EARLY CAUSE

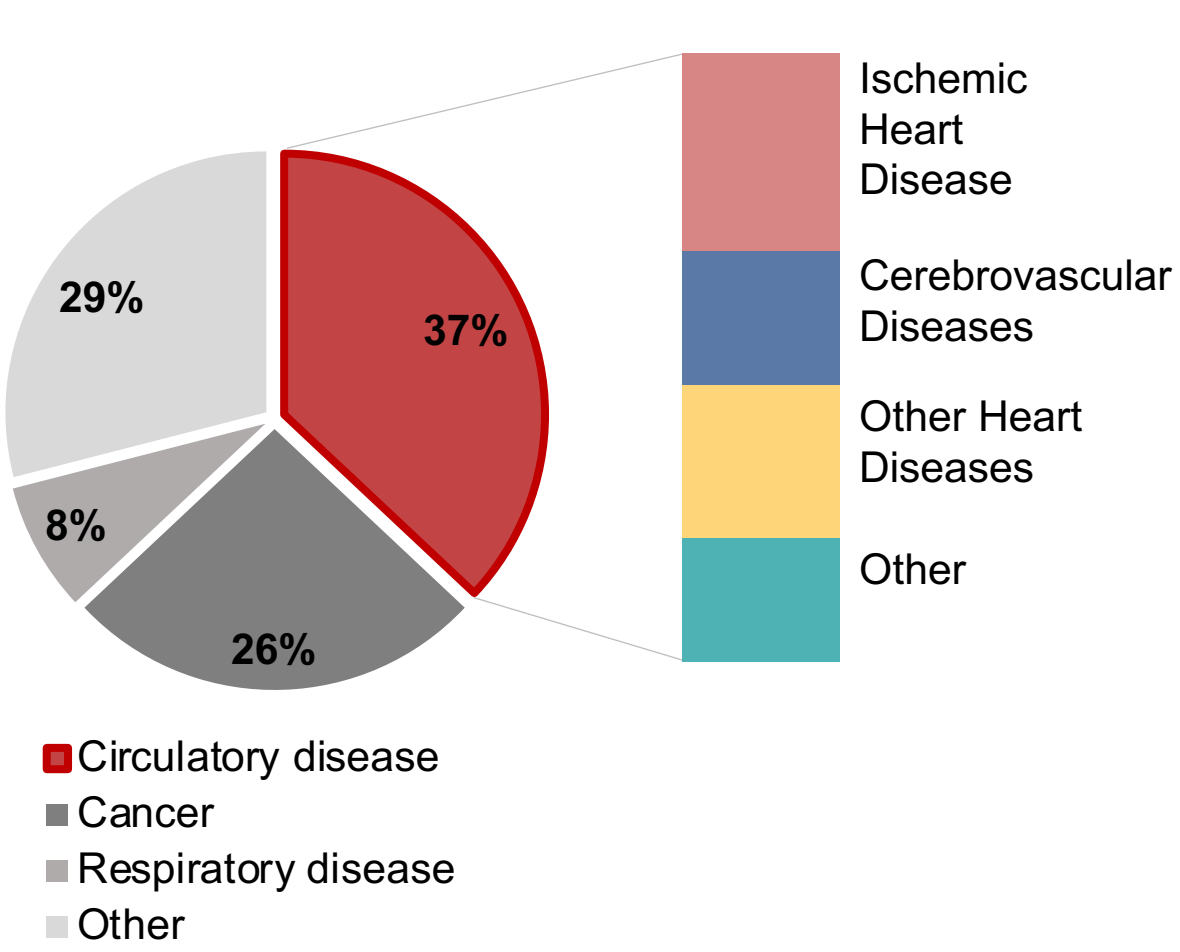
Determinants and consequences of cardiovascular health in childhood

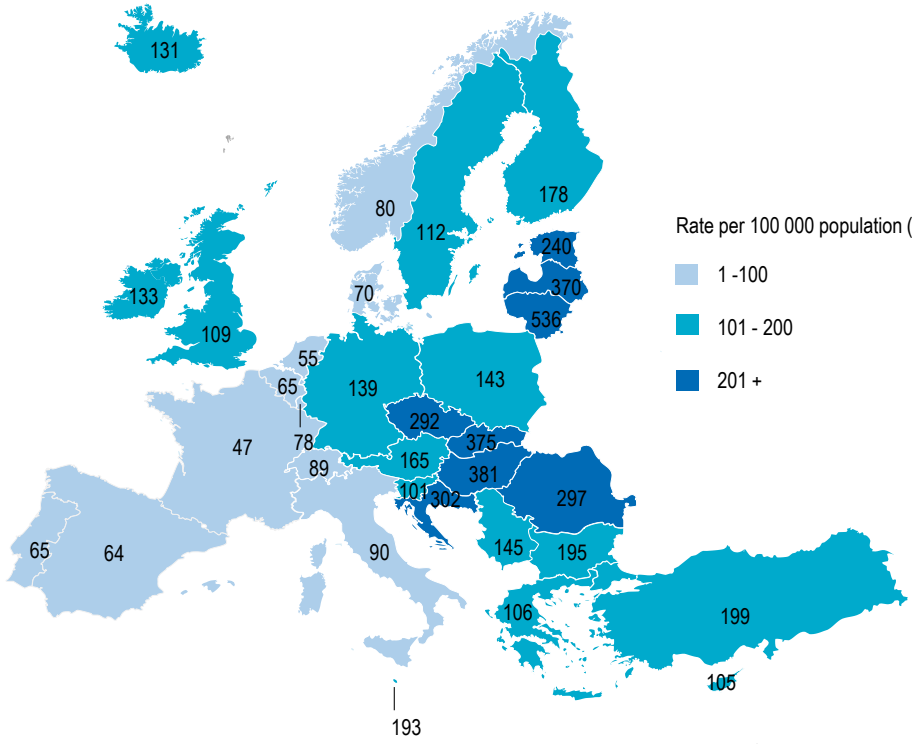
This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement N° 848158.

20/10/2022

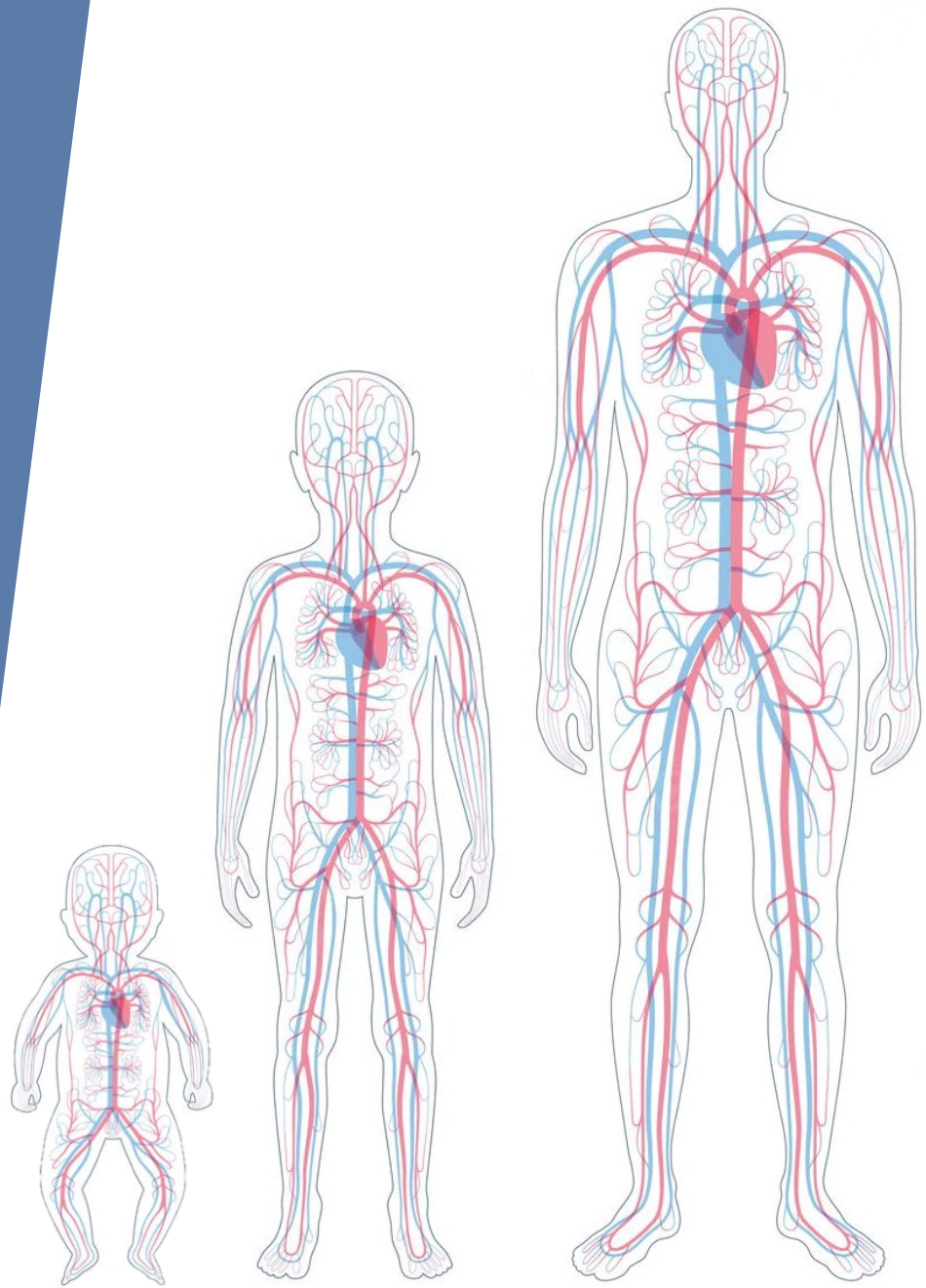
Serena Defina, Erasmus MC

Leading causes of death in Europe (2019)





