, a atividade garimpeira configura-se como uma das principais fontes de emissão de mercúrio (Hg) para a atmosfera, os solos e os corpos d'água da Amazônia, contribuindo diretamente para a contaminação dos rios e de suas cadeias tróficas (Nevado *et al.*, 2010; Crespo-Lopez *et al.*, 2021; Teixeira *et al.*, 2021). Durante o processo de amalgamação do ouro, o mercúrio metálico (Hg^o) é liberado no ambiente e pode ser transportado e redistribuído entre diferentes compartimentos ambientais, ampliando sua área de impacto (Crespo-Lopez *et al.*, 2024).

Já em ambientes aquáticos, parte do mercúrio inorgânico (IHg) pode ser metilado por bactérias metanogênicas, originando o metilmercúrio (MeHg), forma altamente tóxica e com elevado potencial de bioacumulação (Gao *et al.*, 2022; Crespo-Lopez *et al.*, 2024). Esse composto se biomagnifica ao longo da cadeia alimentar, podendo representar até 95% do mercúrio total (THg) presente em tecidos de peixes amazônicos (Maraslis *et al.*, 2025).

A exposição ao MeHg afeta de maneira desproporcional populações tradicionais da Amazônia, especialmente povos indígenas e comunidades ribeirinhas, cuja base alimentar depende fortemente do consumo de peixe (Vasconcellos *et al.*, 2021; Crespo-Lopez *et al.*, 2021; Martoredjo *et al.*, 2024). Esse padrão de exposição crônica eleva o risco de contaminação humana e configura um importante problema de saúde pública (Pierezan *et al.*, 2024).

Os efeitos tóxicos do mercúrio incluem danos neurológicos, alterações sensoriais e motoras, comprometimento renal e cardiovascular, além de potenciais efeitos genotóxicos e carcinogênicos (Wu *et al.*, 2024; Kang *et al.*, 2024). Gestantes, fetos e crianças constituem grupos particularmente vulneráveis, uma vez que o MeHg atravessa a barreira placentária e pode ser transferido também pelo leite materno (Grandjean *et al.*, 1998; Wu *et al.*, 2024).

Diversos estudos têm documentado níveis elevados de contaminação por mercúrio em populações urbanas, garimpeiros, ribeirinhos e diferentes etnias indígenas que vivem próximas a áreas de mineração na Amazônia (Basta *et al.*, 2021; Martoredjo *et al.*, 2024; Pinheiro *et al.*, 2025). Nesses grupos, a exposição crônica tem sido associada a manifestações clínicas relevantes, incluindo déficits cognitivos, alterações motoras e sensoriais, neuropatias periféricas e prejuízos ao desenvolvimento infantil (Hoshino *et al.*, 2015; Kempton *et al.*, 2021; Pinheiro *et al.*, 2025).

Contudo, a magnitude desses efeitos não depende apenas do nível de exposição ambiental, mas também de fatores biológicos individuais que modulam a toxicocinética e a toxicodinâmica do metal (Gundacker *et al.*, 2010; Llop *et al.*, 2014). Nesse sentido, genes envolvidos em processos de absorção, distribuição, biotransformação e excreção do mercúrio, incluindo componentes do sistema antioxidante da glutationa, metaloproteínas e transportadores de membrana, desempenham papel central na resposta biológica ao metal (Kang *et al.*, 2024).

Os genes associados ao metabolismo do mercúrio podem ser organizados em diferentes famílias funcionais de acordo com seus papéis biológicos na resposta ao metal. Os genes da família da glutationa S-transferase e da síntese de glutationa (*GCLC*, *GCLM*, *GSS*) atuam na conjugação de xenobióticos, incluindo o mercúrio, à glutationa, favorecendo sua detoxificação e excreção celular (Hayes; Flunagan; Jowsey, 2005; Ballatori *et al.*, 2009). Os genes do sistema antioxidante, como *GPX1*, *TXNRD* e *GLRX*, participam da neutralização de espécies reativas de oxigênio geradas pela exposição ao mercúrio, protegendo estruturas celulares contra o estresse oxidativo (Barcelos *et al.*, 2013; Maraslis *et al.*, 2025).

Já as metalotioneínas (*MT1A*, *MT2A*, *MT1M*) e o gene *ALAD* estão envolvidos na ligação e captação de metais, contribuindo para a regulação da biodisponibilidade e toxicidade do mercúrio no organismo (Klaassen; Aleksunes, 2010). Os genes da família dos transportadores de membrana, como *ABCB1*, *ABCC2* e os transportadores

SLC, regulam o influxo e efluxo de compostos tóxicos e seus conjugados, influenciando diretamente a distribuição e eliminação do mercúrio (Carvalho *et al*., 2024). O gene *NOS3* atua na produção de óxido nítrico, sendo fundamental para a homeostase vascular, e sua modulação pelo mercúrio está associada a disfunções endoteliais e aumento do risco cardiovascular (Förstermann; Sessa, 2012).

Os genes relacionados ao metabolismo lipídico, como *APOE*, *APOB* e *APOA-V*, desempenham papel no transporte de lipoproteínas e estão associados à susceptibilidade a efeitos neurotóxicos e cardiovasculares induzidos pelo mercúrio (Mahley, 2016; Genchi *et al*., 2017). Por fim, o gene *VDR* - que é um receptor de vitamina D - atua na regulação de processos imunológicos, inflamatórios e metabólicos, podendo influenciar indiretamente a resposta biológica ao mercúrio (Carlberg, 2014; Bouillon *et al*., 2019).

Evidências indicam que polimorfismos nesses genes podem potencializar a retenção corporal de Hg e agravar seus efeitos clínicos em populações expostas (Arrifano *et al.*, 2018; Barcelos *et al.*, 2013; Oliveira *et al.*, 2014). Em comunidades ribeirinhas, variantes em genes como *ALAD*, *APOE*, *GSTM1*, *GSTT1*, *GSTP1*, *SLC6A15*, *TXNRD* e *NOS3* têm sido associadas a maior suscetibilidade à contaminação e a desfechos clínicos adversos relacionados ao mercúrio (Marco *et al.*, 2011; Marco *et al.*, 2012; Maraslis *et al.*, 2025).

De forma semelhante, em diferentes etnias indígenas, polimorfismos em genes como *ABCB1*, *ABCC2*, *ALAD*, *GSTM1*, *GSTT1* e *GSTP1* têm sido relacionados ao aumento da retenção do metal e a manifestações neurológicas e cardiovasculares (Carvalho *et al*., 2024; Klautau-Guimarães *et al*., 2005; Silva *et al.*, 2023; Silva *et al.*, 2024).

Para estruturar o problema de pesquisa, utilizou-se a estratégia PECO (*Population, Exposure, Comparison, Outcome*). Nesse sentido, definiu-se como população (P) indivíduos pertencentes a populações nativas da Amazônia; como exposição (E) a presença de polimorfismos em genes relacionados ao metabolismo do mercúrio; como comparação (C) indivíduos portadores de diferentes genótipos (variantes e selvagens); e como desfecho (O) as concentrações de mercúrio no organismo. A partir dessa estrutura, estabeleceu-se a seguinte pergunta de pesquisa: “Polimorfismos em genes relacionados ao metabolismo do mercúrio estão associados a diferenças nas concentrações desse metal em populações nativas da Amazônia?”.

Apesar do crescimento do número de estudos sobre genética e exposição ao mercúrio na Amazônia, o conhecimento disponível permanece fragmentado e heterogêneo, dificultando a compreensão integrada do papel desses polimorfismos na vulnerabilidade das populações tradicionais (Perini *et al.*, 2021; Rocha *et al.*, 2016). Além disso, diferenças metodológicas, tamanhos amostrais reduzidos e variabilidade nos biomarcadores utilizados contribuem para resultados por vezes discordantes entre os estudos (Barcelos *et al.*, 2015; Lopes-Araújo *et al.*, 2023).

Nesse cenário, abordagens de síntese de evidências, como revisões sistemáticas e metanálises, tornam-se ferramentas fundamentais para consolidar o conhecimento e identificar padrões consistentes de associação genética. Diante dessa lacuna, a presente dissertação reúne e debate criticamente as evidências disponíveis sobre polimorfismos genéticos relacionados ao metabolismo do mercúrio em populações amazônicas expostas, integrando revisão sistemática, metanálise e avaliação funcional dos genes envolvidos.

Ao sintetizar dados de diferentes estudos conduzidos entre 2005 e 2025 na Amazônia brasileira, esta investigação busca contribuir para a compreensão dos mecanismos biológicos que modulam a suscetibilidade individual à contaminação por Hg. Além disso, a identificação de variantes genéticas potencialmente associadas à maior retenção do metal pode subsidiar estratégias de vigilância em saúde e políticas públicas voltadas a populações em situação de vulnerabilidade ambiental (Crespo-Lopez *et al.*, 2024).

Esta dissertação está estruturada da seguinte forma: inicialmente apresenta-se esta introdução geral, que contextualiza o problema da contaminação por mercúrio e o papel dos polimorfismos genéticos nas populações amazônicas; em seguida, é apresentado o capítulo de objetivos do estudo; por fim, é exposto o artigo científico resultante da revisão sistemática, metanálise e avaliação funcional conduzidas nesta pesquisa.

2 OBJETIVO GERAL

Investigar a relação entre polimorfismos genéticos envolvidos no metabolismo do mercúrio e os níveis corporais desse metal em populações amazônicas expostas, por meio de revisão sistemática, metanálise e análise funcional dos genes.

2.1. ESPECÍFICOS

I- Identificar e sintetizar, na literatura científica, os polimorfismos genéticos associados à exposição, retenção e efeitos clínicos do mercúrio em populações urbanas, ribeirinhas e indígenas da Amazônia.

II- Avaliar, por meio de metanálise, a associação entre variantes genéticas selecionadas (especialmente *GSTP1*, *GSTM1* e *GSTT1*) e os níveis corporais de mercúrio.

III- Realizar análise funcional e de enriquecimento gênico para compreender as vias biológicas e processos moleculares envolvidos nos genes associados ao metabolismo e à toxicidade do mercúrio.

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ARTIGO 1

GENETIC POLYMORPHISMS RISK-RELATED TO MERCURY CONTAMINATION IN NATIVE AMAZONIAN POPULATIONS: A SYSTEMATIC REVIEW, META-ANALYSIS AND FUNCTIONAL APPROACH

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Genetic polymorphisms risk-related to mercury contamination in native Amazonian populations: A systematic review, meta-analysis and functional approach

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Abstract:	The relationship between mercury poisoning and genetic polymorphism has been reported in the Amazonian population. However, some studies are dichotomous regarding the real impact of these variants. We combined a systematic review, a meta-analysis and gene enrichment to assess the impact of these variants in exposed individuals from the Amazon. We found one study reported in the urban population, nine in riverside communities and five in indigenous populations. Fifteen genes were significantly related to body mercury levels. In the meta-analysis, GSTP1 (rs1965), GSTT1 (-/-) and GSTM1 (-/-) were related with elevated mercury levels. APOEε4 (rs429358), GSTM1 (-/-), VDR (rs1544410), GCLM-588-TT (rs41303970), NOS3 (rs1799983, rs11771443 and VNTR4a/4b), TXNRD2 (rs5748469), GLRX (rs2007), GLRX2 (rs912071), SLC6A19 (rs9418) and SLC6A15 (rs11116642) were associated with mercury accumulation in riverside people. ALAD (rs1800435), GSTP1 (rs1695) and GSTM1 (-/-) were associated with mercury accumulation in indigenous people. GSTM1 (-/-) was shared for all three groups studied, while ALAD (rs1800435), GSTP1 (rs1695), GSTT1 (-/-) and MT1A (rs11640851) were reported in riverine and indigenous populations, suggesting that these two populations share a common genetic background. GCLM (rs41303970) may facilitate urinary mercury excretion. In genic enrichment, the genes were involved in pathways of metal metabolism, cellular detoxification, oxidative stress, neuronal apoptosis and urinary excretion modulation. The polymorphisms analyzed are important for the toxodynamics of mercury and may be potentially useful as biomarkers of vulnerability in traditional Amazonian populations. These data provided may be useful for health surveillance strategies, public policies and prevention actions targeting Amazonian populations exposed to mercury.

