Using Mendelian randomization estimates to calculate the global burden of endometrial cancer attributable to overweight and obesity in 2020

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I have no disclosures

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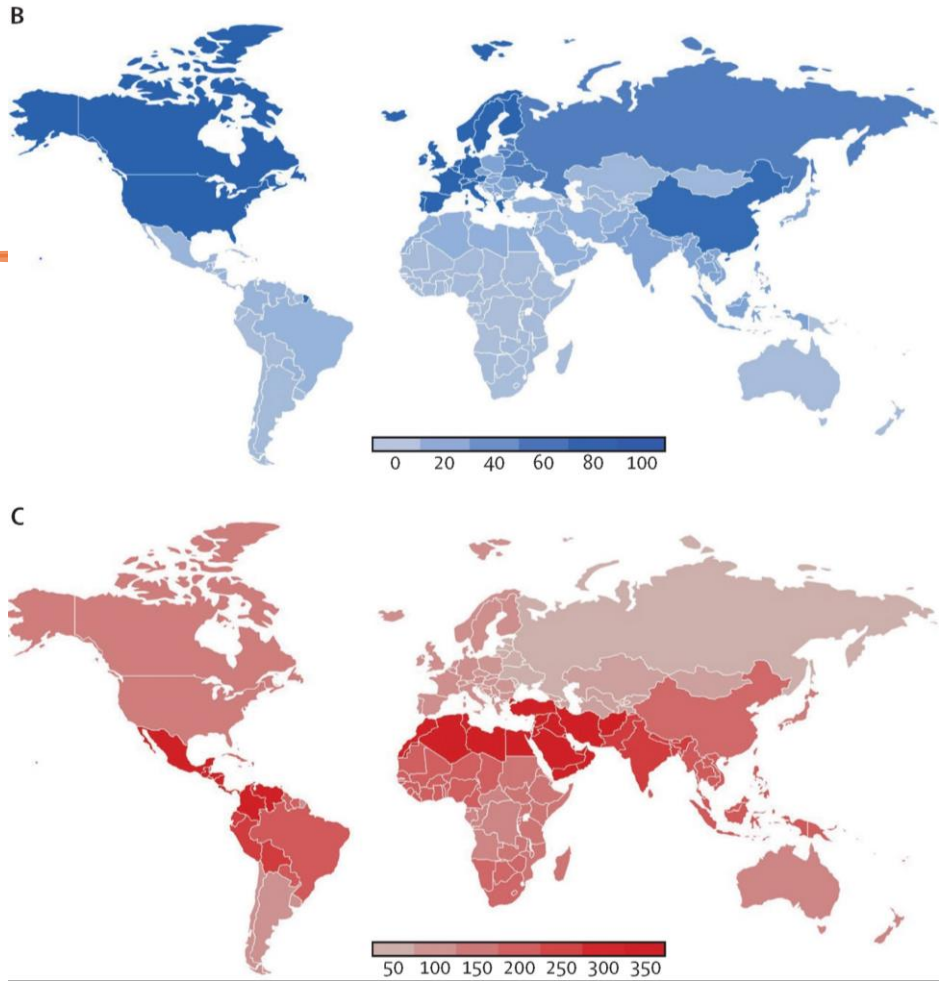
Study aim and overview

To calculate the global burden of endometrial cancer attributable to overweight and obesity in 2020

1. Assess the magnitude of the effect of elevated BMI on endometrial cancer risk using Mendelian randomization
2. Apply these results to calculate the population attributable fraction (PAF) and quantify the proportionate contribution of overweight and obesity to new cases of endometrial cancer worldwide in 2020

Incidence of endometrial cancer is rising

- The global incidence of endometrial cancer rose by 31% between 2012 and 2020 (1,2)
- Endometrial cancer is the 6th most common cancer in women (3)
- Although an ageing population and fewer benign hysterectomies have contributed to this trend, the growing prevalence of obesity is the major underlying cause (4)



Endometrial cancer (EC) risk and elevated BMI

- Elevated BMI is an established risk factor for endometrial cancer (4)
- It has the greatest magnitude of effect on disease risk compared to any other cancer type (5)
- Mendelian randomization (MR) studies have not only confirmed the causal role of elevated BMI but have found a greater magnitude of effect size (6)

