World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival

Body fatness and weight gain and the risk of cancer

2018

World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund 世界癌症研究基金會

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WORLD CANCER RESEARCH FUND NETWORK

Our Vision

We want to live in a world where no one develops a preventable cancer.

Our Mission

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

Our Network

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

Our Continuous Update Project (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (see inside back cover).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the World Cancer Research Fund Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Body fatness and weight gain and the risk of cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see dietandcancerreport.org

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

How to cite the Third Expert Report

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Body fatness and weight gain and the risk of cancer. Available at dietandcancerreport.org

The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at dietandcancerreport.org

Key

See **Glossary** for definitions of terms highlighted in *italics*.

References to other parts of the Third Expert Report are highlighted in purple.

Executive summary

Background and context

In this part of the Third Expert Report from our Continuous Update Project (CUP) – the world's largest source of scientific research on cancer prevention and survivorship through diet, nutrition and physical activity – we analyse global research on how body fatness and weight gain affect the risk of developing cancer.[1] This includes new studies as well as those included in the 2007 Second Expert Report, Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective [1].

Excess *energy* from food and drink is stored in the body as fat in *adipose tissue*. The amount of adipose tissue in the body varies more from person to person than any other type of tissue (such as muscle, bone or blood). The size and location of these fat stores also vary considerably between populations, between people and over the course of a person's life. Excess body fat is a cause of a number of *chronic* diseases and reduces life expectancy.

Overweight and obesity, generally assessed by various *anthropometric measures* including body mass index (BMI) and waist circumference, are now more prevalent than ever. In 2016, an estimated 1.97 billion adults and over 338 million children and adolescents around the world were categorised as overweight or obese. The increase in the proportion of adults categorised as obese has been observed both in *low-* and *middle-income countries* and in *high-income countries*.

Body fatness is difficult to measure directly. However, because body fatness is the most variable determinant of weight, several weight-based measures are used as markers of body fatness. The most common is *body mass index* (BMI), a measure of weight adjusted for height. BMI is calculated as weight in kilograms divided by height in metres squared (kg/m^2). It is the most commonly used marker of *adiposity* in epidemiological studies owing to its simplicity of assessment, low costs, and high precision and accuracy.

Fat is not distributed equally around the body. It accumulates subcutaneously (beneath the skin) around the muscles of the upper arm, buttocks, belly, hips and thighs. It also accumulates intra-abdominally or viscerally (around the organs) and may also be deposited within tissues such as the liver and muscles. Fat stores can be categorised as 'peripheral' (not around the trunk) or 'abdominal' (also called 'central'). Ideal measurements of adiposity include the regional distribution and site of deposition of the adipose tissue, including that within and around specific organs. Measures such as adult weight gain, waist circumference, hip circumference and waist-hip ratio contribute information on adipose tissue distribution.

Excess weight and obesity have been linked to a number of other chronic diseases including cardiovascular disease, diabetes and other metabolic disorders.

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin.

How the research was conducted

The global scientific research on diet, nutrition, physical activity and the risk of cancer was systematically gathered and analysed and then independently assessed by a panel of leading international scientists to draw conclusions about which factors increase or decrease the risk of developing the disease (see Judging the evidence).

This Third Expert Report presents in detail findings for which the Panel considered the evidence strong enough to make cancer prevention recommendations (where appropriate) and highlights areas where more research is required (where the evidence is suggestive of a causal or protective relationship but is limited in terms of amount or by methodological flaws). Evidence that was considered by the Panel but was too limited to draw firm conclusions is not covered in detail in this Third Expert Report.

Findings

There is strong evidence that:

- **being overweight or obese throughout adulthood increases the risk of cancers of the mouth, pharynx and larynx; oesophagus (*adenocarcinoma*); stomach (cardia); pancreas; gallbladder; liver; colorectum; breast (postmenopause); ovary; endometrium; prostate (advanced); and kidney.**
- **greater weight gain in adulthood increases the risk of postmenopausal breast cancer.**
- **being overweight or obese as an adult before menopause decreases the risk of premenopausal breast cancer.**
- **being overweight or obese between the ages of about 18 and 30 years decreases the risk of pre and postmenopausal breast cancer.**

The evidence shows that, in general, the more excess weight people have as adults, the higher the risk of certain cancers, apart from premenopausal breast cancer where the risk is generally lower. The evidence also shows that, in general, the more weight people gain as adults, the higher the risk of postmenopausal breast cancer. In contrast, the evidence shows that, in general, the more excess weight people have as young adults, the lower the risk of breast cancer.

The Panel has used this strong evidence on being overweight or obese and on weight gain when making Recommendations (see below) designed to reduce the risk of developing cancer.

There is also other evidence on being overweight or obese throughout adulthood that is limited (either in amount or by methodological flaws), but is suggestive of an increased risk of cervical cancer for women with a BMI of 29 kg/m^2 or more. Further research is required, and the Panel has not used this evidence to make recommendations.

Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. It is important to keep weight within the healthy range and avoid weight gain in adult life. The Recommendations are listed on the inside back cover.

References

[1] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington DC: AICR, 2007. Available from wcrf.org/about-the-report

1. Body fatness and weight gain and the risk of cancer: a summary matrix

BODY FATNESS AND WEIGHT GAIN AND THE RISK OF CANCER

WCRF/AICR GRADING		DECREASES RISK		INCREASES RISK	
		Exposure	Cancer site	Exposure	Cancer site
STRONG EVIDENCE	Convincing			Adult body fatness	Oesophagus (adenocarcinoma) 2016[1] Pancreas 2012[1] Liver 2015[2] Colorectum 2017[1] Breast (postmenopause) 2017[1,3] Endometrium 2013[4,5] Kidney 2015[1]
				Adult weight gain	Breast (postmenopause) 2017[3]
	Probable	Adult body fatness	Breast (premenopause) 2017[1,3]	Adult body fatness	Mouth, pharynx and larynx 2018[1] Stomach (cardia) 2016[2] Gallbladder 2015[2,7] Ovary 2014[2,5,8] Prostate (advanced) 2014[1,9]
		Body fatness in young adulthood	Breast (premenopause) 2017[3,6] Breast (postmenopause) 2017[3,6]		
LIMITED EVIDENCE	Limited – suggestive			Adult body fatness	Cervix (BMI ≥ 29 kg/m^2) 2017[2,5]
STRONG EVIDENCE	Substantial effect on risk unlikely	None identified			

1 Conclusions for adult body fatness and cancers of the following types were based on evidence marked by body mass index (BMI), waist circumference and waist-hip ratio: mouth, pharynx and larynx; oesophagus (adenocarcinoma); pancreas; colorectum; breast (pre and postmenopause); prostate (advanced); and kidney.

2 Conclusions for adult body fatness and cancers of the following types were based on evidence marked by BMI: stomach (cardia), gallbladder, liver, ovary and cervix (BMI ≥ 29 kg/m^2).

3 Evidence for the link between body fatness, weight gain and breast cancer is presented separately for the risk of pre and postmenopausal breast cancer because of the well-established effect modification by menopausal status.

4 The conclusion for adult body fatness and endometrial cancer was based on evidence marked by BMI (including BMI at age 18 to 25 years), weight gain, waist circumference and waist-hip ratio.

5 There is no evidence of effect modification by menopausal status for body fatness and the risk of endometrial, ovarian or cervical cancer so the evidence for all women (irrespective of menopausal status) is presented together.

6 Evidence for body fatness in young adulthood and breast cancer (pre and postmenopause) comes from women aged about 18 to 30 years and includes evidence marked by BMI.

7 Adult body fatness may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence, to cause gallbladder cancer. It is not yet possible to separate these effects.

8 The effect of adult body fatness on the risk of ovarian cancer may vary according to tumour type, menopausal hormone therapy use and menopausal status.

9 The effect of adult body fatness on the risk of prostate cancer was observed in advanced, high-grade and fatal prostate cancers.

Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the systematic literature review was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

Definitions of World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) grading criteria

'Strong evidence': Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship and generally justify making public health recommendations.

'Convincing': Evidence is strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

'Probable': Evidence is strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies goals and recommendations designed to reduce the risk of cancer.

'Limited evidence': Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations.

'Limited – suggestive': Evidence is inadequate to permit a judgement of a probable or convincing causal (or protective) relationship, but is suggestive of a direction of effect. The evidence may be limited in amount, or by methodological flaws, but shows a generally consistent direction of effect. This judgement generally does not justify making recommendations.

'Limited – no conclusion': There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these. Evidence that was judged to be 'limited – no conclusion' is mentioned in Evidence and judgements (**Section 5**).

'Substantial effect on risk unlikely': Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet, nutrition, body fatness or physical activity is unlikely to have a substantial causal (or protective) relation to a cancer outcome.

For further information and to see the full grading criteria agreed by the Panel to support the judgements shown in the matrices, please see **Appendix 1**.

The next section describes which evidence the Panel used when making Recommendations.

2. Summary of Panel judgements

The conclusions drawn by the CUP Panel are based on the evidence from both epidemiological and mechanistic studies relating body fatness and weight gain to the risk of development of particular cancer types. Each conclusion on the likely causal relationship between body fatness and weight gain and a cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence, and can be found at the end of this Third Expert Report.

The CUP Panel concluded:

STRONG EVIDENCE

Convincing

- **Increased risk**
  - **Adult body fatness:** Greater adult body fatness is a convincing cause of cancers of the oesophagus (*adenocarcinoma*),[1] pancreas,[1] liver,[2] colorectum,[1] breast (postmenopause),[1,3] endometrium[4,5] and kidney.[1]
  - **Adult weight gain:** Adult weight gain is a convincing cause of postmenopausal breast cancer.[3]

Probable

- **Decreased risk**
  - **Adult body fatness:** Greater adult body fatness probably protects against premenopausal breast cancer.[1,3]
  - **Body fatness in young adulthood:** Greater body fatness in young adulthood probably protects against pre and postmenopausal breast cancer.[3,6]
- **Increased risk**
  - **Adult body fatness:** Greater adult body fatness is probably a cause of cancers of the mouth, pharynx and larynx;[1] stomach (cardia);[2] gallbladder;[2,7] ovary[2,5,8] and prostate (advanced).[1,9]

The evidence shows that, in general, the more excess weight people have as adults, the higher the risk of certain cancers, apart from premenopausal breast cancer where the risk is generally lower. The evidence also shows that, in general, the more weight people gain as adults, the higher the risk of postmenopausal breast cancer. In contrast, the evidence shows that, in general, the more excess weight people have as young adults, the lower the risk of breast cancer.

The Panel used this strong evidence on being overweight or obese and weight gain when making Recommendations designed to reduce the risk of developing cancer (See Recommendations and public health and policy implications, Section 2: Recommendations for Cancer Prevention).

See page 10 for footnotes.

LIMITED EVIDENCE

Limited – suggestive

- **Increased risk**
  - **Adult body fatness:** The evidence suggesting that greater adult body fatness increases the risk of cervical cancer[2,5] in people with a BMI ≥ 29 kg/m^2 is limited.

The Panel did not use the limited evidence when making Recommendations designed to reduce the risk of developing cancer. Further research is required into these possible effects on the risk of cancer.

See Definitions of WCRF/AICR grading criteria (**Section 1**: Body fatness and weight gain and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'strong evidence', 'convincing', 'probable', 'limited evidence' and 'limited – suggestive'.

[1] Conclusions for adult body fatness and cancers of the following types were based on evidence marked by body mass index (BMI), waist circumference and waist-hip ratio: mouth, pharynx and larynx; oesophagus (adenocarcinoma); pancreas; colorectum; breast (pre and postmenopause); prostate (advanced); and kidney.

[2] Conclusions for adult body fatness and cancers of the following types were based on evidence marked by BMI: stomach (cardia), gallbladder, liver, ovary and cervix (BMI ≥ 29 kg/m^2).

[3] Evidence for the link between body fatness, weight gain and breast cancer is presented separately for the risk of pre and postmenopausal breast cancer because of the well-established effect modification by menopausal status.

[4] The conclusion for adult body fatness and endometrial cancer was based on evidence marked by BMI (including BMI at age 18 to 25 years), weight gain, waist circumference and waist-hip ratio.

[5] There is no evidence of effect modification by menopausal status for body fatness and the risk of endometrial, ovarian or cervical cancer so the evidence for all women (irrespective of menopausal status) is presented together.

[6] Evidence for body fatness in young adulthood and breast cancer (pre and postmenopause) comes from women aged about 18 to 30 years and includes evidence marked by BMI.

[7] Adult body fatness may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence, to cause gallbladder cancer. It is not yet possible to separate these effects.

[8] The effect of adult body fatness on the risk of ovarian cancer may vary according to tumour type, menopausal hormone therapy use and menopausal status.

[9] The effect of adult body fatness on the risk of prostate cancer was observed in advanced, high-grade and fatal prostate cancers.

3. Definitions and patterns

3.1 Body fatness

Excess *energy* from food and drink is stored in the body as fat in *adipose tissue*. The amount of adipose tissue in the body varies more from person to person than any other type of tissue (such as muscle, bone or blood). The size and location of these fat stores also vary considerably between populations, between people and over the course of a person's life. Excess body fat is a cause of a number of *chronic* diseases and reduces life expectancy [2].

Overweight and obesity, generally assessed by various *anthropometric measures* including BMI and waist circumference, are now more prevalent than ever. In 2016, an estimated 1.97 billion adults and over 338 million children and adolescents around the world were categorised as overweight or obese [3]. The increase in the proportion of adults categorised as obese has been observed both in *low-* and *middle-income countries* and in *high-income countries*.

3.1.1 Body mass index

Body fatness is difficult to measure directly. However, because body fatness is the most variable determinant of weight, several weight-based measures are used as markers of body fatness.

The most common is *body mass index* (BMI), a measure of weight adjusted for height. BMI is calculated as weight in kilograms divided by height in metres squared (kg/m^2). It is the most commonly used marker of *adiposity* in epidemiological studies due to simplicity of assessment, low costs, and high precision and accuracy [2].

In most circumstances, BMI has been shown to be reliably linked to body fatness [4]. However, it does not differentiate between lean and *adipose tissue* mass, the relative proportions of which vary between people, and with age, sex and ethnicity [5, 6]. Unusually muscular and lean people (such as manual workers and power athletes) may have a relatively high BMI, even if they have relatively little body fat [7, 8]. Measures that do not distinguish lean from adipose tissue may obscure any separate roles of low lean mass and high adiposity in determining cancer risk [2].

In addition, BMI provides no information on the distribution of adipose tissue, whether central (in the abdomen, including the abdominal wall and viscera), truncal subcutaneous, peripheral (in the buttocks and extremities), or in organs and tissues. Fat distribution varies between individuals and by ethnicity and stage in the lifespan [2].

