EARLY CAUSE

# Early-life stress (ELS) & psycho-cardiometabolic comorbidity

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29/03/2023

Serena Defina, Erasmus MC

# Backgroud

Pregnancy | Childhood | Adolescence | Adulthood

Early-life stress (ELS)

**Depression**

**Cardio-metabolic disease**

# Backgroud

Pregnancy | Childhood | Adolescence | Adulthood

Early-life stress (ELS)

Internalizing symptoms

Excess adiposity

Depression

Cardio-metabolic disease

# This talk

1

**Differential effects of prenatal and postnatal ELS on internalizing symptoms, adiposity and their comorbidity in early adolescence**

2

**The role of exercise, sleep and diet in the association between ELS and psycho-cardiometabolic health**

3

**Cross-sectional and longitudinal relations between internalizing symptoms and cardiometabolic health from childhood to early adulthood**

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1

# Differential effects of prenatal and postnatal ELS on internalizing symptoms, adiposity and their comorbidity in early adolescence

Serena Defina, Tom Woofenden, Vilte Baltramonaityte, Carmine M. Pariante, Karim Lekadir, Vincent W. V. Jaddoe, Fadila Serdarevic, Henning Tiemeier, Esther Walton, Janine F. Felix, and Charlotte A.M. Cecil

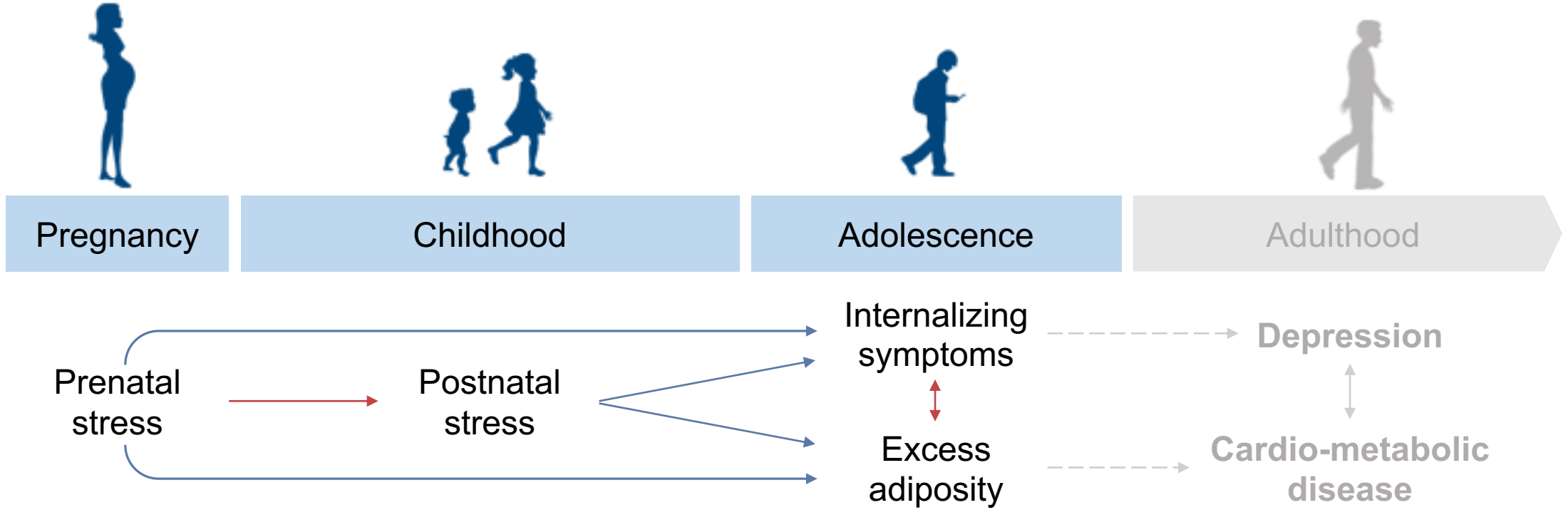
# Backgroud


**Early–life stress (ELS)**

**Depression**

**Cardio-metabolic disease**

# Backgroud



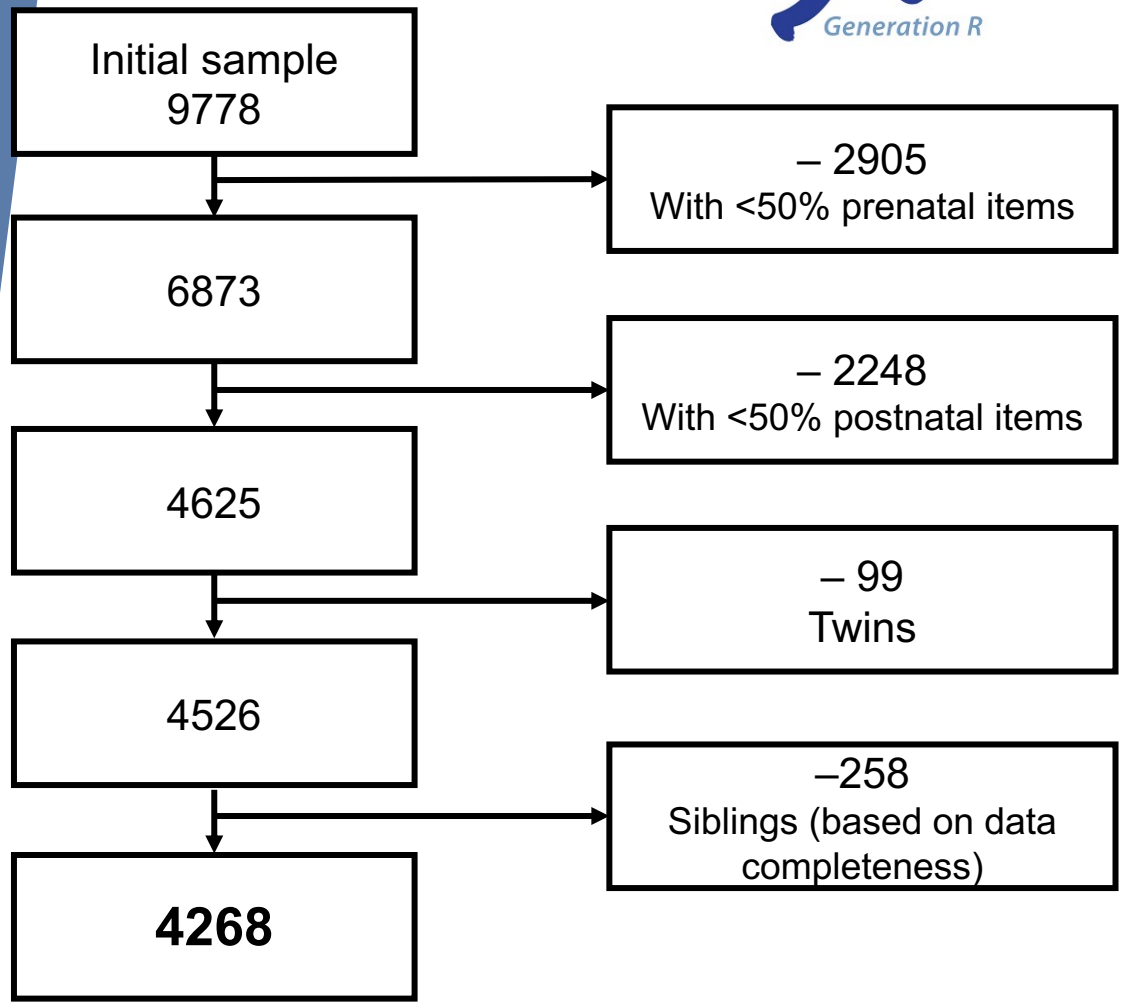

# Aims

I. What is the contribution of prenatal vs. postnatal stress?

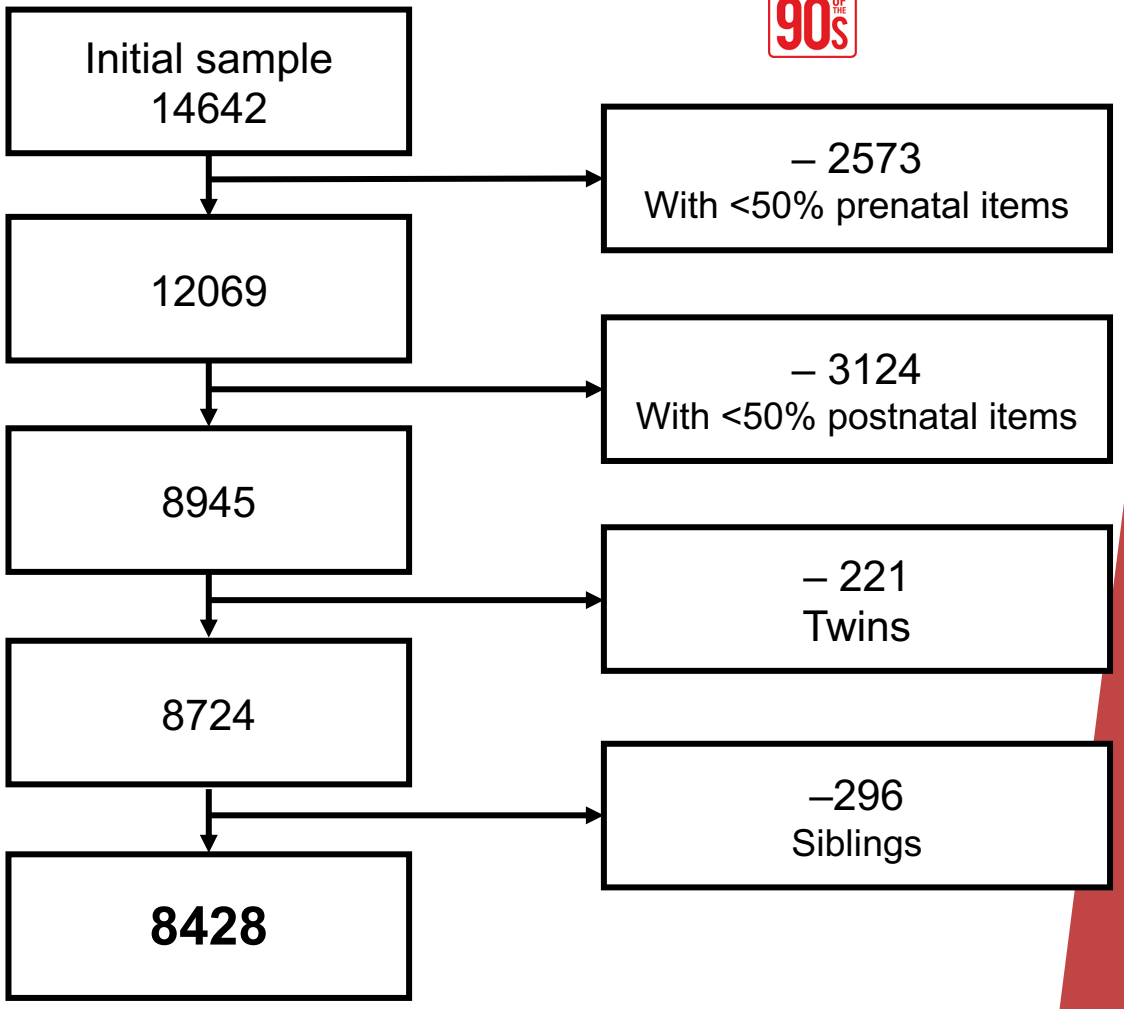
II. Is ELS a risk factor for comorbidity?

