

Obesity & Endometrial Cancer

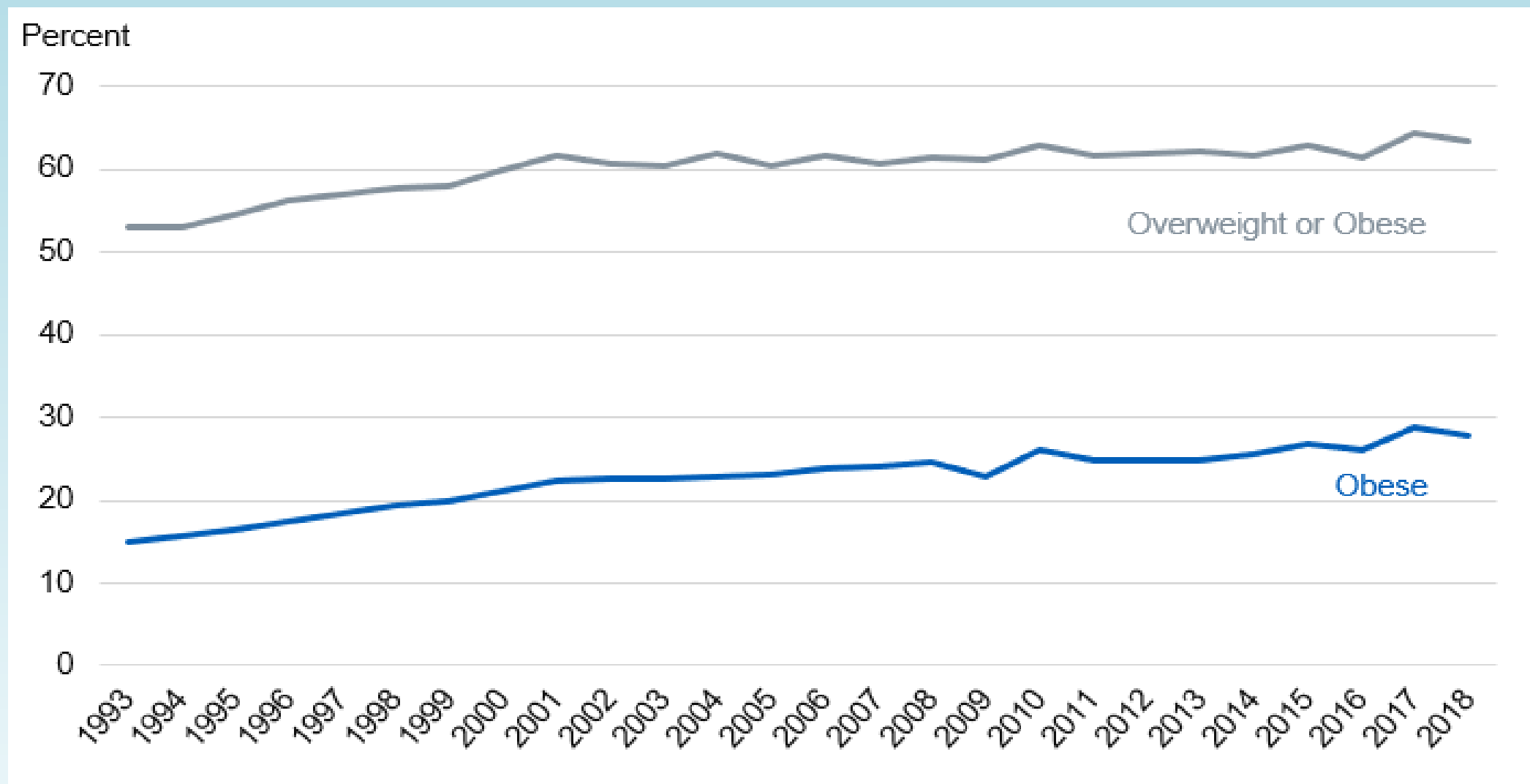