European Commission | eurostat



This talk

1. **Arterial health** and **brain morphology** in early adolescence

2. **Early-life stress** and **cardiac structure and function** in childhood

EARLY CAUSE

1

Arterial health and brain morphology in early adolescence

Serena Defina, Carolina Silva, Henning Tiemeier, Charlotte Cecil, Janine Felix, Ryan Mutzel, Vincent Jaddoe

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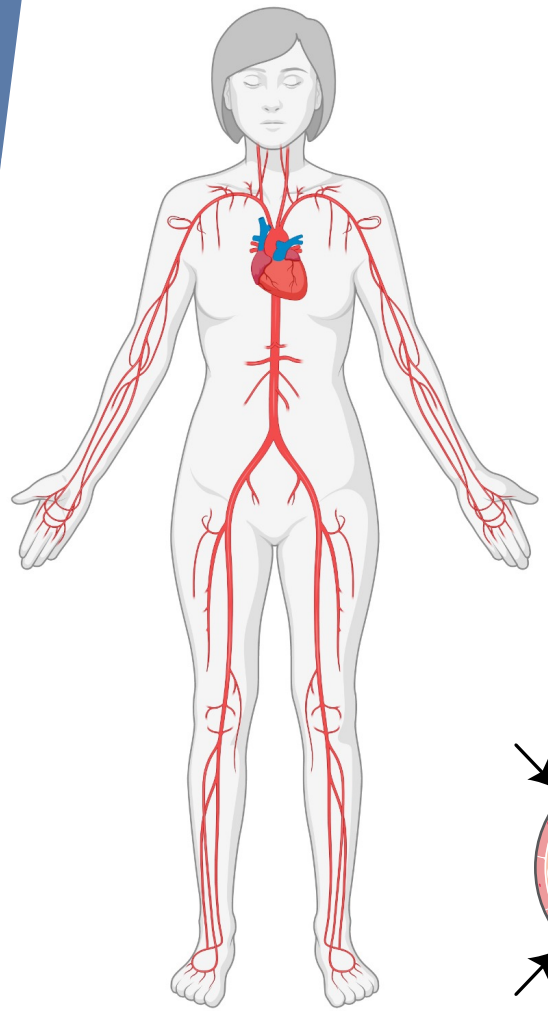
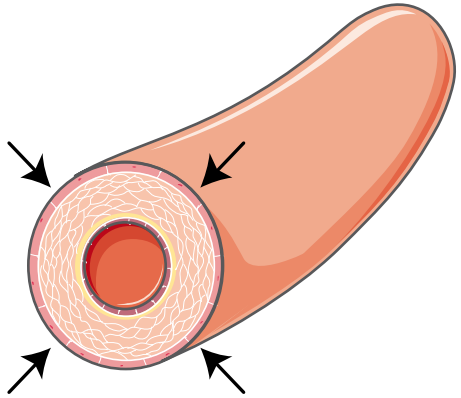
Background

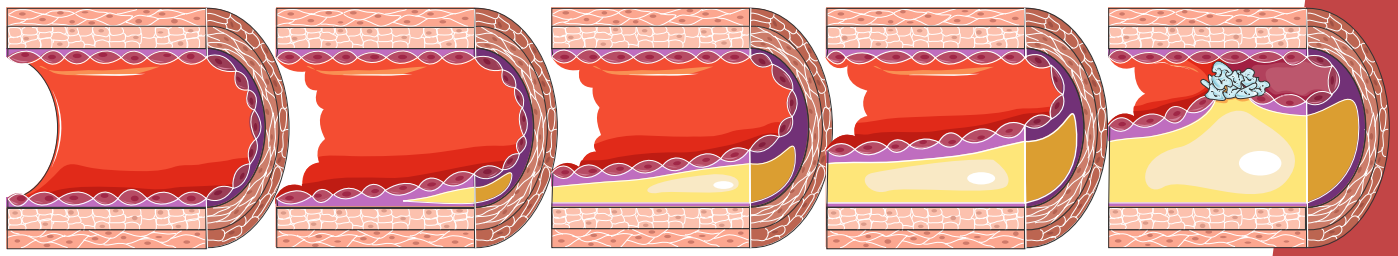


Arterial *aging*

- Arterial wall stiffness
- Atherosclerosis
- ↑ Blood pressure

- **Slow** progression
- **Systemic** nature





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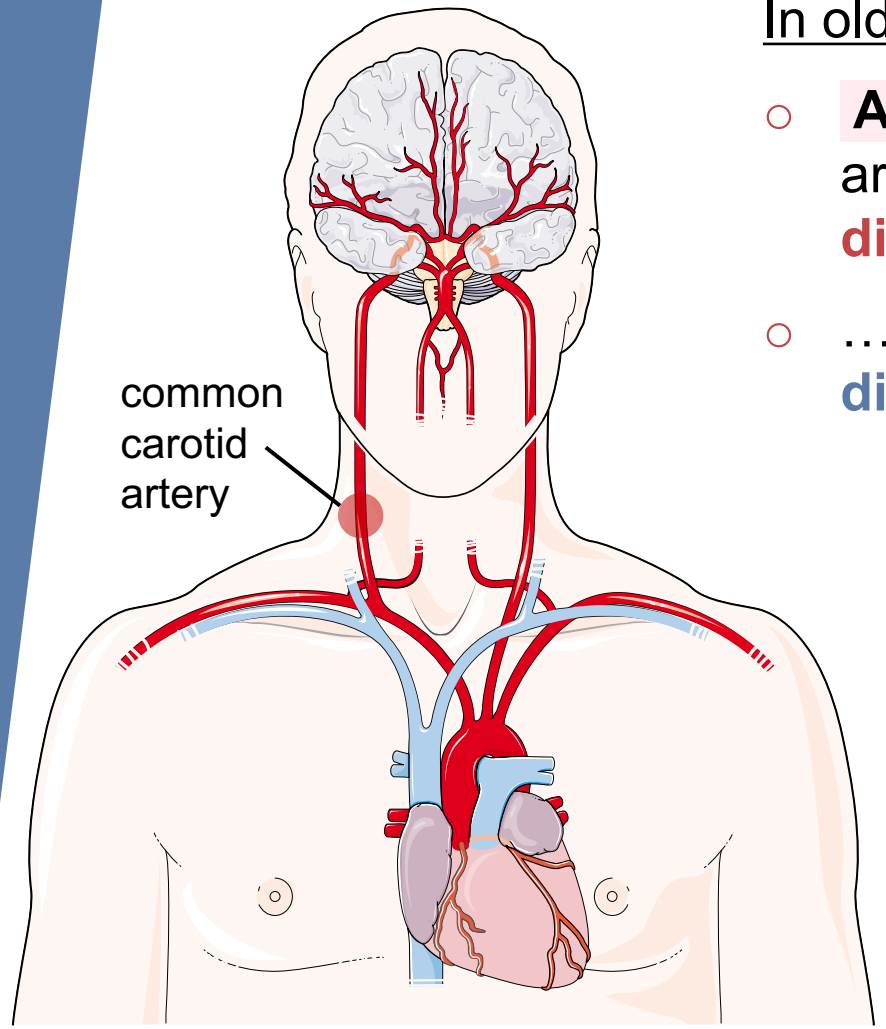


In older and middle age adults:

- **Atherosclerosis**, **arterial stiffness** and **hypertension** are among the strongest predictors of **cardiovascular disease**.
- … they are also known risk factors for **cerebrovascular disease** and **dementia**.

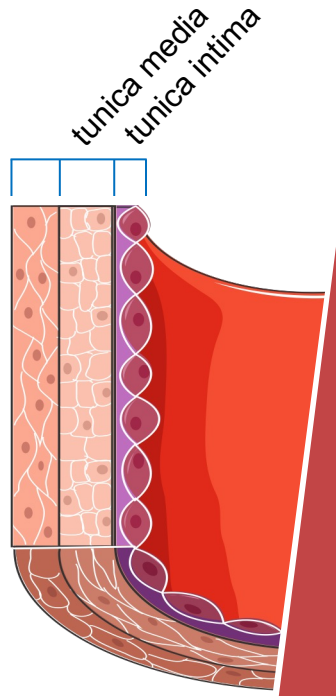
In children and adolescents:

It is yet unclear how early these associations between arterial health and brain heath begin to emerge.

Exposure: arterial health

Age: **10 years**

carotid ultrasound



Arterial structure

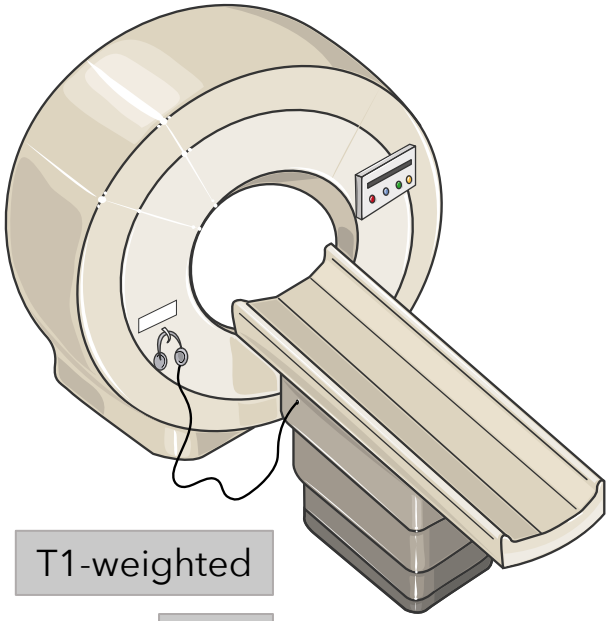
1. **Carotid intima-media thickness (IMT)**

Arterial funtion

2. **Carotid distensibility (Dis)**
3. **Systolic blood pressure (SBP)**
4. **Diastolic blood pressure (DBP)**

Outcome: brain health

Age: **13 years**



T1-weighted

DWI

Brain volume

1. **Total brain volume** (**TBV**)
2. **Grey matter volume** (**GMV**)

White matter microstructure

3. **Global fractional anisotropy** (**FA**)
4. **Mean diffusivity** (**MD**)

Main analysis

TBV **GMV** **FA** **MD**	~	**IMT** **Dis** **SBP** **DBP**	+	Model 0: sex + age + height Model 1: Model 0 + ethnicity + BMI + maternal education + maternal age

↳ FDR correction
↳ non-linear relationships

https://osf.io/ryc7e

Exporatory analyses

- All main analyses will be stratified by **sex**.
- Interaction between IMT and BP.