# Sample

## Generation R




## ALSPAC



# Measures: ELS exposure

Pregnancy

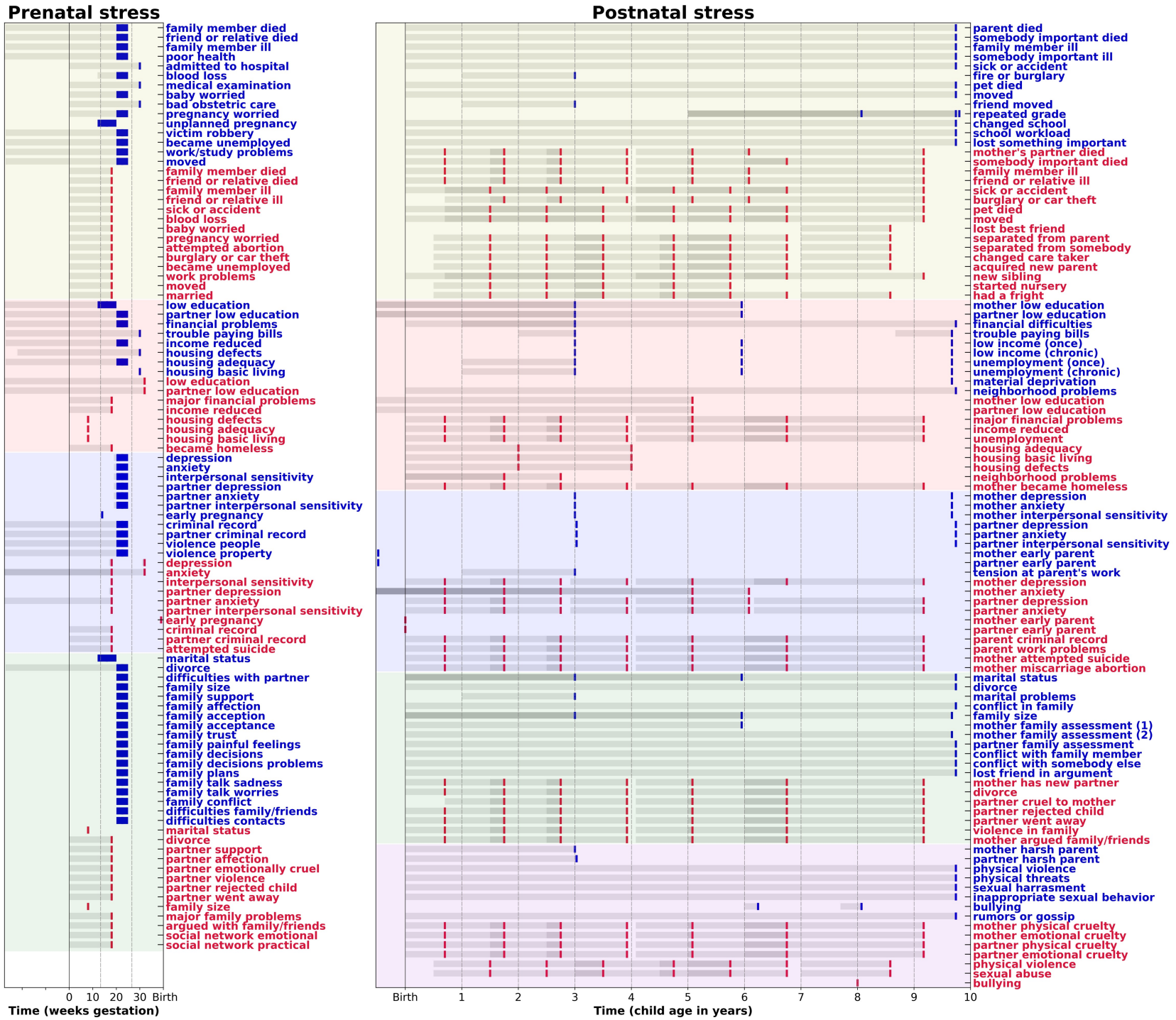
## PRENATAL STRESS

- Life events
  e.g., victim of robbery
- Contextual risk
  e.g., financial difficulties
- Parental risk
  e.g., psychopathology
- Interpersonal risk
  e.g., family conflicts

Childhood (0 – 10 years)

## POSTNATAL STRESS

- Life events
  e.g., death of a relative
- Contextual risk
  e.g., low parental education
- Parental risk
  e.g., parental psychopathology
- Interpersonal risk
  e.g., divorce, overcrowding
- Direct victimization
  e.g., bullying, harsh parenting



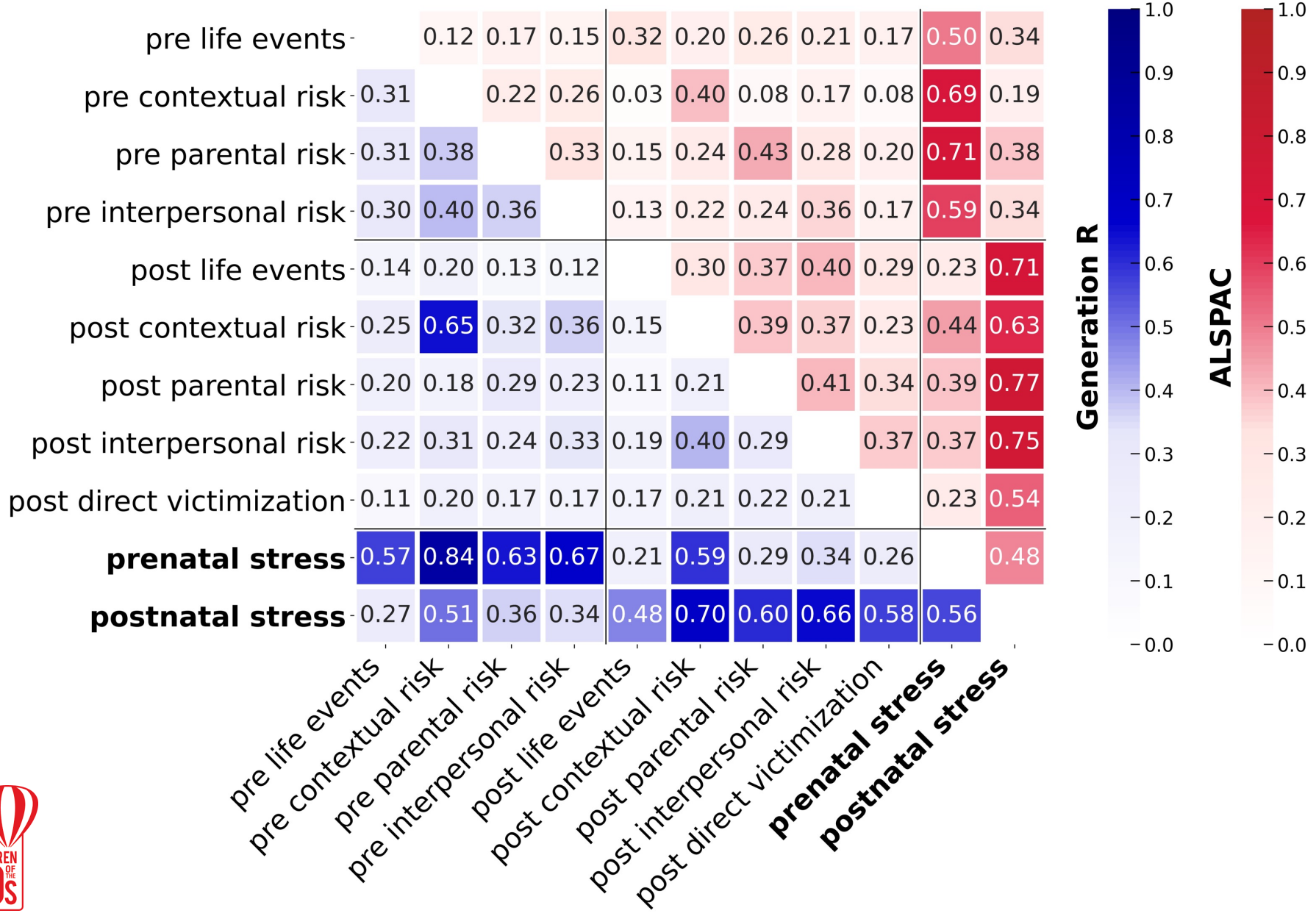

Generation R

CHILDREN OF THE 90S

- Life events
- Contextual risk
- Parental risk
- Interpersonal risk
- Direct victimization

https://github.com/SereDef/cumulative-ELS-score

# Stress score correlation matrix



# Measures: primary health outcomes

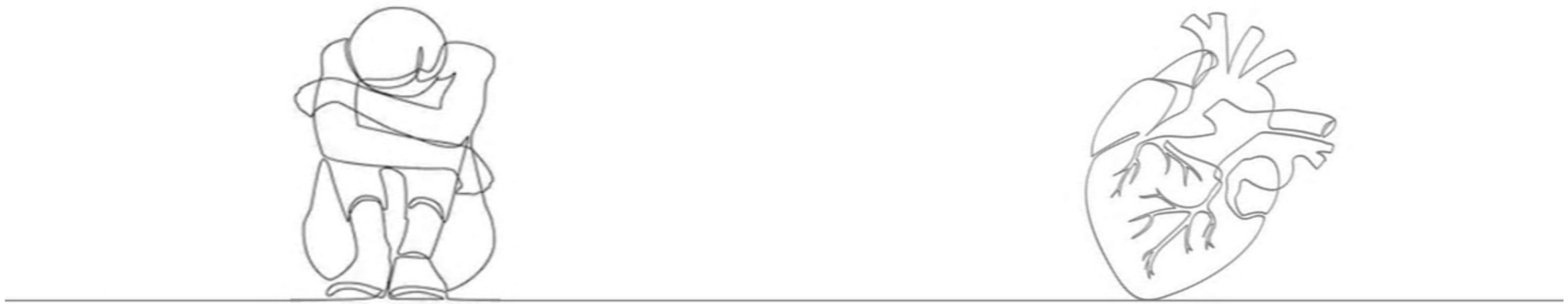
## Internalizing symptoms @13

- Child behaviour checklist (**CBCL**)
  - ⇢ Internalizing subscale
- Strengths and Difficulties Questionnaire (**SDQ**)
  - ⇢ Emotional problems subscale

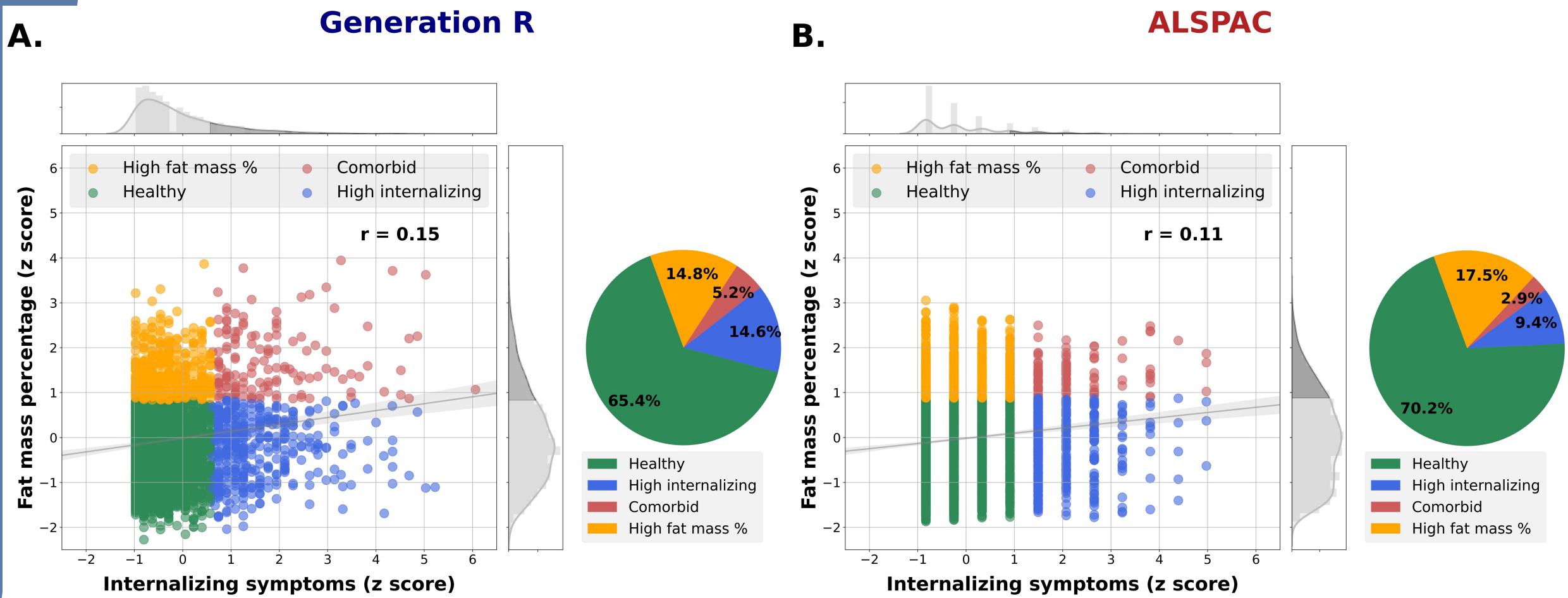
## Cardio-metabolic risk @13

- **Fat mass percentage** =
  total body fat mass (kg)* / weight (kg)
- Android fat mass*

*measured using a dual-energy X-ray absorptiometry (DXA) scanner.



# Measures: comorbidity outcome



# Modeling strategy

**Prenatal** contribution ▶ Causal mediation analysis (CMA)


- Internalizing
- Fat mass %

- Sex
- Age
- Ethnicity
- Maternal BMI (pre-pregnancy)
- Maternal smoking (during pregnancy)
- Maternal drinking (during pregnancy)

**Postnatal** contribution ▶ Hierarchical regression analysis

- Internalizing ~
- Fat mass % ~

0. covariates
1. prenatal stress + covariates
2. **postnatal stress** + covariates
3. **prenatal stress** + **postnatal stress** + covariates

---

**Co-morbidity** ~

1. **prenatal stress** + covariates
2. **postnatal stress** + covariates

# Additional analyses

- Moderation effects of:
  - **Sex**
  - **Ethnic backgroud**
- Individual stress **domains** as predictors;
- Sensitivity analysis:
  - responders only
  - android fat mass

# Results: prenatal contribution

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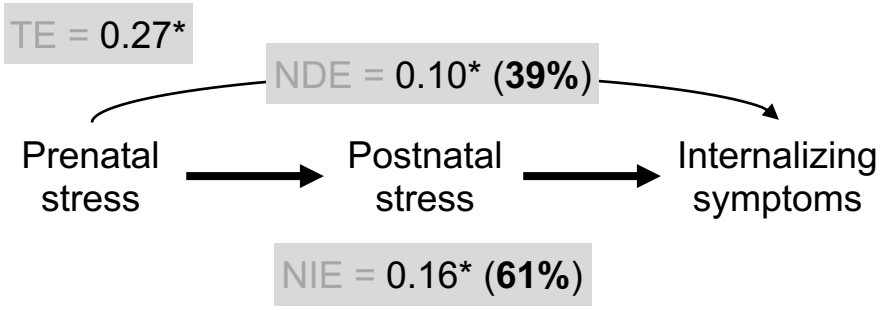
## Generation R

A.

