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Laying the groundwork: Exploring pesticide exposure and genetic factors in south-eastern Brazilian farmers

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ABSTRACT

Brazil is the world leader in pesticide consumption, and its indiscriminate use puts farmers' health at risk. The *CYP2C9* gene encodes the CYP2C9 enzyme, which metabolizes several endogenous substrates and specific xenobiotics, especially pesticides. Our goal is to study the risk of pesticide use, especially the herbicide glyphosate, in the development of diseases and the association with two *CYP2C9* polymorphisms, in farmers living in the southern region of Espírito Santo state, Brazil. The allelic frequency of *CYP2C9**1, *CYP2C9**2 and *CYP2C9**3 was determined in blood samples from individuals exposed or not to pesticides using real-time PCR. 304 blood samples were analyzed, dividing *CYP2C9* genotypes into three metabolization classes: normal, intermediate, and slow. Our results indicate that normal metabolizers may be more susceptible to conditions such as high blood pressure, cardiovascular disease, and kidney problems. Intermediate metabolizers show an association with attention deficit disorder and miscarriages, suggesting that farmers' symptoms correlated with their *CYP2C9* genotype. Insufficient data prevented conclusions about slow metabolizers (*2 and/or *3). These findings suggest that the *CYP2C9* genotype may influence the way farmers exposed to pesticides respond, but more research is needed to clarify causality and investigate other possible health effects. As an introductory effort, this study provides insights into the complex relationship between genetic variations and pesticide exposure, laying the groundwork for future research. This pioneering work on associations between specific genetic variations and health risks with pesticide exposure, emphasizes the importance of personalized medicine and stricter regulation of pesticide use for public health and occupational safety.

1. Introduction

Brazil leads the world rank in pesticide consumption, a worrying fact that is directly related to the country's agricultural policy, focused on increasing productivity to compete in the international market (Bombardi, 2022). Excessive use of pesticides, often without due

Abbreviations: ADHD, Attention deficit hyperactivity disorder; AMPA, aminomethylphosphonic acid; CDC, Centers for Disease Control and Prevention; Co, cobalt; EPSPS, 5-enolpyruvylshikimate-3-phosphate synthase; Mn, manganese; mTOR, mammalian Target of Rapamycin; ASMT, N-acetylserotonin O-methyltransferase; MTNR1A, N-acetylserotonin O-methyltransferase receptor 1A; NNG, N-nitrosoglyphosate; PPE, personal Protection Equipment.

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technical information and without the adequate use of personal protective equipment (PPE), exposes farmers, their families and even the end consumer to significant health risks (Jobim et al., 2010; Pignati et al., 2017; Latt et al., 2023; Lencucha et al., 2020). In the context of farmers in the south of Espírito Santo, a populous region divided into three micro-regions: Alegre, Cachoeiro de Itapemirim and Itapemirim, covering 22 municipalities, there is an additional concern. This region, which occupies 8,844.17 km^2 and represents 19.19 % of the state, with 565,934 inhabitants, 72.35 % urban, faces socioeconomic challenges. The area's human development index (HDI) is lower than the state average, mainly due to education, and data from 2009 showed that many families have a monthly income of up to 2 minimum wages. This reality, combined with the intense use of pesticides, increases the vulnerability of local farmers to health problems related to the use of these chemical substances (BRASIL, 2017). A study carried out by the Territorial Plan for Sustainable Rural Development (PTDRS) in 2009 highlighted that the main problem for rural workers in the Territory of Caparaó – ES is health. In the region, farmers use several pesticides, with glyphosate being one of the most common. This is due to the indiscriminate and inappropriate use of pesticides in coffee monoculture, the unsanitary nature of workplaces and the consequent contamination of food and water (Lopes et al., 2023). These conditions significantly increase the risk of disease among farmers, who are exposed both through direct handling and through inappropriate practices, such as storing and reusing contaminated packaging (PTDRSS, 2017; BRASIL, 2018). Substances widely used in agriculture, such as organophosphates, carbamates, malthion, diazinone, and especially glyphosate, have been classified as probable carcinogens by the International Agency for Research on Cancer (Guyton et al., 2015; Ore et al., 2023; Iwuozor et al., 2023). The Cytochrome P450 family of enzymes, including *CYP2C9*, is essential for xenobiotic metabolism, having a characteristic molecular structure that allows the metabolization of several substances (Rang et al., 2003; Singh et al., 2023; Syed and Mashele, 2014).

