Obesity and endometrial cancer risk:
using plasma proteomics to identify underlying inflammation and immune response pathways

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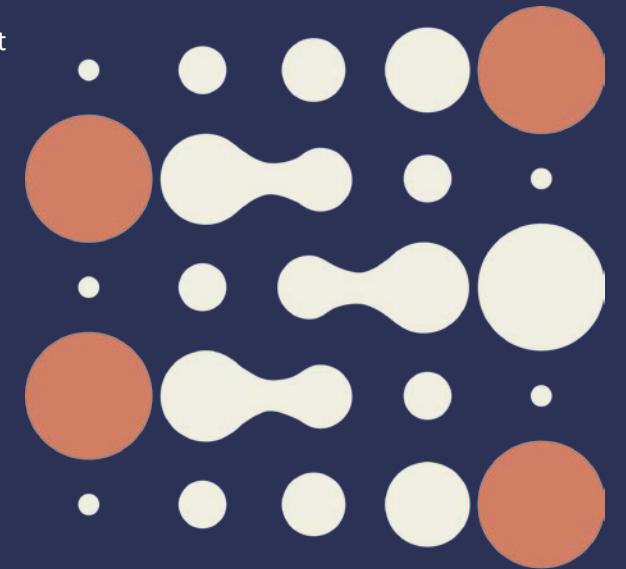4 – West London Gynaecological Cancer Centre, Imperial College Healthcare NHS Trust, London, UK
5 – Gynaecological Oncology Research Group, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, St Mary's Hospital, Manchester, UK
6 – Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
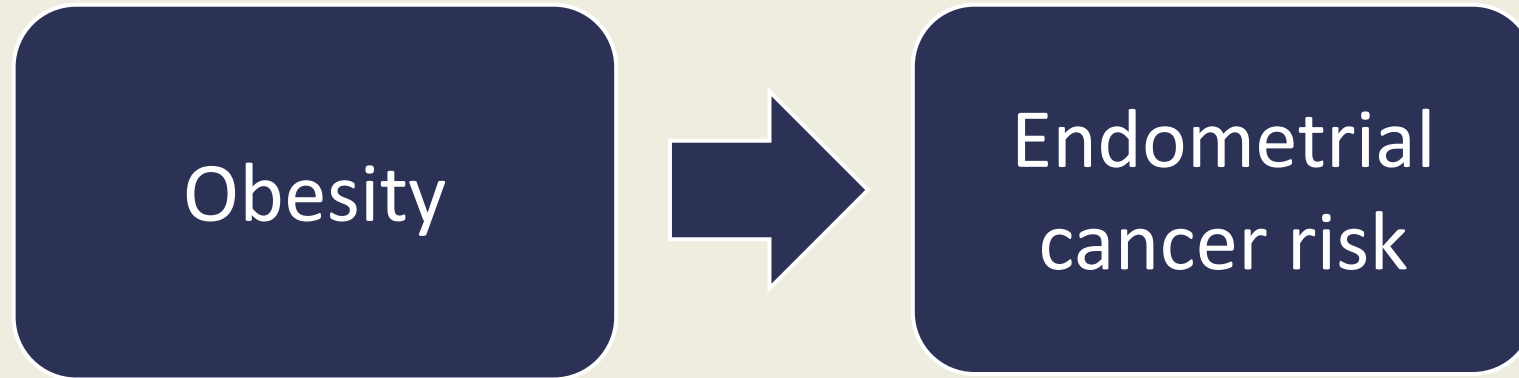7 – Cancer Epidemiology and Prevention Research Unit, School of Public Health, Imperial College London, London, UK
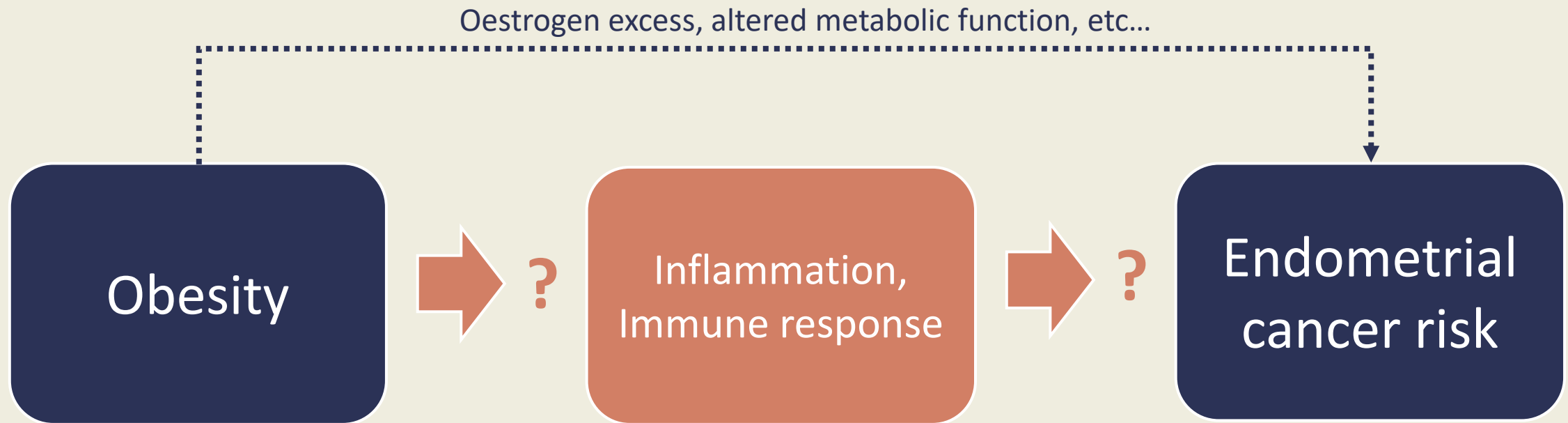
wangs@iarc.who.int

