

Review

Air Pollution, The Nrf2-Ferroptosis Axis, and Neonatal Seizure Susceptibility

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ABSTRACT

Neonatal seizures remain a leading cause of acute neurological morbidity in the newborn period, yet a substantial proportion of cases have no identified structural, infective, or metabolic cause. Air pollution, particularly fine particulate matter of 2.5 micrometers or less in diameter (PM2.5), has recently been implicated as a modifiable environmental contributor to seizure risk across the lifespan, with proposed mechanisms centered on oxidative stress, disrupted iron handling, and regulated cell death. Two convergent bodies of evidence are reviewed here: first, epidemiological and mechanistic work linking PM2.5 exposure to seizure exacerbation through impaired nuclear factor erythroid 2-related factor 2 (Nrf2) signaling; and second, the emerging role of ferroptosis, an iron-dependent form of lipid peroxidation-driven cell death, as a downstream effector of this impairment in hippocampal neurons. Because the fetal and neonatal antioxidant system is developmentally immature and iron handling in the perinatal brain is already in flux, this axis may confer disproportionate vulnerability during gestation and the immediate postnatal period, a population in which direct mechanistic data are still lacking. This review synthesises the current evidence, outlines a plausible developmental extension of the Nrf2-ferroptosis hypothesis to neonatal epileptogenesis, and proposes a research agenda to close the gap between adult mechanistic data and perinatal clinical relevance.

KEYWORDS: Neonatal Seizures, Nrf2, Ferroptosis, PM2.5, Air Pollution.

INTRODUCTION

Seizures occurring in the first 28 days of life are a distinct clinical entity from later-onset epilepsy, both electroclinically and mechanistically, and they carry a disproportionate burden of long-term neurodevelopmental sequelae¹. Established causes include hypoxic-ischaemic encephalopathy, intracranial haemorrhage, infection, and inborn errors of metabolism, but a meaningful fraction of neonatal seizures still occurs without a clearly identified precipitant. Over the past several years, environmental epidemiology has begun to reframe air pollution, and fine particulate matter (PM_{2.5}) in particular, as a plausible and modifiable contributor to seizure risk, largely on the basis of adult and paediatric cohort data^{2,3}.

What has been missing until quite recently is a coherent cellular mechanism connecting inhaled particulate exposure to an altered seizure threshold. Two strands of laboratory work, one on the transcription factor Nrf2 and its role as the master regulator of the cellular antioxidant response, and the other on ferroptosis as an iron-dependent mode of neuronal death, have now been drawn together into a single explanatory framework^{1,4}. This review outlines that framework, then asks a question the existing literature has not yet addressed directly: whether the same pathway operating in the mature or aging brain might also operate, and plausibly with greater consequence, in the developing brain during gestation and the neonatal period.

PM_{2.5} and the Seizure Threshold: What the Epidemiological Evidence Shows

A scoping review of thirty-four epidemiological studies found consistent, if heterogeneous, associations between short-term increases in ambient air pollution and both new-onset seizures and acute exacerbations in people with established epilepsy, alongside a smaller but growing literature on ambient temperature as an independent trigger². A separate narrative review has argued that epilepsy has received comparatively little attention within the air pollution and brain health literature relative to stroke and neurodegenerative disease, despite biologically plausible pathways through inflammation, oxidative stress, and disrupted neurodevelopment, and despite

evidence that prenatal exposure to diesel particulates, carbon black nanoparticles, methylmercury, and dioxin-like compounds interferes with the normal maturation of fast-spiking parvalbumin-positive interneurons, a cell population whose loss is mechanistically tied to network hyperexcitability³. A time-series analysis of hospital seizure presentations against local pollutant and meteorological data reached similar conclusions, reporting associations between particulate and gaseous pollutant levels and short-term fluctuations in seizure-related admissions⁵.

