

The current evidence of the effects of mercury exposure on hypertension

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Hypertension

- Hypertension (high blood pressure), is one of the most common chronic conditions
- The World Health Organization estimated 1.28 billion adults aged 30-79 years have hypertension.

Modifiable risk factors:

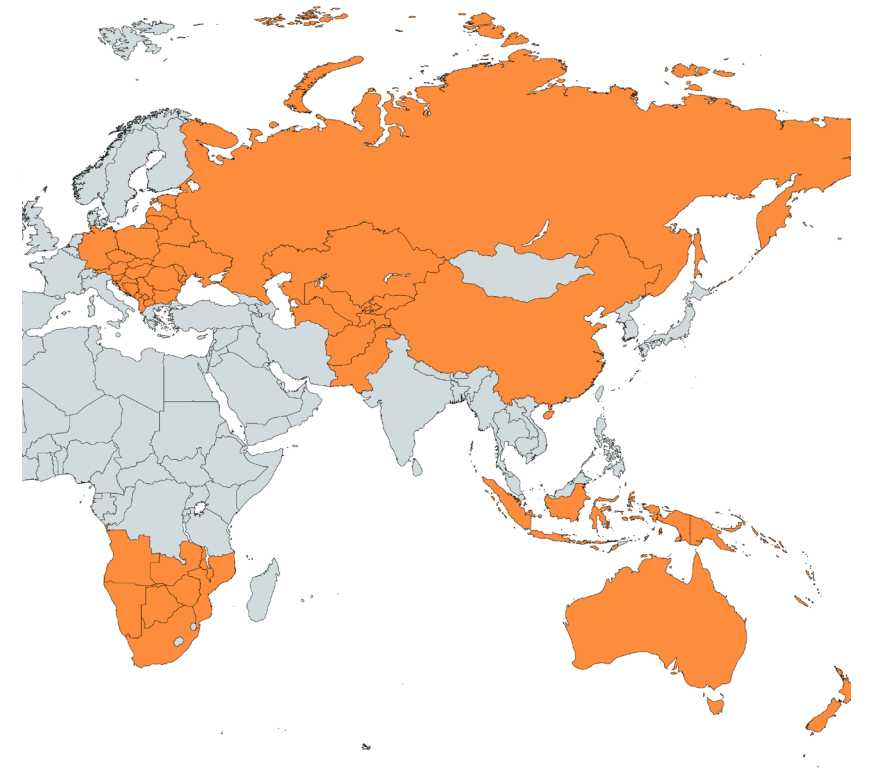
- Unhealthy diet
- Physical inactivity
- Consumption of tobacco and alcohol
- Obesity

Non-modifiable risk factors:

- A family history of hypertension
- 65 years of age or older
- Co-existing diseases

Exposure to environmental chemicals may also play an important role

- Hypertension prevalence is highest throughout central and eastern Europe, central Asia, Oceania, southern Africa
- Many of these areas that have a prevalence of hypertension also have fish and seafood as a staple food



Effect of Mercury (Hg) on hypertension

- Mercury (Hg) is a chemical pollutant of human health concern worldwide.
- Although the health impacts of Hg have been primarily focused on its neurotoxicity, there is increasing evidence that exposure to Hg is a risk factor for hypertension

Fish Consumption, Mercury Exposure, and Heart Diseases

Hing Man Chan; Grace M Egeland
Nutrition Reviews; Feb 2004; 62, 2; Research Library Core
pg. 68

Fish Consumption, Mercury Exposure, and Heart Diseases

Review

A Section 508-conformant HTML version of this article
is available at <https://doi.org/10.1289/EHP2863>.