Genetic polymorphisms risk-related to mercury contamination in native Amazonian populations: A systematic review, meta-analysis and functional approach

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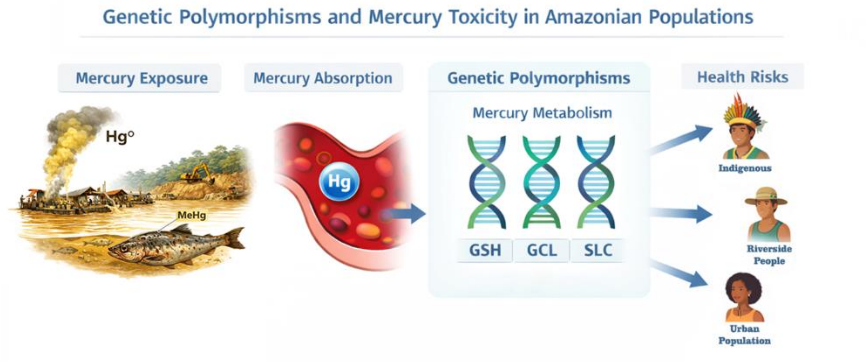
ABSTRACT

The relationship between mercury poisoning and genetic polymorphism has been reported in the Amazonian population. However, some studies are dichotomous regarding the real impact of these variants. We combined a systematic review, a meta-analysis and gene enrichment to assess the impact of these variants in exposed individuals from the Amazon. We found one study reported in the urban population, nine in riverside communities and five in indigenous populations. Fifteen genes were significantly related to body mercury levels. In the meta-analysis, *GSTP1* (rs1965), *GSTT1* (-/-) and *GSTM1* (-/-) were related with elevated mercury levels. *APOEε4* (rs429358), *GSTM1* (-/-), *VDR* (rs1544410), *GCLM-588-TT* (rs41303970), *NOS3* (rs1799983, rs11771443 and VNTR4a/4b), *TXNRD2* (rs5748469), *GLRX* (rs2007), *GLRX2* (rs912071), *SLC6A19* (rs9418) and *SLC6A15* (rs11116642) were associated with mercury accumulation in riverside people. *ALAD* (rs1800435), *GSTP1* (rs1695) and *GSTM1* (-/-) were associated with mercury accumulation in indigenous people. *GSTM1* (-/-) was shared for all three groups studied, while *ALAD* (rs1800435), *GSTP1* (rs1695), *GSTT1* (-/-) and *MT1A* (rs11640851) were reported in riverine and indigenous populations, suggesting that these two populations share a common genetic background. *GCLM* (rs41303970) may facilitate urinary mercury excretion. In genic enrichment, the genes were involved in pathways of metal metabolism, cellular detoxification, oxidative stress, neuronal apoptosis and urinary excretion modulation. The polymorphisms analyzed are important for the toxodynamics of mercury and may be potentially useful as biomarkers of vulnerability in traditional Amazonian populations. These data provided may be useful for health surveillance strategies, public policies and prevention actions targeting Amazonian populations exposed to mercury.

Keywords: Mercury metabolism, genetic variant, genetic susceptibility, Amerindian, riverside population, traditional Amazonian population.



1. Introduction

The Amazon region has historically been the target of economic and strategic interest due to its mineral, biological, and ecosystem service resources (Filho et al., 2025). This scenario poses an imminent danger to its preservation and the maintenance of the lives and customs of the traditional Amazonian populations (Flores et al., 2024; Barreto et al., 2025; Filho et al., 2025).

In recent decades, there has been a dizzying increase in mineral exploration in South America, mainly rudimentary and illegal gold mining (*garimpo*). Approximately 91% of this exploitation occurs within the Amazon Brazilian, and 62% of that total is located in indigenous territories, mainly in Kayapo, Munduruku and Yanomami ethnic groups communities. The Brazilian Amazonian states of Amazonas, Mato Grosso, Pará and Rondônia are the most affected by *garimpo* activity (Neto et al., 2024).

In the Amazon, *garimpo* activity is one of the most important sources of mercury (Hg) emissions to atmosphere, soil and water bodies, and consequently the most important source of contamination of the Amazonian rivers and their tributaries (Neto et al., 2024; Nevado et al*.,* 2010; Crespo-Lopez et al*.,* 2021; Teixeira et al*.,* 2021; Crespo-Lopez et al*.,* 2024). When released into the environment, such as through its use in *garimpo* for gold amalgamation, metallic mercury (Hg^o) can be transported and redistributed in the atmosphere, soil and aquatic systems (Crespo-Lopez et al*.,* 2024). In rivers and sediments, some of the inorganic mercury (IHg) can be methylated by methanogenic bacteria and become bioavailable, giving rise to methylmercury (MeHg), the most toxic form with a high capacity for bioaccumulation along the food chain (Gao et al., 2022; Crespo-Lopez et al*.,* 2024).

The impacts of MeHg exposure disproportionately affect traditional Amazonian populations, such as indigenous peoples and riverside communities, because their livelihoods largely depend on fishing and consuming fish from contaminated rivers (Nevado et al*.,* 2010; Vasconcellos et al., 2021; Crespo-Lopez et al*.,* 2021; Martoredjo et al., 2024). The biomagnification of MeHg in the aquatic food chain can alter the average proportion of this element relative to total mercury (THg) in fish tissues, and can reach up to 95% (Malm et al*.,* 1995). Indeed, contamination and biomagnification by MeHg in fish from different trophic levels in the Brazilian Amazon region was evidenced in a meta-analytic study, which evaluated the contamination scenario reported by experimental studies developed between 2017 and 2022, including the states of Amazonas, Pará, Rondônia and Roraima (Pierezan et al*.,* 2024).

This scenario is particularly worrying because it exposes local populations to an imminent risk of chronic contamination.

The effects of Hg toxicity on the human body include damage to the brain (with cognitive, sensory and motor repercussions), bone marrow, kidneys, lungs, heart, reproductive system, DNA damage and cancer promotion (Wu et al., 2024; Kang et al., 2024). There is particular concern for pregnant women, as MeHg can be easily transferred to the fetus through the placenta. Furthermore, it can also be transferred to babies and children through breast milk, making them a more vulnerable group due to their neurodevelopmental stage (Grandjean et al., 1998; Wu et al*.,* 2024).

Studies have shown widespread Hg contamination in urban populations, gold miners, riverside communities (Malm et al., 1995; Nevado et al., 2010; Martoredjo et al., 2024) and indigenous groups of the Munduruku, Kayabi, Kayapó and Yanomami ethnicities who live near *garimpo* areas in the Amazon (Basta *et al.*, 2021; Martoredjo et al., 2024; Hofer et al., 2025; Pinheiro et al., 2025). The effects of such exposition and contamination become explicit in indigenous and riverside populations, where they have already been associated with neurological clinical manifestations (motor, sensory, cognitive and psychosocial disorders) in adults, as well as impaired motor development, cognitive deficits, short stature and anemia in children (Hoshino et al., 2015; Kempton et al., 2021; Pinheiro et al., 2025).

Hg transit routes (toxicokinetics) in the human body involve pathways related to absorption, distribution, biotransformation and excretion, in which genes linked to the metal conjugation and elimination, such as glutathione antioxidant system (e.g., *GCLC*, *GCLM*, *GST* and *GPX*), metalloproteins and membrane transporters (e.g., ATP-binding cassette (*ABC*) transporters) participate (Gundacker et al., 2010; Llop et al., 2014; Kang et al., 2024). Interestingly, in the Amazonian population, the toxic effects of Hg and its clinical manifestations can be potentiated by the presence of polymorphisms in genes related to Hg metabolism (Arrifano et al., 2018; Barcelos et al., 2013; Barcelos et al., 2015a; Barcelos et al., 2015b; Carvalho et al., 2024; Klautau-Guimarães et al., 2005; Lopes-Araújo et al., 2023; Marco et al., 2011; Marco et al., 2012; Oliveira et al., 2014; Perini et al., 2021; Rocha et al., 2016; Silva et al., 2023; Silva et al., 2024; Maraslis et al., 2025).

Studies in riverside populations have associated these polymorphisms (e.g., *ALAD*, *APOE*, *GSTM1*, *GSTT1*, *GSTP1*, *SLC6A15*, *TXNRD* and *eNOS*) with increased susceptibility to contamination, body retention and clinical manifestations of Hg toxic effects, such as cognitive deficits, memory and attention impairments, peripheral neuropathy, motor and sensory disorders, reduced nitric oxide bioavailability, increased cardiovascular risk, Hg-related dyslipidemias, higher prevalence of hypertension and increased risk of acute myocardial infarction (Arrifano et al., 2018; Barcelos et al., 2013; Barcelos et al., 2015a; Barcelos et al., 2015b; Lopes-Araújo et al., 2023; Marco et al., 2011; Marco et al., 2012; Oliveira et al., 2014; Maraslis et al., 2025). Similarly, in various indigenous ethnic groups, studies have associated these polymorphisms (e.g., *ABCB1*, *ABCC2*, *ALAD*, *GSTM1*, *GSTT1* and *GSTP1*) with increased susceptibility to metal contamination and retention, and clinical manifestations such as cognitive deficits, somatosensory alterations, distal peripheral neuropathy, motor disorders, visual field alterations, hypertension and delayed neurodevelopment in children (Carvalho et al., 2024; Klautau-Guimarães et al., 2005; Perini et al., 2021; Silva et al., 2023; Silva et al., 2024). Therefore, there is a significant amount of research that has assessed the impact of genetic polymorphisms in genes related to Hg metabolism in traditional Amazonian populations; however, this information remains scattered and lacks consistent meta-analytic analysis.

In this study, we conducted a systematic review that provides a current overview of the impacts of these polymorphisms on the clinical manifestations induced by Hg poisoning in traditional Amazonian populations. Furthermore, we developed a meta-analysis in order to strengthen the relationship between these polymorphisms and increased susceptibility to Hg contamination. Finally, we performed a functional analysis using all polymorphic genes, demonstrating that they are closely related to metal detoxification. Our results demonstrate that these polymorphisms are important for these populations living in vulnerable situations and imminent contamination, and we provide suggestions and future perspectives for public policies related to this important environmental and public health problem in the Amazon.

2. Materials and methods

2.1. Protocol Registration

This meta-analysis is registered in the PROSPERO database with identification number: CRD420251245623 and followed the guidelines and checklist of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* - PRISMA (Page et al., 2021).

