

# Hypertensive Disorders of Pregnancy and Environmental Exposures: Disease as a Toxicology Focus

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# Overview of hypertensive disorders of pregnancy

## What are hypertensive disorders of pregnancy (HDP)?



- **Gestational hypertension**
  - Hypertension after 20 weeks gestation
- **Preeclampsia/eclampsia**
  - Hypertension after 20 weeks gestation
  - Proteinuria
  - Multiorgan dysfunction (liver, kidney)
  - Seizures (eclampsia)
- **Chronic hypertension**
  - Hypertension that predates pregnancy that continues through pregnancy
- **Chronic hypertension with superimposed preeclampsia**
  - Hypertension that predates pregnancy that continues though pregnancy
  - Proteinuria, multiorgan dysfunction



# Overview of hypertensive disorders of pregnancy

## Global impact

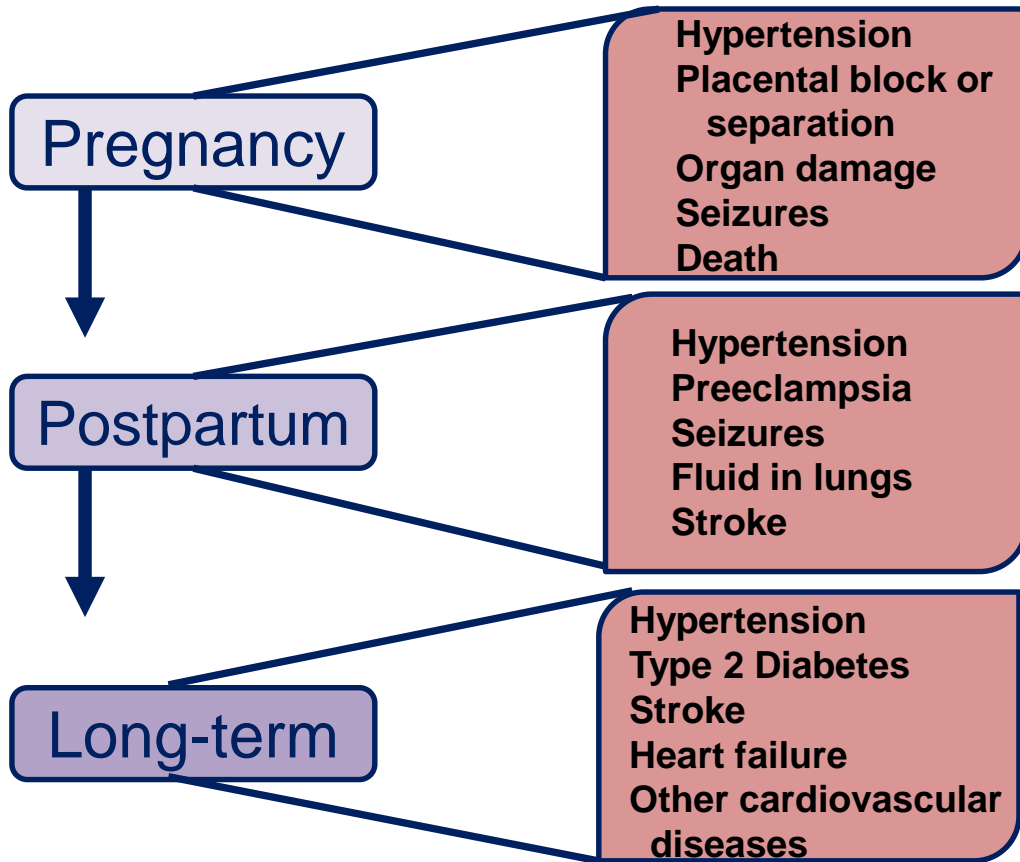


- Affects up to 10% of pregnancies worldwide
- A leading cause of maternal and fetal morbidity and mortality worldwide
- Preeclampsia is the most common form of hypertension during pregnancy
- Preeclampsia: 60,000+ maternal deaths and 500,000 fetal deaths each year