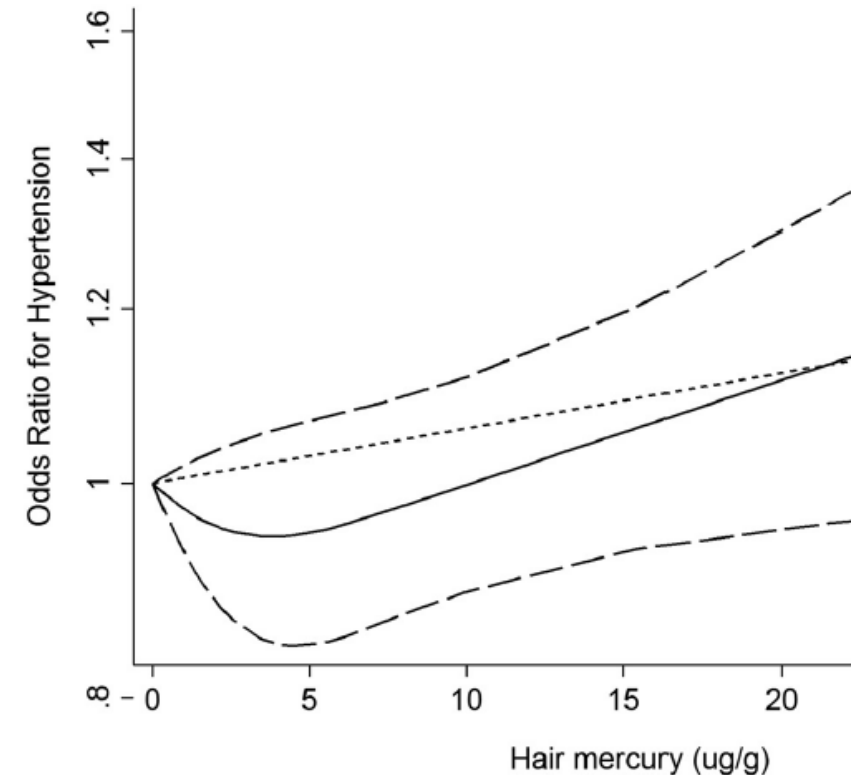
Mercury Exposure, Blood Pressure, and Hypertension: A Systematic Review and Dose-response Meta-analysis

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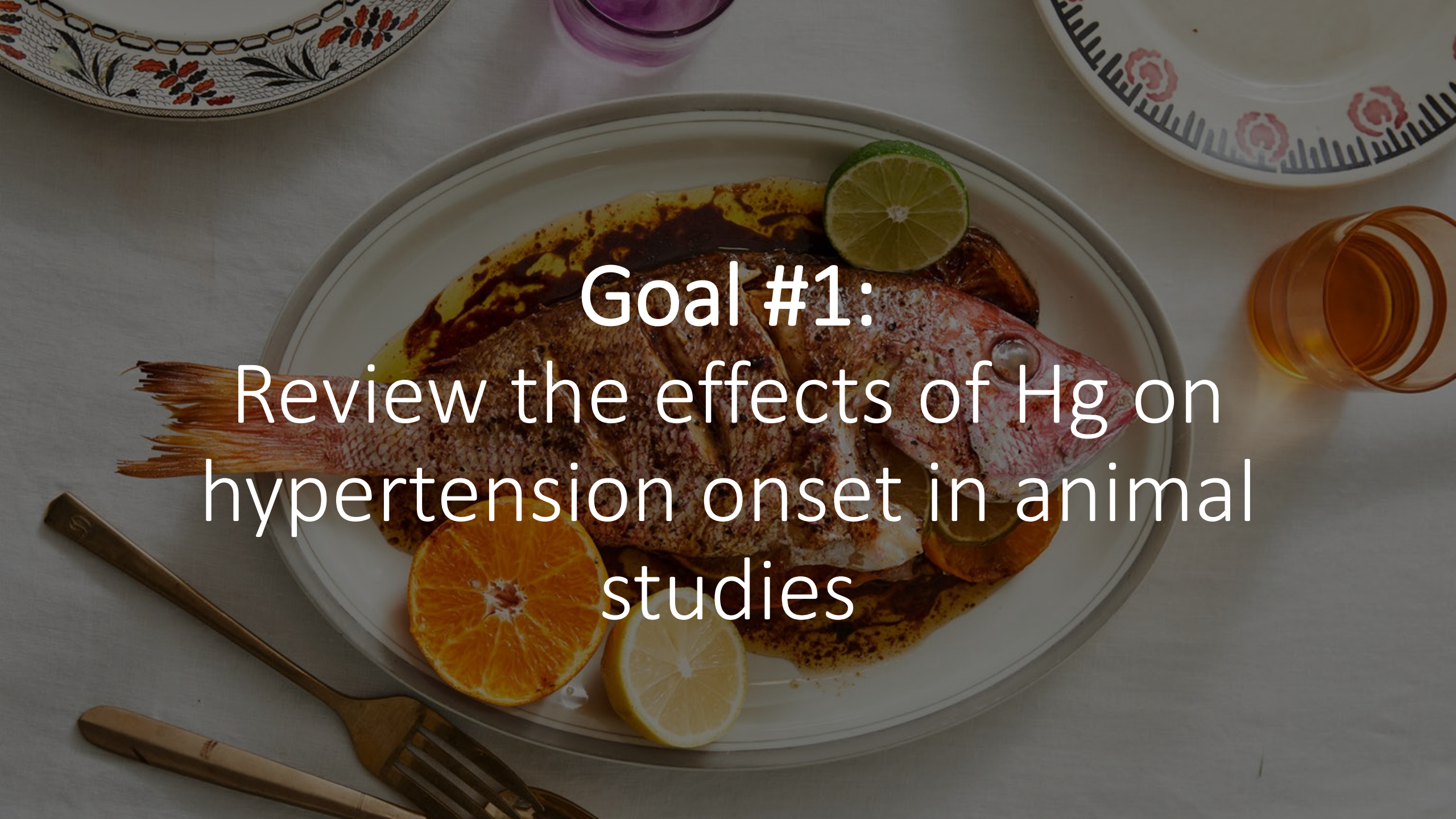
29 studies showed a significant positive association between Hg and blood pressure