2.2. Eligibility Criteria

The following inclusion criteria were adopted in the literature search process: (1) case-control studies or cohort studies; (2) studies that documented the genotypic frequency in detail of the polymorphisms analyzed; (3) studies conducted on human populations from areas susceptible to Hg exposure and contamination in the Amazon.

2.3. Exclusion Criteria

The following exclusion criteria were adopted during the searches: (1) systematic, narrative or scoping review studies; (2) studies that did not provide the genotypic frequencies of genetic polymorphisms in the studied population; (3) studies that did not relate Hg contamination and genetic polymorphisms.

2.4. Search Strategy

The search for studies was conducted independently by three authors (E.K.S.L., F.R.P.S. and A.L.P.) in the following medical and scientific databases: Google Scholar, PubMed, ScienceDirect and Web of Science. The following combination of keywords and Boolean operators was used: "genetic variation or polymorphism or gene variation" and "mercury or heavy metal" and "contamination or body levels". The search included studies published up to December 31, 2025.

No language restrictions were applied during the searches, and the references of the included studies were evaluated to gather possible additional studies.

2.5. Data Collection Process

Three researchers (E.K.S.L., F.R.P.S. and A.L.P.) collected the data following a standardized form, which comprised the table of characteristics of the included studies, presented in the results (Table 1). The data were extracted by author, year of publication, ethnicity/country of participants, form of Hg presentation, source of exposure and main outcomes.

2.6. Assessment Of The Risk Of Bias

The methodological quality of the studies included was assessed independently by three reviewers (E.K.S.L., F.R.P.S. and A.L.P.) using the Newcastle-Ottawa Scale (NOS), widely recognized for assessing bias in observational studies, such as case-control and cohort studies, which comprised this meta-analysis.

The NOS scale considers three main domains: (1) participant selection, (2) comparability between groups and (3) exposure or outcome. Each study can receive a total of up to nine points, with four points for the selection domain, two for comparability and three for exposure or outcome.

Studies of high methodological quality were those that obtained seven or more points in the final score. Studies with scores below seven were classified as moderate quality and, therefore, were reviewed with greater caution in the sensitivity analyses. The complete assessment of the methodological quality of each study is presented in the results (Table 2).

2.7. Statistical Analysis

For the meta-analysis, the Review Manager v.5.4 software (RevMan, Nordic Cochrane Centre, The Cochrane Collaboration, 2012) was used. The presence or absence of true heterogeneity (I^2) was calculated using Cochran's Q test or the chi-square-based Q statistical test, and Funnel plot. When the observed value of I^2 showed no statistical significance and was defined as mild or moderate ($I^2 < 50\%$, $p > 0.05$), the fixed effects model was used to calculate the combined Odds Ratio (OR). When I^2 showed a statistically significant value and was defined as high ($I^2 > 50\%$, $p < 0.05$), the random effects statistical model was used to calculate the OR.

A *p-value* < 0.05 was considered significant in all heterogeneity and association calculations.

To quantify the influence of genetic variation on the risk of Hg exposure, six genetic models were calculated based on “M” as the mutated allele and “m” as the wild-type allele. Therefore, the calculations were composed of allelic comparisons: (I) M *versus* m, (II) m *versus* M; genotypic comparisons: (III) MM *versus* mm, (IV) mm versus MM; and combinations between genotypic variations: (V) MM *versus* mm+Mm and (VI) Mm *versus* MM+mm. In addition, a sensitivity analysis was performed, omitting one included study at a time to check for any possible significant changes in the OR value.

All data included in the studies were dichotomous data expressed as OR with 95% confidence intervals (CI) in order to determine the possible association between these genetic variations and Hg contamination.

2.8. Computational Analysis

Polymorphic genes were used to perform functional analyses in Kyoto Encyclopedia of Genes and Genomes (KEGG; https://www.genome.jp/kegg/), Reactome (https://reactome.org/) pathways, biological process of the Gene Ontology (GO; http://geneontology.org/) and Human Phenotype Ontology of the Monarch Initiative (https://monarchinitiative.org/) through

STRING: functional protein association networks v.12.0 tool (https://string-db.org/) (Szklarczyk et al., 2025). For the statistical significance of genetic enrichment, the STRING v.12.0 default was applied, with a statistical significance of $FDR_{adj}<0.05$. For the adjustment of the false discovery rate (FDR_{adj}) p-*value*, the Benjamini-Hochberg correction method was used.

In addition, we used The Genotype-Tissue Expression (GTEx; https://gtexportal.org/home/) database for the gene expression profile avaliation these genes in tissues that may be afeccted by mercury acumulation and toxicity.

3. Results

3.1. Characteristics of the included studies

Fifteen studies that met the inclusion criteria were identified and comprised the results (Figure 1). The studies were published between 2005 and 2025 and included a total of 3,507 individuals from urban areas, traditional riverside communities and indigenous populations in the Amazon region, encompassing the states of Mato Grosso, Pará and Rondônia, in Northern Brazil (Figure 2). Only one study analyzed individuals from the urban population of Porto Velho city, state of Rondônia, northern region of Brazil, which included 149 women who self-identified as mulatto (n=133), white (n=12), Afro-Brazilian (n=3) and Asian (n=1) (Rocha *et al.*, 2016).

FIGURE 1. Study flow diagram following PRISMA guidelines

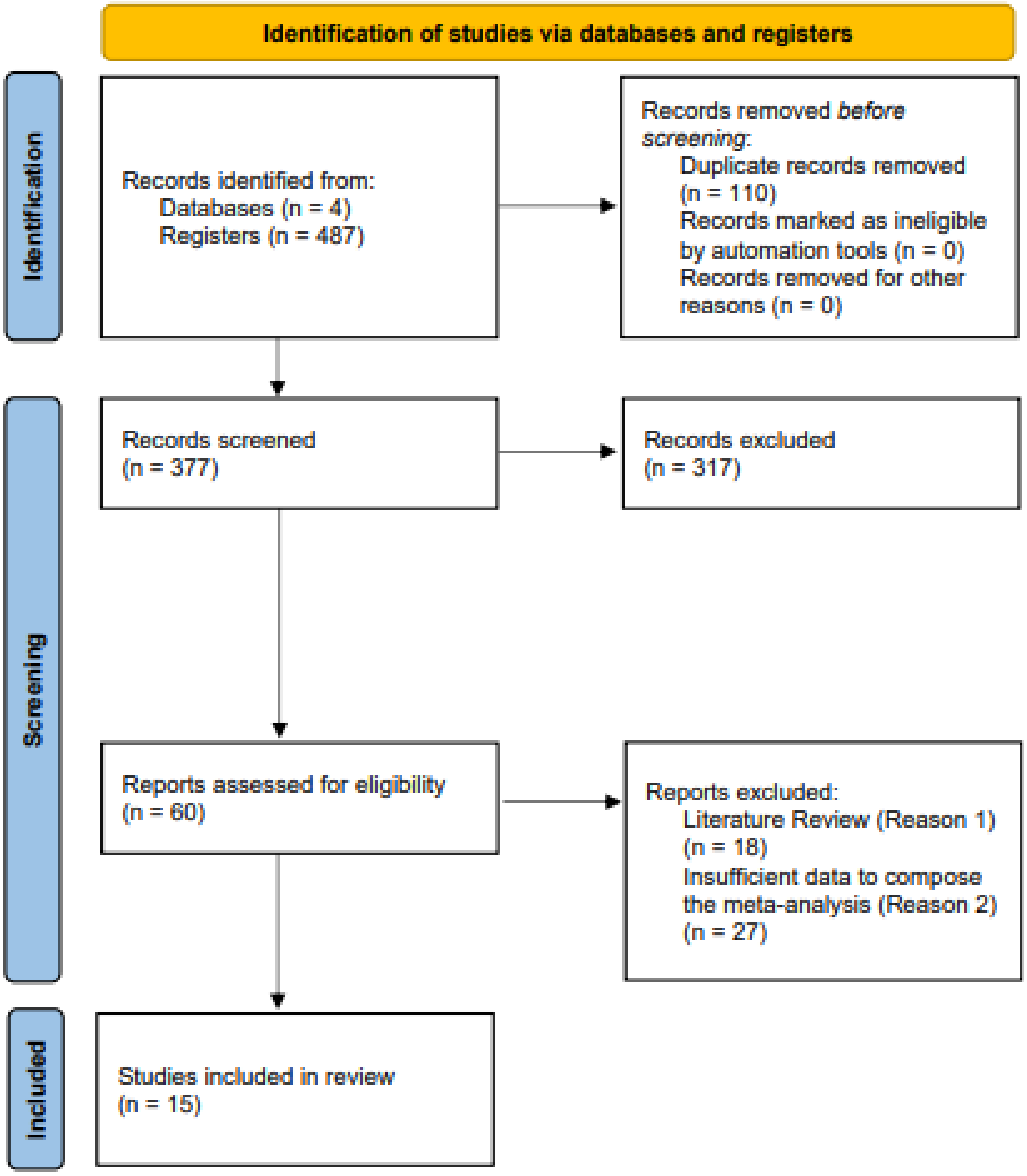
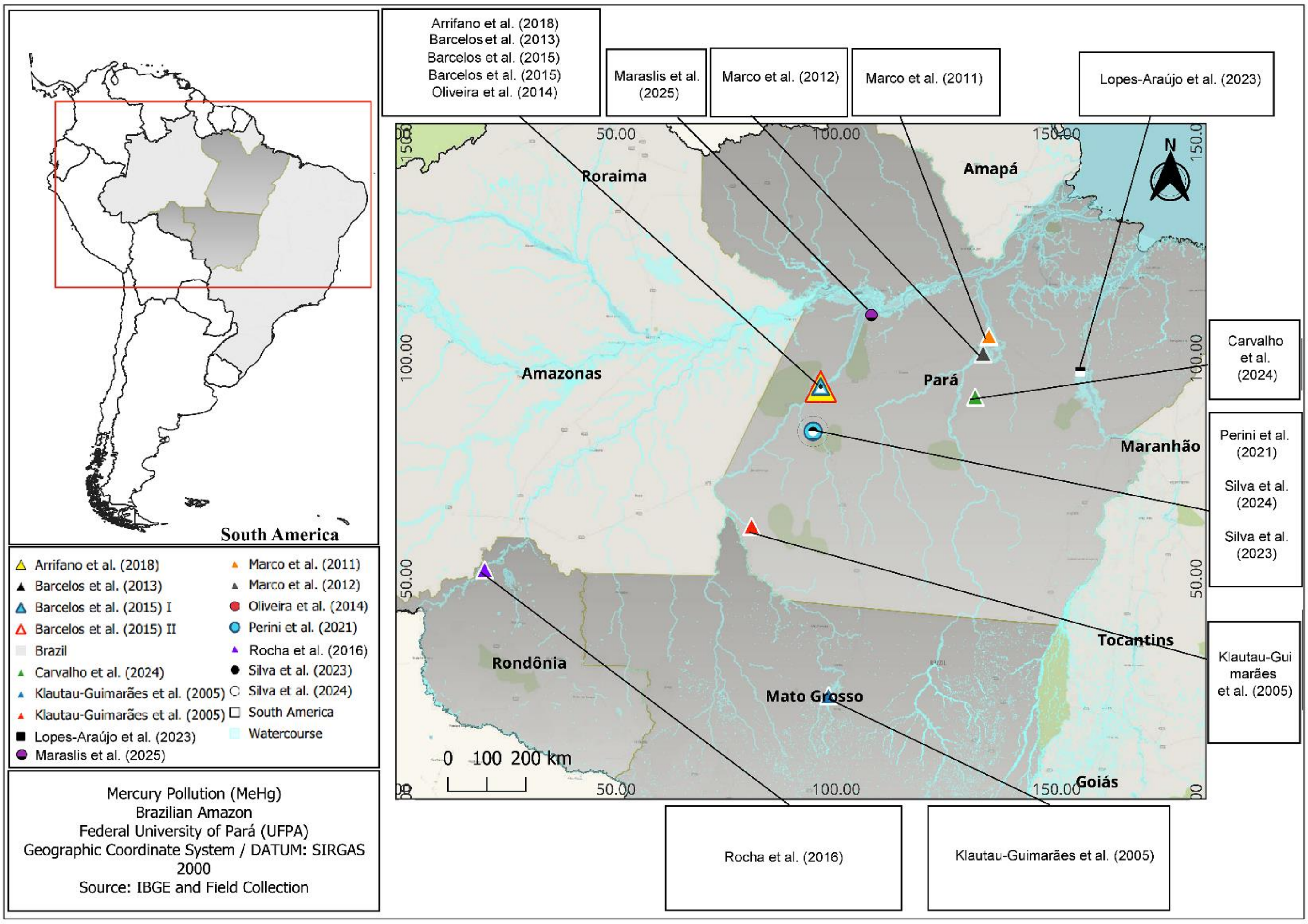