- **Subcortical** brain structures (volumes):
  ① Accumbens, ② Amygdala, ③ Caudate, ④ Hippocampus, ⑤ Pallidum,
  ⑥ Putamen, ⑦ Thalamus

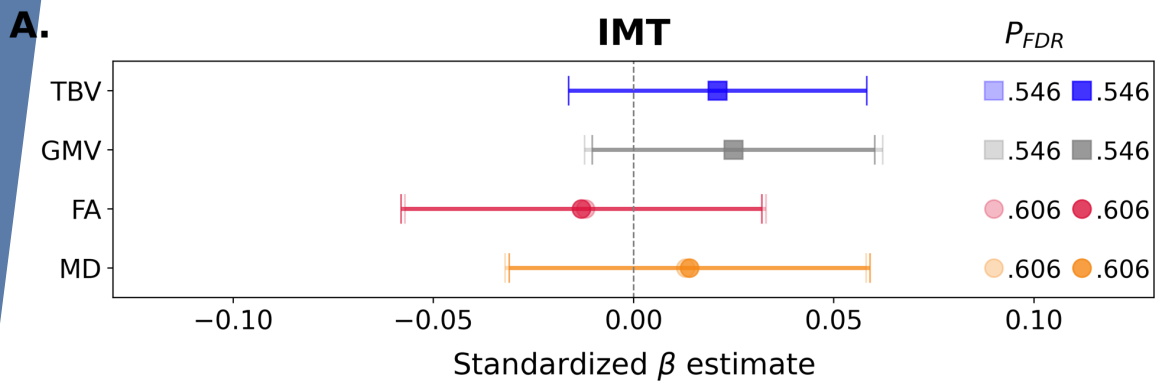
- **White matter tracts** (FA and MD):
  ① Cingulate gyrus, ② Cortico-spinal tract, ③ Uncinate fasciculus,
  ④ Inferior & ⑤ Superior longitudinal fasciculus,
  ⑥ Major & ⑦ Minor forceps.

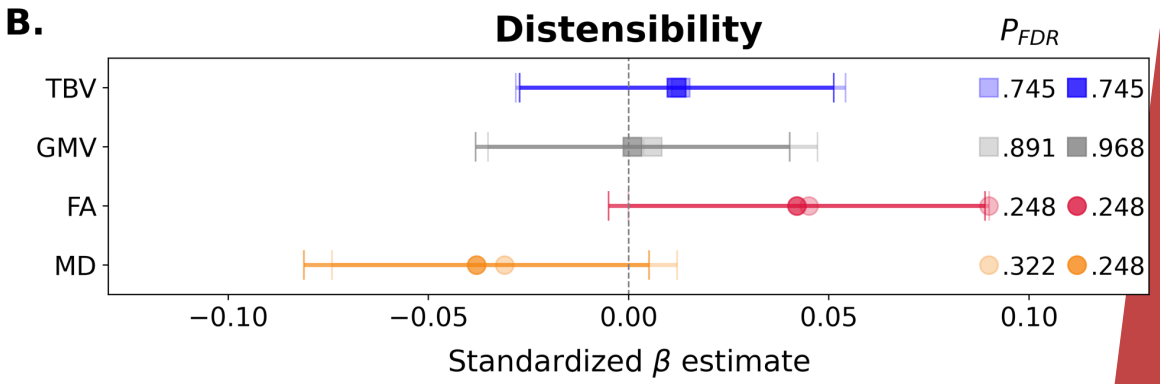
- Vertex-wise **cortical thickness.**
- Longitudinal analyses (brain trajectory from 10 to 13)

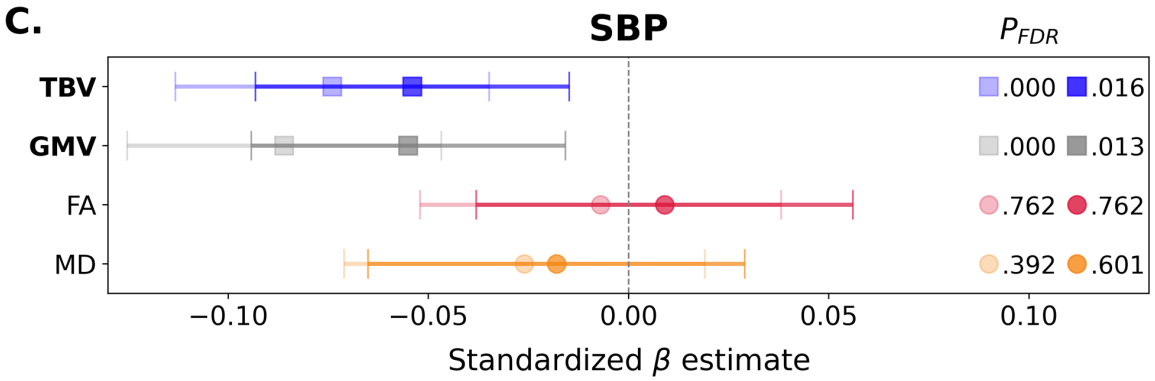
Results

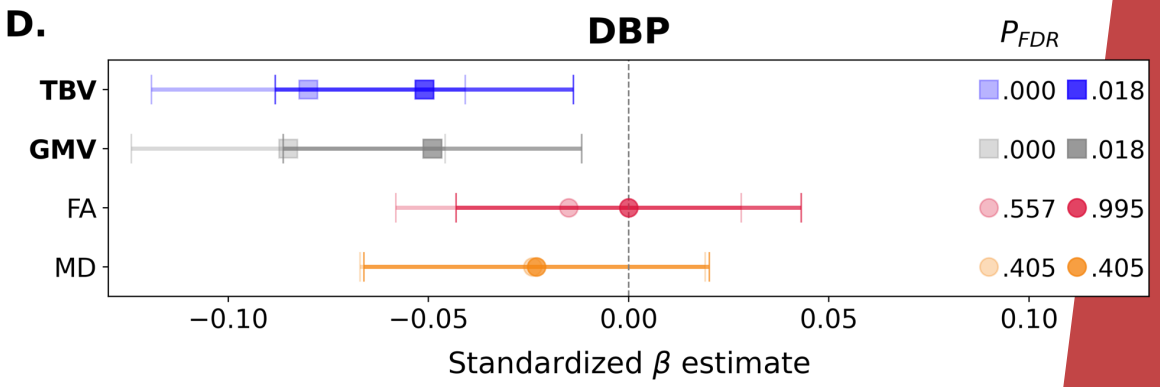
Base model (+ sex + age + height)

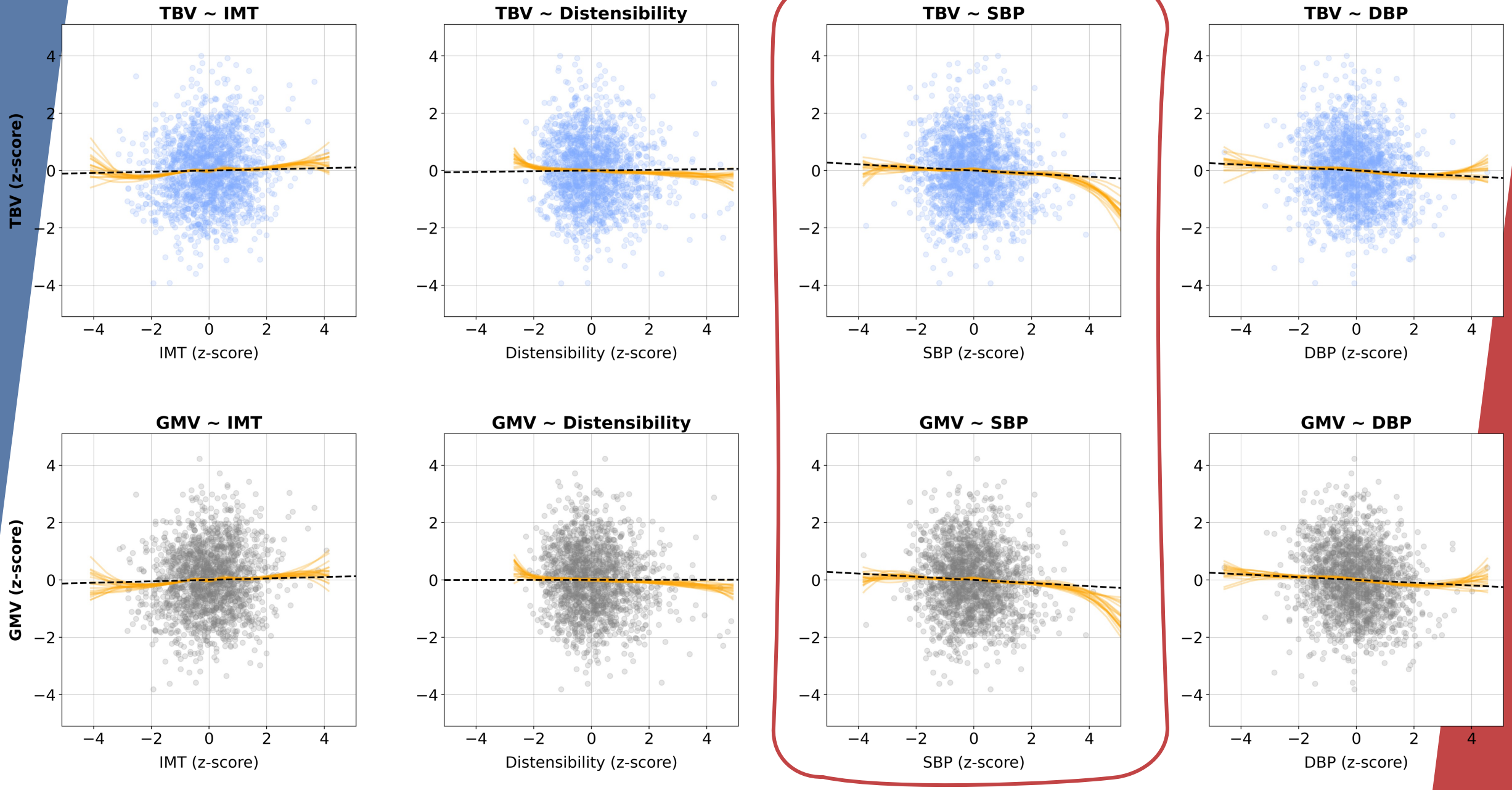
Adjusted model (+ ethnicity + BMI + maternal education + maternal age)



