WORLD STATISTICS CONGRESS 2025 THE HAGUE

Benchmark dose contours for bivariate exposures : application to maternal drinking patterns and childhood cognition

Session: CPS16
Experimental Design and Clinical Trials

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Motivation

- **Fetal Alcohol Syndrome (FAS):** craniofacial dysmorphology, growth restriction, neurobehavioral dysfunction

- **Partial FAS:** dysmorphology + neurobehavioral dysfunction

- **Alcohol-Related Neurotal Disorder (ARND):** cognitive/behavioral impairment without dysmorphology (most prevalent)

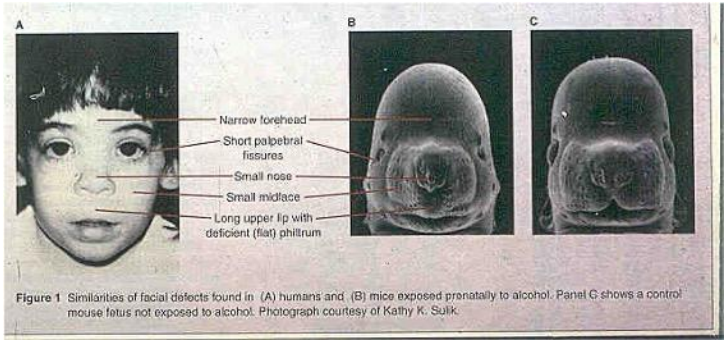
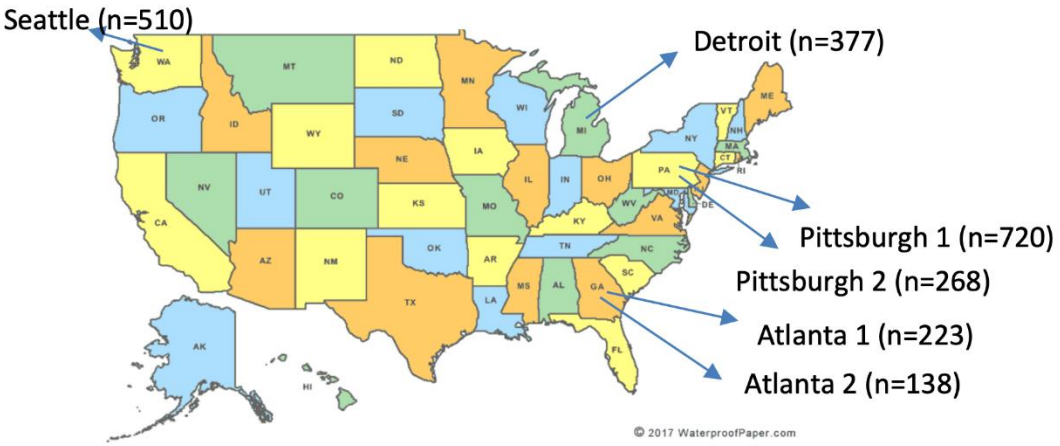


Figure 1 Similarities of facial defects found in (A) humans and (B) mice exposed prenatally to alcohol. Panel C shows a control mouse fetus not exposed to alcohol. Photograph courtesy of Kathy K. Sulik.

Diagnostic Challanges

- FASD not officially recognized in DSM-5
- ND-PAE introduced (condition for further study)
- Criteria lower than earlier cutoffs and NIAAA binge definition
- Screening & referral recommended, but underdiagnosis persists due to lack of dose–response guidance

NIH Study



- Six longitudinal U.S. cohorts combined (N = 2226 mother–child pairs).
- Offspring followed from infancy to childhood. \item
- Outcomes: IQ + 4 cognitive domains (learning, memory, exec. function, academic achievement).

