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# Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe

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## ABSTRACT

Standard approaches to estimating population-attributable risk (PAR) include modelling estimates of exposure prevalence and relative risk. Here, we examine the associations between body mass index (BMI) and cancer risk and how effect modifications of these associations impact on PAR estimates. In 2008, sex- and population-specific risk estimates were determined for associations with BMI in a standardised meta-analysis for 20 cancer types. Since then, refinements of these estimates have emerged: (i) absence of menopausal hormonal therapy (MHT) is associated with elevated BMI associations in post-menopausal breast, endometrial and ovarian cancers; (ii) current smoking attenuates the BMI associations in oesophageal squamous cell carcinoma, lung and pancreatic cancers; (iii) prostate screening attenuates BMI associations when all prostate cancers are considered together; and (iv) BMI is differentially associated with different histological subtypes within the same cancer group. Using secondary analyses of the aforementioned meta-analysis, we show 2–3-fold shifts in PAR estimations for breast and endometrial cancers depending on the MHT usage in European countries. We also critically examine how to best handle exposures (in this example, BMI distributions) and relative risk estimates in PAR models, and argue in favour of a counterfactual approach based around BMI means. From these observations, we develop a research framework in which to optimally evaluate future trends in numbers of new cancers attributable to excess BMI. Overall, this framework gives conservative estimates for PAR – nonetheless, the numbers of avoidable cancers across Europe through avoidance of excess weight are substantial.

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## 1. Introduction

Standard approaches to estimating population-attributable risk (PAR) include modelling estimates of prevalence of the exposure and relative risk. The simplest formula for such a model was described half a century ago by Levin,<sup>1</sup> as follows:

$$PAR = \frac{P_e(RR - 1)}{P_e(RR - 1) + 1}$$

where  $P_e$  is the prevalence of exposure and RR is the relative risk. The derived PAR is defined as the proportion of all cases that would not have occurred if the exposure had been absent,<sup>2</sup> and is thus relevant in cancer prevention research.

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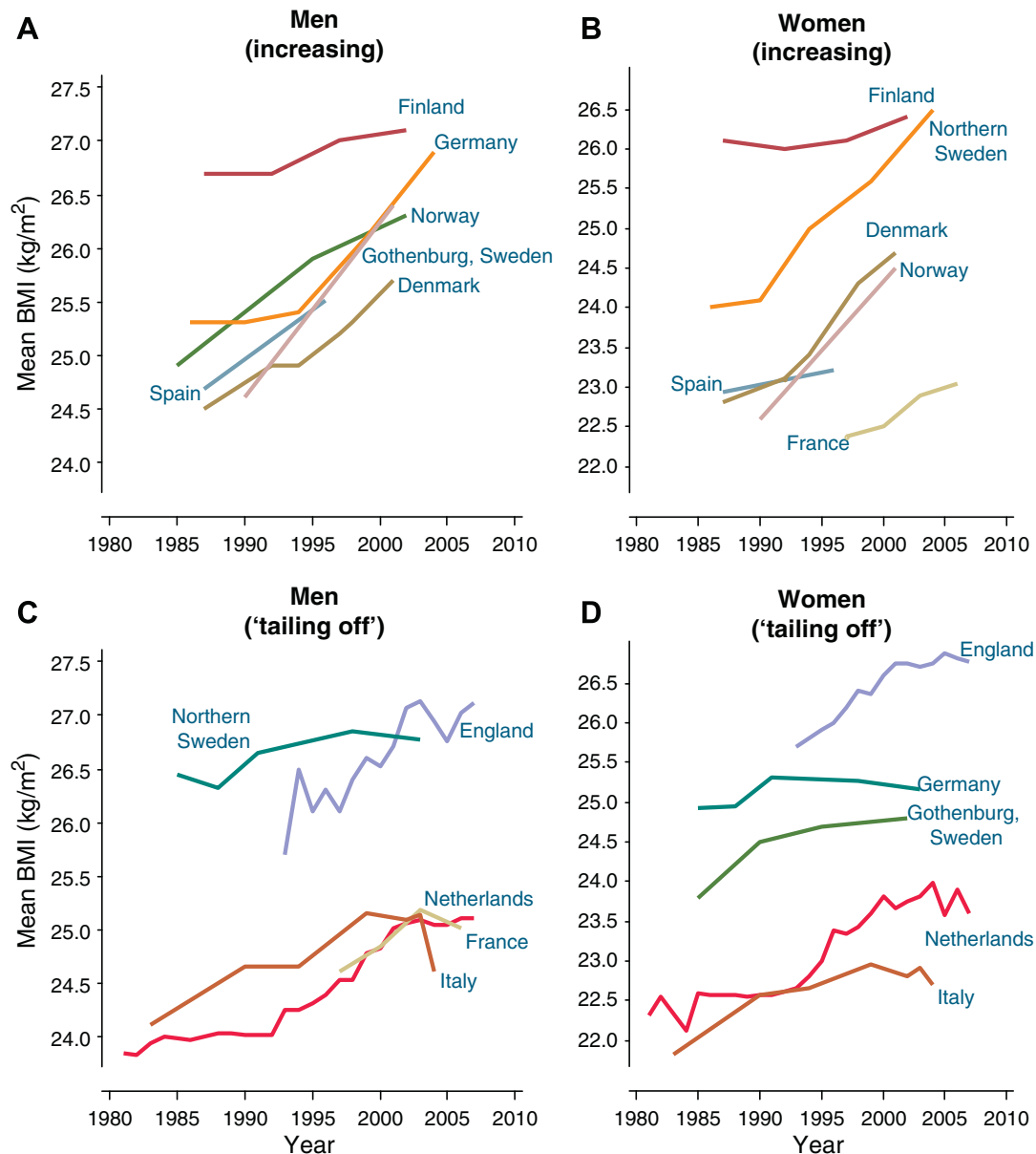
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The prevalence exposure of interest in the present example is body adiposity, which may be approximated by a number of anthropometric measures, including body mass index (BMI: expressed in  $\text{kg}/\text{m}^2$ ), waist circumference (WC: expressed in cm) and waist-hip ratio (WHR). By far the most commonly reported index is the BMI, and this will be the main focus of the current review. Using this metric, there is a well-established World Health Organisation (WHO) classification of four broad categories: underweight ( $\text{BMI} < 18.5 \text{ kg}/\text{m}^2$ ); normal weight ( $18.5\text{--}24.9 \text{ kg}/\text{m}^2$ ); overweight ( $25.0\text{--}29.9 \text{ kg}/\text{m}^2$ ) and obese ( $\geq 30 \text{ kg}/\text{m}^2$ ).<sup>3</sup> Combined overweight and obesity may be expressed as excess body weight (EBW). Limitations of using BMI to express disease risk are recognised in the context of cardiovascular disease<sup>4</sup> – for example central obesity determined by WC or WHR may be a more

sensitive disease predictor than BMI – and this may also be true for certain cancer types where distinguishing between fat mass and fat-free mass is critical, although the volume of available evidence is small.<sup>5–9</sup>