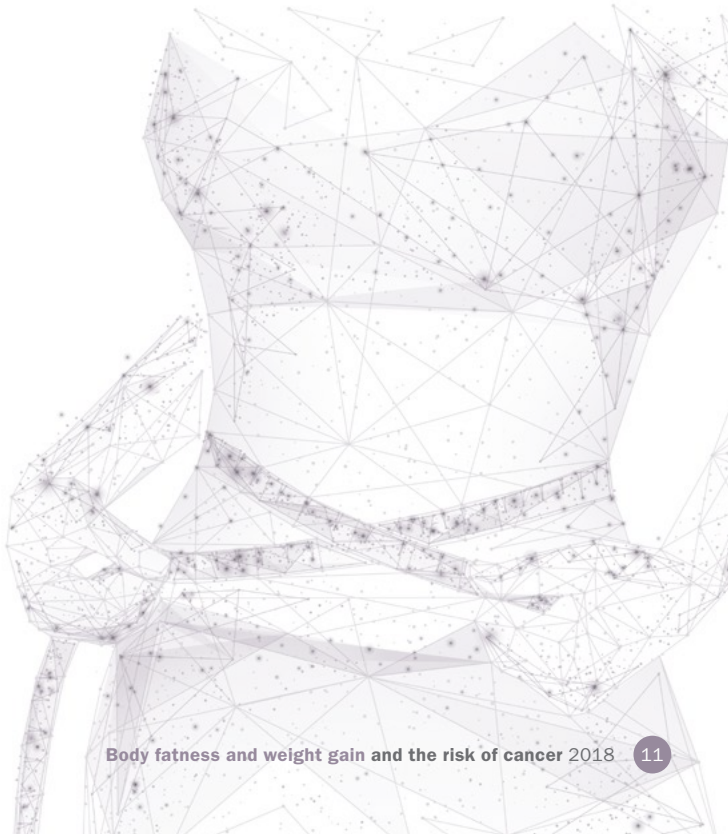
Definitions for classifying and reporting population-level healthy weight, overweight and obesity have historically been based on *anthropometric measures*, including BMI [2].

The World Health Organization defines BMI between 18.5 and 24.9 kg/m^2 as 'healthy' or 'normal' for most populations [9]. This is roughly equivalent to 15 to 20 per cent body fat in adult men and 25 to 30 per cent in adult women [10]. The 'underweight' or 'thin' range is a BMI below 18.5 (low body fatness). Above a BMI of 25, there are common gradings for overweight (25 to 29.9) and obesity (30 or more); see **Figure 3.1**. The risk of type 2 diabetes and high blood pressure increases with BMI, with no clear threshold but with a marked increase in risk as BMI approaches 25 [11].

These BMI cut-offs are based on data primarily derived from populations of European origin living in *high-income countries*, so they may not apply globally. Because the relationship between BMI and body composition varies between ethnic groups, different reference ranges have been proposed for Asian populations [9]. For further information about variation in anthropometric measures due to sex and ethnicity, see **Box 1**.

3.1.2 Body fat distribution

Fat is not distributed equally around the body. It accumulates subcutaneously (beneath the skin) around the muscles of the upper arm, buttocks, belly, hips and thighs. It also accumulates intra-abdominally or viscerally (around the organs) and may also be deposited within tissues such as the liver and muscles. Fat stores can be categorised as 'peripheral' (not around the trunk) or 'abdominal' (also called 'central'). The pattern of fat stores is determined largely by genetic factors, with a typically different pattern in men and women, which tends to change with age. Women tend to store more subcutaneous fat around their hips, buttocks and thighs than men, producing a body profile known as a 'pear shape' (or 'gynoid' pattern of fat distribution). Men are more likely to store fat around their abdomen, producing an 'apple shape' (or 'android' pattern).



Ideal measurements of *adiposity* include the regional distribution and site of deposition of the *adipose tissue*, including that within and around specific organs. Measures such as adult weight gain, waist circumference, hip circumference and waist-hip ratio contribute information on adipose tissue distribution [2].

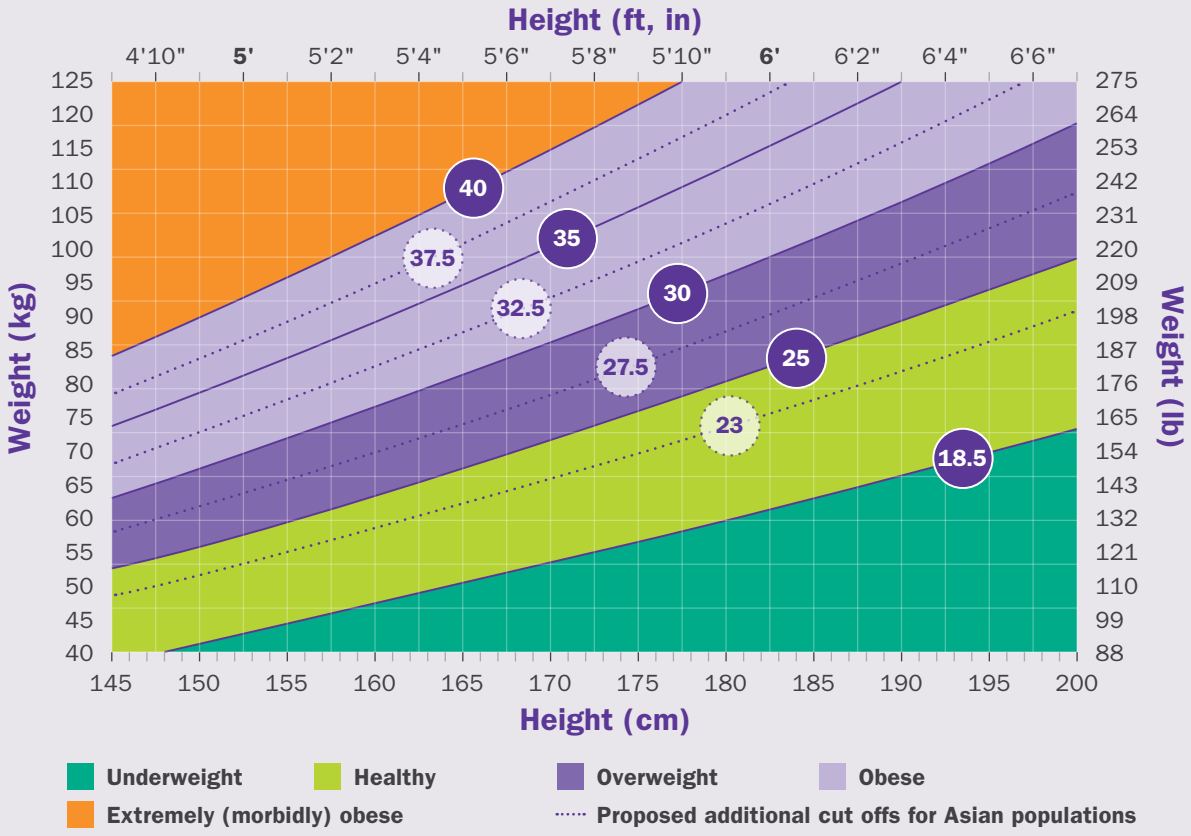
The size of peripheral fat stores can be used as a measure of total body fatness, although the proportion of total to abdominal fat varies between people. Waist circumference is a measure that includes subcutaneous fat stores, as well as the more metabolically active intra-abdominal fat stores, which have high lipolytic activity and release large amounts of free *fatty acids* [12, 13].

3.1.2.1 Waist circumference and waist-hip ratio

Crude estimates of excess abdominal fat can be made either by measuring waist circumference

Figure 3.1: Adult height, weight and ranges of body mass index (BMI)

Body mass index (BMI) is a simple index of weight-for-height used to classify underweight, healthy weight and overweight in adults. BMI is defined as weight in kilograms divided by the square of height in metres (kg/m^2).



It is not possible to specify a single BMI goal that applies to all people, because healthy people vary in their proportion of lean to fat tissue at any BMI. We recommend that people aim to keep their BMI as low as possible within the healthy BMI range. People who have gained weight, even within the healthy range, are advised to aim to return to their original weight.

Adults above the healthy range of BMI are recommended to lose weight to approach the healthy range; general information is available from several reliable sources, such as government guidelines and the WCRF Network, but individually tailored advice is best sought from appropriately qualified professionals.

or by calculating the ratio of this measurement to hip circumference (the 'waist-hip' ratio), although this ratio is no longer recommended as a better indicator of abdominal obesity than waist circumference alone. Waist circumference is a better single indicator.

Waist and hip circumference measures are useful to identify abdominal obesity, commonly defined as waist measurement cut-offs of 94 centimetres for men and 80 centimetres for women based on a rough equivalence to a BMI of 25 kg/m^2 and a waist-hip ratio of ≥ 0.90 for males and ≥ 0.85 for females [14].

Asian populations appear to have an increased metabolic risk at a lower waist circumference than European populations. This is probably due to higher levels of intra-abdominal *adipose tissue* for the same BMI. These data indicate a lower waist circumference cut-off point for Asian populations; for example, waist circumference values of 90 centimetres and 80 centimetres, for men and women, respectively [14]. For further information about variation in *anthropometric measures* by sex and ethnicity, see **Box 1**.

Waist and hip circumference measures cannot differentiate between visceral and subcutaneous adipose compartments [15]. Waist circumference and waist-hip ratio should be interpreted as markers of risk [2].

3.2 Adult weight gain

Increases in body weight during adulthood depend mostly on accumulation of fat rather than lean tissue, and therefore any change may better reflect fatness than adult attained weight itself, which is more dependent on lean mass. For this reason, evidence of associations specifically between adult weight gain and cancers was sought in the CUP.

Box 1: Anthropometric measures: variation with sex and ethnic groups

Several studies across the world have shown that body composition varies by sex and by ethnicity [14]. At the same BMI level, for example, women tend to have a higher body fat percentage than do men [16].

Variations in the relationship between BMI and body fat percentage have been observed between Caucasian, African and Asian populations [17, 18]. In addition, body composition and fat distribution appear to vary for different ethnic groups at similar BMIs [18–20]. For example, Asian Indian men with a BMI of 24 kg/m^2 and women with a BMI of 26 kg/m^2 have the same percentage body fat as European men and women with a BMI of 30 kg/m^2 and Pacific men and women with a BMI of 34 and 35 kg/m^2 respectively [18].

In addition, ethnic variation in circulating levels of obesity-related *biomarkers* is apparent after controlling for BMI [21], and Asian populations have a higher risk of cardiovascular disease and its comorbidities than Europeans at a given BMI, waist circumference or waist-hip ratio [18, 21]. These factors may contribute to observed ethnicity-related differences in cancer risk at similar levels of *anthropometric measures* of *adiposity*.

4. Interpretation of the evidence

4.1 General

For general considerations that may affect interpretation of the evidence in the CUP, see Judging the evidence.

'Relative risk' (RR) is used in this Third Expert Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios' and *'odds ratios'*.

4.2 Specific

Specific factors that the Panel bears in mind when interpreting evidence on whether adult body fatness and weight gain increase or decrease the risk of developing cancer are described in this section. Factors that are relevant to specific cancers are presented here too.

4.2.1 Exposures

4.2.1.1 Adult body fatness

Definitions. The CUP interpreted BMI, waist circumference, waist-hip ratio and adult weight gain as indicating interrelated aspects of body fatness and fat distribution. BMI was consistently used as a measure of adult body fatness in the CUP, most commonly in conjunction with waist circumference and waist-hip ratio.

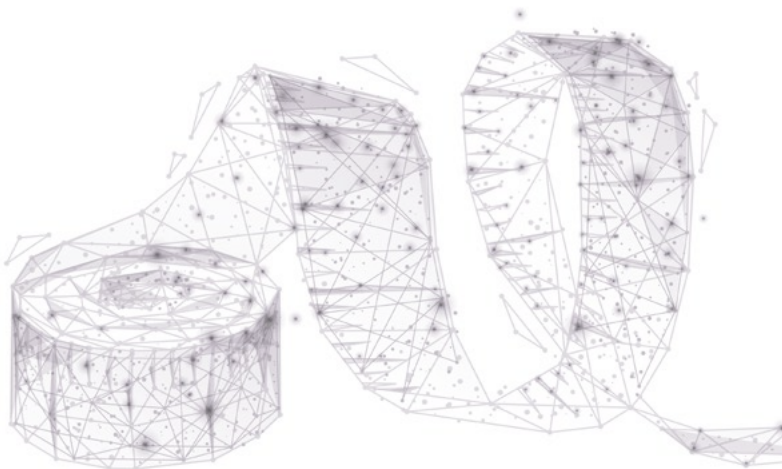
The system of classifying underweight, 'normal' weight, overweight, and degrees of obesity as discrete ranges of BMI is in general use. However, as shown in this part of the Third Expert Report, the relationship between body fatness and cancer is continuous across the range of BMI. For this reason, the Panel has chosen to use the term 'body fatness' rather than 'overweight' or 'obesity'.

Measurement. Anthropometric measures are imperfect and cannot distinguish reliably between lean mass and body fat, between total and abdominal fat, or between visceral and subcutaneous fat. Increases in body weight during adulthood depend on accumulation of fat more than of lean tissue, and therefore any such change may better reflect fatness than adult weight itself [2].

BMI is not a perfect marker of body fatness, but more precise techniques such as underwater weighing, magnetic resonance imaging, computerised tomography or dual-energy X-ray absorptiometry are rare in large-scale epidemiological studies due to their logistical difficulties and expense.

The relationship between waist circumference and the size of intra-abdominal fat stores (as opposed to subcutaneous abdominal fat stores) may vary between ethnic groups [22]. As body fatness tends to increase with age in most populations and is characteristically higher in women than in men, it is important that studies take into account both age and sex.

The association between *adiposity*, growth and maturational events is complex. Single *anthropometric measures* do not capture maturational events, including the presence of critical windows of susceptibility (age of *menarche* and *menopause*).



Reporting bias. Some epidemiological studies rely on self-reported height and weight, which may include systematic errors in calculations of BMI; people tend to under-report weight and over-report height, especially individuals in overweight or obese categories [23]. BMI cut-offs are therefore useful at the population level but may not accurately reflect adiposity of individuals [2].

4.2.1.2 Body fatness in young adulthood

Definition. Body fatness in young adulthood is marked by BMI in the CUP and is based on data available for participants aged between about 18 and 30 years.

Measurement. Anthropometric measures are imperfect and cannot distinguish reliably between lean mass and body fat, between total and abdominal fat, or between visceral and subcutaneous fat. For information on measurement, see **Section 4.2.1.1**.

The association between *adiposity*, growth and maturational events is complex. Single *anthropometric measures* do not capture maturational events, including the presence of critical windows of susceptibility (age of *menarche*).

Reporting bias. In most studies included in the CUP analyses, participants were asked to recall weight in young adulthood; hence, there is a possibility of recall bias and errors may be greater than for self-reported current weight.

4.2.1.3 Adult weight gain

Definition. Increases in body weight during adulthood depend on accumulation of fat more than of lean tissue, and therefore any such change may better reflect fatness than adult weight itself. For this reason, evidence of associations specifically between adult weight gain and cancers was sought in the CUP.

Reporting bias. The assessment of weight gain in most studies has been based on recall, which may have led to measurement error but is generally expected to be random and result in attenuation of effect estimates [24].

For information on measurement, see **Section 4.2.1.1**.

4.2.2 Cancers

The information provided here on 'Other established causes' of cancer is based on judgements made by the International Agency for Research on Cancer (IARC) [25], unless a different reference is given. For more information on findings from the CUP on diet, nutrition, physical activity and the risk of cancer, see other parts of this Third Expert Report.