Evidence on Prenatal Alcohol Exposure and Outcomes

- Jacobson et al. (2021) meta-analysis (N>2000, 6 cohorts)
  - Modest, robust effects of PAE on cognitive function (after adjustment)

- Nonlinear dose-response suggested by semi-parametric models:
  - Little/no effect at low exposure
  - Stronger effects at moderate/heavy levels (Jacobson & Jacobson 1994; Goldschmidt 1996)

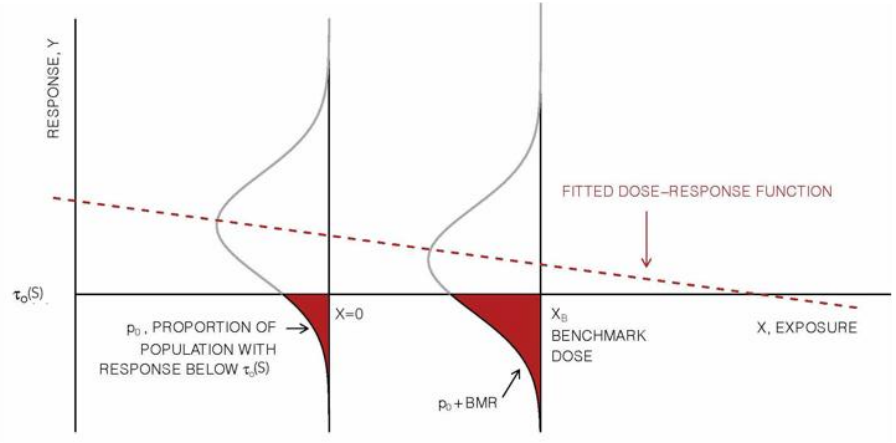
- Animal studies: acute high-dose exposure more damaging than gradual intake (Bonthius 1990; Goodlett 1987)

Why Benchmark Dose?

- Evidence shows nonlinear effects of prenatal alcohol exposure.
- Traditional cutoffs (e.g., binge/no binge) may miss gradual risks.
- Need a data-driven threshold:
  - Captures low-level risk often overlooked.
  - Provides transparent, reproducible cutoff for public health and clinical guidelines.

Benchmark Dose (BMD)

- BMD: exposure level at which risk of adverse response increases by a chosen benchmark response (BMR).
- Traditionally: estimated for a single exposure.
- Public health use: lower confidence limit (BMDL) applied for safety margins.



Limitations of current methods

- Most methods univariate.
- Real exposures often multidimensional
(e.g. dose/occasion & frequency).
- Need: BMD surfaces/contours for bivariate exposures.

Our framework

- Generalized additive models (GAMs):

  Flexible, nonlinear dose-response surfacess for alcohol dose/occasion × drinking frequency

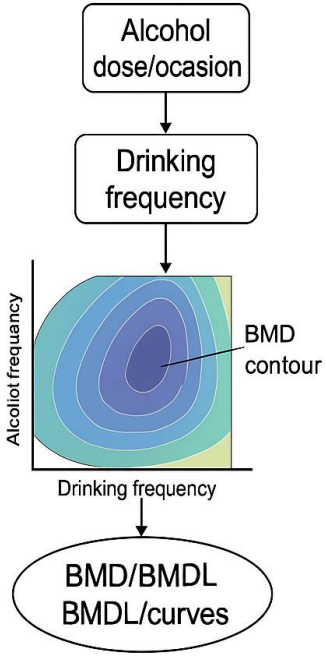
- Confounder adjustment via propensity scores:

  Account for potential sociodemographic and risk factor confounding

- Extension to bivariate BMD analysis:

  Define BMD contours at specified risk increase
  Parametric bootstrap for BMDL confidence contors