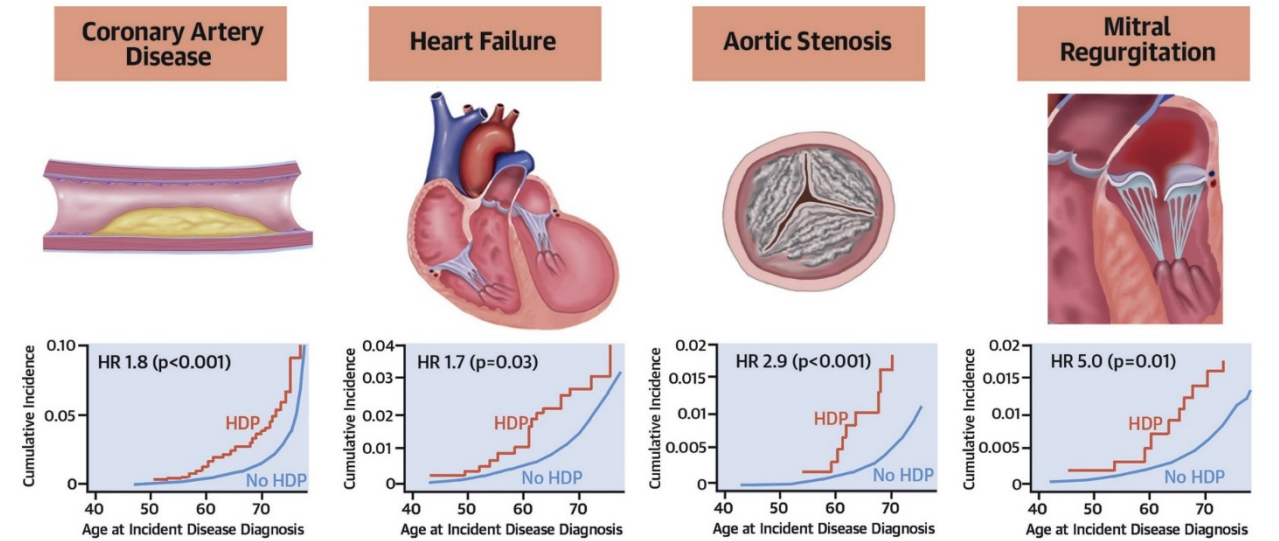


# Hypertensive disorders of pregnancy health effects

## Short- and long-term effects on maternal health



### CENTRAL ILLUSTRATION: Hypertensive Disorders of Pregnancy Are Associated With Long-Term Risk of Diverse Cardiovascular Diseases

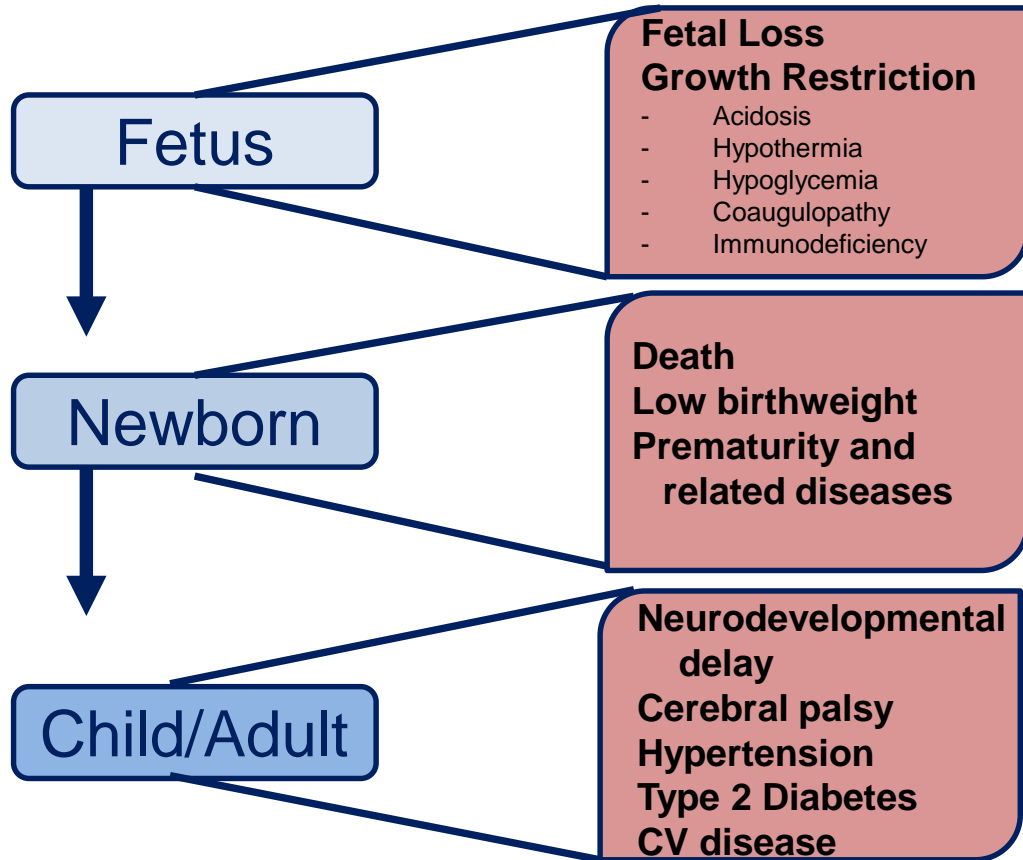


Honigberg, M.C. et al. J Am Coll Cardiol. 2019;74(22):2743-54.



