

Exploring Multifactorial Contributors to
Disease Outcomes:
The Possible Role of Acetaminophen in
Asthma and Autism

CHE Partnership Call June 7, 2016
Part 1: David Kriebel

Multifactorial causal webs

- Like the weather!
 - “everybody talks about it, but nobody does anything!”
- In particular:
 - How much evidence do we need to decide that factor X contributes to causal web Y before we act to prevent exposure?

Does Acetaminophen contribute to Asthma & Autism?

- Important question!
- Also, a useful model for thinking about hazards from harder-to-measure exposures like:
 - PFOA
 - BPA
 - PBDE
 - Etc.

To Begin: Acetaminophen & Asthma?

- Plenty of epidemiologic evidence for an association, but
 - Medical community remains unconvinced
- Why?

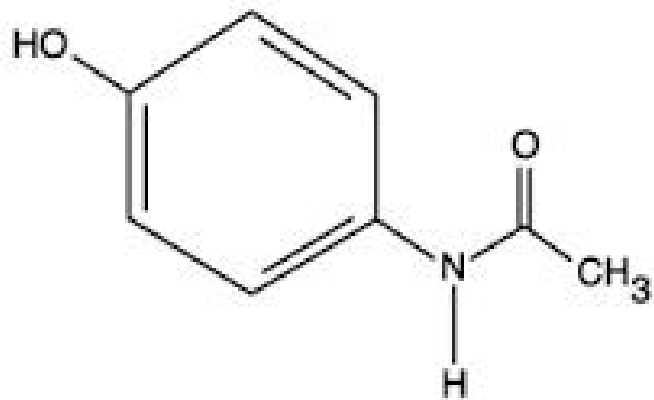
Asthma incidence is rising – especially in children

- Asthma is a chronic lung disease causing airway hyper-responsiveness, inflammation, and airway obstruction.
- Affects 9.5% of US children
- Affects 8.0% of US adults



What is Acetaminophen?

- *N-acetyl-para-aminophenol Paracetamol, Tylenol (will use APAP)*
- *An antipyretic- **NOT AN ANTI-INFLAMMATORY***



Acetaminophen
 $C_8H_9NO_2$ MW = 151.16



Acetaminophen has a very narrow safety margin

FDA in 2009- As little as 25% above the maximum daily dose (4000mg) has been reported to cause liver damage



8 Extra-strength (500mg)



+ just **2** more

Acetaminophen is the leading cause of acute liver failure and is widely used



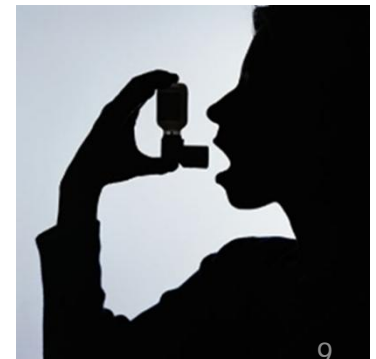
65% of US women will take it during pregnancy



