Preterm birth, early environmental risks and ADHD

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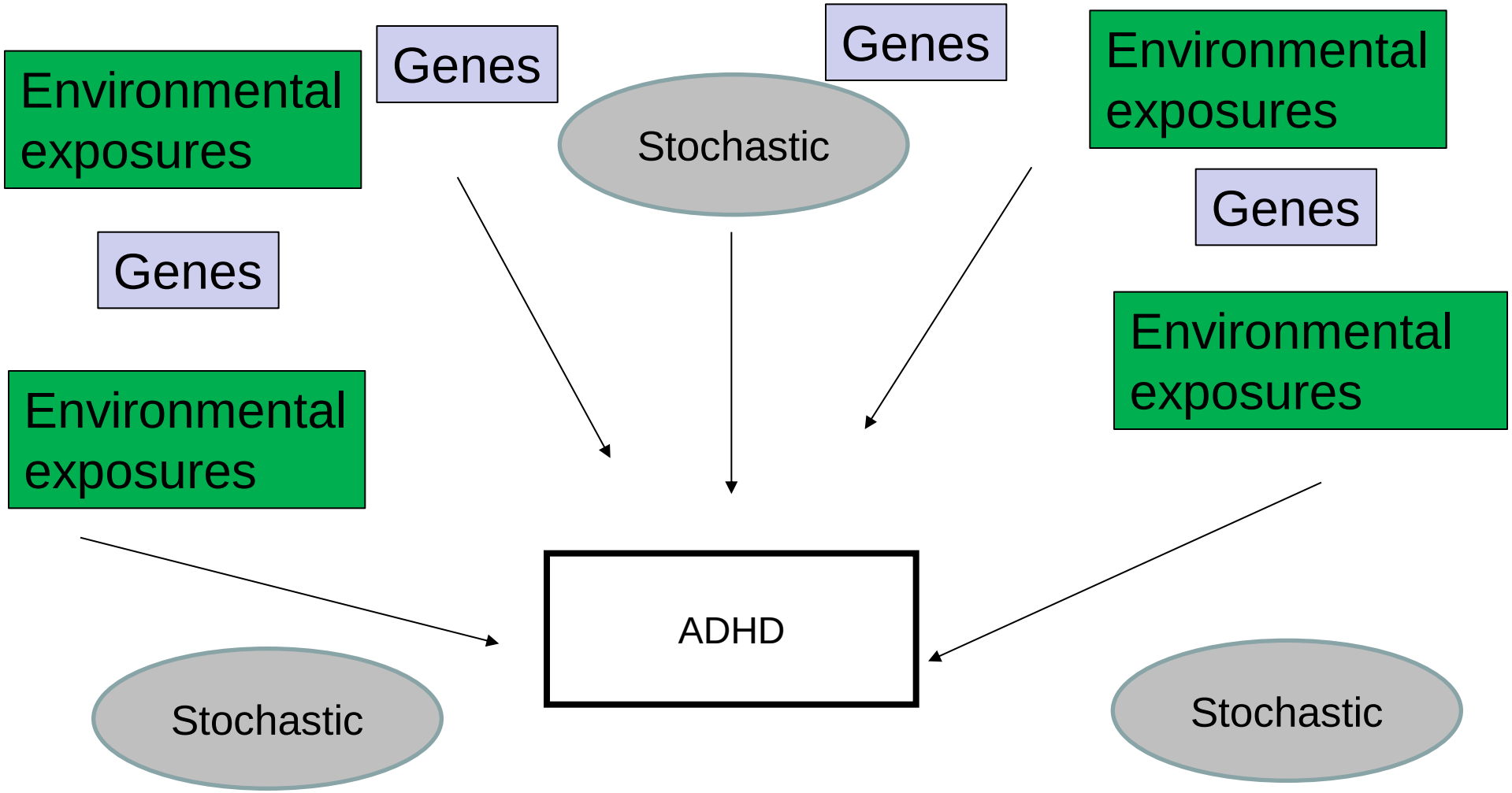
Overview