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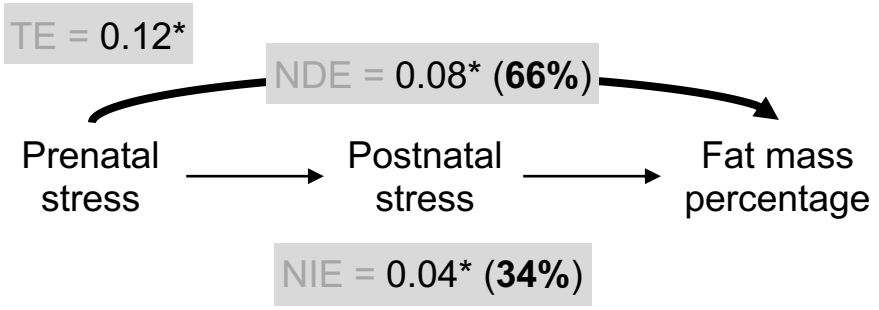
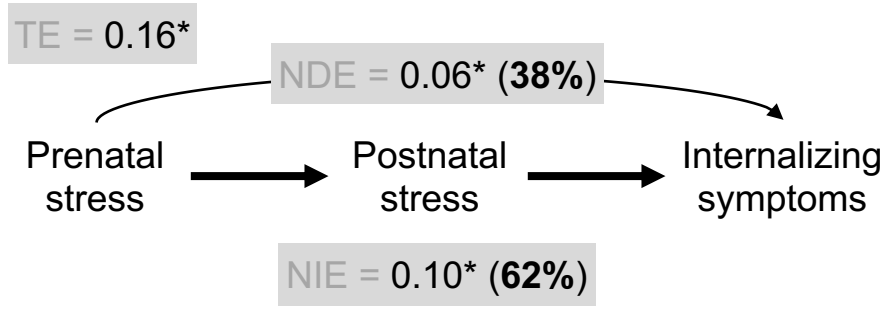



## ALSPAC

B.

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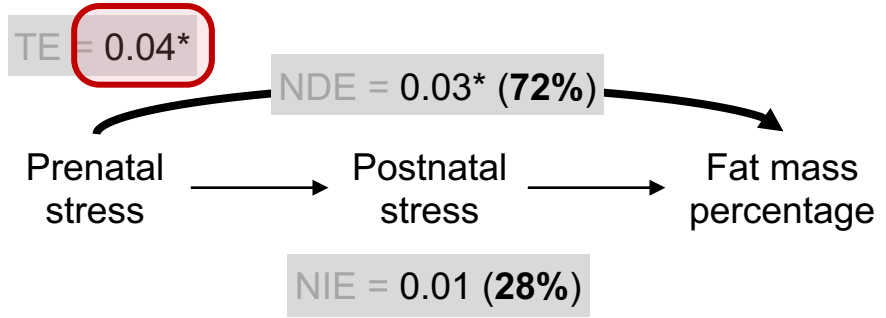
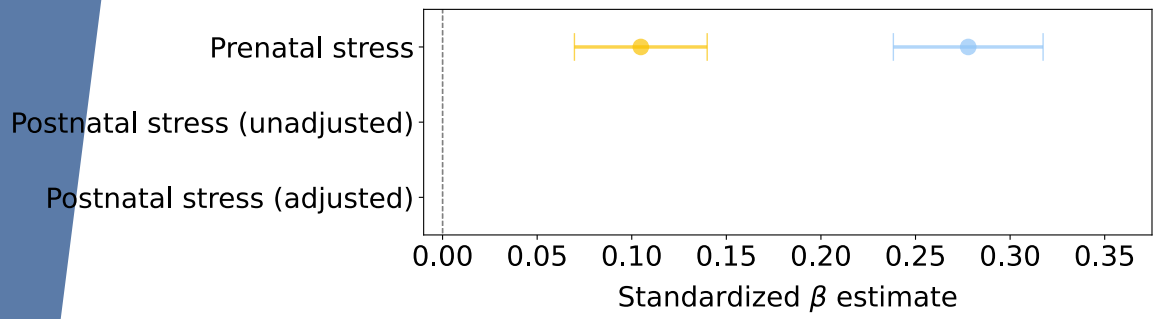


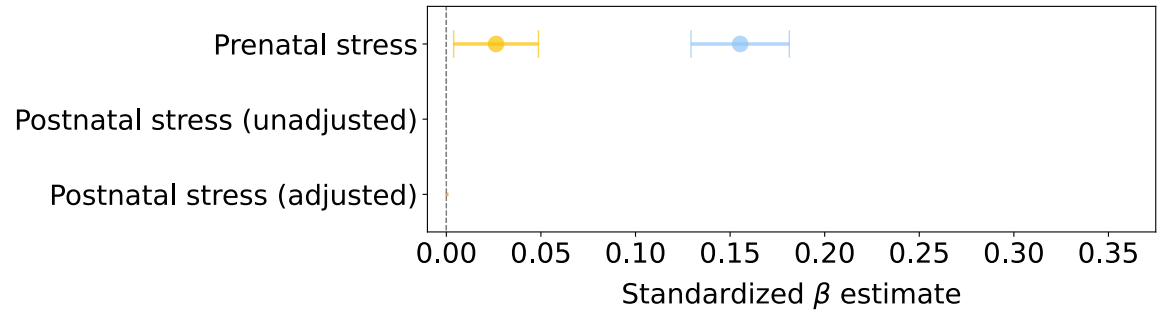
# Results: postnatal contribution

## Generation R




| Adiposity | | Internalizing | |
|---|---|---|---|
| $R^2 = 0.25$; | $R^2_{inc} = 0.01$ | $R^2 = 0.07$; | $R^2_{inc} = 0.06$ |
| $R^2 = 0.25$; | $R^2_{inc} = 0.01$ | $R^2 = 0.10$; | $R^2_{inc} = 0.09$ |
| $R^2 = 0.25$; | $R^2_{inc} = 0.01$ | $R^2 = 0.11$; | $R^2_{inc} = 0.10$ |

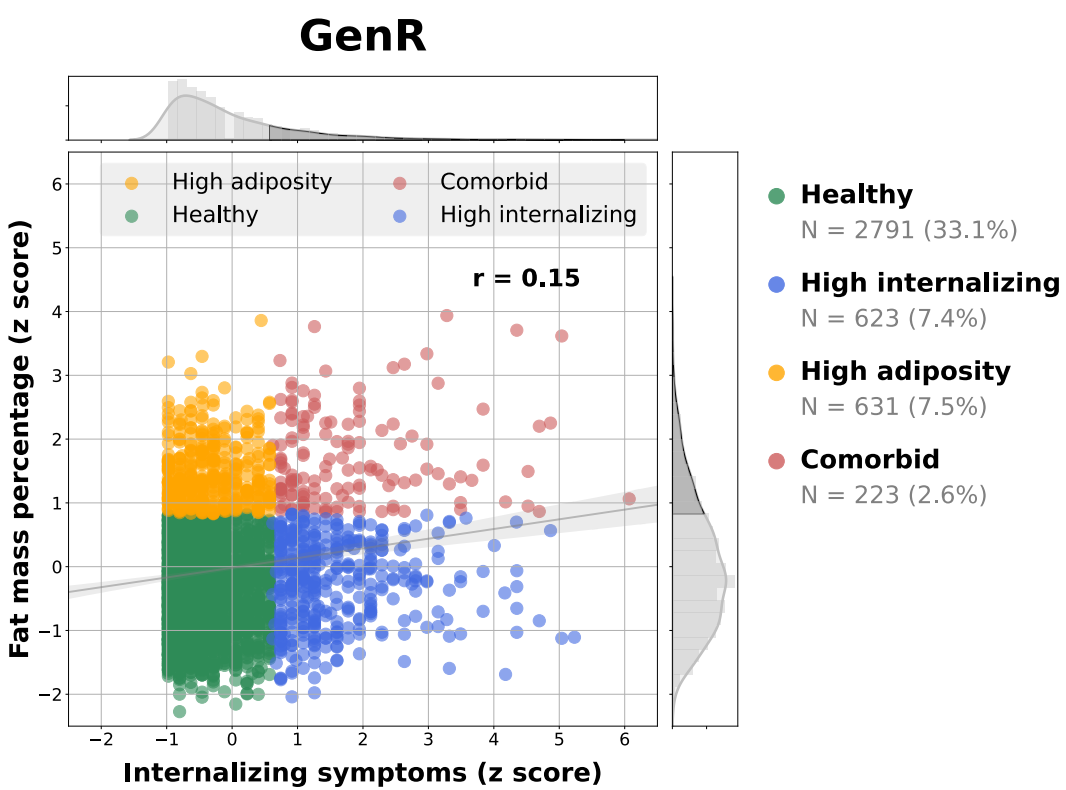
## ALSPAC




| Adiposity | | Internalizing | |
|---|---|---|---|
| $R^2 = 0.33$; | $R^2_{inc} < 0.01$ | $R^2 = 0.04$; | $R^2_{inc} = 0.02$ |
| $R^2 = 0.33$; | $R^2_{inc} < 0.01$ | $R^2 = 0.06$; | $R^2_{inc} = 0.05$ |
| $R^2 = 0.33$; | $R^2_{inc} < 0.01$ | $R^2 = 0.07$; | $R^2_{inc} = 0.05$ |

# Results: comorbidity

A.

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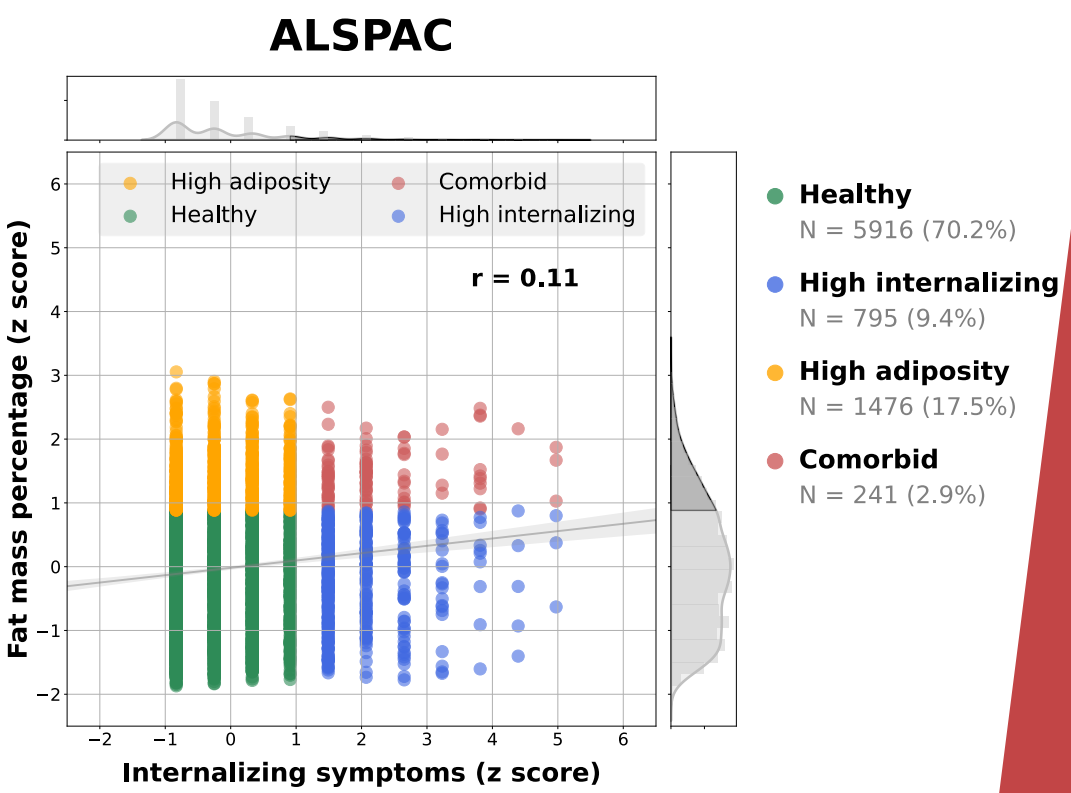


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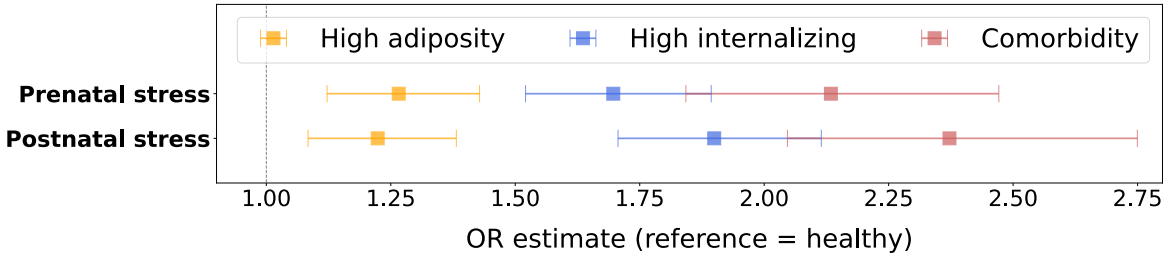