FIGURE 2. Amazon geographic distribution of the studies included in the systematic review



The figure illustrates the spatial distribution of the selected studies, providing a global overview of the investigated areas and supporting the understanding of the geographic scope of the evidence on mercury exposure.

The fifteen studies identified the following polymorphisms in genes related to Hg metabolism: (1) *APOE* (rs429358 e *rs7412* — alleles ε2, ε3, ε4) (Arrifano et al., 2018); (2) *GSTM1* (-/-), *GSTT1* (-/-), *GSTP1* (rs1695) and *GCLM* (rs41303970) (Barcelos et al., 2013); (3) *GSTM1* (-/-), *GSTT1* (-/-), *GSTM1*/*GSTT1* (double deletion), *GSTP1* (rs1695), *GCLM* (rs41303970), *GCLC* (rs17883901), *GPx1* (rs1800668), *ALAD* (rs1800435), *VDR* (rs1544410) and *MDR1* (rs2032582) (Barcelos et al., 2015a); (4) *eNOS* (rs11771443, rs1799983, VRTN 27-pb (intron 4): 4a/4b) (Barcelos et al., 2015b); (5) *GSTA1* (rs1051775), *GSTM1* (rs1183423000, rs1241704212, rs1065411, rs1179816349, rs1363667431, rs202002774), *ABCB1* (rs2032582), *ABCC2* (rs2273697, rs79183306), *ATP7B* (rs1801243, rs732774, rs7334118), *GPx1* (rs17838762), *GSTP1* (rs1695, rs4147581, rs1871042, rs762803, rs8191439), *MT1A* (rs11640851, rs8052394), *MT1M* (rs1827210), *NFE2L2* (rs35248500), *SEPP1* (rs3877899) and

SLC7A8 (rs144958980) (Carvalho et al., 2024); (6) *GSTM1* (-/-), *GSTT1* (-/-) and *GSTP1* (rs1695) (Klautau-Guimarães et al., 2005); (7) *APOA-V* (rs662799), *APOB* (rs693) and *APOE* (rs429358, rs7412) (Lopes-Araújo et al., 2023); (8) *eNOS* (rs2070744, rs1799983) (Marco et al., 2011); (9) *eNOS* (VRTN 27-pb (intron 4): 4a/4b) (Marco et al., 2012); (10) *GSTM1* (-/-), *GSTT1* (-/-), *GSTP1* (rs1695), *GCLM* (rs41303970) and *GCLC* (rs17883901) (Oliveira et al., 2014); (11) *ALAD* (rs1800435) (Perini et al., 2021); (12) *GPx1* (rs1050450) and *GSTM1* (-/-) (Rocha et al., 2016); (13) *GSTP1* (rs1695) (Silva et al., 2023); (14) *GSTP1* (rs1695) (Silva et al., 2024); (15) *GSS* (rs6088660), *GLRX* (rs2007), *GLRX2* (rs912071), *TXNRD1* (rs11111979), *TXNRD2* (rs5748469), *SELENOP* (rs3877899), *MT1A* (rs11640851), *MT1M* (rs2270837), *MT2A* (rs10636), *SLC6A15* (rs11116642), *SLC6A19* (rs9418, rs7732589), *SLC11A1* (rs17235409) and *SLC11A2* (rs149411, rs11169654) (Maraslis et al., 2025).

Nine studies were conducted in traditional riverside populations in the Brazilian Amazon region, totaling 2,822 individuals. Most investigations have focused on the state of Pará, especially in communities located along the Tapajós River banks and its tributaries, as well as in areas associated with the Tucuruí hydroelectric dam reservoir (Barcelos et al., 2013; Barcelos et al., 2015a; Barcelos et al., 2015b; Arrifano et al., 2018; Oliveira et al., 2014; Maraslis et al., 2025; Lopes-Araújo et al., 2023). Two studies include riverside communities in the Amazon region of the state of Pará, without specifying the exact river or location (Marco et al., 2011; Marco et al., 2012).

Considering indigenous populations, five studies evaluated 536 individuals from the following ethnic groups: (1) Asurini from the Koatinemo (n=5), Arara/Arara from the Iriri (n=7), Araweté (n=6), Asurini from the Trocará (n=16), Awá-Guajá (n=7), Munduruku (n=1), Xikrin from the Cateté (n=6), Xikrins Odjá (n=2), Zo'é (n=5), Wajãpi Karipuna (n=5), Karipuna (n=2) and Juruna (n=2) (Carvalho et al., 2024); (2) Kayabi (n=65) and Munduruku (n=117) (Klautau-Guimarães et al., 2005); (3) Children of the Munduruku ethnic group from the Sawré Muybu villages (n=44), Poxo Muybu (n=38) and Sawré Aboy (n=19), Sawré Muybu indigenous territory, in the Middle Tapajós River, state of Pará (Perini et al., 2021); (4) Munduruku from the Poxo Muybu villages (n=34), Sawré Aboy (n=23) and Sawré Muybu (n=50), from the Middle Tapajó River, state of Pará (Silva et al., 2023); (5) Munduruku from the villages of Poxo Muybu (n=28), Sawré Aboy (n=15) and Sawré Muybu (n=39), from the Middle Tapajó River, state of Pará (Silva et al., 2024). Details on the included studies are found in Table 1.

TABLE 1. Characterization of the qualitative data from the studies included in the present systematic review

Author and Year	Gene + Polymorphism	Population	Form of Mercury	Source of Exposure	Main Outcomes
Arrifano et al., 2018	APOE* (rs429358 e rs7412)	823 adults (>18 years), Amazonian riverside residents (Tapajós and Tucuruí), living in the area for ≥2 years	Methylmercury (MeHg)	Consumption of contaminated fish (regions impacted by mining and dams)	APOE4 → ↑Hg + pharmacokinetic effect with ↑metal accumulation. APOE2 → ↓Hg under high exposure. APOE4 associated with higher risk of neurotoxicity.
Barcelos et al., 2013	GSTM1* (-/-), GSTT1 (-/-), GSTP1* (rs1695), GCLM* (rs41303970)	400 adults (>18 years) from 12 riverside communities in the Tapajós River region, Brazilian Amazon	Methylmercury (MeHg)	Chronic consumption of contaminated fish (no local mining, only natural biomagnification)	GSTM1 (-/-) → ↑Hg + pharmacokinetic effect with ↑retention. GCLM-588 C allele → ↑Hg. GCLM TT → ↓Hg, but ↑accumulation with increased fish intake. GSTP1 Val/Val → tendency toward ↓Hg.
Barcelos et al., 2015 (a)	GSTM1* (-/-); GSTT1 (-/-); GSTM1/GSTT1 (double deletion); GSTP1* (rs1695); GCLM* (rs41303970); GCLC* (rs17883901); GPx1 (rs1800668); ALAD* (rs1800435); VDR* (rs1544410); MDR1 (rs2032582)	395 adults (>18 years) from 12 riverside communities in the Tapajós River region (PA)	Methylmercury (MeHg)	Dietary intake of contaminated fish (MeHg naturally biomagnified in the ecosystem)	GSTM1 (-/-) → ↑Hg + pharmacokinetic effect with ↑retention. ALAD 1/2 → ↑Hg. VDR A allele → ↑Hg. GSTM1 (-/-) → ↑CAT (antioxidant enzyme), possible compensation for Hg-induced oxidative stress.

Barcelos et al., 2015 (b)	eNOS* (rs11771443, rs1799983, 27-pb (intron 4): 4a/4b)	113 adults (>18 years) from 12 riverside communities in the Tapajós River region (PA)	Methylmercury (MeHg)	Fish consumption (MeHg) and, to a lesser extent, cassava flour (Pb)	Hg → ↓plasma NO (nitric oxide). Hg + eNOS 4b/4b → ↑systolic and diastolic blood pressure. Hg + C allele (-786 T/C) → ↓NO in alcohol users.
Carvalho et al., 2024	1. High impact: GSTA1 (rs1051775); GSTM1* (rs1183423000, rs1241704212). 2. Moderate impact: ABCB1 (rs2032582); ABCC2 (rs2273697, rs79183306); ATP7B (rs1801243, rs732774, rs7334118); GPX1 (rs17838762); GSTM1 (rs1065411, rs1179816349, rs1363667431, rs202002774); GSTP1* (rs1695, rs4147581, rs1871042, rs762803, rs8191439); MT1A (rs11640851, rs8052394);	64 Indigenous individuals from 12 ethnic groups in the Brazilian Amazon (Asurini, Arara, Araweté, Munduruku, Zo’é, etc.)	Methylmercury (MeHg)	Consumption of contaminated fish (MeHg via bioaccumulation); indirect exposure from mining and deforestation	GSTM1 (rs1183423000 and rs1241704212) → ↑susceptibility to Hg + probable ↓elimination (pharmacokinetic effect). GSTA1 rs1051775 → possible ↓enzymatic activity. Variants in the 3'/5'UTR may modulate gene expression related to the Hg response.