# Hypertensive disorders of pregnancy health effects

## Short- and long-term effects on offspring health



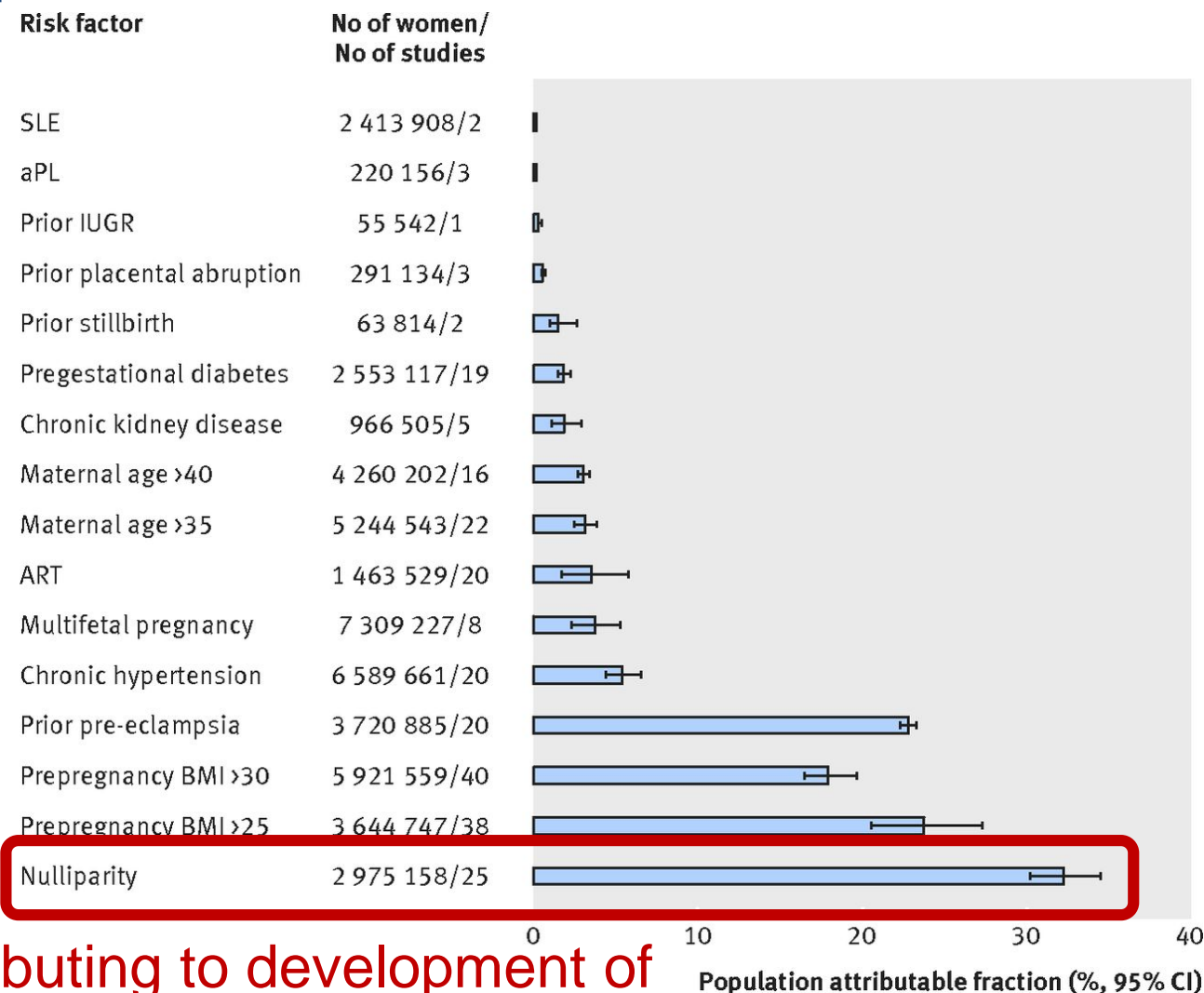




# Unknown risk factors for hypertension in pregnancy

## What is the role of the environment?

- Most HDP cases (up to 80%\*) are in first pregnancies with no other known risk factors
- Known risk factors explain only a fraction of cases
  - Co-morbidities (obesity, diabetes, hypertension)
  - Age (over 40)
  - Multifetal pregnancy



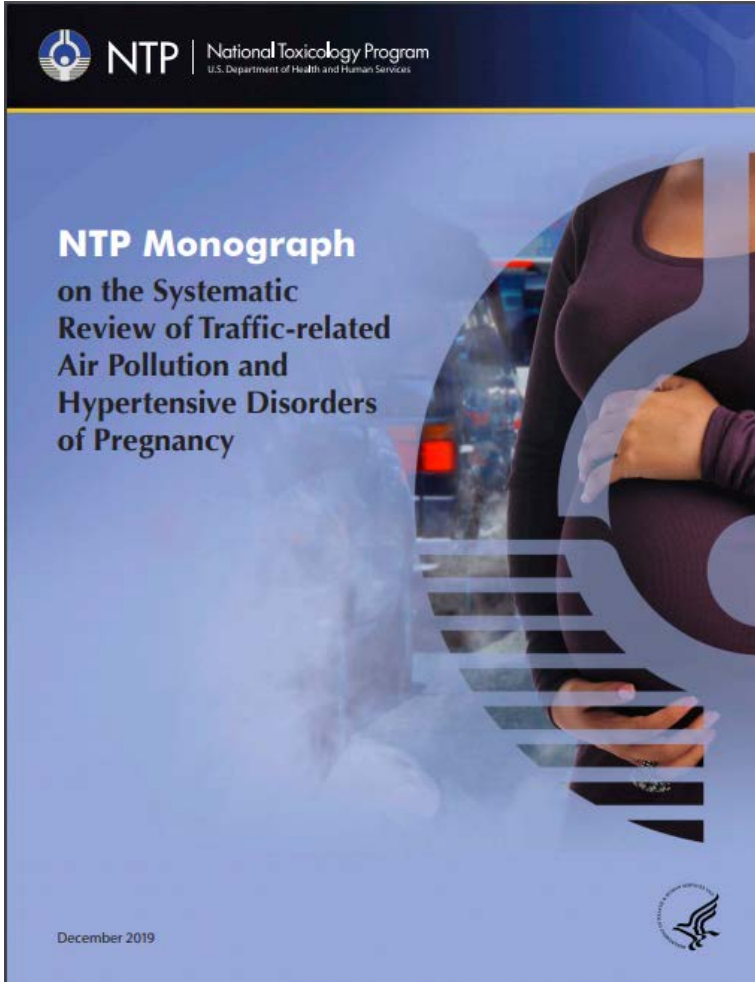
Are environmental exposures contributing to development of hypertensive disorders of pregnancy?