Nrf2: The Cell's Oxidative Stress Sensor

Nrf2 is a transcription factor that, under basal conditions, is held in the cytoplasm by its repressor Keap1 and targeted for degradation. Oxidative or electrophilic stress disrupts this interaction, allowing Nrf2 to translocate to the nucleus and drive transcription of antioxidant and cytoprotective genes through the antioxidant response element, including glutathione peroxidase 4 (GPX4), the cystine-glutamate antiporter subunit SLC7A11, and heme oxygenase-1 (HO-1)^{1,4}. In the context of epilepsy, reduced expression of components of the Nrf2 pathway has been documented in temporal lobe epilepsy and after traumatic brain injury, while pharmacological activation of Nrf2 has been shown to reduce seizure severity, limit microglial activation, and preserve learning and memory in animal models¹.

The relevance to air pollution is that Nrf2 activation is itself triggered by PM_{2.5} exposure, positioning the pathway as a point of convergence between an external environmental insult and an endogenous disease process. Transcriptomic comparisons between individuals exposed to high ambient PM_{2.5} and those with newly diagnosed epilepsy have shown overlapping changes in Nrf2 pathway components, suggesting the two conditions may perturb a shared molecular substrate rather than acting through entirely separate mechanisms¹. Critically, the direction of that perturbation appears to matter: acute or adaptive Nrf2 activation is protective, but chronic or overwhelming particulate exposure has instead been associated with suppression of Nrf2 pathway proteins, tipping the balance toward injury rather than defence¹.

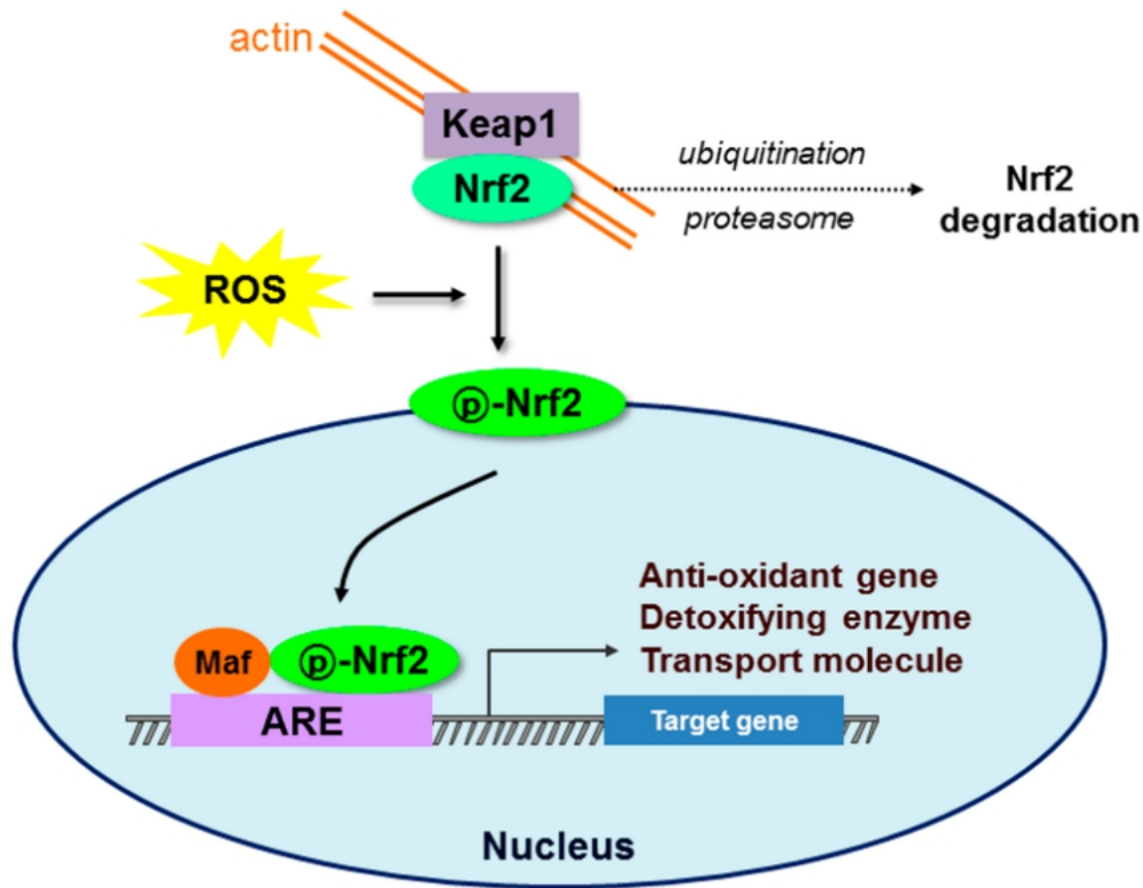


Figure 1: The Nrf2-Keap1-ARE Antioxidant Signaling Pathway under Normal Conditions