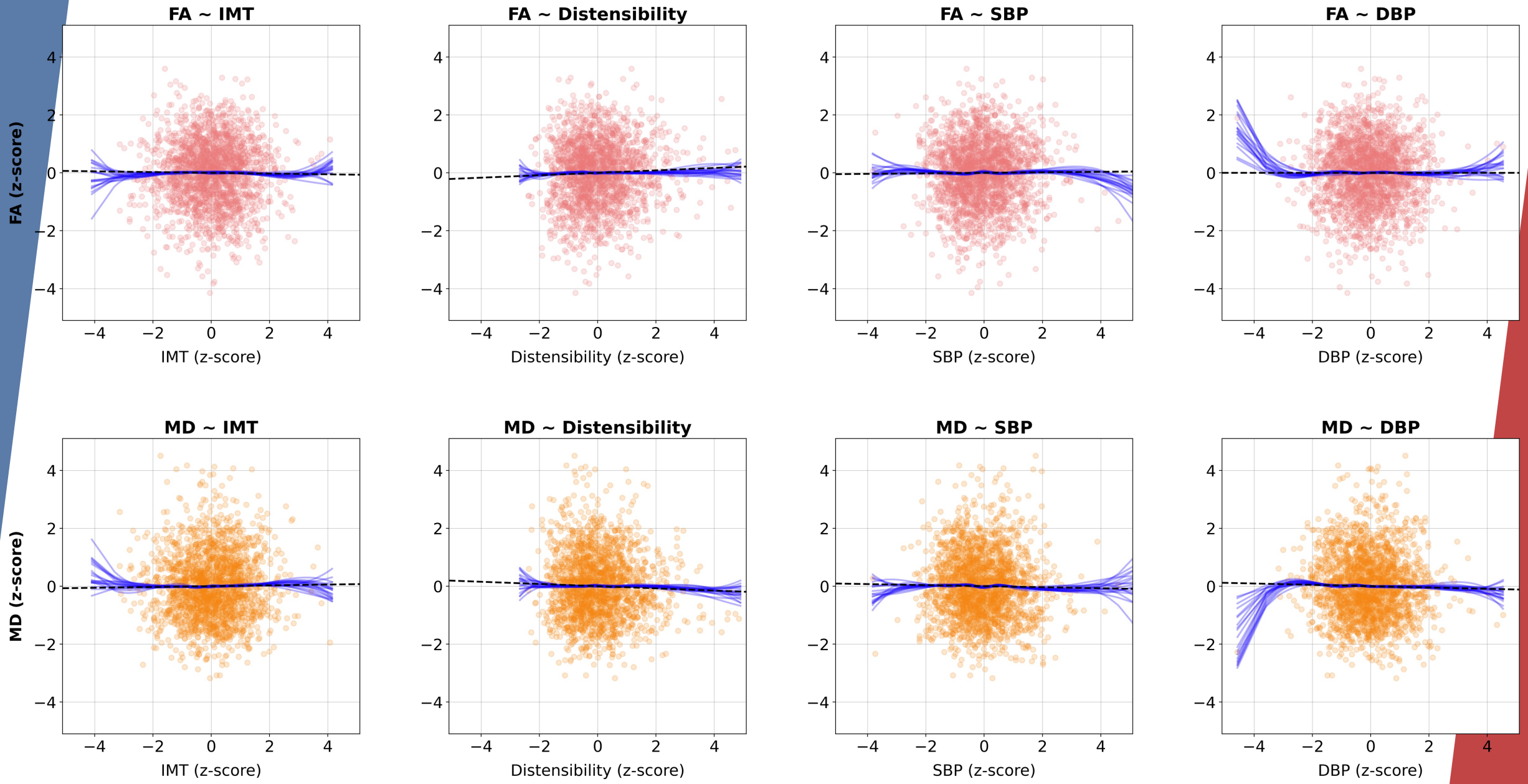




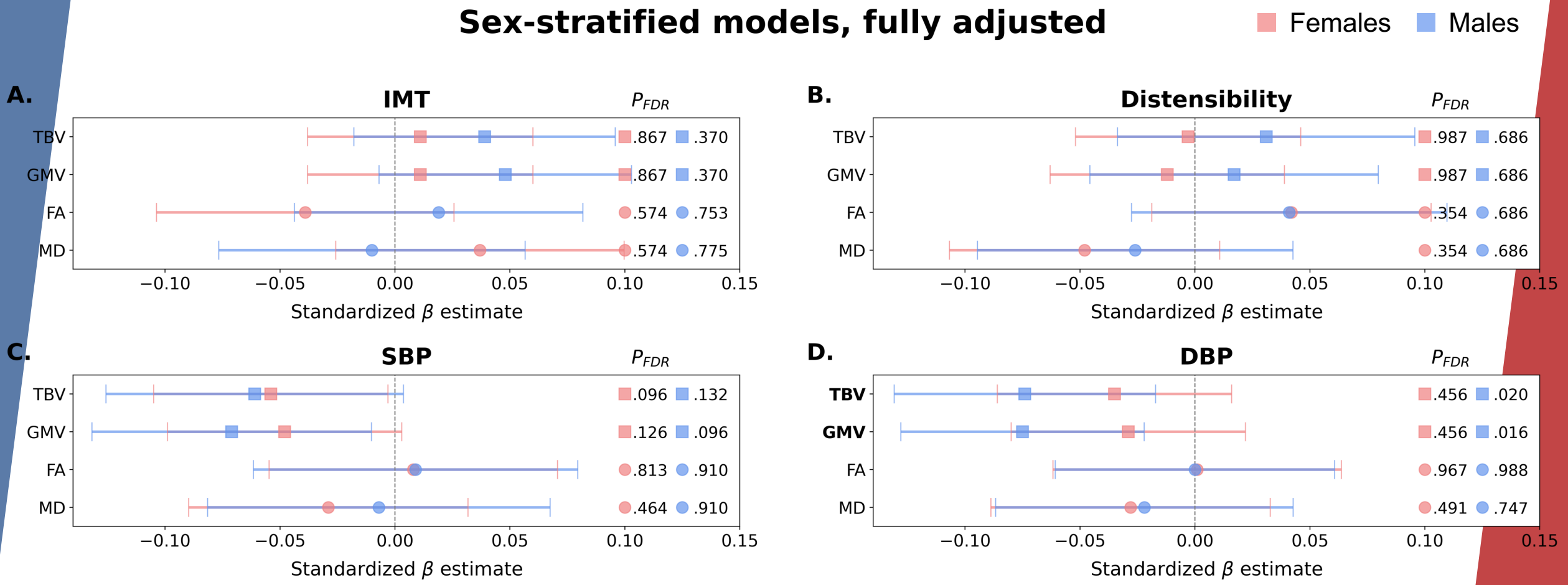



TBV ~ IMT
TBV ~ Distensibility
TBV ~ SBP
TBV ~ DBP
GMV ~ IMT
GMV ~ Distensibility
GMV ~ SBP
GMV ~ DBP
TBV (z-score)
GMV (z-score)
IMT (z-score)
Distensibility (z-score)
SBP (z-score)
DBP (z-score)