\*<https://www.preeclampsia.org/health-information/faqs/>



# Hypertensive disorders of pregnancy and the environment

## Traffic-related air pollution and hypertensive disorders of pregnancy



**Nomination:** Evaluate emerging children's health issues associated with ambient air pollution

Broad topic

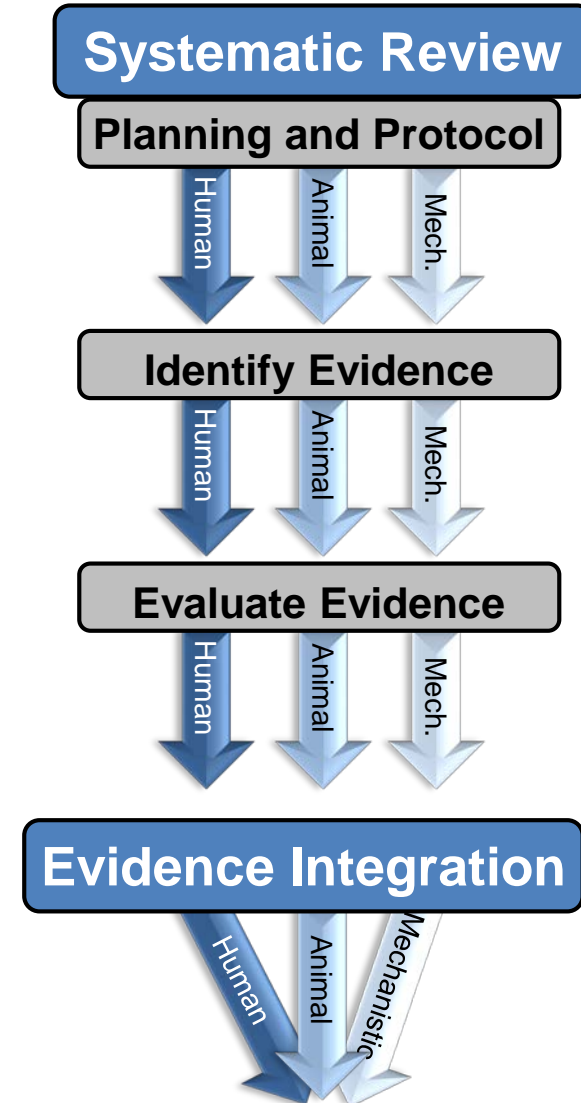
- Hypertensive disorders of pregnancy were identified as emerging air pollution-related health issue affecting mother and child
- Studies found during scoping efforts report that traffic-related air pollution (TRAP) is potentially associated with hypertensive disorders of pregnancy

**Objective:** Evaluate the evidence for associations between exposure to traffic-related air pollution and hypertensive disorders of pregnancy