4.2.2.1 Mouth, pharynx and larynx

Definitions. Organs and tissues in the mouth include the lips, tongue, inside lining of the cheeks (buccal mucosa), floor of the mouth, gums (gingiva), palate and salivary glands. The pharynx (throat) is the muscular cavity leading from the nose and mouth to the larynx (voice box), which includes the vocal cords. Cancers of the mouth, pharynx and larynx are types of *head and neck cancer*.

Classification. In sections of this Third Expert Report where the evidence for cancers of the mouth, pharynx and larynx is discussed, the term 'head and neck cancer' includes cancers of the mouth, larynx, nasal cavity, salivary glands and pharynx, and the term 'upper aerodigestive tract cancer' includes head and neck cancer together with oesophageal cancer. Nasopharyngeal cancer is reviewed separately from other types of head and neck cancer in the CUP.

Other established causes. Other established causes of cancers of the mouth, pharynx and larynx include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of cancers of the mouth, pharynx and larynx. Chewing betel quid (nuts wrapped in a betel leaf coated with calcium hydroxide), with or without added tobacco, is also a risk factor for cancers of the mouth and pharynx. Smoking tobacco is estimated to account for 42 per cent of deaths from mouth and oropharynx (the part of the throat just behind the mouth) cancers worldwide [26].

Infection

Some human papilloma viruses (HPV) are carcinogenic, and oral infection with these types is a risk factor for mouth, pharynx, and larynx cancer. The prevalence of carcinogenic HPV types in oropharyngeal cancer is estimated to be about 70 per cent in Europe and North America [27].

Environmental exposures

Exposure to asbestos increases the risk of laryngeal cancer.

Confounding. Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than people who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects by smoking tobacco; that is, not a direct result of the exposure examined.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.8**).

The characteristics of people developing cancers of the mouth, pharynx and larynx are changing. Increasingly, a large cohort of younger people who are infected with the carcinogenic HPV types 16 or 18, and who do not smoke and do not consume a large amount of alcohol, are now developing these cancers. As far as possible, the conclusions for mouth, pharynx and larynx take account of this changing natural history. However, most published epidemiological studies reviewing body fatness and cancers of the mouth, pharynx and larynx have not included data on HPV infection.

4.2.2.2 Oesophagus

Definition. The oesophagus is the muscular tube through which food passes from the pharynx to the stomach.

Classification. The oesophagus is lined over most of its length by squamous *epithelial* cells, where *squamous cell carcinomas* arise. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar epithelial cells, from which *adenocarcinomas* arise. The oesophageal-gastric junction and gastric cardia are also lined with columnar epithelial cells.

Globally, squamous cell carcinoma is the most common type and accounts for 87 per cent of cases [28]; however, the proportion of adenocarcinomas is increasing dramatically in affluent nations.

Squamous cell carcinomas have different geographic and temporal trends from adenocarcinomas and follow a different disease path. Different approaches or definitions in different studies are potential sources of heterogeneity.

Other established causes. Other established causes of oesophageal cancer include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is a cause of oesophageal cancer. *Squamous cell carcinoma* is more strongly associated with smoking tobacco than *adenocarcinoma* [29]. It is estimated that 42 per cent of deaths of oesophageal cancer are attributable to tobacco use [26].

Infection

Between 12 and 39 per cent of oesophageal squamous cell carcinomas worldwide are related to carcinogenic types of HPV [30]. *Helicobacter pylori (H. pylori)* infection, an established risk factor for *non-cardia stomach cancer*, is associated with a 41 to 43 per cent decreased risk of oesophageal adenocarcinoma [31, 32].

Other diseases

Risk of adenocarcinoma of the oesophagus is increased by gastro-oesophageal reflux disease, a common condition in which stomach acid damages the lining of the lower part of the oesophagus [29]. This type of oesophageal cancer is also increased by a rare condition, oesophageal achalasia (in which the valve at the end of the oesophagus called the 'cardia' fails to open and food gets stuck in the oesophagus) [29].

Family history

Tylosis A, a late-onset, inherited *familial* disease characterised by thickening of the skin of the palms and soles (hyperkeratosis), is associated with a 25 per cent lifetime incidence of oesophageal squamous cell carcinoma [33].

Confounding. Smoking tobacco is a potential *confounder*. People who smoke tend to have less healthy diets, less physically active ways of life and lower body weight than those who do not smoke. Therefore a central task in assessing the results of studies is to evaluate the degree to which observed associations in people who smoke may be due to residual confounding effects by smoking tobacco; that is, not a direct result of the *exposure* examined.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.1**).

4.2.2.3 Stomach

Infection with *H. pylori* is strongly implicated in the aetiology of intestinal *non-cardia stomach cancer*. The role of any other factor is to enhance risk of infection, integration and/or persistence.

Definition. The stomach is part of the digestive system, located between the oesophagus and the small intestine. It secretes enzymes and gastric acid to aid in food digestion and acts as a receptacle for masticated food, which is sent to the small intestines though muscular contractions.

Classification. Stomach cancer is usually differentiated by the anatomical site of origin: *cardia stomach cancer* (cardia cancer), which occurs near the gastro-oesophageal junction, and *non-cardia stomach cancer* (non-cardia cancer), which occurs outside this area, in the lower portion of the stomach. Cardia and non-cardia stomach cancer have distinct *pathogeneses* and aetiologies, but not all studies distinguish between them, particularly older studies. For these studies, there is a greater likelihood that the general term 'stomach cancer' may reflect a combination of the two subtypes, and therefore results may be less informative. Furthermore, definitions of cardia cancer classifications sometimes vary according to distance from the gastro-oesophageal junction, raising concerns about misclassification [34].

Cardia cancer shares some risk factors with oesophageal adenocarcinoma, in particular body fatness and smoking tobacco, and may have a common aetiology. Some studies examine cases of cardia cancer concurrently with oesophageal adenocarcinoma.

Other established causes. Other established causes of stomach cancer include the following:

Smoking tobacco

Smoking tobacco is a cause of stomach cancer. It is estimated that 13 per cent of deaths worldwide are attributable to smoking tobacco [26].

Infection

Persistent colonisation of the stomach with *H. pylori* is a risk factor for non-cardia stomach cancer, but in some studies has been found to be inversely associated with the risk of cardia stomach cancer [35, 36].

Industrial chemical exposure

Occupational exposure to dusty and high-temperature environments – as experienced by wood-processing and food-machine operators – has been associated with an increased risk of stomach cancer [37]. Working in other industries, including rubber manufacturing, coal mining, metal processing and chromium production, has also been associated with an elevated risk of this cancer [38, 39].

Family history and ethnicity

Inherited *mutations* of certain genes, particularly the glutathione S-transferase (GSTM1)-null *phenotype*, are associated with an increased risk of stomach cancer [40]. Certain *polymorphisms* of interleukin genes (IL-17 and IL-10) have also been associated with increased risk of stomach cancer, particularly in Asian populations. These polymorphisms may interact with *H. pylori* infection [41] and smoking tobacco [42] to affect cancer risk.

Pernicious anaemia

People with the autoimmune form of pernicious anaemia have an increased risk of stomach cancer [43, 44]. This form of pernicious anaemia involves the autoimmune destruction of parietal cells in the gastric mucosa [44, 45]. These cells produce intrinsic factor, a protein that is needed to absorb vitamin B_{12} from foods, so the resultant vitamin B_{12} deficiency hinders the production of fully functioning red blood cells.

Confounding. Smoking tobacco and *H. pylori* infection are possible *confounders* or *effect modifiers*.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.9**).

4.2.2.4 Pancreas

Definition. The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, *exocrine* and *endocrine*. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas produce *hormones* including *insulin* and glucagon, which influence glucose metabolism.

Classification. Over 95 per cent of pancreatic cancers are *adenocarcinomas* of the exocrine pancreas, the type included in the CUP.

Other established causes. Other established causes of pancreatic cancer include the following:

Smoking tobacco, chewing tobacco and snuff

Smoking tobacco (or use of smokeless tobacco, sometimes called 'chewing tobacco' or 'snuff') is an established cause of pancreatic cancer, and approximately 22 per cent of deaths from pancreatic cancer are attributable to smoking tobacco [26].

Family history

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited *mutations*), although a family history increases risk, particularly where more than one family member is involved [46].

Confounding. Smoking tobacco is a possible *confounder*.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, See Evidence and judgements (**Section 5.1.2**).

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed.

4.2.2.5 Gallbladder

Definition. The gallbladder is a small sac-like organ that forms part of the biliary tract. *Bile*, produced in the liver, flows into the gallbladder, where it is stored and concentrated until released into the small intestine.

Classification. Approximately 90 to 95 per cent of gallbladder cancers are *adenocarcinomas*, whereas only a small proportion are *squamous cell carcinomas*.

Other established causes. Other established causes of gallbladder cancer include the following:

Gallstones

Having gallstones increases the risk of gallbladder cancer [47].

Ethnicity

A congenital deformity to the pancreatic ducts is associated with most gallbladder cancers in eastern Asia [48].

Confounding. Exposures with an apparent link to gallbladder cancer may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence. It is not yet possible to separate these effects.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.10**).

4.2.2.6 Liver

Definition. The liver is the largest internal organ in the body. It processes and stores nutrients and produces *cholesterol* and proteins such as albumin, clotting factors and the lipoproteins that carry cholesterol. It also secretes *bile* and performs many metabolic functions, including detoxification of several classes of *carcinogens*.

Classification. Most of the available data are on *hepatocellular carcinoma*, the best characterised and most common form of liver cancer. However, different outcomes are reported for unspecified primary liver cancer than for hepatocellular carcinoma and *cholangiocarcinoma* so the different types of liver cancer may be a cause of heterogeneity among the study results.

Other established causes. Other established causes of liver cancer include the following:

Disease

Cirrhosis of the liver increases the risk of liver cancer [49].

Medication

Long-term use of oral contraceptives containing high doses of *oestrogen* and *progesterone* increases the risk of liver cancer [50].

Infection

Chronic infection with the *hepatitis* B or C virus is a cause of liver cancer [51].

Smoking tobacco

Smoking tobacco increases the risk of liver cancer generally, but there is a further increase in risk among people who smoke and have the hepatitis B or hepatitis C virus infection and also among people who smoke and consume large amounts of alcohol [52, 53]. It is estimated that 14 per cent of deaths worldwide from liver cancer are attributable to smoking tobacco [26].

Confounding. Smoking tobacco and hepatitis B and C viruses are possible *confounders* or *effect modifiers*.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.3**).

The Panel is aware that alcohol is a cause of *cirrhosis*, which predisposes to liver cancer. Studies identified as focusing exclusively on patients with hepatic cirrhosis (including only patients with cirrhosis), hepatitis B or C viruses, alcoholism or history of alcohol abuse were not included in the CUP.

4.2.2.7 Colon and rectum

Definition. The *colon* (large intestine) is the lower part of the intestinal tract, which extends from the *caecum* (an intraperitoneal pouch) to the rectum (the final portion of the large intestine that connects to the anus).

Classification. Approximately 95 per cent of colorectal cancers are *adenocarcinomas*. Other types of colorectal cancers include *mucinous carcinomas* and *adenosquamous carcinomas*. *Carcinogens* can interact directly with the cells that line the colon and rectum.

Other established causes. Other established causes of colorectal cancer include the following:

Other diseases

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of, and so may be seen as a cause of, colon cancer [54].

Smoking tobacco

There is an increased risk of colorectal cancer in people who smoke tobacco. It has been estimated that 12 per cent of cases of colorectal cancer are attributable to smoking cigarettes [55].

Family history

Based on twin studies, up to 45 per cent of colorectal cancer cases may involve a heritable component [56]. Between five and 10 per cent of colorectal cancers are consequences of recognised hereditary conditions [57]. The two major ones are *familial* adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.

Confounding. Smoking tobacco is a possible *confounder*. In postmenopausal women, *menopausal hormone therapy (MHT)* use decreases the risk of colorectal cancer and is a potential confounder.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.4**).

4.2.2.8 Breast

Definition. Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts and connective tissue. Breast tissue develops in response to *hormones* such as *oestrogens*, *progesterone*, *insulin* and growth factors. The main periods of development are during puberty, pregnancy and *lactation*. The glandular tissue atrophies after *menopause*.

Classification. Breast cancers are almost all *carcinomas* of the *epithelial* cells lining the breast ducts (the channels in the breast that carry milk to the nipple). Fifteen per cent of breast cancers are lobular carcinoma (from lobes); most of the rest are ductal carcinoma. Although breast cancer can occur in men, it is rare (less than one per cent of cases) and thus is not included in the CUP.

Breast cancers are classified by their receptor type; that is, to what extent the cancer cells have receptors for the sex hormones oestrogen and progesterone, and the growth factor human epidermal growth factor (hEGF), which can affect the growth of the breast cancer cells. Breast cancer cells that have oestrogen receptors are referred to as oestrogen-receptor-positive (ER-positive), while those containing progesterone receptors are called progesterone-receptor-positive (PR-positive) cancers, and those with receptors for hEGF are HER2-receptor-positive (HER2-positive). Hormone-receptor-positive cancers are the most common subtypes of breast cancer but vary by population (60 to 90 per cent of cases). They have a relatively better prognosis than hormone-receptor-negative cancers, which are likely to be of higher pathological grade and can be more difficult to treat.

Most data come from *high-income countries*. Breast cancer is hormone related, and factors that modify risk may have different effects on cancers diagnosed in the pre and postmenopausal periods.

Due to the importance of menopausal status as an *effect modifier*, studies should stratify for *menopause* status, but many do not. Breast cancer is now recognised as a heterogeneous disease, with several subtypes according to hormone receptor status or molecular intrinsic markers. Although there is growing evidence that these subtypes have different causes, most studies have limited statistical power to evaluate effects by subtype.

There is growing evidence that the impact of *obesity* and dietary exposures on the risk of breast cancer may differ according to these particular molecular subtypes of cancer, but currently there is no information on how nutritional factors might interact with these characteristics.

Other established causes. Other established causes of breast cancer include the following:

Life events

Early *menarche* (before the age of 12), late natural *menopause* (after the age of 55), not bearing children and first pregnancy over the age of 30 all increase lifetime exposure to oestrogen and progesterone and the risk of breast cancer [58–60]. The reverse also applies: late menarche, early menopause, bearing children and pregnancy before the age of 30 all reduce the risk of breast cancer [58, 59].

Because nutritional factors such as obesity can influence these life course processes, their impact on breast cancer risk may depend on the maturational stage at which the exposure occurs. For instance, obesity before menopause is associated with reduced breast cancer risk, probably due to reduced ovarian progesterone production, while in postmenopausal women, in whom ovarian oestrogen production is low, obesity increases breast cancer risk by increasing production of oestradiol through the action of aromatase in *adipose tissue*.

Radiation

Exposure to ionising radiation from medical treatment such as X-rays, particularly during puberty, increases the risk of breast cancer [61, 62].

Medication

MHT (containing oestrogen or progesterone) increases the risk of breast cancer [63]. Oral contraceptives containing both oestrogen and progesterone also cause a small increased risk of breast cancer in young women, among current and recent users only [64].

Family history

Some inherited mutations, particularly in BRCA1, BRCA2 and p53, result in a very high risk of breast cancer. However, germline mutations in these genes are infrequent and account for only two to five per cent of all cases of breast cancer [65].