- Meta-analysis of 9 studies with 55,000 participants from 17 countries
- Non-linear relationship between Hair Hg concentrations and Odd Ratio for hypertension with a threshold of 2-3 ug/g
- Hair Hg > 2 ug/g is associated with a 59% increase in Odd Ratio for hypertension with an increase of 2.2 mm Hg (SBP) and 1.24 mm Hg (DBP)



Goals for this review paper

- We aim to:
 - Review the effects of Hg on hypertension onset in animal studies
 - Summarize the potential underlying mechanisms that contribute to hypertension onset
 - Update the latest epidemiological evidence between Hg exposure and hypertension



Goal #1:
Review the effects of Hg on
hypertension onset in animal
studies

Hypertension in rodents exposed to inorganic Hg

Reference	Species	Exposure route	Form	Outcome
Carmignani et al. 1983	Sprague-Dawley rats	Drinking water	Inorganic	No significant change in BP
Machado et al. 2007	Wistar rats	Intravenous injection	Inorganic	SBP/DBP increase
Wildemann et al. 2015a	Wistar rats	Drinking water	Inorganic	No significant change in BP
Wildemann et al. 2015b	Wistar rats	Drinking water	Inorganic	No significant change in BP
Wildemann et al. 2016	Wistar rats	Drinking water	Inorganic	Increased DBP
Simões et al. 2016	Wistar rats	Intramuscular injections	Inorganic	Diastolic arterial BP increase
Rizzetti et al. 2017b	Wistar rats	Intramuscular injections	Inorganic	SBP increase after 60 days only
Vassallo et al. 2019	Spontaneously hypertensive rats (Wistar rats (control))	Intramuscular injections	Inorganic	SBP increase in spontaneously hypertensive rats only
Fardin et al. 2020	Spontaneously hypertensive rats	Intramuscular injections	Inorganic	SBP increase
Simões et al. 2020	Spontaneously hypertensive rats (Wistar rats (control))	Intramuscular injections	Inorganic	SBP increase in spontaneously hypertensive rats only
Schreider et al. 2021	Wistar rats (female)	Intramuscular injections	Inorganic	No significant change in SBP
Bello et al. 2023	Wistar rats	Intramuscular injections	Inorganic	SBP/DBP increase

8/12 studies show that inorganic Hg causes increased blood pressure in rodent models

Hypertension in rodents exposed to MeHg

Reference	Species	Exposure route	Form	Outcome
Wakita 1987	Wistar rats	Subcutaneous injection Oral gavage	Methyl	SBP increase following cessation
Grotto et al. 2009	Wistar rats	Oral gavage	Methyl	SBP increase
Grotto et al. 2011	Wistar rats	Oral	Methyl	SBP increase
Wildemann et al. 2015a	Wistar rats	Drinking water	Methyl	SBP/DBP increase
Wildemann et al. 2015b	Wistar rats	Drinking water	Methyl	SBP increase
Wildemann et al. 2016	Wistar rats	Drinking water	Methyl	SBP/DBP increase

6/6 studies show that MeHg causes increased blood pressure in rodent models

Hypertension in spontaneously hypertensive rats

Reference	Species	Exposure route	Form	Outcome
Vassallo et al. 2019	Spontaneously hypertensive rats (Wistar rats (control))	Intramuscular injections	Inorganic	SBP increase in spontaneously hypertensive rats only
Fardin et al. 2020	Spontaneously hypertensive rats	Intramuscular injections	Inorganic	SBP increase
Simões et al. 2020	Spontaneously hypertensive rats (Wistar rats (control))	Intramuscular injections	Inorganic	SBP increase in spontaneously hypertensive rats only