Recent studies have changed the perception about pesticide toxicity to humans, with evidence that substances such as glyphosate can inhibit the activity of the *CYP2C9* enzyme (Abass et al., 2009; Elmadani et al., 2011; Foldager et al., 2021). Furthermore, there is an association between central nervous system neoplasms and chemically exposed occupations, such as agriculture (Alavanja and Bonner, 2012; Clapp, 2006; Nichols and Sorahan, 2005). Symptoms of pesticide poisoning can range from acute effects, such as headaches and nausea, to chronic conditions, including liver and kidney damage (Augusto et al., 2012; Londres, 2011).

Indifferent to the great awareness movements about the toxicity of pesticides, Brazil remains the largest consumer of pesticide products in the world, reaching alarming levels in terms of environmental damage resulting from contamination of soil and water (BRASIL, 2018).

Given this context, the project aims to verify mainly what is the role (if there is an association between the use of pesticides and the development of diseases/symptoms) of pesticides in the development of diseases/symptoms in farmers in the south of Espírito Santo due to their daily use in their work environment, and assess whether there is an association between the presence or emergence (or worsening) of diseases with polymorphisms in the *CYP2C9* gene, which encodes the enzyme CYP2C9 (a member of the Cytochrome P450 family of proteins), extremely important for the metabolization of xenobiotics.

In this study, the impact of pesticides on the development of diseases/symptoms in farmers of the south of Espírito Santo was evaluated, focusing on the relationship between daily exposure and *CYP2C9* polymorphisms and seeking to correlate the emergence or worsening of diseases with these polymorphisms, analyzing a total of 43 variables related to diseases and symptoms.

2. Materials and methods

2.1. Study population

This research was submitted to the research ethics committee of the Federal University of Espírito Santo and approved according to opinion number 3.378.510 and the resolutions of the National Health Council n° 466 (of December 12, 2012) and n° 510 (of April 7, 2016). Inclusion criteria were men and women over 18 years of age, resident farmers of the south of the Espírito Santo state. Exclusion criteria were individuals who did not have the cognitive conditions to understand the research, those who refused to participate and in situations in which it was not possible to identify their place of residence or occupation.

A questionnaire was filled out by each volunteer, and then blood was collected and DNA extraction and genotyping of samples were analyzed. A total of 304 participants aged over 18 years were randomized. Most of the interviewed workers (72.01 %) were males, and 27.99 % were females. The control group consists of individuals who do not use pesticides on their coffee plantations and other vegetable monocultures, while the exposed group is made up of individuals who are in contact with pesticides on crops and choose to use synthetic pesticides. Farmers were predominantly aged between 34 and 50 years, having worked as such for 26 to 50 years, with 86 of them being in both groups (32.21 %).

The percentage of rural workers who use pesticides was as high as 90.27 %. Glyphosate was the most used (79.66 %), followed by flutriafol (32.85 %), thiamethoxam (26.91 %) and cyproconazole (22.34 %). Behavioral variables such as alcohol consumption and tobacco use were not correlated with genotypes and diseases/symptoms emergence.

Symptoms/diseases addressed were eye irritation, skin lesions/allergies, skin burns, nausea/vomiting, phlegm, abdominal pain, diarrhea, difficult digestion, wheezing, asthma, gastric inflammations, liver diseases, blood pressure changes, infertility, tearing, dizziness/vertigo, cough, shortness of breath/dyspnea, blurred vision, tremors, vomiting, joint pain, hepatitis, osteoarthritis/osteoporosis, kidney diseases, respiratory diseases, attention deficit, miscarriages, headache, excessive sweating, salivation, agitation/irritability, tingling, miosis, cramps, body/muscle pain, depression, cardiovascular diseases, cancer, heart palpitations, salivary gland damage, malformation and hyperactivity. Significant correlations ($P < 0.05$) between the use of pesticides and symptoms/diseases were tested for each genotype group ("A", "B" and "C").

