Relationships between adiposity and left ventricular function in adolescents: mediation by blood pressure and other cardiovascular measures

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Avon Longitudinal Study of Parents and Children

Body composition and cardiovascular health

↑BMI

↑Risk of developing cardiovascular disease

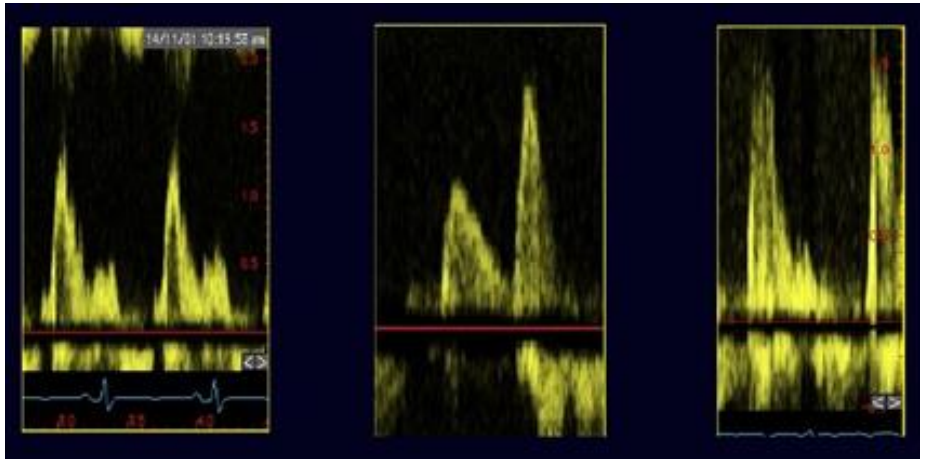
Including ↑risk of developing LV diastolic dysfunction

Study Outline

- No studies have considered the role of mediators in the association observed between fat mass and E/A

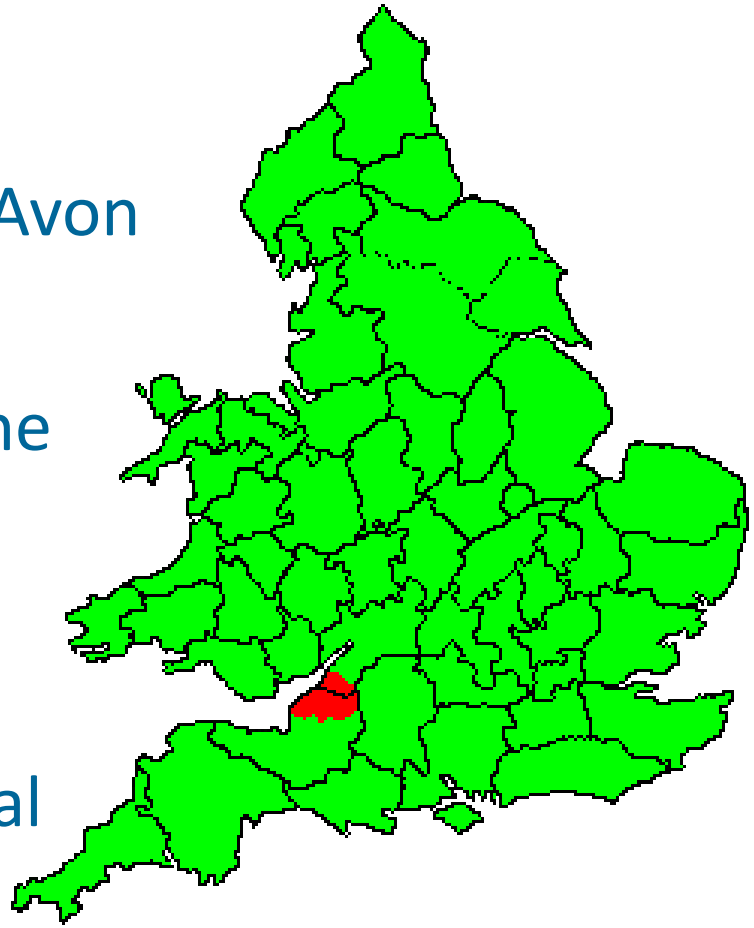
- **Youth** is an important period for consideration in the development of cardiovascular risk

- *Do haemodynamic risk factors for heart disease mediate the effect of total fat mass on mitral inflow (E/A) in adolescents?*



The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort

- 14541 pregnant women were recruited in 1990s from Avon
- 13988 infants have been followed up, at intervals, to the present time, participating in over 90 questionnaires, 10 clinical assessment visits and genetics
- Large range of data available (behavioural and biological factors (inc. biometric and genomic data))



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Methods

- Body composition was assessed by dual energy X-ray absorptiometry (DXA) in 2,068 individuals (age 17.7(SD 0.32) years; 45% male; weight 67(SD 13) kg)

- Sedentary blood pressure was measured and echocardiography was performed

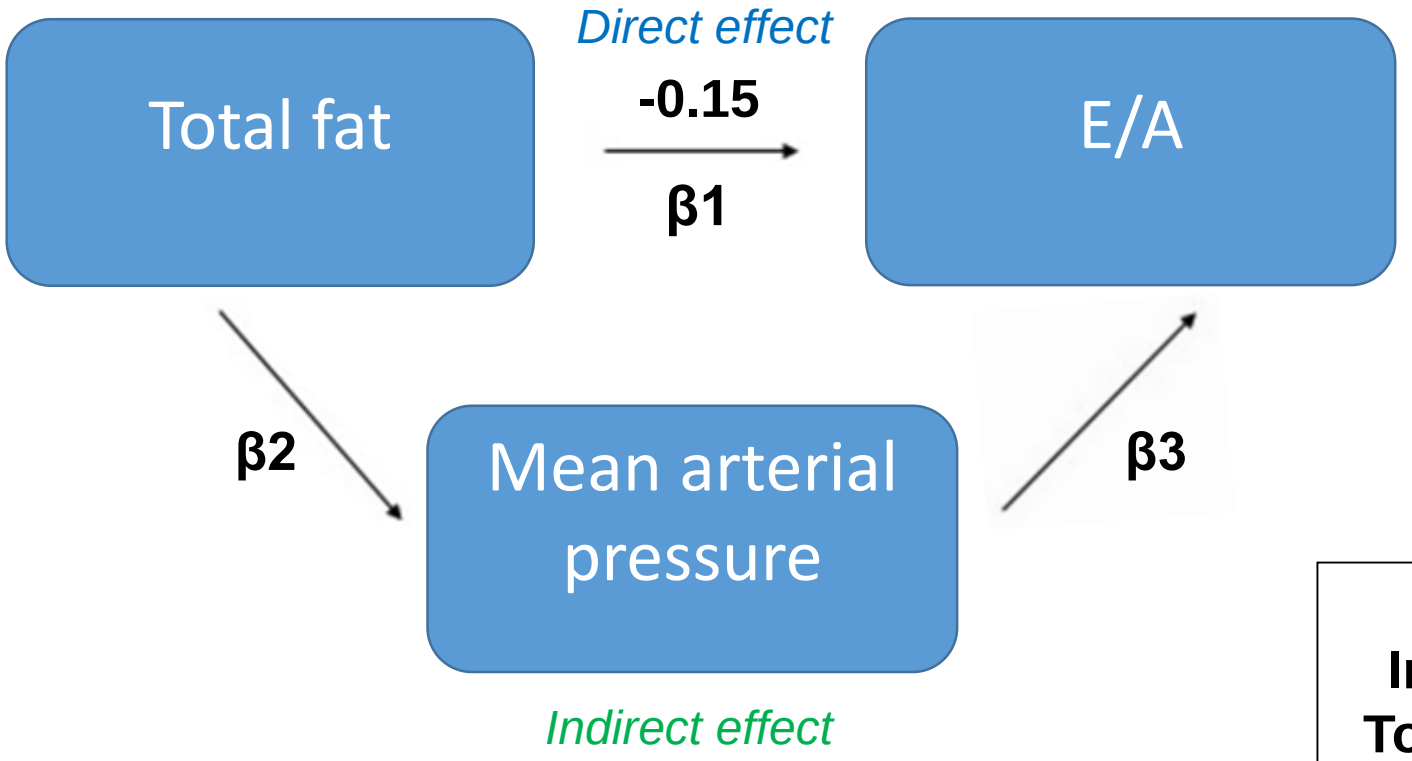
- Associations between total fat mass and transmitral E/A and the extent of mediation by individual risk factors were estimated using structural equation modelling (SEM)

Introduction to SEM

- SEM is used to quantify the extent of mediation by a particular variable of interest

- Directed acyclic graphs (DAGs) are constructed to represent the known causal relationships between different variables

Mediation – A basic model:

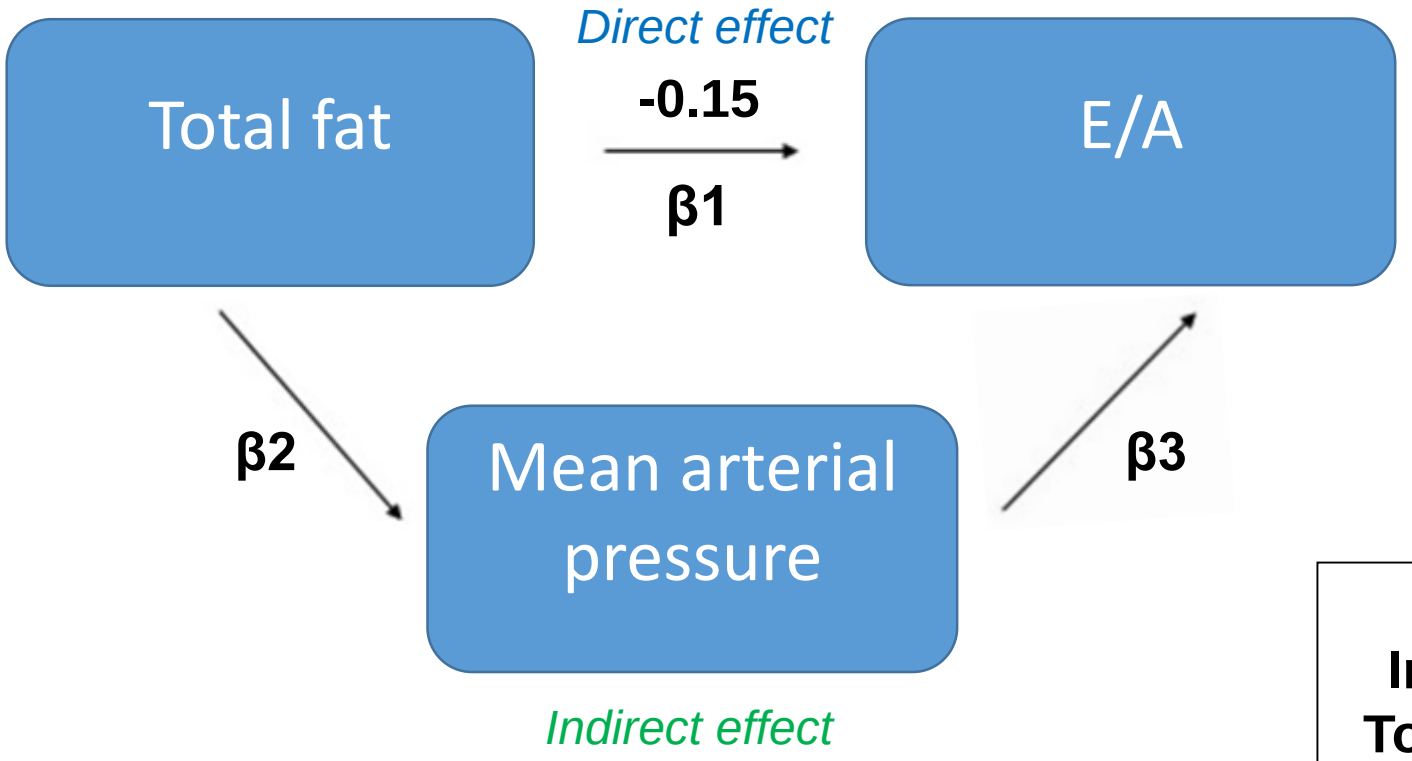


β1 (males) = -0.13
β1 (females) = -0.16

Direct effect = β1
Indirect effect = β2 * β3
Total effect = β1 + β2*β3

Indirect effect = difference between the direct and total effects

Mediation – A basic model:



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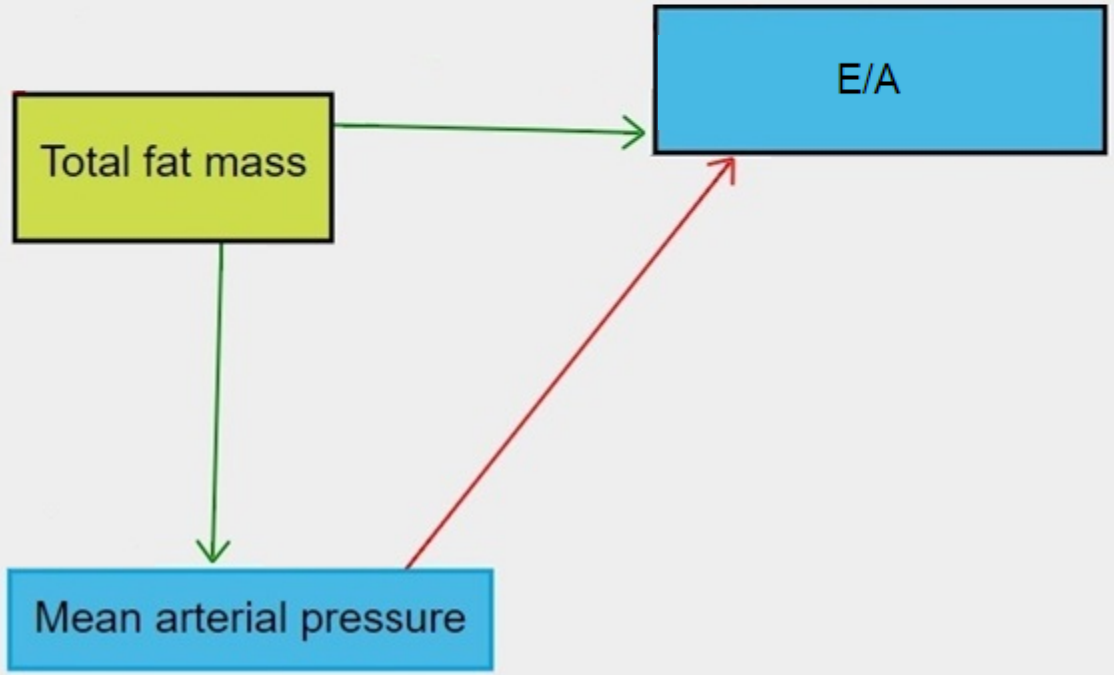
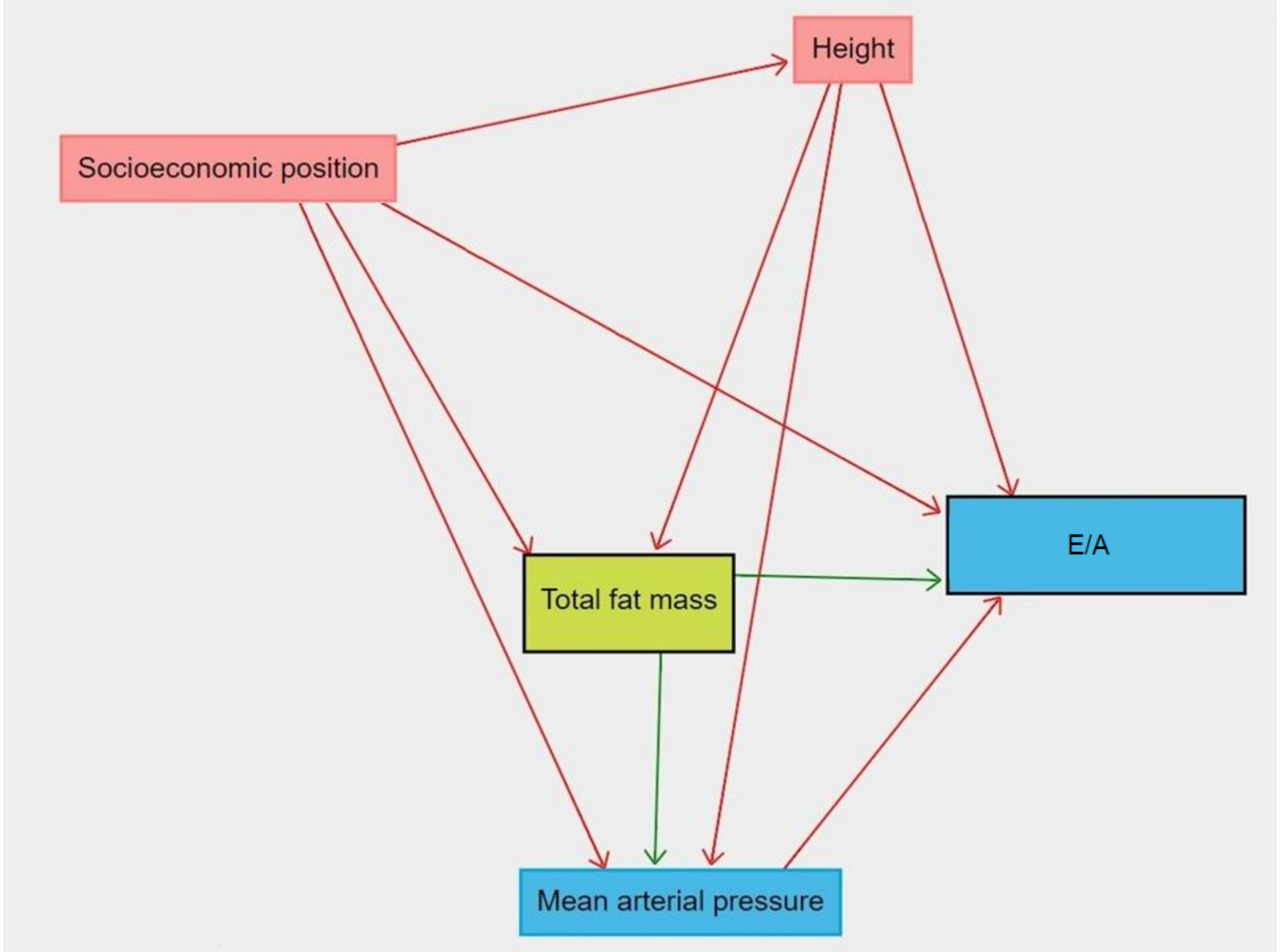
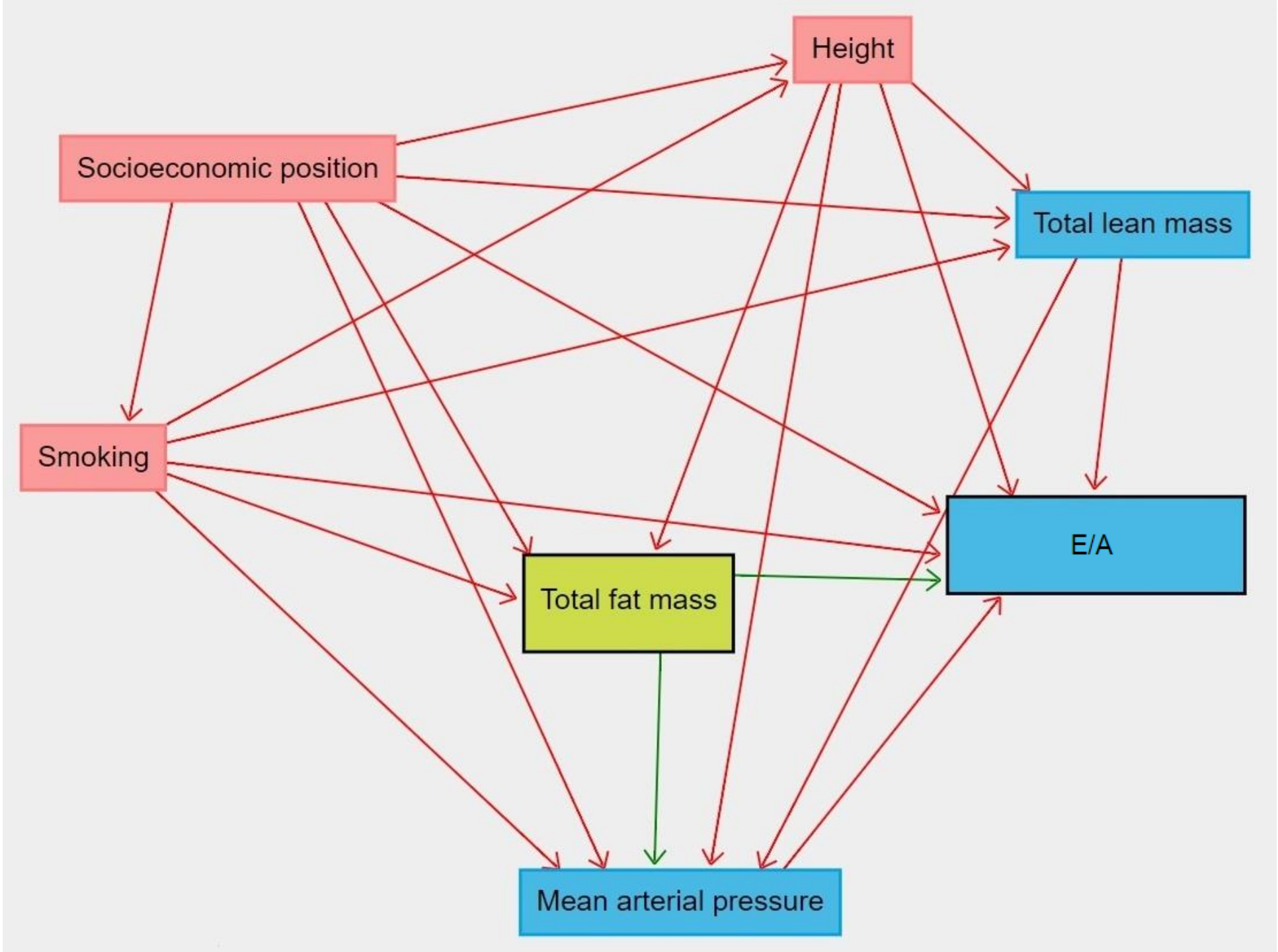
More sophisticated models must account for confounders…