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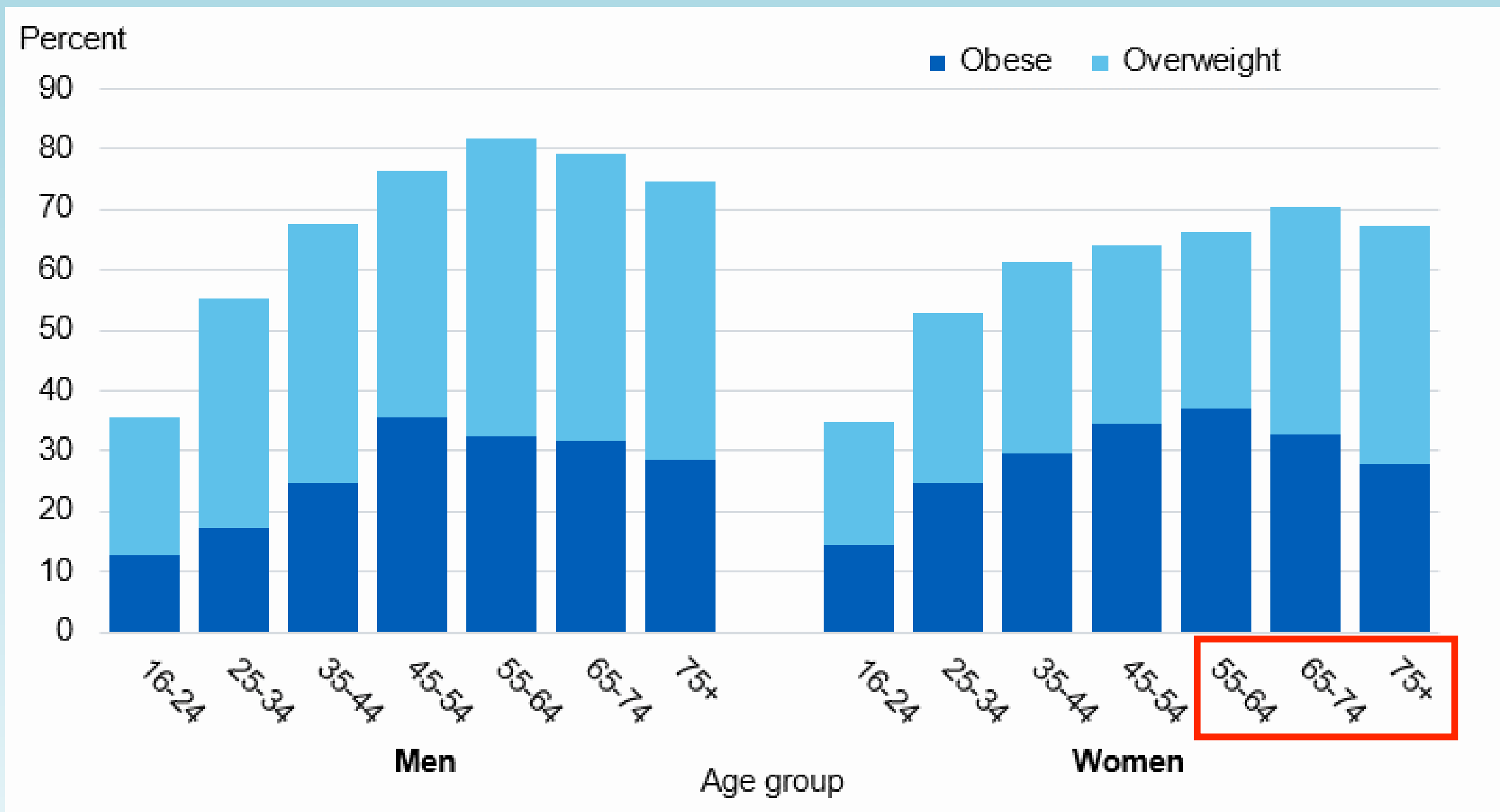
Aims