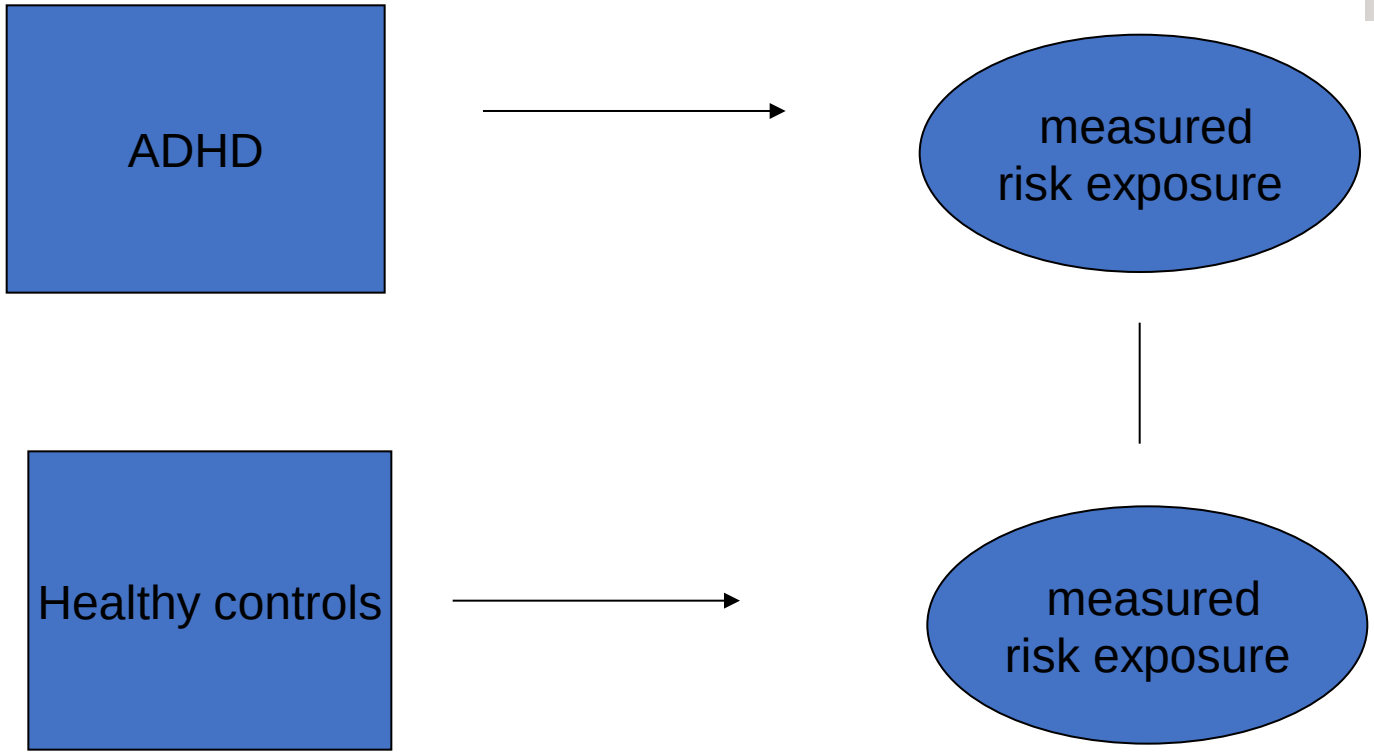
- Environmental risks associated with ADHD
  - -Preterm birth
  - -Other early life factors
- Why association is not causation
- What different research designs have taught us about likely ADHD environmental causes
- What scientific findings mean for clinical practice

Early environmental factors -which ones are associated with ADHD?