E/A
Total fat mass
Mean arterial pressure


Height
Socioeconomic position
E/A
Total fat mass
Mean arterial pressure


Height
Socioeconomic position
Total lean mass
Smoking
E/A
Total fat mass
Mean arterial pressure

Methods

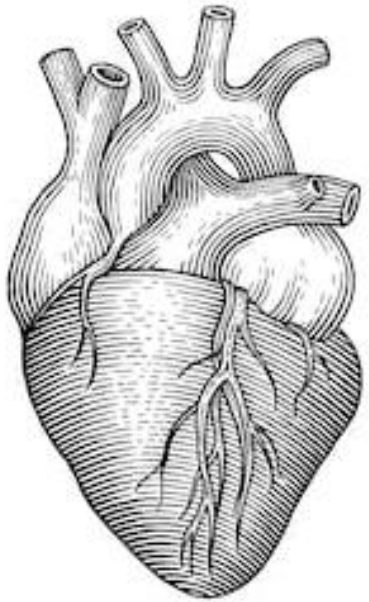
- STATA SE(15) was used to construct SEM models
- Height, smoking, socioeconomic position and lean mass were included as potential confounders in all models
- Analyses were also stratified by sex to assess the possible existence of a gender difference

Mediators

- We investigated the role of the following haemodynamic risk factors as mediators:

  - **Mean arterial pressure**
  - **Pulse pressure**
  - **Heart rate**

  - **End-diastolic volume**
  - **Total arterial elastance**
  - **Total peripheral resistance**

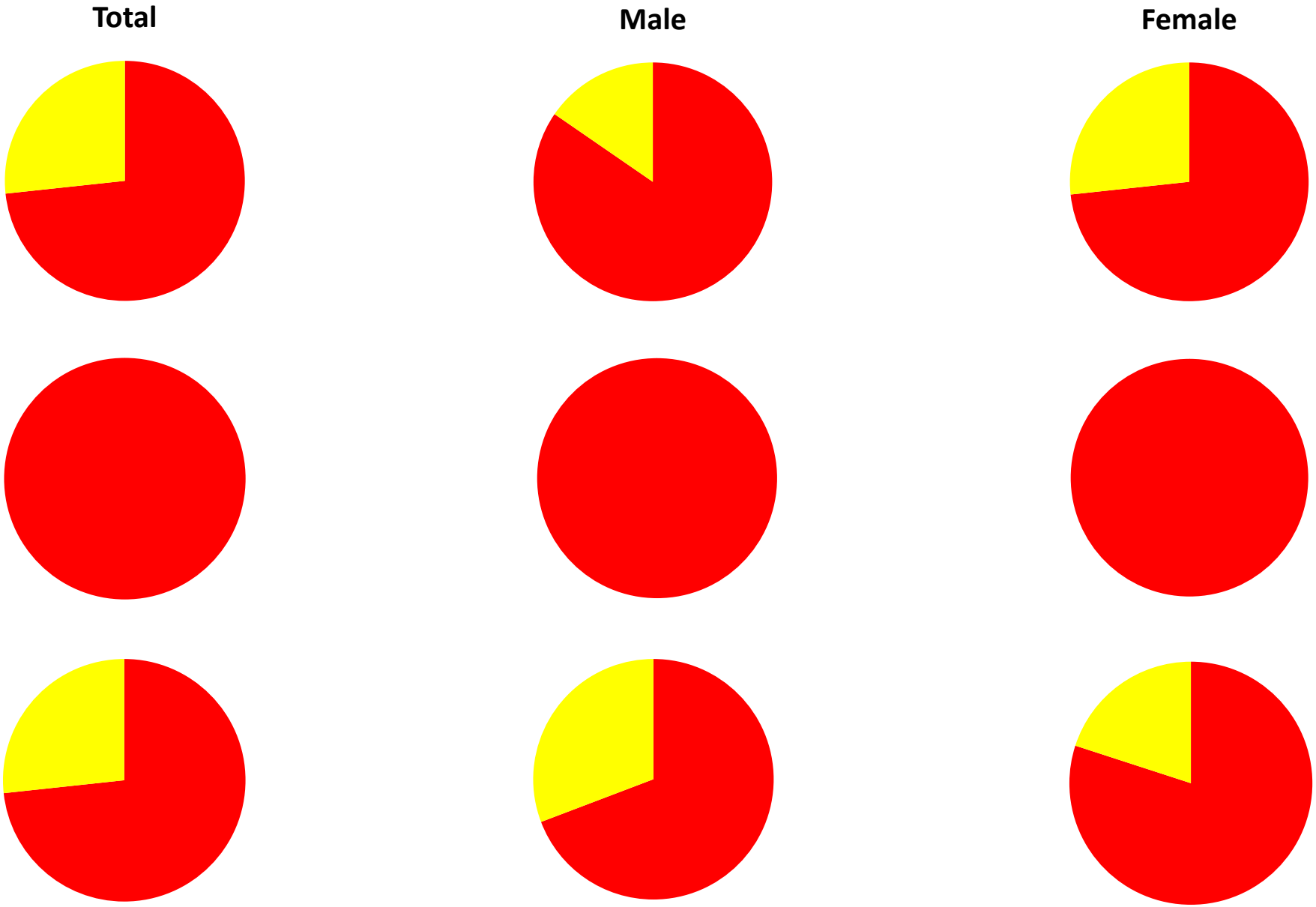


Descriptive Characteristics

	N	Mean ± SEM
Age (years)	2,057	17.7 ± 0.007
Males (n)	941 (45%)	
Height (cm)	2,057	171.20 ±0.21
Total body mass (kg)	2,056	67.09 ± 0.29
Body mass index (kg/m^2)	2,056	22.90 ± 0.09
Left ventricular mass	2,057	124 ± 0.72
Fat mass (kg)	2,030	18.30 ± 0.23
Lean mass (kg)	2,030	45.60 ± 0.22
SBP (mmHg)	2,057	117 ± 0.25
DBP (mmHg)	2,057	65 ± 0.17
HR (bpm)	1,692	69 ± 0.26
Moderate to vigorous physical activity (minutes/day)	960	23.9 ± 0.62

		N	%
Smoking			
	Never	991	53.17
	Ever	402	21.57
	Current	471	25.27
	Total	1864	100
Socioeconomic status			
	I - Professional	220	11.48
	II - Mangerial and technical	762	39.77
	IIINM - Skilled non-manual	223	11.64
	IIIM - Skilled manual	527	26.51
	IV - Partly skilled	132	6.89
	V - Unskilled	52	2.71
		1916	100