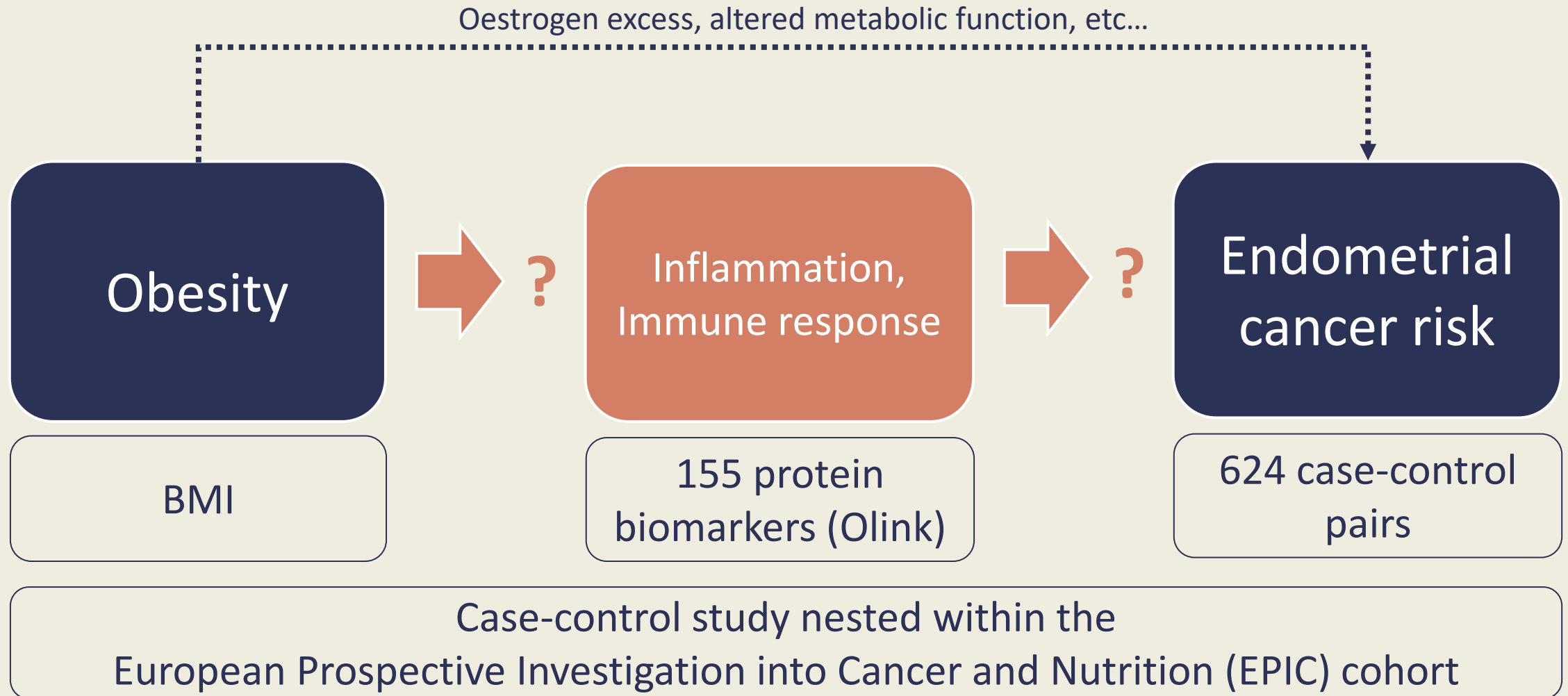International Agency for Research on Cancer

World Health Organization

RÉPUBLIQUE FRANÇAISE
Liberté
Égalité
Fraternité

INSTITUT NATIONAL DU CANCER

World Cancer Research Fund International

Introduction/Background/Motivation

Obesity → Endometrial cancer risk

Oestrogen excess, altered metabolic function, etc…

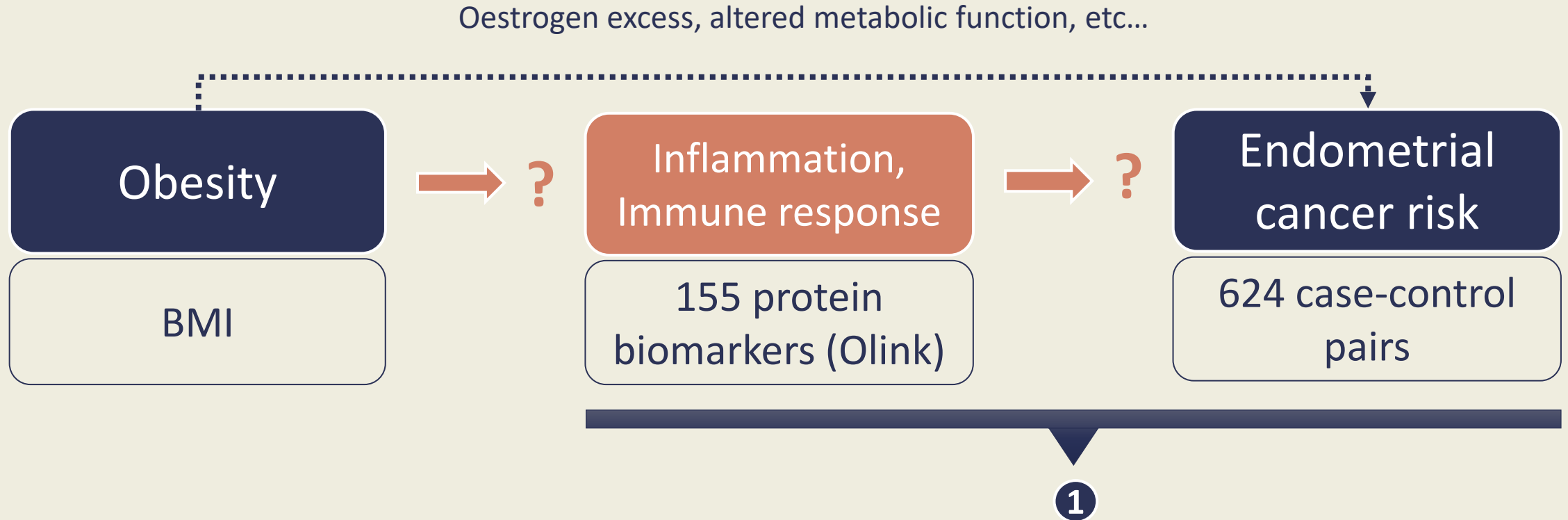| Obesity | ? | Inflammation, Immune response | ? | Endometrial cancer risk |