ADHD is heritable and multifactorial
No single cause



Environmental “causes” Observational designs



Preterm birth

Preterm birth

- 11% of live births and rising
- < 37 weeks gestation
- Very preterm < 32 weeks
- Extremely preterm < 28 weeks

t we know about preterm birth and ADHD

- Robust association with increased ADHD risk
  - odds ratio = 3.04
- ↑ASD, cognitive and learning problems
- Highest risk in those born very/extremely preterm

Franz et al. 2018

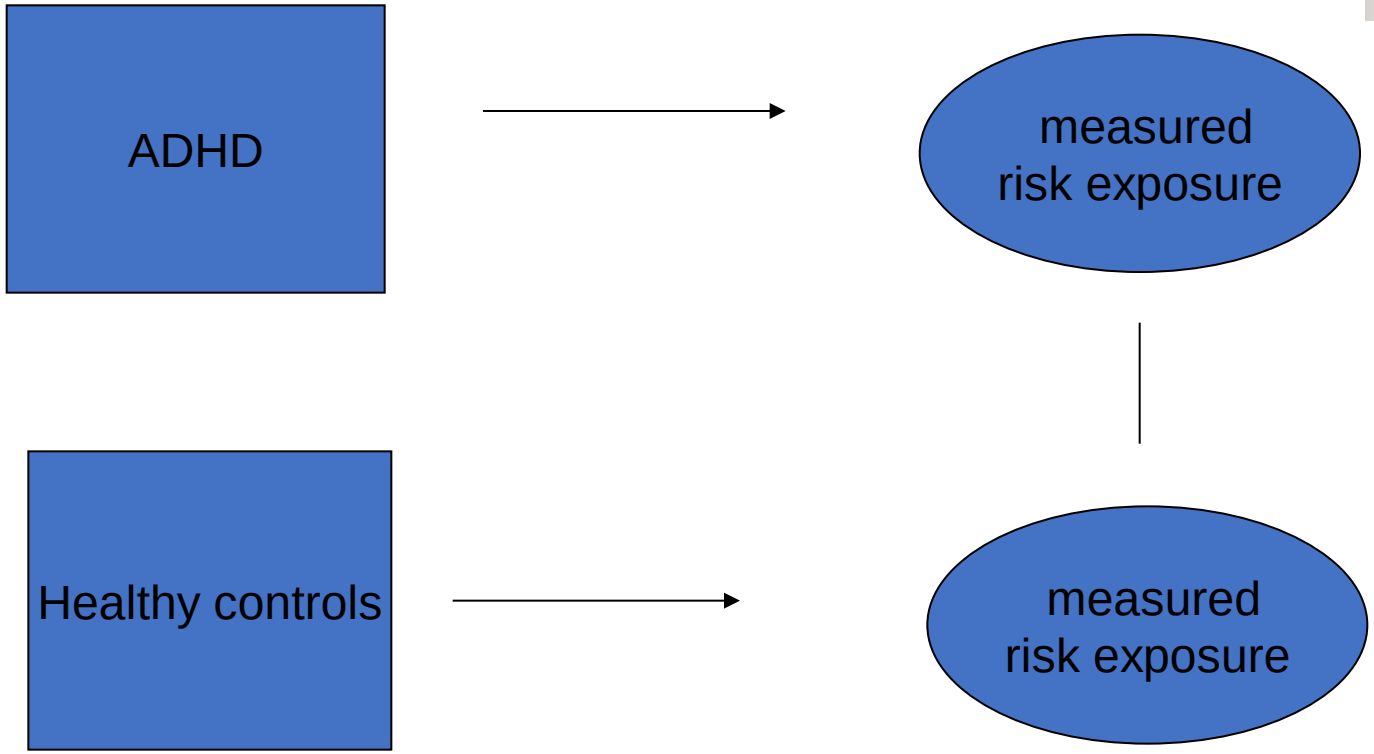
What we know about preterm birth and ADHD

- Most babies born preterm do not develop ADHD
- What explains variation in mental health outcomes?
- Additional background risks?
  - genetic liability
  - additional early adversities

Early environmental risk exposures and ADHD

What else?