Under normal conditions, nuclear erythroid-2 like factor-2 (Nrf2) is constantly ubiquitinated through Kelch-like ECH-associated protein1 (Keap1) and degraded in the proteasome. After exposure to oxidative stress (ROS), Keap1 is inactivated and Nrf2 becomes phosphorylated. Phosphorylated Nrf2 (p-Nrf2) accumulates in the nucleus and binds to antioxidant response element (ARE) sites, subsequently activating many genes including antioxidants, detoxifying enzymes, and transport molecules.

[Adapted from Oh and Jun¹⁰]

Ferroptosis as the Downstream Effector

Ferroptosis is a form of regulated cell death driven by iron-catalysed lipid peroxidation, distinct from apoptosis or necrosis, and dependent on the balance between pro-oxidant iron flux and the antioxidant capacity of the GPX4-glutathione system⁴. Because Nrf2 transcriptionally regulates several nodes of this system, including GPX4, SLC7A11, and proteins governing cellular iron storage and export, loss of Nrf2 activity removes a key brake on ferroptotic vulnerability⁴.

Direct evidence that PM2.5 induces ferroptosis in neural tissue has accumulated rapidly. In murine hippocampal HT22 cells, PM2.5 exposure increased intracellular iron content and lipid peroxidation while disturbing the expression of iron-handling

genes, with the resulting neurotoxicity partially reversible by ferroptosis inhibitors⁶. In a combined clinical and animal study, patients with seizures living in areas of high ambient PM2.5 showed greater disturbance of iron homeostasis and the Nrf2-dependent ferroptosis pathway than those in less polluted areas, and PM2.5-exposed epileptic mice showed worsened seizure severity and cognitive performance on the Morris water maze alongside electroencephalographic and histological evidence of hippocampal ferroptosis⁷. A broader review of pollutant-induced ferroptosis situates these hippocampal findings within a wider pattern in which PM2.5 drives ferroptotic injury across multiple organ systems through convergent disruption of the Nrf2-SLC7A11-GPX4 axis⁴.