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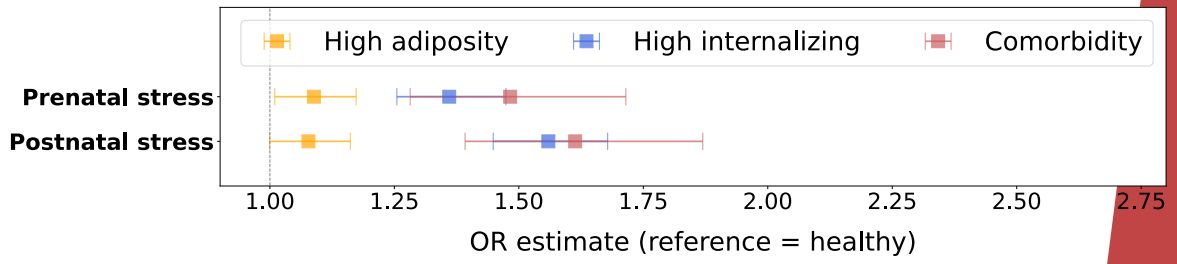

# A peek across the lifespan...

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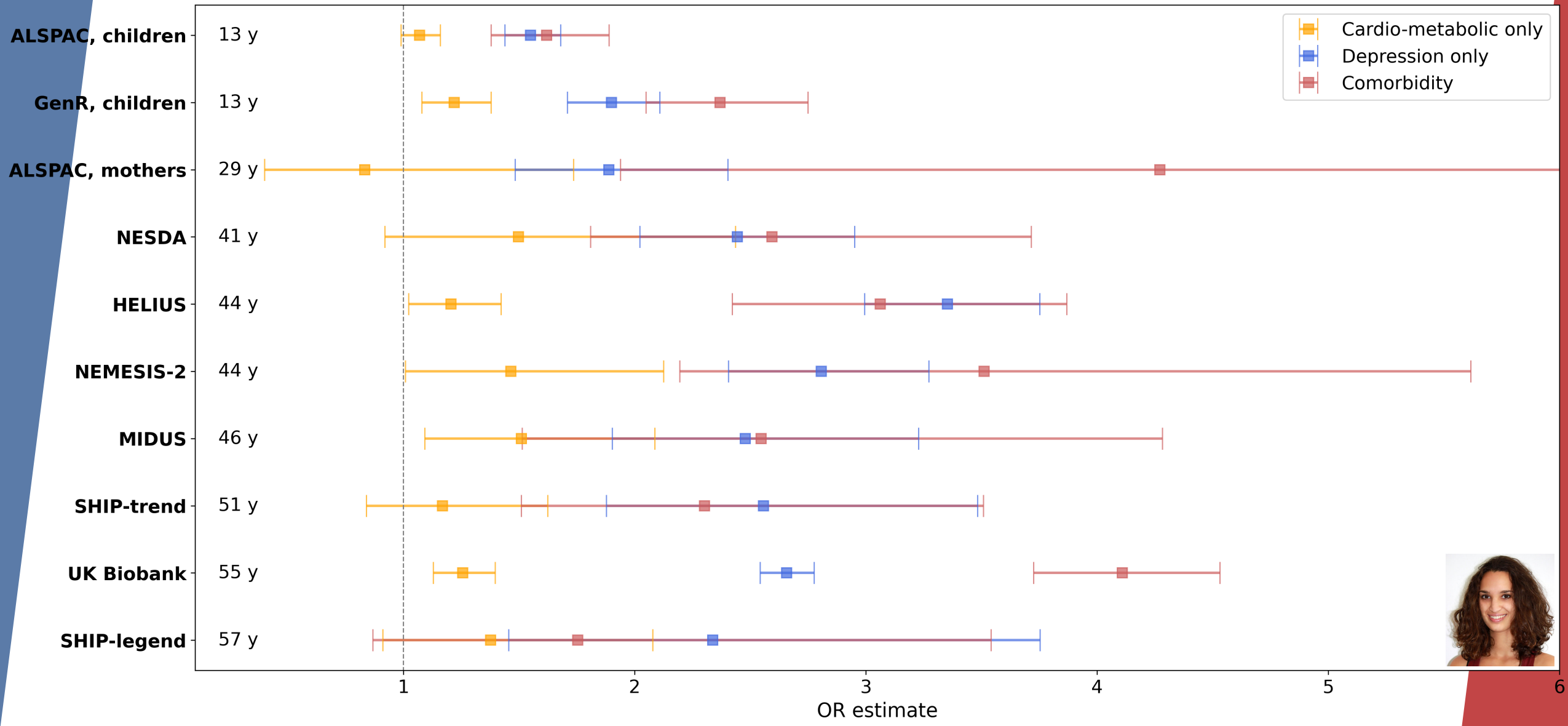


# Results: adiposity by sex

## Generation R

A.

Male

TE = 0.10*

NDE = 0.04 (**43%**)

Prenatal stress → Postnatal stress → Fat mass percentage

NIE = 0.06* (**57%**)

C.

Female

TE = 0.14*

NDE = 0.12* (**82%**)

Prenatal stress → Postnatal stress → Fat mass percentage

NIE = 0.02 (**18%**)

## ALSPAC

B.

TE = 0.03

NDE = 0.01 (**46%**)

Prenatal stress → Postnatal stress → Fat mass percentage

NIE = 0.01 (**54%**)

D.

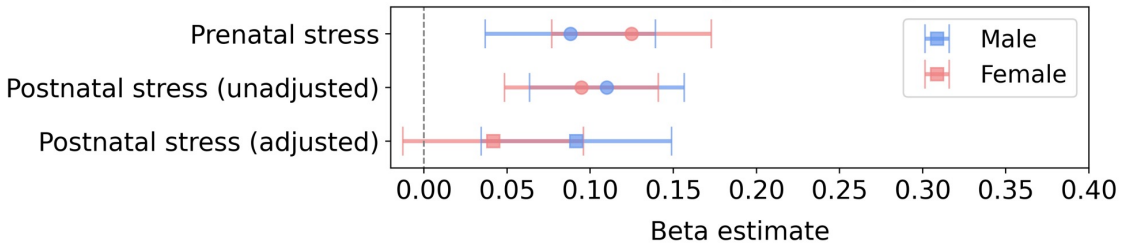
TE = 0.06*

NDE = 0.05* (**83%**)

Prenatal stress → Postnatal stress → Fat mass percentage

NIE = 0.01 (**17%**)

E.

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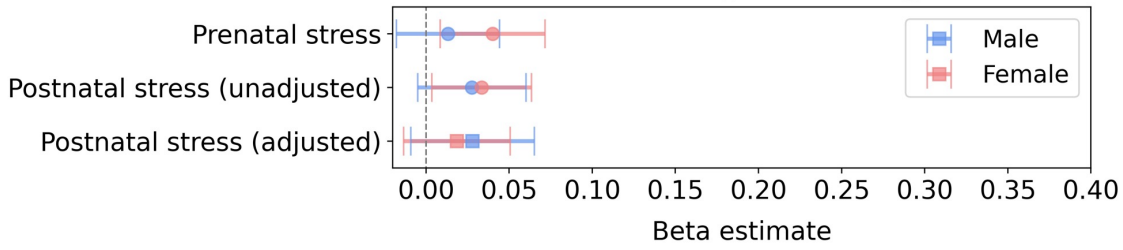

# Summary: main findings

- Both pre- and postnatal ELS predict **internalizing**, with ~60% of the effect of prenatal stress mediated through postnatal exposure.

- Prenatal ELS predicts **adiposity**, and ~70% of its effect is direct (*not* mediated through postnatal stress). Postnatal ELS was significantly associated with adiposity in Generation R only.

- Both pre- and postnatal stress predict **comorbidity**, but *not* significantly more than internalizing problems only (overlapping 95%CIs).

Sex-stratified analyses

- There was some evidence of **sex-specific timing effects** on adiposity, but not internalizing or comorbidity.

# Summary: additional analyses

## Stress domain contribution

- Pre- and postnatal **parental risk***, postnatal **life events** and **direct victimation** consistently associated with internalizing.
- No consistent domain-specific associations for adiposity.
- Only **postnatal parental risk*** associated with comorbidity in both cohorts.

## Sensitivity analyses

- Estimates did not change when restricting to respondents only or using android fat mass.

* i.e. parental psychopathology

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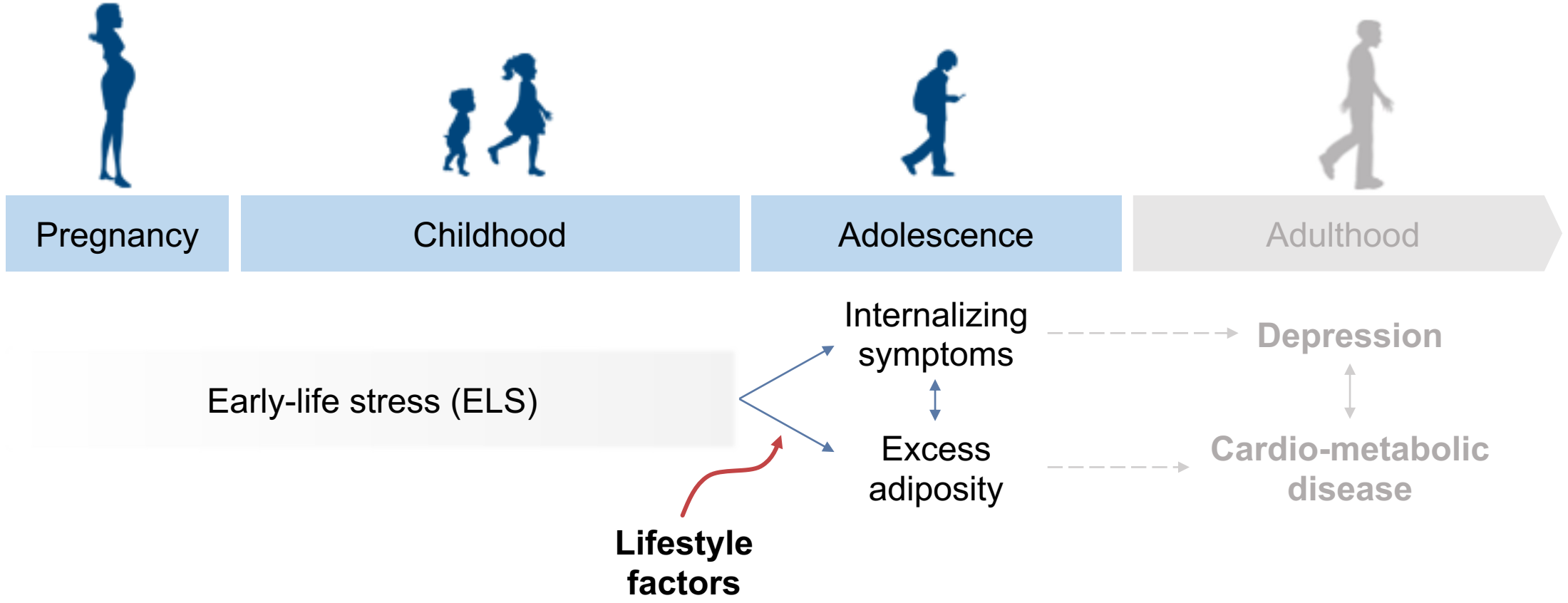
2

# The role of exercise, sleep and diet in the association between ELS and psycho-cardiometabolic comorbidity

Serena Defina, Tom Woofenden, Vilte Baltramonaityte, Janine F. Felix, Charlotte A.M. Cecil, and Esther Walton

*not final byline

# Backgroud




# Aims

I. What is the role of exercise, sleep and diet in the association between ELS and adolescent health?

# Main analyses

**Comorbidity**
**Internalizing**
**Adiposity**

~

**ELS**
Prenatal
Postnatal

*

1. **Exercise**
2. **Sleep**
3. **Diet**

+

**Covariates**
- Sex
- Age
- Ethnicity
- Maternal BMI (pre-pregnancy)
- Maternal smoking (during pregnancy)
- Maternal drinking (during pregnancy)

- 3 comorbidty models + 6 primary outcomes models
- 6 pre-/postnatal stress exposure models