2.2. DNA extraction

DNA extraction and purification were carried out using a Qiagen® commercial kit, following manufacturer's recommendations (Qiagen, USA).

2.3. Real-time PCR to assess CYP2C9 polymorphisms

CYP2C9 polymorphisms were identified by real-time PCR as previously described by Perini et al., (2009). Validated TaqMan® assays (Applied Biosystems, USA) were used to discriminate *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) alleles. For both assays, real-time PCR reactions were performed in a final volume of 10 µl containing 30 ng of DNA, 1X Taqman Universal Master Mix (Applied Biosystems, USA), 1X of each specific assay and H_2O q.s.p. PCR conditions were initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 92 °C for 15 s and annealing/extending at 60 °C for 1 min. All samples were analyzed using the Fast 7500 Real-Time System (Applied Biosystems, USA). Genotypes were determined by analyzing the allelic discrimination plots. According to each sample's alleles, individuals were classified into different categories regarding their

metabolization capacity:

Category	Metabolization	Genotype(s)
A	Normal	*1/*1
B	Intermediate	*1/*2; *1/*3
C	Slow	*2/*2; *2/*3; *3/*3

It is important to emphasize the scarcity of cases in category C, making future analysis essential for possible connections with experiments not addressed in this study. In this context, we focused primarily on groups A and B, recognizing the need for comprehensive understanding to explore potential correlations and broader implications.

2.4. Data analysis methodology

For bivariate statistical analysis, the Chi-square test and, when necessary, Fisher's exact test was applied, with a 5 % margin of error. To carry out the analyses, the free R version 3.6.1 software was used. The software can be obtained from the website https://cran.r-project.org/bin/windows/base/. Furthermore, all results derive from the bivariate analysis between "use of pesticides" and "appearance of a certain symptom" for each genotype group.

3. Results

Allelic and genotypic frequencies were calculated and are presented in Tables 1 and 2.

As shown in Table 3, "B" intermediate metabolizers (who use pesticides) are associated with attention deficit (Chi-square P = 0.01782 / Fisher P = 0.02008) and miscarriages (Chi-square P = 0.00070 / Fisher P = 0.00409), and in normal "A" metabolizers (who use pesticides) an association with blood pressure alteration (Chi-square P = 0.00371 / Fisher P = 0.00305), cardiovascular diseases (Chi-square P = 0.04308 / Fisher P = 0.03319) and kidney diseases (Chi-square P = 0.06536 / Fisher P = 0.02635) was found.

As an introductory effort, this study provides preliminary insights into the intricate relationship between genetic variations and pesticide exposure, highlighting potential health risks associated with specific *CYP2C9* genotypes. The findings, although limited by sample size and the need for further comprehensive data, underscore the relevance of genetic predisposition in mediating individual susceptibility to pesticide-related health effects. By identifying genotype-specific trends, such as the increased vulnerability of normal metabolizers to cardiovascular and kidney conditions and the association of intermediate metabolizers with neurocognitive and reproductive outcomes, this research establishes a foundation for future studies. These future investigations should aim to elucidate causality, expand the understanding of slow metabolizers, and explore broader implications for public health. This work sets the stage for advancing personalized medicine approaches and supports the imperative for stricter pesticide regulation to safeguard vulnerable populations.

4. Discussion

In this paper, we have investigated a possible link between exposure to glyphosate and other pesticides among agricultural workers in Brazil and various health issues and have explored specifically whether different polymorphisms of the *CYP2C9* liver enzyme might play a role in how pesticides impact health. We have found a statistically significant increase in blood pressure issues (hypotension/hypertension), cardiovascular disease, kidney disease, attention deficit, and miscarriages, when comparing pesticide-exposed agricultural workers with controls who worked on organic farms, with interesting differences observed between normal metabolizers (*1 alleles only) and intermediate metabolizers (*1 and either *2 or *3).

The unexposed group, made up of farmers who work on organic farms and do not use pesticides, serves as a reference to compare the effects observed in the exposed group. The main function of this group is to help identify which health problems can be attributed to exposure to pesticides, discounting other factors that could influence the results. Therefore, the control group includes farmers who do not use pesticides and who correspond to the exposed group based on factors such as age, lifestyle and environmental background. In particular, normal metabolizers (group A) are more susceptible to hypertension, cardiovascular disease and kidney disease, whereas intermediate metabolizers (group B) are more susceptible to attention deficit and miscarriages.