- Demonstrate link between obesity and development of endometrial cancer
- Obesity-related carcinogenesis

Obesity epidemic

- Rising overweight/obese population in UK

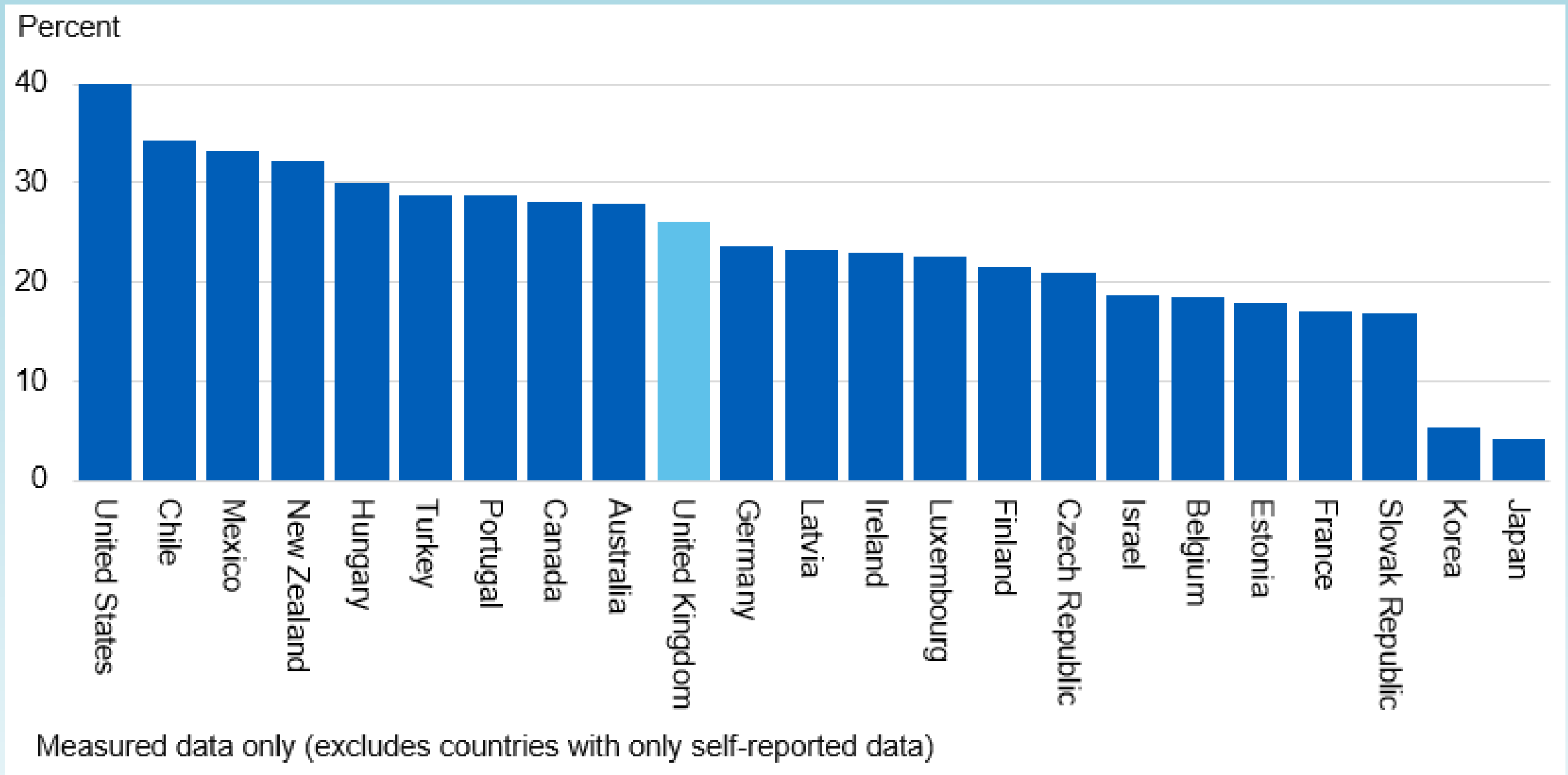




NHS Digital



Obesity: UK vs OECD



NHS Digital



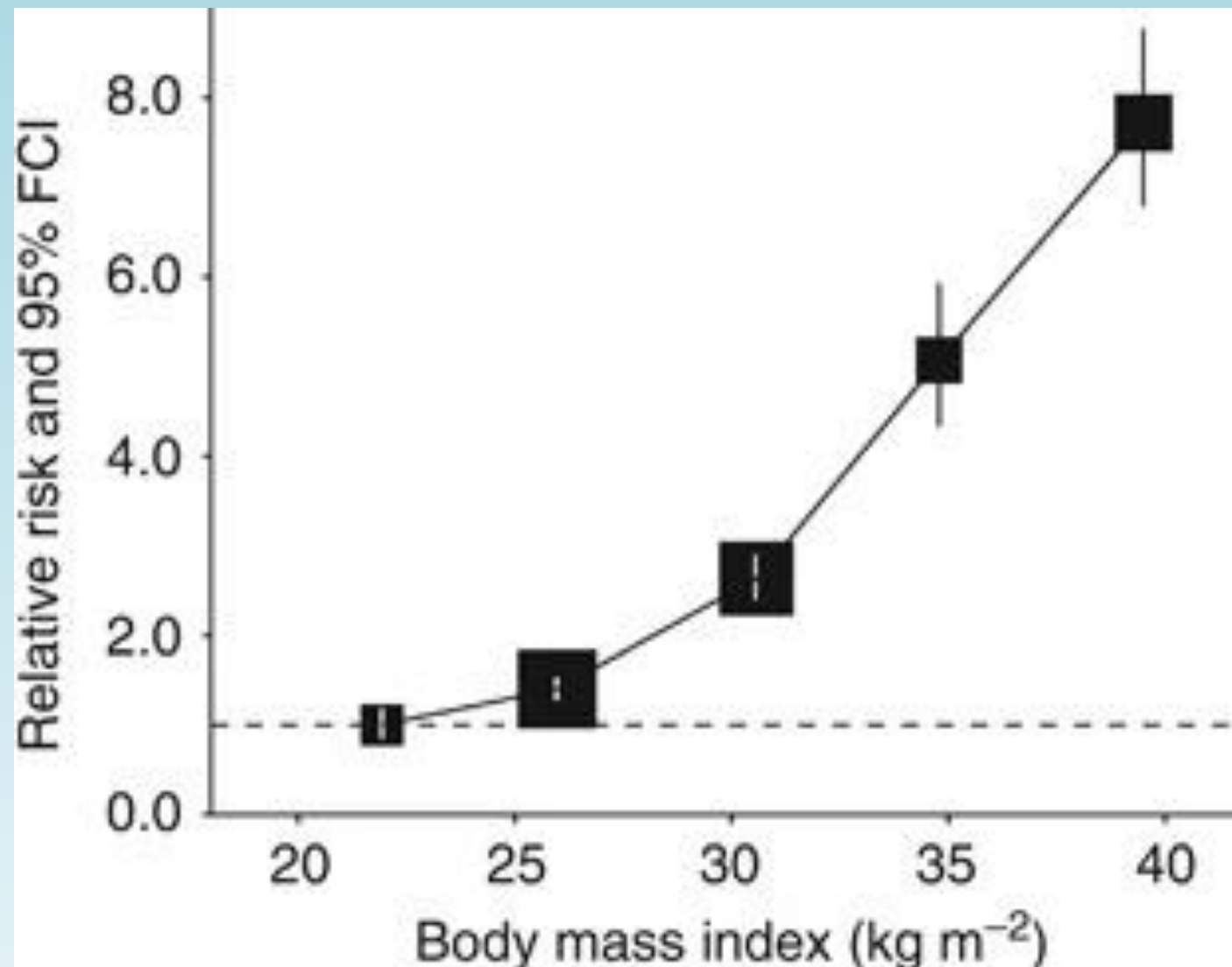
Background

- Endometrial Ca (EC) is the most common gynaecological cancer in developed world
- Incidence rates are rising

EC Risk factors

- **Obesity**
- Age
- Hormones (HRT, Tamoxifen, PCOS)
- Parity
- Diabetes
- Previous breast or ovarian cancer
- Family history