# Lifestyle factors

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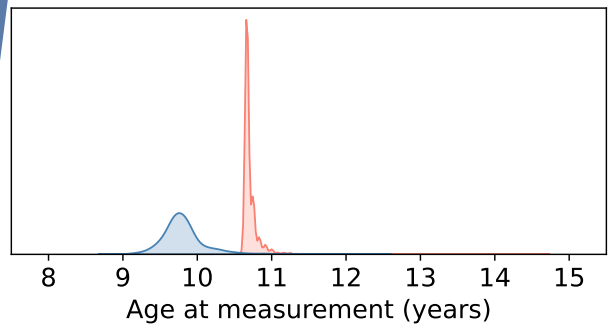
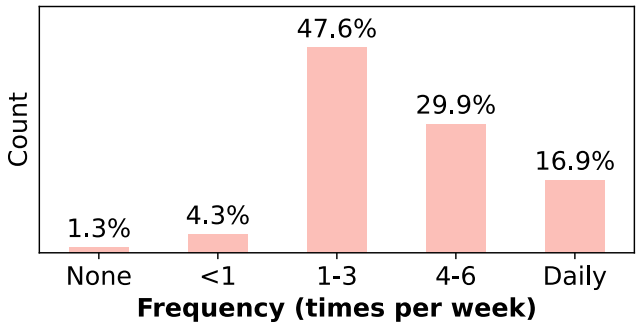
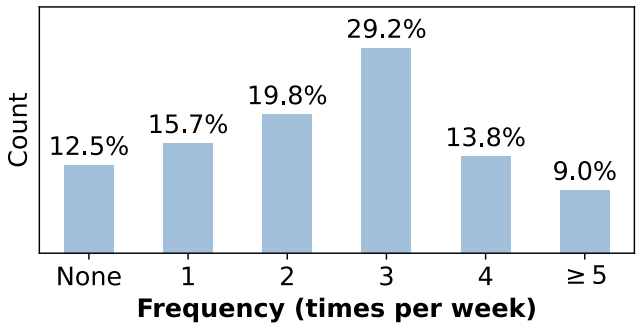
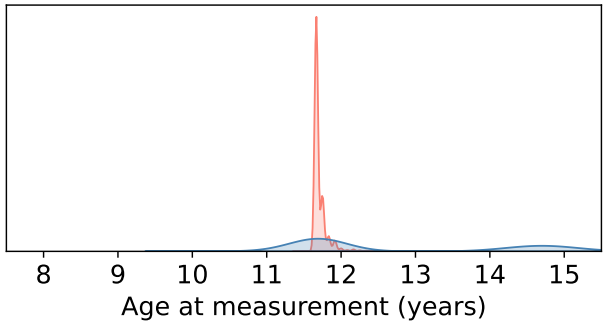
## Exercise

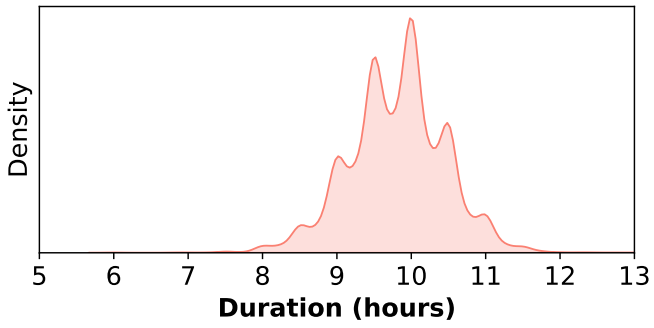


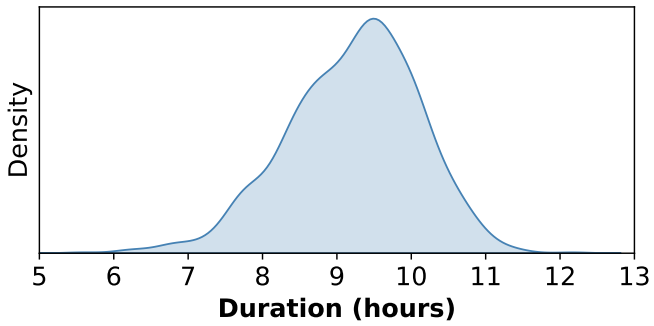



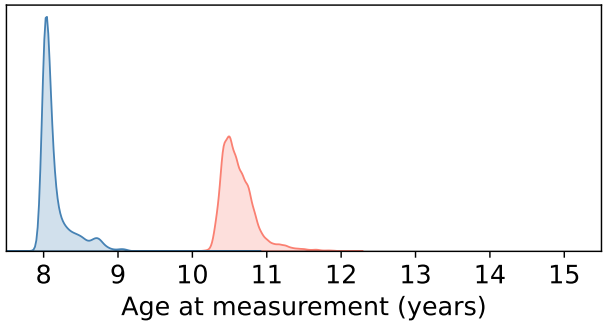

## Sleep

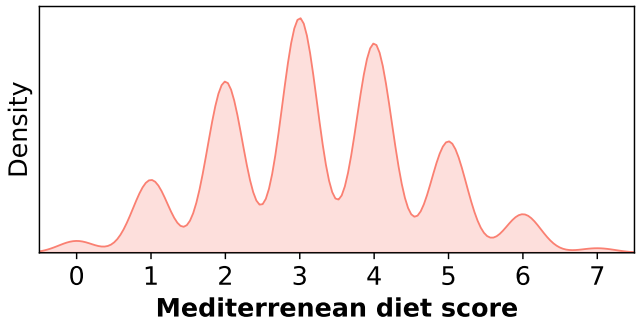


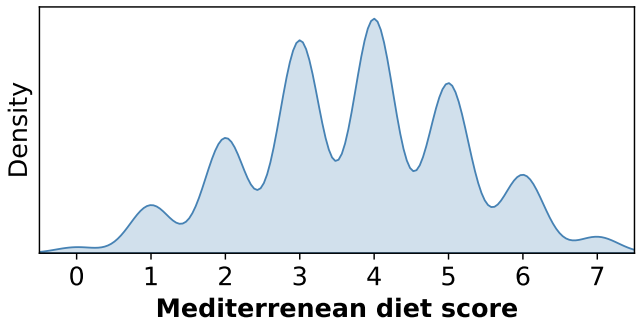




## Diet



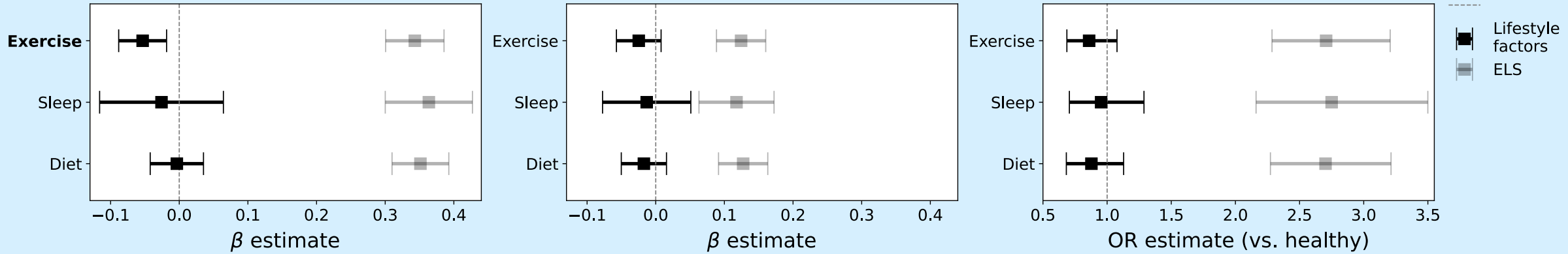




ALSPAC
Generation R

# Results

**MAIN EFFECTS**

**GENERATION R**

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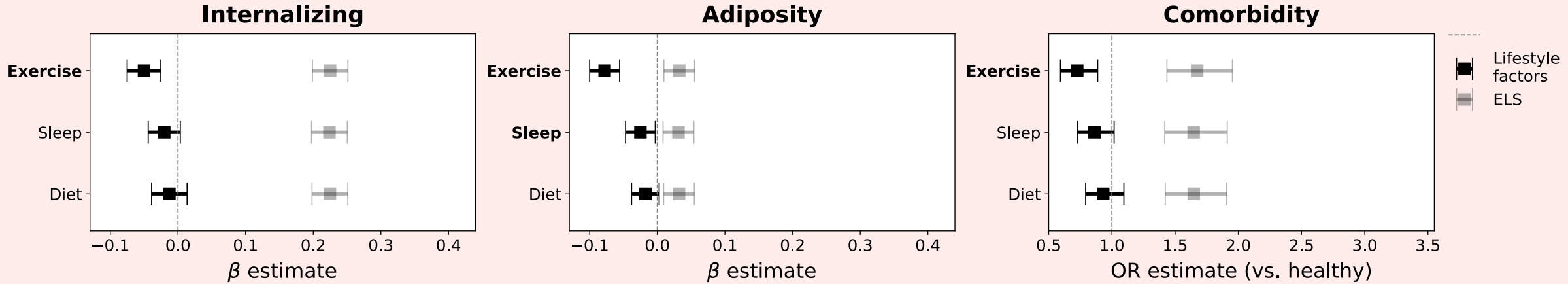
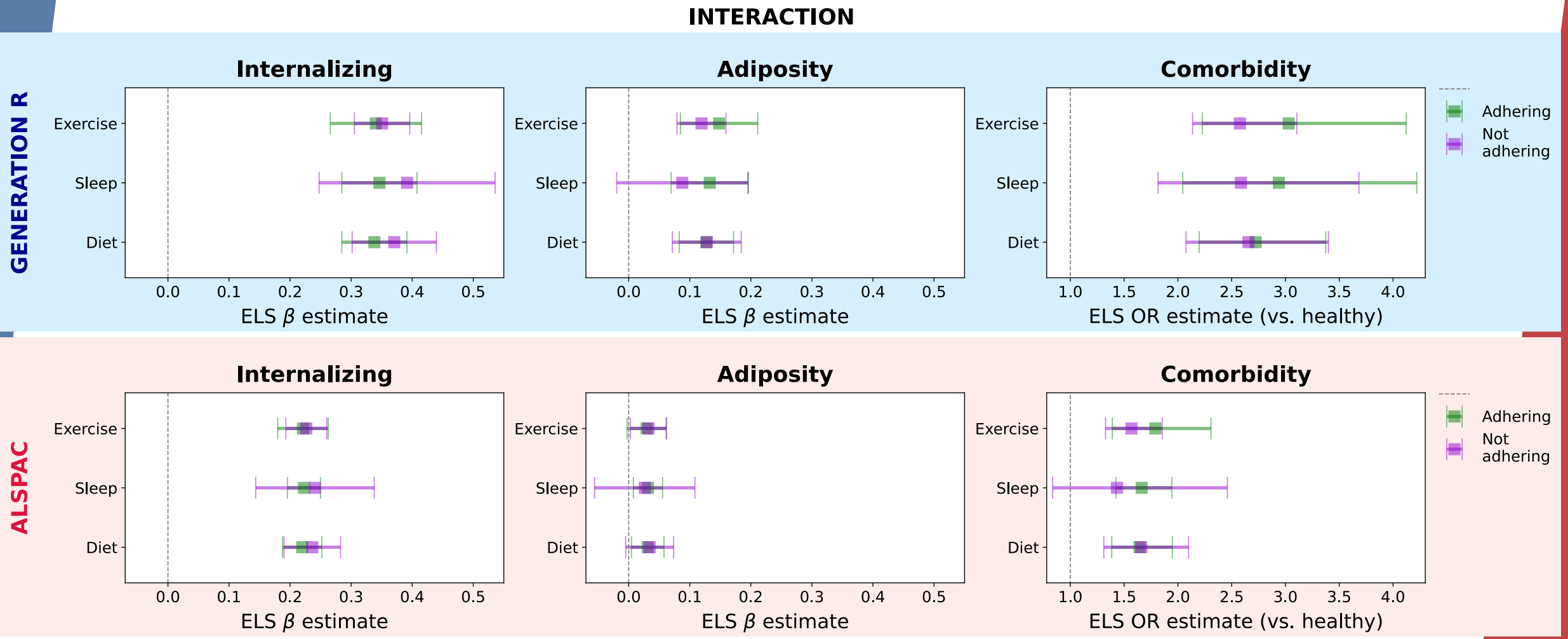



[ outcome ] ~ ELS * [ lifestyle factor ] + sex + age + ethnicity
+ maternal BMI + maternal smoking + maternal alcohol consumption

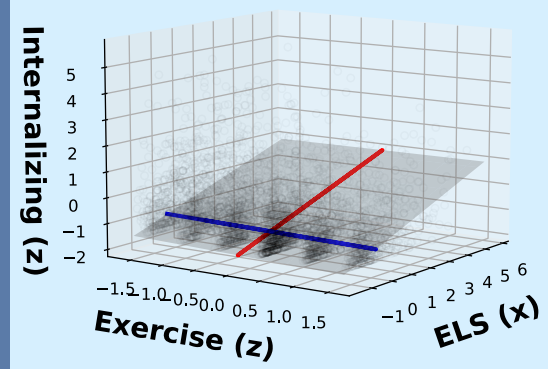
# Results

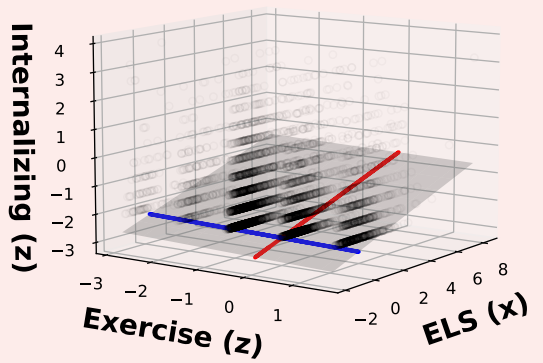


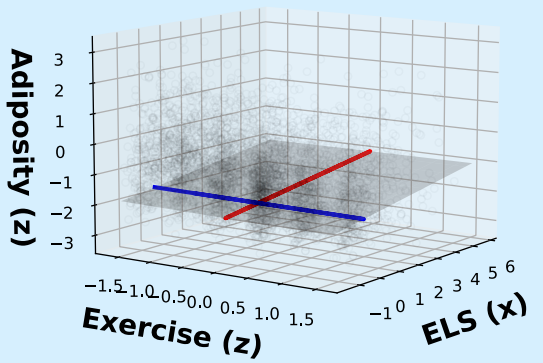

[ outcome ] ~ ELS * [ lifestyle factor (dichotomized) ] + sex + age + ethnicity
+ maternal BMI + maternal smoking + maternal alcohol consumption