## OHAT Approach to Systematic Review and Evidence Integration

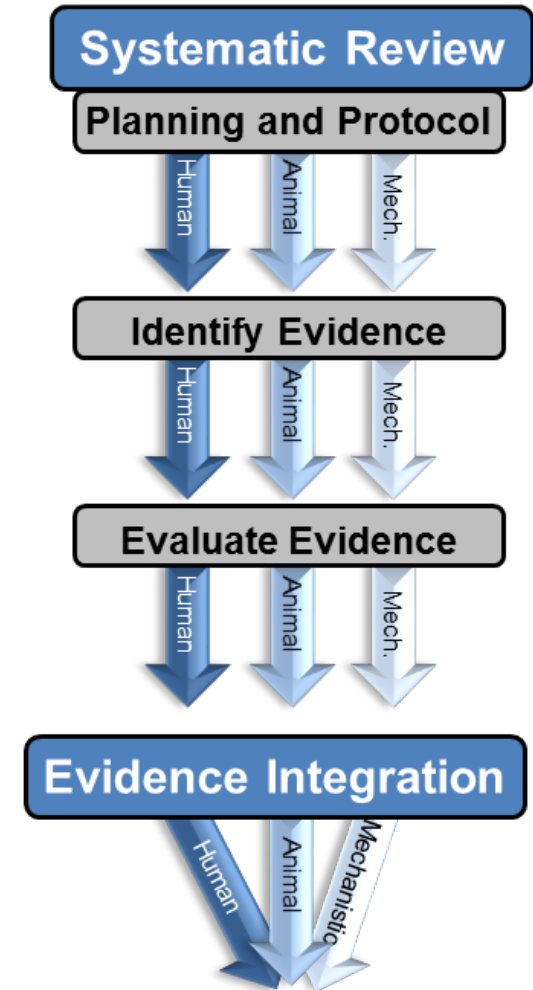
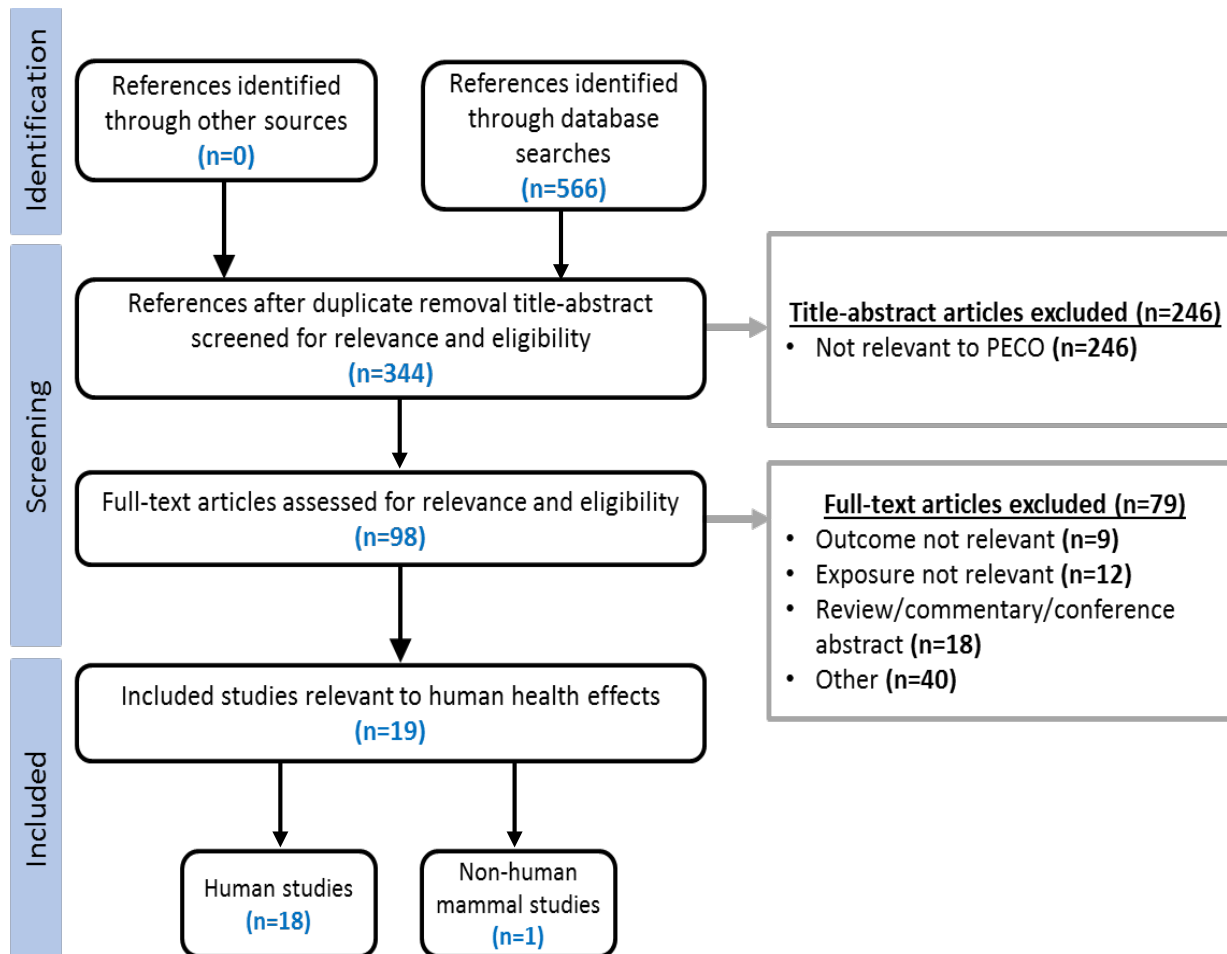
- **Problem formulation and protocol development**
  - Refine research question and develop systematic review protocol
  - Peer review and posting revised protocol
- **Identifying evidence**
  - Perform comprehensive literature search
  - Select relevant studies
  - Extract data
- **Evaluating evidence**
  - Assess individual study quality/risk of bias
- **Integrating evidence**
  - Identify bodies of evidence
  - Develop confidence ratings for bodies of evidence
  - Translate confidence rating into levels of evidence
  - Develop hazard identification conclusion