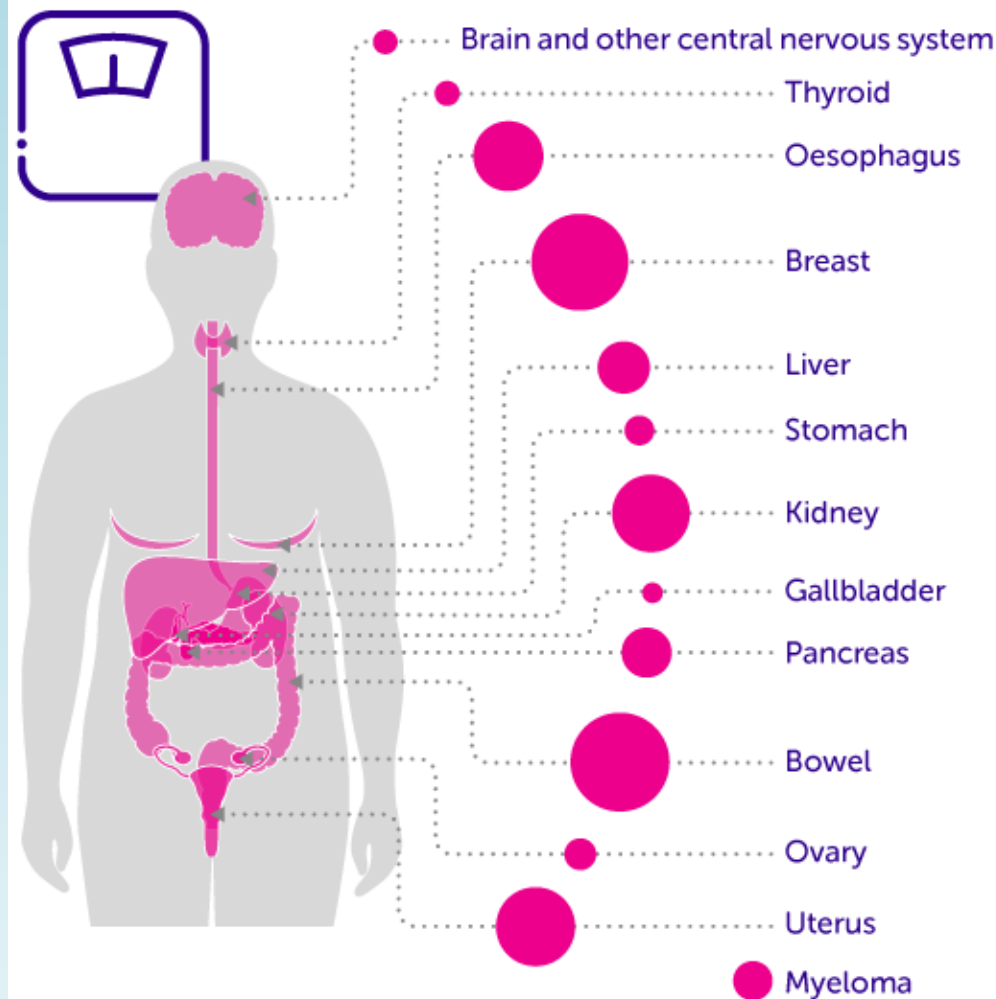
Obesity and EC



Yang *et al* BJC 2012 – from Million Women study

Obesity as a carcinogen?

Overweight and obesity is the UK's biggest cause of cancer after smoking



●●● Larger circles indicate more UK cancer cases

Circle size here is not relative to other infographics based on Brown et al 2018.
Source: Brown et al, British Journal of Cancer, 2018