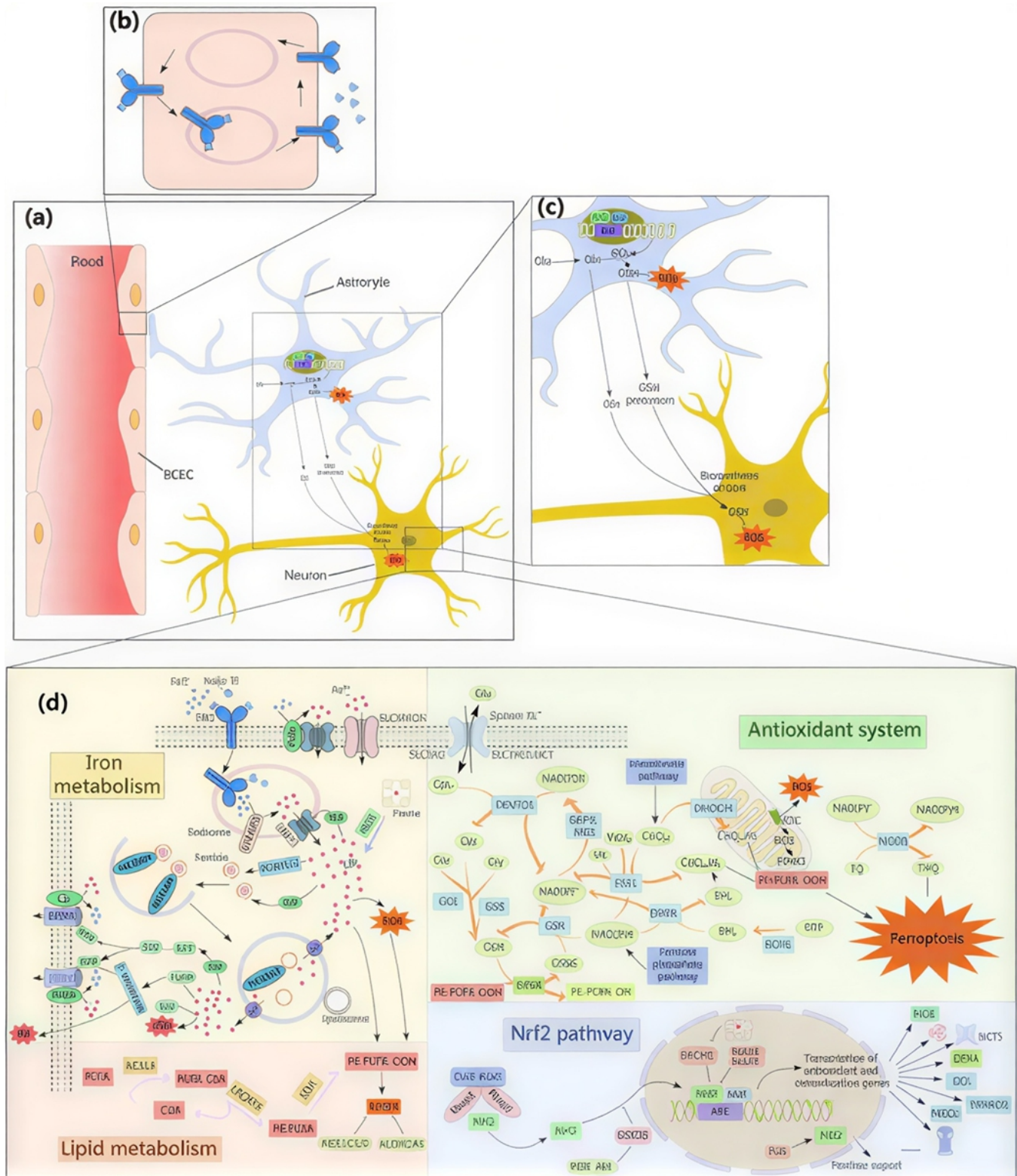


Figure 2: Regulation of Iron Homeostasis and Ferroptosis by Nrf2 in the Context of Neurodegenerative Diseases

- (a) Neurogliovascular unit (BMECs, astrocytes and neurons) are the main players of iron transport across the BBB. The brain parenchyma iron homeostasis is maintained through astrocyte-mediated uptake and neuronal delivery, and the limiting of the harmful effects of the excess iron by astrocytes.
- (b) Iron in the circulation is bound by Tfs and reaches BMECs via Tf/TfR1. Iron is delivered to parenchyma by endocytosis.
- (c) Through the generation of antioxidant molecules, mainly the supply of glutathione (GSH) precursors, activation of antioxidant defenses by Nrf2 in astrocytes leads to neuronal protection against oxidative stress.
- (d) The iron uptake through Tf-TfR1 system and the consequent reduction of Fe^{3+} to Fe^{2+} in neurons contributes to the formation of the labile pool of iron. This pool is mainly under the control of ferritin, NCOA4-ferritinophagy, and FPN1-export of iron. Increased ROS and PUFA peroxidation by an excessive Fe^{2+} lead to ferroptosis. ACSL4, LPCAT3 and the lipoxygenases are among the lipid peroxidation enhancers responsible for driving ferroptosis while GSH, GPX4, FSP1, CoQ10, DHODH, CoQ10H and GCH1, BH4 pathways counteract ferroptosis. Nrf2 dependent antioxidant and cytoprotective genes are triggered by the Keap1, Nrf2, ARE pathway under oxidative stress conditions, thereby limiting the iron-induced oxidative damage and ferroptosis.