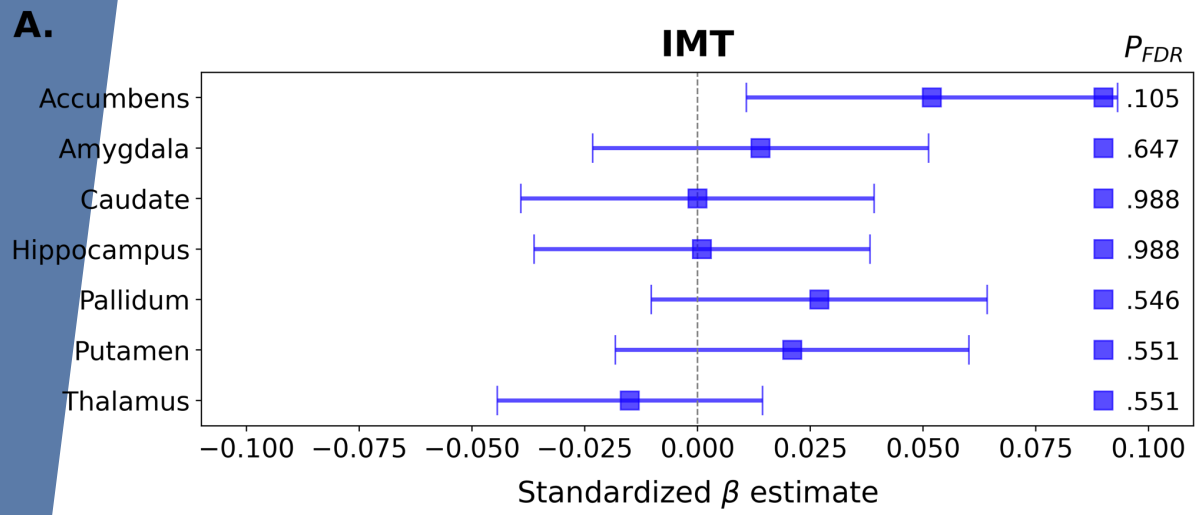
EARLY CAUSE

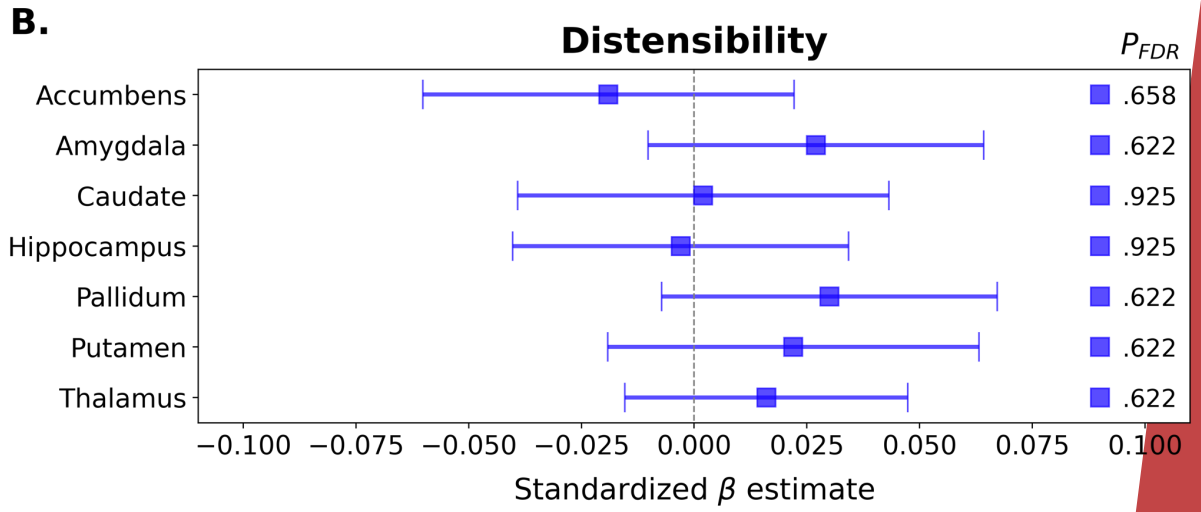

FA ~ IMT
FA ~ Distensibility
FA ~ SBP
FA ~ DBP
MD ~ IMT
MD ~ Distensibility
MD ~ SBP
MD ~ DBP
FA (z-score)
MD (z-score)
IMT (z-score)
Distensibility (z-score)
SBP (z-score)
DBP (z-score)

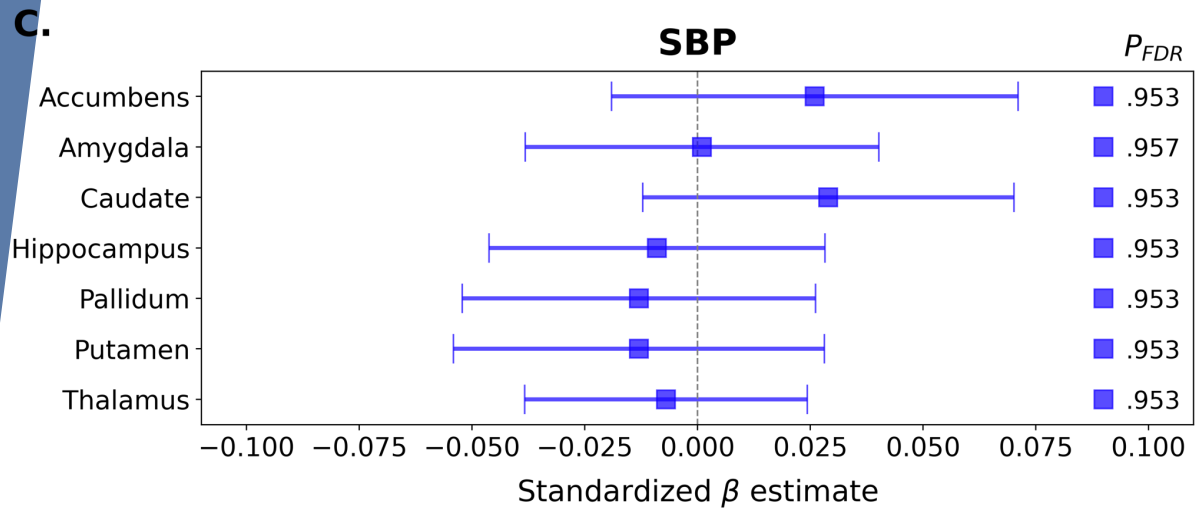
Exploratory results

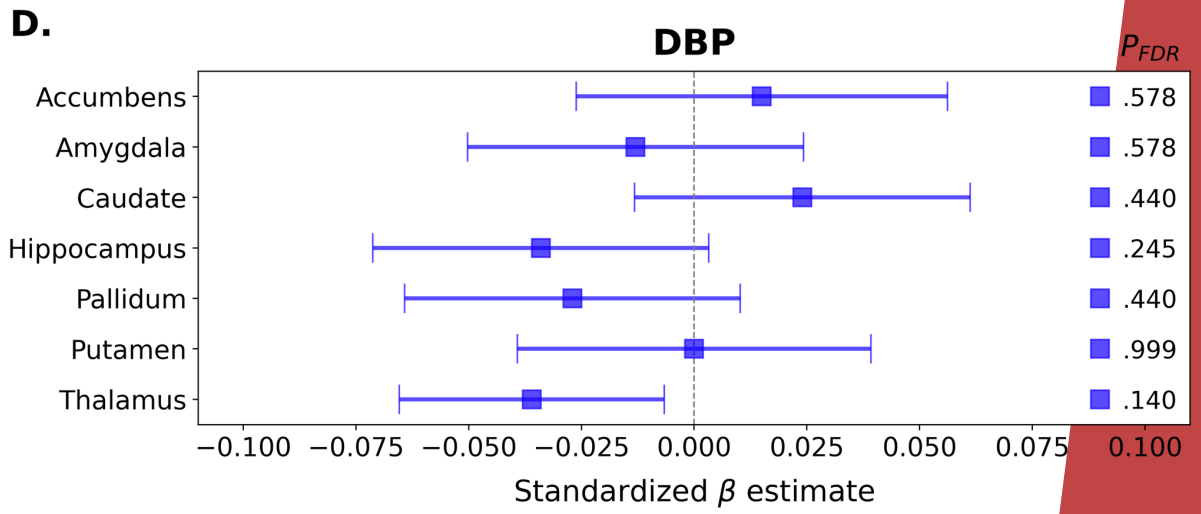


Subcortical brain volumes, fully adjusted





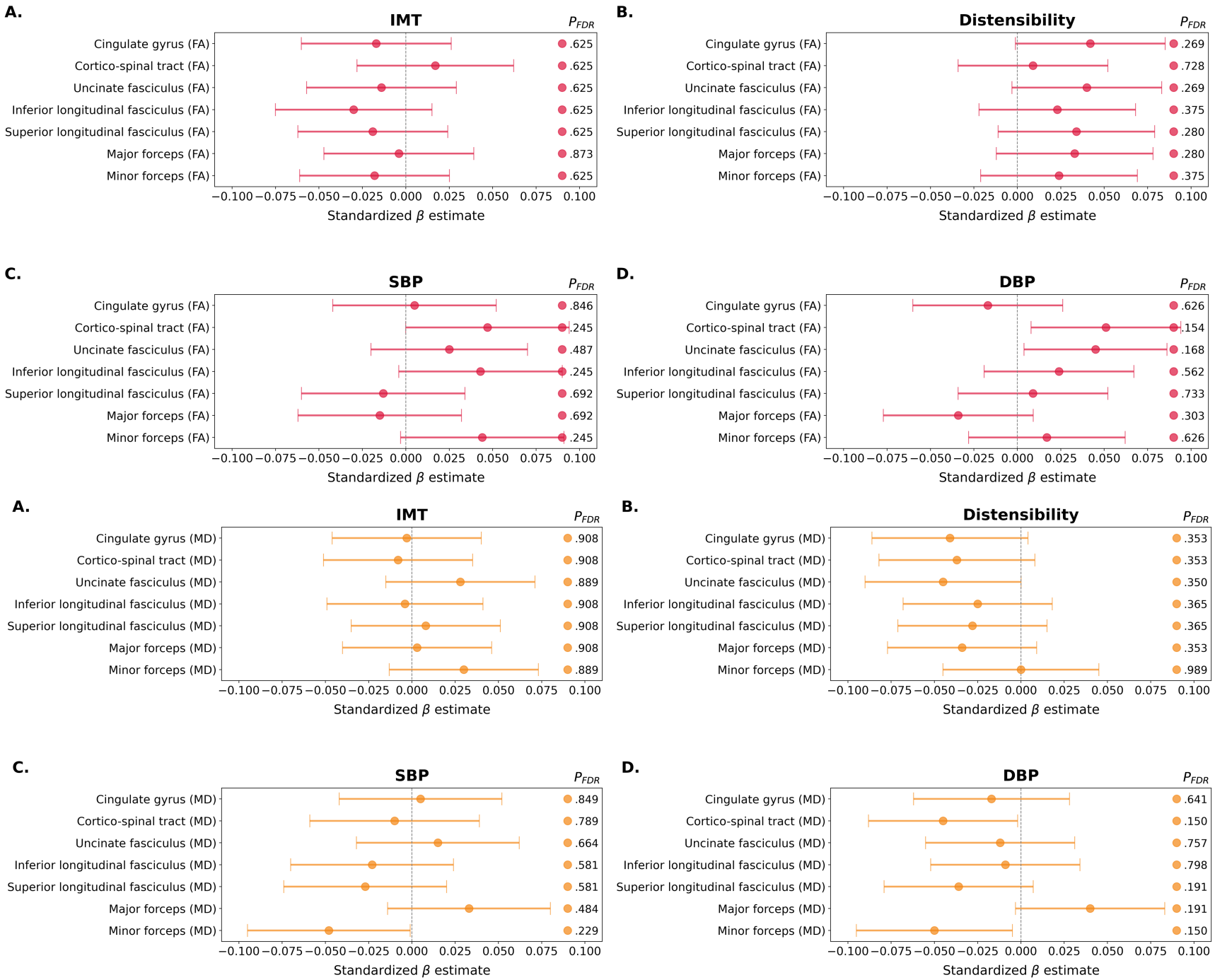




White matter tracts

FA

MD



In summary…

- 1 mm Hg increase in **DBP** is associated with –990,8 mm^3 TBV and –554,9 mm^3 GMV.
  - More pronounced in *boys* (observational !)
  - Not uniform across subcortical regions:
    - ↑ Accumbens, caudate
    - ↓ Thalamus, hippocampus, pallidum
- 1 mm Hg increase in **SBP** is associated with –880.6 mm^3 TBV and –519,9 mm^3 GMV.
  - Non-linear relationship.
  - Not uniform across subcortical regions:
    - ↑ Accumbens, caudate
    - ↓ Pallidum, putamen, hippocampus, thalamus…