Confounding. Use of MHT is an important possible *confounder* or *effect modifier* in postmenopausal breast cancer. High-quality studies adjust for age, number of reproductive cycles, age at which children were born and the use of hormone-based medications.

For more detailed information on *adjustments* made in CUP analyses, see Evidence and judgements adult body fatness (**Sections 5.1.5** and **5.1.13**), body fatness in young adulthood (**Sections 5.2.1** and **5.2.2**) and adult weight gain (**Section 5.3.1**).

4.2.2.9 Ovary

Definition. The ovaries are the sites of ovum (egg) production in women. They are also the main source of the *hormones oestrogen* and *progesterone* in premenopausal women.

Classification. Cancers may arise from three types of ovarian tissue: *epithelial* cells, which cover the ovary; stromal cells, which produce hormones; and *germ cells*, which become ova (eggs). About 85 to 90 per cent of ovarian cancers are epithelial *carcinomas* [66]. Because ovarian cancer is hormone related, factors that modify risk might have different effects at different times of life.

Other established causes. Other established causes of ovarian cancer include the following:

Life events

The risk of ovarian cancer is affected by the number of menstrual cycles during a woman's lifetime [67–69]. Not bearing children, early *menarche* (before the age of 12) and late natural *menopause* (after the age of 55) all increase the risk of ovarian cancer [45–47]. The reverse also applies: bearing children, late menarche and early menopause all reduce the risk of ovarian cancer [45–47]. Tubal ligation (sterilisation) also decreases the risk of ovarian cancer [70].

Medication

Oral contraceptives protect against ovarian cancer [71]. Use of *menopausal oestrogen hormone therapy* has been shown to increase risk.

Smoking tobacco

Smoking tobacco increases the risk of *mucinous ovarian cancer* [53]. It is estimated that 17 per cent of mucinous ovarian cancer cases are due to smoking tobacco [72].

Family history

Most ovarian cancers occur spontaneously, although five to 10 per cent of cases develop due to a genetic predisposition [73]. The latter, involving dysfunctional BRCA1 or BRCA2 genes produces high-grade carcinomas, with poorer prognosis [74].

Confounding. Including data on women who were at high risk of ovarian cancer who have had oophorectomies (surgical removal of one or both ovaries) may have influenced the results of some studies.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.11**).

Tumour heterogeneity. There is growing evidence that different histologic subtypes of ovarian cancer have different aetiologies and clinical courses. However, most studies lack the statistical power to evaluate associations by histologic subtype [75].

4.2.2.10 Endometrium

Definition. The endometrium is the lining of the uterus (womb). It is subject to a process of cyclical change during the fertile years of a woman's life.

Classification. The majority of cancers that occur in the body of the uterus are endometrial cancers, mostly *adenocarcinomas* [66]. Because endometrial cancer is *hormone* related, factors that modify risk might have different effects at different times of life.

Other established causes. Other established causes of endometrial cancer include the following:

Life events

Not bearing children and late natural *menopause* (after the age of 55) both increase the risk of endometrial cancer [76]. The reverse also applies: bearing children and early menopause both reduce the risk of endometrial cancer [71, 77–80].

Medication

Oral contraceptives, which contain either a combination of *oestrogen* and *progesterone*, or progesterone only, protect against endometrial cancer [80, 81]. Menopausal oestrogen hormone therapy unaccompanied by progesterone is a cause of this cancer. Menopausal oestrogen-only hormone therapy is normally prescribed only to women who have had a hysterectomy [80, 81]. Tamoxifen, a hormonal therapy used for breast cancer, can also increase the risk of endometrial cancer.

Family history

Women with a family history of endometrial or colorectal cancer have a higher risk of endometrial cancer [82]. Lifetime risk of endometrial cancer in women with Lynch syndrome *mutations* MLH1 or MSH2 is approximately 40 per cent, with a median age of 49. Women with MSH6 mutations have a similar risk of endometrial cancer but a later age of diagnosis [83].

Confounding. Including data on women who were at high risk of endometrial cancer who have had hysterectomies may have influenced the results. MHT is an *effect modifier*; in women who have never used MHT, there is a stronger association between BMI and endometrial cancer than in women who have ever used it [84].

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.6**).

4.2.2.11 Cervix

Infection with a carcinogenic HPV type is found in women with cervical cancer; however, most infections with HPV do not lead to cancer. The role of any other factors is to enhance risk of infection, integration and/or persistence.

Definition. The cervix is the neck of the womb. The part of the cervix inside the cervical canal is called the endocervix. The part on the outside is the ectocervix. Most cervical cancers start where these two parts meet.

Classification. Approximately 80 per cent of cervical cancers are *squamous cell carcinomas*, with the majority of the rest being *adenocarcinomas*.

Other established causes. Other established causes of cervical cancer include the following:

Life events

Early sexual experience and a relatively high number of sexual partners increase the risk and severity of HPV infection and may be seen as indirect causes of cervical cancer [58, 59].

Smoking tobacco

Smoking tobacco increases the risk of cervical cancer. It is estimated that two per cent of deaths from cervical cancer worldwide are attributable to smoking tobacco [26]. The effect of smoking tobacco is independent to that of viral infection.

Infectious agents

Infection with a carcinogenic HPV type is a necessary, but not sufficient, cause of cervical cancer [85]. Virtually all cervical cancers are associated with a carcinogenic HPV type [85]. Women become susceptible to developing cervical cancer following infection with a carcinogenic HPV type, but other environmental factors are required for the cancer to develop [86].

Medication

Dethylstilboestrol (a synthetic *oestrogen*, now withdrawn) used by women during pregnancy is a cause of vaginal and cervical clear-cell adenocarcinoma in their daughters [87].

Confounding. Smoking tobacco is a possible *confounder*.

4.2.2.12 Prostate

Definition. The prostate is a walnut-sized gland in men that surrounds the top of the urethra just below the bladder outlet; it produces seminal fluid. Male hormones, such as testosterone, control its growth and function.

Classification. Almost all cases of prostate cancer are *adenocarcinoma*, a glandular *malignancy*. The clinical course and natural history of diagnosed prostate cancer vary considerably. Although prostate cancer can spread locally and metastasise, and may be fatal, many men, especially at older ages, are found to have previously undetected and presumably asymptomatic prostate cancers at autopsy.

There are several ways of characterising prostate cancers according to grade (aggression) or stage. The term 'advanced' prostate cancer is sometimes employed in epidemiologic studies and is variably defined as higher grade, later stage, presence of *metastatic* disease or death. Further research is needed to better define the biological potential of newly diagnosed prostate cancer.

In the CUP, advanced prostate cancer is defined as cancers reported in any of the following ways:

- stage 3–4 in the American Joint Committee on Cancer (AJCC) 1992 classification
- advanced cancer
- advanced or metastatic cancer
- metastatic cancer
- stage C or D on the Whitmore/Jewett scale
- fatal cancer (prostate specific mortality)
- high stage or grade
- Gleason grade ≥ 7

Other established causes. Other established causes of prostate cancer include the following:

Family history and ethnicity

Approximately nine per cent of all prostate cancers may result from heritable susceptible genes [88]. Genetic susceptibility has been linked to African heritage and familial disease [89]. In the USA, African American men are 1.6 times more likely to develop prostate cancer than Caucasian men. A large number of single-nucleotide *polymorphisms* that modestly affect risk has also been identified [90].

Confounding. Screening for prostate cancer is a potential *confounder* or *effect modifier*.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.12**).

Prostate-specific antigen (PSA) screening. Prostate cancer leads to an elevated blood concentration of PSA. Although it is highly sensitive for prostate cancer, it is not specific. Levels may be raised due to non-malignant disease, for example, benign prostatic *hyperplasia*. Furthermore, when only modestly raised, PSA alone cannot be used to distinguish between early stage or indolent tumours (which may never be of clinical significance) and more aggressive or later stage cancers.

Cancers detected at an older age with indolent features can be monitored by a process called active surveillance. Consequently, studies of the natural history of screen-detected cancers, and of prostate cancers generally in screened populations, will be dominated by the behaviour of the more common but less clinically relevant low-grade or indolent tumours. In some populations, such as in the USA, PSA screening is widely used. However, in other populations, such as in Europe, PSA screening is less common. The number of cases of prostate cancer identified by PSA screening is not consistently reported in studies, and few report epidemiological results based on the grade or stage of cancer detected.

4.2.2.13 Kidney

Definition. The kidneys are a pair of organs located at the back of the abdomen outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureters.

Classification. Different subtypes of kidney cancer likely have different aetiologies, yet some epidemiologic studies do not distinguish the *clear cell* subtype, the predominant parenchymal renal cancer, from *papillary* or other subtypes. Cancers of the renal pelvis are typically *transitional cell carcinomas*, which probably share aetiologic risk factors such as smoking tobacco with other transitional cell carcinomas of the ureter and bladder.

Other established causes. Other established causes of kidney cancer include the following:

Smoking tobacco

Smoking tobacco is a cause of kidney cancer. People who smoke have a 52 per cent increased risk of kidney cancer, and people who used to smoke have a 25 per cent increased risk, compared with those who have never smoked [91].

Medication

Painkillers containing phenacetin are known to cause cancer of the renal pelvis. Phenacetin is no longer used as an ingredient in painkillers [92].

Kidney disease

Polycystic kidney disease predisposes people to developing kidney cancer [93].

Hypertension

High blood pressure is associated with a higher risk of kidney cancer [94].

Family history

Inherited genetic predisposition accounts for only a minority of kidney cancers [95]. Von Hippel-Lindau syndrome is the most common, with up to 40 per cent of those inheriting the mutated gene developing kidney cancer [96].

Confounding. Smoking tobacco is a possible *confounder*.

For more detailed information on *adjustments* made in CUP analyses on adult body fatness, see Evidence and judgements (**Section 5.1.7**).

5. Evidence and judgements

For information on study types, methods of assessment of exposures and methods of analysis used in the CUP, see Judging the evidence.

Full systematic literature reviews (SLRs) for each cancer are available online. For most cancer sites considered in the CUP,[1] there is also a CUP cancer report. CUP cancer reports summarise findings from the SLRs, again focusing on a specific cancer site. This section also presents findings from the SLRs, but from a different perspective: it brings together all of the key findings on body fatness and weight gain and the risk of cancer.

Note that, throughout this section, if *Egger's test*, *non-linear analysis* or stratified analyses are not mentioned for a particular exposure and cancer, it can be assumed that no such analyses were conducted. This is often because there were too few studies with the required information.

5.1 Adult body fatness

Table 5.1 summarises the main findings from the CUP *dose–response meta-analyses* of *cohort studies* on adult body fatness. Measures of adult body fatness presented in this section include body mass index (BMI), waist circumference, waist-hip ratio and weight gain.

Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[2]: nasopharynx (2017), oesophagus (squamous cell carcinoma; 2016), lung (2017), stomach (non-cardia; 2016), prostate (non-advanced; 2014), bladder (2015) and skin (2017).

[1] Cancers at the following sites are reviewed in the CUP: mouth, pharynx and larynx; nasopharynx; oesophagus; lung; stomach; pancreas; gallbladder; liver; colorectum; breast; ovary; endometrium; cervix; prostate; kidney; bladder; and skin. CUP cancer reports not are currently available for nasopharynx, cervix and skin.

[2] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

Table 5.1: Summary of CUP dose–response meta-analyses of adult body fatness and the risk of cancer

Cancer	Measure	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% confidence intervals [CI])	Increment	I^2 (%)	Conclusion[1]	Date of CUP cancer report[2]
Oesophagus (*adenocarcinoma*)	BMI	9	9	1,725	1.48 (1.35–1.62)	5 kg/m^2	37	**Convincing: Increases risk**	2016
	Waist circumference	2	2	335	1.34 (1.17–1.52)	10 cm	10		
	Waist-hip ratio	3	3	380	1.38 (1.10–1.73)	0.1 unit	27		
Pancreas	BMI (cancer incidence)	30	23	9,504	1.10 (1.07–1.14)	5 kg/m^2	19	**Convincing: Increases risk**	2012
	BMI (cancer mortality)	30	7	8,869	1.10 (1.02–1.19)	5 kg/m^2	61		
	Waist circumference	5	5	949	1.11 (1.05–1.18)	10 cm	0		
	Waist-hip ratio	4	4	1,047	1.19 (1.09–1.31)	0.1 unit	11		
Liver	BMI	15	12	14,311	1.30 (1.16–1.46)	5 kg/m^2	78	**Convincing: Increases risk**	2015
Colorectum	BMI	57	38	71,089	1.05 (1.03–1.07)	5 kg/m^2	74	**Convincing: Increases risk**	2017
	Waist circumference	13	8	4,301	1.02 (1.01–1.03)	10 cm	0		
	Waist-hip ratio	6	4	2,564	1.02 (1.01–1.04)	0.1 unit	17		
Breast (postmenopause)[3]	BMI	156	56	80,404	1.12 (1.09–1.15)	5 kg/m^2	74	**Convincing: Increases risk**	2017
	Waist circumference	27	11	14,033	1.11 (1.09–1.13)	10 cm	0		
	Waist-hip ratio	29	18	15,643	1.10 (1.05–1.16)	0.1 unit	60		
Endometrium[4]	BMI	34	26	18,717	1.50 (1.42–1.59)	5 kg/m^2	86	**Convincing: Increases risk**	2013
	BMI (age 18 to 25 years)	8	7	3,476	1.42 (1.22–1.66)	5 kg/m^2	79		
	Weight gain	5	5	1,971	1.16 (1.10–1.22)	5 kg	66		
	Waist circumference	4	4	1,641	1.13 (1.08–1.18)	5 cm	71		
	Waist-hip ratio	5	5	2,330	1.21 (1.13–1.29)	0.1 unit	0		

Cancer	Measure	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% confidence intervals [CI])	Incre-ment	I^2 (%)	Conclusion[1]	Date of CUP cancer report[2]
Kidney	BMI	28	23	15,575	1.30 (1.25–1.35)	5 kg/m^2	39	**Convincing: Increases risk**	2015
	Waist circumfer-ence	3	3	751	1.11 (1.05–1.19)	10 cm	0		
	Waist-hip ratio	4	3	751	1.26 (1.18–1.36)	0.1 unit	0		
Mouth, pharynx and larynx[5]	BMI	20	20	796	1.15 (1.06–1.24)	5 kg/m^2	–	**Probable: Increases risk**	2018
Stomach (cardia)	BMI	10	7	2,050	1.23 (1.07–1.40)	5 kg/m^2	56	**Probable: Increases risk**	2016
Gallbladder[6]	BMI	11	8	6,004	1.25 (1.15–1.37)	5 kg/m^2	52	**Probable: Increases risk**	2015
Ovary[4,7]	BMI	26	25	15,899	1.06 (1.02–1.11)	5 kg/m^2	55	**Probable: Increases risk**	2014
Prostate (advanced)[8]	BMI	24	23	11,149	1.08 (1.04–1.12)	5 kg/m^2	19	**Probable: Increases risk**	2014
	Waist circumfer-ence	5	4	1,781	1.12 (1.04–1.21)	10 cm	15		
	Waist-hip ratio	4	4	1,781	1.15 (1.03–1.28)	0.1 unit	0		
Cervix[4,9]	BMI	10	9	5,144	1.02 (0.97–1.07)	5 kg/m^2	69	**Limited – suggestive: Increases risk**	2017
Breast (premeno-pause)[3]	BMI	128	37	16,371	0.93 (0.90–0.97)	5 kg/m^2	55	**Probable: Decreases risk**	2017
	Waist circumfer-ence	6	6	2,423	0.99 (0.95–1.04)	10 cm	0		
	Waist-hip ratio	11	11	3,465	1.06 (0.98–1.16)	0.1 unit	27		

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Body fatness and weight gain and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing', 'probable' and 'limited – suggestive'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

3 Evidence for the link between body fatness, weight gain and breast cancer is presented separately for the risk of pre and postmenopausal breast cancer because of the well-established effect modification by menopausal status.