3/3 studies show that inorganic Hg causes increased blood pressure in spontaneously hypertensive rat models

Summary of Animal Studies

- There is a strong cause-effect relationship between MeHg and hypertension onset (6/6 studies finding an effect)
- There is a moderate cause-effect relationship between inorganic Hg and hypertension onset (8/12 studies finding an effect)
- Spontaneous hypertensive rats are more affected by Hg exposure than normotensive rats



A top-down view of a white oval plate containing a whole cooked fish, likely a sea bream, garnished with slices of lime, orange, and lemon. The fish is served on a bed of yellowish sauce. The plate is set on a white tablecloth. In the background, there are other plates with decorative borders and a glass of orange juice. The text is overlaid on the center of the image.

Goal #2:
Summarize potential underlying mechanisms that contribute to hypertension onset

Identifying studies which investigated the effect of Hg on the cardiovascular system

In total we found 36 *in vitro* and *in vivo* studies reporting the effect of Hg on the cardiovascular system

15 studies found mitochondrial disruption or oxidative stress following Hg exposure

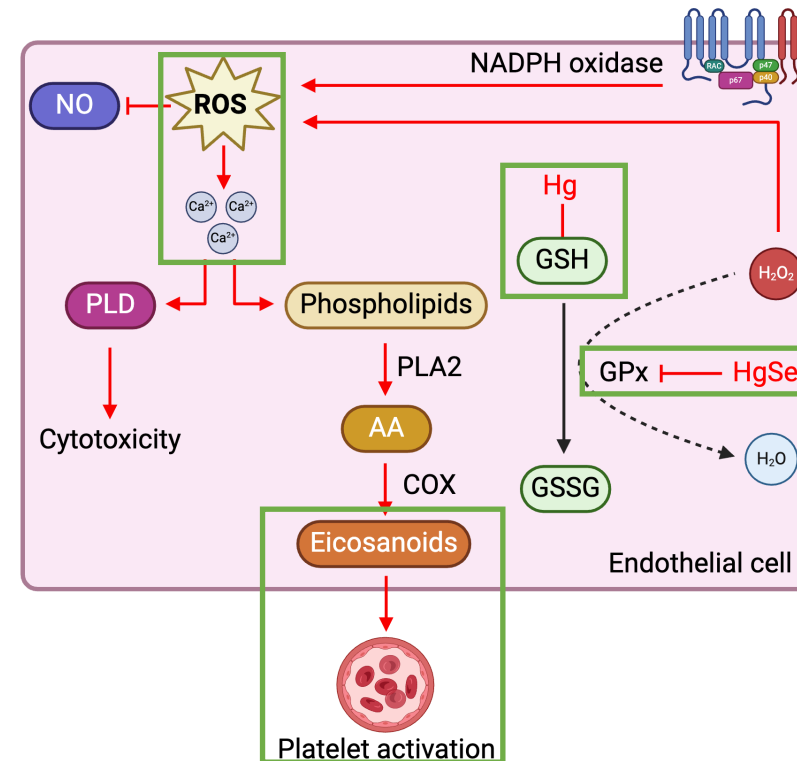
15 studies identified endothelial dysfunction