Glyphosate stands out as the most used pesticide by Espírito Santo farmers. According to Boocock et al. (Boocock and Coggins, 1983), glyphosate inhibits plant growth by interfering with the production of essential aromatic amino acids, primarily through suppression of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). In the terrestrial environment, glyphosate is mainly biodegraded into aminomethylphosphonic acid (AMPA). When metabolized by soil bacteria, glyphosate can cause several toxicological problems if absorbed. It can leak into groundwater and be transformed into formaldehyde, which is carcinogenic and neurotoxic (Bohrer, 2005). Another problem with glyphosate-based herbicides is the presence of N-nitrosoglyphosate (NNG) as a contaminant (0.1 ppm), which is a highly carcinogenic substance (Bohrer, 2005). NNG can also be formed in soil, water or in the human body when glyphosate combines with nitrates and nitrites (Bohrer, 2005).

Glyphosate is a glycine molecule with a methyl-phosphonyl group attached to the nitrogen atom. By acting as a glycine analogue, it is possible that glyphosate can displace glycine at random points during protein synthesis, with unknown consequences. Several synthetically produced amino acids, close structural analogues of natural amino acids, can be erroneously incorporated into peptides (Rubenstein, 2000; Samsel and Seneff, 2015). The correlations between glyphosate use and the recent alarming rise in several modern diseases are striking, as presented by Swanson et al. (Swanson et al., 2014) These include

Table 1
Genotypic frequencies (N = 304).

Genotypes	N	Frequency
*1/*1	196	0.645
*1/*2	68	0.224
*1/*3	28	0.092
*2/*2	5	0.016
*2/*3	5	0.016
*3/*3	2	0.007

N: total number of individuals; n: sample subtotal; Frequency = n/N.

Table 2
Allelic frequencies (N = 608).

Allele	*N*	*Frequency*
1	*488*	*0.803*
2	*83*	*0.137*
3	*37*	*0.061*

N: total number of individuals; n: sample subtotal; Frequency = n/N.

Table 3
Diseases and symptoms of intermediate metabolizers "B" and normal metabolizers "A" of *CYP2C9*.

Disease/Symptoms	Group	P-value (Chi-square)	P-value (Fisher)
Blood pressure alterations	A	0.00371	0.00305
Cardiovascular diseases	A	0.04308	0.03319
Kidney diseases	A	0.06536	0.02635
Attention deficit	B	0.01782	0.02008
Miscarriages	B	0.00070	0.00409

obesity, diabetes, end-stage renal disease, kidney failure, autism, Alzheimer's disease, dementia, Parkinson's disease, multiple sclerosis, intestinal infection, inflammatory bowel disease, stroke, leukemia, thyroid cancer, liver cancer, pancreatic cancer and kidney cancer (Swanson et al., 2014).

We found a highly statistically significant correlation with pesticide use among Group A farmers for blood pressure alterations ($p = 0.003$). As early as 1974, hypertension had been identified as the most common and most potent contributor to cardiovascular mortality (Kannel, 1974). There is a 30–55 % prevalence of hypertension in the general population in Europe, with higher rates in the elderly (Kjeldsen, 2018). As of 2018, half the people in the United States over 20 years old suffers from hypertension (Chobufo et al., 2020). A study based in China evaluated health risks of glyphosate exposure in factory workers involved in the production of glyphosate. Compared to workers at the same company who were not exposed to glyphosate, the exposed group had statistically significant higher rates of hypertension, coronary artery disease, elevated liver enzymes, and renal disease (Pan et al., 2017).