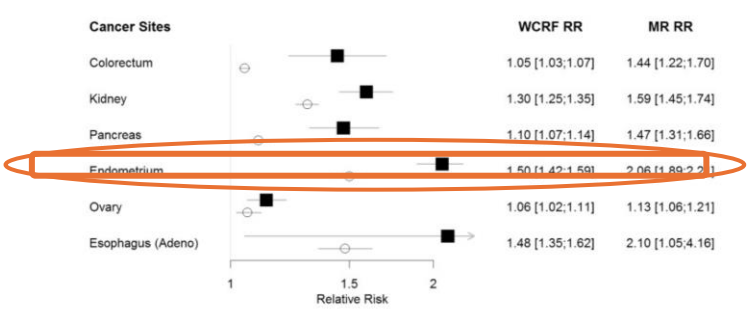


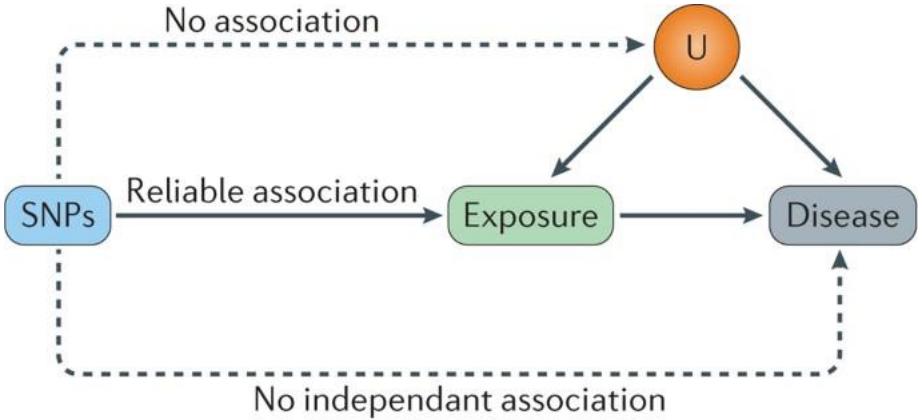
Figure 2. WCRF (circles) and MR (squares) relative risks for the association between a 5-unit BMI increase and cancer risk by cancer site.

Table 2. Strength of the Evidence for a Cancer-Preventive Effect of the Absence of Excess Body Fatness, According to Cancer Site or Type.*

Cancer Site or Type	Strength of the Evidence in Humans†	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: squamous-cell carcinoma	Inadequate	NA
Gastric noncardia	Inadequate	NA
Extrahepatic biliary tract	Inadequate	NA
Lung	Inadequate	NA
Skin: cutaneous melanoma	Inadequate	NA
Testis	Inadequate	NA
Urinary bladder	Inadequate	NA
Brain or spinal cord: glioma	Inadequate	NA

Methods 1. Mendelian randomization

- We used two-sample MR to quantify the effect of elevated BMI on endometrial cancer risk (8,9)



Holmes MV, Ala-Korpela M, Smith GD. *Mendelian randomization in cardiometabolic disease: challenges in evaluating causality*. Nat Rev Cardiol. 2017 Oct;14(10):577–90.

Methods 2. Calculating the population attributable fraction (PAF)

- We adapted the formula described by Parkin to calculate PAFs (10)
  - In our analysis, exposure level 1 denoted overweight, and exposure level 2 denoted obesity
- BMI data included the prevalence of overweight and obesity in adult women aged 18 years or older in 2010, by country
- The incidence of EC in 2020 by country were obtained from GLOBOCAN 2020 (11)

$$\frac{(p_1 \times \mathrm{ERR}_1) + (p_2 \times \mathrm{ERR}_2) + (p_3 \times \mathrm{ERR}_3) \ldots + (p_n \times \mathrm{ERR}_n)}{1 + [(p_1 \times \mathrm{ERR}_1) + (p_2 \times \mathrm{ERR}_2) + (p_3 \times \mathrm{ERR}_3) \ldots + (p_n \times \mathrm{ERR}_n)]}$$

Parkin DM. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer*. 2011 Dec 6;105(Suppl 2):S2–5.