- Carotid **IMT** and **distensibility** were *not* significantly associated with TBV or GMV.
- No arterial health exposure was significantly associated with global FA or MD.

EARLY CAUSE

2

ELS and cardiac structure and function in children

Analysis plan & preliminary results

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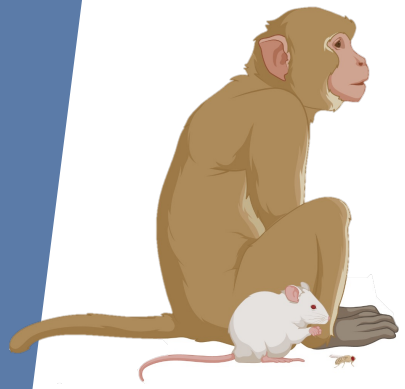
Backgroud




Pregnancy | Childhood | Adolescence | Adulthood



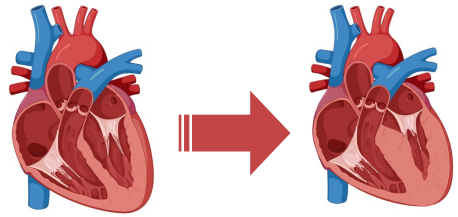
Early–life stress (ELS)

Cardiovascular disease

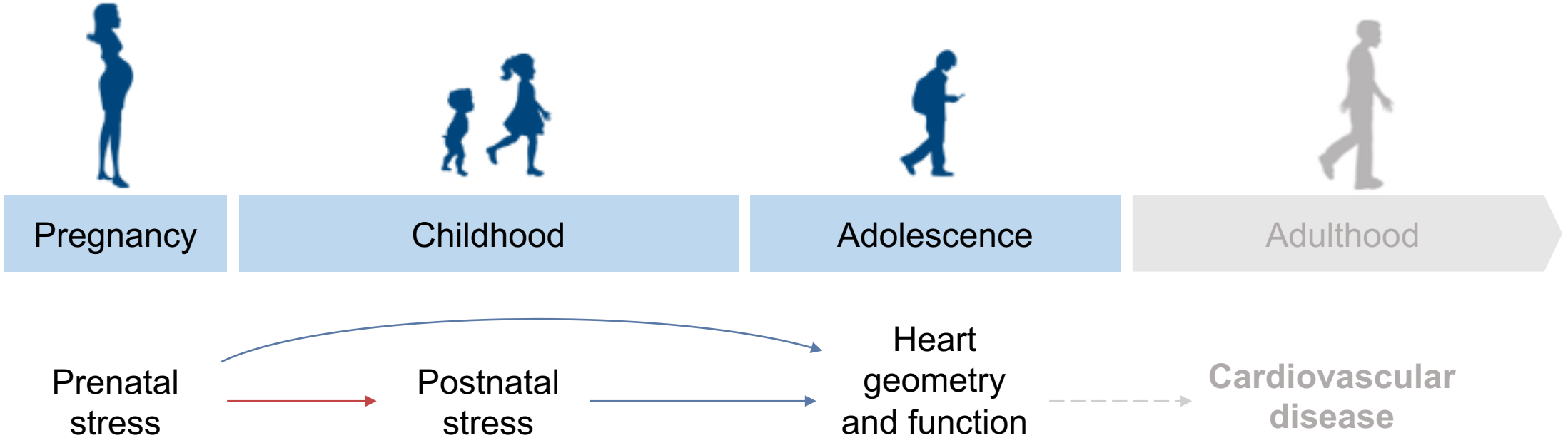
e.g. heart failure, CHD, stroke, CVD

Prenatal stress

Postnatal stress



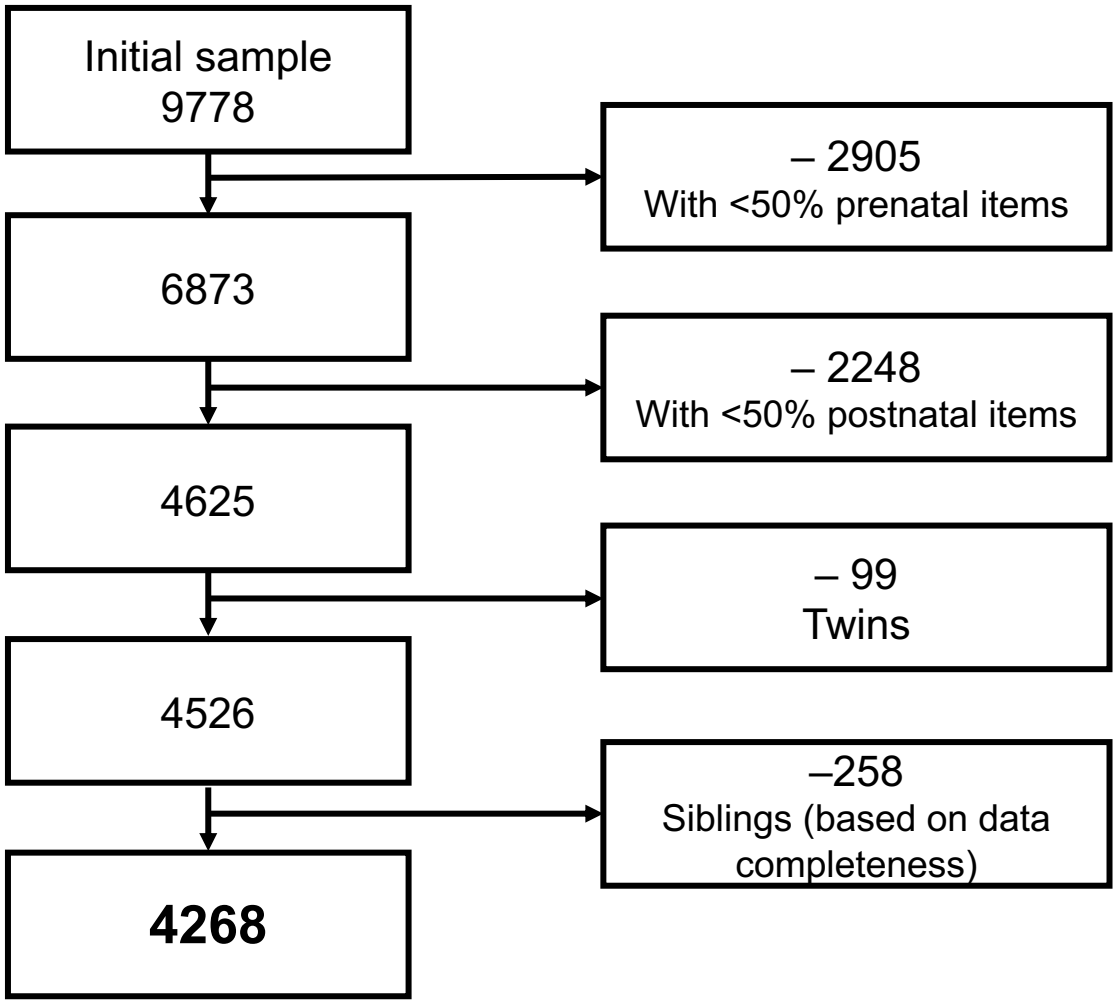
Backgroud



Aims

I. What is the contribution of ***prenatal*** *vs.* ***postnatal*** **stress** exposure to **heart morphology** in childhood?