	MT1M (rs1827210); NFE2L2 (rs35248500); SEPP1 (rs3877899); e SLC7A8 (rs144958980)				
Klautau-Guimarães et al., 2005	GSTM1* (-/-), GSTT1 (-/-), GSTP1* (rs1695)	65 Kayabi and 117 Munduruku individuals (Amazonian Indigenous populations from the Teles Pires River, MT and PA)	Methylmercury (MeHg)	Intake of contaminated fish and indirect environmental exposure from nearby artisanal mining	GSTM1 (-/-) → ↑hair Hg (Kayabi: 14 ppm vs 8 ppm in GSTM1+). GSTT1 and GSTP1 → no association with Hg. G6PD, Hb, and Hp → no significant effect on Hg variation.
Lopes-Araújo et al., 2023	APOA-V (rs662799), APOB (rs693), APOE* (rs429358 e rs7412)	414 adults (18–70 years) from riverside communities on the islands of Tucuruí Lake (PA, Brazil)	Methylmercury (MeHg)	Chronic consumption of contaminated fish (bioaccumulation in the lake ecosystem)	Hg → ↑ApoB and ↑ApoB/ApoA-I → increased cardiovascular risk. Hg ≥10,000 ng/g → ↑total cholesterol, ↑LDL, ↑non-HDL. Analyzed polymorphisms did not

					directly influence Hg effects, indicating a dominant environmental effect.
Marco et al., 2011	eNOS* (rs2070744, rs1799983)	202 adults (98 men, 104 women) from riverside communities in the Amazon region (PA, Brazil)	Methylmercury (MeHg)	Consumption of MeHg-contaminated fish (environmental bioaccumulation)	Hg → ↓plasma NO (via ↓nitrite). eNOS polymorphisms → did not influence NO levels, indicating a direct Hg effect independent of genetics.
Marco et al., 2012	eNOS (27-pb (intron 4): 4a/4b)	202 adults (98 men, 104 women) from riverside communities in the Amazon region (PA, Brazil)	Methylmercury (MeHg)	Consumption of MeHg-contaminated fish (environmental bioaccumulation)	eNOS intron 4 (4a/4b) → ↓NO (plasma nitrite) + pharmacodynamic effect with ↑cardiovascular risk due to ↓eNOS activity. eNOS intron 4 polymorphisms → ↑Hg + negative modulation of NO production.
Oliveira et al., 2014	GSTM1* (-/-), GSTT1 (-/-), GSTP1* (rs1695), GCLM* (rs41303970), GCLC* (rs17883901)	88 adults residing in riverside communities along the Tapajós River (Amazonas, Brazil), with high fish consumption	Methylmercury (MeHg) and inorganic mercury (IHg)	Consumption of fish contaminated with MeHg	GSTM1 (-/-) → ↑THgP and ↑MeHgP + pharmacokinetic effect with ↑MeHg retention. GCLC (T allele) → ↑THgP and ↑MeHgP + modification of Hg distribution in plasma. GCLM (T allele) →

					↓THgP/THgB + altered Hg partitioning in blood.
Perini et al., 2021	ALAD* (rs1800435)	103 Indigenous children (Munduruku), under 15 years old, from the villages of Sawré Muybu, Poxo Muybu, and Sawré Aboy, in the middle Tapajós River region (PA)	Methylmercury (MeHg)	Consumption of contaminated fish due to illegal gold mining activity	ALAD (CG) → ↑Hg (hair) + pharmacokinetic effect with ↑half-life and ↑MeHg retention. ALAD (CG) → neurological symptoms (memory deficit, distal neuropathy, muscle atrophy, visual alterations).
Rocha et al., 2016	GPX1 (rs1050450), GSTM1* (-/-)	149 women (18–48 years) living in Porto Velho (RO), urban residents, non-smokers, and without chronic diseases	Methylmercury (MeHg)	Diet (mainly occasional supermarket fish consumption) – low environmental exposure	GPx1 (Pro198Leu) → ≈Hg + absence of relevant pharmacokinetic effect under low exposure. GSTM1 (-/-) → ≈Hg + no difference in mercury retention under low exposure.

Silva et al., 2023	GSTP1* (rs1695)	107 Munduruku Indigenous individuals (>12 years) from the villages of Sawré Muybu, Poxo Muybu, and Sawré Aboy, in the middle Tapajós River region, Pará	Methylmercury (MeHg)	Consumption of contaminated fish due to proximity to illegal mining sites	GSTP1 (GG) → ↓Hg + pharmacokinetic effect with ↑MeHg elimination. GSTP1 (GA) → ↑risk of somatosensory signs + pharmacodynamic effect with ↑neurological vulnerability.
Silva et al., 2024	GSTP1* (rs1695)	82 Munduruku Indigenous children (0–11 years) living in the villages of Poxo Muybu, Sawré Aboy, and Sawré Muybu, in the middle Tapajós River region (PA)	Methylmercury (MeHg)	Consumption of contaminated fish due to illegal mining activity in the region	GSTP1 (AA) → ↑Hg (hair) + pharmacokinetic effect with ↑MeHg accumulation and ↑half-life. GSTP1 (AA or AG) → ↑risk of neurodevelopmental delay + pharmacodynamic effect with ↑early neurological vulnerability.

Maraslis et al., 2025	GSS (rs6088660); GLRX* (rs2007); GLRX2* (rs912071); TXNRD1 (rs11111979); TXNRD2* (rs5748469); SELENOP (rs3877899); MT1A (rs11640851); MT1M (rs2270837); MT2A (rs10636); SLC6A15* (rs11116642); SLC6A19* (rs9418; rs7732589); SLC11A1 (rs17235409); SLC11A2 (rs149411; rs11169654)	329 riverside residents (“Caboclos”) distributed across villages located along the Tapajós River and its tributaries, in the state of Pará, aged between 15 and 87 years	Total mercury (THg)	Diet based on frequent fish consumption	GLRX (CC) → ↑Hg (whole blood); ↑systemic accumulation; ↑circulating availability of Hg in the body / SLC6A15 (CT) → ↓Hg (whole blood); ↓bioaccumulation and ↑elimination/differential distribution of Hg / General population → high Hg (elevated dietary exposure).

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*: gene with statistical significance for mercury

3.2. Meta-analysis

To better describe and understand the relationship among *GSTP1* (rs1965), *GSTT1* (+/+, -/-) and *GSTM1* (+/+, -/-) and different levels of Hg contamination, we developed a meta-analysis including studies published between 2005 and 2025.

Of the 15 studies identified in the systematic review for the Amazon region, only three presented data suitable for association calculations, thus comprising the results of the meta-analysis. The three studies evaluated a total of 377 individuals from the Brazilian Amazon region, including: (1) Indigenous people of the Kayabi (n=66) and Munduruku (n=117) ethnicities, both from the Teles Pires River region, state of Pará, Northern Brazil (Klautau-Guimarães et al*.,* 2005); (2) 87 people from riverside communities located along the Tapajós River, state of Pará, Northern Brazil (Oliveira et al*.,* 2014); e (3) 107 indigenous people of the Munduruku ethnicity, from villages located in the Middle Tapajós River region, state of Pará, Northern Brazil (Silva et al*.,* 2023).

We identified four studies in other populations from other countries that evaluated polymorphisms in Hg metabolism genes and that met the established inclusion criteria, being therefore included. These studies evaluated a total of 782 individuals, including: (1) 139 pregnant women from the coastal region of Indonesia (Armatussolikha et al*.,* 2024); (2) 309 artisanal mining workers and gold buyers from Ecuador (Custódio et al*.,* 2005); (3) 112 people from riverside communities in Colombia (Espitia-Pérez et al*.,* 2024); (4) 222 university students from Austria (Gundacker et al*.,* 2007). Overall, one can analyze the following polymorphisms:

3.3. Hg concentration and GSTP1 (rs1965) polymorphism

Meta-analysis calculations showed that the mutated allele in the *GSTP1* gene polymorphism was associated with higher levels of Hg accumulation (OR 1.06, 95%CI 0.68-1.64, *p-value*: 0.79) (Figure 3A). The wild-type allele was associated with lower concentrations of Hg in the participants' bodies (OR 0.94, 95%CI 0.61-1.46, *p-value*: 0.79) (Figure 3B). However, these associations were not statistically significant. These associations were calculated using the random effects model due to high heterogeneity ($I^2 = 69\%$; *p-value*: 0.01), and did not reach statistical significance (*p-value*: 0.79). The high heterogeneity suggests that differences in exposure levels, the types of samples used (e.g., blood *versus* hair), and the ethnic composition of the populations may have influenced the magnitude of the observed effects.

3.4. Hg concentration in blood and GSTT1 (+/+, -/-) polymorphism

Meta-analysis calculations showed that *GSTT1* (+/+) was associated with higher levels of Hg in the body (OR: 1.16, 95%CI: 0.70-1.91, *p-value*: 0.56) (Figure 3C), whereas the GSTT1 (-/-) polymorphism was associated with the lowest concentrations (OR: 0.86, 95%CI: 0.52-1.42, *p-value*: 0.56) (Figure 3D). However, these associations were not statistically significant. These associations were calculated using the fixed-effects model due to the reduced heterogeneity ($I^2 = 0\%$, *p-value*: 0.87), which suggests consistency among the included studies. However, the small sample size may have limited the statistical power to detect modest associations (Hedges; Pigott, 2001).

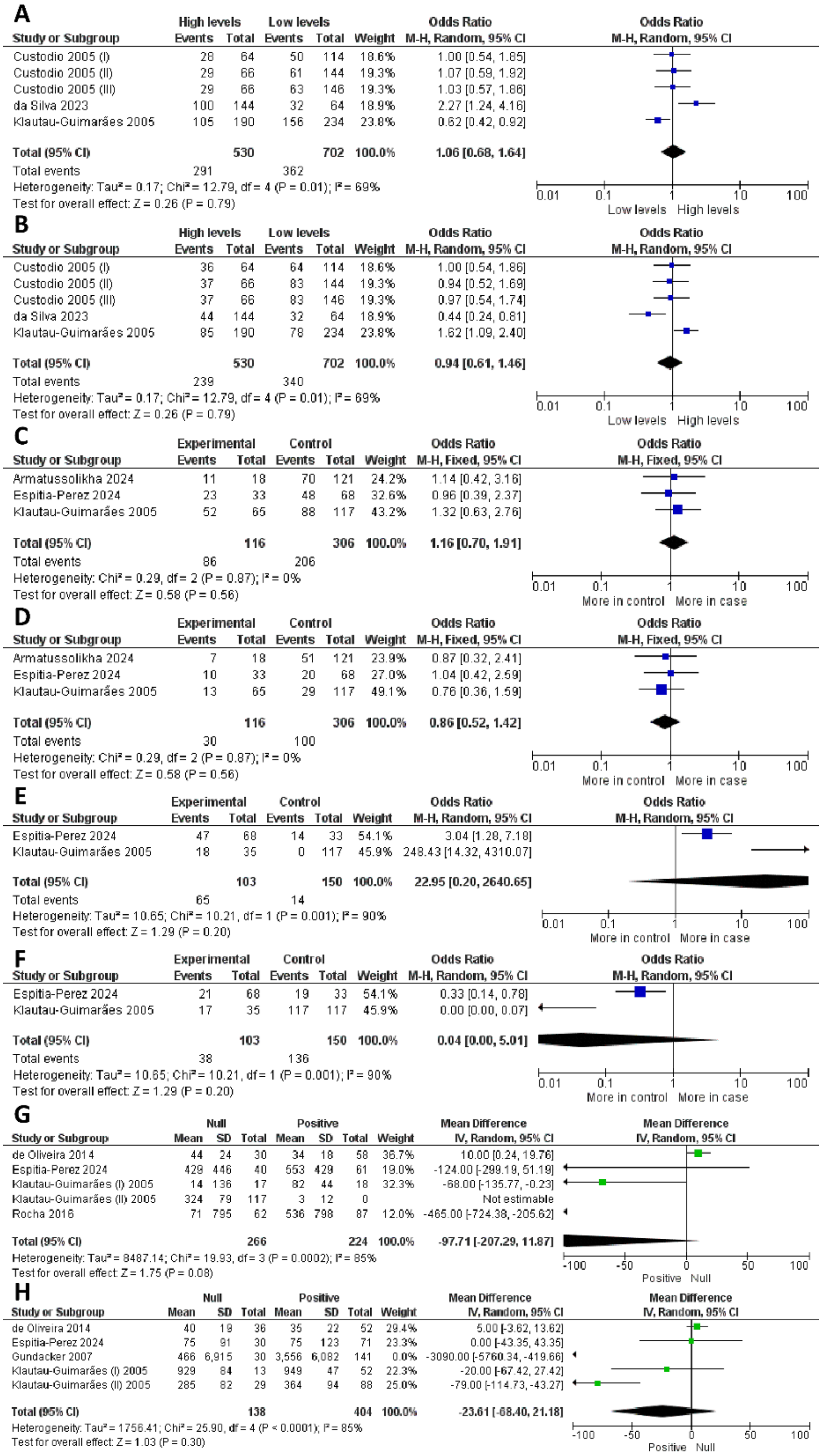
3.5. Hg concentration and GSTM1 (+/+, -/-) polymorphism