cruk.org/prevention
Together we will beat cancer



Adipose

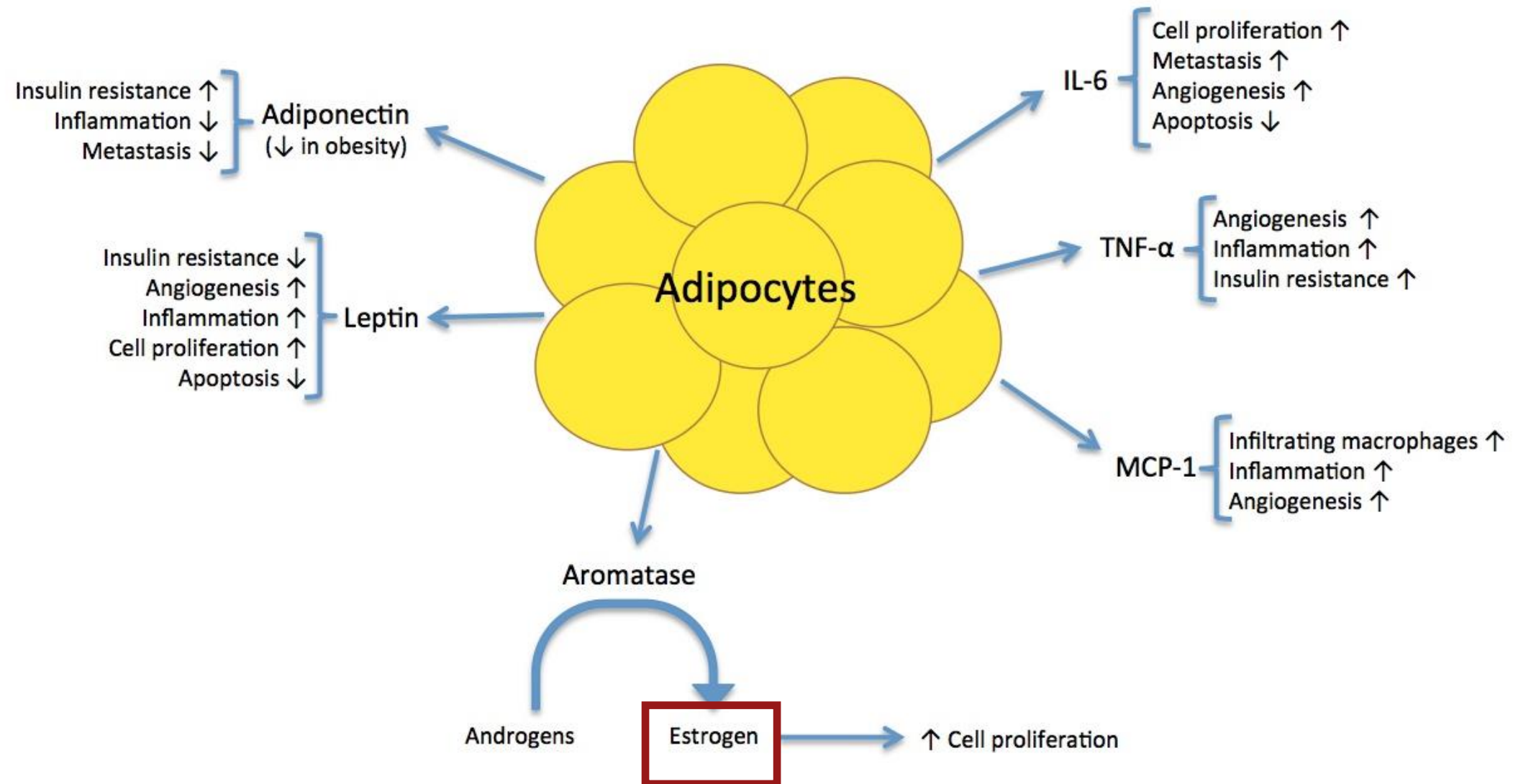
Highly vascularised endocrine organ

Brown (generates heat) vs White (generates energy)

Functions vary according to location:

- Subcutaneous
- Visceral

Adipose's Secretory Activity



Mechanisms of action

3 main accepted pathways:

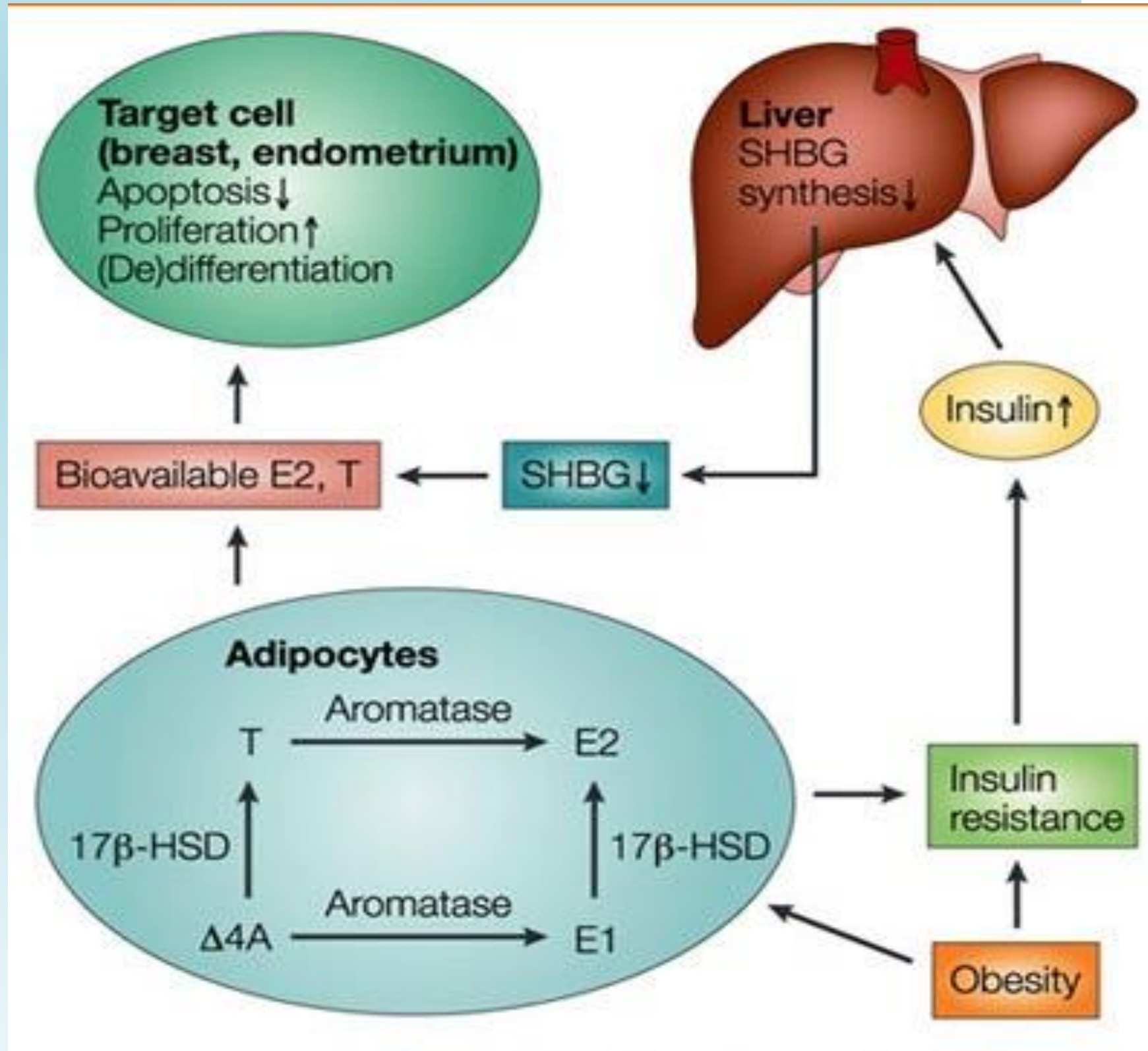
- Excess estrogen production
- Hyperinsulinaemia
- Chronic inflammation

Estrogen excess

- Adipose produces aromatase and 17 β -HSD which converts androgens to estrogens
- Contribution of steroid hormones from adipose can be significant - upto 100% of circulating estrogen in postmenopausal women

Hyperinsulinaemia

- Increased insulin resistance from excess adipose tissue leads to chronic hyperinsulinaemia
- This causes decrease circulating SHBG levels, which in turn increases the bioavailability of estrogen
- Insulin also increases bioactive IGF-1
 - plays a key role in cell proliferation