This review updates the epidemiology linking obesity and cancer risk (which establishes the relative risk component of the Levin formula) focusing mainly on the large volume of association data linking BMI with several cancer types. The smaller volume of data linking WC or WHR and cancer risk will also be discussed. Additionally, it is becoming clear that associations between EBW and cancer risk, at specific sites, may be considerably modified by other site-specific risk factors – and examples will be listed and discussed. As a prerequisite to these discussions, some key aspects of the epidemiology of EBW in Europe are summarised.



**Fig. 1 – Epidemiology of body mass index in Europe.** Trends in means of body mass index (BMI) distributions for 12 datasets across ten European countries shown for men and women. Trends are all increasing and generally linear (A and B), with some countries demonstrating plateau effects or 'tailing off' (C and D). References for studies are cited in the supplemental material of Renehan et al.<sup>52</sup> or are available from the author. Note: different y-axis ranges for men and women.

## 2. Prevalence of excess body weight

Globally for 2005, 23.2% (937 million) of the world's adult population was overweight (24.0% in men; 22.4% in women) and 9.8% (396 million) was obese (7.7% in men; 11.9% in women).<sup>10</sup> In many industrialised countries, over a fifth of adult populations are obese – for example 24.2% in men and 23.5% in women in the United States (2005)<sup>11</sup>; and 21.9% in men and 24.4% in women in the United Kingdom (2007)<sup>12</sup> – but obesity is also prevalent in developing world countries. There are complex inter-relationships between socio-educational stratifications and EBW prevalence, but in general, outside the context of very low income populations, obesity is more prevalent among lower socio-educational classes.<sup>13</sup>

Across Europe, trends in mean BMI have been increasing since the 1980s, though from different starting points and at different rates, as shown in Fig. 1. However, two country patterns have emerged – those with increasing mean BMI over the past two to three decades and evidence now of ‘tailing off’ (England; Netherlands; Italy; Northern Sweden and France in men; Germany and Gothenburg, Sweden in women); and those with continuing upward increases in BMI trends (Norway; Spain; Denmark; Finland; Germany and Gothenburg, Sweden in men; Northern Sweden in women).

## 3. Associations between adiposity and cancer risk

### 3.1. Body mass index (BMI)

In 2002, the International Agency for Research into Cancer (IARC)<sup>14</sup> concluded, from a semi-quantitative review of the lit-

erature, that EBW is associated with increased risk of developing cancers of the postmenopausal breast, colorectum, endometrium, kidney and oesophageal adenocarcinoma. In 2007, the World Cancer Research Fund (WCRF)<sup>15</sup> used a more standardised approach to review the literature and reported that the evidence that body fatness is associated with increased risk of oesophageal adenocarcinoma and with cancers of the pancreas, colorectum, postmenopausal breast, endometrium and kidney is ‘convincing’, and that a ‘probable’ association exists between body fatness and risk of gallbladder cancer.

At the same time, one of the present authors, with collaborators from the University of Bern (Switzerland), reported in the *Lancet*<sup>16</sup> a systematic review and meta-analysis of prospective observational studies (221 datasets including 281,137 incident cases) quantifying associations with a 5 kg/m<sup>2</sup> BMI increase and risk of incident cancer for 20 cancer types. The summary of the risk estimates by gender is shown in Table 1. By using a standardised approach across a large number of cancer types and an updated literature search (to December 2007, capturing several studies from Asia-Pacific populations not included in previous meta-analyses), the study<sup>10</sup> demonstrated that associations:

- are sex specific – for example associations are consistently stronger for men than women for colon cancer risk,
- are site specific – for example associations are consistently stronger for colon versus rectal cancer,
- exist for a wider range of malignancies than previously thought – ‘new’ obesity-related cancers added to the list were thyroid cancer, malignant melanoma in men, multiple myeloma, leukaemia and non-Hodgkin's lymphoma,

**Table 1 – Sex-specific estimated risk ratios by cancer types.**

	Men			Women		
	n <sup>a</sup>	Risk ratio (95% CIs)	I <sup>2</sup> (%) <sup>b</sup>	n <sup>a</sup>	Risk ratio (95% CIs)	I <sup>2</sup> (%) <sup>b</sup>
<i>Colorectal cancer</i>						
Colon	22	1.24 (1.20, 1.28)	21	19	1.09 (1.05, 1.13)	39
Rectum	18	1.09 (1.06, 1.12)	3	14	1.02 (1.00, 1.05)	0
Gallbladder cancer		No association		2	1.59 (1.02, 2.47)	67
Leukaemia	7	1.08 (1.02, 1.14)	0	7	1.17 (1.04, 1.32)	80
Malignant melanoma	6	1.17 (1.05, 1.30)	44		No association	
Multiple myeloma	7	1.11 (1.05, 1.18)	7	6	1.11 (1.07, 1.15)	0
Non-Hodgkin's lymphoma	6	1.06 (1.03, 1.09)	0	7	1.07 (1.00, 1.14)	47
Oesophageal adenocarcinoma	5	1.52 (1.33, 1.74)	24	3	1.51 (1.31, 1.74)	0
Pancreatic cancer		No association		11	1.12 (1.02, 1.22)	43
Renal cancer	11	1.24 (1.15, 1.34)	37	12	1.34 (1.25, 1.43)	45
Thyroid cancer	4	1.33 (1.04, 1.70)	77	3	1.14 (1.06, 1.23)	5
Prostate cancer	27	1.03 (1.00, 1.07)	73		NA	
Post-menopausal breast cancer		NA		31	1.12 (1.08, 1.16)	64
Endometrial cancer		NA		19	1.59 (1.50, 1.68)	77

Risk estimates are per increase in 5 kg/m<sup>2</sup> BMI (body mass index).