23% of infants given it in any given week

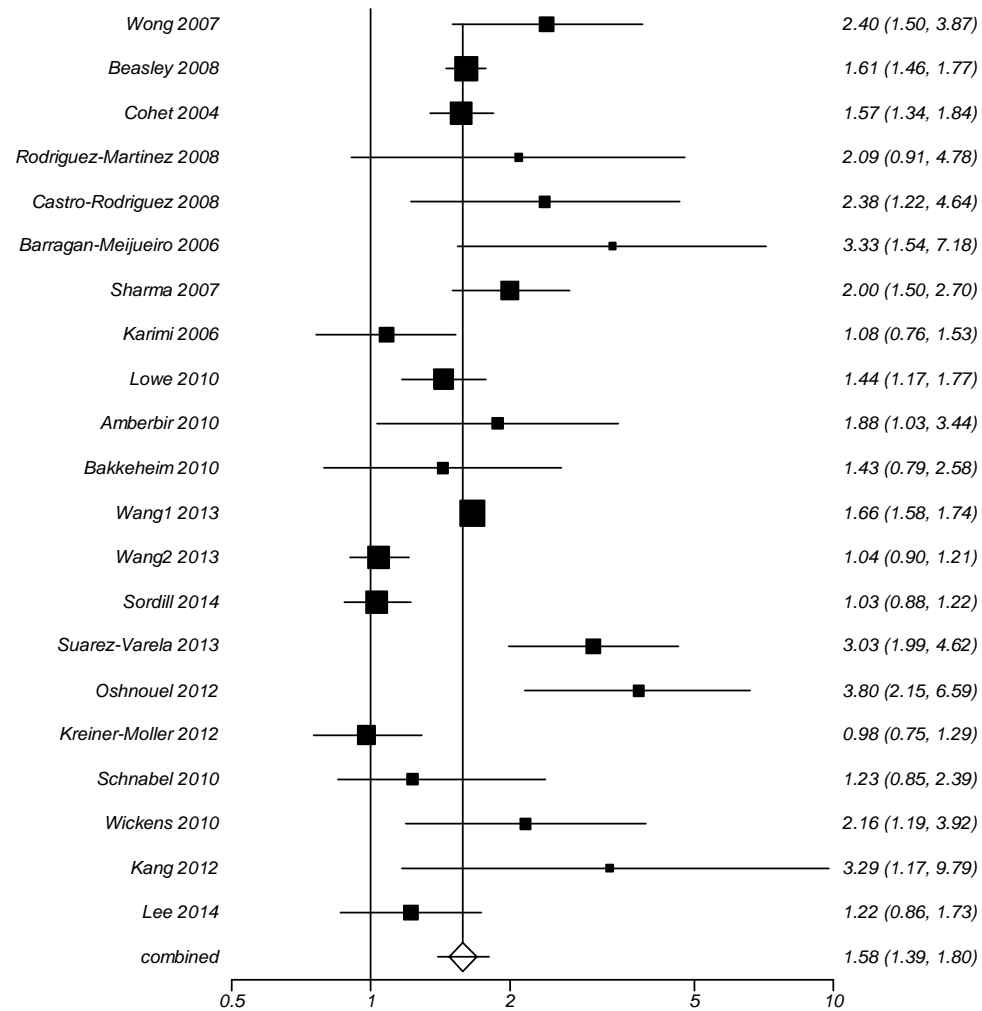
There have been > 42 studies of acetaminophen & asthma risk

- Most find a modest but increased risk
 - Consistent findings for
 - prenatal,
 - children and
 - adult exposures
 - Evidence of “dose response”
 - Biologic plausibility



Childhood exposure and asthma

Summary meta-analysis plot [random effects]



Summary Risk Estimate = 1.58 95% CI (1.30 to 1.80)

There are plausible biologic mechanisms

Acetaminophen has been shown to decrease glutathione levels leading to oxidative injury.

Acetaminophen-induced oxidative stress may enhance Th2 cell polarization and mediation of non-eosinophilic inflammatory responses.

Prenatal APAP mouse model recently developed (Karimi et al. 2015)

Despite this evidence, many researchers remain skeptical about the link between acetaminophen and asthma

RESEARCH ARTICLE

Prenatal Paracetamol Exposure and Wheezing in Childhood: Causation or Confounding?

Enrica Migliore^{1*}, Daniela Zugna¹, Claudia Galassi¹, Franco Merletti¹, Luigi Gagliardi², Laura Rasero³, Morena Trevisan¹, Franca Rusconi⁴, Lorenzo Richiardi¹