Total Fat -> E/A

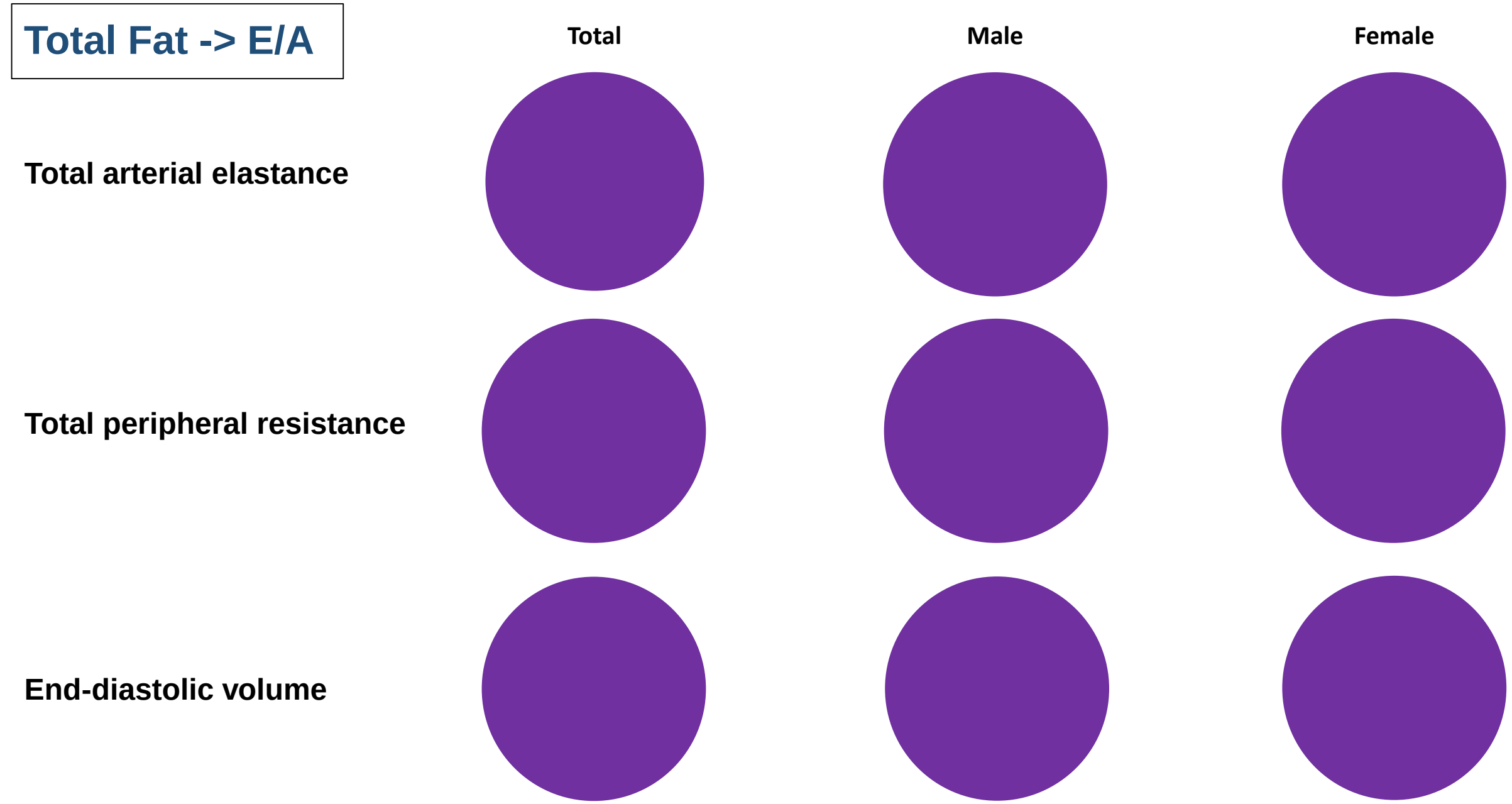


= extent of mediation

***All p values <0.05**

Greatest mediative effect is by *heart rate* (male): 31%

Total Fat -> E/A



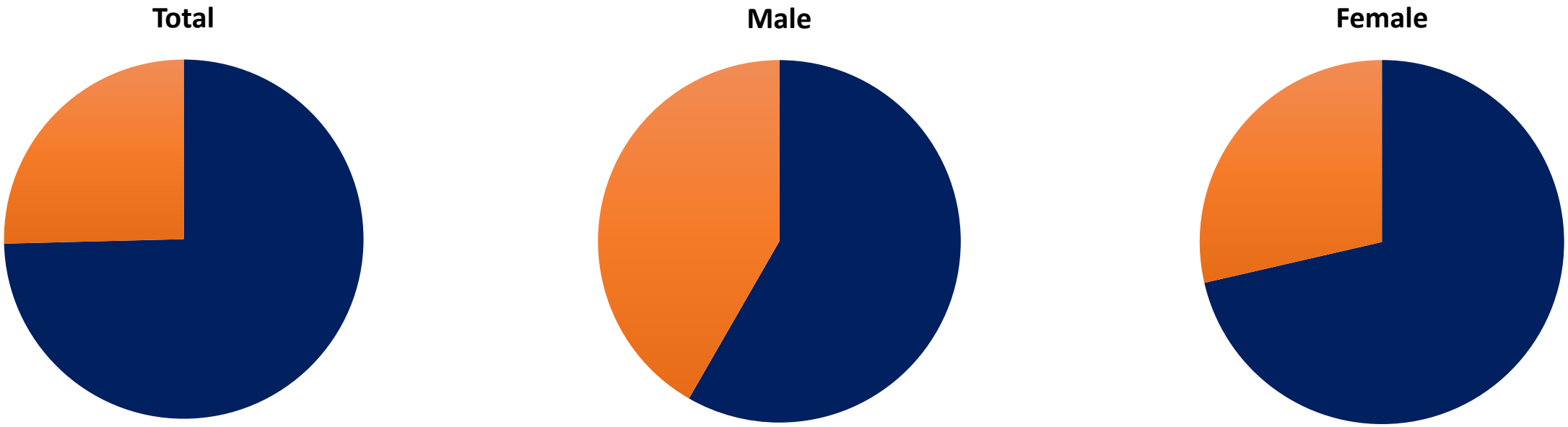
*All p values <0.05

No evidence of any mediative effect by TAE, TPR or EDV

Total Fat -> E/A

Complete models

= extent of mediation



Variable but considerable mediation – greatest effect can be seen in the male group: **42%**

In the association between total fat and E/A…

- MAP and HR showed the greatest mediative effects individually (MAP = 27% (in both total and female groups); HR = 31% (male group))

- There was no evidence of any mediative effect by pulse pressure, total arterial elastance, total peripheral resistance or end-diastolic volume

- Collectively, mediators appear to have the greatest effect (42%, male group)

Concluding Remarks

- MAP and HR are important mediators of the effect of adiposity on diastolic function in adolescence

- These findings emphasise the importance of monitoring adiposity, cardiac function and risk factor control through adolescence

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University College London

All ALSPAC clinic staff and participants!

Dr Laura Howe
Dr Abigail Fraser
Prof Debbie Lawlor
Prof George Davey Smith

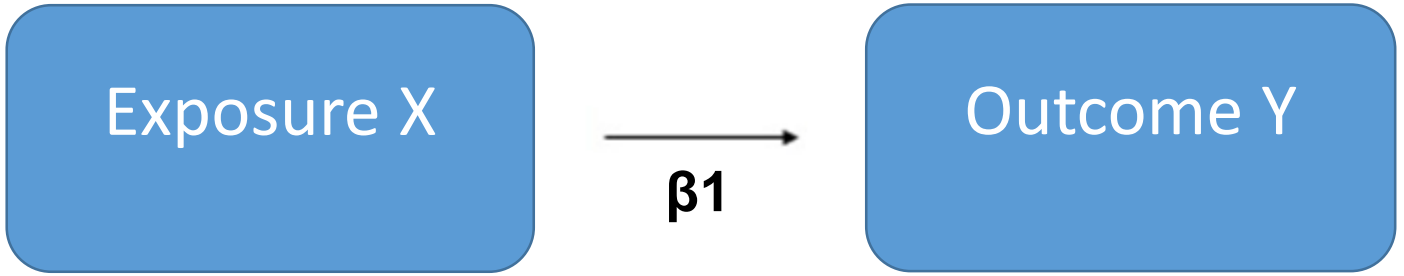
MRC Integrative Epidemiology Unit,
University of Bristol

Any questions?

Strengths and Weaknesses

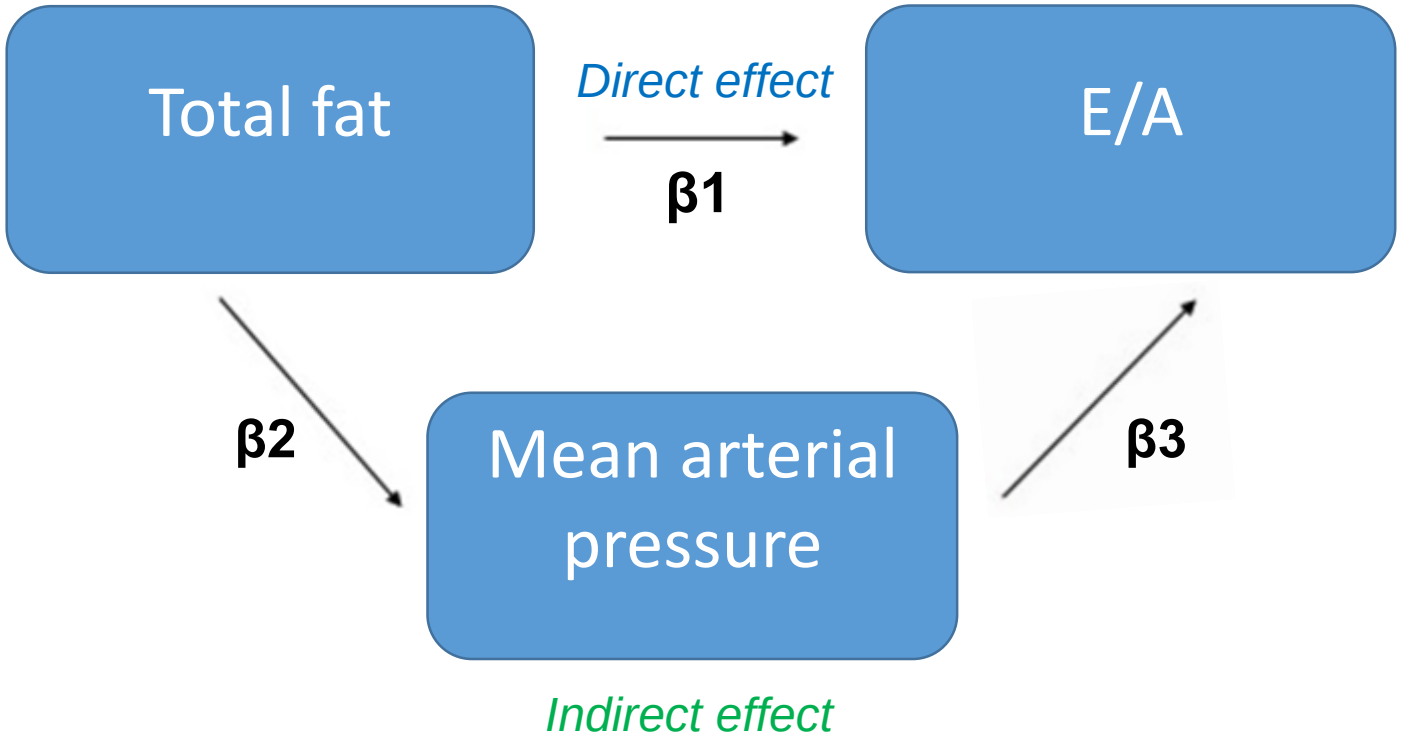
- Observational mediation is weakened by measurement error
- Possibility of collider bias
- Age, ethnicity, sample size
- With a larger sample size it would be possible to interrogate mediation through Mendelian randomisation (using genetic data)

Mediation – A basic model:



Provided that X is a significant predictor for Y, X is a significant predictor for M and M is a significant predictor for Y

Mediation – A basic model:



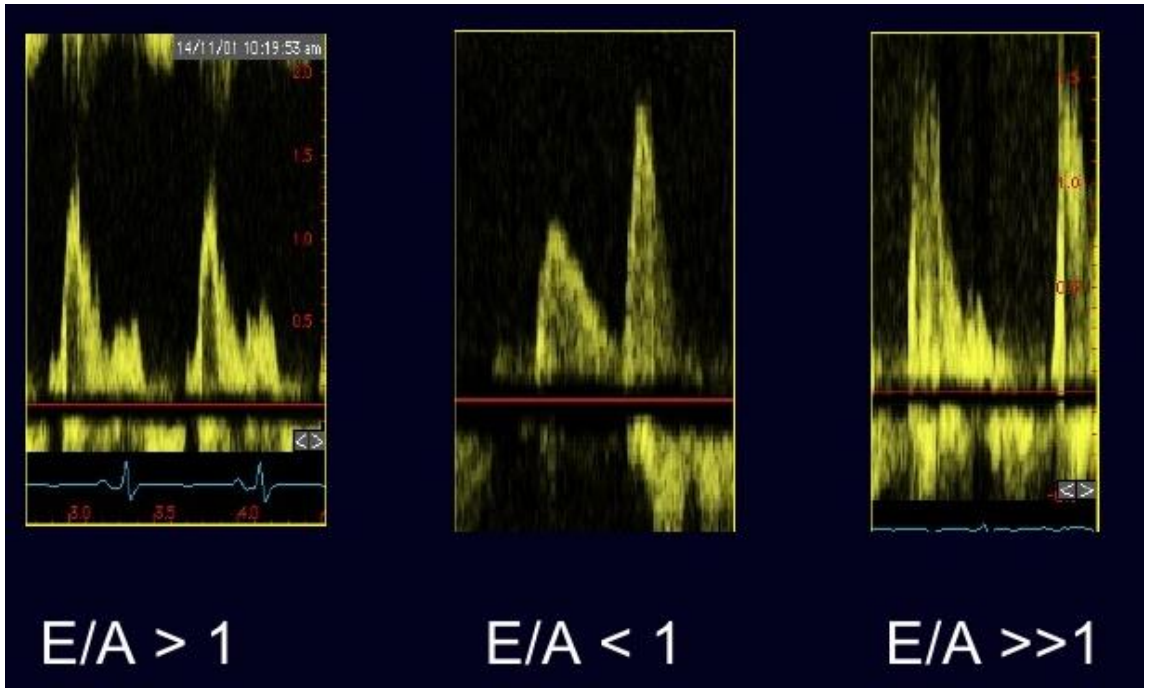
Provided that X is a significant predictor for Y, X is a significant predictor for M and M is a significant predictor for Y

Mitral inflow (measured by E/A)

- Numerous factors impact mitral inflow as measured by E/A

Congenital heart disease

Genetic disposition



Infectious disease e.g. rheumatic fever

Persistent inflammatory valve damage & haemodynamic injury

- No studies have considered the role of mediation by other cardiovascular risk factors during **youth**, when risk may emerge