Meta-analysis calculations showed that the *GSTM1* (+/+) gene was associated with higher levels of Hg accumulation in the body (OR: 22.95; 95%CI: 0.20-2.640,65; *p-value:* 0.20) (Figure 3E). *GSTM1* (-/-) was associated with lower concentrations of Hg in the participants' bodies (OR: 0.04; 95%CI: 0.00-5.01; *p-value:* 0.20) (Figure 3F). However, the associations were not statistically significant. These associations were calculated using the random effects model due to the high heterogeneity ($I^2 = 90\%$; *p-value:* 0.001). On account of the extremely variable confidence intervals and high heterogeneity of these findings, the lack of statistical significance of the estimates may be due to the small number of studies and the large variability among highly exposed populations, such as indigenous people and riverside communities of the Tapajós River.

3.6. Hg levels and GSTM1(+/+, -/-) and *GSTT1 (+/+, -/-) polymorphism association*

Meta-analysis calculations showed that *GSTM1* (+/+) was associated with lower levels of Hg accumulation (MD: -97.71; 95%CI: -207.29-11.87, *p-value:* 0.08) (Figure 3G). *GSTT1* (-/-) was associated with lower concentrations of Hg in the bodies of the participants (MD: -23.61; 95%CI: -68.40-21.18; *p-value:* 0.30) (Figure 3H). However, these associations were not statistically significant. Additionally, both analyses were calculated using the random effects model due to the high heterogeneity. The *GSTM1* (+/+) genotype was associated with lower Hg levels when compared to the null genotype (MD: 7.36; 95%CI: -2.28–17.00; *p-value*: 0.13). Similarly, the *GSTT1* (-/-) genotype was associated with lower concentrations of Hg in the body (MD -0.26; 95%CI: -8.36–7.85; *p-value*: 0.95). However, none of the associations showed statistical significance.

FIGURE 3. Forest plots of the association between genetic polymorphisms and mercury concentrations



The plot displays individual effect sizes and the pooled estimate with 95% confidence intervals and heterogeneity measures, quantitatively synthesizing the studies that met the criteria for statistical pooling. A) Association between the mutated allele of *GSTP1* (rs1695) and Hg levels. B) Association between the wild-type allele of *GSTP1* (rs1695) and Hg levels. C) Association between *GSTT1* (+/+) genotype and Hg concentrations in blood. D) Association between *GSTT1* (-/-) genotype and Hg concentrations in blood. E) Association between *GSTM1* (+/+) genotype and Hg accumulation. F) Association between *GSTM1* (-/-) genotype and Hg accumulation. G) Mean difference in Hg levels associated with *GSTM1* (+/+). H) Mean difference in Hg levels associated with *GSTT1* (-/-).

3.7. Newcastle-Ottawa Scale (NOS) evaluation

The methodological assessment by NOS of the quality of the studies included in the meta-analysis showed that only one study reached the highest level of quality, whose results for "selection" and "comparability" obtained all scores. Four studies achieved six points on the NOS scale, and two studies only five points, and were classified as having a quality moderate level (Table 2).

TABLE 2. Methodological quality assessment of the studies included in the meta-analysis using the Newcastle-Ottawa Scale (NOS)

Author	**Categorie Case Control**									
	Selection				**Comparability**		**Exposure**			**Total**
	I	II	III	IV	Ia	Ib	I	II	III	
Armatussolikha et al 2024	•	•			•	•			•	5
Custodio et al 2005	•	•	•		•	•			•	6
Espitia-Pérez et al 2024	•	•	•	•	•	•			•	7
Gundacker et al 2007	•	•			•	•			•	5
Klautau-Guimarães et al 2005	•	•	•		•	•			•	6
Oliveira et al 2014	•	•	•		•	•			•	6
Silva et al 2023	•	•	•		•	•			•	6

3.8. Functional assessment of polymorphic genes

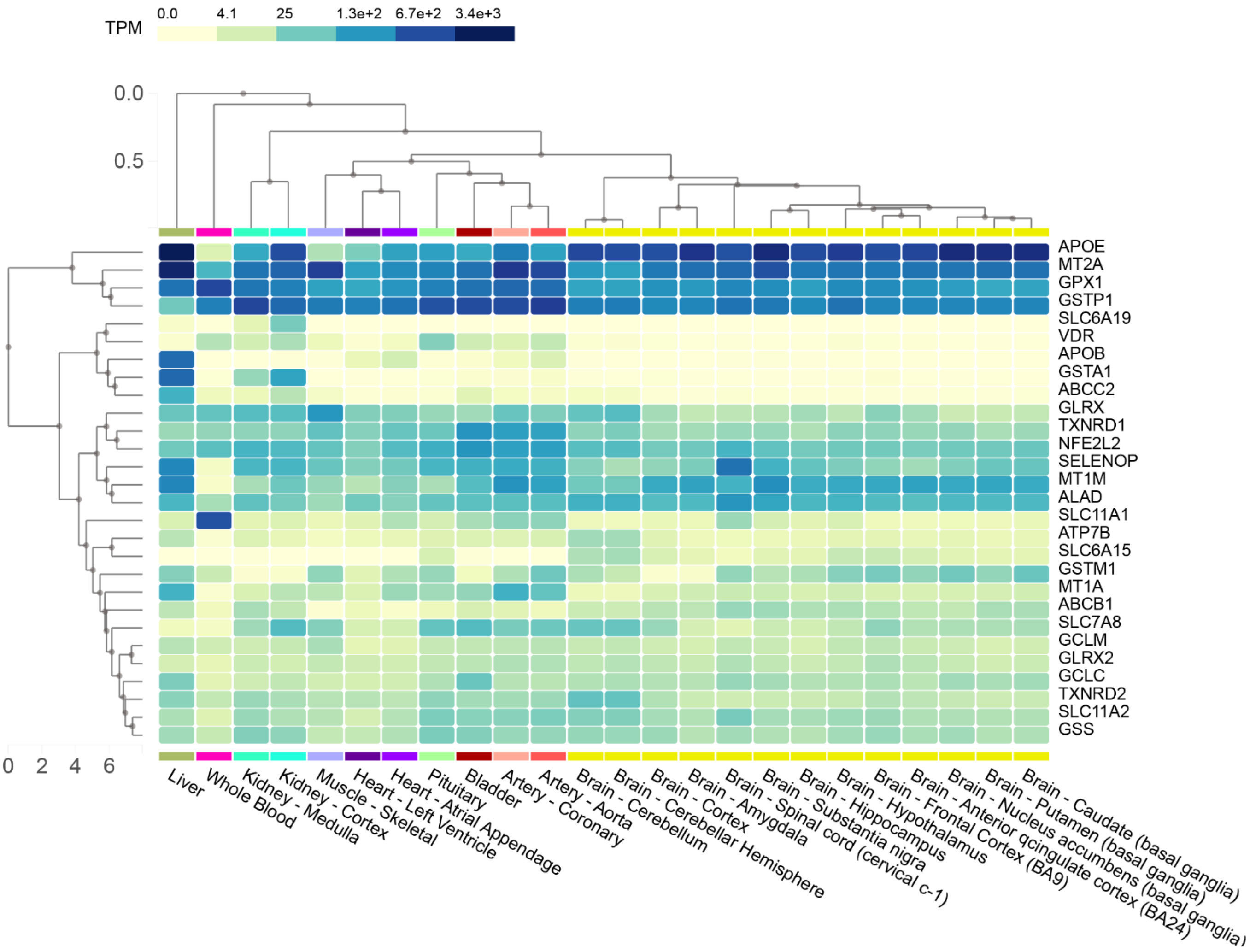
To evaluate the involvement of the polymorphic genes *APOA*, *APOB*, *APOE*, *ABCB1*, *ABCC2*, *ALAD*, *ATP7B*, *eNOS*, *GCLC*, *GCLM*, *GPx1*, *GSTA1*, *GSTM1*, *GSTP1*, *MT1A*, *MT1M*, *NFE2L2*, *SEPP1*, *SLC7A8*, *VDR*, *GSS*, *GLRX*, *GLRX2*, *TXNRD1*, *TXNRD2*, *SELENOP*, *MT2A*, *SLC6A15*, *SLC6A19*, *SLC11A1* and *SLC11A2* in pathways and biological processes, we performed gene enrichment in Reactome and KEGG pathways, and GO biological processes. Considering the biological processes of GO, these genes were enriched mainly in processes of metal metabolism, homeostasis and response, cellular detoxification, xenobiotic export from the cell, response to oxidative stress, xenobiotic transport across the blood-brain barrier and apoptosis control of neurons (Figure 4A). These genes were enriched mainly in Reactome and KEGG biological pathways related to xenobiotic metabolism, mineral absorption and glutathione synthesis, recycling, conjugation and metabolism (Figure 4B-C). Regarding the human phenotype, some of the analysed genes (*ABCC2*, *ALAD*, *ATP7B*, *APOE*, *APOB*, *CYP27B1*, *GCLC*, *LPA*, *NFE2L2*, *SLC6A19*, *SLC11A1*, *SLC11A2* and *TXNRD1*) are mainly involved in the modulation of the urinary excretion homeostasis (Figure 4D).

FIGURE 4. Gene set enrichment of polymorphic genes associated with mercury metabolism

The figure summarizes the main functional involvement of the identified polymorphisms. A) Biological process of Gene Ontology enrichment. B) REACTOME pathways enrichment. C) KEGG pathways enrichment. D) Human Phenotypes (Monarch) enrichment.

Additionally, we observed that a large proportion of these genes are highly expressed in healthy tissues such as the bladder, brain, liver, skeletal muscle, cardiac muscle, kidney, whole blood, and blood vessels, which are susceptible to the accumulation and damage caused by Hg. Among them, *APOE*, *MT2A*, *GPX1*, and *GSTP1* stand out as the most highly expressed genes (Figure 5).

FIGURE 5. Heatmap of the expression of genes associated with mercury metabolism



TPM: Transcripts Per Million. Heatmap created in the GTEx database.

4. Discussion

In recent decades, the Amazonian biome has been suffering from uncontrolled and illegal gold mining (Basta, et al., 2023; Neto et al., 2024), and this has a direct impact on human health (Bakker et al., 2021), since this metal can be converted into MeHg and bioaccumulate in living organisms, both animal and human (Crespo-Lopez et al., 2021).