[Adapted from Xiang *et al.*¹¹]

Extending the Model to the Perinatal and Neonatal Period

None of the mechanistic studies cited above were conducted in neonatal or fetal tissue, and this is the central gap this review seeks to make explicit rather than to paper over. Several lines of indirect evidence nonetheless make a perinatal extension of the Nrf2-ferroptosis hypothesis plausible, and arguably urgent. First, PM2.5 and its carbon-based components are able to cross the placental barrier and have been detected directly on the fetal side of the human placenta, establishing a physical route of exposure during gestation rather than a purely maternal one⁸. Second, gestational PM2.5 exposure in rodent models produces hippocampal neurodevelopmental impairment in offspring, including reduced neurogenesis, increased apoptotic markers, and elevated neuroinflammatory signaling, changes that overlap substantially with the injury pattern described in ferroptosis-mediated models⁹. Third, the fetal and neonatal antioxidant system, including glutathione synthesis capacity and Nrf2-responsive gene expression, is developmentally immature relative to the adult system, which would be expected to lower the exposure threshold at which pro-oxidant insults overwhelm cytoprotective capacity.

Iron handling in the perinatal brain adds a further layer of plausibility. The third trimester and early postnatal period are characterised by active iron accretion to support myelination and oxidative metabolism, meaning that regional iron availability in the neonatal brain is, if anything, higher relative to antioxidant buffering capacity than in the mature brain. A pathway whose central toxic mechanism is iron-catalysed lipid peroxidation would be expected to find fertile ground under these conditions. Several of the exposures already linked to disrupted interneuron development and network hyperexcitability, including diesel particulates and other combustion-derived pollutants, are also established inducers of the Nrf2-ferroptosis cascade in non-neural tissue, raising the possibility that interneuronopathy and ferroptotic injury are not

competing explanations for pollutant-associated seizure risk but two visible faces of the same underlying redox failure³.

Sex-dependent susceptibility is a further recurring theme worth carrying into any neonatal-focused review. Male fetuses tend to accumulate higher body burdens of several persistent pollutant classes, and gestational PM2.5 exposure produces sex-divergent glial and cognitive outcomes in animal models, with male offspring more often showing microglial dysfunction and female offspring showing transient astroglial reactivity⁹. Whether this pattern holds for ferroptotic markers specifically in the neonatal hippocampus has not, to our knowledge, been tested.

Gaps in the Evidence and a Proposed Research Agenda

Three gaps stand out as priorities for future work. The first is direct mechanistic confirmation: no published study has yet measured Nrf2 pathway activity or ferroptotic markers, such as tissue GPX4, SLC7A11, malondialdehyde, or labile iron, in fetal or neonatal brain tissue following gestational or early postnatal PM2.5 exposure, in either animal models or archived human material. The second is temporal specificity: because Nrf2 activation is protective at physiological levels of stress and only becomes pathological under sustained or high-dose exposure, dose-response and timing studies are needed to establish whether typical ambient exposure in high-pollution settings, as opposed to experimentally concentrated PM2.5, is sufficient to tip the balance toward ferroptotic injury in the developing brain. The third is translational relevance to regions with the highest ambient PM2.5 burden and the least epidemiological surveillance of neonatal seizure outcomes, where household and ambient particulate exposure, heavy-metal co-exposure, and limited access to continuous EEG monitoring may combine to produce a population at particularly high and currently invisible risk.

CONCLUSION

The Nrf2-ferroptosis axis offers one of the more mechanistically coherent explanations to have emerged for how an entirely modifiable environmental exposure, fine particulate air pollution, might lower the seizure threshold in the brain. The evidence base for this pathway is currently strongest in adult and juvenile animal models and in epidemiological data drawn from established epilepsy populations. Extending it to the neonatal period rests, for now, on developmental plausibility rather than direct proof: an immature antioxidant system, an active perinatal iron pool, a documented ability of particulate matter to cross the placenta, and overlapping injury patterns in gestationally exposed rodent hippocampus. Testing this extension directly, in fetal and neonatal tissue and in populations with high ambient exposure, is a tractable and clinically important next step for research into the environmental contributors to neonatal seizures.