4 There is no evidence of effect modification by menopausal status for body fatness and the risk of endometrial, ovarian or cervical cancer so the evidence for all women (irrespective of menopausal status) is presented together.

5 A dose–response meta-analysis of cohort studies could not be conducted in the CUP. Evidence is from a published pooled analysis of head and neck cancer of people who have never smoked [97].

6 Adult body fatness may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence to cause gallbladder cancer. It is not yet possible to separate these effects.

7 The effect of adult body fatness on the risk of ovarian cancer may vary according to tumour type, menopausal hormone therapy use and menopausal status.

8 The effect of adult body fatness on the risk of prostate cancer was observed in advanced, high-grade and fatal prostate cancers.

9 The conclusion for body fatness and cervical cancer was based on evidence for BMI ≥ 29 kg/m^2. No conclusion was possible for BMI < 29 kg/m^2.

The strong evidence on the effects of adult body fatness on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and/or other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

For more information on the evidence for adult body fatness and the risk of cancer that was graded by the Panel as 'limited – suggestive' and suggests a direction of effect, see the following CUP document:

- CUP cervical cancer SLR 2017: Section 8.1.1.

Also, for information on mechanisms that could plausibly influence the risk of cancer, see **Appendix 2**.

Please note that the information on mechanisms included in the following subsections and in the appendix supersedes that in CUP cancer reports published before this Third Expert Report.

5.1.1 Oesophagus (adenocarcinoma)

(Also see CUP oesophageal cancer report 2016: Section 7.7 and CUP oesophageal cancer SLR 2015: Sections 8.1.1, 8.2.1 and 8.2.3)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. For information on the risk of oesophageal *squamous cell carcinoma*, see the relevant sections from the CUP oesophageal cancer report 2016 and the CUP oesophageal cancer SLR 2015.

[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

5.1.1.1 Body mass index

5.1.1.1.1 CUP dose–response meta-analyses

All nine identified studies were included in the dose–response meta-analysis, which showed a statistically significant 48 per cent increased risk of oesophageal *adenocarcinoma* per 5 kg/m^2 increase in BMI (*relative risk* [RR] 1.48 [95% CI 1.35–1.62]; n = 1,725 cases) (see **Figure 5.1**). Moderate *heterogeneity* was observed (I^2 = 37%), and there was no evidence of small study bias with *Egger's test* (p = 0.69).

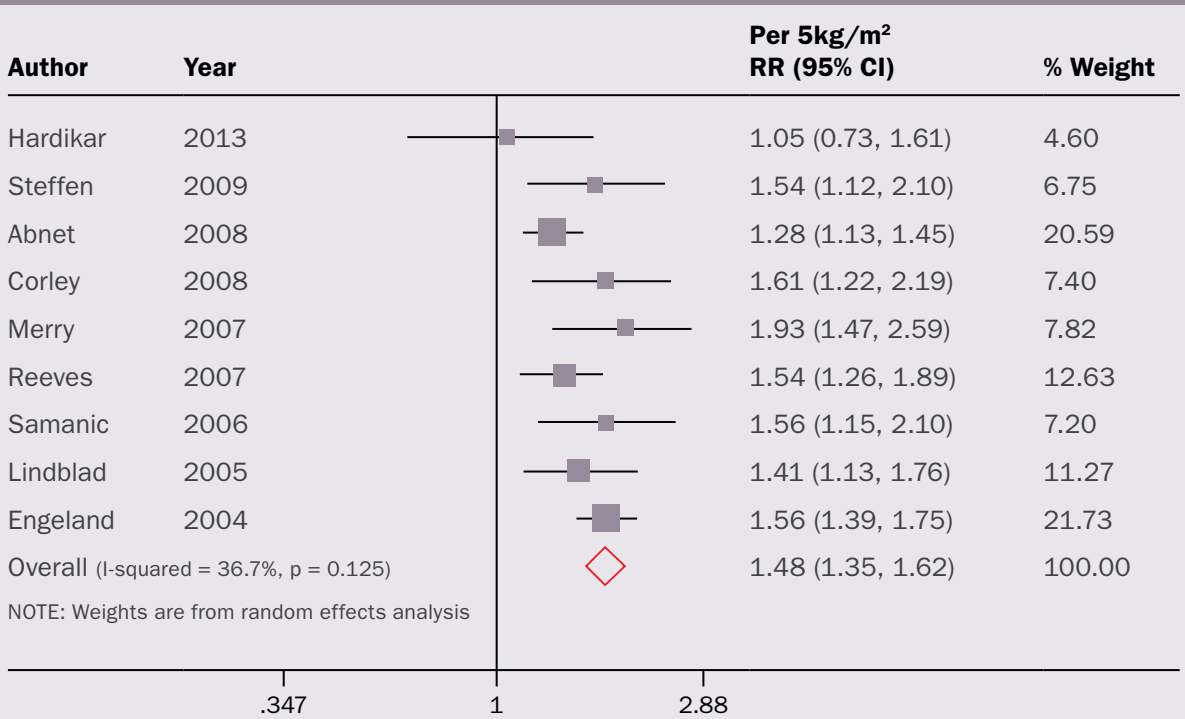
Stratified analyses for the risk of oesophageal adenocarcinoma per 5 kg/m^2 increase in BMI were conducted for sex, geographic location and tobacco smoking. For details of other stratified analyses that have been conducted, see CUP oesophageal cancer SLR 2015, Section 8.1.1.

When stratified by sex, a statistically significant increased risk was observed for men (RR 1.56 [95% CI 1.39–1.74]) and women (RR 1.48 [95% CI 1.29–1.71]; see CUP oesophageal cancer SLR 2015, Figure 81). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.56 [95% CI 1.44–1.69]) and North America (RR 1.32 [95% CI 1.10–1.57]; see CUP oesophageal cancer SLR 2015, Figure 84). When stratified by tobacco smoking, a significant increased risk was observed for people who do not smoke (RR 1.62 [95% CI 1.23–2.13]; see CUP oesophageal cancer report 2016, Figure 4).

There was no evidence of a non-linear dose–response relationship (p = 0.07).

All studies included in the dose–response meta-analysis adjusted or accounted for age and sex, most also adjusted for tobacco smoking. In addition, some studies adjusted for alcohol consumption. For information on the adjustments made in individual studies, see CUP oesophageal cancer SLR 2015, Table 74.

Figure 5.1: CUP dose–response meta-analysis for the risk of oesophageal adenocarcinoma, per 5 kg/m^2 increase in body mass index



Source: Hardikar, 2013 [98]; Steffen, 2009 [99]; Abnet, 2008 [100]; Corley, 2008 [101]; Merry, 2007 [102]; Reeves, 2007 [103]; Samanic, 2006 [104]; Lindblad, 2005 [105]; Engeland, 2004 [106].

5.1.1.1.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* (see **Table 5.2**) and four other published meta-analyses on BMI and the risk of oesophageal adenocarcinoma were identified. Both published pooled analyses [107, 108] reported a statistically significant increased risk in dose–response meta-analyses, consistent with the CUP. All four published meta-analyses also reported a significant increased risk in dose–response and in highest compared with lowest meta-analyses [109–112] (see CUP oesophageal cancer SLR 2015, Table 73).

When the studies identified in the CUP (but not in the pooled analysis) were combined with the results of the pooled analysis of the Me-Can project (European cohorts) [107], a significant increased risk of oesophageal adenocarcinoma per 5 kg/m^2 increase in BMI was observed (RR 1.51 [95% CI 1.38–1.65]; n = 1,839 cases).

5.1.1.2 Waist circumference

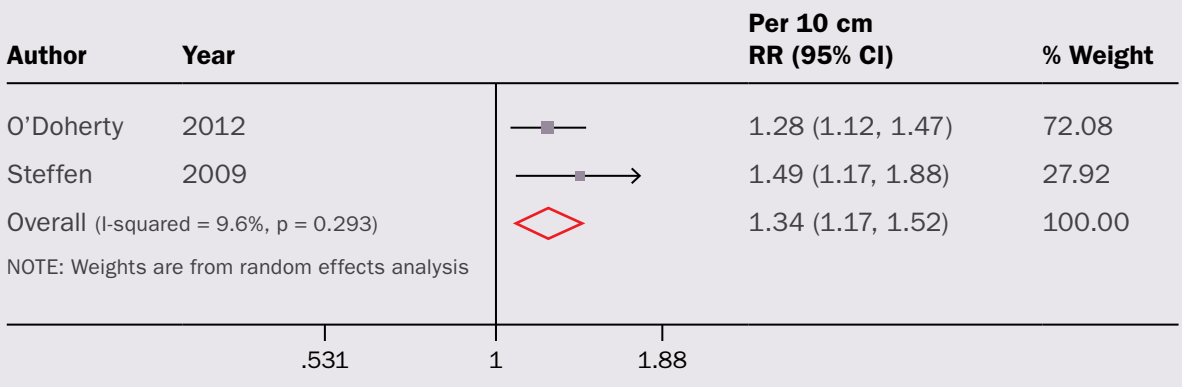
5.1.1.2.1 CUP dose–response meta-analysis

Both studies identified were included in the dose–response meta-analysis, which showed a statistically significant 34 per cent increased risk of oesophageal adenocarcinoma per 10 centimetre increase in waist circumference (RR 1.34 [95% CI 1.17–1.52]; n = 335 cases) (see **Figure 5.2**). Low *heterogeneity* was observed (I^2 = 10%).

Table 5.2: Summary of published pooled analyses of body mass index and the risk of oesophageal adenocarcinoma

Publication	Increment	RR (95% CI)	I^2 (%)	No. of studies	No. of cases
Me-Can [107]	5 kg/m^2	1.78 (1.45–2.17)	–	7 cohort	114
BEACON Consortium [108]	1 kg/m^2	1.09 (1.06–1.12)	76	2 cohort, 10 case-control	1,897

Figure 5.2: CUP dose–response meta-analysis for the risk of oesophageal adenocarcinoma, per 10 centimetre increase in waist circumference



Source: O'Doherty, 2012 [113]; Steffen, 2009 [99].

One published study that was included in the dose–response meta-analysis [99] analysed data by tobacco smoking; a statistically significant increased risk was observed in people who smoke for the highest compared with the lowest BMI (RR 4.14 [95% CI 1.14–15.10]). No significant association was observed in people who do not smoke.

Both studies included in the dose–response meta-analysis adjusted for age, sex, tobacco smoking and alcohol consumption. For full information on the *adjustments* made in individual studies see CUP oesophageal cancer SLR 2015, Table 86.

5.1.1.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis of cohort and case-control studies on central *adiposity* (measured by abdominal fat accessed by computed tomography, waist circumference or waist-hip ratio) and the risk of oesophageal adenocarcinoma has been identified [114]. It reported a statistically significant increased risk when comparing the highest with the lowest level of central adiposity (RR 2.51 [95% CI 1.56–4.04]).

5.1.1.3 Waist-hip ratio

5.1.1.3.1 CUP dose–response meta-analysis

All three identified studies were included in the dose–response meta-analysis, which showed a statistically significant 38 per cent increased risk of oesophageal adenocarcinoma per 0.1 unit increase in waist-hip ratio (RR 1.38 [95% CI 1.10–1.73]; n = 380 cases) (see **Figure 5.3**). Low *heterogeneity* was observed (I^2 = 27%).

All studies included in the dose–response meta-analysis adjusted for age, sex and tobacco smoking; two studies also adjusted for alcohol consumption. For information on the *adjustments* made in individual studies, see CUP oesophageal cancer SLR 2015, Table 91.

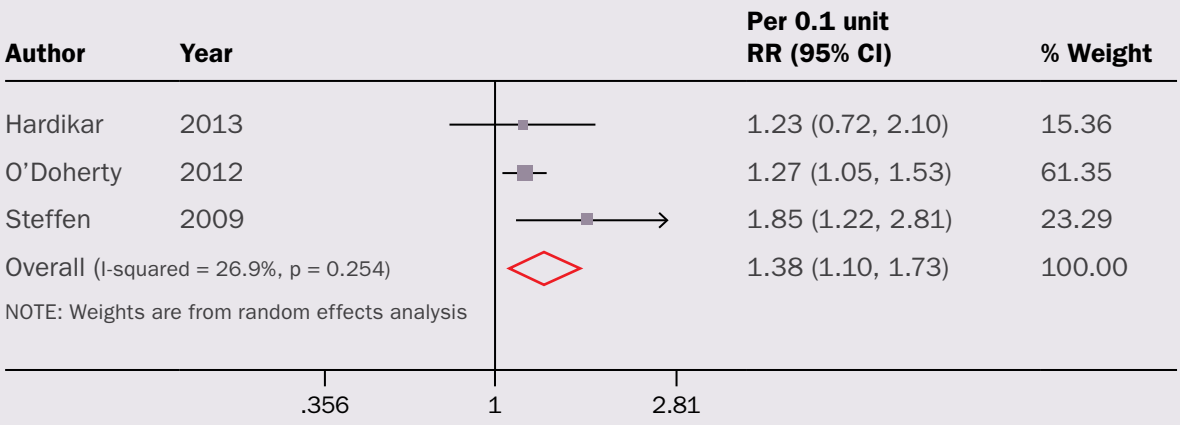
5.1.1.3.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. For information on the published meta-analysis of cohort and case-control studies on central *adiposity* [114], see **Section 5.1.1.2.2**.

5.1.1.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary

Figure 5.3: CUP dose–response meta-analysis for the risk of oesophageal adenocarcinoma, per 0.1 unit increase in waist-hip ratio



Source: Hardikar, 2013 [98]; O'Doherty, 2012 [113]; Steffen, 2009 [99].

hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Increased body fatness may promote *chronic* gastroesophageal reflux disease or *inflammation* of the oesophagus; this may lead to the development of Barrett's oesophagus, which has been shown to increase the risk of developing oesophageal adenocarcinoma [115]. Greater body fatness is also associated with higher circulating *insulin* levels and inflammation, both of which have been proposed as plausible mechanisms linking body fatness to cancers at other sites. However, to date there are limited data to support a direct link between elevated insulin or inflammation and oesophageal adenocarcinoma. Further research is needed to better understand the biological mechanisms that underlie the association of body fatness with oesophageal adenocarcinoma.

5.1.1.5 CUP Panel's conclusion

For oesophageal adenocarcinoma, the epidemiology was consistent, reflecting a graded increase in risk with increasing body fatness that is attributable to increased adiposity, for which plausible mechanisms in humans exist. The dose–response meta-analyses showed a statistically significant increased risk for BMI, waist circumference and waist-hip ratio and low or moderate heterogeneity was observed. There was no evidence of non-linearity for BMI.