Sample



Generation R

Exposure: ELS

Pregnancy

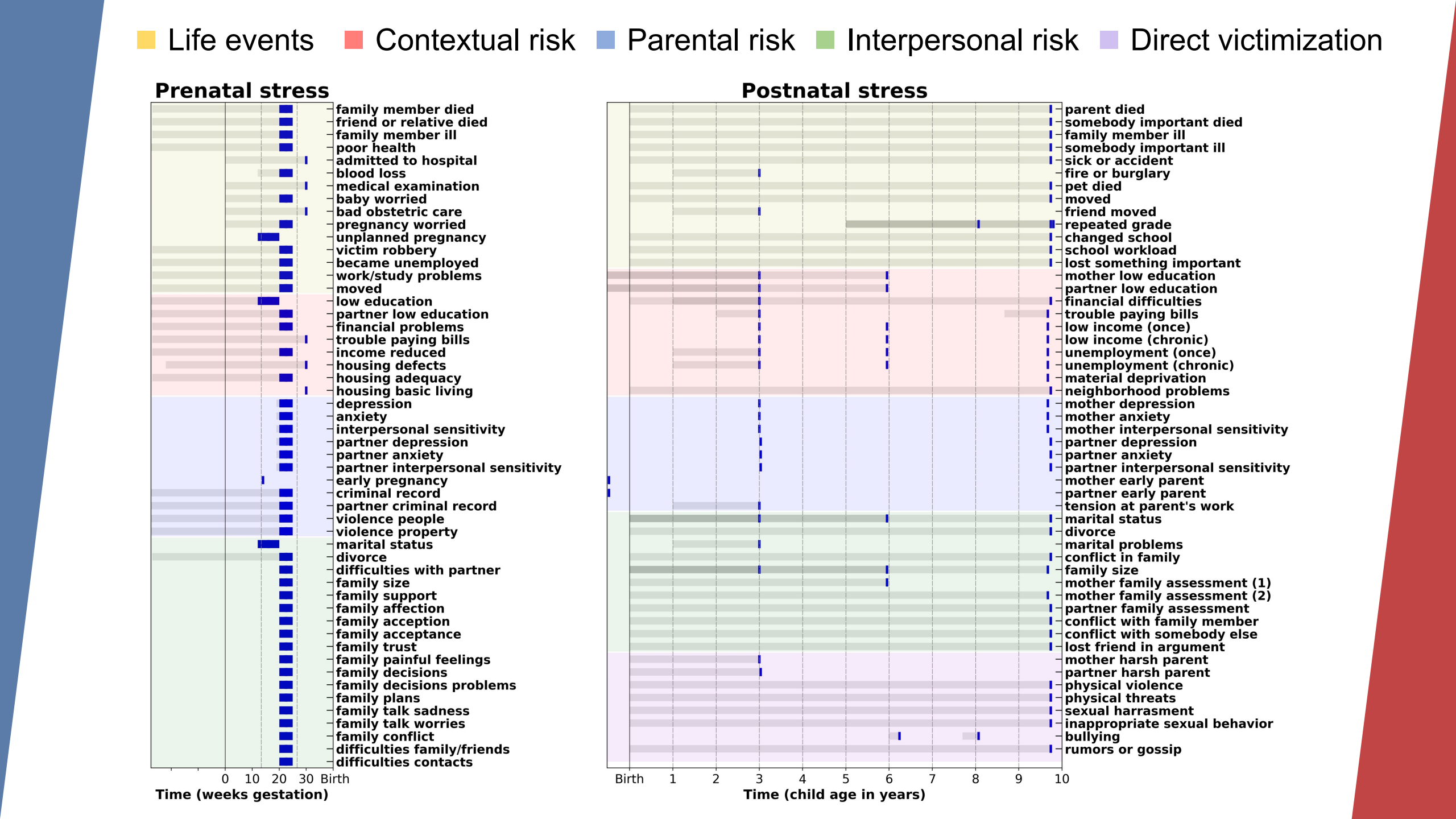
PRENATAL STRESS

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

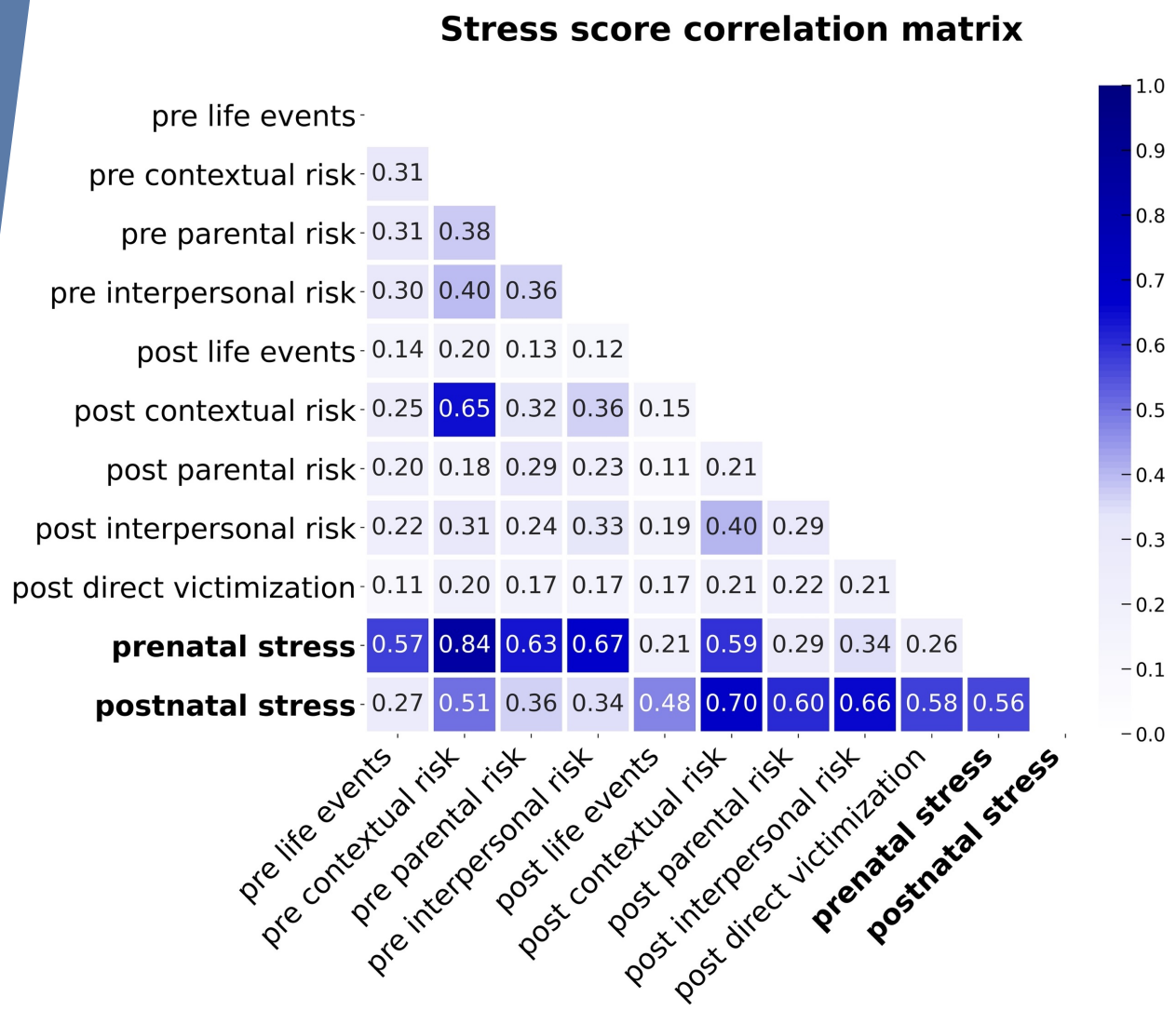
Childhood (0 – 10 years)

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

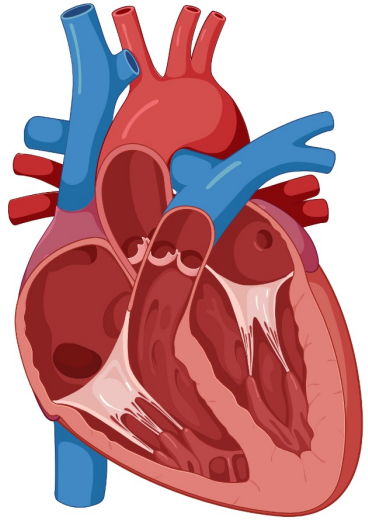

Life events
Contextual risk
Parental risk
Interpersonal risk
Direct victimization
Prenatal stress
family member died
friend or relative died
family member ill
poor health
admitted to hospital
blood loss
medical examination
baby worried
bad obstetric care
pregnancy worried
unplanned pregnancy
victim robbery
became unemployed
work/study problems
moved
low education
partner low education
financial problems
trouble paying bills
income reduced
housing defects
housing adequacy
housing basic living
depression
anxiety
interpersonal sensitivity
partner depression
partner anxiety
partner interpersonal sensitivity
early pregnancy
criminal record
partner criminal record
violence people
violence property
marital status
divorce
difficulties with partner
family size
family support
family affection
family acception
family acceptance
family trust
family painful feelings
family decisions
family decisions problems
family plans
family talk sadness
family talk worries
family conflict
difficulties family/friends
difficulties contacts
0
10
20
30
Birth
Time (weeks gestation)
Postnatal stress
parent died
somebody important died
family member ill
somebody important ill
sick or accident
fire or burglary
pet died
moved
friend moved
repeated grade
changed school
school workload
lost something important
mother low education
partner low education
financial difficulties
trouble paying bills
low income (once)
low income (chronic)
unemployment (once)
unemployment (chronic)
material deprivation
neighborhood problems
mother depression
mother anxiety
mother interpersonal sensitivity
partner depression
partner anxiety
partner interpersonal sensitivity
mother early parent
partner early parent
tension at parent's work
marital status
divorce
marital problems
conflict in family
family size
mother family assessment (1)
mother family assessment (2)
partner family assessment
conflict with family member
conflict with somebody else
lost friend in argument
mother harsh parent
partner harsh parent
physical violence
physical threats
sexual harrasment
inappropriate sexual behavior
bullying
rumors or gossip
Birth
1
2
3
4
5
6
7
8
9
10
Time (child age in years)