## TRAP considered PM2.5, NOx, traffic measures in main findings



**18 Human Studies, 1 Animal Study**



## Hazard conclusion and main takeaways

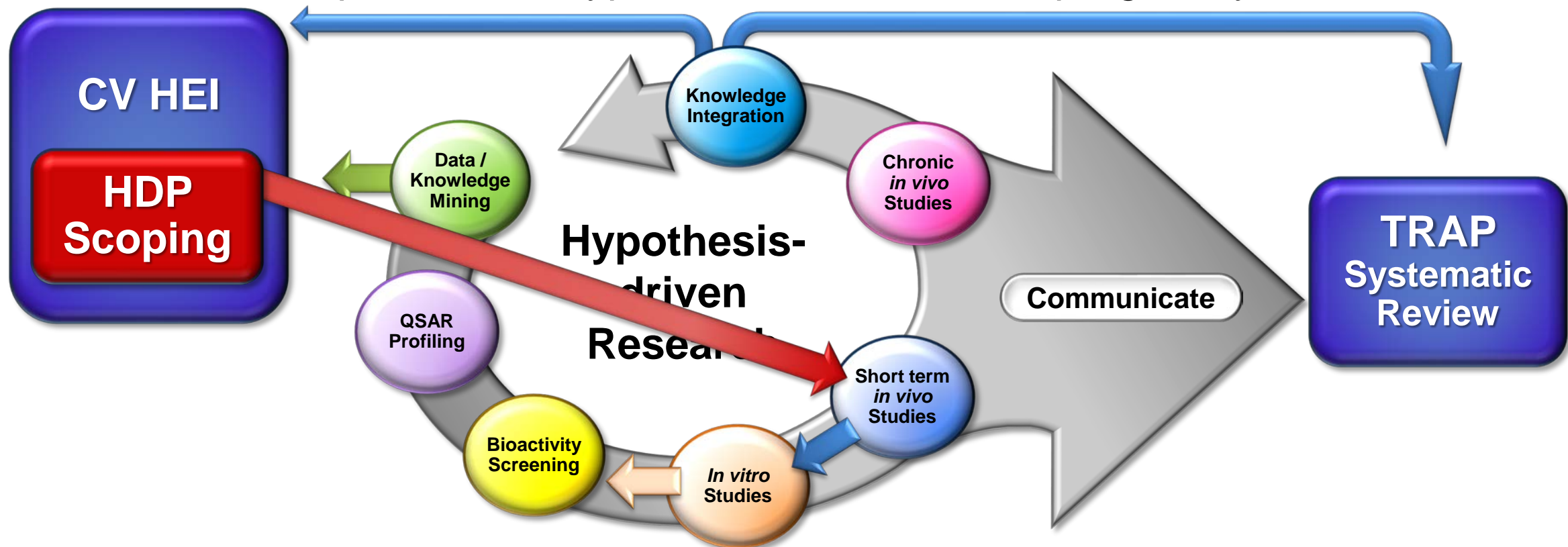


- Exposure to TRAP is ***presumed to be a hazard to pregnant women*** based on the collective evidence outlining that exposure to components of TRAP are associated with an increased odds for developing HDP.
- Conclusion based on human data only
- There was only one animal study that evaluated the effects of TRAP on blood pressure parameters during pregnancy
- TRAP is playing a role in HDP

**Are there other environmental exposures of concern?**



- Alignment with new programmatic direction and NTP pipeline (i.e., Cardiovascular Health Effects Innovation, CV HEI)
  - Paradigm shift: chemical focus → disease focus
- Leverage understanding of (patho)physiology to better understand the impact of environmental exposures on hypertensive disorders of pregnancy





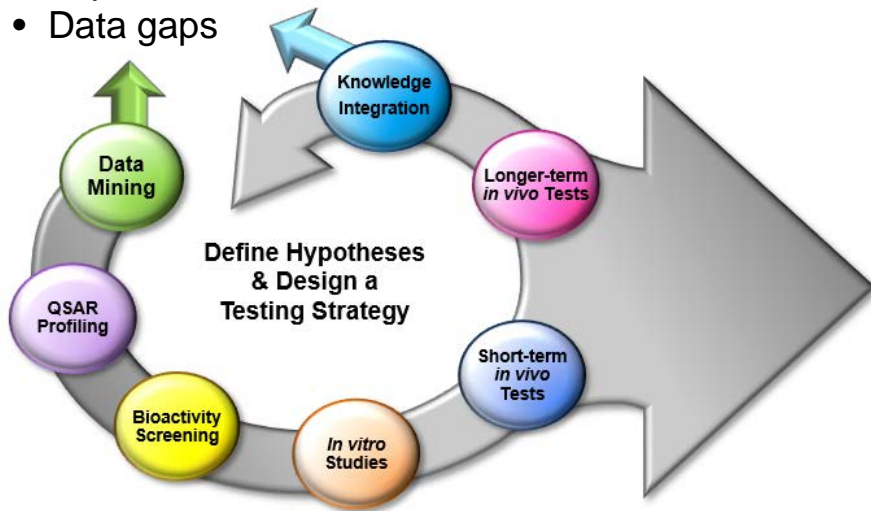
# Proposed Scoping Review and Evidence Mapping

## Identification of Biomarkers of HDP for Use in Animal Studies

- What are human-relevant biomarkers and mechanisms of hypertensive disorders of pregnancy that can be evaluated using animal models?

### Evidence Mapping

- Inform Research and Analysis
  - Biomarkers
  - Exposures
  - Data gaps



- Categorize and display – Evidence Map
  - Contemporary biomarkers associated with HDP
  - Exposures that have been evaluated with HDP
- Summarize data – Scoping Review
  - Characterizes generalizability of biomarkers and mechanisms from human to animal and across species
  - Describe research gaps to inform future research
- Output – Manuscript

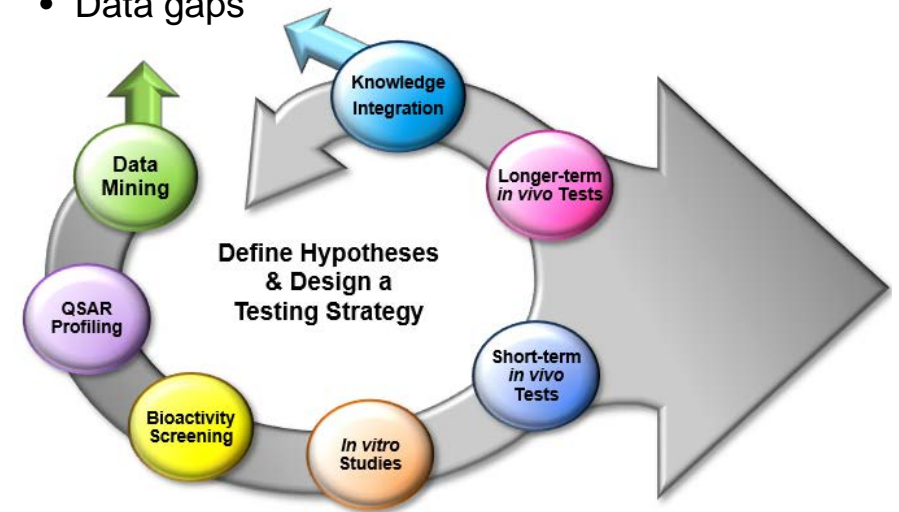




- 21<sup>st</sup> century toxicology (in vitro, in silico, organ on a chip, etc.)
  - In-house expertise and external relationships
- Systems biology approaches to address the issue
  - In-house expertise and external relationships
- Engagement of stakeholders and institutes/agencies