All risk estimates are taken from the *Lancet* meta-analysis<sup>16</sup>.

Only risk estimates for cancer types with a significant positive association with BMI are shown.

NA: not applicable.

<sup>a</sup> Number of studies.

<sup>b</sup> I<sup>2</sup> is a statistic, expressed as a percentage, that is widely used in meta-analysis to describe statistical differences between study heterogeneity – conventionally values of 25%, 50% and 75% correspond to cut-off points for low, moderate and high degrees of heterogeneity.

- are broadly consistent across geographic populations, namely, North American, European and Australian, and Asian-Pacific,
- may be ranked per given change in BMI across the cancer types by gender.

### 3.2. Other adiposity-related anthropometric measures

Body adiposity is often sub-classified as subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT); WHR and WC measurements are thought to better reflect central adiposity or VAT, whereas BMI reflects total body fatness (combined SAT and VAT). WHR or WC might therefore be superior measures of adiposity than BMI in terms of cancer risk, as is the case for cardiovascular risk,<sup>17</sup> but the number of cohort studies relating these parameters to subsequent cancer development is relatively small.

Two previous meta-analyses,<sup>5,7</sup> both including case-control and cohort studies, examined the cumulative evidence linking WHR and breast cancer risk. For pre-menopausal breast cancer risk, both analyses arrived at the same conclusion: namely, that adiposity determined by WHR reverses the inverse association noted with BMI to either a null or a positive association. For post-menopausal breast cancer risk, the findings were less straightforward: the analysis by Connolly and colleagues<sup>5</sup> suggested that WHR may have a stronger positive association with breast cancer than BMI, whereas the analysis by Harvie and colleagues,<sup>7</sup> having adjusted for BMI, found a null association for WHR.

For colorectal cancer, two meta-analyses<sup>6,8</sup> addressed risk associations with WHR and/or WC, both limiting their inclusions to cohort studies. Dai and colleagues<sup>6</sup> concluded that indices of abdominal obesity are more sensitive than BMI for predicting cancer risk, but this conclusion was based on analyses of uppermost categories versus lowermost categories of distributions for BMI, WHR and WC – however, these may not be directly comparable categories. The analysis reported by Moghaddam and colleagues<sup>8</sup> used a dose-response approach and arrived at a more cautious conclusion – namely, that for a 2-kg/m<sup>2</sup> increase in BMI, the risk of colorectal cancer increased by 7% and for a 2-cm increase in WC, the risk increased by 4%. Here again, however, it is unclear whether a 2-kg/m<sup>2</sup> increase in BMI and a 2-cm increase in WC equate to equivalent quantities of ‘fatness’.

The European Prospective Investigation into Cancer and Nutrition (EPIC) recently examined the role of indices of central adiposity and associations for oesophageal cancer, recognising that two main histological types exist – adenocarcinoma (EAC) and squamous cell carcinoma (ESCC) – and that associations with BMI are positive for EAC, yet inverse for ESCC.<sup>9</sup> The EPIC analysis found that where WHR was the anthropometric measure of adiposity, the inverse association with ESCC disappeared.

In summary, in at least two examples – pre-menopausal breast cancer and ESCC – indices of central adiposity may provide more appropriate approximations of body fatness and cancer risk, i.e. the true association with adiposity is probably null. However, whether indices of central adiposity represent

a more valid measure of adiposity (for example in colon cancer) is not clear.

### 3.3. Developments since the Lancet meta-analysis

In the commentary that accompanied the *Lancet* meta-analysis in 2008, Larsson and Wolk<sup>18</sup> stated that there were several questions remaining. These included: (i) is the obesity-cancer association modified by other risk factors? (ii) does the effect of excess body weight on cancer risk vary by specific cancer subtypes? and (iii) does weight loss in overweight or obese people reduce the risk of cancer? These questions have been diligently pursued by researchers with some emerging answers.

#### 3.3.1. Effect modification of menopausal hormone therapy (MHT)

As hyper-oestrogenaemia secondary to increased aromatase activity in peripheral adipose tissue is relevant to the development of obesity-related post-menopausal breast cancer,<sup>19</sup> it is reasonable to hypothesise that MHT use may influence this association. This hypothesis has been tested in at least six cohort studies,<sup>20–25</sup> where risk estimates were reported stratified by MHT status. Table 2 summarises these studies and demonstrates that MHT is an effect modifier for the associations between BMI and post-menopausal breast cancer; namely, risk estimates per 5 kg/m<sup>2</sup> increase are higher among never users compared with ever users (where associations are generally null).

Similar to breast cancer risk, MHT use may influence the association between BMI and endometrial cancer risk. Three cohort studies<sup>26–28</sup> have reported risk estimates stratified by MHT status, and similar findings to those for breast cancer emerge (Table 2); namely, the risk estimates per 5 kg/m<sup>2</sup> increase in BMI are higher among never users compared with ever users (but there is some residual risk in ever users). When these data are taken together with the findings from the Million Women Study<sup>29</sup> (which reported on the interaction among BMI, MHT and endometrial cancer risk among ever users only), it appears that the risk estimates per 5 kg/m<sup>2</sup> for cyclical combined MHT were similar to those for oestrogen only (approximately 1.20), but have a null association for continuous combined MHT.