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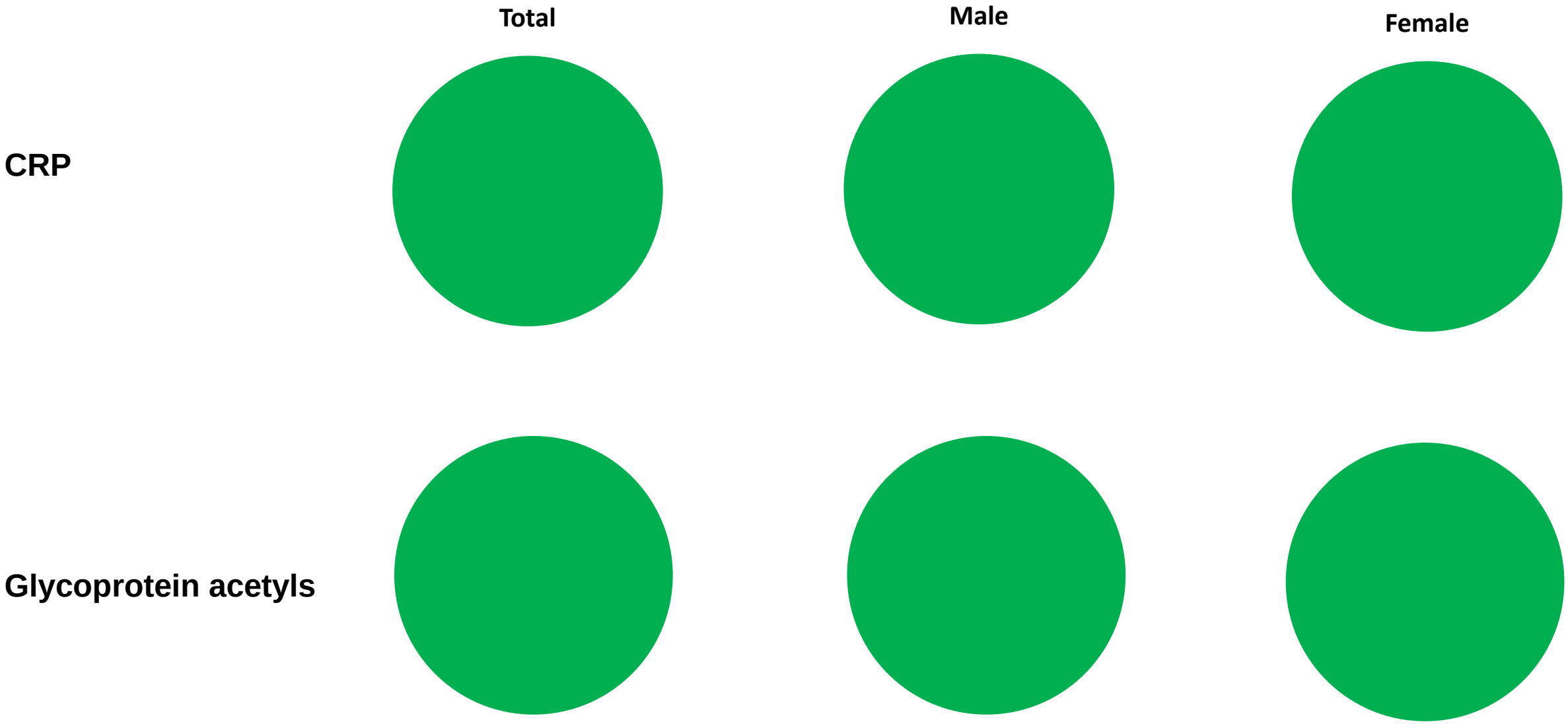
Total Fat -> LVM

Inflammatory mediators:

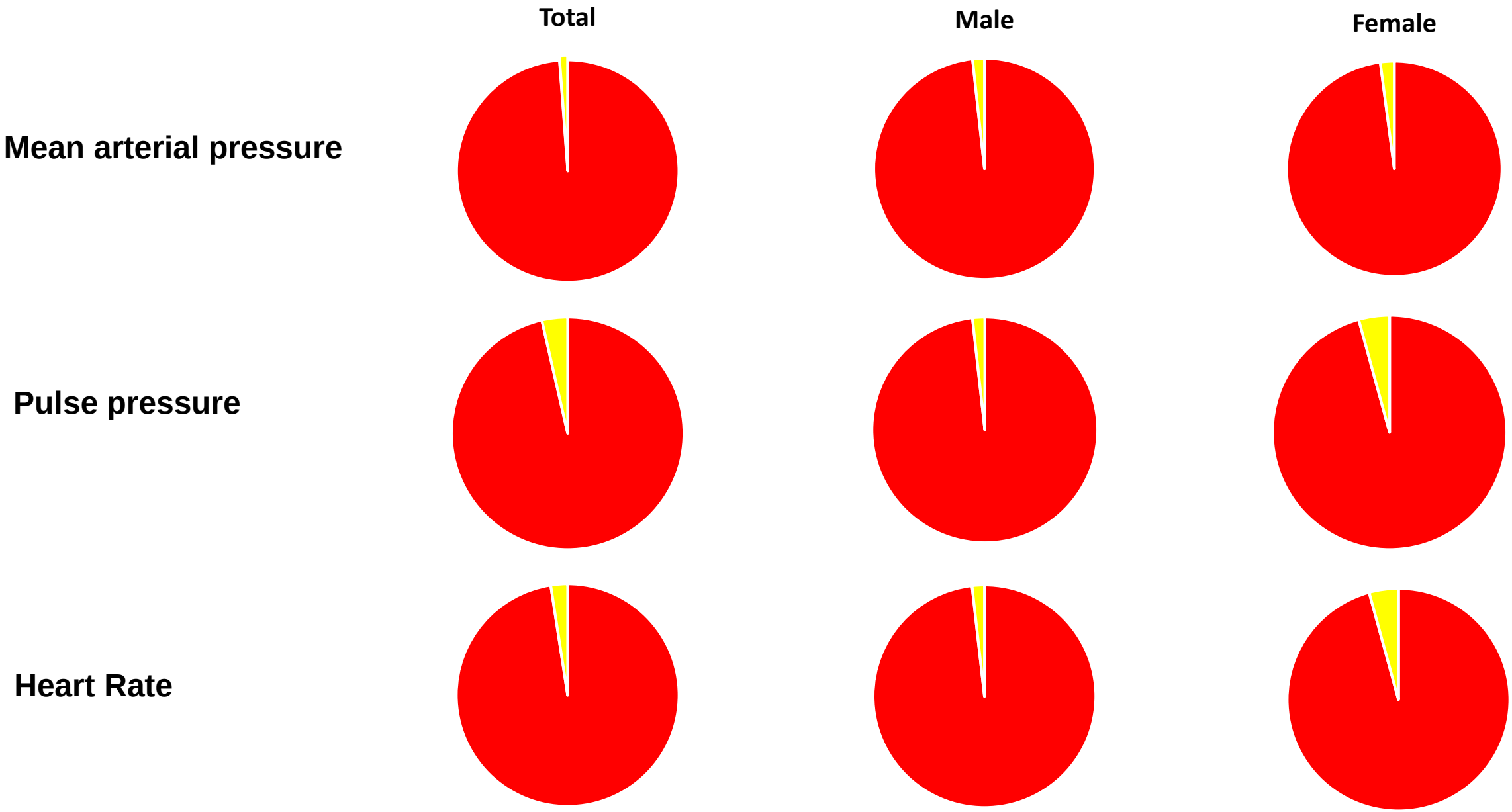
- No evidence of any mediative effect by either CRP or glycoprotein acetyls



Total Lean -> LVM

Haemodynamic mediators:

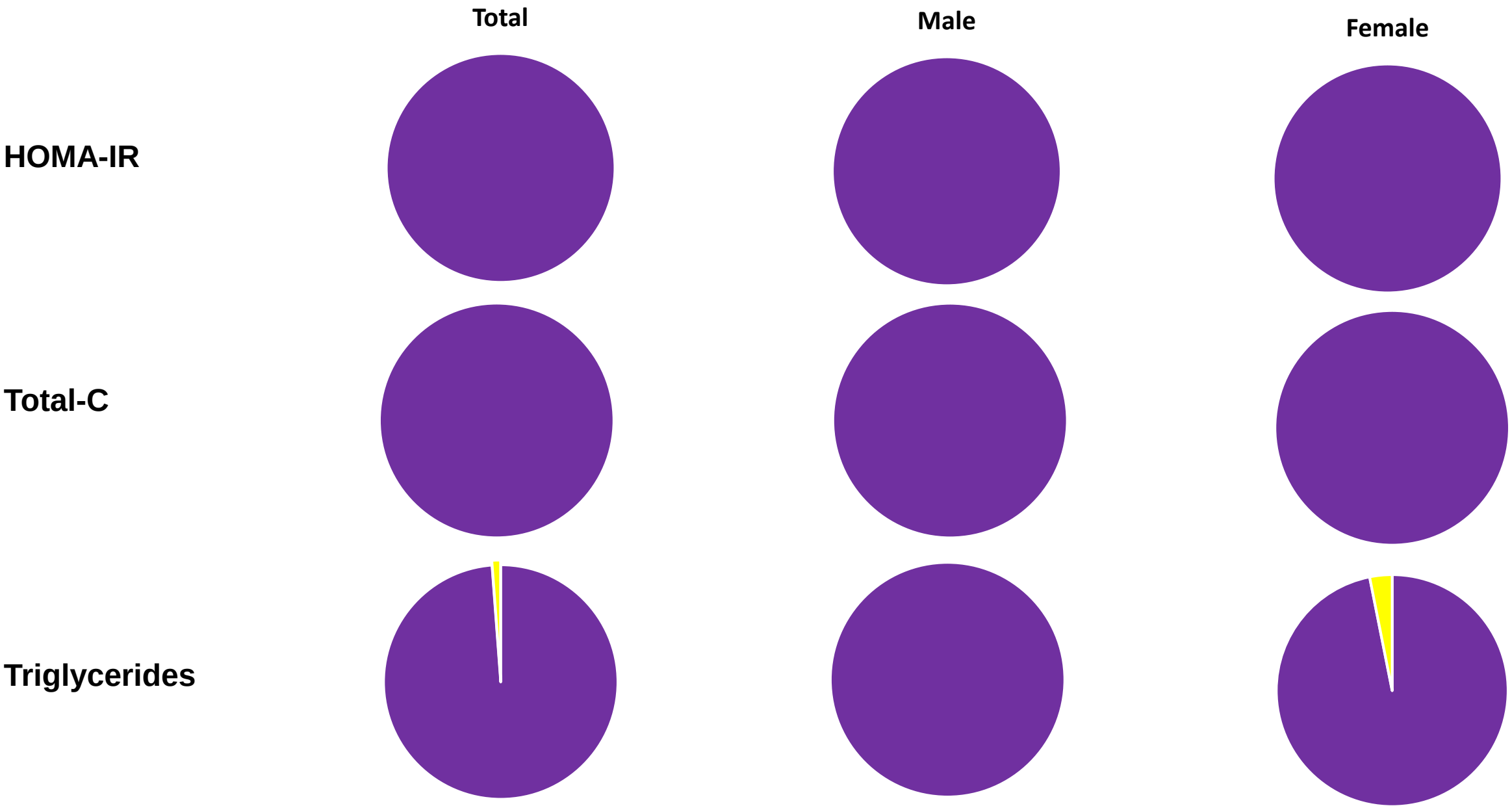
- Negligible mediation - greatest mediative effect is by pulse pressure (female): 4.3%