10 studies found a link to inflammation

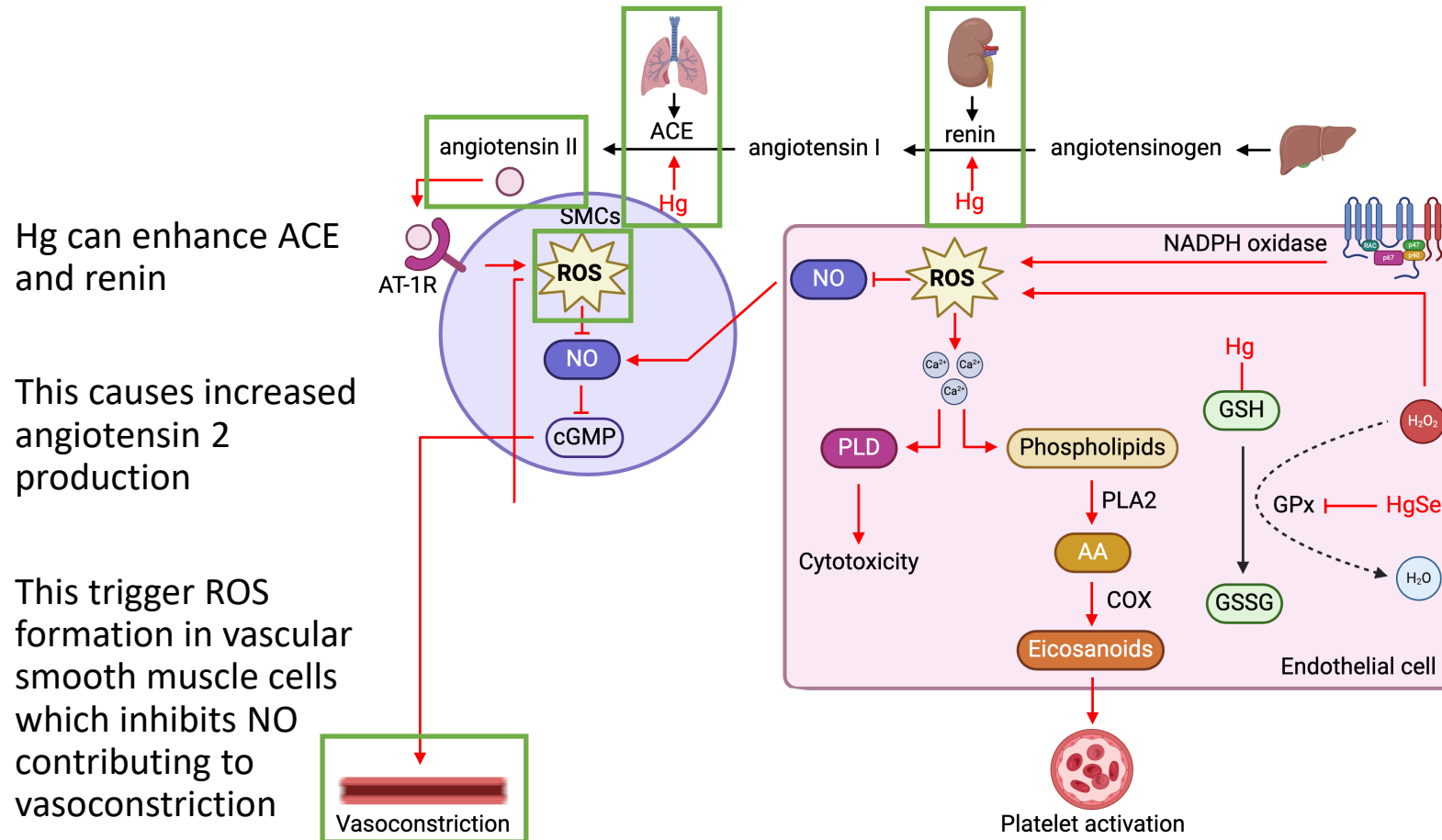
5 studies found a link to lipid peroxidation

Endothelial dysfunction

- In vascular endothelial cells Hg forms complexes with GSH and selenium inhibiting ROS reduction
- Intracellular Ca^{2+} caused by increased ROS has been shown to lead to eicosanoid production.
- This ultimately results in in platelet activation which causes vasoconstriction and ultimately elevates blood pressure



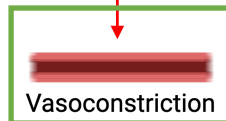
Renin-angiotensin system



Hg can enhance ACE and renin

This causes increased angiotensin 2 production

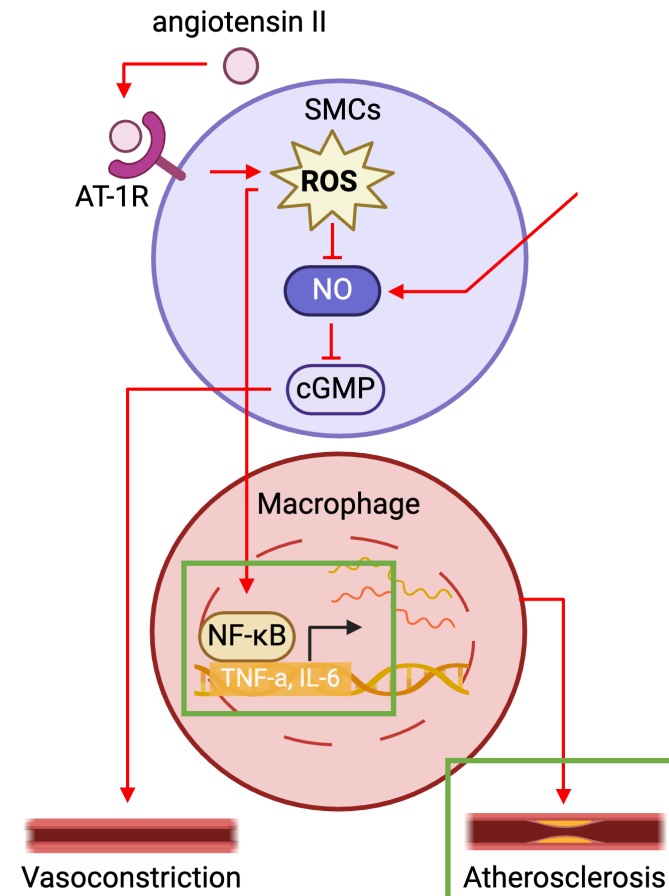
This trigger ROS formation in vascular smooth muscle cells which inhibits NO contributing to vasoconstriction