Associations between BMI and ovarian cancer are unclear – one meta-analysis,<sup>30</sup> including cohort and case-control studies, found an overall positive association; whereas another<sup>16</sup> found a null association when only cohort studies were included. These inconsistencies may be partly explained by prevalence of MHT usage in the cohort studied. Recent data from the NIH-AARP Diet and Health Study showed that among women who never used MHT, the relative risk for obese versus normal weight women was 1.83 (95% CI, 1.18–2.84), whereas there was no relation between BMI and ovarian cancer in ever users (RR=0.96; 95% CI, 0.65–1.43; P interaction=0.02).<sup>31</sup> These observations partly explain apparently higher point estimates per 5 kg/m<sup>2</sup> for risk of post-menopausal breast and ovarian cancers observed among cohorts from Asia-Pacific populations (areas of low MHT use) in our meta-analysis.<sup>16</sup>

**Table 2 – Associations between BMI and risk of post-menopausal breast, endometrial and ovarian cancers stratified by menopausal hormonal therapy (MHT) usage.**

	Total post-menopausal		Never users		MHT type	Ever users	
	n <sup>a</sup>	Risk ratio (95% CIs)	n <sup>a</sup>	Risk ratio (95% CIs)		n <sup>a</sup>	Risk ratio (95% CIs)
<b>Post-menopausal breast cancer</b>							
Morimoto et al. (2002) <sup>20</sup>	1030	1.11 (0.83, 1.50)	319	1.34 (1.18, 1.52)	MHT, NOS	711	1.00 (0.91, 1.10)
Feigelson et al. (2004) <sup>21</sup>	1934	1.08 (0.98, 1.19)	1182	1.22 (1.14, 1.30)	EO and EP combined <sup>b</sup>	752	0.94 (0.85, 1.03)
Lahmann et al. (2004) <sup>22</sup>	1402	1.05 (0.86, 1.28)	911	1.14 (1.04, 1.26)	MHT, NOS	494	0.88 (0.77, 1.01)
Mellemkjaer et al. (2006) <sup>23</sup>	633	1.02 (0.93, 1.12)	217	1.08 (0.93, 1.24)	MHT, NOS	416	0.98 (0.86, 1.11)
Tehard and Clavel-Chapelon. (2006) <sup>24</sup>	860	1.13 (0.97, 1.31)	271	1.03 (0.89, 1.20)	Non-transdermal MHT users	285	1.01 (0.85, 1.20)
Ahn et al. (2007) <sup>25</sup>	2087	1.10 (0.95, 1.28) <sup>c</sup>	925	1.19 (1.13, 1.27)	MHT, NOS	1162	1.02 (0.95, 1.09)
<b>Endometrial cancer</b>							
Chang et al. (2007) <sup>26</sup>	677	1.40 (1.17, 1.67)	358	2.26 (1.87, 2.73)	EO	34	1.19 (0.93, 1.53)
Chang et al. (2007) <sup>26</sup>	NA		NA		EP, NOS	242	1.25 (1.05, 1.47)
Friedenreich et al. (2007) <sup>27</sup>	567	1.34 (1.22, 1.47)	151	1.61 (1.151, 1.85)	MHT, NOS	186	1.10 (0.88, 1.38)
McCullough et al. (2008) <sup>28</sup>	318	1.89 (1.64, 2.17)	207	1.93 (1.64, 2.28)	EP, NOS	186	1.29 (0.82, 2.01)
<b>Ovarian cancer</b>							
Leitzmann et al. (2009) <sup>31</sup>	303	1.10 (0.96, 1.26)	125	1.33 (1.08, 1.26)	EO and EP	178	0.93 (0.78, 1.12)

Risk estimates are per increase in 5 kg/m<sup>2</sup> BMI (body mass index) as per methods used in Renehan et al.<sup>16</sup>  
CI: confidence intervals. MHT, NOS: menopausal hormone therapy, not otherwise specified.  
<sup>a</sup> Number of cases.  
<sup>b</sup> EO (oestrogen only) and EP (oestrogen and progesterone) reported together as 'risk ratio estimates were similar in the two groups'.  
<sup>c</sup> This risk estimate is not reported directly in the paper – instead this has been calculated combining the estimates for never and ever MHT (random effects).

### 3.3.2. BMI, smoking and cancer risk

In the *Lancet* meta-analysis,<sup>16</sup> the associations between BMI and risk were apparently inverse for two smoking-related cancers, namely, ESCC and lung cancer; and for pancreatic cancer risk (another smoking-related malignancy), there were positive BMI associations in women but not men. These observations raised some questions; and recent studies have clarified these interpretations.

When sex-specific risk estimates per 5 kg/m<sup>2</sup> (derived from the analysis in Renehan et al.<sup>16</sup>) are plotted against the prevalence of smoking in the sex-specific populations of each study, greater percentage of ever smoking was related to a more pronounced inverse association.<sup>32</sup> In the absence of smoking, the association between BMI and lung cancer was null. Interestingly, when the EPIC investigators<sup>9</sup> examined the relationship between adiposity and oesophageal cancer risk, recognising two main histological types (EAC and ESCC), they found a strong association between BMI and EAC, which in turn, was unaffected when the data were analysed according to smokers and non-smokers. In sharp contrast, the association between BMI and ESCC, which was significantly inverse among smokers (RR for uppermost versus lowermost quintile = 0.09, 95% CI, 0.03–0.29), was null among non-smokers. Recently, a pooled analysis of seven prospective studies on pancreatic cancer risk presented BMI data stratified by smoking status, finding that a 5 kg/m<sup>2</sup> BMI increment was associated with an increased risk of pancreatic cancer among never and former smokers, but not among current smokers (P interaction = 0.08).<sup>33</sup>

Taken together, the above data on BMI in relation to lung cancer, ESCC and pancreatic cancer are consistent with residual negative confounding of the BMI and cancer association by smoking intensity. There may be at least two explanations: smokers have a lower mean BMI than non-smokers matched for age and gender,<sup>34</sup> such that lower BMI categories have a 'artificially' higher risk of smoking-related cancer compared with higher BMI categories; or alternatively, smoking may be a key competing risk factor for mortality such that age-related malignancies fail to manifest.