Total Lean -> LVM

Metabolic mediators:

- Negligible mediation - greatest mediative effect is by triglycerides (female): 2.13%



Total Lean -> LVM

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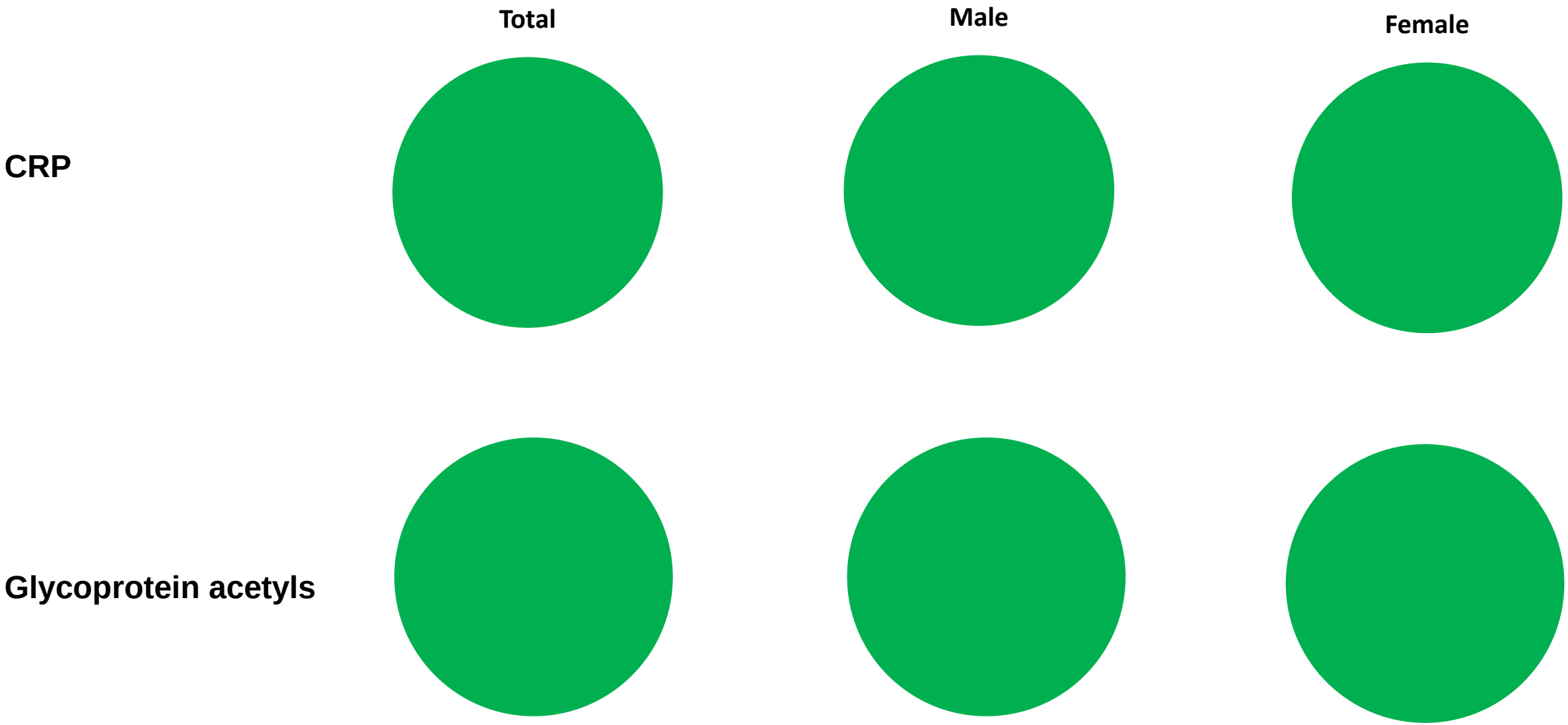
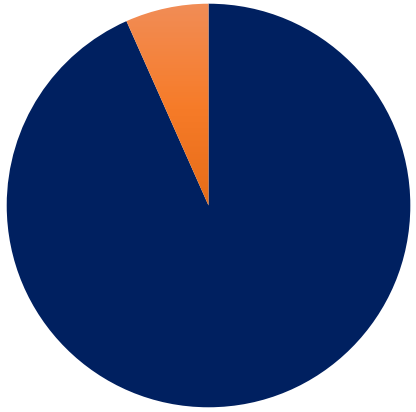


Total Fat -> LVM

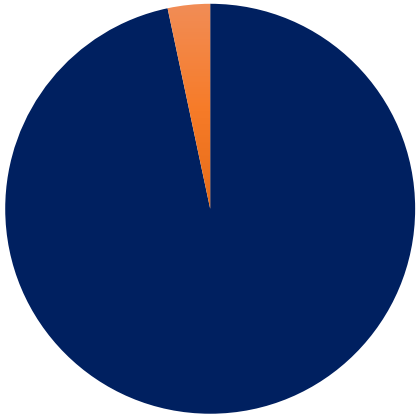
Complete models:

- Variable mediation – greatest collective effect is in the female lean subgroup: **8.9%**