Results 1.

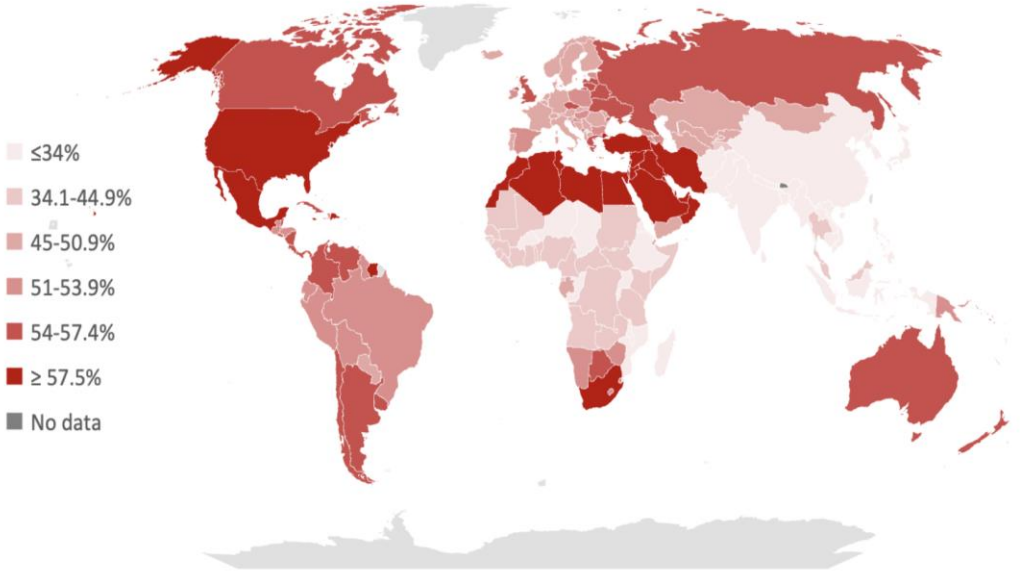
- Our MR analyses confirmed a strong association between elevated BMI and EC risk
- To aid our calculations, these results were scaled to a 5kg/m^2 increase in BMI:
  - **OR: 1.95 (95% CI 1.76-2.16)**
- This result was consistent across sensitivity analyses for evidence of pleiotropy, including weighted median, weighted mode and MR-Egger

Method	**OR (95% CI)**	***P* value**
Inverse variance weighted	**1.83 (1.65 - 2.04)**	3.79 x 10^{-30}
Weighted median	1.89 (1.59 - 2.24)	2.72 x 10^{-13}
Weighted mode	1.88 (1.39 - 2.53)	3.97 x 10^{-5}
MR Egger	2.09 (1.58 - 2.09)	2.48 x 10^{-7}

ORs are shown per standard deviation 4.7kg/m^2 increase in BMI

Results 2.

- We found that an estimated **184,241/ 413,179 (45%)** of all new cases of EC in female adults in 2020 worldwide were attributable to elevated BMI
- Country-specific PAF ranged from 17% to 69%, with a median value of 51%
- North America had the highest regional PAF at 60%, narrowly followed by the Middle East and north Africa at 59%



PAF of new endometrial cancer cases in 2020 caused by elevated BMI in adult women (aged 30 years +), by country

Discussion

- Our results confirm that elevated BMI is strongly associated with risk of endometrial cancer
- Our MR findings conferred a greater magnitude of effect than those of conventional observational studies, and were similar to a previous analysis by Hazelwood et al (12), and in keeping with a further MR study which used a different genetic instrument for BMI (13)
- Arnold et al (14) estimated the global PAF of new EC cases in 2012 attributable to elevated BMI to be 34% based on a relative risk obtained from observational studies
- Our study found that elevated BMI accounted for nearly half (45%) of new EC cases worldwide

Conclusions

- Our study adds to the significant body of evidence concerning elevated BMI and endometrial cancer risk
- We used novel MR methods to clarify the intensity of this association and found that 45% of global endometrial cancer cases in 2020 were caused by elevated BMI
- In the face of rising levels of overweight and obesity globally, our results highlight an important target for cancer prevention and should inform health policy

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