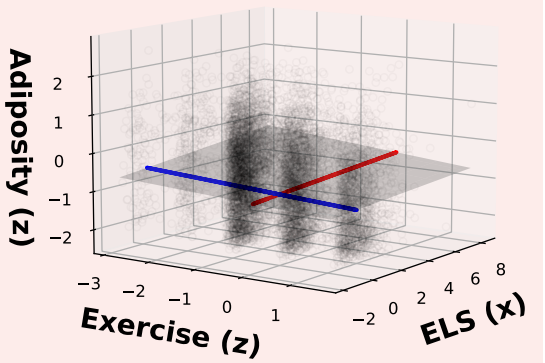
## INTERNALIZING

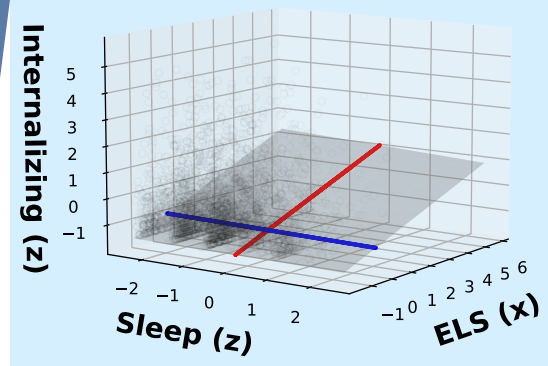
## ADIPOSITY

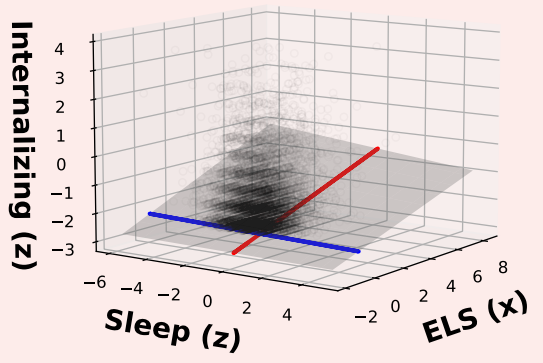


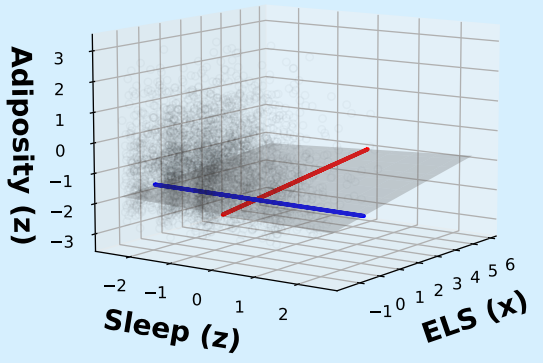



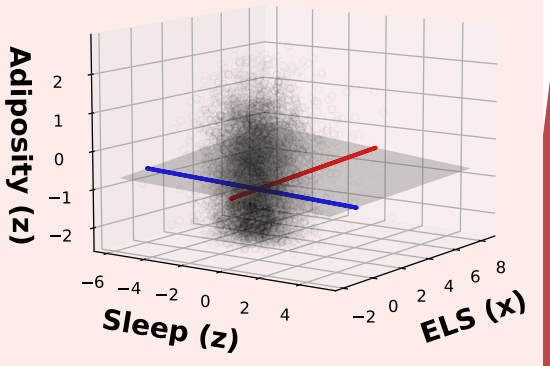



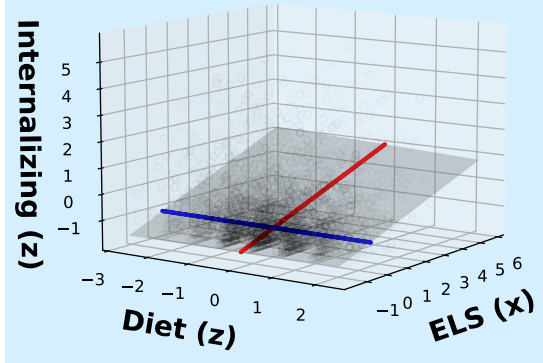



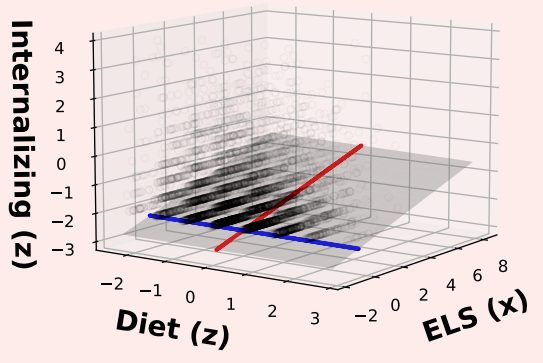



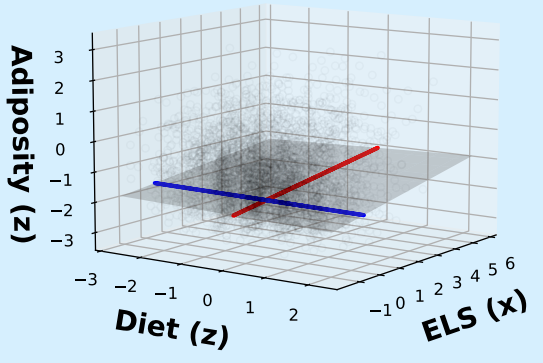



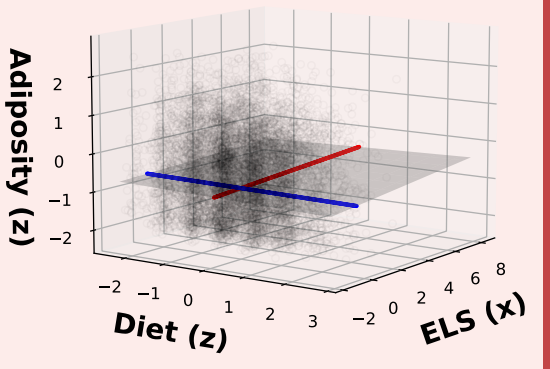



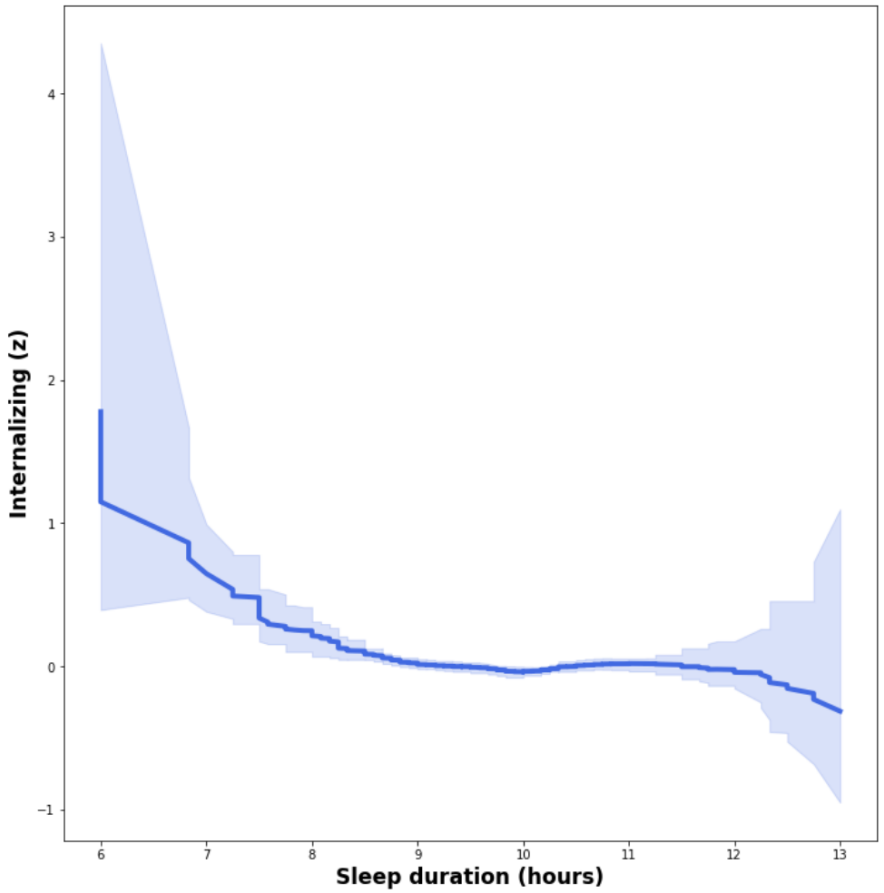



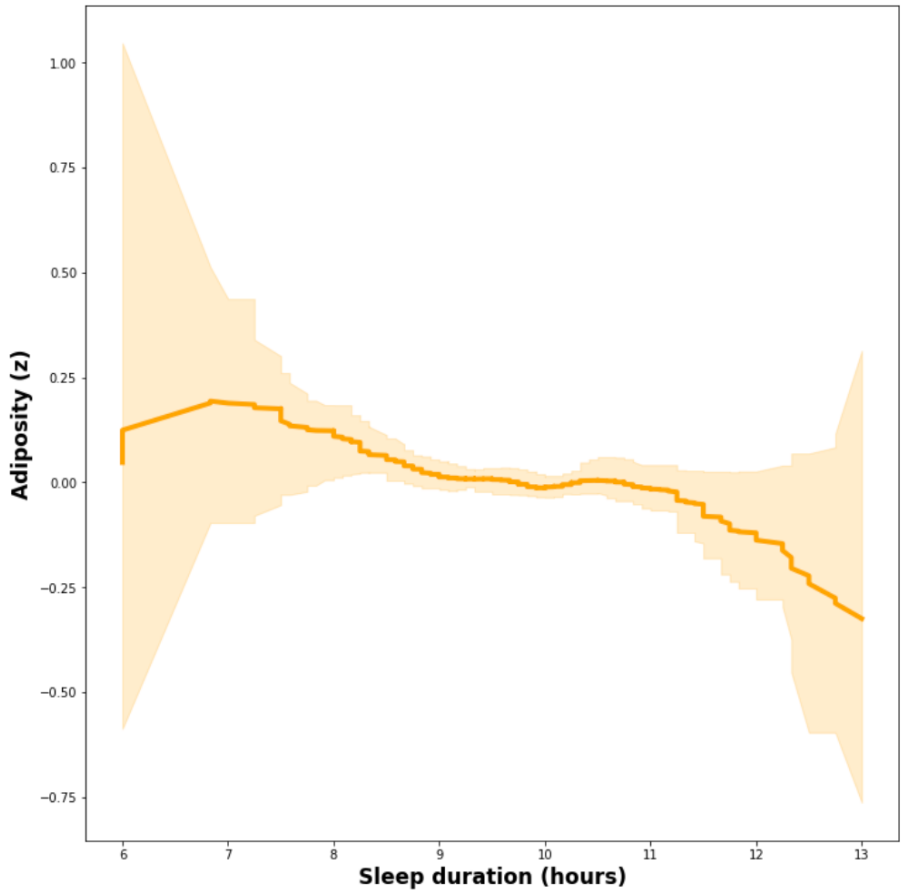




Internalizing (z)
4
3
2
1
0
−1
6
7
8
9
10
11
12
13
Sleep duration (hours)


Adiposity (z)
1.00
0.75
0.50
0.25
0.00
−0.25
−0.50
−0.75
6
7
8
9
10
11
12
13
Sleep duration (hours)

# In summary…

- We did *not* find evidence supporting the hypothesis that lifestyle factors may attenuate the association between ELS and adolescent physical or mental health
- Sensitivity: this did not differ when prenatal and postnatal stress were examined individually