Inflammation

In macrophages ROS production can trigger NF- κ B leading to transcription of pro-inflammatory cytokines and atherosclerosis.

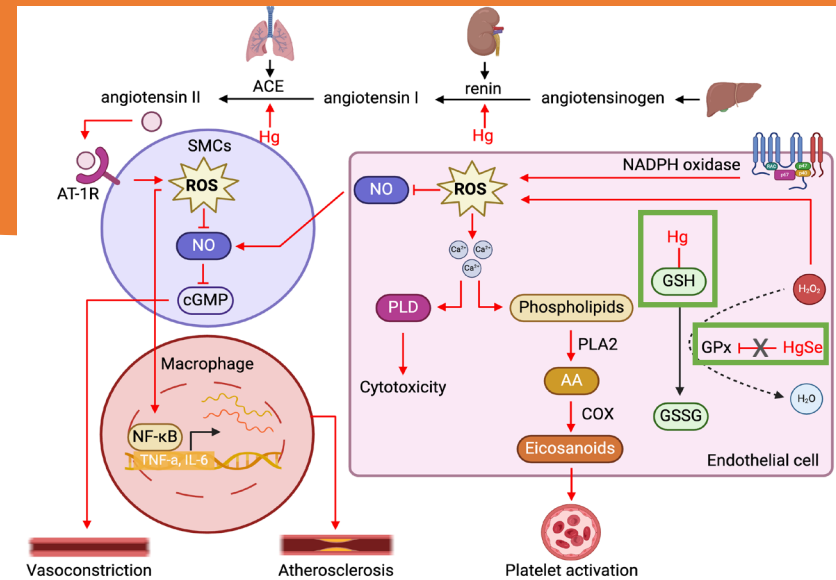
Atherosclerosis is the thickening or hardening of arteries where plaques, which consist of cholesterol and other substances, form in the arteries. This results in reduced blood flow which could potentially contribute to or be caused by hypertension development