What are the underlying inflammation and immune response pathways that could mediate the effect of obesity on endometrial cancer risk?
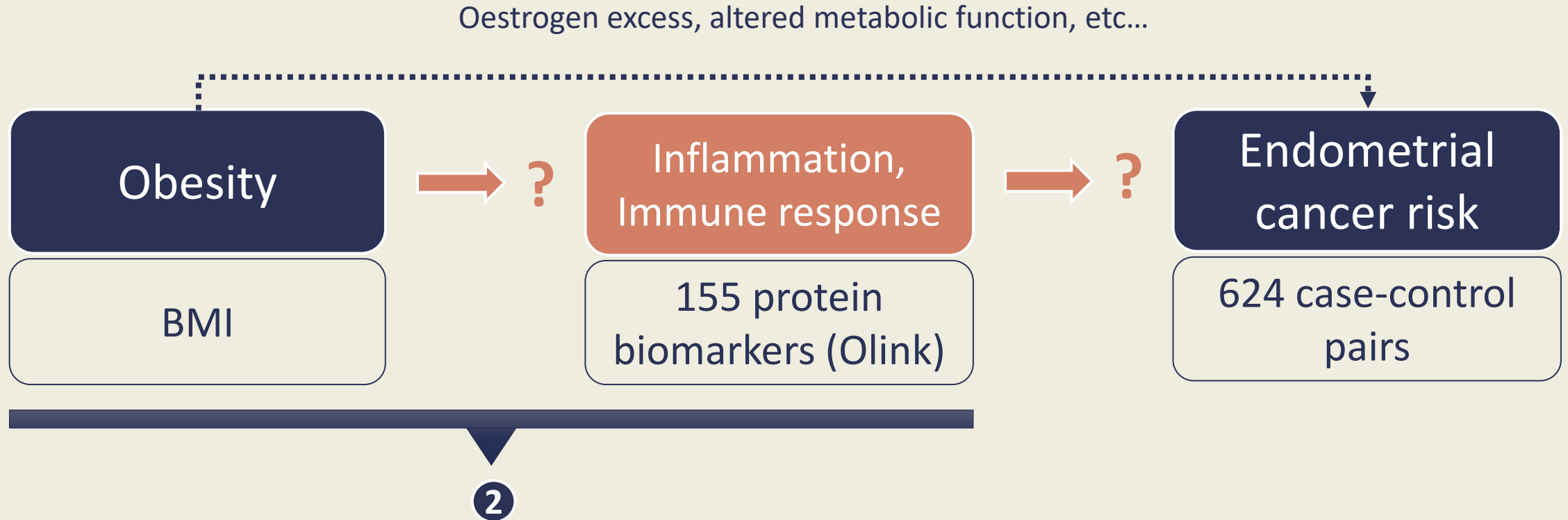
Design

Oestrogen excess, altered metabolic function, etc…

Obesity ❓ **Inflammation, Immune response** ❓ **Endometrial cancer risk**

BMI

155 protein biomarkers (Olink)

624 case-control pairs

Case-control study nested within the
European Prospective Investigation into Cancer and Nutrition (EPIC) cohort

3

Design

Oestrogen excess, altered metabolic function, etc…

Obesity

BMI

Inflammation, Immune response

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Endometrial cancer risk

624 case-control pairs

①

1. **Protein-EC** associations, adjusted for **BMI**, using conditional logistic regression
2. **BMI-Protein** associations, among EC controls, using linear regression
3. **Estimate effect mediated** by each identified protein (mediation analysis)

All regression models included reproductive and lifestyle factors as covariates
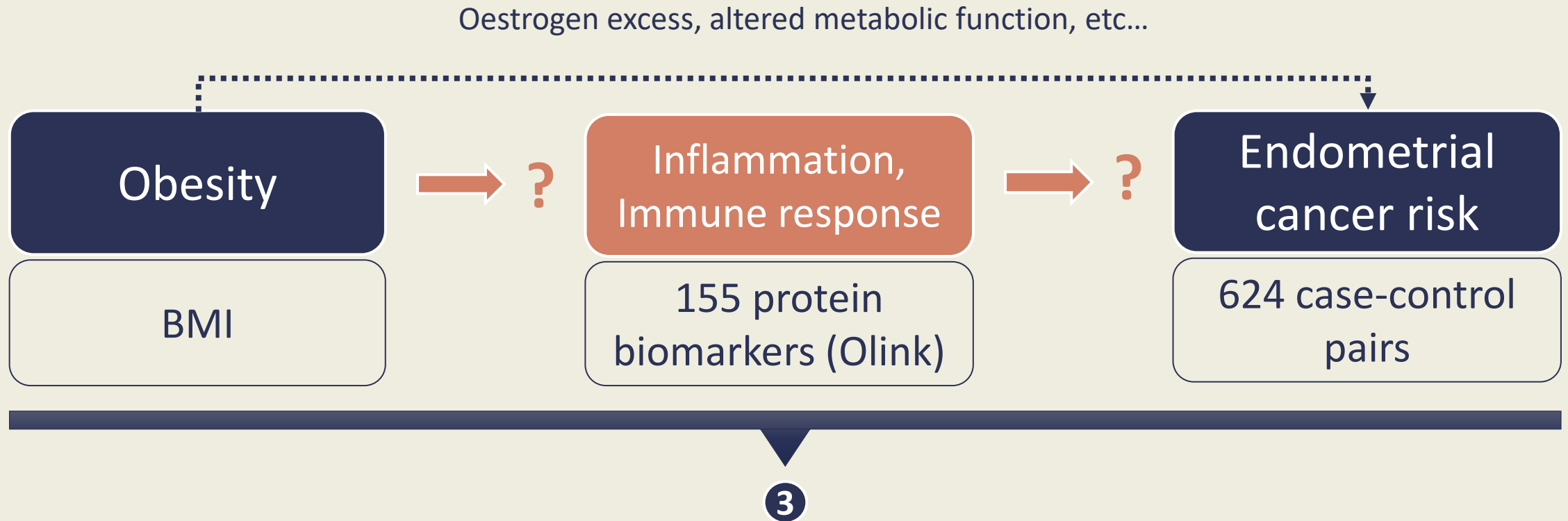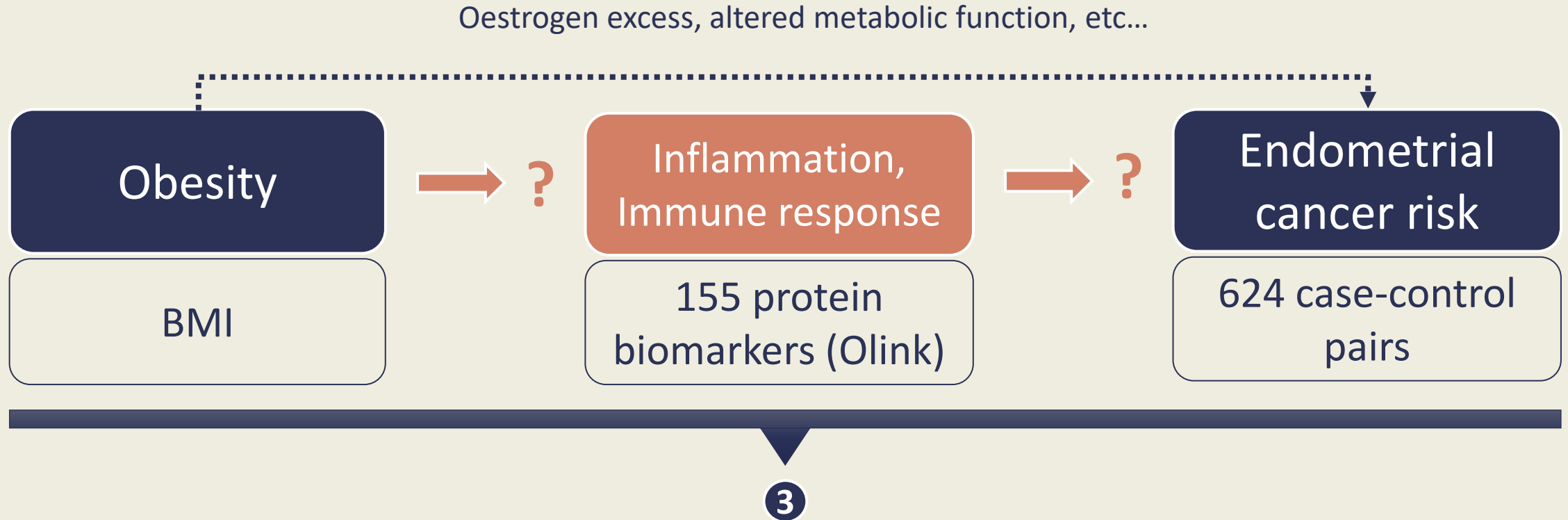
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Oestrogen excess, altered metabolic function, etc…