### 3.3.3. Screening and cancer risk

For prostate cancer, initial epidemiological data suggested that increasing BMI was positively associated with increased risk. When all invasive cancers were analysed, the summary risk estimate in the *Lancet* meta-analysis (27 cohorts)<sup>16</sup> was modest (1.03, 95% CI, 1.00–1.07). However, there was considerable heterogeneity ( $I^2 = 73\%$ ). A variety of commentaries<sup>35–37</sup> suggest that BMI is associated with high-grade and/or aggressive histological types of prostate cancer (and possibly a reduced risk of low-grade/less aggressive prostate cancer). Supporting this posit, obesity is consistently associated with an increased risk of prostate cancer progression and mortality.<sup>37</sup> However, the proportion of high-grade/aggressive histology prostate cancers in a cohort may reflect the level of prostate-specific antigen (PSA) screening in that population and hence the high level of heterogeneity noted may be partly explained by the level of PSA screening. Secondary analyses of the *Lancet* meta-analysis data suggest this is the case<sup>32</sup>



(Fig. 2). In recent studies with large sample sizes and greater than 50% prevalence of PSA screening in the populations, the associations between overall prostate cancer risk and BMI are essentially null.

For breast cancer, there are emerging data that mammographic screening utility rates are lower among obese women (particularly white women),<sup>38</sup> and this may partly explain higher breast cancer-related mortality in obese women.<sup>39</sup>

### 3.3.4. BMI–cancer associations and histological sub-types

There are now several examples where the BMI–cancer association favours specific histological sub-types within a site-specific cancer. These examples include:

- A dose–response meta-analysis (9 cohorts: 22 case–control studies) showed that the BMI–breast cancer association is stronger for oestrogen receptor-positive/progesterone receptor-positive (ER+PR+) tumours (33% increase per 5 kg/m<sup>2</sup> increment for post-menopausal breast cancer). There were no significant BMI–cancer associations for ER–PR– and ER+PR– tumours.<sup>40</sup>
- Detailed pathological examination of a Swedish population-based prospective cohort (9685 postmenopausal women not using MHT) showed that the highest quartiles of BMI were associated with tumours of ductal type, Grade II, low Ki67 index, HER2 negativity, low cyclin D1 expression, ER $\alpha$  and PR immune-positivities, but not ER $\beta$  tumours.<sup>41</sup>
- For endometrial cancer, obesity is predominantly a risk factor for Type I endometrioid tumours (accounting for 70% of endometrial cancers) rather than Type II.<sup>42</sup>
- BMI associations are stronger for the papillary subtype of thyroid carcinoma.<sup>43</sup>

- Positive associations exist between BMI and cardia gastric adenocarcinomas, but not non-cardia gastric malignancies.<sup>44</sup>

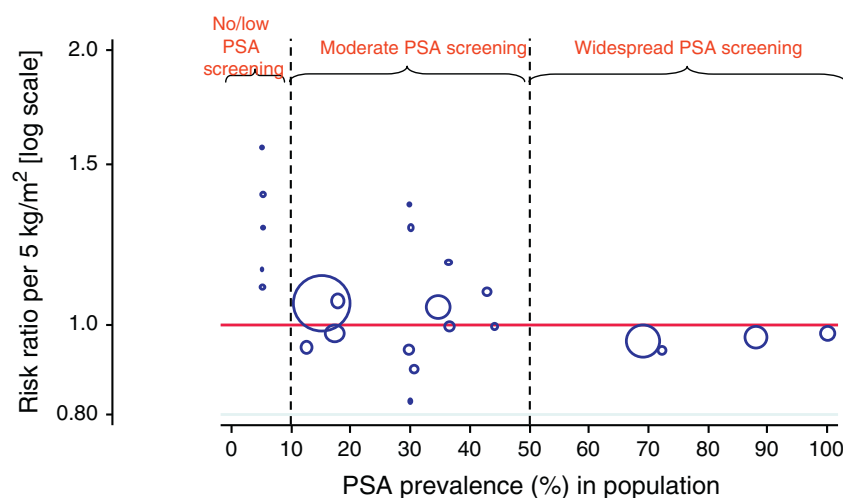
### 3.3.5. Additional cancer types for the ‘possible’ list

In addition, there may be more obesity-related cancers on the risk list. Thus, for example analyses from the NIH-AARP Diet and Health Study reported a modest increased risk BMI association for bladder cancer,<sup>45</sup> conventionally considered a smoking-related malignancy. Further data from the NIH-AARP Study show that increased BMI, particularly at an early age, might be associated with an increased risk of glioma,<sup>46</sup> an uncommon brain tumour.

## 4. Attributable risk modelling and assumptions

### 4.1. General considerations

Given the plausibility of the biological explanations,<sup>47</sup> the consistency of associations<sup>16</sup> and the sufficiently long latency times between BMI measurement and cancer occurrence,<sup>16</sup> many of the above associations are probably causal. Thus, it is reasonable to ask the question, what proportion of cancers in a population is attributable to EBW, as this in turn relates to the potential number of avoidable incident cancers in future intervention studies. While in its simplest format (the Levin formula), PAR could be derived by knowledge of the prevalence of exposure (in this example, EBW) and risk estimates, the discussions above demonstrate that this is not a simple model and that several time-related and population-related factors need to be incorporated into the model. In addition, the Levin formula only partially adjusts for confounding and



**Fig. 2 – BMI, prostate-specific antigen (PSA) screening and prostate cancer risk. Plot of sex-specific risk ratios per 5-kg/m<sup>2</sup> increment increase in BMI (i.e. ‘slopes’) for cohort studies of prostate cancer risk versus prevalence of PSA screening per study based on a secondary analysis of the meta-analysis in Renehan et al.<sup>16</sup> The size of each circle is proportional to the sample size of each cohort. Where exact prevalence was not reported in each paper, the prevalence was allotted to the mid-point of the respective categories: ‘no routine PSA screening or very low prevalence’; ‘moderate level of PSA screening’; or ‘widespread PSA screening’. The plot demonstrates that as the level or prevalence of PSA screening in a population increases, the ‘study-slope’ or BMI–cancer association approaches null association.**