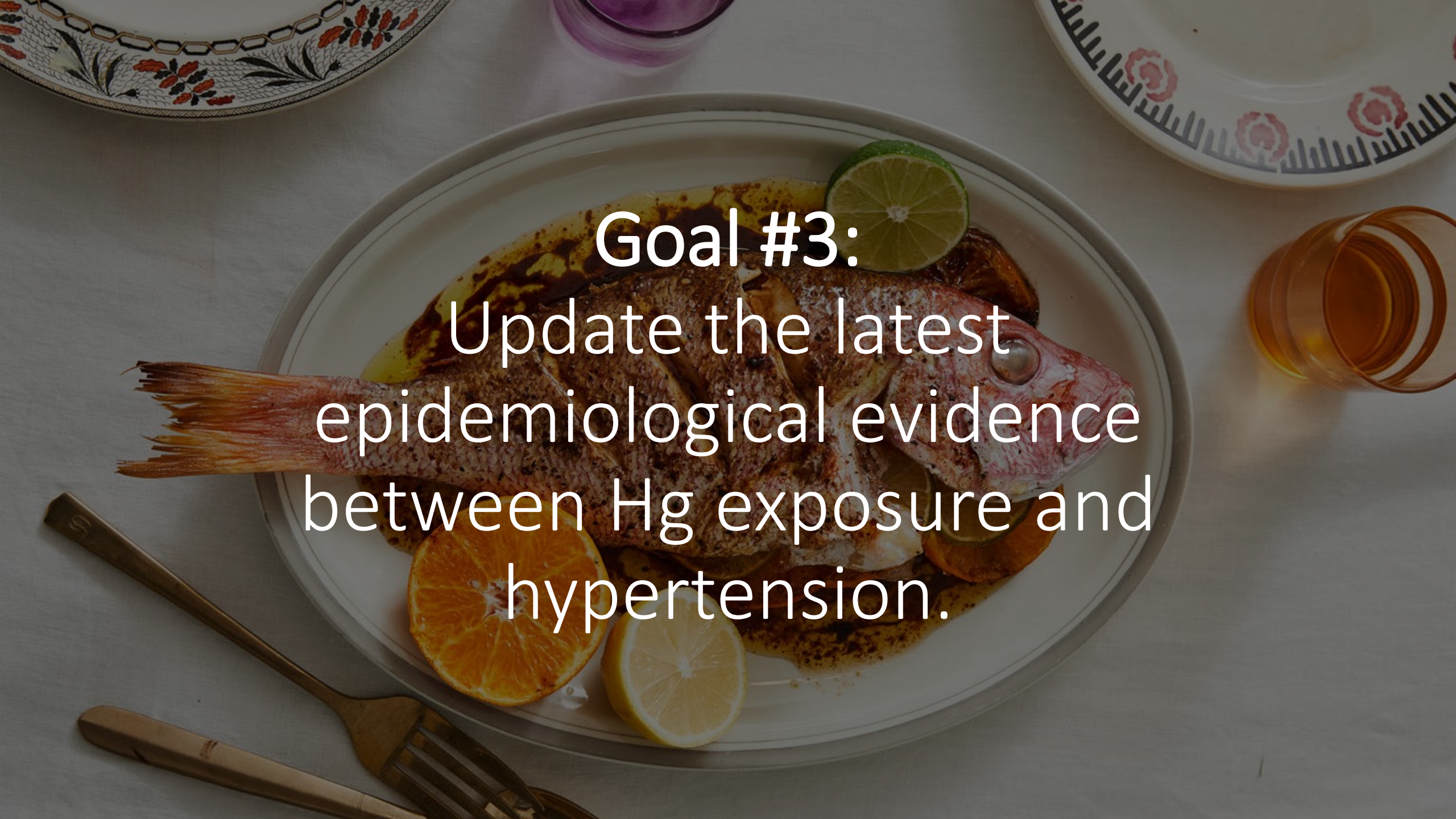
Summary

We have identified a mechanism for Hg exposure causing ROS in various cell types, leading to cellular dysfunction, including endothelial dysfunction, inflammation, and lipid peroxidation.

We propose an Adverse Outcome Pathway with a key initiating event thiol depletion which ultimately causes increased ROS and oxidative stress