## Evidence Mapping

- Inform Research and Analysis
  - Biomarkers
  - Exposures
  - Data gaps

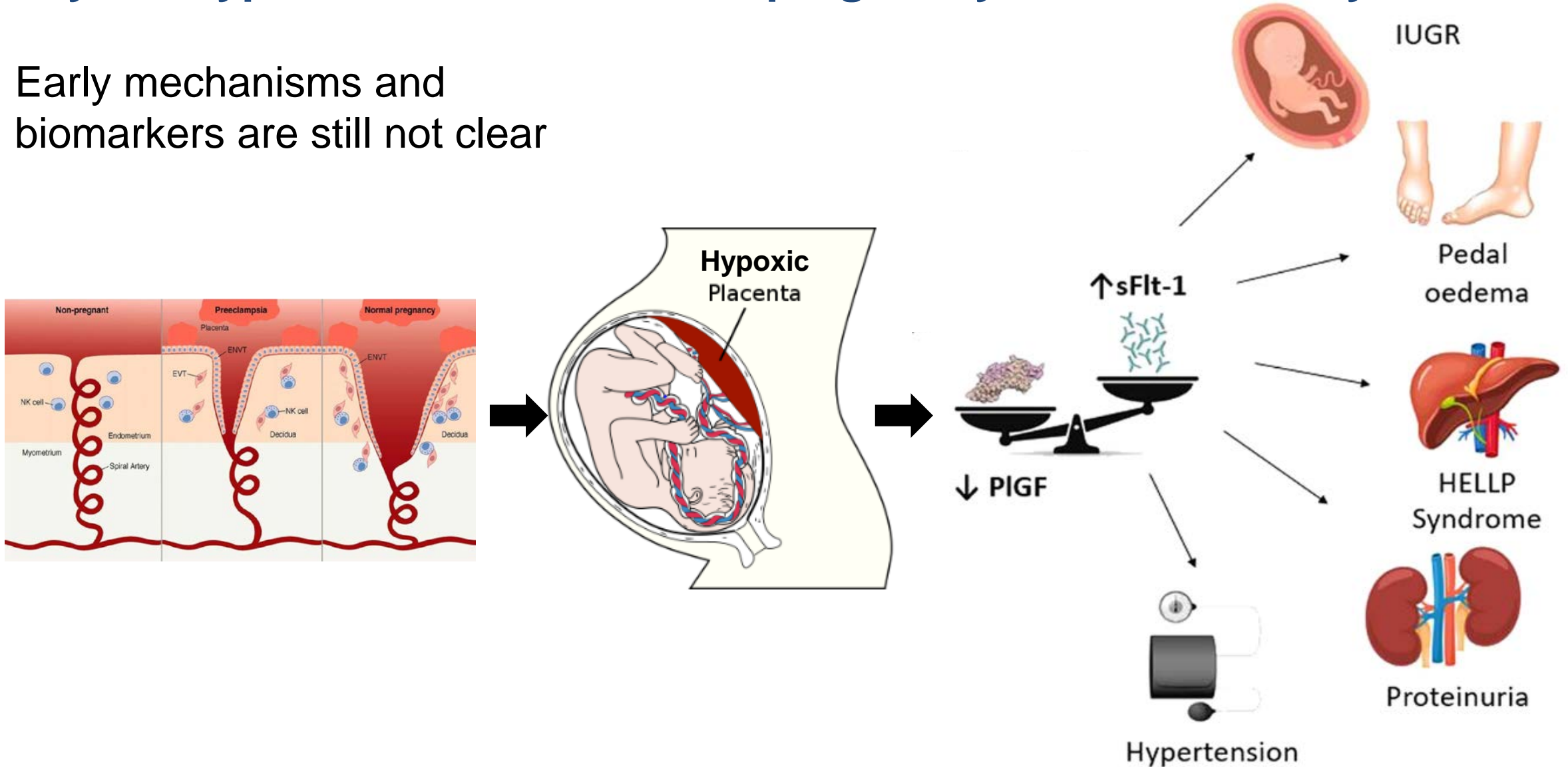






## Why are hypertensive disorders of pregnancy difficult to study?

Early mechanisms and biomarkers are still not clear





## Why are hypertensive disorders of pregnancy difficult to study?

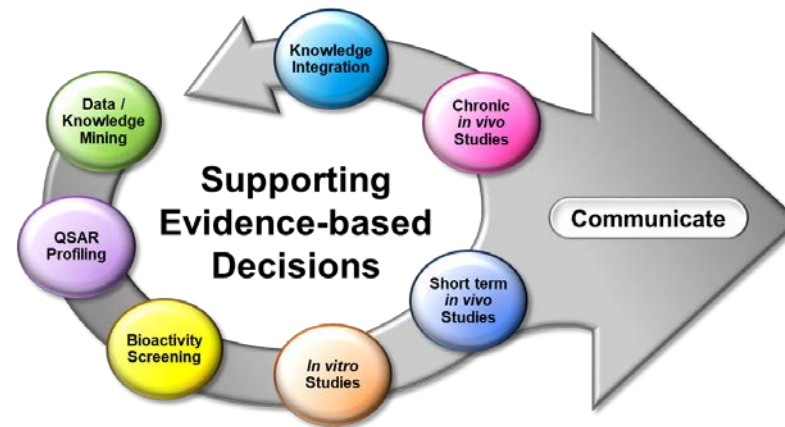
- Experimental interventions during pregnancy that can characterize phenotypes related to the maternal syndrome
  - Reduced Uterine Perfusion Pressure (RUPP) rat
  - N(G)-Nitro-L-arginine-methyl-ester (L-NAME) rat
  - Genetic knock-out mice
  - Cardiotonic steroid-induced hypertensive rats/mice
- Models that can potentially characterize early abnormal placentation
  - Dahl Salt Sensitive rat?