- Work in progress: non-linearities

EARLY CAUSE

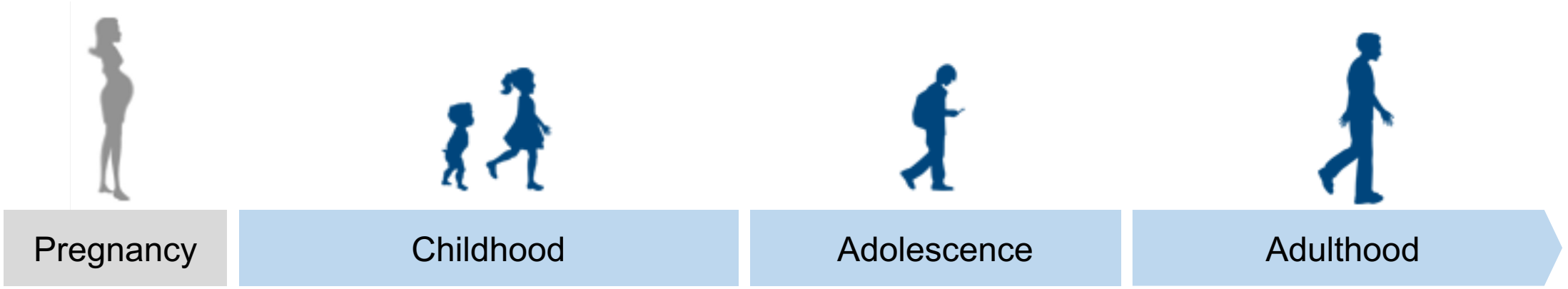
3

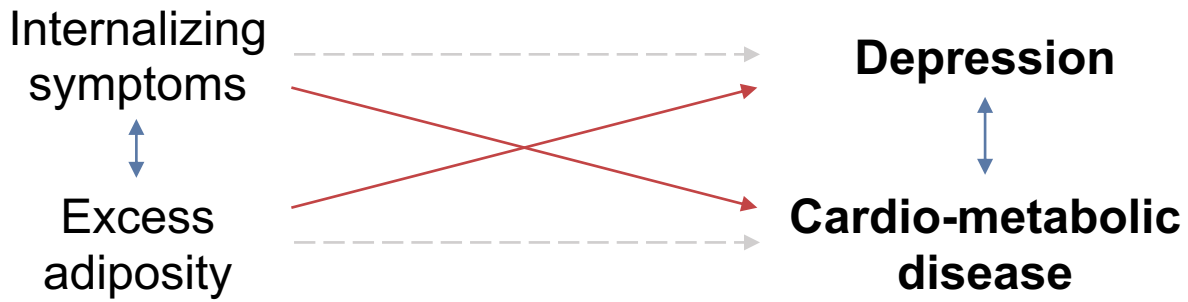
# Cross-sectional and longitudinal relations between internalizing symptoms and cardiometabolic health from childhood to early adulthood

Serena Defina, Vilte Baltramonaityte, Janine F. Felix, Charlotte A.M. Cecil, Esther Walton, and Henning Tiemeier

*not final byline

# Backgroud



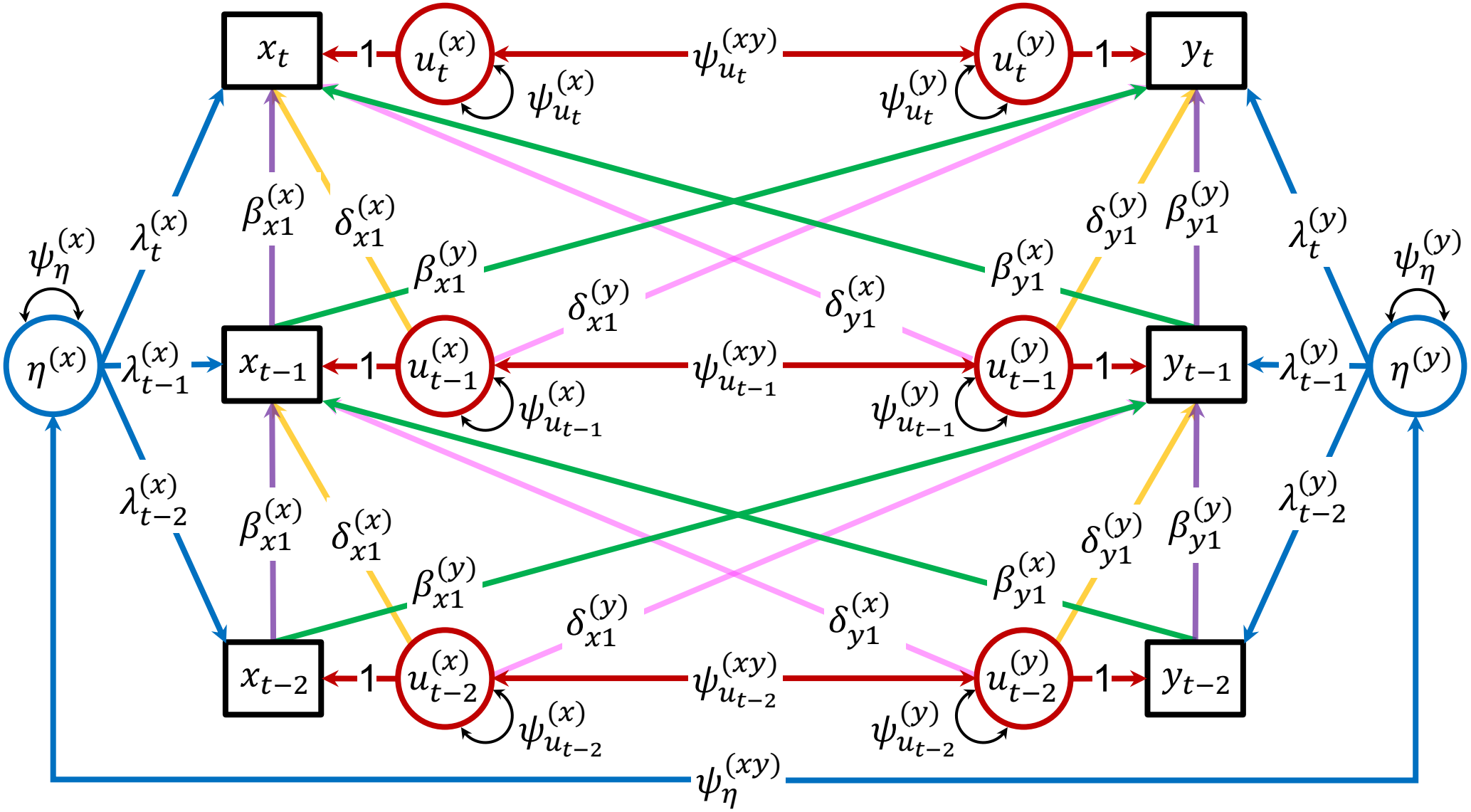

# Aims

I. Cross-sectional relationship between internalizing symptoms and cardio-metabolic health markers?

II. Longitudinal relationship between internalizing symptoms and cardio-metabolic health?

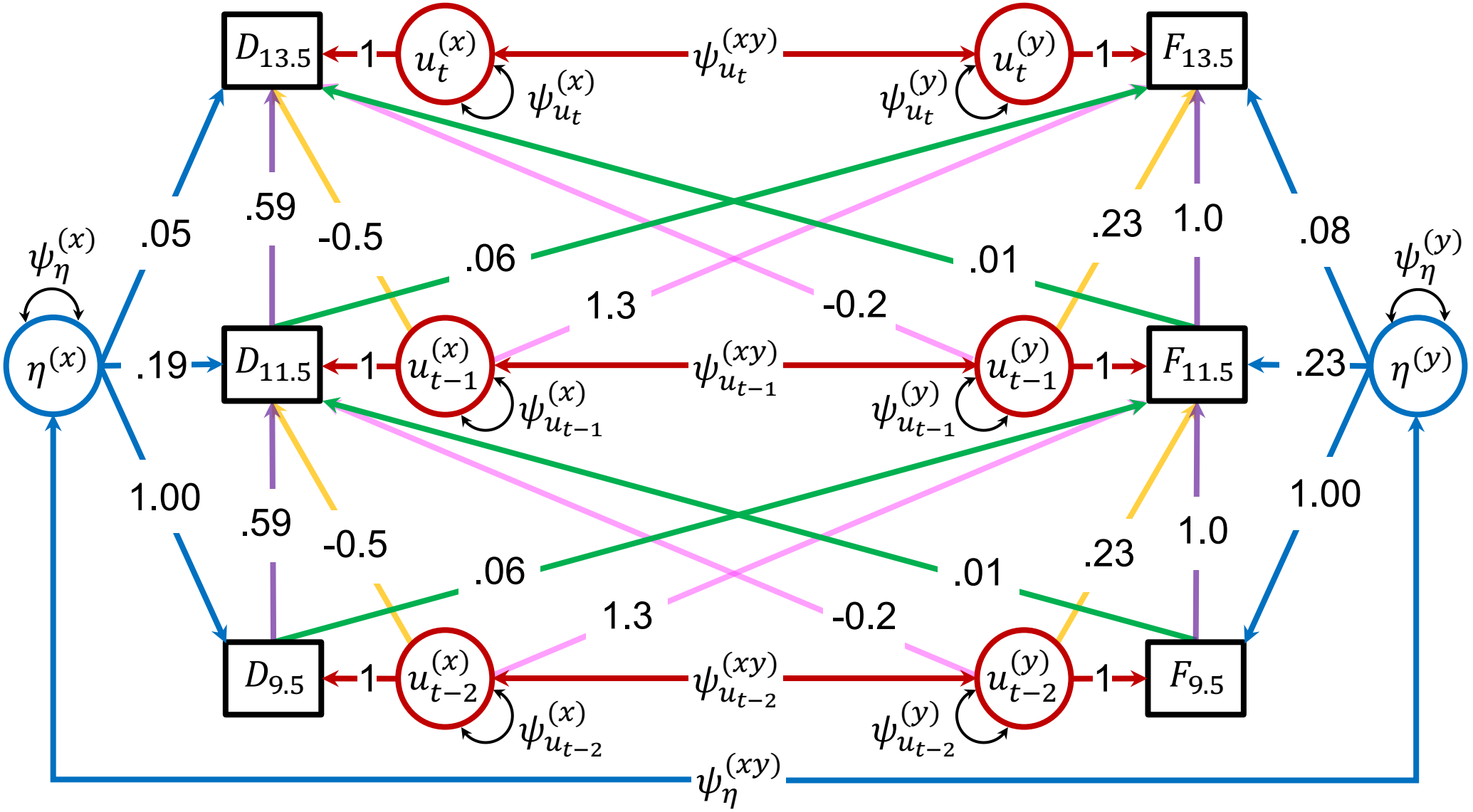
EARLY CAUSE

?




$$x_{it} = \alpha_t^{(x)} + \lambda_t^{(x)}\eta_i^{(x)} + \delta_{x1}^{(x)}u_{it-1}^{(x)} + \beta_{x1}^{(x)}x_{it-1} + \beta_{y1}^{(x)}y_{it-1} + \delta_{y1}^{(x)}u_{it-1}^{(y)} + u_{it}^{(x)}$$

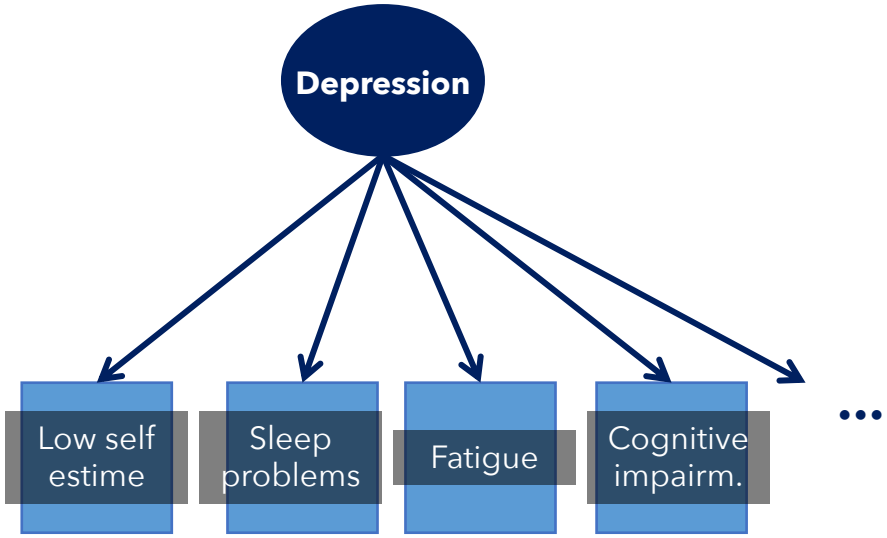
$$y_{it} = \alpha_t^{(y)} + \lambda_t^{(x)}\eta_i^{(x)} + \delta_{y1}^{(y)}u_{it-1}^{(y)} + \beta_{y1}^{(y)}y_{it-1} + \beta_{x1}^{(y)}x_{it-1} + \delta_{x1}^{(y)}u_{it-1}^{(x)} + u_{it}^{(y)}$$

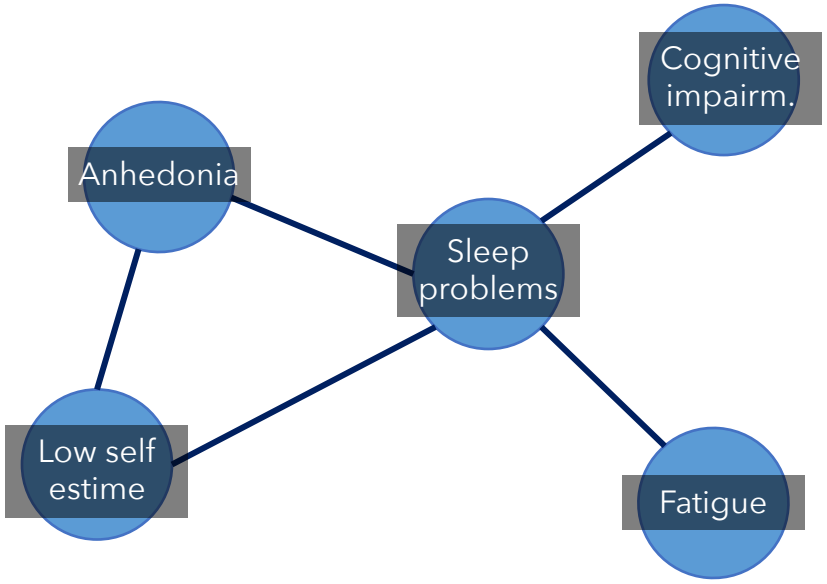



$$x_{it} = \alpha_t^{(x)} + \lambda_t^{(x)}\eta_i^{(x)} + \delta_{x1}^{(x)}u_{it-1}^{(x)} + \beta_{x1}^{(x)}x_{it-1} + \beta_{y1}^{(x)}y_{it-1} + \delta_{y1}^{(x)}u_{it-1}^{(y)} + u_{it}^{(x)}$$

$$y_{it} = \alpha_t^{(y)} + \lambda_t^{(x)}\eta_i^{(x)} + \delta_{y1}^{(y)}u_{it-1}^{(y)} + \beta_{y1}^{(y)}y_{it-1} + \beta_{x1}^{(y)}x_{it-1} + \delta_{x1}^{(y)}u_{it-1}^{(x)} + u_{it}^{(y)}$$