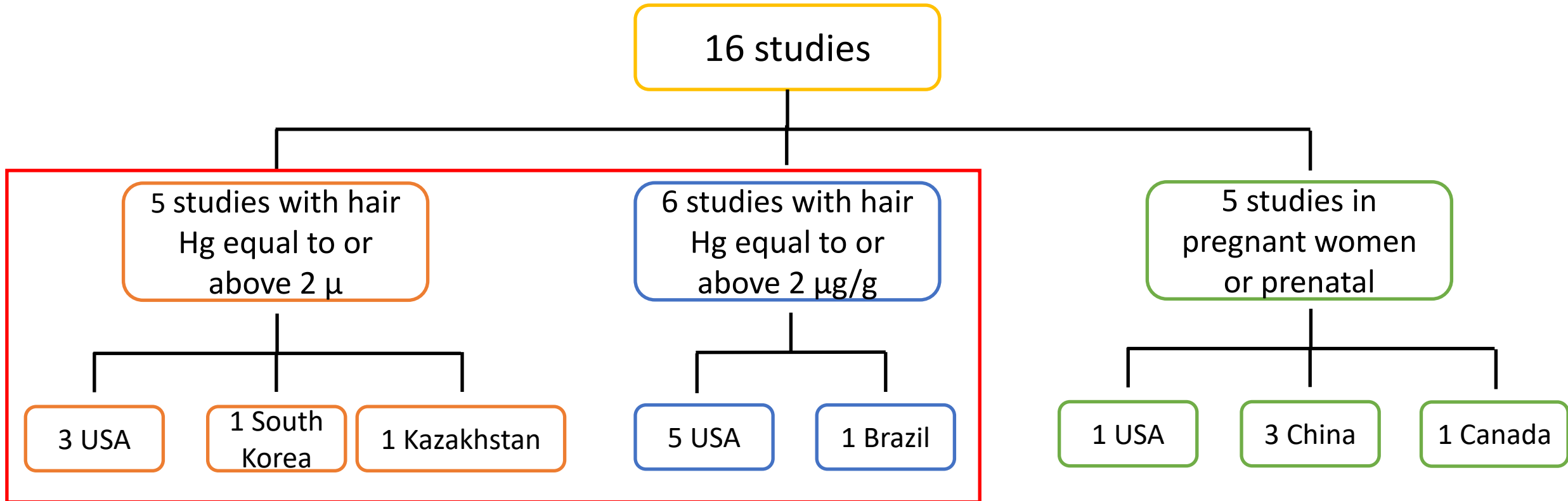


Level of Organization	AOP Diagram	
Molecular	MIE	Thiol sequestering
Cellular/Tissues	KE1	ROS overproduction
	KE2	Increased renin and ACE
	KE3	Increased angiotensin 2
	KE4	Decreased NO production
Organ/Organ System	KE5	Vasoconstriction
Individual	AO	Hypertension

A top-down view of a white oval plate containing a whole cooked fish, likely a sea bream, garnished with slices of lime and orange. The fish is served on a white tablecloth. In the background, there are other plates with decorative borders and a glass of orange juice. The text is overlaid on the fish.

Goal #3:
Update the latest
epidemiological evidence
between Hg exposure and
hypertension.

We found 16 studies 2018-2024



Studies with hair Hg equal to or above 2 $\mu\text{g/g}$

5 studies with hair Hg equal to or above 2 μ

Reference	Population	Exposure route	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Outcome
Bulka et al. 2019	USA	General population	54.8	52.7	1088	Urine ($\mu\text{g/h}$)	Inorganic	HPT
Kim et al. 2019	South Korea	Polluted regions	≈ 65	31.6	7822	Blood ($\mu\text{g/L}$)	Total	HPT
Shinetova et al. 2020	Kazakhstan	Polluted regions	54	56	84	Urine ($\mu\text{g/L}$)	Inorganic	HPT
Farzan et al. 2021	USA	General population	5.5	48.6	395	Urine ($\mu\text{g/L}$)	Inorganic	BP
Wang et al. 2021	USA	General population	49.4	0	1317	Urine ($\mu\text{g/L}$)	Inorganic	BP

These five studies all reported a positive association between Hg and either SPB/DBP or hypertension

Studies with hair Hg below 2 µg/g

6 studies with hair Hg equal to or above 2 µg/g

Reference	Population	Exposure route	Mean age or age range (years)	Male (%)	N	Biomarker (unit)	Form	Outcome
Yao et al. 2020	USA	General population	45	50.9	7076	Blood (µg/L)	Total/Methyl	BP
Desai et al. 2021	USA	General population	12.5	49.8	1642	Blood (µg/L)	Total	BP
Xu et al. 2021	USA	Occupational population	>30	74	957	Blood (µg/L)	Total	HPT, BP
Guo et al. 2022	USA	General population	≥20	49.6	8371	Blood (µg/L)	Total	BP
Nunes et al. 2022	Brazil	General population	59	42	112	Urine (µg/g creatinine)	Inorganic	BP
Tang et al. 2022	USA	Asian population	>20	47.3	1422	Blood (µg/L)	Total/Methyl	HPT, BP

Studies that reported no or inverse association between Hg and hypertension
One study reported a positive association in a subgroup of participants

Summary

- The findings of the 11 additional studies in adult reconfirmed our conclusion on the overall association between Hg exposure and hypertension
- **Hair Hg 2 µg/g** was a reasonable cut-off for the association between Hg exposure, BP, and hypertension

A top-down view of a white oval plate containing a whole cooked fish, likely a sea bream, with a golden-brown crust. The fish is garnished with several slices of citrus fruit: a lime slice at the top right, a large orange slice at the bottom left, and a lemon slice at the bottom center. The plate is set on a white tablecloth. In the background, there are other plates with decorative borders and a glass of amber beer. In the foreground, a wooden fork and knife are visible.

Significance and conclusion

Conclusion and Significance

Conclusive evidence on the cause-effect of Hg exposure and hypertension in animal studies, including the mechanistic studies that provide supportive evidence on this association

Strong evidence from epidemiological studies shows that Hg exposure is associated with an increased risk of hypertension with a dose-response relationship

However, the association between Hg exposure and BP is mixed at lower exposure levels

The current evidence continues to support the **2 µg/g hair Hg** or equivalent as the cut-off level for public health regulation for male adults and women older than child-bearing age