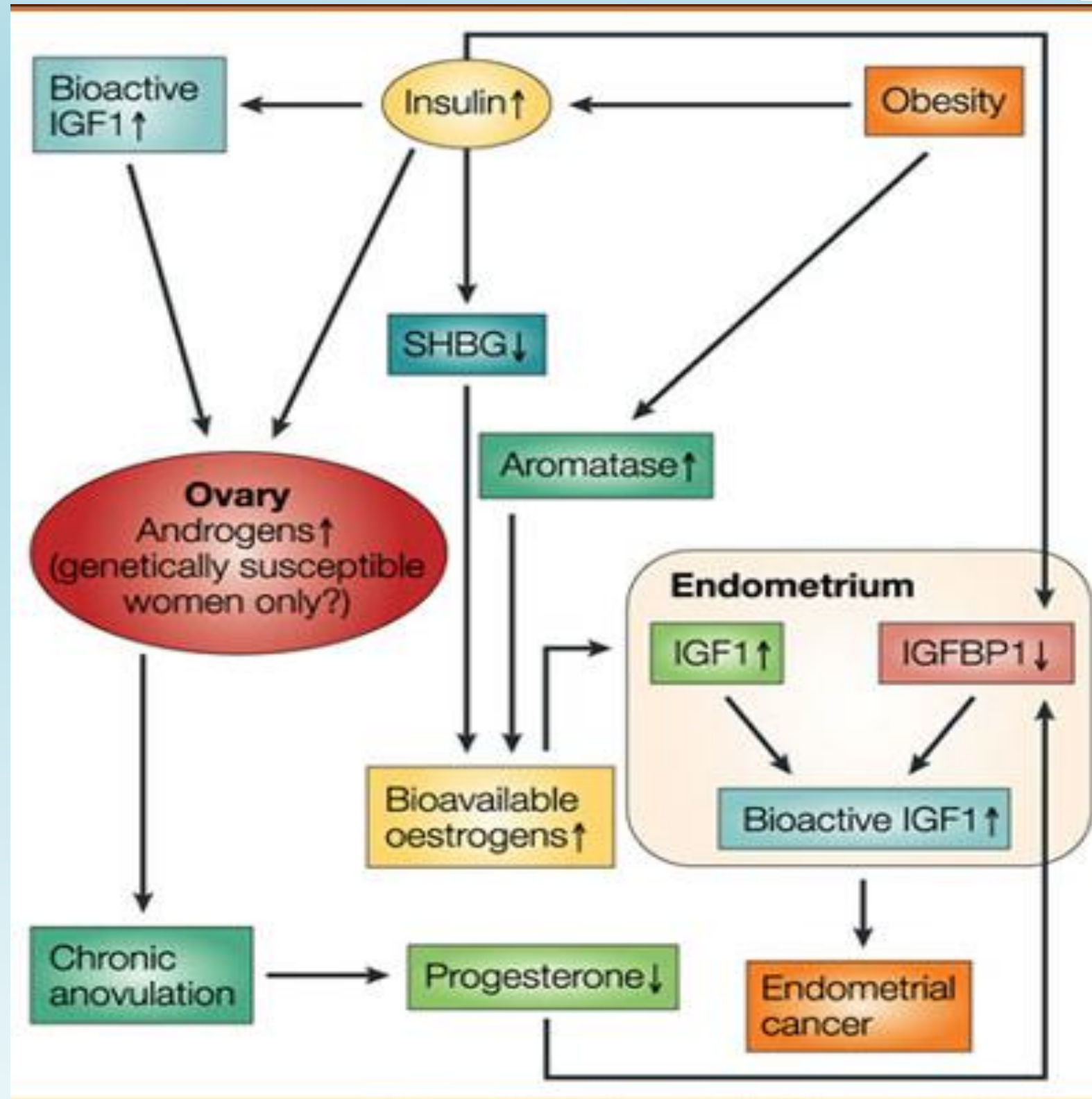


Net effect of estrogen excess

- Both pathways leads to estrogen excess without progesterone counterbalance
- This drives endometrial proliferation whilst inhibiting apoptosis

At the endometrium level

- Estrogens increase local IGF-1 synthesis, which is further exacerbated with hyperinsulinaemia
- New evidence suggests that local endometrial insulin receptor is activated insulin and IGF-1 via MAPK pathways
- Increases risk of accumulation of mutation in key proto-oncogenes and TSG
- This in turn encourages modulation of cellular apoptosis, differentiation and angiogenesis



Chronic inflammation

- Accumulation of adipose releases FFA, which activates macrophages
- Thereby releasing pro-inflammatory cytokines (IL-6, TNF- α)
- Leading to activation of NF κ B – which in turn activates aromatase and estrogen synthesis

New concepts

- Adiponectin an adipose-derived factor
- Levels reduced with obesity
- Thought to promote insulin sensitivity, thereby decreasing IGF-1's role in hyperplasia
- New studies also suggest anti-angiogenic properties by inhibiting VEGF

Obesity reduces adiponectin – a protective factor against cancer

Conclusion

- Understanding of how obesity can lead to neoplastic changes in the endometrium
- Rethink of obesity as carcinogen