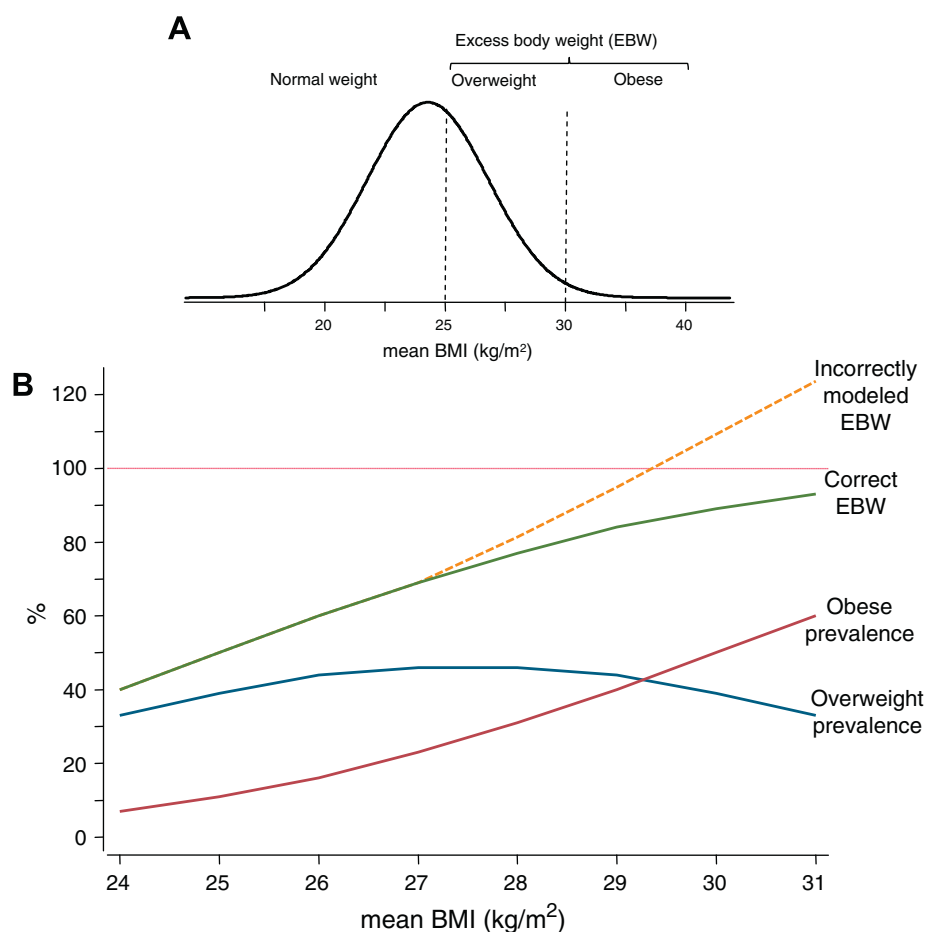
does not allow for effect modification, which can result in biased PAR estimates (generally overestimated), as has been extensively described by Flegal and colleagues.<sup>48</sup> A common remedy is to employ a fully saturated model that accounts for both confounding and interaction by allowing for different risk estimates within each population subgroup, as described by Benichou.<sup>49</sup>

The issue of the lag period for cancer development in the presence of excess adiposity has received little attention, yet is crucial to modelling population-attributable risk and further population intervention studies. Studies on the relationship between obesity and increased cardiovascular disease risk suggest lag periods of the order of 4–5 years.<sup>50</sup> In cohorts assessing cancer risk, the typical follow-up is greater than 10 years<sup>51</sup>, and it is thought that this is an ‘average’ lag period for obesity-related cancer development.<sup>52</sup> However, where hyper-oestrogenaemia is a predominant mechanism (for example post-menopausal breast and endometrial can-

cer), the lag period may be shorter. Thus, for example ecological<sup>53</sup> and observational<sup>54</sup> data suggest that large-scale cessation in MHT usage in a population translates into reductions in breast cancer incidences within 3–4 years. The observations of cancer risk reductions limited to women (where breast and endometrial cancer predominate) after bariatric surgery may be partly explained by the failure of sufficiently long follow-up to observed reductions in cancer risk in men (where colorectal and kidney are numerically the commonest obesity-related cancers).<sup>55</sup>

#### 4.2. Assumptions on the exposure: BMI distributions

Published articles<sup>39,56</sup> and reports<sup>57</sup> on PAR cancer estimates often cite outcomes in terms of excess cancers attributable to overweight and/or obesity states. This approach has several limitations when one wants to examine changes in time due to an intervention, or changes in an exposure. This