Environmental “causes” Observational designs



Early life exposures associated with ADHD

- maternal smoking in pregnancy **
- maternal stress/anxiety in pregnancy*
- maternal health e.g. hypertension in pregnancy
- Toxins and medications in pregnancy
  - Antidepressants: pooled adjusted relative risk 1.4
  - Paracetamol
- Lead*, PCB exposure

Thapar et al JCPP 2013
Maher et al, JAMA Psychiatry 2018
Sujaan et al. 2019

Association of risk exposure with ADHD is **not causation**

Limitations to observational science and epidemiology

..and jumping to conclusions in clinical practice

Why testing causation is important

- If they are genuine causes, reducing exposure could help prevent ADHD
- Inform health and environmental policies
- Examples in medicine: cigarette smoking and lung cancer causal
- Increased levels of quitting smoking in California led to reduced lung cancer compared to rest of USA

Maternal or fetal genetic liability

environmental causation
e.g. brain structure alterations

Early life risk exposure

Child ADHD

environmental causation

e.g. brain structure alterations

Early risk exposure

Child ADHD

Unmeasured Confounders

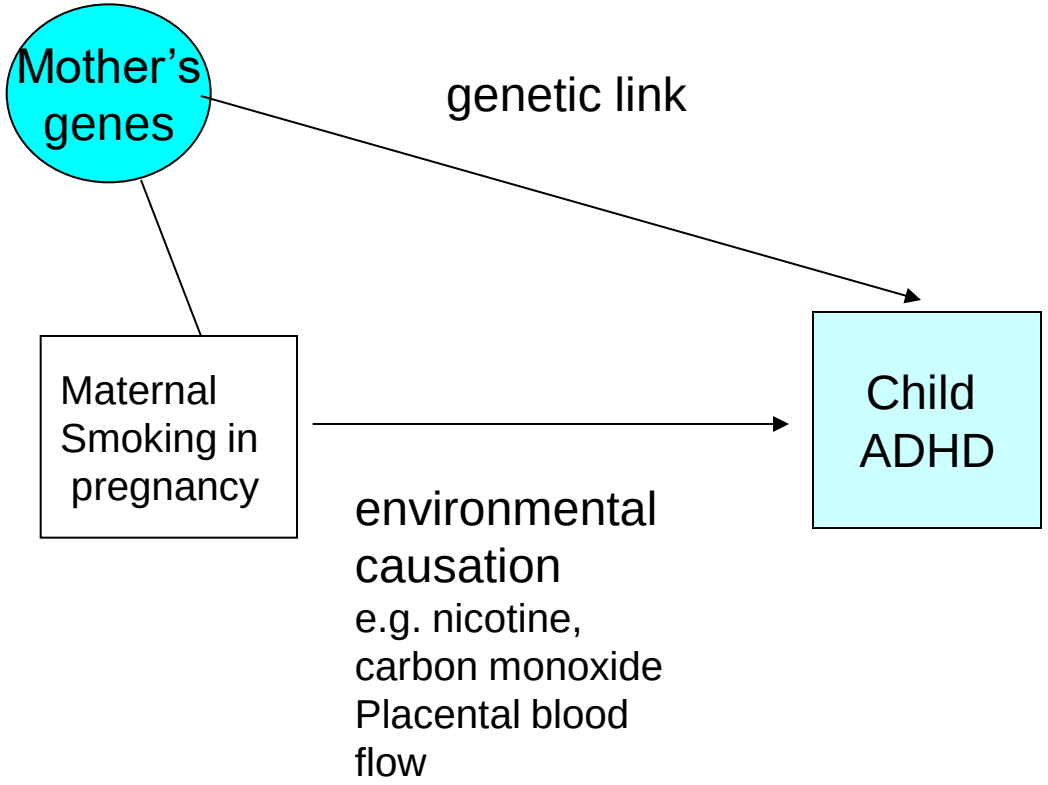
e.g. social disadvantage

Need alternative designs that remove confounders to observational studies

Quasi-experimental designs, using genetic designs to test environment

Rutter M. 2007. Proceeding From Observed Correlation to Causal Inference: The Use of Natural Experiments.

Association ≠ causation: need quasi experimental designs and triangulation of evidence to remove unmeasured confounders etc.