- R package *semibmd*



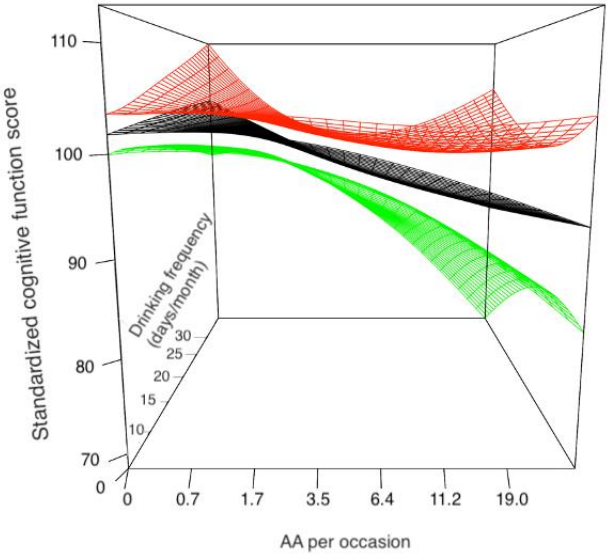
Application: Prenatal Alcohol Exposure

- 2226 children across 6 cohorts

- Exposure metrics:
  - Dose per drinking occasion
  - Drinking frequency (days/month)

• Outcome: Composite cognitive function (standardized)

• Method: Bivariate GAM → flexible nonlinear dose–response



Benchmark Dose (BMD) Approach

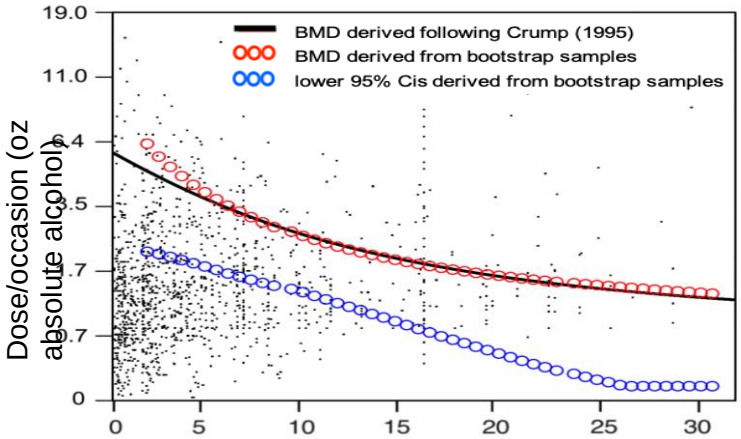
- Defines exposure that increases impairment risk by ~1%

- Cutoffs:
  - Intellectual disability: IQ < 70
  - Poor intellectual function: IQ ≈ 77

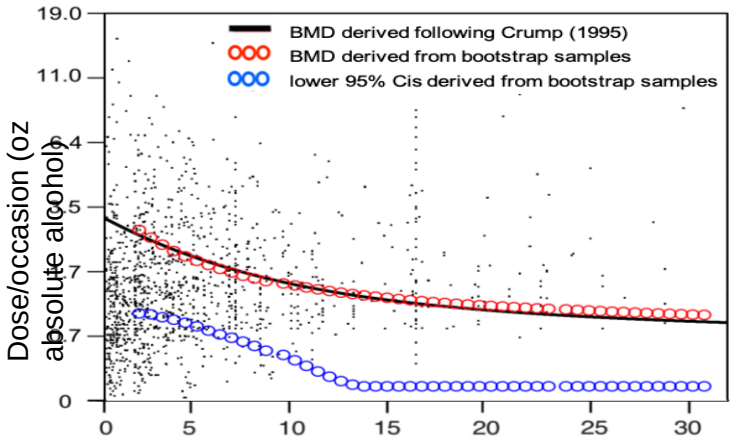
- BMDL: lower confidence bound for policy thresholds

Application: Prenatal Alcohol Exposure

Intellectual disability



Poor intellectual function



Discussion

- Developed bivariate BMD analysis framework.
- Provides clinically interpretable exposure thresholds.
- Flexible, extends to more exposures with modification.
- R implementation available: semibmd.

QUESTIONS?

THANK YOU.