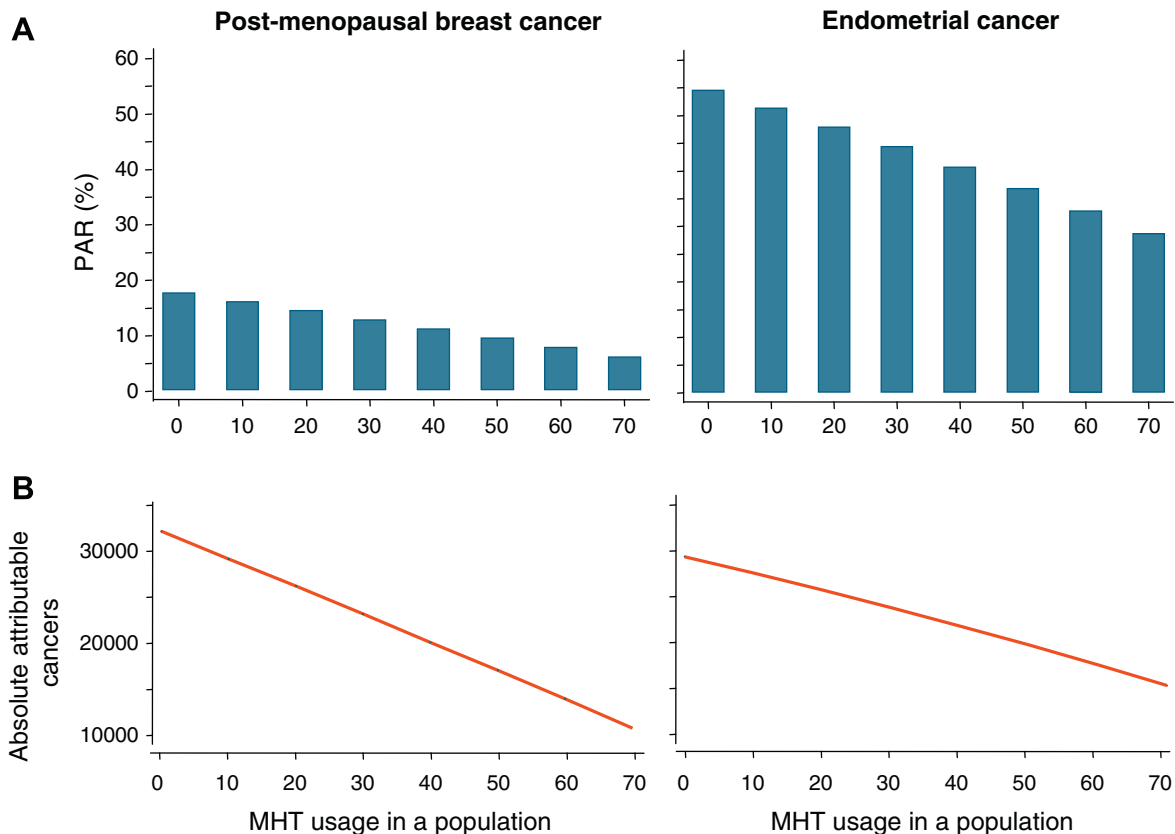
**Fig. 3 – Modelling the BMI distribution in population-attributable risk (PAR) estimations.** (A) Shows BMI distribution in a population handled as a normal distribution (mean = 24 kg/m<sup>2</sup>; standard deviation (SD) = 4 kg/m<sup>2</sup>, values common for many European countries in the mid-1990s, see Renehan et al. (52). ‘Overweight’ is the prevalence of the population with a BMI between 25.0 and 29.9 kg/m<sup>2</sup>; ‘obese’ is the prevalence of the population with a BMI greater than 30 kg/m<sup>2</sup> (for simplicity, the SD remains the same). (B) As mean BMI values increase with time (x-axis), the corresponding prevalence of the WHO ‘overweight’ (blue) and ‘obese’ (purple) categories increase, but then with increasing mean BMI, the prevalence of ‘overweight’ declines as the proportion in the ‘obese’ category continues to increase. The sum of the prevalence of ‘overweight’ and ‘obese’ (excess body weight, EBW), therefore, does not exceed 100% (correct EBW: green). However, if the future trend modelling is simply handled as linear extrapolation of the prevalence of the ‘overweight’ and ‘obese’ categories, the EBW incorrectly exceeds 100%.

is illustrated in Fig. 3. First, taking a normal BMI distribution as the simplest model, and modelling an increasing mean BMI over time, the corresponding prevalence of WHO overweight (blue) and obese (purple) categories increases, but then with further increases in mean BMI, the prevalence of overweight declines as the prevalence of obese continues to increase. The EBW, therefore, does not exceed 100% (correct EBW). However, if future trend modelling is simply handled as linear extrapolations of the prevalence of the overweight and obese categories, the EBW incorrectly exceeds 100%.

Second, the categorisation of the BMI distribution into normal weight, overweight and obese weight renders the parameter trichotomous or polychotomous. Barendregt and Veerman<sup>58</sup> have shown that using categorical distribution to calculate PAR may cause a non-linear result. With a small reduction in BMI, the modelled PAR is overestimated because of the higher weight of RR in the calculation. This is followed by an underestimation of PAR. This trend will end with an overestimation when reduction in weight is very large, as shown by Hanley.<sup>2</sup>

#### 4.3. Assumptions on relative risk

When we calculated PAR using one risk function we assumed linearity in the model. Although this model is most often justified, we showed that this is not always the case<sup>16</sup> – thus, the risk of endometrial cancer increases exponentially with increasing weight, and risk function should be adjusted for calculating PAR for the higher EBW level, otherwise PAR might be underestimated. Another assumption in calculating PAR using the general formulas described earlier is risk reversibility. For smoking and cancer, risk reversibility has been reported before, i.e. stopping smoking at a young age reduces cancer risk compared to that of non-smokers.<sup>59</sup> Yet, for obesity evidence of reversibility remains limited, mostly because large weight loss is difficult and hard to maintain.<sup>60</sup> The Swedish trial on bariatric surgery gives a clue here, although whether reversibility is partial or total when the desired BMI was maintained remains unclear.<sup>61</sup> To assess this a control group with normal BMI and a larger cohort that represent groups having surgery at different ages with a long follow-up period are needed.<sup>58</sup>



**Fig. 4 – Impact of varying MHT usage in Europe on PAR and absolute attributable numbers of cancers. (A) Secondary analyses from data in Renehan et al.<sup>16</sup> were performed evaluating the relationship between study-specific menopausal hormone therapy (MHT) use (as a percentage) and risk of post-menopausal breast and endometrial cancers. A meta-regression was then performed to derive an RR value for each MHT percentage use. The resulting risk estimates were then populated into the PAR modelling used in Renehan et al.<sup>52</sup> (for 30 European countries) based on 2008 BMI exposure estimates. In essence, this is an RR effect approach described by Barendregt and Veerman.<sup>58</sup> (B) In Europe 2008, which has low MHT usage, the absolute numbers of cancers attributable to excess body weight are greater than 32,000 for post-menopausal breast cancer, and greater than 29,000 for endometrial cancer.**



4.4. Assumptions about the model

Currently, calculation of PAR is most commonly done using counterfactual analysis. The contribution of a risk factor to a health measure is estimated by comparing the current or future level of the health measure under alternative hypothetical scenarios including the absence of the exposure. This hypothetical scenario is referred to as counterfactual analysis,<sup>62,63</sup> where PAR is expressed as follows:

$$PAR = \frac{\int_{x=0}^m RR(x)P_e(x)dx - \int_{x=0}^m RR(x)P_{ne}(x)dx}{\int_{x=0}^m RR(x)P_e(x)dx}$$

where  $RR(x)$  is the relative risk of the exposure level  $x$ ,  $P_e(x)$  is the population distribution of exposure,  $P_{ne}(x)$  is the counterfactual distribution of the exposure (hypothetical rather than to the actual condition)<sup>64</sup> and  $m$  is the maximum exposure level. Before determining the counterfactual scenario, one has to determine the *theoretical minimum risk*, which is the exposure distribution that would result in the lowest population risk. In the example of smoking, this would be never smokers. To determine theoretical minimum risk for BMI, the fact that there are hazards associated with low as well as high BMI should be taken into account.<sup>65</sup> Because of these considerations the WHO has advised a theoretical minimum value

of 21–22 kg/m<sup>2</sup> for BMI.<sup>66</sup> The difference in the theoretical minimum risk group or reference group is probably one of the causes of the variations of attributable cancer incidence or mortality due to EBW.