de Marins et al. (de Marins et al., 2023), Ojelade et al. (Ojelade et al., 2022) and Gress et al. (Gress et al., 2015) have published literature reviews addressing potential cardiac issues associated with glyphosate exposure, and they found evidence of long QT syndrome, conduction blocks, arrhythmias, and cardiac arrest in cases of acute glyphosate exposure. These studies delved into the potential arrhythmogenic mechanism of glyphosate in mammalian cardiac tissues. Considering the rising use of synthetic molecules in agriculture, the review by Ojelade et al. (Ojelade et al., 2022) highlighted the adverse impact on human health and ecosystems (Ojelade et al., 2022). Recently, the enzyme 21-hydroxylase, encoded by the *CYP21A2* gene, was implicated in steroid hormone synthesis, suggesting that glyphosate's inhibition of *CYP2C9* could impact endocrine regulation and influence farmers' blood pressure (Neves Cruz et al., 2020). Glyphosate-based herbicides, widely used in woodlands and farmlands, have raised concerns due to toxicological issues of glyphosate and its metabolite AMPA in the food chain. Glyphosate has been linked to various health problems, necessitating a comprehensive review of its use, associated risks, and maximum residue limits. The compilation of such data aims to guide regulatory agencies in advising safe glyphosate usage practices (Ojelade et al., 2022).

Catani et al. (Cattani et al., 2023) have shown that perinatal exposure of rats to glyphosate causes oxidative damage in the brain associated with reduced melatonin levels. Low urinary melatonin levels are associated with essential hypertension (Forman et al., 2010). Melatonin supplementation in the evening has been shown to reduce nighttime blood pressure in men suffering from essential hypertension (Scheer et al., 2004).

Gunatilake et al. (Gunatilake et al., 2019) proposed that glyphosate, even without added formulators, has a unique insidious mechanism of toxicity that involves the erroneous substitution for the coding amino acid glycine during protein synthesis, which in certain circumstances can lead to nearly complete inactivation of the affected protein's enzymatic activity. Glyphosate's inhibition of cytochrome P450 enzymes in the liver would disrupt the liver's ability to detoxify and eliminate fat soluble toxic exposures, including pathogenic metabolites, toxic environmental chemicals, and prescription drugs (Guengerich, 2022), causing them to be much more nephrotoxic than they would normally be (Fathy and El-Rahman, 2023).

In this study, we observed that farmers classified as intermediate metabolizers (B) who used pesticides presented more "attention deficit" when compared to farmers who did not use pesticides. Although we did not find a direct correlation with this symptom in the literature, we observed that several researchers have found correlations between the use of pesticides and psychiatric diseases such as autism and Alzheimer's disease (Xu et al., 2023; Seneff et al., 2024).

Attention deficit hyperactivity disorder (ADHD) has been conceptualized as a childhood disorder that diminishes with age. However, there is less awareness of adult ADHD as a condition, but a systematic study determined that 2.58 % of the population worldwide continues to have symptoms of ADHD even after they age out of a childhood diagnosis, and, overall, 6.76 % of the global adult population suffers from symptomatic adult ADHD (Song et al., 2021). A study of the trends over time in the United States of ADHD prevalence (according to US Centers for Disease Control and Prevention (CDC) data) showed a rising trend over time from 1990 to 2010, which correlated very strongly with the rising use of glyphosate on corn and soy crops ($R = 0.9466$, $p \leq 0.000036$) (Seneff et al., 2015). While correlation does not necessarily mean causation, there is an increasing number of peer-reviewed publications showing evidence that glyphosate causes specific pathologies that are linked with ADHD.

The incidence of ADHD in children is rising rapidly, from about 12 cases per 1000 people 30 years ago to about 35 cases per 1000 people in the late 1990 s (Zhang et al., 2021). Learning and memory impairment are common ADHD symptoms. While ADHD has become very common in both children and adults, the causes of ADHD and the underlying brain pathology are still poorly understood. Recently, evidence is building to support the idea that ADHD is caused by an interaction between genetics and environmental factors linked to the Wnt and mammalian Target of Rapamycin (mTOR) signaling pathways, both of which are heavily involved in neurodevelopment (Yde Ohki et al., 2020). Glyphosate exposure during pregnancy in rat dams caused suppression of the Wnt signaling pathway in exposed embryos, leading to behavioral and cognitive issues in the offspring (Coullery et al., 2020). Glyphosate exposure during pregnancy and lactation leads to abnormalities in the Wnt/β-catenin and Notch pathways in the prefrontal cortex of mouse offspring, potentially contributing to neurodevelopmental disorders (Ji et al., 2017).