Mother's genes

~~genetic link~~

Maternal Smoking in pregnancy

Child ADHD

environmental causation
e.g. nicotine, carbon monoxide
Placental blood flow

Genetically informative designs show including measured confounders NOT enough

- Maternal vs. paternal exposures

  e.g. Langley et al. 2012

Genetically informative designs show including measured confounders NOT enough

- Siblings discordant for exposure

  Mother smoking in one pregnancy vs. not the other

- IVF design

  Offspring genetically related vs. unrelated to mother

e.g. d'Onofrio et al, 2014; Obel et al, 2016; Thapar et al 2009

Maternal smoking in pregnancy and ADHD

- 12 genetically informative studies
- 8 discordant sibling studies, 2 maternal vs. paternal exposure studies, one IVF
- 11 report no causal association

Rice et al, Development and Psychopathology, In press. 2018

Maternal smoking in pregnancy

- Still observational studies reporting associations between smoking in pregnancy and ADHD
- Larger ones and meta-analyses will not answer the question
- Confuses the field, wastes time and resources that could be spent on finding real causes or providing interventions
- We know smoking in pregnancy is no good for other reasons
- Not just psychopathology e.g. vitamin E and heart disease

Proceeding From Observed Correlation to Causal Inference: The Use of Natural Experiments. Rutter M. 2007
Identifying the environmental causes of disease: how should we decide what to believe and when to take action? Academy of Medical Sciences Report. Chaired by Rutter M.

Other prenatal risk exposures that quasi-experimental designs suggest may not be causal

- Maternal stress in pregnancy
- Maternal antidepressant use in pregnancy

e.g. Rice et al. 2010; Rosenqvist et al. 2019; Sujan et al. 2019

Preterm birth and ADHD

Causal?

Preterm birth and ADHD

- 2 discordant sibling studies: one sibling born preterm, the other full term
- Increased rates of ADHD/ADHD symptoms in preterm offspring
- Consistent with causal explanation; unlike studies on smoking in pregnancy

D'Onofrio et al, 2013; James et al. 2019

Preterm birth and ADHD

- High-income vs. middle-income country cohort
- Different structure of confounders
- Increase ADHD risk in both contexts
- Different designs consistent with inferring causal relationship

D'Onofrio et al, 2013; James et al. 2019; Murray et al, 2016

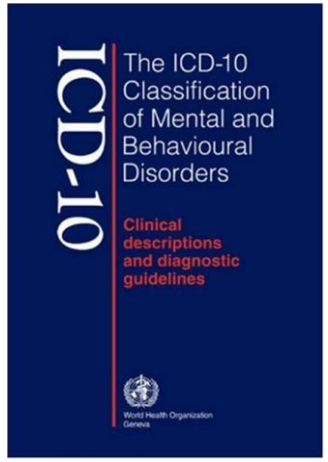
Preterm birth and ADHD

- Causal mechanisms however remain unknown
- Brain alterations due to direct insult?
- Fetal developmental liability co-acts with additional risks e.g. genetic liability, other adversities

ADHD environmental risk factors

- Causality needs rigorous testing
- No single design sufficient
- Combine methods to assess causality e.g. discordant sib pair designs, longitudinal tests, cross-country comparisons
- Looking for convergence of findings across different designs: triangulation
- Preterm birth most consistent