A significant increased risk was observed for BMI in people who do not smoke, in men and women, and in Europe and North America. The CUP findings for BMI were supported by two published pooled analyses and other published meta-analyses, and some evidence of plausible mechanisms.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of oesophageal adenocarcinoma.**

5.1.2 Pancreas

(Also see CUP pancreatic cancer report 2012: Section 7.7 and CUP pancreatic cancer SLR 2011: Sections 8.1.1, 8.2.1 and 8.2.3)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. For information on BMI at age about 20 years and change in body composition (including weight gain), see CUP pancreatic cancer SLR 2011, Sections 8.1.1 and 8.1.6, respectively.

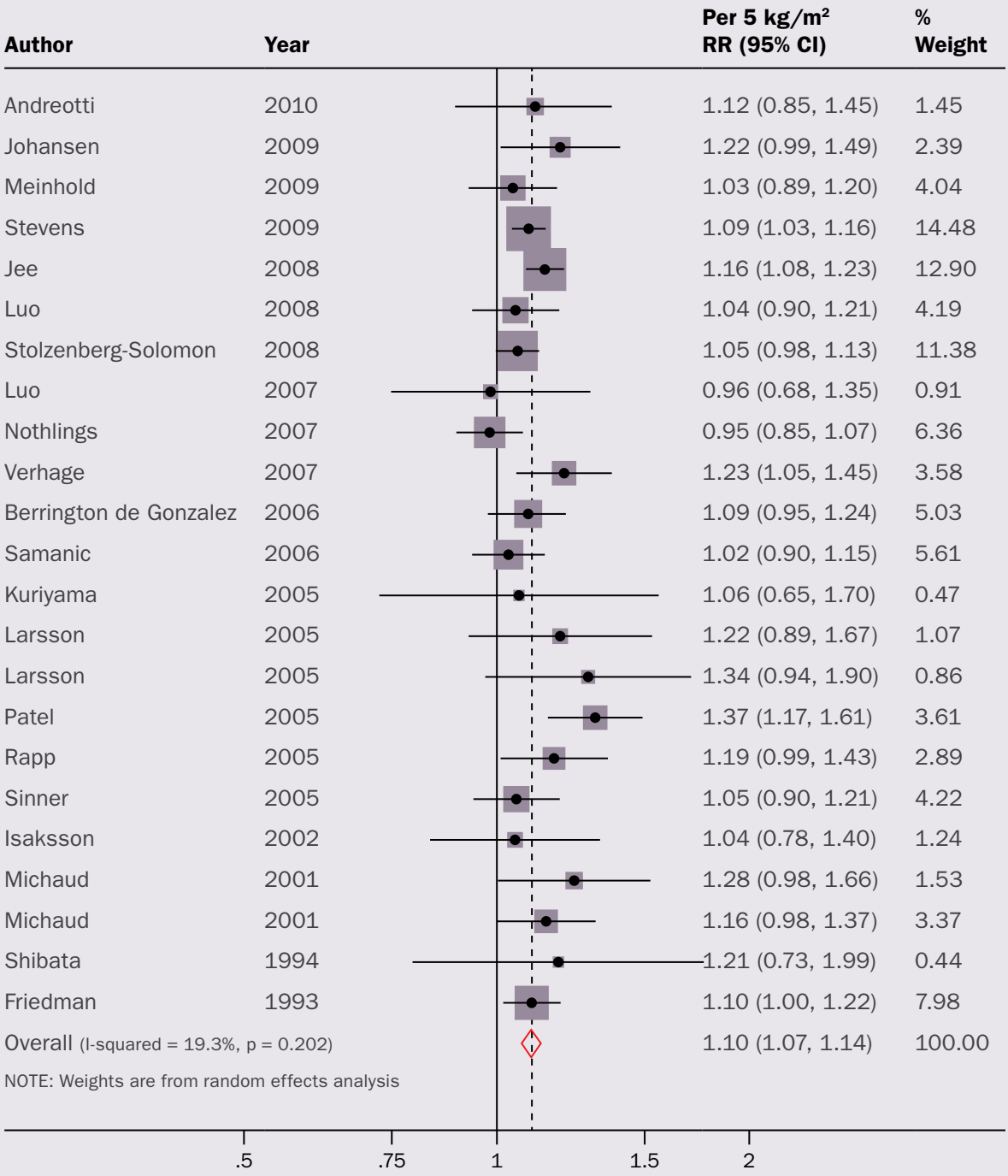
5.1.2.1 Body mass index

5.1.2.1.1 CUP dose–response meta-analyses

Twenty-three of 30 identified studies were included in the dose–response meta-analysis for pancreatic cancer incidence, which showed a statistically significant 10 per cent increased risk per 5 kg/m^2 increase in BMI (RR 1.10 [95% CI 1.07–1.14]; n = 9,504 cases) (see **Figure 5.4**). Low *heterogeneity* was observed (I^2 = 19%), and there was no evidence of small study bias with *Egger's test* (p = 0.36).

Seven of 30 identified studies reported on mortality and all were included in the dose–response meta-analysis for pancreatic cancer mortality, which showed a statistically significant 10 per cent increased risk per 5 kg/m^2 increase in BMI (RR 1.10 [95% CI 1.02–1.19]; n = 8,869 cases) (see **Figure 5.5**). High *heterogeneity* was observed (I^2 = 61%).

Figure 5.4: CUP dose–response meta-analysis[1] for the risk of pancreatic cancer incidence, per 5 kg/m² increase in body mass index



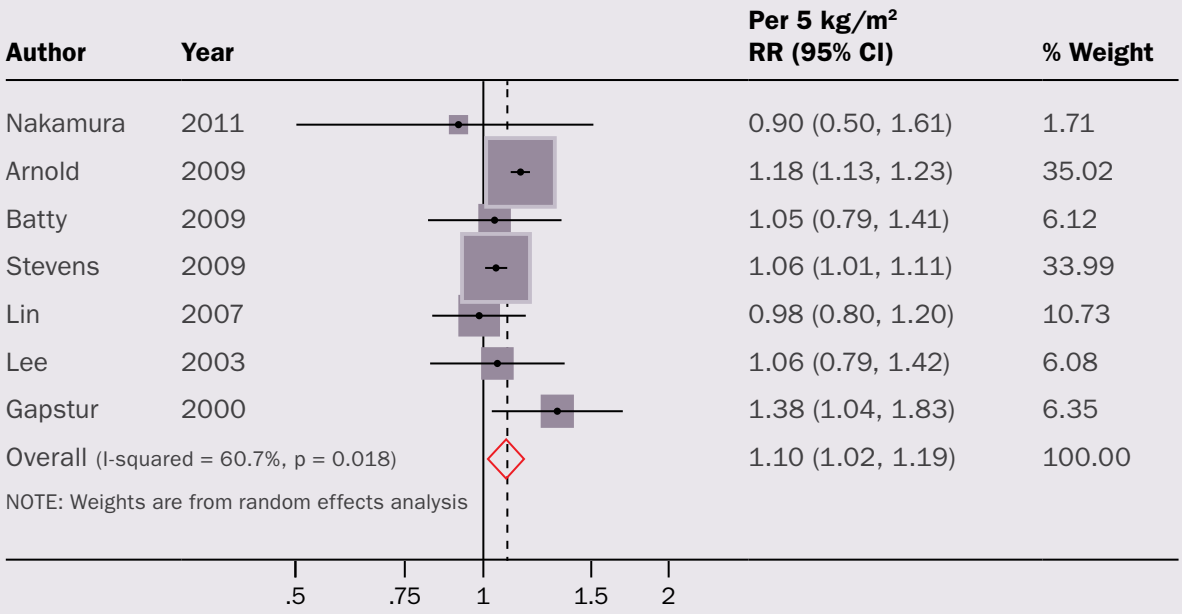
Source: Andreotti, 2010 [116]; Johansen, 2009 [117]; Meinhold, 2009 [118]; Stevens, 2009 [119]; Jee, 2008 [120]; Luo, 2008 [121]; Stolzenberg-Solomon, 2008 [122]; Luo, 2007 [123]; Nothlings, 2007 [124]; Verhage, 2007 [125]; Berrington de Gonzalez, 2006 [126]; Samanic, 2006 [104]; Kuriyama, 2005 [127]; Larsson, 2005 [128]; Patel, 2005 [129]; Rapp, 2005 [130]; Sinner, 2005 [131]; Isaksson, 2002 [132]; Michaud, 2001 [133]; Shibata, 1994 [134]; Friedman, 1993 [135].

A stratified analysis for pancreatic cancer incidence per 5 kg/m² increase in BMI was conducted for sex; a statistically significant increased risk was observed for both men (RR 1.13 [95% CI 1.04–1.22]) and women (RR 1.10 [95% CI 1.04–1.16]; see CUP pancreatic cancer SLR 2011, Figure 184). No analysis was possible for pancreatic cancer mortality.

[1] Larsson 2005 [128] and Michaud 2001 [133] reported separate RRs for two studies.

There was evidence of a non-linear dose–response relationship for pancreatic cancer incidence (p = 0.005; see **Figure 5.6**) and mortality (p = 0.0001; see **Figure 5.7**), with an increased risk apparent for a BMI greater or equal to 25 kg/m^2.

Figure 5.5: CUP dose–response meta-analysis[1] for the risk of pancreatic cancer mortality, per 5 kg/m^2 increase in body mass index



Source: Nakamura, 2011 [136]; Arnold, 2009 [137]; Batty, 2009 [138]; Stevens, 2009 [119]; Lin, 2007 [139]; Lee, 2003 [140]; Gapstur, 2000 [141].

Figure 5.6: CUP non-linear dose–response association of body mass index and the risk of pancreatic cancer incidence

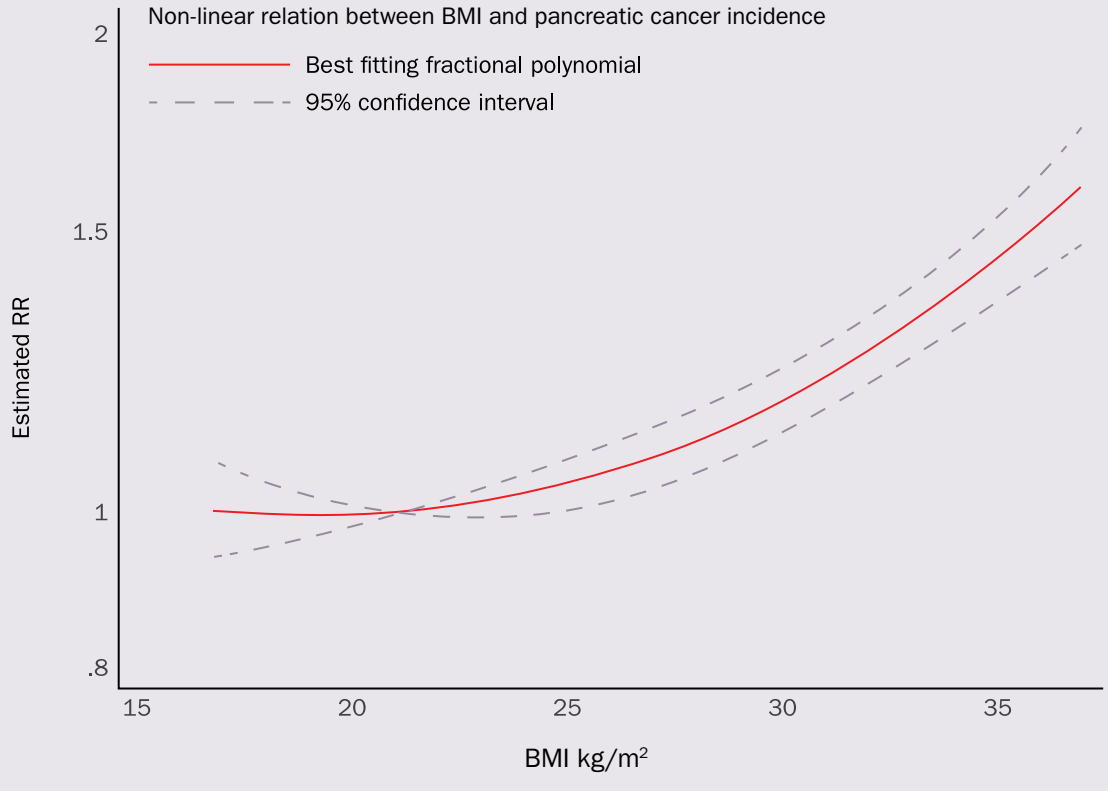
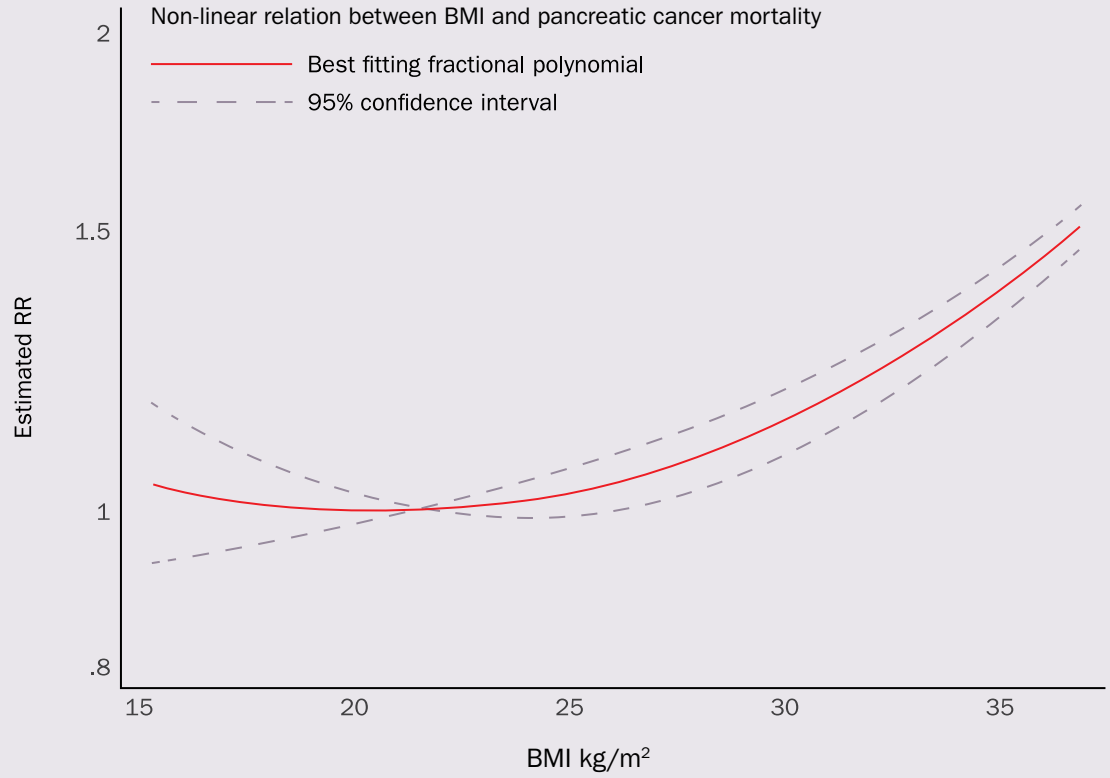


Figure 5.7: CUP non-linear dose–response association of body mass index and the risk of pancreatic cancer mortality



All studies included in the dose–response meta-analysis adjusted or accounted for age, sex and tobacco smoking.