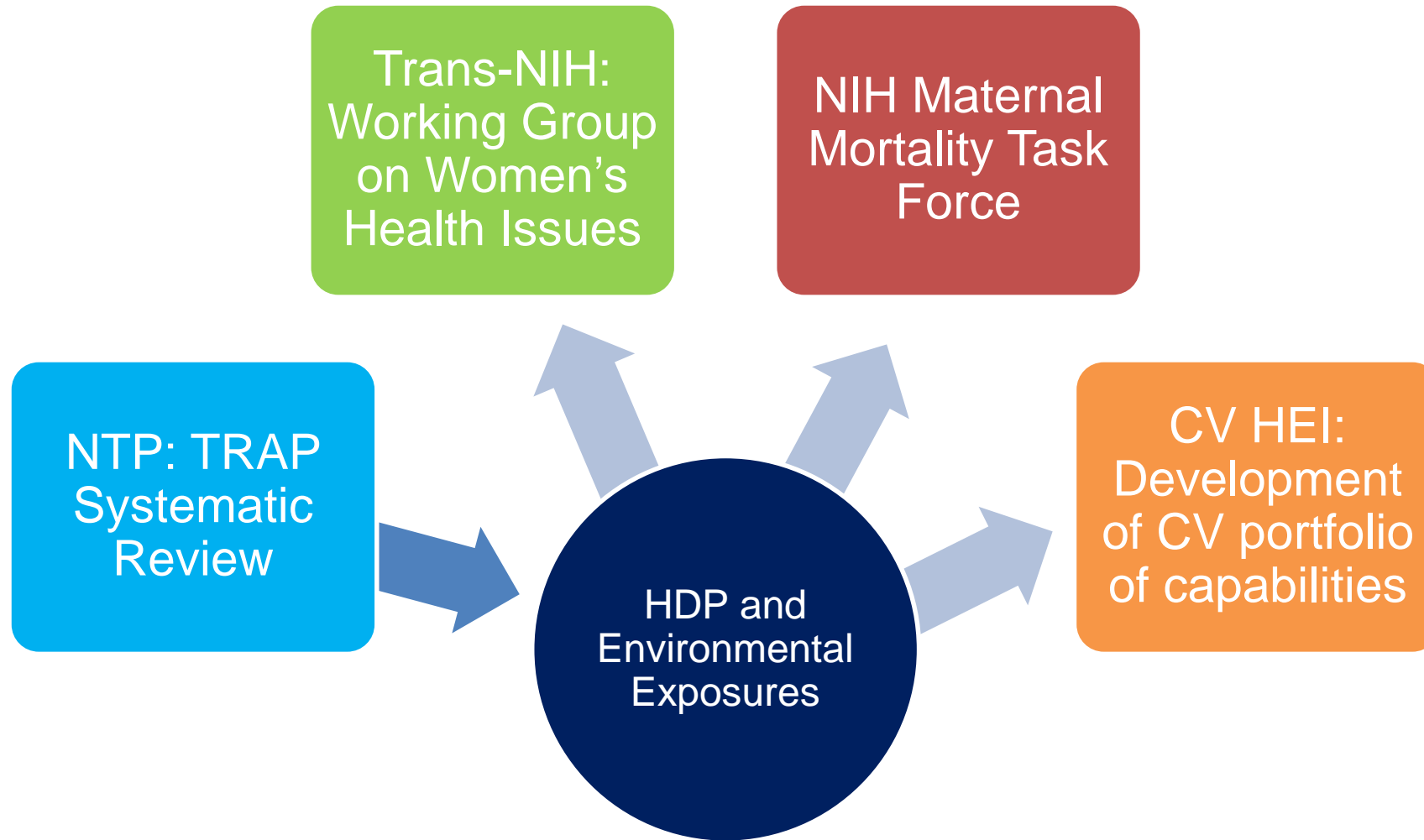




## Potential Goals and Impact

- Case example of how to engage the pipeline to address a contemporary issue
  - Development of a strategy and portfolio of capabilities to address cardiovascular toxicity-relevant questions
- Better understand how environment affect HDP and the contribution of HDP in overall cardiovascular disease risk in women (esp. minority women)
- Communication strategies to better incorporate environmental health considerations in public health, patient care





**Addressing research gaps to better understand the impact of environmental exposures on HDP**



- One of the aims of our Health Effects Innovation efforts is to shift our focus from ‘agents of concern’ to ‘environmental effects on diseases of concern’. How does this change in focus influence the questions we ask in our hazard characterization studies?
- If you consider environmental effects on hypertensive disorders of pregnancy as an exemplar, how does that change our approach to hazard characterization (e.g., approach to evidence development, modeling systems, human contextualization, stakeholders, etc.)?
- Are there unique technical capabilities or approaches that we’ll need to develop to be successful?
- What challenges are we likely to encounter in making this fundamental shift in focus?





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# Thank you Questions?