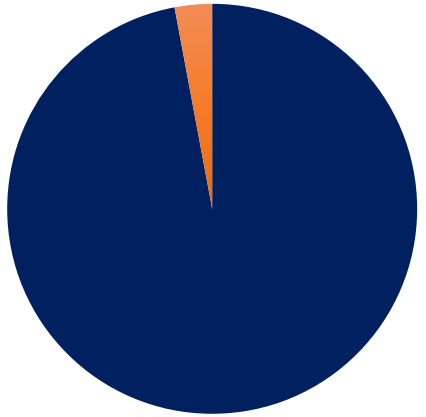
Total



Male

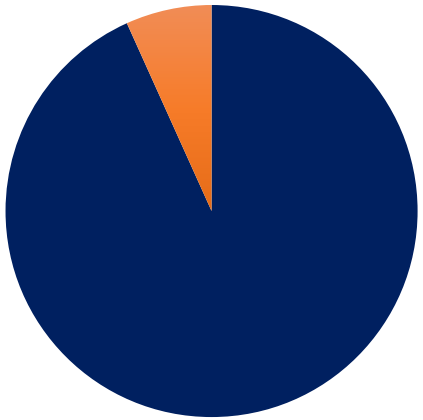


Female

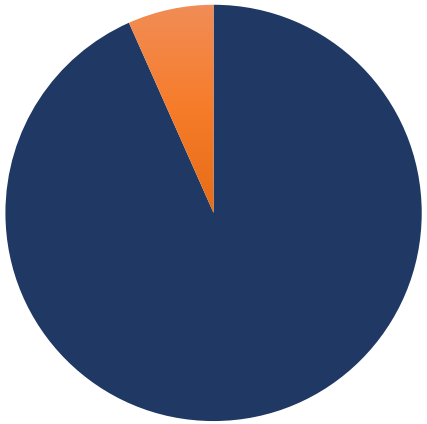


Total Lean -> LVM

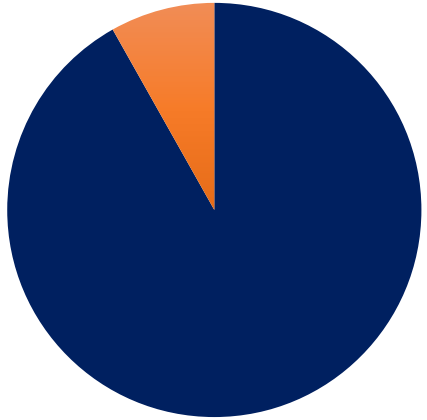
Total



Male



Female



Strengths and Weaknesses

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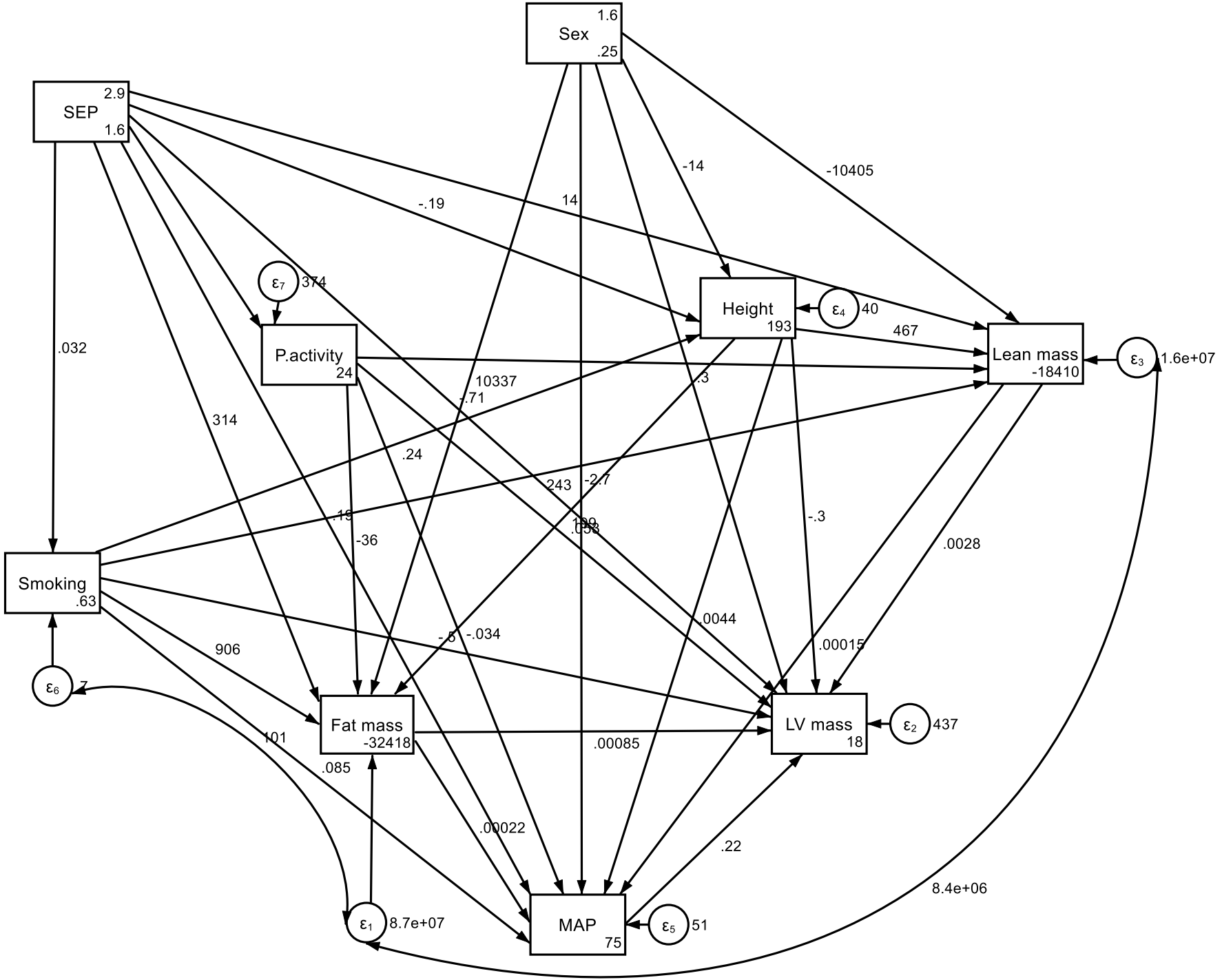
Sex
1.6
.25
SEP
2.9
1.6
Height
193
ε4
40
Lean mass
-18410
ε3
1.6e+07
P.activity
24
ε7
374
Smoking
.63
ε6
7
Fat mass
-32418
LV mass
18
ε2
437
MAP
75
ε5
51
ε1
8.7e+07
-14
-10405
-.19
14
.032
314
10337
.71
.3
.24
243
-2.7
-.3
-36
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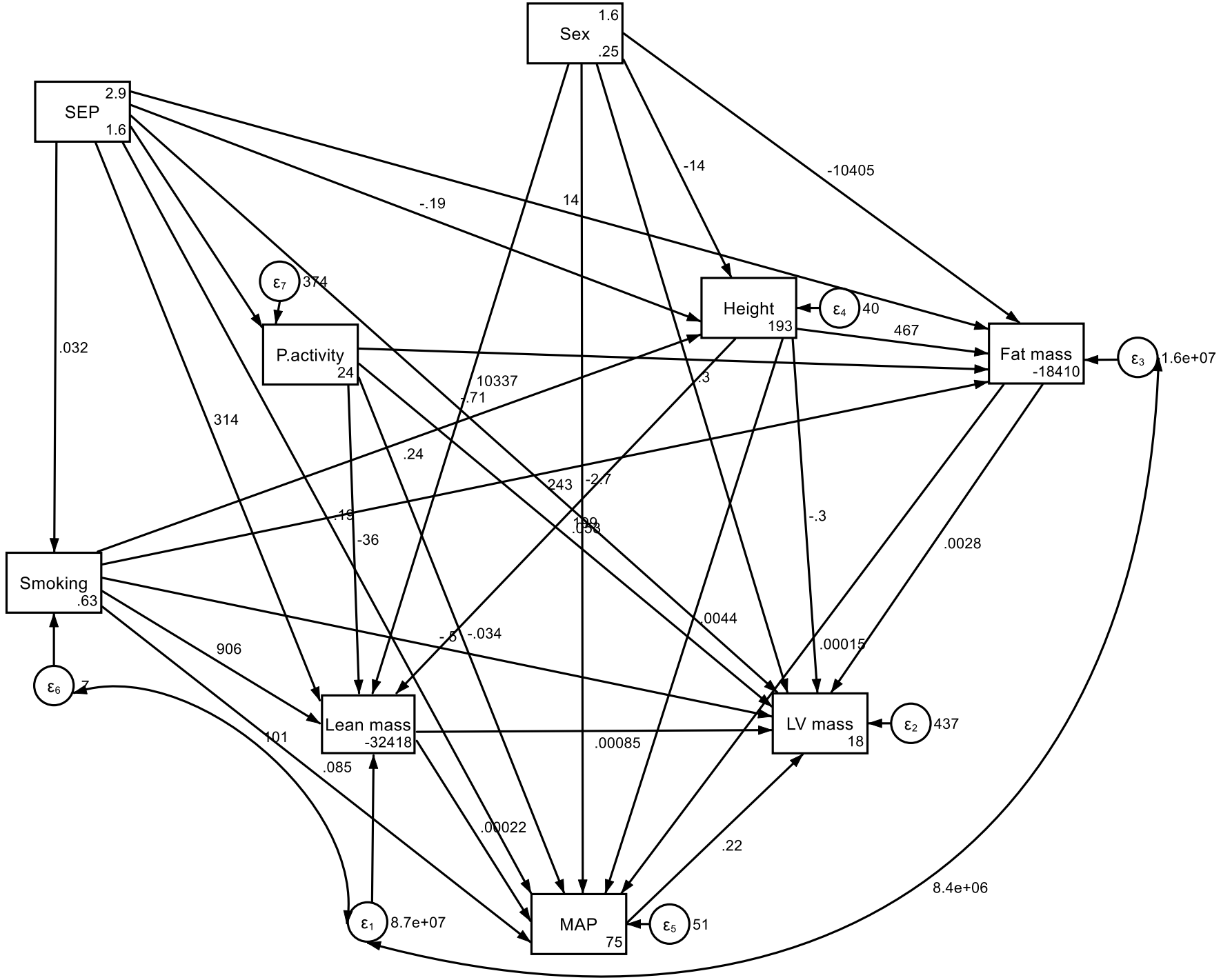
.0044
-.5
-.034
.00015
906
101
.085
.00085
.00022
.22
8.4e+06

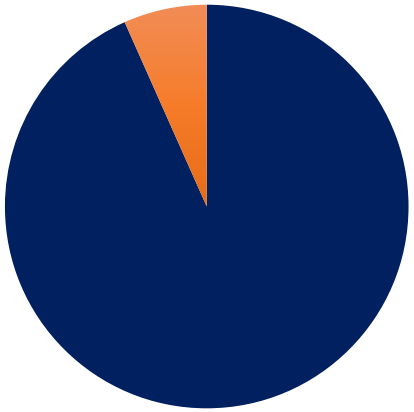

Sex
1.6
.25
SEP
2.9
1.6
-14
-10405
-.19
14
ε7
374
Height
193
ε4
40
467
P.activity
24
Fat mass
-18410
ε3
1.6e+07
.032
10337
.71
.3
314
.24
243
-2.7
-.3
.0028
-36
Smoking
.63
.0044
-.034
906
.00015
ε6
7
Lean mass
-32418
LV mass
18
ε2
437
101
.00085
.085
.00022
.22
8.4e+06
ε1
8.7e+07
MAP
75
ε5
51

Total Fat -> LVM

Complete models:

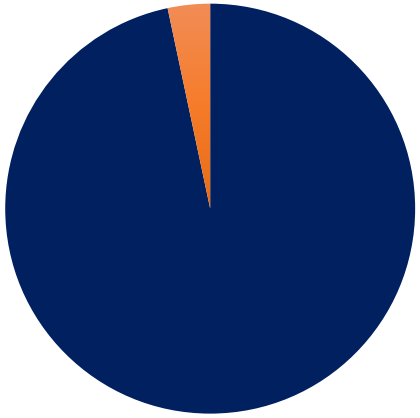
- Variable mediation – greatest mediative effect is by mediators for female lean: **8.9%**