5.1.2.1.2 Published pooled analyses and meta-analyses

Four published *pooled analyses* (see **Table 5.3**) and four other published meta-analyses on BMI and the risk of pancreatic cancer were identified. Results from three of the pooled analyses were consistent with the CUP [142–144] and showed a statistically significant increased risk in dose–response or highest compared with lowest meta-analyses. The fourth pooled analysis on pancreatic cancer mortality showed no significant association [145] but had fewer cases than the other published pooled analyses and the CUP meta-analysis.

All four published meta-analyses [110, 146–148] reported a significant increased risk of pancreatic cancer in dose–response meta-analyses of BMI (in one study the significant observation was only in women and in another study only in obese men and women; see CUP pancreatic cancer SLR 2011, Section 8.1.1).

Table 5.3: Summary of published pooled analyses of body mass index and the risk of pancreatic cancer

Publication	Increment/ contrast	RR (95% CI)	I^2 (%)	No. of studies	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [142]	5 kg/m^2	1.14 (1.07–1.21)	–	14 cohort	2,135 diagnoses
National Cancer Institute pooled analysis [144]	5 kg/m^2	1.08 (1.03–1.14)	0	7 cohort	2,454 diagnoses
Asia-Pacific Cohort Studies Collaboration [145]	5 kg/m^2	1.02 (0.83–1.25)	–	39 cohort	301 deaths
Pancreatic Cancer Cohort Consortium (PanScan) [143]	BMI > 35 vs 18.5–24.9 kg/m^2	1.55 (1.16–2.07)[1]	–	12 cohort, 1 case-control	2,095 diagnoses

5.1.2.2 Waist circumference

5.1.2.2.1 CUP dose–response meta-analysis

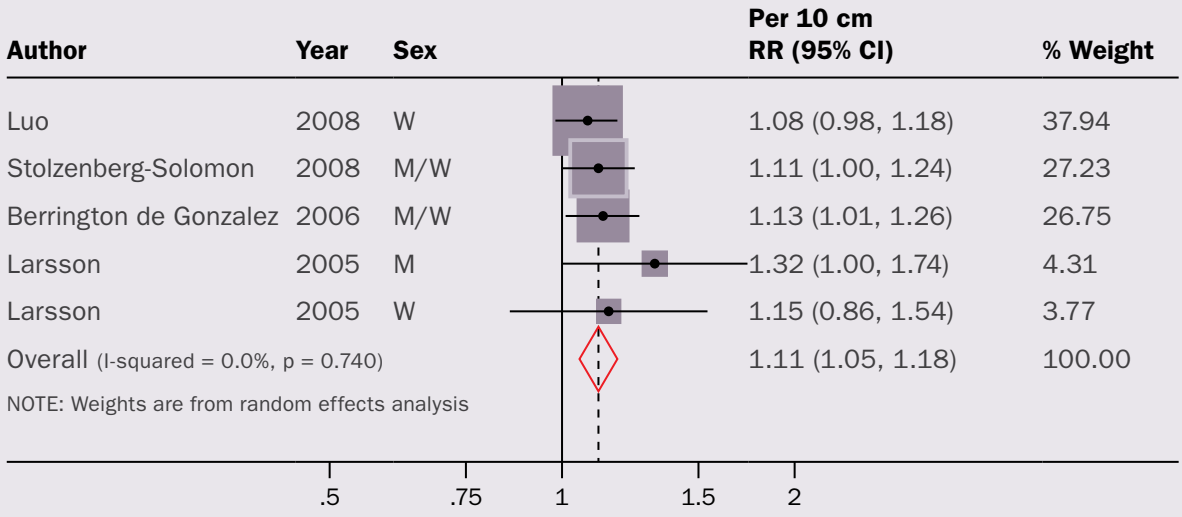
All five identified studies were included in the dose–response meta-analysis, which showed a statistically significant 11 per cent increased risk of pancreatic cancer per 10 centimetres increase in waist circumference (RR 1.11 [95% CI 1.05–1.18]; n = 949 cases) (see **Figure 5.8**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.11).

There was no evidence of a non-linear dose–response relationship (p = 0.28).

A stratified analysis for the risk of pancreatic cancer per 10 centimetres increase in waist circumference was conducted for sex; a statistically significant increased risk was observed for women (RR 1.14 [95% CI 1.02–1.28]) but not men; see CUP pancreatic cancer SLR 2011, Figure 204.

All studies included in the dose–response meta-analysis adjusted or accounted for age, sex and tobacco smoking.

Figure 5.8: CUP dose–response meta-analysis[2] for the risk of pancreatic cancer, per 10 centimetre increase in waist circumference



Source: Luo, 2008 [121]; Stolzenberg-Solomon, 2008 [122]; Berrington de Gonzalez, 2006 [126]; Larsson, 2005 [128].

[1] Risk was attenuated when adjusting for history of diabetes mellitus (RR 1.26 [95% CI 0.93–1.71]).
[2] Larsson 2005 [128] reported separate RRs for two studies.

Table 5.4: Summary of published pooled analyses of waist circumference and the risk of pancreatic cancer

Publication	Contrast	RR (95% CI)	I^2 (%)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [142]	Highest vs lowest	1.16 (0.92–1.46)	10	7	743
	Highest vs lowest (additionally adjusted for BMI)	1.04 (0.73–1.47)	26		
Pancreatic Cancer Cohort Consortium (PanScan) [143]	Highest vs lowest	1.23 (0.94–1.62) ptrend = 0.04	–	6	812

5.1.2.2.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* on waist circumference and the risk of pancreatic cancer were identified (see **Table 5.4**). No other published meta-analyses have been identified. Both pooled analyses reported no significant association for the highest compared with the lowest measure of waist circumference [142, 143]. However, one of the pooled analyses [143] reported a statistically significant positive trend with greater waist circumference (p_{trend} = 0.04). No single study was included in both pooled analyses and the CUP.

5.1.2.3 Waist-hip ratio

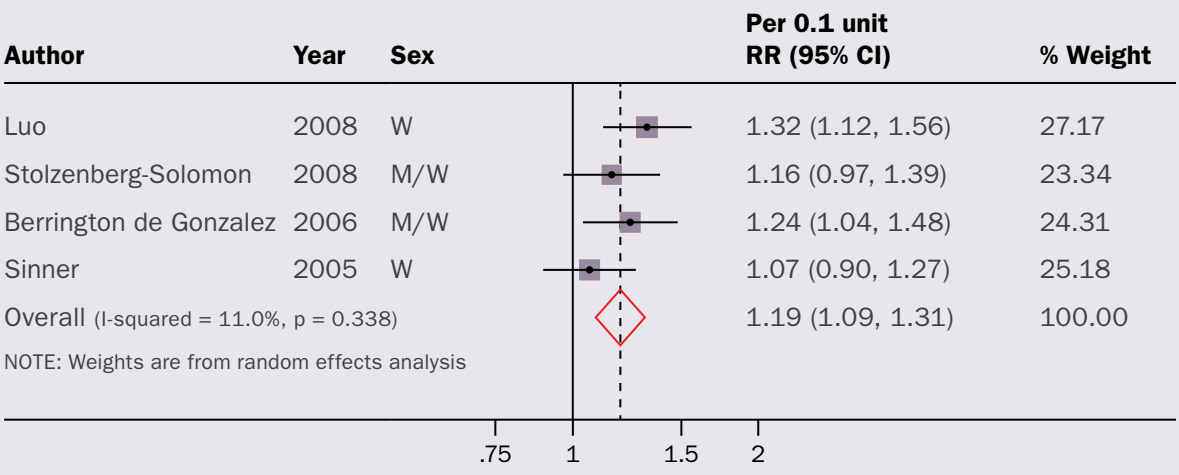
5.1.2.3.1 CUP dose–response meta-analyses

All four identified studies were included in the dose–response meta-analysis, which showed a statistically significant 19 per cent increased risk of pancreatic cancer per 0.1 unit increase in waist-hip ratio (RR 1.19 [95% CI 1.09–1.31]; n = 1,047 cases) (see **Figure 5.9**). Low *heterogeneity* was observed (I^2 = 11%).

There was no evidence of a non-linear dose–response relationship (p = 0.29).

All studies included in the dose–response meta-analysis adjusted or accounted for age, sex and tobacco smoking.

Figure 5.9: CUP dose–response meta-analysis for the risk of pancreatic cancer, per 0.1 unit increase in waist-hip ratio



Source: Luo, 2008 [121]; Stolzenberg-Solomon, 2008 [122]; Berrington de Gonzalez, 2006 [126]; Sinner, 2005 [131].

Table 5.5: Summary of published pooled analyses of waist-hip ratio and the risk of pancreatic cancer

Publication	Contrast	RR (95% CI)	I^2 (%)	No. of studies (cohort)	No. of cases
Pooling Project of Prospective Studies on Diet and Cancer [142]	Highest vs lowest	1.35 (1.03–1.78)	0	6	552
	Highest vs lowest (additionally adjusted for BMI)	1.34 (1.00–1.79)	0		
Pancreatic Cancer Cohort Consortium (PanScan) [143]	Highest vs lowest	1.71 (1.27–2.30)	–	6	750

5.1.2.3.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* on waist-hip ratio and the risk of pancreatic cancer were identified (see **Table 5.5**). No other published meta-analyses have been identified. Both pooled analyses reported a statistically significant increased risk for the highest compared with the lowest measure of waist-hip ratio [142, 143]. No single study was included in both the pooled analyses and the CUP.

5.1.2.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Body fatness may influence the development of pancreatic cancer through similar and diverse mechanisms purported to underlie its cancer-promotive role at other anatomical sites. Elevated *chronic inflammation* with activation of NF-kappaB signaling, increased production of pro-inflammatory *cytokines* and pancreatic infiltration of immunosuppressive cells have all been proposed as possible mechanisms [149–151]. In addition, higher body fatness has been associated with increased levels of hormones such as *insulin*, which can promote cell growth and inhibit *apoptosis*, and hence could be cancer promotive [152, 153]. A recent Mendelian randomisation analysis performed in a study of more than 7,000 pancreatic cancer cases and 7,000 controls found robust evidence for a strong association between genetic variants that determine higher body fatness and circulating insulin levels and pancreatic cancer risk, suggesting a causal role for body fatness in pancreatic cancer development [154].

5.1.2.5 CUP Panel's conclusion

Overall the evidence from the CUP for an association between body fatness was consistent, and there was a dose–response relationship. For BMI, low heterogeneity was observed for incidence and high heterogeneity was observed for mortality. Also for BMI there was evidence of a non-linear association with an increased risk apparent for a BMI greater or equal to 25 kg/m^2. Results from several published pooled analyses and other published meta-analyses were also consistent with the CUP findings.

The evidence for waist circumference and waist-hip ratio was less robust than BMI when used as the measure of body fatness but supports the evidence for an association between overall body fatness and pancreatic cancer risk. There is evidence for plausible mechanisms that operate in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of pancreatic cancer.**

5.1.3 Liver

(Also see CUP liver cancer report 2014: Section 7.6 and CUP liver cancer SLR 2014: Section 8.1.1.)

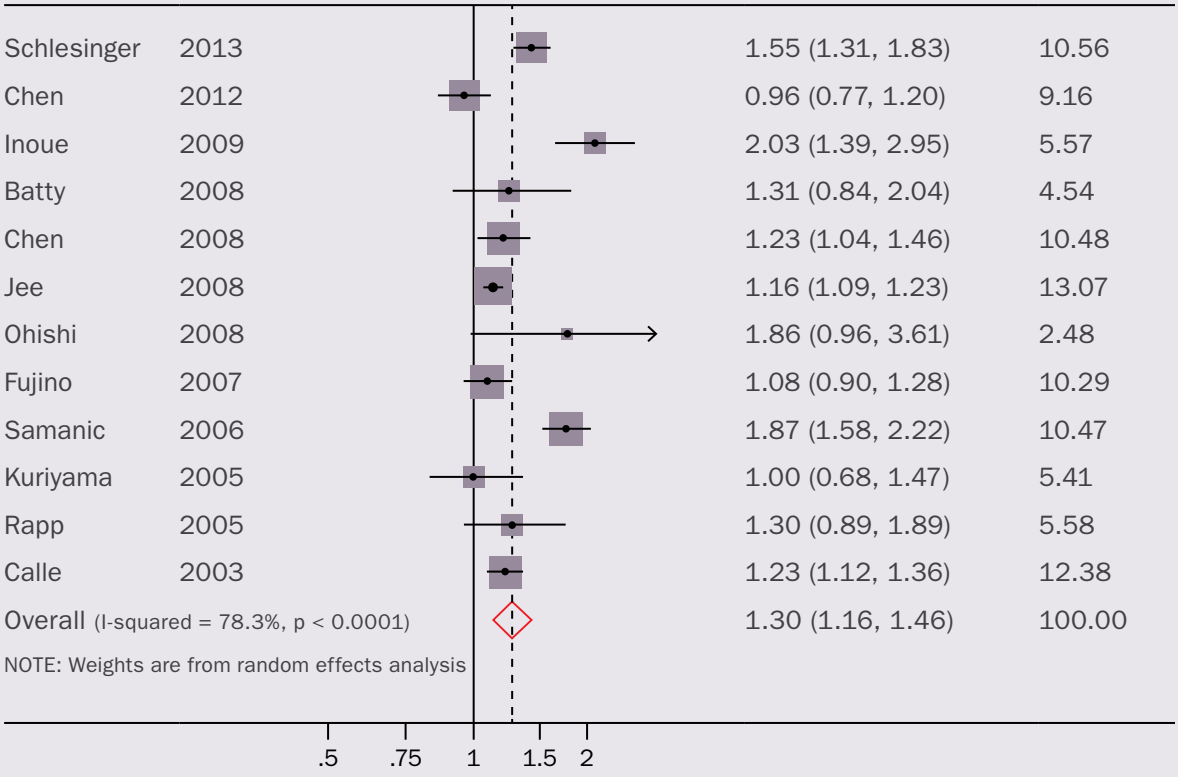
The evidence for BMI is presented in the following subsection.