Obesity → ? → Inflammation, Immune response → ? → Endometrial cancer risk

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Decompose the total effect (TE) of obesity on EC risk into:

➡ Natural indirect effect (NIE) mediated by protein

┈► Natural direct effect (NDE) not mediated by protein

TE = NIE + NDE
% mediated = NIE/TE

Results
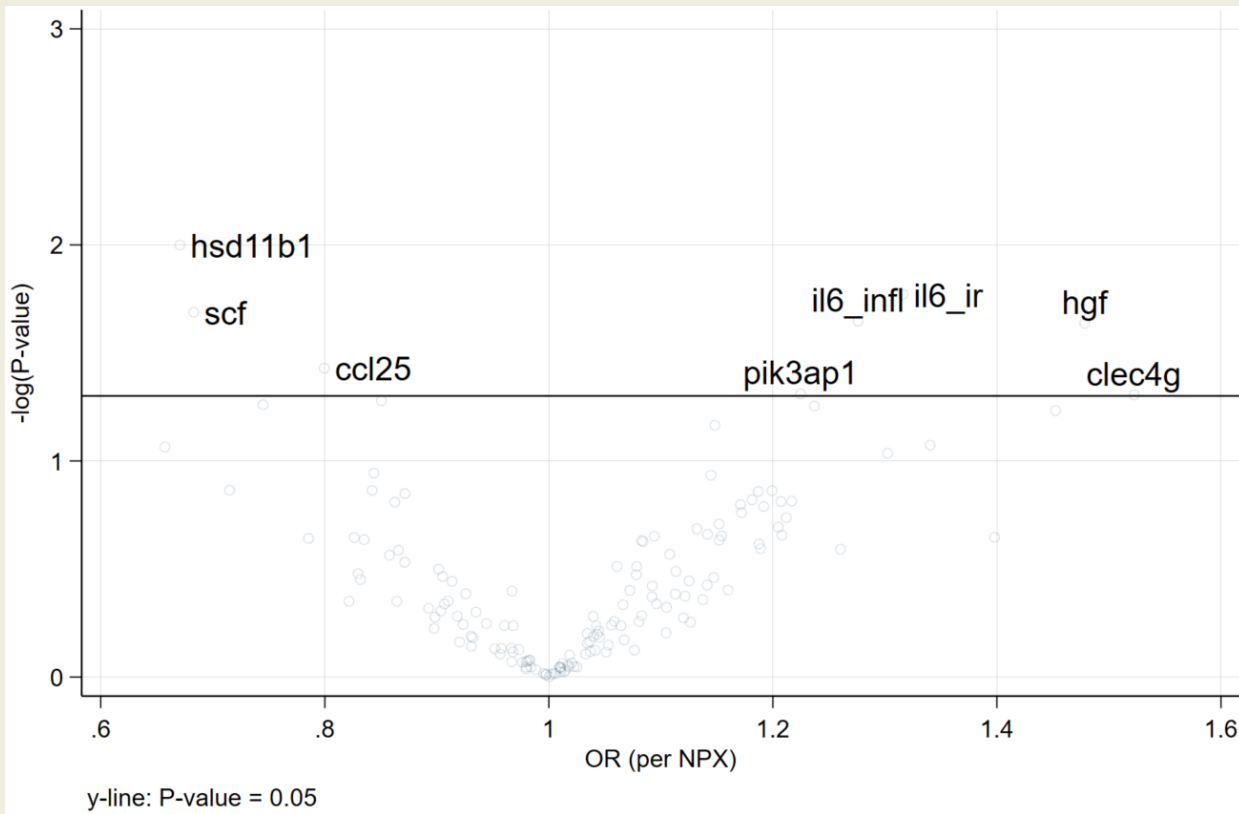
❶ Protein-EC, adjusted for BMI
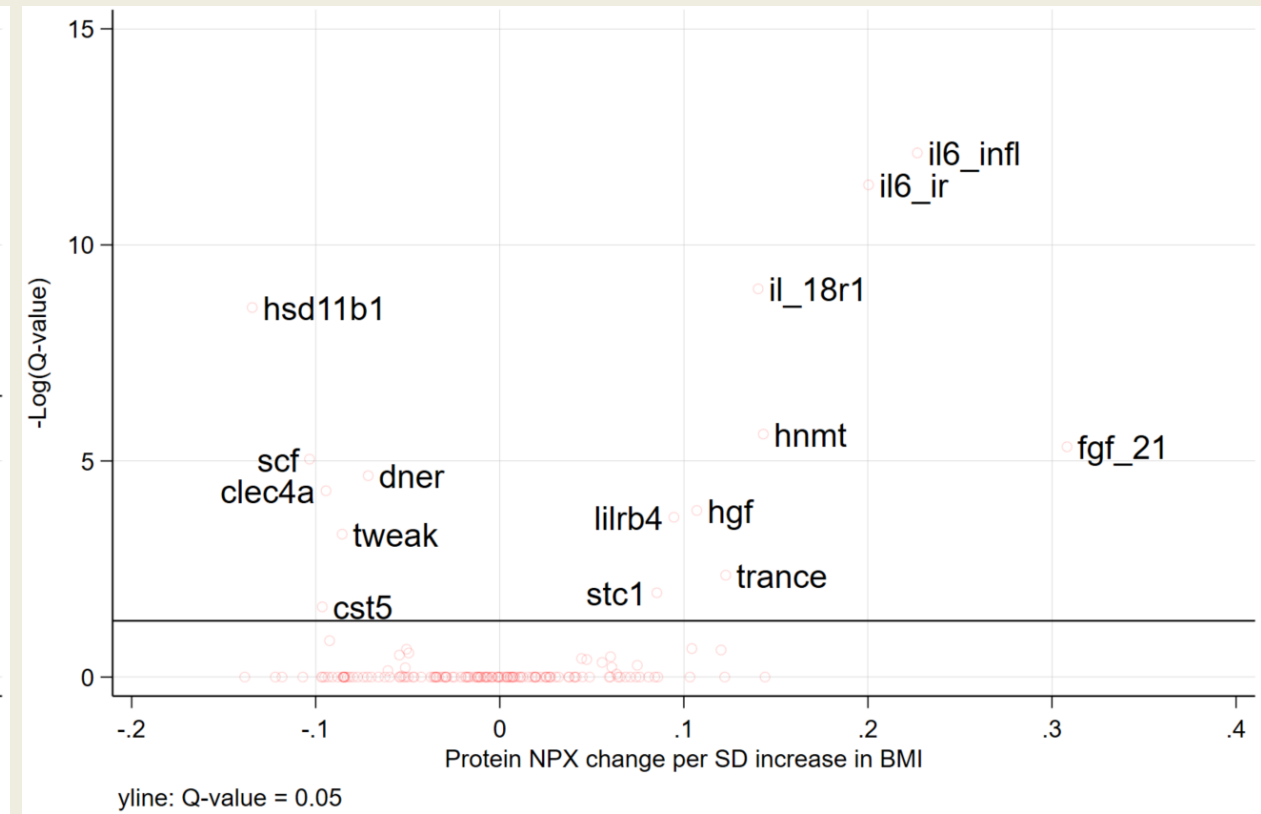
❷ BMI-Protein