Glyphosate has been linked to gut dysbiosis through suppression of critical beneficial microbes and overgrowth of pathogenic species. Pathogenic Clostridia species can produce toxic metabolites that cause neurological deviations in the brain, particularly when CYP enzymes are compromised (Rueda-Ruzafa et al., 2019). Imbalances in the gut microbiome observed in association with ADHD could be related to impairments in dopaminergic signaling (Shirvani-Rad et al., 2022).

Glyphosate exposure in rats causes neurotoxicity by altering serotonergic, dopaminergic, and noradrenergic systems, with dose-related changes in neurotransmitter levels (Martínez et al., 2018). As early as 1999, dysregulation of central noradrenergic networks has been linked to ADHD (Biederman and Spencer, 1999). These networks are involved in modulating high level cortical functions such as attention, alertness, vigilance, and executive function. Furthermore, disruptions in the dopaminergic system, particularly genetic defects in critical genes involved in dopamine signaling regulation, have been implicated in ADHD (Li et al., 2006). Genetic mutations involved in serotonin signaling have also been implicated in the etiology of ADHD (Quist et al., 2003). In a machine learning model, serotonin transporter gene SNPs were linked to ADHD (Kautzky et al., 2020).

Arnsten et al. hypothesized in 2009 that a weakness in the prefrontal association cortex characterizes ADHD. This center is particularly dependent on dopaminergic stimulation and adrenergic stimulation for proper function. Stimulants that have been widely used to treat ADHD specifically enhance catecholamine signaling in the prefrontal cortex, increasing expression of both dopamine and norepinephrine (Arnsten, 2009).

Glyphosate has been shown experimentally to cause melatonin deficiency. Glyphosate exposure to rats prenatally and perinatally caused a 43 % reduction in melatonin serum levels measured after pups had matured, likely through epigenetic effects (Cattani et al., 2023). The mechanism might be traced to the shikimate pathway, which glyphosate suppresses in gut microbiota. Melatonin is derived from the amino acid tryptophan, which is one of the three aromatic amino acids synthesized by gut microbes via the shikimate pathway. *In vitro* studies with rat pinealocytes exposed to 50 μm glyphosate showed that glyphosate activated metabotropic glutamate receptors, and that this caused a

reduction in melatonin synthesis (Cattani et al., 2023). Metabotropic glutamate receptor activation suppresses melatonin synthesis in rat pinealocytes (Yamada et al., 1998).

According to a review paper published in 2022, glyphosate exposure can cause many neurotoxic effects, affecting cell development, neurotransmission, and causing neuronal death, and behavioral and motor disorders in humans, rodents, fish, and invertebrates (Costas-Ferreira et al., 2022). All these disruptions could adversely impact brain development, leading to symptoms of ADHD. Based on an extensive literature review, Seneff et al. (Seneff et al., 2024) provided a theoretical argument for how glyphosate's suppression of melatonin synthesis and induction of oxidative stress in the brain through glutamate neuroexcitotoxicity could lead to the neurodevelopmental defects associated with autism. Glyphosate exposure to neurons disrupts synaptic assembly, and glyphosate reduces synaptic protein expression in the hippocampus, likely contributing to cognitive impairment observed in glyphosate-exposed developing rats (Luna et al., 2021).

Through genetic studies, deficiencies in melatonin signaling have been found in association with ADHD. In one experiment, 101 patients with ADHD were compared to 220 controls from the general population. Several damaging mutations were found in patients with ADHD. A specific mutation in N-acetylserotonin O-methyltransferase (ASMT) and another in melatonin receptor 1A (MTNR1A) were detected exclusively in ADHD patients, and both of these mutations were determined to abolish enzyme activity (Chaste et al., 2011). Melatonin therapy has been found to be beneficial for ADHD patients, particularly for treating insomnia (Van der Heijden et al., 2007).