The studies existing to date in traditional Amazonian populations (riverine and indigenous peoples) that associate polymorphisms in genes related to Hg metabolism, the retention of this metal in the body, and its toxic and clinical effects, were developed among the years 2005 to 2025, in the Brazilian states of Mato Grosso, Pará, and Rondônia. Interestingly, Neto et al., (2024) assessed the distribution and extent of mining activity in Brazil over a historical period (1985 to 2022), and observed that artisanal and *garimpo*, which is the most polluting due to the indiscriminate release of Hg into the environment, has increased dramatically in the Amazon region and is mainly concentrated in the states and regions where the studies reported in this review were conducted (Mato Grosso, Pará, and Rondônia states). Therefore, traditional Amazonian populations from the states of Mato Grosso, Pará, and Rondônia who reside near mining areas with high and chronic contamination, and who carry these polymorphisms, may be more vulnerable to Hg retention in the body and, consequently, more prone to associated clinical manifestations. In fact, the effects of chronic exposure in indigenous and riverside populations are associated with neurological manifestations such as motor, sensory, cognitive, and psychosocial disorders in adults, and impaired motor development, cognitive deficits, short stature, and anemia in children (Hoshino et al., 2015; Kempton et al., 2021; Pinheiro et al., 2025).

To date, at least 31 polymorphisms related to Hg metabolism have been found in traditional Amazonian populations; however, only 15 polymorphisms have been significantly associated with Hg levels in the body.

4.1. Polymorphisms associated with Hg retention in people from urban areas

In the urban population of Porto Velho, state of Rondônia, Brazil, the presence of *GSTM1* (-/-) and *GPx1* (rs1050450) polymorphisms did not show a significant effect on Hg poisoning biomarkers (Rocha et al., 2016). However, in the riverside population of the Tapajós River, state of Pará, the *GSTM1* (-/-) polymorphism was associated with body Hg retention (Barcelos et al., 2013). Furthermore, *GPx1* (rs1050450) was associated with low levels of MeHg in the hair of individuals from Hong Kong, what supports the influence of this polymorphism in Hg metabolism (Chan et al., 2020). Therefore, new studies in urban populations from the regions affected by illegal mining, such as in cities from the Tapajós region, may confirm these associations in this group of people.

4.2. Polymorphisms associated with Hg retention in riverside peoples

In riverside communities located in the Tapajós River basin and along the Tucuruí Hydroelectric Power Plant reservoir in the state of Pará, the frequency of *APOEε4* (rs429358-C allele) was higher among individuals with pronounced indigenous (Amerindian) ancestry. In this population, *APOEε4* (rs429358-C allele) was associated with higher concentrations of THg in hair when compared to *APOEε2* carriers and was also associated with vulnerability to the neurotoxic effects of Hg, such as poor motor performance and neuropsychological deficits (Arrifano et al., 2018). However, another study with riverside people from the same region did not identify an association between *APOEε4* and/or its haplotypes (ε2, ε3 and ε4) and Hg levels (Lopes-Araújo et al., 2023). In children from Taiwan, it was observed that *APOEε4* can modify the adverse effect of MeHg on child neurodevelopment, and carriers of this polymorphism are more susceptible to Hg contamination (Ng et al., 2013). In Croatian mothers carrying the ε4 allele, elevated levels of MeHg were found in peripheral venous blood, umbilical cord blood and hair (Trdin et al., 2020). Contrary to these findings, in Italian mothers the ε4 allele (rs429358-C and rs7412-C) was associated with lower levels of MeHg in blood and umbilical cord blood (Palir et al., 2023). Interestingly, the mercury ion (Hg2+) has a binding affinity for *APOEε4*, and is able to change its structural conformation and function in oxidizing extracellular environments (Berntsson et al., 2022). Although findings of the impact of *APOEε4* on Hg retention in the body are dichotomous, the strong binding affinity to IHg may make this polymorphism a risk factor for IHg intoxication and accumulation.

Considering the genes of the glutathione system, the double deletion *GSTM1* (-/-) and *GSTT1* (-/-) in riverside people was related to susceptibility to oxidative stress due to reduced glutathione peroxidase activity; however, no direct association was found with Hg concentrations (Barcelos et al., 2015a). In riverside communities along the Tapajós River chronically exposed to MeHg due to frequent fish consumption, the *GSTM1* (-/-) deletion was associated with elevated plasma concentrations of THg and MeHg (Oliveira et al., 2014). In Austrian students, the combined deletion of *GSTM1* (-/-) and *GSTT1* (-/-) was associated with higher concentrations of MeHg in hair (Gundacker et al., 2007). In pregnant Korean women, the double deletion was associated with elevated maternal blood MeHg levels and negative perinatal outcomes linked to Hg exposure, such as decreased birth weight in newborns (Lee et al., 2010). In people from Temirtau, Kazakhstan, *GSTM1* (-/-) was associated with higher levels of Hg in the body and greater susceptibility to oxidative stress (Serik et al., 2025). In pregnant women in Indonesia, these deletions have been associated with elevated levels of MeHg in the hair and clinical aspects, such as hypertension (Armatussolikha et al., 2024). Therefore, *GSTM1* (-/-) may be important for Hg toxicodynamics in Amazonian riverine populations.

Considering the vitamin B receptor (*VDR*) gene, *VDR* carriers (rs1544410; allele A) showed higher concentrations of Hg in the blood compared to homozygous GG individuals (Barcelos et al., 2015a). In contrast, in pregnant Italian women exposed to Hg, rs1544410 did not have a significant association with body Hg levels (Palir et al., 2023). Interestingly, in dolphin cells, MeHg impairs the ability of 1,25-dihydroxyvitamin D3 (a bioactive metabolite of vitamin D3) to positively regulate the *VDR*, causing the inhibition of the expression of specific target genes important for the cell (Ellis et al., 2010). Therefore, although the direct relationship between rs1544410 and Hg concentrations in the body is unknown, this gene is directly affected by MeHg and may play a relevant role in the toxic effects of Hg in exposed populations.

The *GSTP1* (rs1695) polymorphism is generally associated with Hg levels (Chan et al., 2020; Silva et al., 2023; Silva et al., 2024); however, in at least three independent studies in riverside populations, this polymorphism did not show a significant association with Hg levels (Barcelos et al., 2013; Oliveira et al., 2014; Barcelos et al., 2015a).

Considering *GCLM*-588-TT (rs41303970) in riverside people of the Tapajós region, the TT genotype was associated with a lower concentration of MeHg in blood plasma (Oliveira et al., 2014), and in blood and hair (Barcelos et al., 2013) when compared to carriers of the C allele. Interestingly, in pregnant women from the Seychelles archipelago, *GCLM* (rs41303970; TT genotype) was associated with lower concentrations of MeHg in the hair (Wahlberg et al., 2018). In contrast, individuals from Sweden carrying *GCLM* (rs41303970; TT genotype) showed higher levels of MeHg in erythrocytes (Engström et al, 2008). In people from Temirtau, Kazakhstan, *GCLM* (rs41303970) was associated with higher Hg levels and greater susceptibility to oxidative stress (Serik et al., 2025). In Colombian mining workers, *GCLM* (rs41303970; T allele) was associated with increased urinary excretion of IHg (Medina Pérez et al., 2021). Individuals from Ecuador carrying *GCLM* (rs41303970; T allele) had elevated levels of MeHg in their blood, plasma and urine (Custódio et al., 2005; Harari et al., 2012). Therefore, these results suggest that this polymorphism favors urinary excretion of IHg (Custódio et al., 2005; Harari et al., 2012; Medina Pérez et al., 2021), but not of MeHg (Custódio et al., 2004).

Considering *GCLC* (rs17883901) in the riverine population of Tapajós, carriers of *GCLC* (rs17883901; T allele) presented increased levels of THg and MeHg in plasma (Oliveira et al., 2014). People from Sweden carrying *GCLC* (rs17883901; T allele) had elevated levels of MeHg in erythrocytes (Custódio et al., 2004). In contrast, Hong Kong women carrying *GCLC* (rs17883901; T allele) had lower levels of MeHg in the hair (Chan et al., 2020). Furthermore, some studies have found no association between *GCLC* (rs17883901) and Hg concentrations in the body (Custódio et al., 2005; Engström et al, 2008; Gundacker te al., 2009). *CGLC* is crucial for the formation of reduced glutathione (GSH), which is able to bind to MeHg and form GSH-MeHg conjugates that are easily transported and excreted by the body. Interestingly, an experimental study in *Drosophila melanogaster* demonstrated that *GCLC* is important for the tolerance, toxicokinetics and toxicodynamics of MeHg, since this gene increases the availability of GSH for the formation of GSH-MeHg conjugates (Rand et al., 2019). Therefore, *GCLC* (rs17883901) may be important for the accumulation of this metal in the body in riverside people by elevating GSH and, consequently, elevating GSH-MeHg conjugates.

Regarding the endothelial nitric oxide synthase gene (*NOS3/eNOS*), responsible for the synthesis of nitric oxide (NO) and which is responsible for endothelial homeostasis, it was observed that in riverine people of the Tapajós River, the polymorphisms rs1799983, rs11771443 and VNTR4a/4b (intron 4) were associated with elevated levels of Hg in hair, nitrite concentrations in blood plasma and markers of endothelial dysfunction. The rs1799983 polymorphism has been associated with reduced NO levels, headache and hypertension, suggesting that Hg accumulation is favored by this polymorphism, which interferes with NO bioavailability and potentiates clinical manifestations such as increased blood pressure (Marco et al., 2011; Marco et al., 2012). Interestingly, in an experimental murine model, Hg treatment did not interfere with systolic blood pressure, but increased vascular reactivity due to reduced NO bioavailability resulting from increased reactive oxygen species from the eNOS enzyme uncoupling (Schereider et al., 2020. Uncoupling is an error (which can be potentiated by Hg) of the eNOS enzyme, which produces superoxide anion ($O2\cdot-$) instead of producing vasodilator NO, resulting in oxidative stress and endothelial dysfunction (Förstermann; Münzel, 2006).

The *TXNRD2* (rs5748469), *GLRX* (rs2007), *GLRX2* (rs912071) and *SLC6A19* (rs9418) polymorphisms were associated with higher concentrations of THg in whole blood and/or plasma, and in the hair of riverside people in the Tapajós River region, in the state of Pará. While *SLC6A15* (rs11116642) was associated with lower levels of THg in blood and hair, and higher glutathione peroxidase activity (Maraslis et al., 2025).

4.3. Polymorphisms associated with Hg retention in indigenous populations

Considering Amazonian indigenous populations, five studies have associated polymorphisms with Hg accumulation and susceptibility to neurological damage. For example, in Munduruku children, the rare presence of the *ALAD* polymorphism (rs1800435) in heterozygous carriers was associated with hair MeHg levels above acceptable limits and alterations in the visual field, memory deficit, distal neuropathy and toe amyotrophy, consistent with chronic exposure, suggesting that this polymorphism may modulate neurobehavioral effects in exposed populations (Perini et al., 2021). Interestingly, the Hg2+ has a binding affinity for *ALAD* and, consequently, can inhibit its enzymatic activity (Farina et al., 2003; Brandão; Nogueira, 2011). Therefore, new studies in Amazonian indigenous populations exposed to Hg should analyze this polymorphism in order to better characterize its relationship with Hg.