Thus, where the exposure of interest is BMI (or other anthropometric indices), to avoid inaccuracies in trends modelling prevalence rates and to avoid polychotomous parameters, we recommend the use of dynamic modelling with counterfactual approaches, e.g. Prevent (model described elsewhere in this Special Issue).<sup>67</sup>

4.5. PAR cancer estimates for Europe

Using the risk estimates derived from our meta-analysis,<sup>16</sup> we recently estimated sex-specific population-attributable risks across 30 European countries.<sup>52</sup> Our estimates for incident cancers were 3.2% in men and 8.6% in women, and this amounted to over 124,000 avoidable cancer cases per year (based on 2008 risk exposures). Cancers of the post-menopausal breast, colorectal and endometrium accounted for two-thirds of new cases attributable to EBW. Importantly, this analysis showed that estimates were most sensitive to changes in risk estimates – for example an increase in relative risk of 0.20 caused a 133% shift in PAR estimates.

**Table 3 – Framework for the evaluation of excess body weight (EBW) and attributable risk of cancer.**

Examples relevant to EBW	
<i>Demographic factors</i>	
Sex-specific risk exposures	BMI distribution standard deviations (SDs) are consistently larger in women than men
Age-group-specific exposures	In general, mean BMI increases with age
<i>Cancer registry details</i>	
Cancer sub-sites	Distinguish colon and rectal cancer
Histological sub-types	Oesophageal SCC and adenocarcinoma; breast cancer ER/PR status; endometrial cancer Type I and II
<i>Trend data</i>	
Exposure trends	Preference to use mean BMI (+SD) rather than overweight and obese WHO categories. Explore data prior to analysis for linearity; exponential trends; piecewise changes
Exposure distribution changes	As populations change weight, they tend to shift from a normal to a gamma distribution
<i>Covariates</i>	
Menopausal hormone therapy(MHT)	This is a major effect modifier for breast and endometrial cancers. Future detail needs to disentangle effects of oestrogen alone versus combined MHT, and in turn, cyclical versus continuous combined MHT
Smoking	Key confounder for smoking-related cancers
Medical practice trends	For example as hysterectomy rates for benign disorder decline, this may impact on endometrial cancer rates in obese populations
<i>Model assumption</i>	
Lag period	May vary between different cancers for the same apparent exposure
Lead period	For obesity-related cancers, this is broadly unknown
Handling exposure	Preference to use counterfactual approach, determine theoretical minimum risk
Relative risk	Based on meta-analysis corrected for confounders. Consider the possibilities of non-linear relationship, e.g. endometrial cancer
Risk reversibility	For obesity-related cancers, this is broadly unknown?

BMI: body mass index.  
 ER: oestrogen receptor. PR: progesterone receptor.  
 SCC: squamous cell carcinoma.  
 WHO: World Health Organisation.

#### 4.6. Why PAR cancer estimates vary in different papers

Our above-mentioned estimates for Europe were conservative. The media often highlight the fact that obesity is linked to 20% of all cancer deaths in women and 14% in men, quoting the large US Cancer Prevention Study II.<sup>39</sup> However, estimates based on mortality data cannot be used to infer incident cancers as: (i) they are reported against the background of a number of high smoking-attributable cancer deaths (which tend to dilute other attributable factors) and (ii) relative risk of cancer mortality may overinflate those of cancer incidence,<sup>39,56</sup> as increased adiposity may itself unfavourably impact upon cancer treatment selection and outcome. Based on a denominator of obesity-related incident cancers, the World Cancer Research Fund (WCRF)<sup>57</sup> calculated UK population-attributable fractions of 18% in men and 16% in women. The equivalent UK estimates (6.9% and 8.0%, respectively) in our analysis were more conservative, reflecting that the WCRF included relative risks from selected studies (which tend to bias overestimation).

With regard to post-menopausal breast cancer, the present Europe-wide estimate is conservative (4.9%) compared with that of 10.2% from an Italian population<sup>68</sup> – as we will see below, this may in part reflect that traditionally Italy has had a low usage of MHT.<sup>69</sup>

So why is there so much variation? One clear possibility is that each study used a different framework and thus different assumptions in calculating PAR. Based on the observations in the section “Developments since the *Lancet* meta-analysis”, we undertook a secondary analysis of those data,<sup>16</sup> evaluating the relationship between MHT and study-specific risk estimates, using meta-regressions. The findings were similar for post-menopausal breast cancer and endometrial cancer – namely, increasing MHT use in a population attenuates the risk ratio. The resulting risk estimates were then populated into the PAR modelling used in our previous analysis<sup>52</sup> based on 2008 BMI exposure estimates. As women in Europe have been moving from high towards low MHT use, PARs may increase 3-fold for post-menopausal breast cancer and 2-fold for endometrial cancer (Fig. 4A). In absolute cases attributable to EBW, the shifts are from 10,000 to 32,000 for post-menopausal breast cancer; and 15,000–29,000 for endometrial cancer (Fig. 4B).

### 5. Framework for future evaluation

From the above observations, the effect modifications in risk estimates and our modelling experience, we have developed a research framework in which to optimally evaluate future trends in numbers of new cancers attributable to EBW. This is shown in Table 3. This list emphasises that PAR estimations are not a simple input of two variables (exposure and risk). Rather, there are multiple covariates that input into these variables, which importantly may vary with time. The last subheading in the evaluation list emphasises, for the example of obesity, the importance of considering the BMI distribution in a population. Thus, for example BMI distribution shifts from a normal to gamma parameterisation as adiposity increases in populations.<sup>70</sup>

Finally, while public health policies aimed at curbing the underlying causes of the obesity epidemic are being suggested and implemented, it is important not to forget the parallel need to better understand the biological processes linking obesity and cancer<sup>19,47</sup> as a prerequisite to the development of new approaches to the prevention and treatment of obesity-related cancers.

#### Conflict of interest statement

None declared.

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