# Health is complicated...

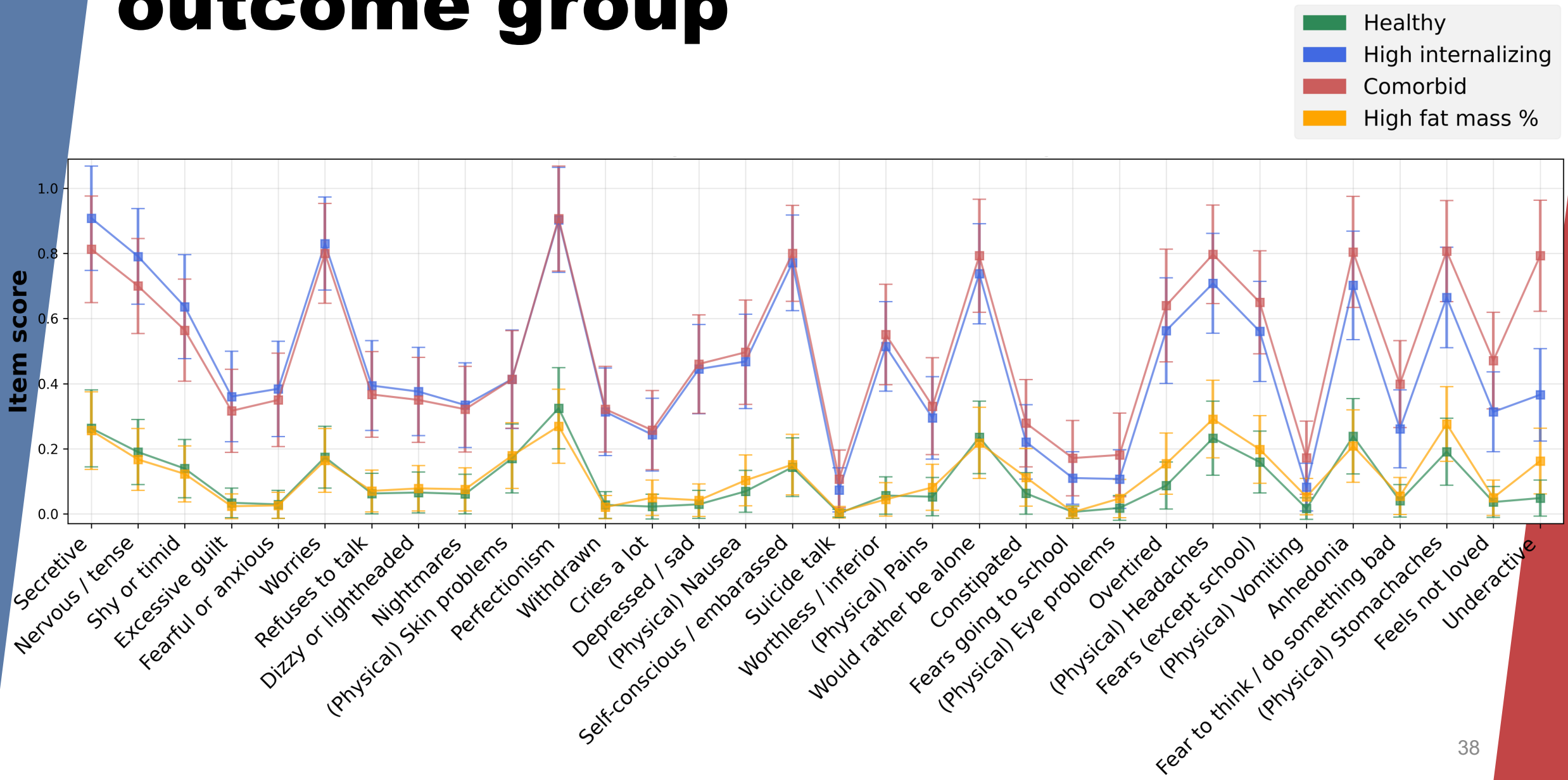


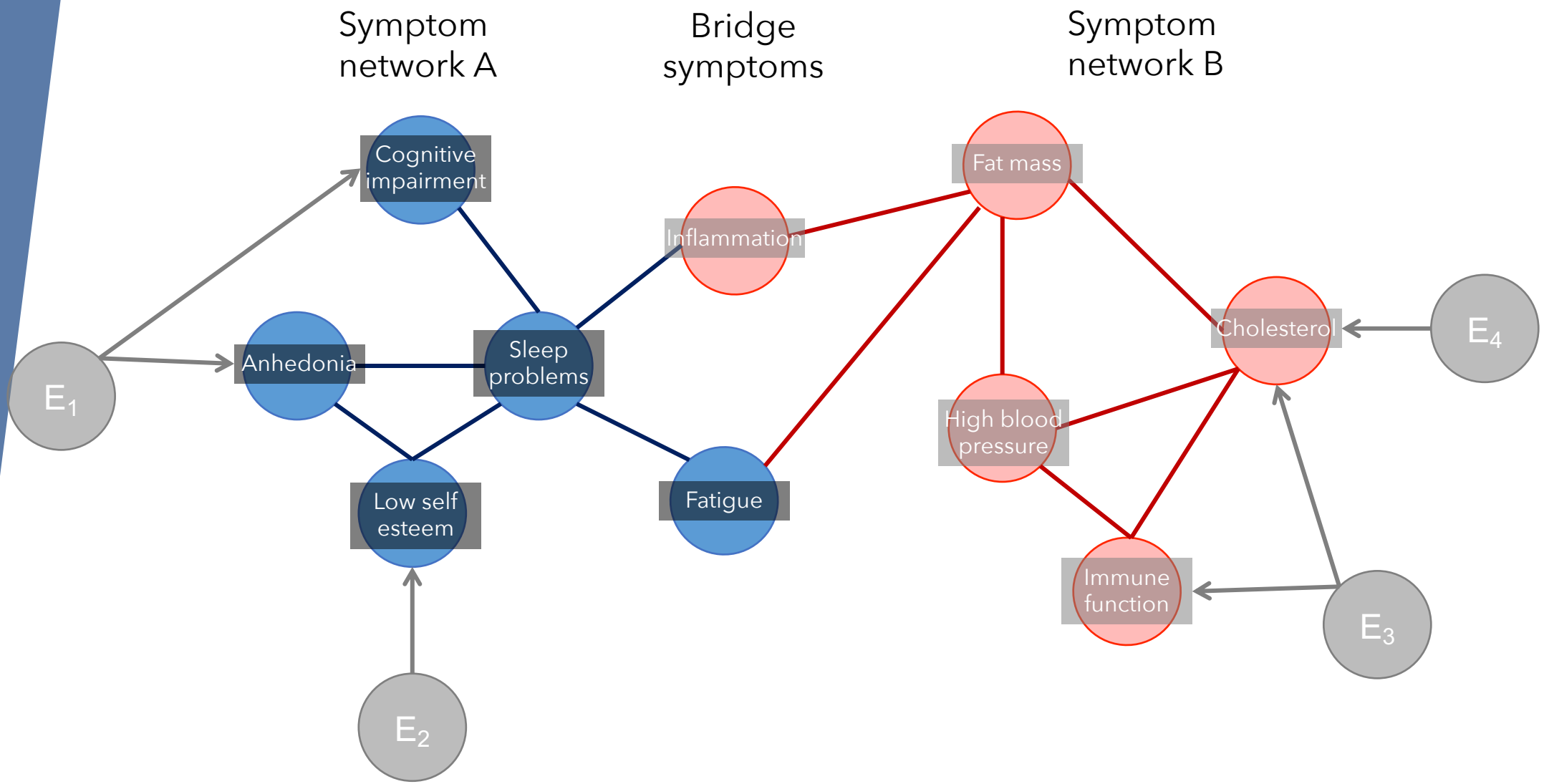

Cramer, A. O. J., Waldorp, L., van der Maas, H., & Bors- boom, D. (2010). Comorbidity: A Network Perspective. *Behavioral and Brain Sciences*, *33*(2-3), 137– 150. doi: 10.1017/S0140525X09991567

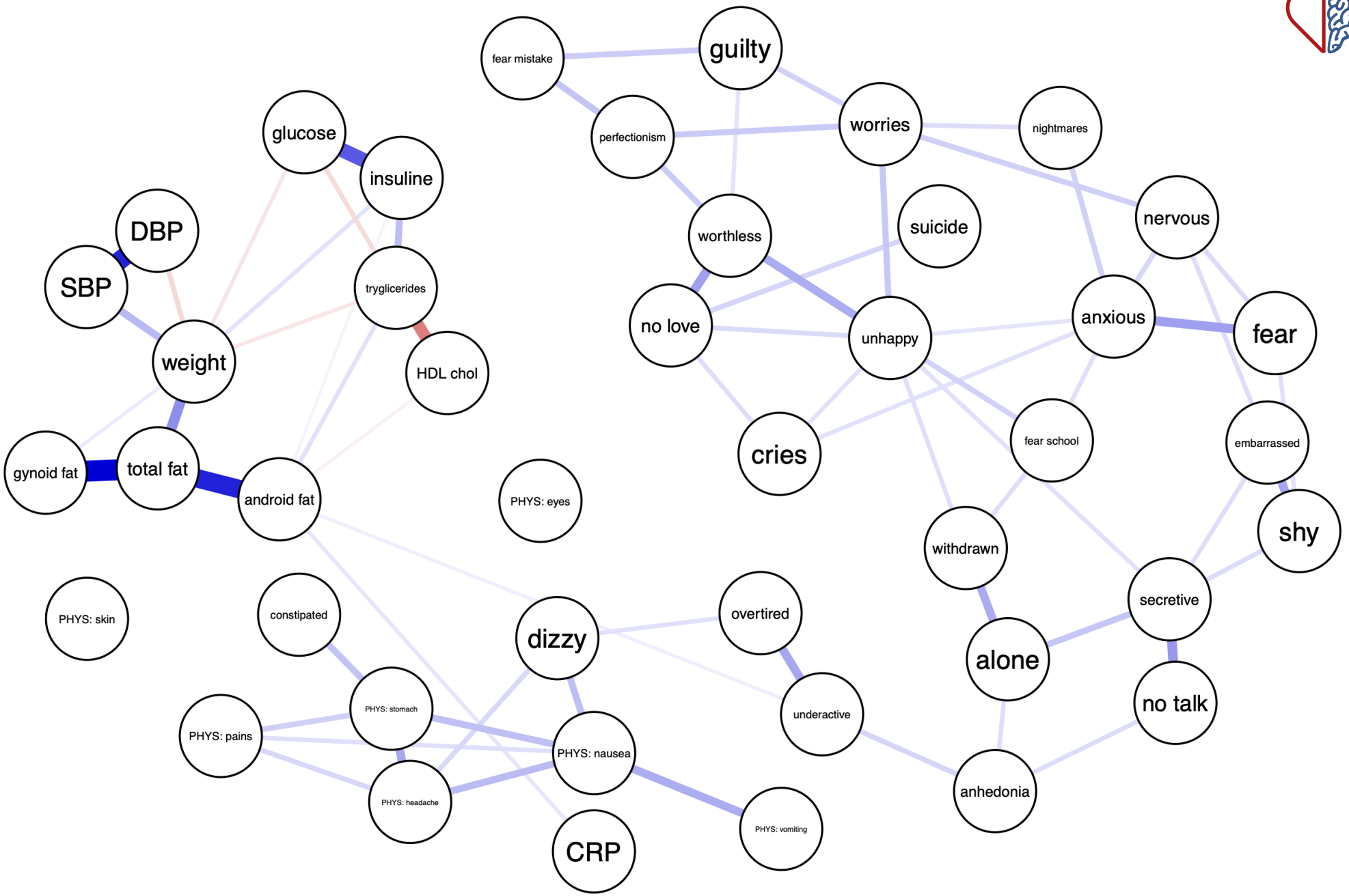
Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, 16(1):5–13.

# Internalizing symptoms per outcome group



# Network models of comorbidity




fear mistake
guilty
perfectionism
worries
nightmares
glucose
insuline
DBP
SBP
worthless
suicide
nervous
tryglicerides
no love
unhappy
anxious
fear
weight
HDL chol
cries
fear school
embarrassed
gynoid fat
total fat
android fat
PHYS: eyes
withdrawn
shy
PHYS: skin
constipated
dizzy
overtired
secretive
alone
PHYS: stomach
underactive
no talk
PHYS: pains
PHYS: nausea
anhedonia
PHYS: headache
PHYS: vomiting
CRP

# Questions?