Results

Step ❶ & ❷
Identify potential mediators ...
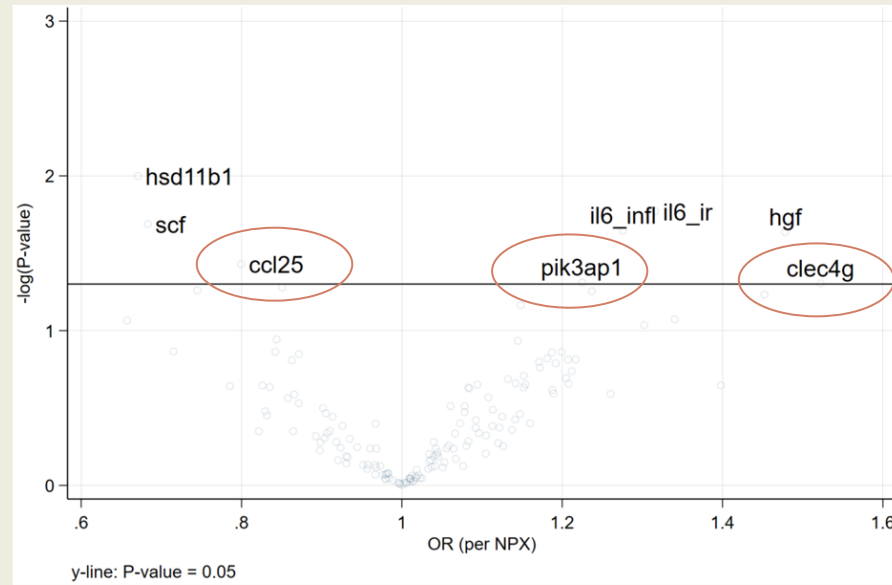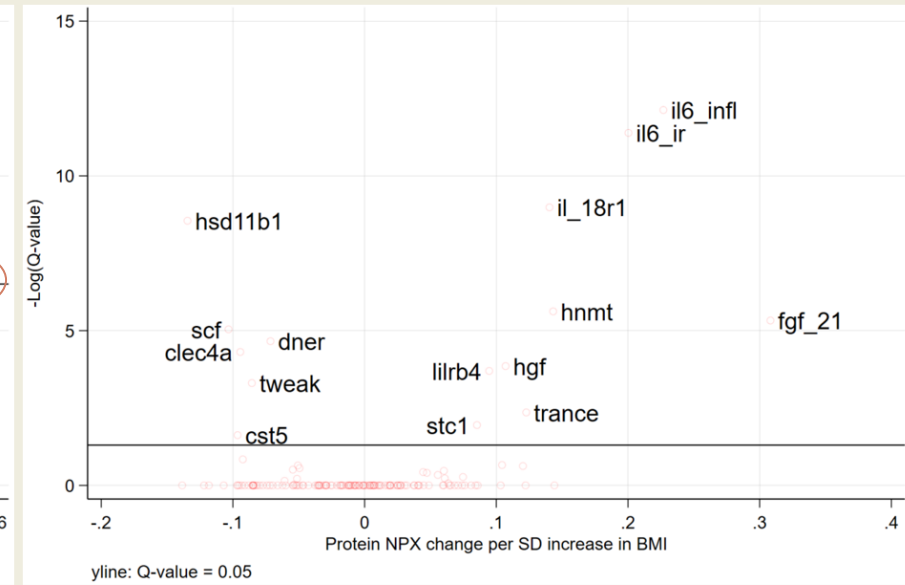
❶ Protein-EC, adjusted for BMI   ❷ BMI-Protein