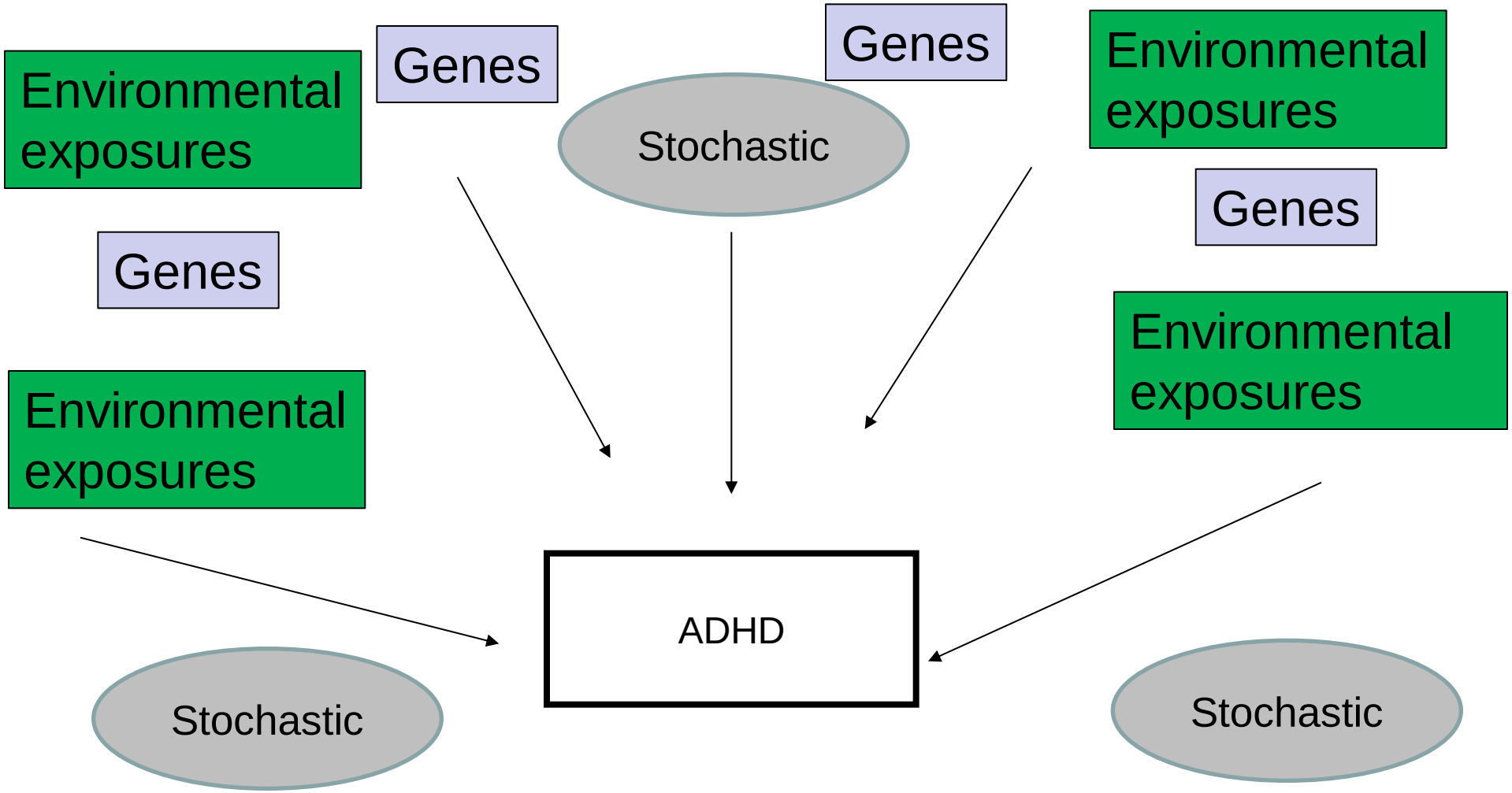
What does this mean clinically?



We assess and treat ADHD symptoms/functioning

Regardless of cause

ADHD is heritable and multifactorial
No single cause



Assessment and Treatment of ADHD in those born preterm

- Assessment of ADHD: as usual
- Look out for additional cognitive/ neurodevelopmental difficulties and comorbidity: as usual
- Treat: as usual

High-risk groups for early monitoring

- Preterm birth: developmental checks and high index of suspicion for ADHD and other neurodevelopmental problems

Preterm birth and ADHD

- Primary care/schools: higher index of suspicion
- Developmental immaturity in those born early
- ↑ADHD diagnosis and mental health problems in children born in August (young in school year)

Sayal et al. 2017; Layton et al. 2018; Root et al. 2019

Conclusions

Conclusions

- Early life exposures reported as being associated with ADHD risk
- Many of these are not necessarily causal
- Observational designs alone have limitations
- Be wary of jumping to conclusions about causes: from own observations and literature
- Strongest evidence to date of causal link with ADHD: preterm birth

Does causality matter?

- What we tell our patients and public understanding of ADHD
- Smoking cessation programs in pregnancy, parenting programs helpful for improving infant health and conduct problems
- Not effective for preventing ADHD

Preterm birth assessment and treatment

- Preterm birth: higher index of suspicion
- Assess and treat as usual

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