Total



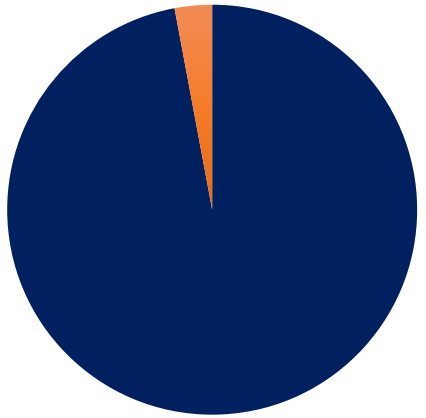
7.14%

Male



3.33%

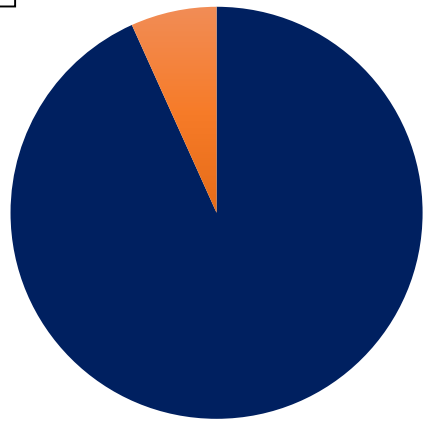
Female



3.03%

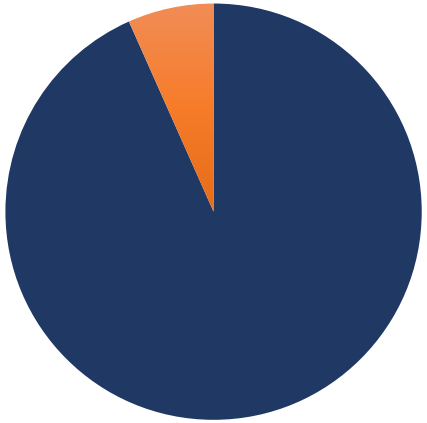
Total Lean -> LVM

Total



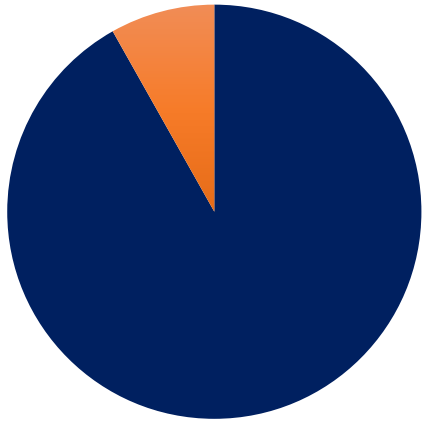
7.22%

Male



7.14%

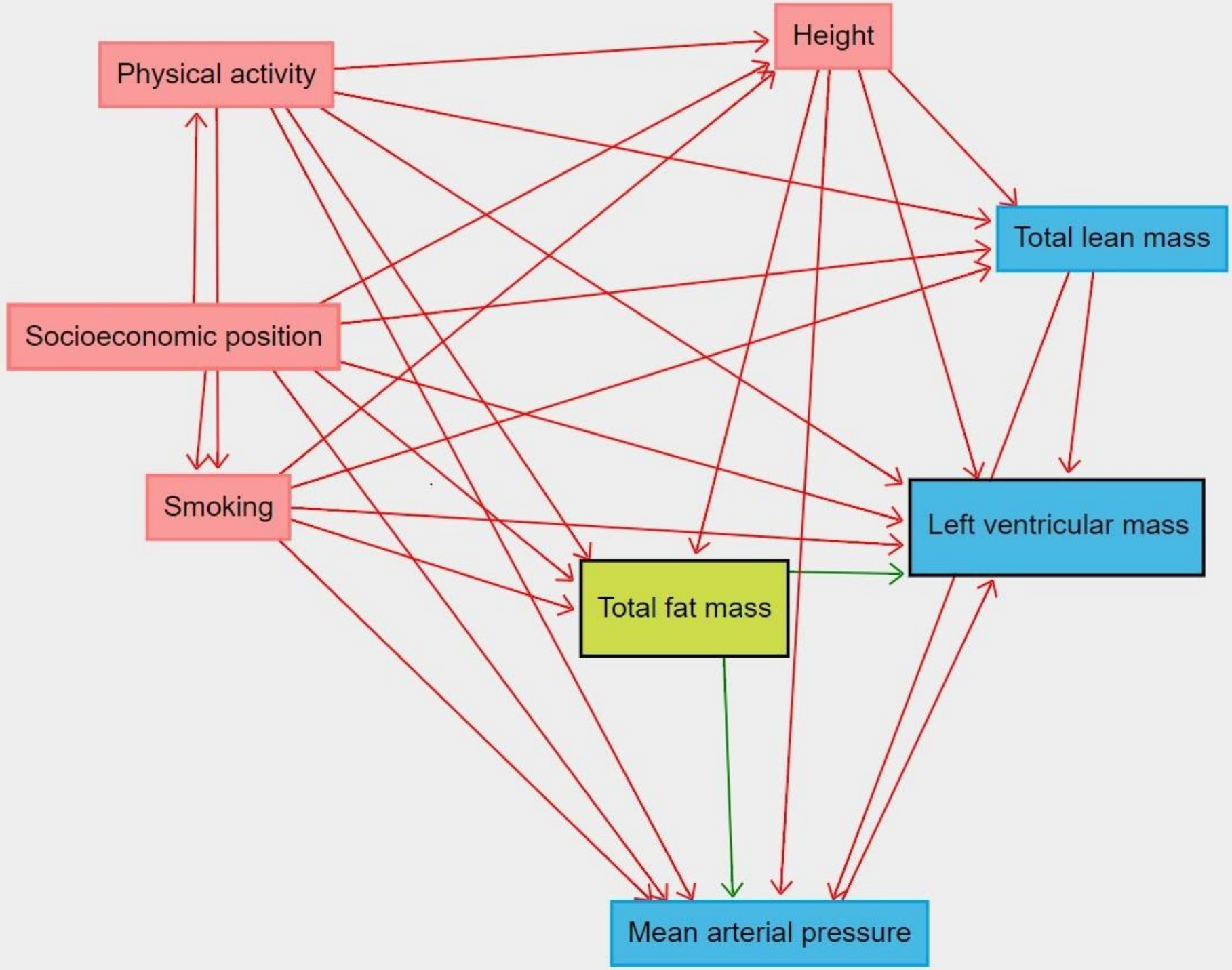
Female



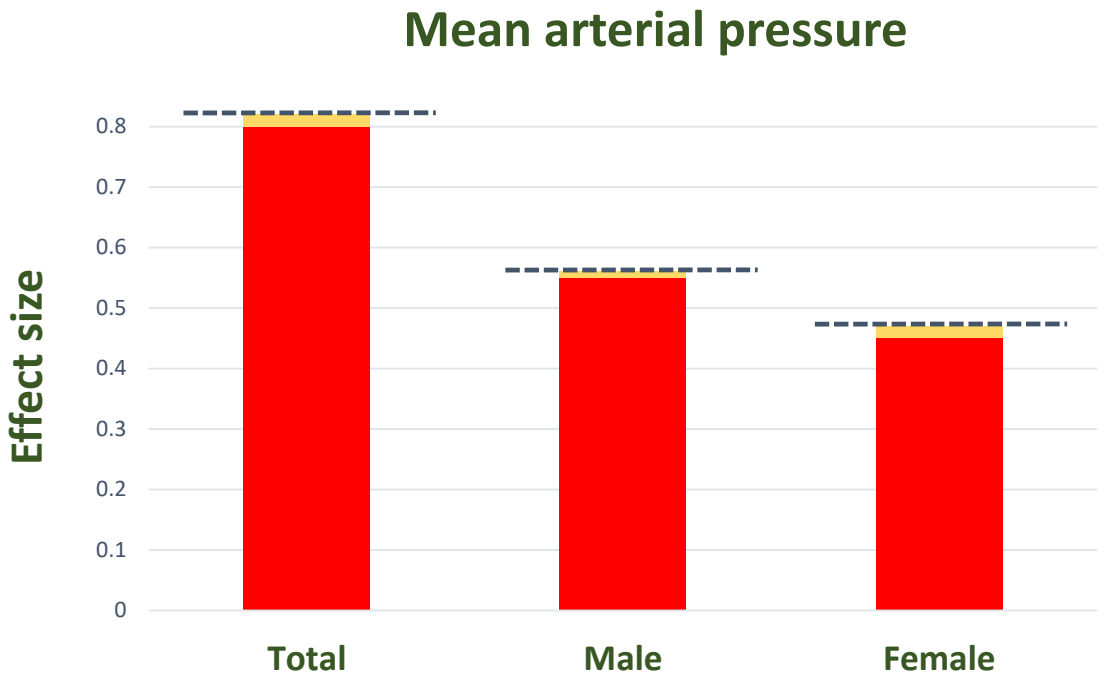
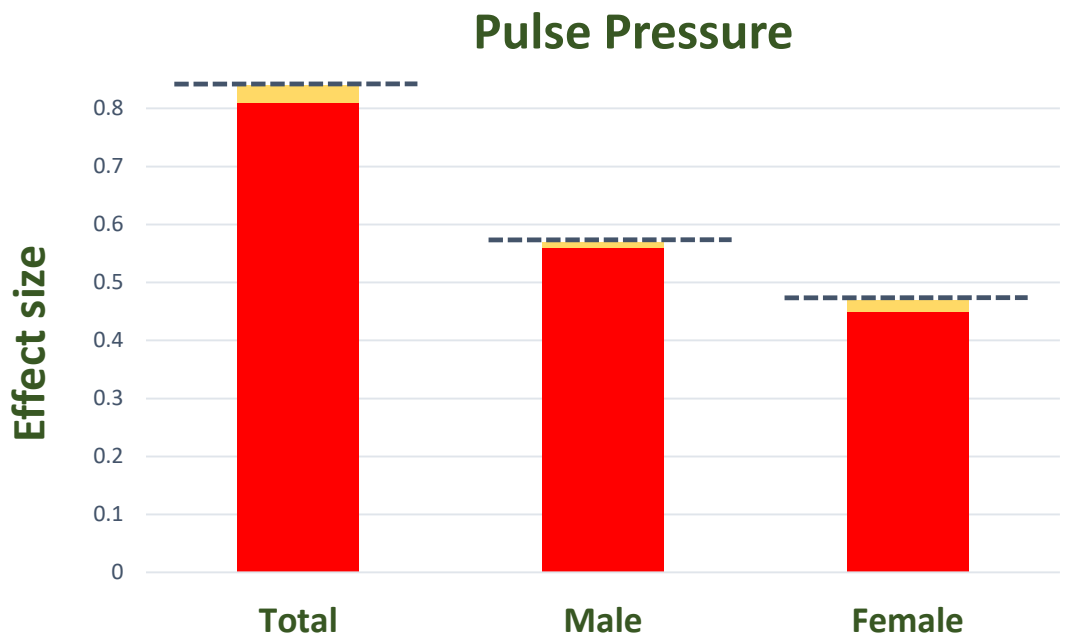
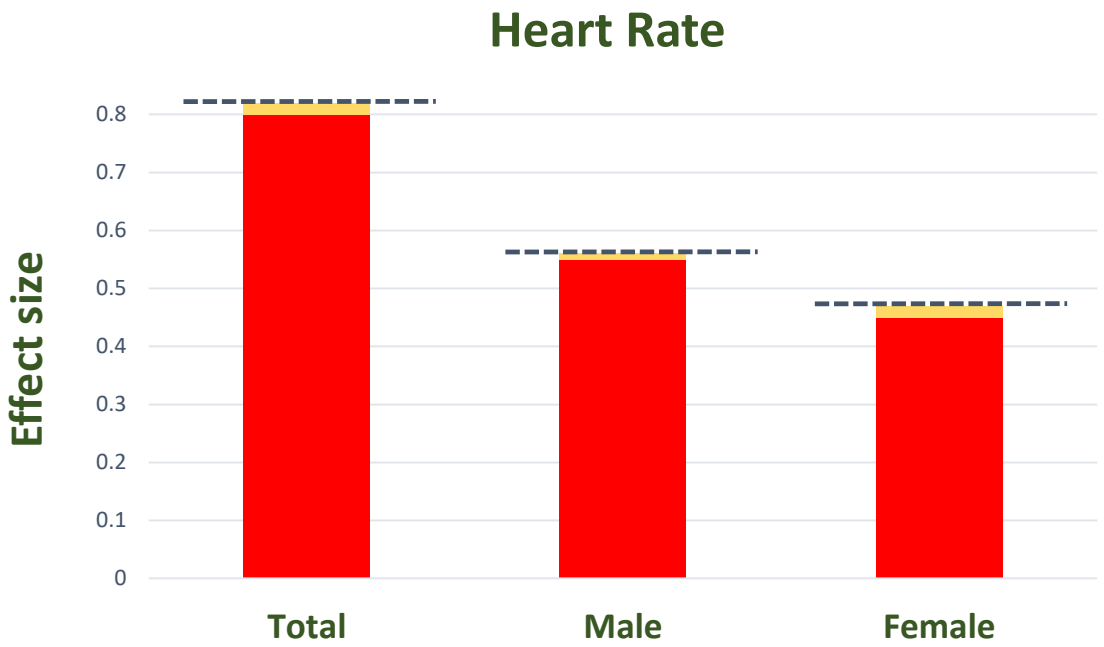
8.89%

Biomarker	Total Fat Mass		Male Fat Mass		Female Fat Mass	
NB: All p < 0.001	Direct effect	Total effect	Direct effect	Total effect	Direct effect	Total effect
Mean arterial Pressure	0.27	0.28	0.31	0.33	0.31	0.33
Pulse pressure	0.28	0.28	0.28	0.33	0.33	0.34
Heart rate	0.30	0.28	0.34	0.33	0.35	0.34
Insulin	0.28	0.28	0.31	0.32	0.36	0.33
HOMA-IR	0.28	0.28	0.31	0.32	0.36	0.33
HDL cholesterol	0.28	0.28	0.34	0.32	0.34	0.33
Total cholesterol	0.27	0.28	0.31	0.32	0.33	0.33
Triglycerides	0.28	0.28	0.33	0.33	0.32	0.33
C-reactive protein	0.28	0.28	0.32	0.32	0.32	0.33
Glycoprotein acetyls	0.27	0.28	0.32	0.32	0.31	0.33

Biomarker	Total Lean Mass		Male Lean Mass		Female Lean Mass	
NB: All p < 0.001	Direct effect	Total effect	Direct effect	Total effect	Direct effect	Total effect
Mean arterial Pressure	0.83	0.84	0.57	0.58	0.47	0.48
Pulse pressure	0.81	0.84	0.56	0.57	0.45	0.47
Heart rate	0.80	0.82	0.55	0.56	0.44	0.46
Insulin	0.84	0.84	0.58	0.58	0.47	0.46
HOMA-IR	0.84	0.84	0.58	0.58	0.47	0.46
HDL cholesterol	0.84	0.83	0.58	0.57	0.47	0.47
Total cholesterol	0.84	0.83	0.57	0.57	0.47	0.47
Triglycerides	0.83	0.84	0.57	0.57	0.46	0.47
C-reactive protein	0.84	0.84	0.57	0.57	0.47	0.47
Glycoprotein acetyls	0.84	0.83	0.57	0.57	0.47	0.47


Height
Physical activity
Total lean mass
Socioeconomic position
Smoking
Left ventricular mass
Total fat mass
Mean arterial pressure

Total Lean -> LVM

Haemodynamic factors:

- Minimal mediation
- Greatest effect in pulse pressure (total group) (2.5%)