✓ **Protein-EC**
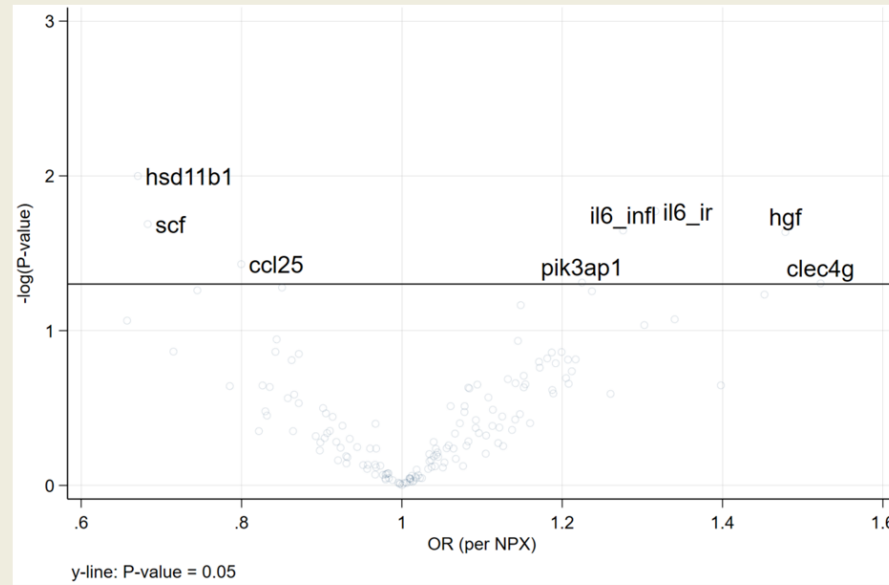
✗ **BMI-Protein**

  • Protein not associated with BMI
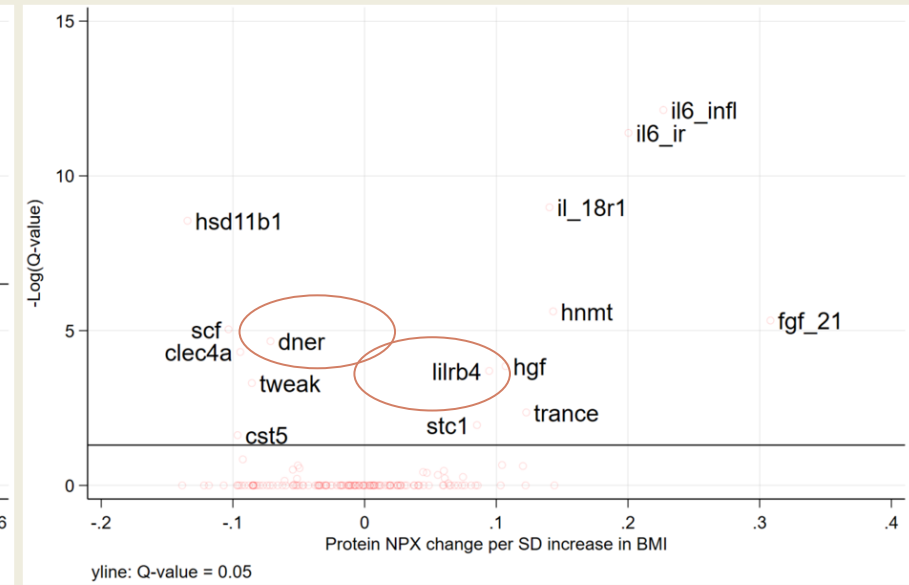
Association with EC not related to BMI
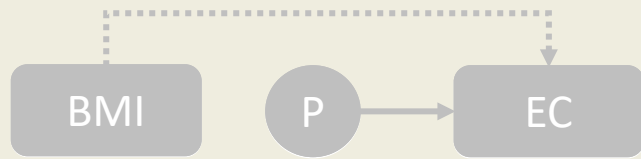**Interesting, but not mediators... will investigate in a separate analysis**

Results

Step ① & ②
Identify potential mediators ...

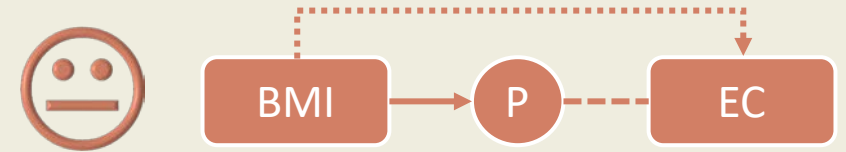① **Protein-EC, adjusted for BMI**

② **BMI-Protein**

✕ **Protein-EC**

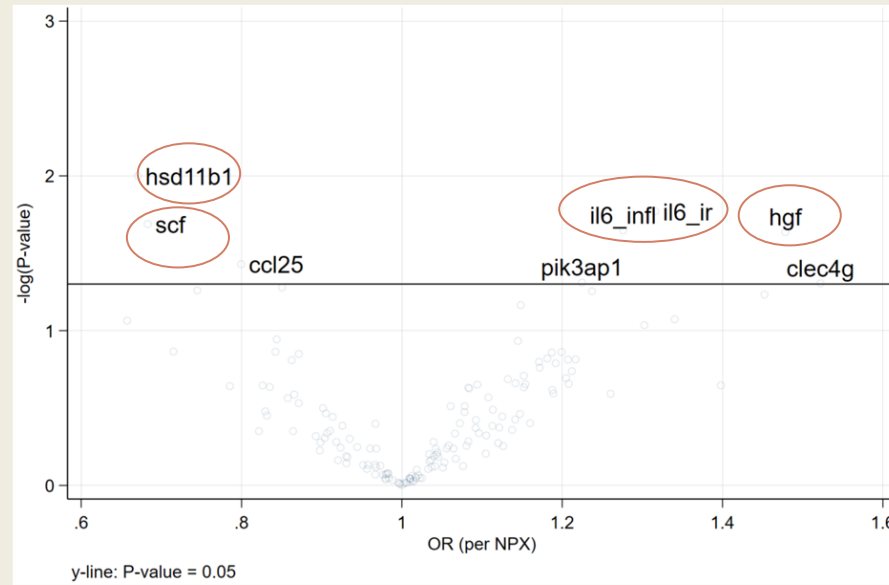- Protein not associated with EC risk when model adjusted for BMI
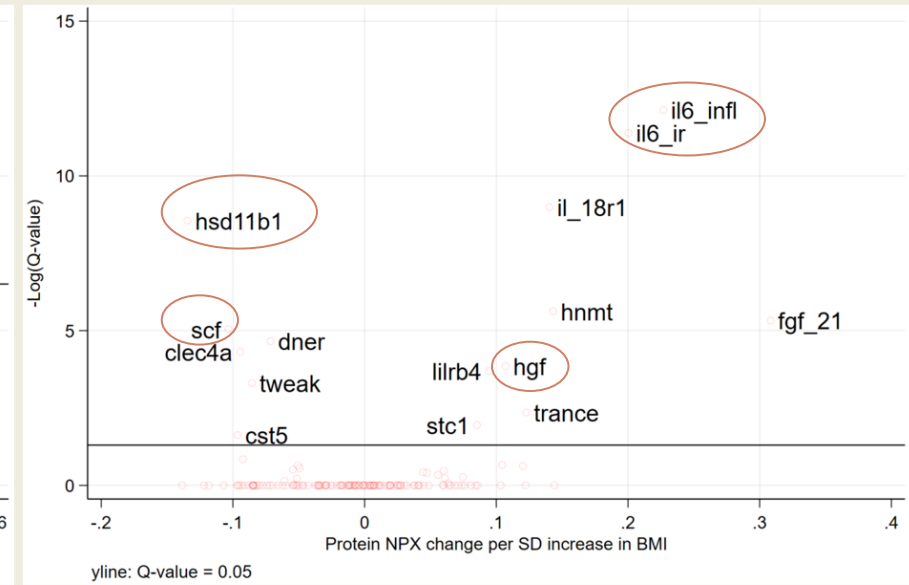
✓ **BMI-Protein**