One of the mechanisms involved in the emergence of these diseases is the ability of glyphosate to chelate metals. A study on Danish dairy cattle investigated the mineral composition in the serum of cattle fed feed containing traces of glyphosate in which cobalt (Co) and manganese (Mn) were deficient (Foldager et al., 2021; Krüger et al., 2013; Heymann et al., 2023). According to Samsel and Seneff (Samsel and Seneff, 2015), manganese (Mn) is one of the 14 essential trace elements in the human body, and its deficiency can explain pathologies associated with glyphosate use, notably autism and Alzheimer's disease, as well as attention deficit (Maleki et al., 2023; Polańska et al., 2013; Bartholomew et al., 2024). Another concern is that the glyphosate breakdown product AMPA can leak into groundwater and be transformed into formaldehyde, which is neurotoxic (Bohrer, 2005).

In this study, correlations were found between the use of pesticides and spontaneous abortions in group "B" of *CYP2C9* genotypes (intermediate metabolizers). Swanson et al. (Swanson et al., 2014) showed that the endocrine disrupting properties of glyphosate can lead to reproductive problems, such as infertility, miscarriage, birth defects and changes in sexual development. Glyphosate has also been linked to polycystic ovary syndrome, a major factor in female infertility, through its estrogenic properties (Jozkowiak et al., 2022). Muñoz published a review paper showing that glyphosate has the key characteristics of an endocrine disruptor, based on its observed toxic effects (Muñoz et al., 2021).

Vianna-Jorge et al. (Vianna-Jorge et al., 2004) and Perini et al. (Perini et al., 2008) describe the frequencies of *1, *2 and *3 alleles in the Brazilian population, which was in accord with the frequencies we found in this study. Our results show that normal metabolizers "A" for *CYP2C9* (*1/*1) are more susceptible to developing a disease/symptom in relation to individuals carrying polymorphic variants of metabolizer groups "B" (*1/*2, *1/*3). To date, no metabolizing enzymes (including all CYPs) have been described to metabolize glyphosate in mammals. Secondary glyphosate metabolites generated by soil and intestinal bacteria, as well as glyphosate itself, have high toxicity (Matsuzaki et al., 2023). The next step of this research should include the evaluation of *CYP2C9* polymorphism in the general population to verify a correlation with symptoms/diseases observed in Espírito Santo farmers. Additionally, we would like to evaluate other diseases, particularly neurodevelopmental diseases such as autism, for their possible association with pesticides (Rueda-Ruzafa et al., 2019; Maleki et al., 2023).

The limitations of this study include the lack of complete responses from some participants, which may have impacted the results. The sample of 304 people may not be representative of all agricultural workers in Brazil, limiting the generalization of the findings. Furthermore, information about slow metabolizers (*2 and/or *3) was not included, which makes broader conclusions about their health difficult. Data accuracy depends on participants' self-reporting, which may introduce errors. Although significant correlations have been observed between pesticide exposure and health problems, causality has not been established, requiring further investigation to clarify these links. Finally, other environmental and lifestyle factors that may influence workers' health were not sufficiently controlled or analyzed, which may affect the validity of the results. These limitations indicate the need for further studies that address these issues and provide a more complete understanding of the impacts of pesticide exposure on the health of agricultural workers.

5. Conclusion

We have found that individuals who use pesticides and have *CYP2C9* "A" normal metabolizer (*1/*1) are more likely to develop diseases and symptoms compared to those who carry polymorphic variants "B" (*1/*2, *1/*3). We observed that Espírito Santo farmers exposed to pesticides manifested changes in blood pressure, cardiovascular and kidney diseases, miscarriages and attention deficit, correlating with their *CYP2C9* genotypes. Continued research about the impacts of pesticide uses on global health and the role of genetics in altering susceptibility will help guide new pesticide use policies.

6. Patents

Not applicable.

Supplementary Materials**:** Not applicable.

All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement Not applicable.

Informed Consent Statement: Not applicable.

Ethical approval

This work was approved by the Research Ethics Committee (CEP) of the Federal University of Espírito Santo and under opinion number 3.378.510 and resolutions of the National Health Council n° 466 (of December 12, 2012) and n° 510 (April 7, 2016).

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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.

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Data availability

Our ethics committee asks that we not share sensitive participant data. We are willing to address any inquiries regarding the study methodology or results to the best of our ability. For further information, please contact Débora Dummer Meira (debora.dummer.meira@gmail.com).

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