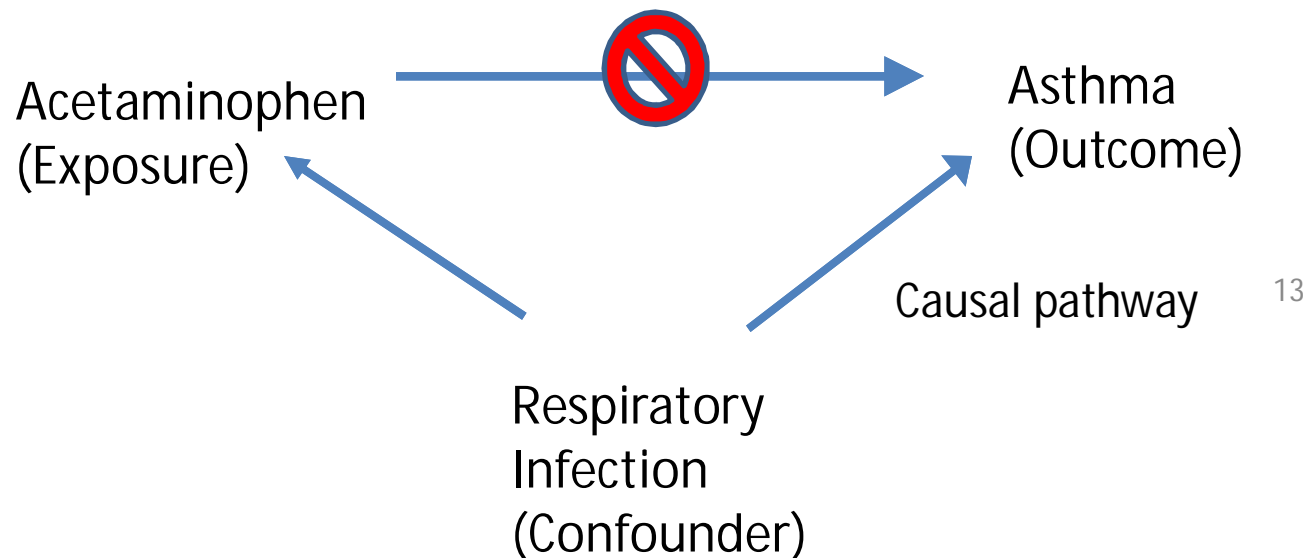
Conclusion

The association between maternal paracetamol use during pregnancy and infant wheezing is mainly, if not completely explained by confounding.

“Confounding by Indication”

Suppose the apparent association is false -- acetaminophen is an innocent bystander.

This could happen if the reason (indication) for taking the acetaminophen is the real cause.



But asthma incidence is rising while infectious diseases are falling (in developed countries)

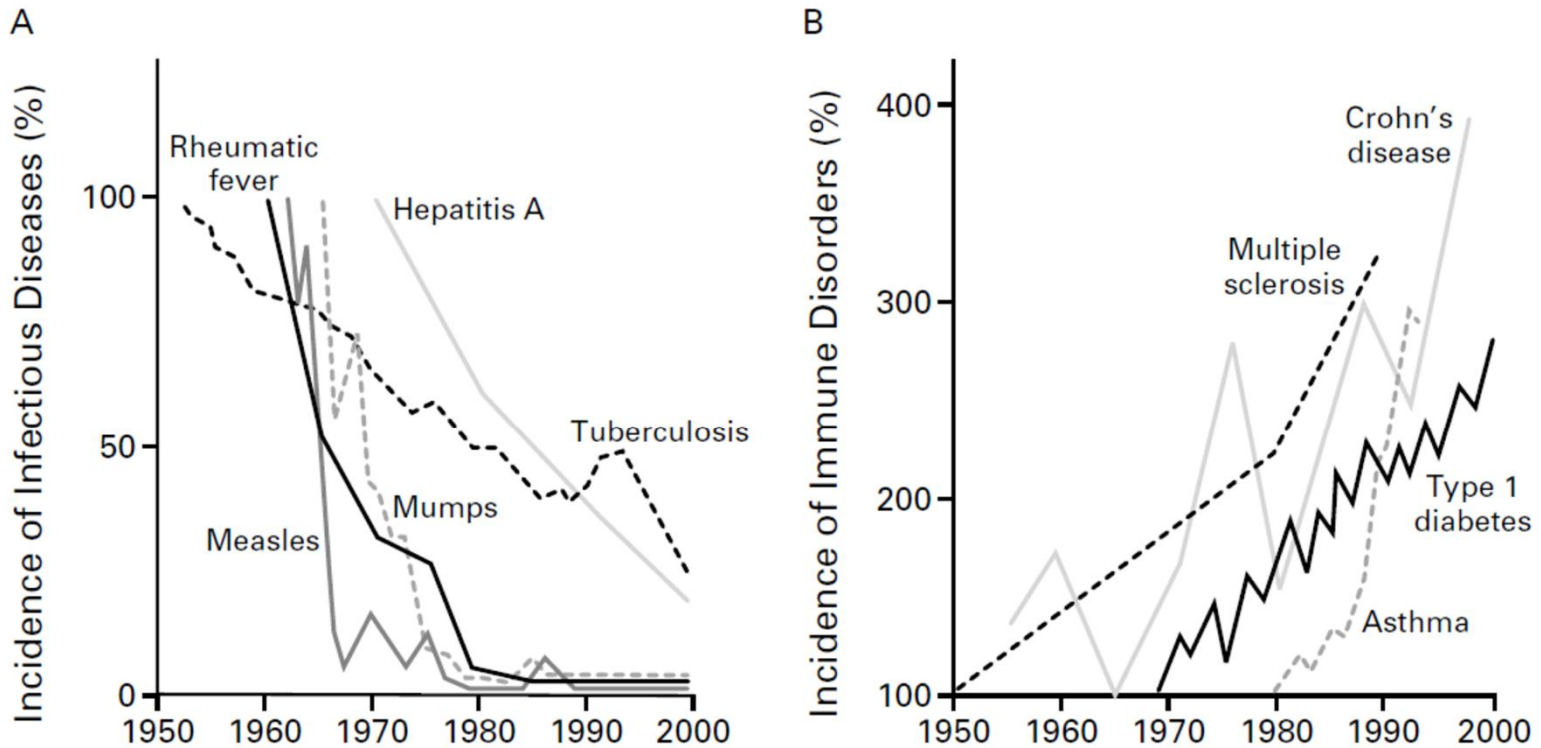


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Bach J-F. N Engl J Med 2002; Vol. 347, No. 12

We propose instead that both acetaminophen & infection may contribute to a multi-factorial causal web for asthma

Infection may cause “immune dysregulation” or activation.