Association with EC largely driven by BMI
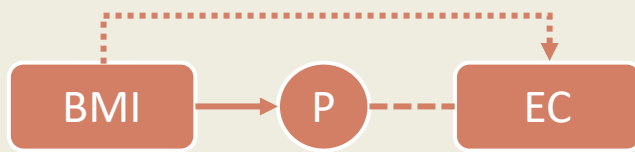**Unlikely to be mediators... but will investigate in mediation analysis**
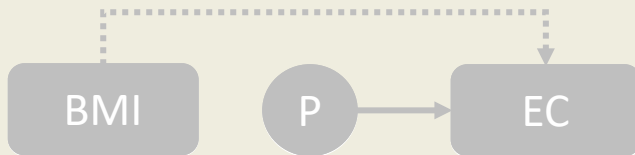
Results

Step ① & ②
Identify potential mediators ...

① **Protein-EC, adjusted for BMI**

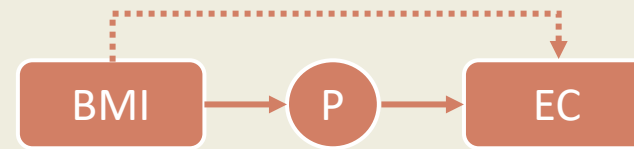② **BMI-Protein**

✓ **Protein-EC**
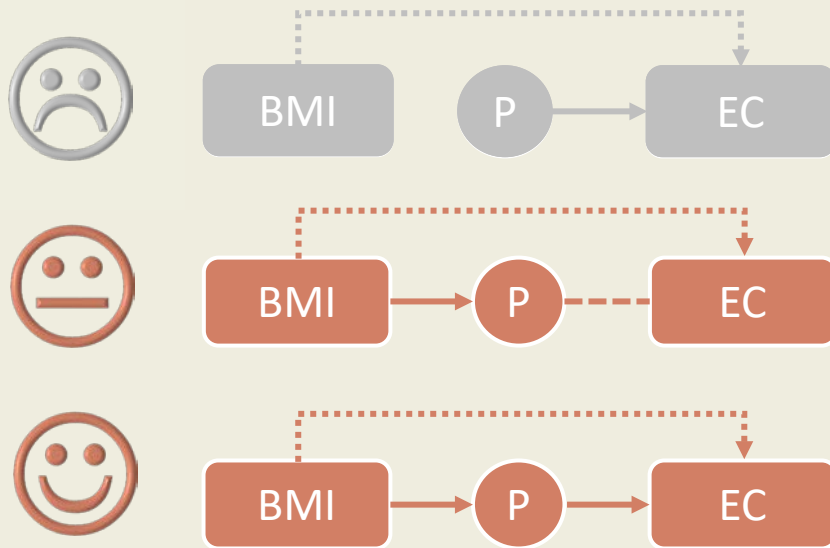   ✓ Protein associated with EC risk, adjusted for BMI

✓ **BMI-Protein**

Potential mediators of the BMI-EC effect

4

Results

Step ❶ & ❷
Identify potential mediators …
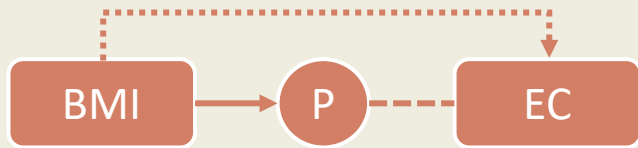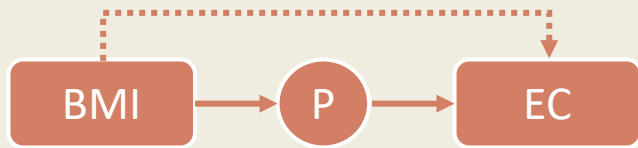

Mediation analysis

Results

Step ③
Estimate effect mediated ...

Decompose the total effect (TE) of obesity on EC risk into:

→ Natural indirect effect (NIE) mediated by protein

┈┈▶ Natural direct effect (NDE) not mediated by protein

TE = NIE + NDE
% mediated = NIE/TE

TE ≈ 3.17 (2.68 – 3.75)
% mediated = NIE/TE
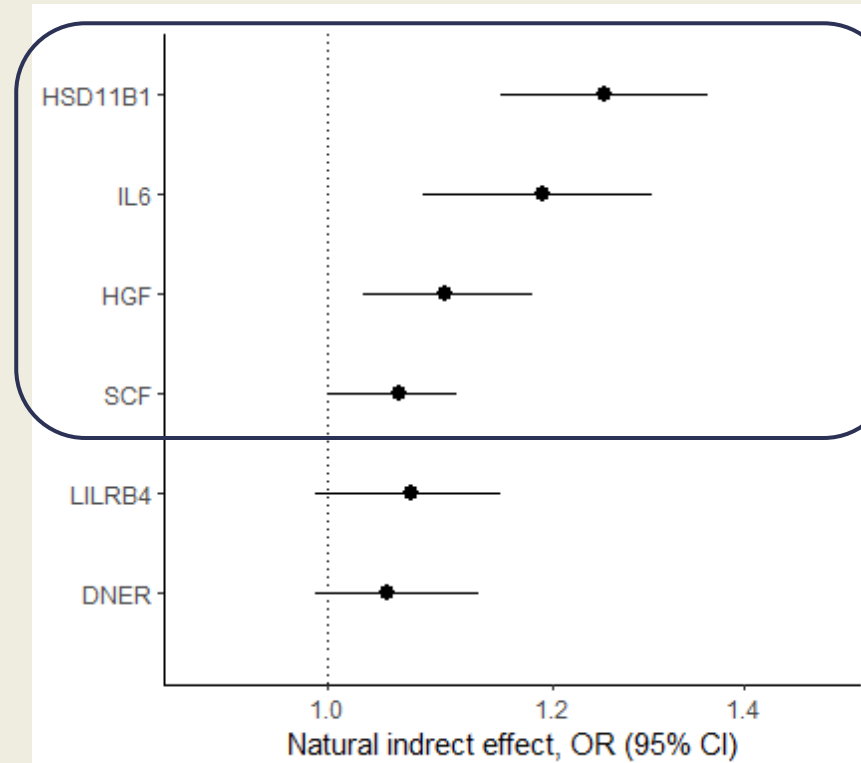
	% mediated
HSD11B1	**19%**
IL6	**15%**
HGF	**8%**
SCF	**5%**
LILRB4	
DNER	