DECLARATIONS

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REFERENCES

1. Sri Hari A, Metcalf CS. Environmental Pollutants and Epilepsy: Is It Nrf or Nothing? *Epilepsy Curr.* 2024 Nov 12;25(1):76-78. doi: 10.1177/15357597241293295. PMID: 39545018; PMCID: PMC11558652.
2. Sharma R, Schinasi LH, Lee BK, Weuve J, Weisskopf MG, Sheffield PE, Clougherty JE. Air Pollution and Temperature in Seizures and Epilepsy: A Scoping Review of Epidemiological Studies. *Curr Environ Health Rep.* 2024 Dec 10;12(1):1. doi: 10.1007/s40572-024-00466-3. PMID: 39656387; PMCID: PMC11631820.
3. Jareonsettasin P, Ji JS, Zhou X, Ding D, Sander JW; SdHIELD (Social determinants of Health In EpiLeptic Disorders) Research Group. The role of air pollution in epilepsy: a better understanding is needed. *Arq Neuropsiquiatr.* 2025 Jun;83(6):1-12. doi: 10.1055/s-0045-1809663. Epub 2025 Jul 2. PMID: 40602803; PMCID: PMC12221694.
4. Gong FH, Liu L, Wang X, Xiang Q, Yi X, Jiang DS. Ferroptosis induced by environmental pollutants and its health implications. *Cell Death Discov.* 2025 Jan 24;11(1):20. doi: 10.1038/s41420-025-02305-2. PMID: 39856053; PMCID: PMC11759704.
5. Llobet C, Martinez-Alonso M, Justríbó E, Ortet J, Yuguero O. Seizures, climate and pollution: is there evidence of an association? *Front Public Health.* 2025 Nov 13;13:1708538. doi: 10.3389/fpubh.2025.1708538. PMID: 41323586; PMCID: PMC12658456.
6. Liu S, Wang A, Zhou D, Zhai X, Ding L, Tian L, Zhang Y, Wang J, Xin L. PM_{2.5} induce neurotoxicity via iron overload and redox imbalance mediated-ferroptosis in HT22 cells. *J Environ Sci Health A Tox Hazard Subst Environ Eng.* 2024;59(2):55-63. doi: 10.1080/10934529.2024.2331938. Epub 2024 Mar 26. PMID: 38532551.
7. Mei H, Wu D, Yong Z, Cao Y, Chang Y, Liang J, Jiang X, Xu H, Yang J, Shi X, Xie R, Zhao W, Wu Y, Liu Y. PM_{2.5} exposure exacerbates seizure symptoms and cognitive dysfunction by disrupting iron metabolism and the Nrf2-mediated ferroptosis pathway. *Sci Total Environ.* 2024 Feb 1;910:168578. doi: 10.1016/j.scitotenv.2023.168578. Epub 2023 Nov 18. PMID: 37981141.
8. Bové H, Bongaerts E, Slenders E, Bijmens EM, Saenen ND, Gyselaers W, et al. Ambient black carbon particles reach the fetal side of human placenta. *Nat Commun.* 2019 Sep 17;10(1):3866. doi:10.1038/s41467-019-11654-3.

9. Zheng X, Wang X, Wang T, Zhang H, Wu H, Zhang C, Yu L, Guan Y. Gestational Exposure to Particulate Matter 2.5 (PM_{2.5}) Leads to Spatial Memory Dysfunction and Neurodevelopmental Impairment in Hippocampus of Mice Offspring. *Front Neurosci.* 2019 Jan 7;12:1000. doi: 10.3389/fnins.2018.01000. PMID: 30666183; PMCID: PMC6330280.
10. Oh YS, Jun HS. Effects of Glucagon-Like Peptide-1 on Oxidative Stress and Nrf2 Signaling. *Int J Mol Sci.* 2017 Dec 22;19(1):26. doi: 10.3390/ijms19010026. PMID: 29271910; PMCID: PMC5795977.
11. Xiang Y, Song X, Long D. Ferroptosis regulation through Nrf2 and implications for neurodegenerative diseases. *Arch Toxicol.* 2024 Mar;98(3):579-615. doi: 10.1007/s00204-023-03660-8. Epub 2024 Jan 24. PMID: 38265475; PMCID: PMC10861688.