Acetaminophen may be a final “trigger” that leads to asthma



Extending the Hypothesis-we propose:

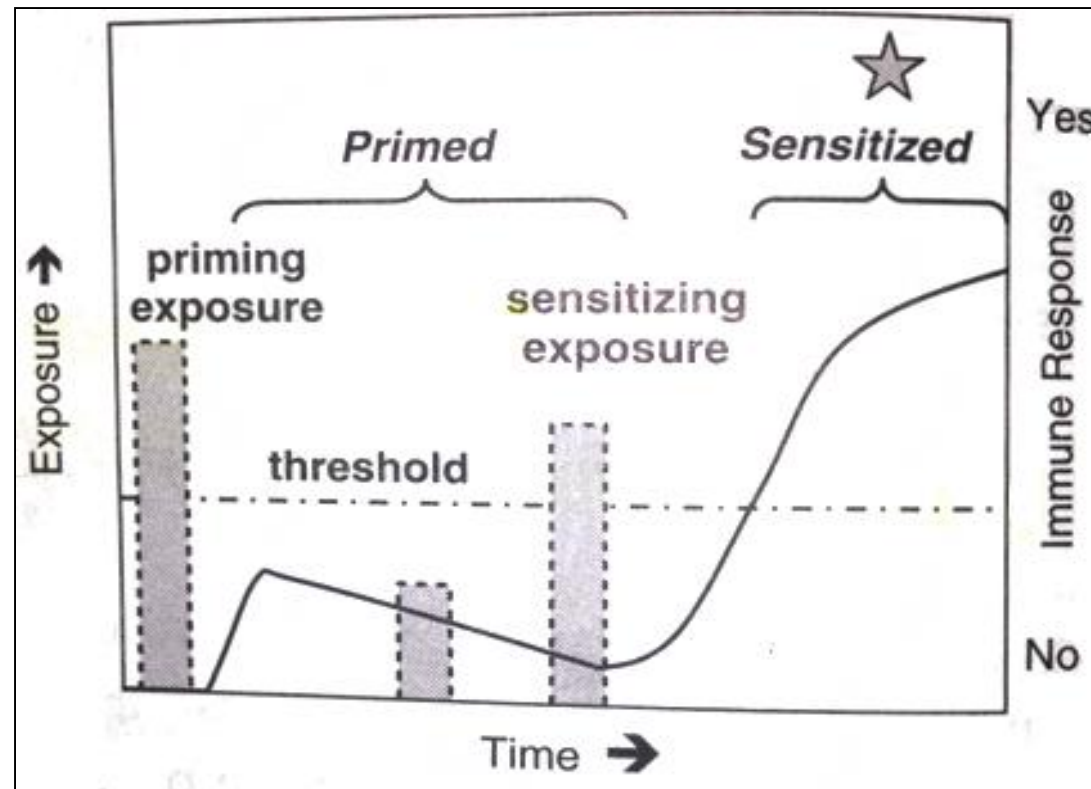
Asthma, attention deficit hyperactivity disease (ADHD) and autism may be two-stage diseases:

An initial intense exposure produces an immune priming response. This could be an infection, environmental exposure, or other stressor

A second intense exposure – possibly acetaminophen - produces a systemic immune sensitizing response that leads to the disease

Idealized typical Time Course

- Irreversible Discrete Disease Process



From: Smith & Kriebel. A Biologic Approach to Environmental Assessment & Epidemiology. Oxford Univ. Press, 2010.

Important aspect of 2-stage model

- Removal of either of the two exposures- the priming exposure OR the sensitizing exposure can decrease disease incidence
- Conversely, a rising trend in one (acetaminophen use) could drive increase in the outcome even if the other exposure is stable or falling (infection).

The best evidence of two-stage etiology is for asthma:

- Four epidemiologic studies have identified antioxidant genetic polymorphisms that interact with acetaminophen to elevate risk beyond the risk associated with the polymorphism or APAP independently
- Environmental tobacco smoke and APAP interacted similarly to elevate oxidant and irritant respiratory tract responses in mice

Conclusions

- A multi-stage disease model suggests it is plausible that there is a true causal relationship between acetaminophen and asthma
- More generally, when multifactorial causal webs have critical temporal sequences, these will be easier to identify through animal experiments and human epidemiology.