Although the *GSTP1* (rs1695) polymorphism has not been related to Hg concentrations in riverside people (Barcelos et al., 2013; Oliveira et al., 2014; Barcelos et al., 2015a), in adults and children of the Munduruku ethnic group, it has been associated with elevated MeHg levels and neurological changes in adults and alterations in neuropsychomotor development in children (Silva et al., 2023; Silva et al., 2024). Interestingly, *GSTP1* (rs1695) has been associated with higher levels of MeHg in the hair of Hong Kong women (Chan et al., 2020) and in the blood of Jamaican children with autism spectrum disorder (Rahbar et al., 2021). Jamaican children with *GSTP1* (rs1695) who were exposed to MeHg had higher blood Hg levels compared to unexposed children (Zaman et al., 2024). In contrast, in mothers from the Seychelles archipelago, this polymorphism was not associated with Hg levels, but it was associated with a reduced mental development index among children (Wahlberg et al., 2018). Therefore, *GSTP1* (rs1695) may confer greater susceptibility to Hg contamination and its neurological clinical outcomes in Munduruku indigenous people and other populations around the world.

The *GSTM1* (-/-) polymorphism present in individuals of the Munduruku and Kayabi ethnicities has been associated with elevated levels of MeHg in hair. Furthermore, individuals of the Kayabi ethnic group carrying the polymorphism showed a higher average Hg contraction than that found in the Munduruku (Klautau-Guimarães et al., 2005). Interestingly, this polymorphism has also been associated with Hg levels in riverside people (Barcelos et al., 2013; Barcelos et al., 2015a; Oliveira et al., 2014) and in other populations around the world (Gundacker et al., 2007; Lee et al., 2010; Armatussolikha et al., 2024; Serik et al., 2025). Therefore, *GSTM1* (-/-) can be considered a key alteration for the toxicodynamics, toxicokinetics and bioaccumulation of Hg in humans.

A genome-wide study revealed 23 polymorphisms in genes associated with Hg metabolism (*ABCB1*, *ABCC1*, *ABCC2*, *ATP7B*, *GCLC*, *GCLM*, *GPX1*, *GPX4*, *GSS*, *GSTA1*, *GSTM1*, *GSTP1*, *GSTT1*, *MT1A*, *MT1M*, *MT2A*, *MT4*, *NFE2L2*, *SEPP1*, *SLC22A6*, *SLC22A8*, *SLC7A5* and *SLC7A8*) in 64 indigenous people from 12 different ethnic groups in the Amazon.

A high frequency of the *GSTA1* (rs1051775) and *GSTM1* (rs1183423000 and rs1241704212) variants was observed in the studied individuals, and these may have a high impact on the phenotype of carriers. In addition, seven new polymorphisms (*ABCC2*, *ATP7B*, *GCLC*, *GPX4*, *GSTT1* and *SLC7A8*) were identified in genes associated with Hg metabolism that are unique to these populations (Carvalho et al*.,* 2024). Although these authors did not directly link these polymorphisms to the participants' Hg levels, these data suggest that these populations may be more susceptible to Hg body retention when exposed.

4.4. Polymorphisms in genes related to Hg metabolism in urban, riverside and indigenous people

We identified that only the *GSTM1* (-/-) polymorphism was common to urban, riverside and indigenous populations. In the only study conducted in an urban population, this polymorphism did not have a statistically significant association with the Hg levels of the participants (Rocha et al., 2016). However, in studies conducted in riverside (Barcelos et al., 2013; Barcelos et al., 2015a; Oliveira et al., 2014) and indigenous (Carvalho et al., 2024; Klautau-Guimarães et al., 2005) populations, an association was found. The limited number of studies in individuals from urban populations in Hg-contaminated regions of the Amazon may have reduced the statistical power of the association between this polymorphism and body Hg levels. Therefore, this polymorphism may play a central role in Hg metabolism in traditional Amazonian populations.

ALAD (rs1800435), *GSTP1* (rs1695), *GSTT1* (-/-) and *MT1A* (rs11640851) have been identified in indigenous (Carvalho et al., 2024; Klautau-Guimarães et al., 2005; Perini et al., 2021; Silva et al., 2023; Silva et al., 2024) and riverside people (Barcelos et al., 2015a; Oliveira et al., 2014; Barcelos et al., 2013; Maraslis et al., 2025), suggesting that these two groups share greater genetic proximity considering genes related to detoxification pathways and metabolism of metals and xenobiotics, and consequently, making them more vulnerable to Hg contamination than the urban population.

4.5. Polymorphisms associated with Hg retention evidenced by meta-analysis

The meta-analysis indicates a trend towards associations of *GSTM1* (-/-), *GSTT1* (-/-) and *GSTP1* (rs1695) with susceptibility to Hg accumulation, yet without statistical significance. The lack of statistical significance observed in the meta-analysis does not invalidate these associations, but reflects structural limitations of the dataset available to date, including low statistical power, high heterogeneity among studies, differences in the analysis of environmental exposure levels and genetic variability among traditional Amazonian populations. Therefore, the results of the meta-analysis tend to corroborate the results of the studies gathered here, which indicate an association between these polymorphisms and a greater susceptibility to Hg poisoning.

4.6. Biological role of the polymorphisms associated with Hg metabolism

The genes used in functional analysis can modulate biological pathways and processes associated with homeostasis, metabolism and metal detoxification (Figure 4A-D). Thus, gene enrichment analysis corroborates previous studies demonstrating that these genes are important for Hg metabolism, since they can interact with different forms of Hg, helping to modulate toxicity, storage, transport and body elimination (Kang et al., 2024).

These genes are also involved in regulating urinary homeostasis, suggesting that they may aid in the excretion of Hg in urine (Figure 4D). Indeed, studies show that polymorphism in genes related to *ABC* and *SLC* transporters (Engström et al., 2013; Rodréguez et al., 2020) and in *GCLM* (rs41303970) of the glutathione pathway (Custódio et al., 2005; Harari et al., 2012) directly influences the concentration of Hg excreted in urine. Therefore, these polymorphisms can alter the activity of these genes and, consequently, interfere with the toxicodynamics, toxicokinetics and excretion of this metal.

Gene expression analysis demonstrated that the studied genes are highly expressed in tissues (e.g., brain, kidney, liver, and whole blood) that are directly affected by Hg accumulation and toxicity. Therefore, these polymorphisms may promote Hg accumulation in target tissues, contributing to clinical phenotypes associated with intoxication, such as neurological alterations and hypertension.

4.7. Study limitations

Considering the meta-analysis, the high heterogeneity, the limited number of eligible studies and the methodological variability among the studies, may have impacted the level of statistical significance and, consequently, may not have allowed the confirmation of the trends in associations and their observed biological contexts. The limited number of studies with complete data restricts the statistical power to detect consistent associations, especially for low-frequency polymorphisms. For example, we identified 15 studies during the systematic review; however, only three met the inclusion criteria for the meta-analysis. Among the excluded studies, many did not provide the allelic and/or genotypic frequencies of the associated polymorphisms. Therefore, the scarcity or absence of information and small sample sizes may have difficult causal statistical inferences and the generalization of results to different populations in the Amazon region.

4.8. Future perspectives and recommendations

The findings of this study point to the need for further investigation into the genetic mechanisms that modulate Hg biodynamics in exposed populations in the Amazon. For example, functional studies using *in vitro* and *in vivo* experimental models could clarify the molecular mechanisms by which these variants interact with Hg in the body and promote the observed clinical effects.

Genomic studies in the Brazilian population, including traditional Amazonian populations (riverine and indigenous communities), will allow the identification of new variants and haplotypes associated with Hg toxicokinetics. The national program for genomics and precision public health - The Genomes Brazil Program, governed by GM/MS No. 6,581 of January 2025 from the Brazilian Ministry of Health, will provide large-scale genomic data that will serve as a basis for identifying new associated genetic variants. For example, in a first genome-wide study of the Brazilian population, approximately 2,723 whole genomes were sequenced from individuals across all Brazilian geographic regions, including the Amazon region. This study identified nearly 9 million new, previously unknown variants, of which more than 36,000 are presumably deleterious (Nunes et al., 2025). Thus, the integration of genomic data with environmental and epidemiological data will contribute to the development of predictive models that can estimate the genetic risk of MeHg bioaccumulation, with the aim of assisting public policies aimed especially at populations vulnerable to chronic exposure, such as the Brazilian Amazonian population.

Therefore, beyond the scientific contribution and from an environmental and socioeconomic perspective, Brazilian public policies should include the implementation of monitoring programs (e.g., genetic and epidemiological) in populations and regions subject to Hg contamination, associated with public policies that combine mitigation and recovery of contaminated areas and the fight against illegal mining. These actions can promote social and environmental justice and reduce health inequalities among historically neglected traditional Amazonian populations.

5. Conclusions

This is the first systematic review study combined with meta-analysis and functional analysis of polymorphisms, which seeks to associate genetic variants with Hg contamination levels in traditional human populations of the Brazilian Amazon at imminent risk of contamination.

The systematic review revealed that only 15 studies that assessed and identified the association between genetic polymorphism and Hg contamination were conducted over the past 20 years in Amazonian populations at risk of contamination. The meta-analysis tended to corroborate the associations between *GSTP1* (rs1965), *GSTT1* (-/-) and *GSTM1* (-/-) polymorphisms and Hg retention; however, the lack of statistical significance reveals the weakness in the structuring of the data from the studies available to date. Thus, there is a need for new, well-designed experimental and epidemiological studies with robust data that can be incorporated into future meta-analyses involving these and/or new markers.

APOEε4 (allele rs429358-C), *GSTM1* (-/-), *VDR* (rs1544410), *GCLM*-588-TT (rs41303970), *NOS3* (rs1799983, rs11771443 and VNTR4a/4b), *TXNRD2* (rs5748469), *GLRX* (rs2007), *GLRX2* (*rs912071*), *SLC6A19* (*rs9418*) and *SLC6A15* (rs11116642) were associated with Hg accumulation and clinical manifestations in riverside communities. *ALAD* (rs1800435), *GSTP1* (rs1695) and *GSTM1* (-/-) were significantly associated with Hg accumulation and clinical manifestations in indigenous people.

The *GSTM1* (-/-) association is present in all three populations (urban, riverside and indigenous Amazon people), while *ALAD* (rs1800435), *GSTP1* (rs1695), *GSTT1* (-/-), and *MT1A* (rs11640851) are shared by both riverside and indigenous populations. Functional analysis of the biological role of these genes demonstrated that they are essentially involved in metal metabolism, detoxification, oxidative stress and modulation of cell death in neurons. *GCLM* (rs41303970) may facilitate urinary Hg excretion. Therefore, these polymorphisms are important for Hg metabolism and may be useful as susceptibility markers in populations at risk of contamination in the Amazon.

CRediT authorship contribution statement

Enzo Kaique da Silva Lopes: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Hianca Marcela Viana dos Santos:** Methodology. **Márcia Socorro Silva Lima Duarte:** Data curation, **Alessandro Luiz Bentes Araújo:** Methodology, Data curation, **Felipe Rodolfo Pereira da Silva:** Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Adenilson Leão Pereira**: Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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