Natural indirect effect, OR (95% CI)

Effect mediated by protein (NIE)

BMI → P → EC

BMI → P ┈┈▶ EC

Results

BMI ⟶ ⊖ HSD11B1 ⟶ EC

BMI ⟶ ⊕ IL6 ⟶ EC

BMI ⟶ ⊕ HGF ⟶ EC

BMI ⟶ ⊖ SCF ⟶ EC

Effect mediated by protein (NIE)
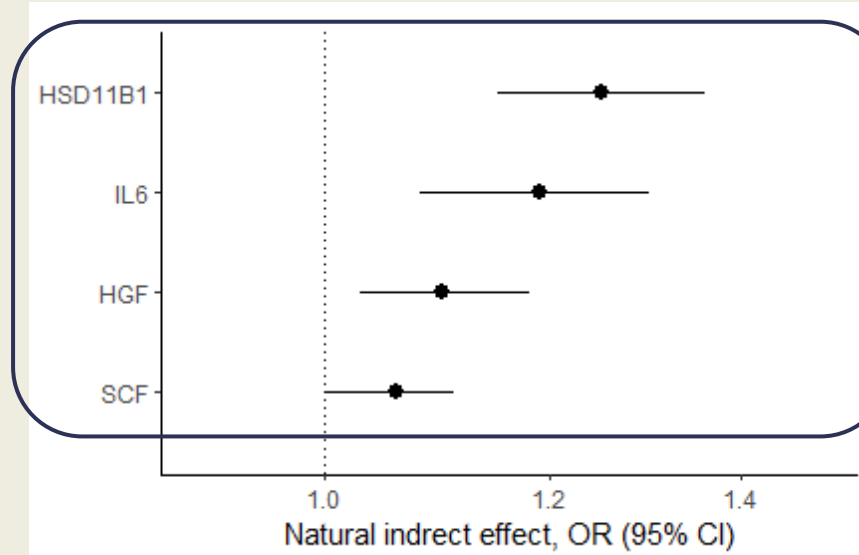
	% mediated	
HSD11B1	19%	Glucocorticoid activating enzyme
IL6	15%	Interleukin-6
HGF	8%	Hepatic growth factor
SCF	5%	Stem cell factor

Discussion and Conclusions
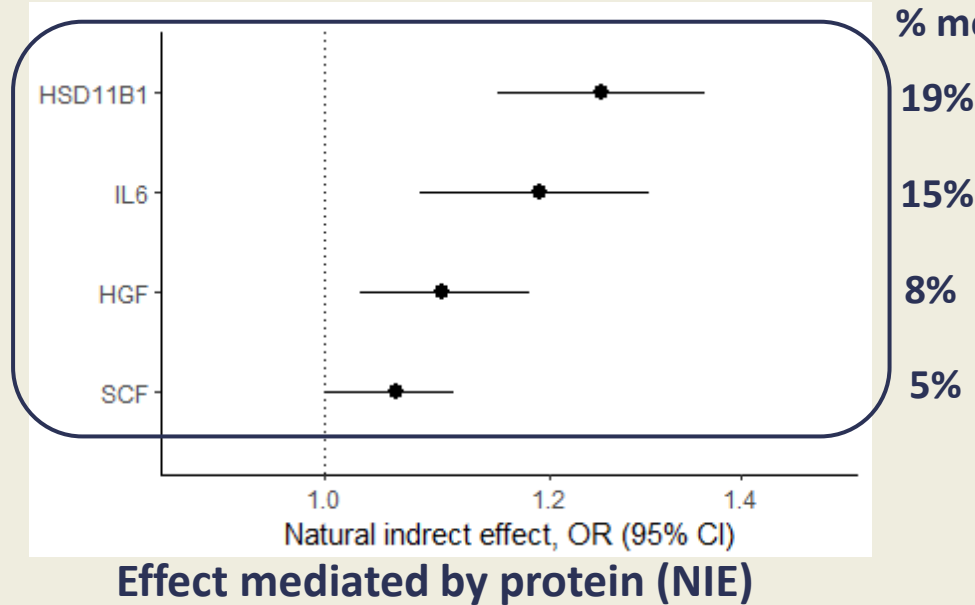
BMI → ⊖ HSD11B1 → EC

BMI → ⊕ IL6 → EC

BMI → ⊕ HGF → EC

BMI → ⊖ SCF → EC

% mediated

19% **Glucocorticoid activating enzyme**

15% **Interleukin-6**

8% **Hepatic growth factor**

5% **Stem cell factor**

Effect mediated by protein (NIE)

Significance
- Understanding underlying pathways linking obesity and endometrial cancer
- Identifying high risk women for prevention
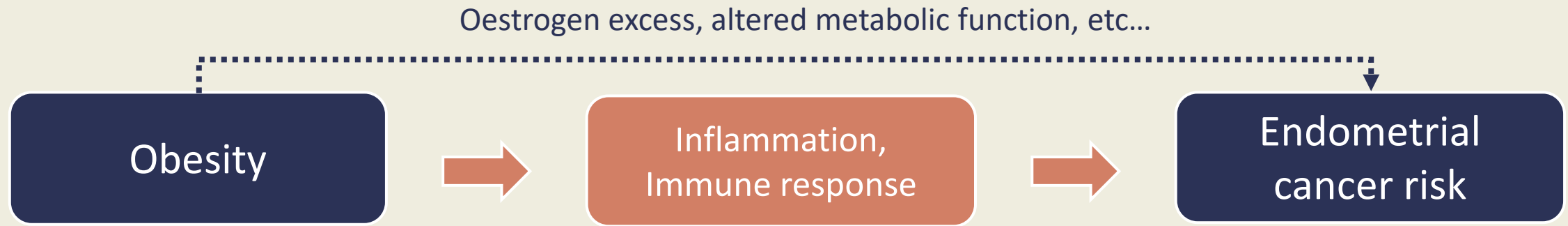- Exploring modifiable risk factors

Limitation
- Examined one biomarker at a time
- Cannot tease out interaction with other biomarkers

Next step...
- Analysis with multiple biomarkers as mediators (plus sex hormones and insulin biomarkers)
- Adiposity-Protein signatures: using UKB data and PLS method

Key take-home messages

Oestrogen excess, altered metabolic function, etc…

| Obesity | → | Inflammation, Immune response | → | Endometrial cancer risk |

Inflammation and altered immune response, as measured by plasma protein biomarkers, might play a role in mediating the effect of obesity on endometrial cancer risk.

- ***In particular:*** *altered glucocorticoid activity (HSD11B1) & interleukin-6 (IL-6) signalling*