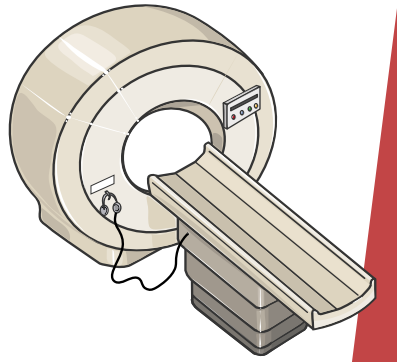
Exposure: ELS



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

Outcome: cardiac MRI



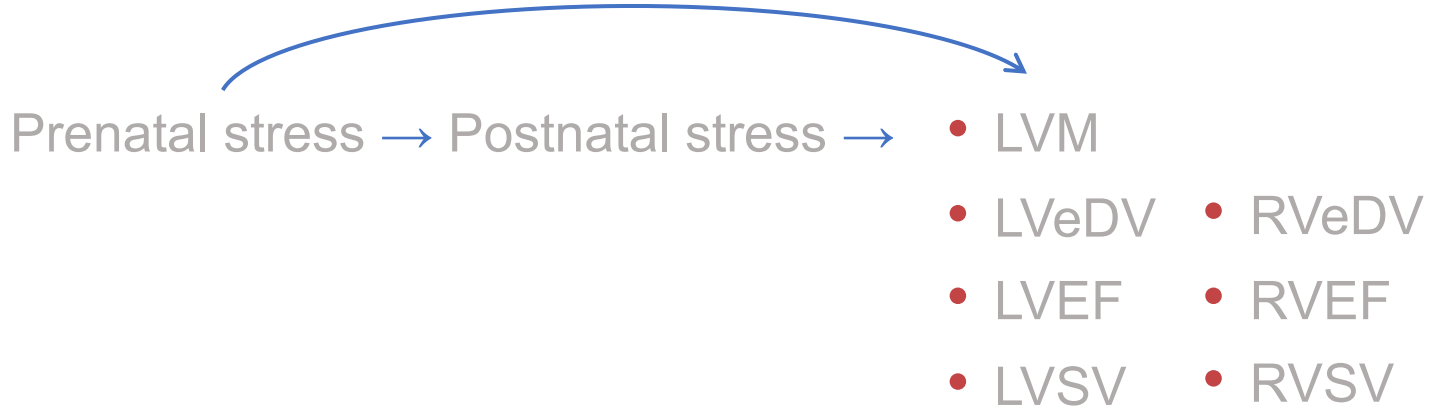


Age: **10 years**

1. Left ventricular **mass (LVM)**
2. Left ventricular **end-diastolic volume (LVeDV)**
3. Left ventricular **stroke volume (LVSV)**
4. Left ventricular **ejection fraction (LVEF)**
5. Right ventricular **end-diastolic volume (RVeDV)**
6. Right ventricular **stroke volume (RVSV)**
7. Right ventricular **ejection fraction (RVEF)**

Modeling strategy

Prenatal contribution ▶ Causal mediation analysis (CMA)



Postnatal contribution ▶ Hierarchical regression analysis

- LVM
- LVeDV
- RVeDV
- LVEF
- RVEF
- LVSV
- RVSV

~

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

Covariates

Model 0: sex + age + height (?)

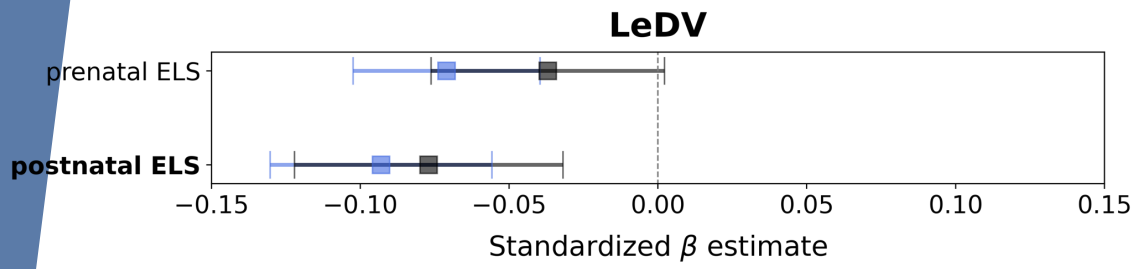
Model 1: Model 0 + ethnicity + BMI + SBP + DBP + Lean body mass %

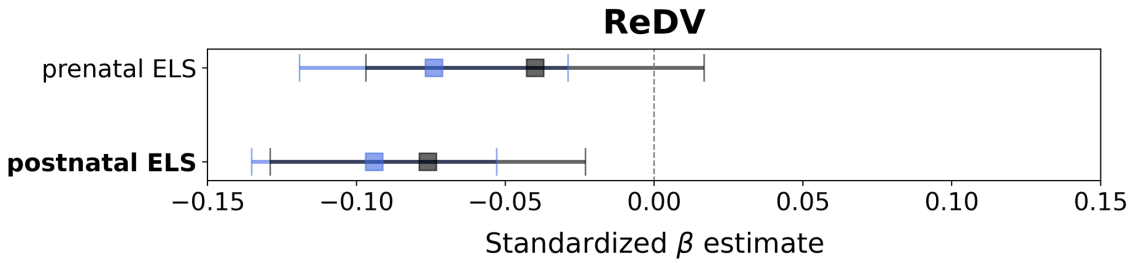
Model 2: Model 1 + maternal BMI + maternal smoking + maternal alcohol consumption

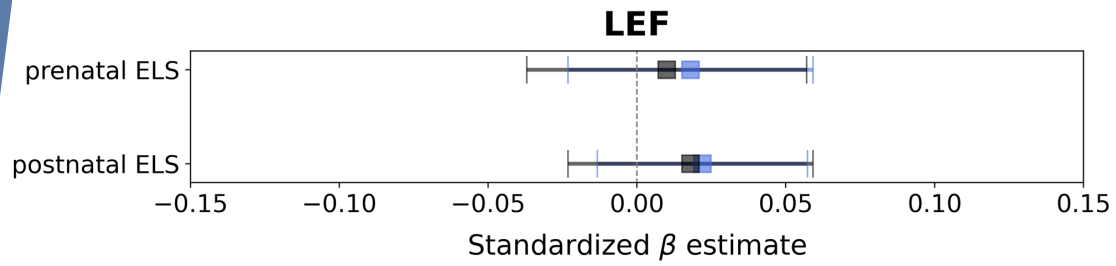
Additional analyses

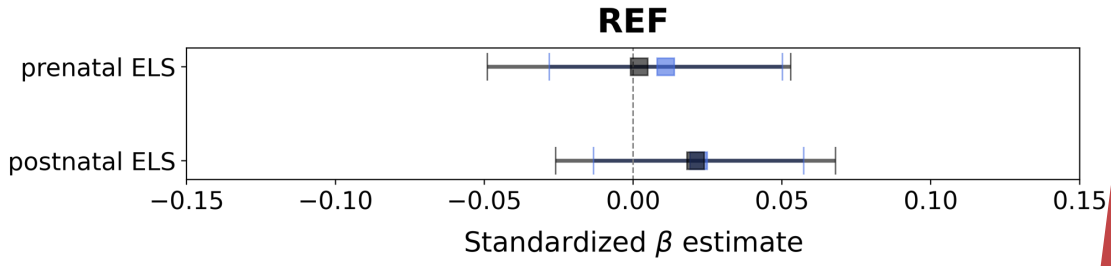
- Main models **stratified by sex**;
- Individual stress **domains** as predictors;
- Sensitivity analysis: responders only;
- Sensitivity analysis: heart ultrasound.

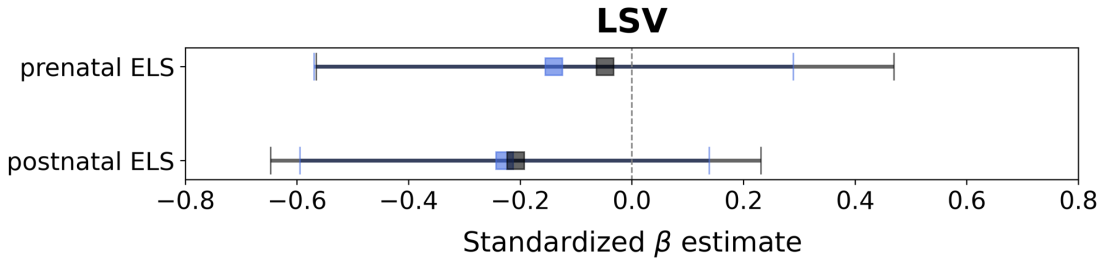
Preliminary results

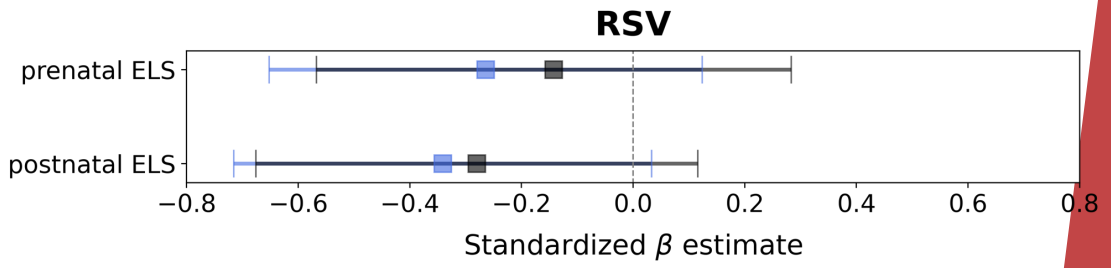


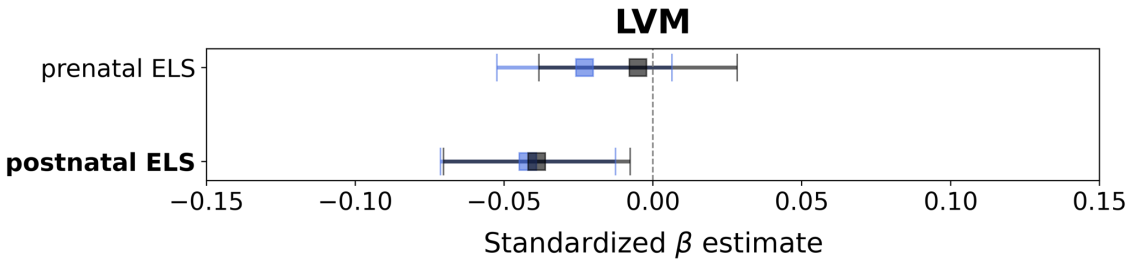












Before mutual adjustment

Mutually adjusted

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Thanks! ☺

Questions?