5.1.3.1 Body mass index

5.1.3.1.1 CUP dose–response meta-analyses

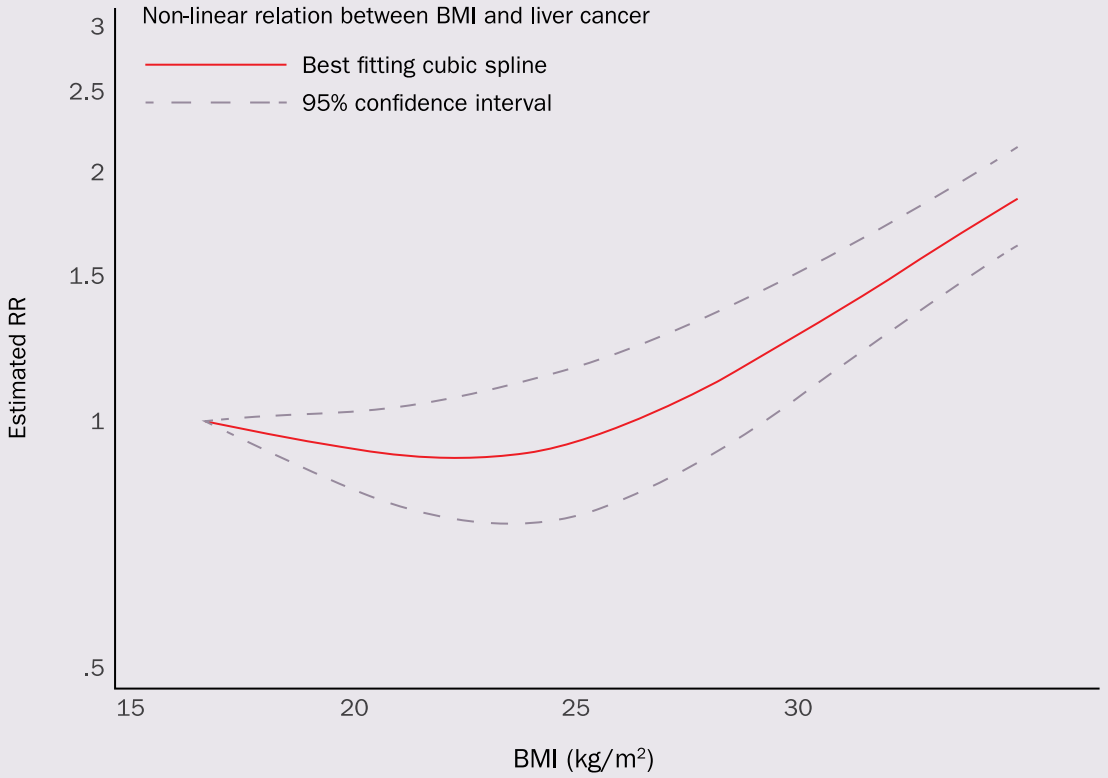
Twelve of 15 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 30 per cent increased risk of liver cancer per 5 kg/m^2 increase in BMI (RR 1.30 [95% CI 1.16–1.46]; n = 14,311 cases) (see **Figure 5.10**). High *heterogeneity* was observed (I^2 = 78%), which appeared to be mainly due to the size of the effect. There was no evidence of small study bias with *Egger's test* (p = 0.27).

Figure 5.10: CUP dose–response meta-analysis for the risk of liver cancer, per 5 kg/m^2 increase in body mass index



Source: Schlesinger, 2013 [156]; Chen, 2012 [155]; Inoue, 2009 [157]; Batty, 2008 [158]; Chen, 2008 [159]; Jee, 2008 [120]; Ohishi, 2008 [160]; Fujino, 2007 [161]; Samanic, 2006 [104]; Kuriyama, 2005 [127]; Rapp, 2005 [130]; Calle, 2003 [162].

Figure 5.11: CUP non-linear dose–response association of body mass index and the risk of liver cancer



Stratified analyses for the risk of liver cancer per 5 kg/m^2 increase in BMI were conducted for sex, geographic location and outcome.

When stratified by sex, a statistically significant increased risk was observed for both men (RR 1.21 [95% CI 1.02–1.44]) and women (RR 1.21 [95% CI 1.10–1.33]). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.59 [95% CI 1.35–1.87]) and Asia (RR 1.18 [95% CI 1.04–1.34]). When stratified by outcome, a significant increased risk was observed for liver cancer incidence (RR 1.43 [95% CI 1.19–1.70]), but not mortality (see CUP liver cancer report 2015, Table 5 and CUP liver cancer SLR 2014, Figures 54, 55 and 56).

There was evidence of a non-linear dose–response relationship ($p < 0.0001$; see **Figure 5.11**), with a steeper increase in risk at higher BMI levels (see CUP liver cancer SLR 2014, Figure 60 and Table 56).

All studies included in the dose–response meta-analysis adjusted or accounted for age and sex; all except for one adjusted for tobacco smoking [161].

Table 5.6: Summary of published pooled analyses of body mass index and the risk of liver cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Asia-Pacific Cohort Studies Collaboration [165]	≥ 25 vs 18.5–22.9 kg/m^2	1.27 (0.93–1.74)	44	420 deaths
Prospective Studies Collaboration [163]	5 kg/m^2	1.47 (1.26–1.71)	57	422 deaths
Asia-Pacific Cohort Studies Collaboration [145]	30–60 vs 18.5–24.9 kg/m^2	1.10 (0.63–1.91)	39	744 deaths
	5 kg/m^2	1.11 (0.63–1.91)		
European cohorts [164]	Highest vs lowest quintile (median) BMI 31.3 vs 20.7 kg/m^2	1.92 (1.23–2.96)	7	266 diagnoses

5.1.3.1.2 Published pooled analyses and meta-analyses

Four published *pooled analyses* (see **Table 5.6**) and five other published meta-analyses on BMI and the risk of liver cancer were identified. Two of the published pooled analyses reported a statistically significant increased risk in dose–response or highest versus lowest meta-analyses [163, 164]; the other two reported no significant association [145, 165]. The CUP included more liver cancer cases than any of the published pooled analyses.

Four of the published meta-analyses reported a significant increased risk of liver cancer in dose–response or highest versus lowest meta-analyses for BMI [155, 166–168] (see CUP liver cancer SLR 2014, Section 8.1.1). The other published meta-analysis reported no significant association [110].

5.1.3.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Although the exact mechanisms linking obesity and liver cancer development are still unclear, recent evidence supports a role for greater body fatness in the development of non-alcoholic fatty liver disease (NAFLD), which is strongly linked to metabolic syndrome and which can lead to a complex dysregulation of hepatic lipid metabolism. In its more aggressive forms, NAFLD can drive *inflammation* and hepatic tissue damage by increasing endoplasmic reticulum stress, elevating production of reactive oxygen species (increased oxidative stress), and higher inflammation [169, 170].

Body fatness is associated with host chronic inflammation and *insulin resistance* [171, 172] and may contribute to the hepatic dysfunction underlying this relationship. Obesity is associated with increased levels of pro-inflammatory *cytokines* (for example, TNF-alpha and IL-6) and *insulin*, which can promote *hepatocyte* growth and malignant transformation through activation of the oncogenic transcription factor Signal Transducer and Activator of Transcription-3 [173]. The resulting chronic liver injury due to

chronic inflammatory processes can promote compensatory hepatocyte injury, death, tissue remodeling and regeneration, which has been shown in animal models to be a necessary factor for liver cancer development [174, 175]. Animal studies also suggest that gut bacterial dysbiosis within the context of NAFLD may also propagate liver injury [176].

5.1.3.3 CUP Panel's conclusion

The evidence for BMI and the risk of liver cancer was consistent, and the dose–response relationship in the CUP showed a statistically significant increased risk. High heterogeneity was observed, which appeared to be mainly due to the size of the effect. A significant increased risk was still apparent when stratified by sex and geographic location. Results from several published pooled analyses and published meta-analyses were also generally consistent with the CUP findings. Non-linear analysis in the CUP showed a steeper increase in the risk of liver cancer at higher BMI levels. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI) is a convincing cause of liver cancer.**

5.1.4 Colorectum

(Also see CUP colorectal cancer report 2017: Section 7.14 and CUP colorectal cancer SLR 2016: Sections 8.1.1, 8.2.1 and 8.2.3)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections.

5.1.4.1 Body mass index

5.1.4.1.1 CUP dose–response meta-analyses

Thirty-eight of 57 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant five per cent increased risk of colorectal cancer per 5 kg/m^2 of BMI (RR 1.05 [95% CI 1.03–1.07]; n = 71,089 cases) (see **Figure 5.12**).

High *heterogeneity* was observed (I^2 = 74%), and there was no evidence of small study bias with *Egger's test* (p = 0.16). However, the funnel plot was asymmetric. Inspection of the funnel plot showed that the asymmetry was driven by smaller studies [177–179], a study in northern China [180] and the Japanese pooled analysis of eight cohorts [181] that reported a larger increased risk than the average (see CUP colorectal cancer SLR 2016, Figure 521).

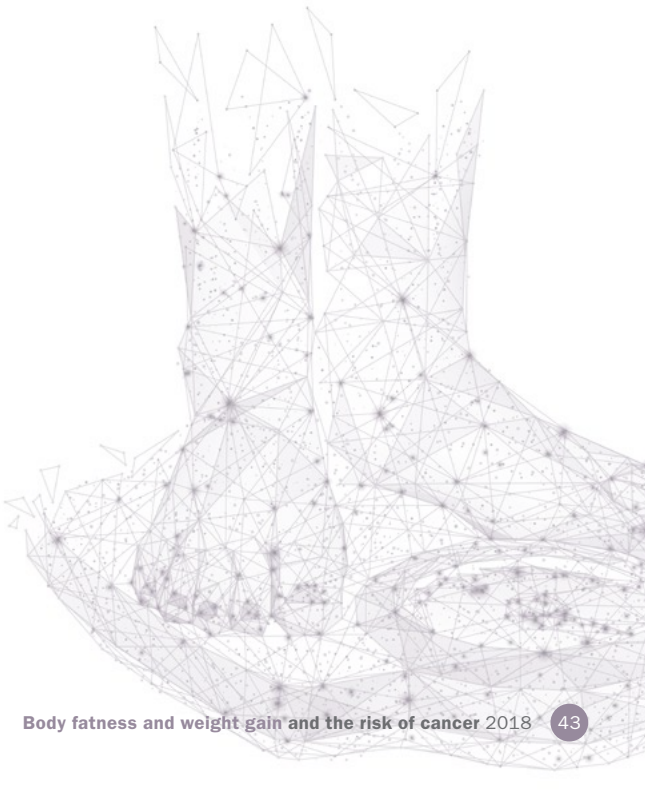
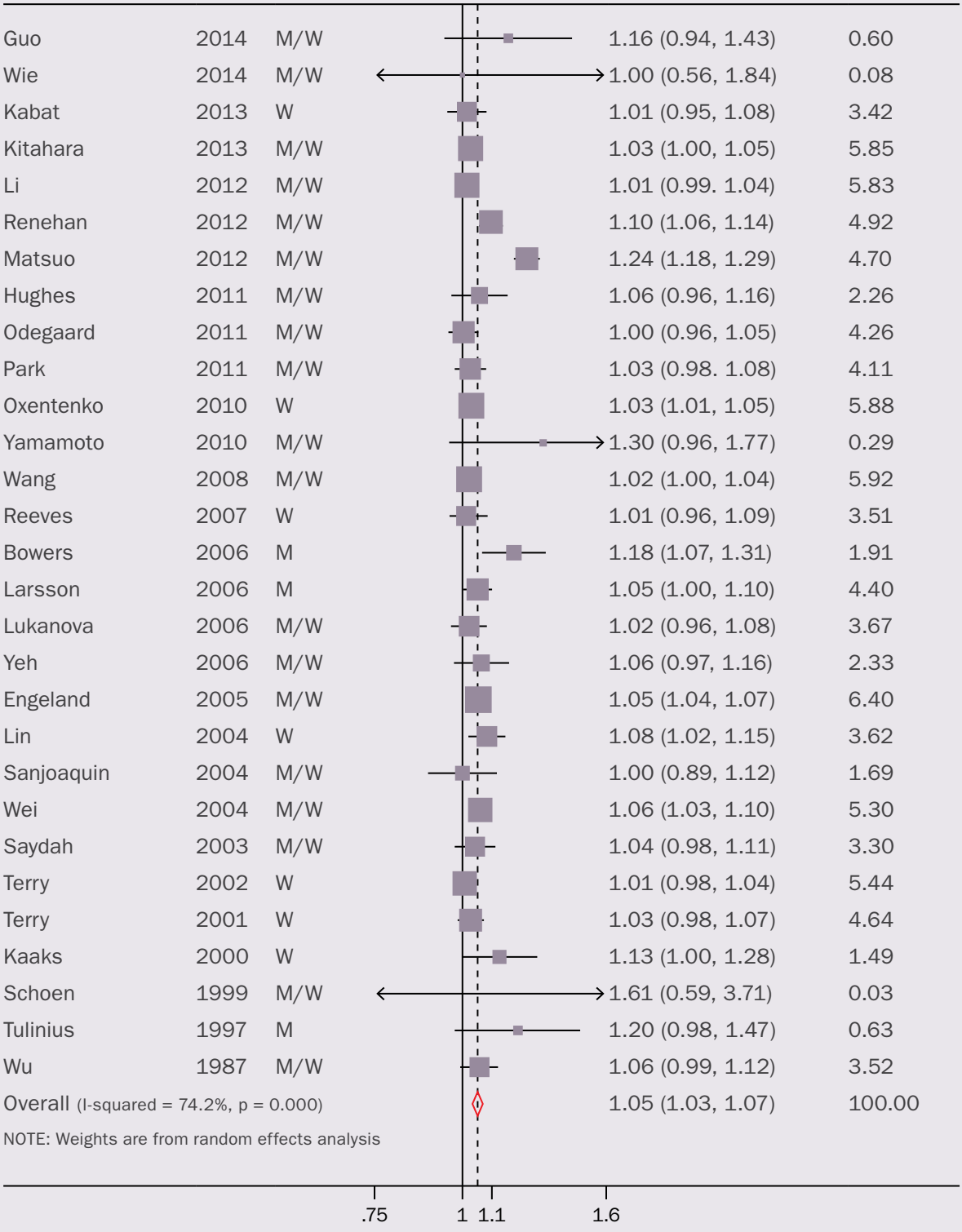


Figure 5.12: CUP dose–response meta-analysis[1,2] for the risk of colorectal cancer, per 5 kg/m² increase in body mass index



Source: Guo, 2014 [180]; Wie, 2014 [182]; Kabat, 2013 [183]; Kitahara, 2013 [184]; Li, 2012 [185]; Renehan, 2012 [186]; Hughes, 2011 [187]; Matsuo, 2012 [181]; Odegaard, 2011 [188]; Park, 2011 [189]; Oxentenko, 2010 [190]; Yamamoto, 2010 [179]; Wang, 2008 [191]; Reeves, 2007 [103]; Bowers, 2006 [192]; Larsson, 2006 [193]; Lukanova, 2006 [194]; Yeh, 2006 [195]; Engeland, 2005 [196]; Lin, 2004 [197]; Sanjoaquin, 2004 [198]; Wei, 2004 [199]; Saydah, 2003 [200]; Terry, 2002 [201]; Terry, 2001 [202]; Kaaks, 2000 [203]; Schoen, 1999 [178]; Tulinius, 1997 [177]; Wu, 1987 [204].

[1] Nineteen studies could not be included in the dose–response meta-analysis; two reported on gene mutations, three reported on specific populations or subtypes of colorectal cancer and 14 did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 323.

[2] The CUP dose–response meta-analysis included one pooled analysis (Matsuo, 2012 [181]), which included eight of the identified studies. For both Li, 2012 [185] and Wei, 2004 [199], the RR for two individual cohorts was reported in one single publication.

Stratified analyses for the risk of colorectal cancer per 5 kg/m^2 increase in BMI were conducted for sex, geographic location and cancer site. For details of other stratified analyses that have been conducted, see CUP colorectal cancer SLR 2016, Section 8.1.1.

When stratified by sex, a statistically significant increased risk was observed in both men (RR 1.08 [95% CI 1.04–1.11]) and women (RR 1.05 [95% CI 1.02–1.08]). When stratified by geographic location, a significant increased risk was observed in North America (RR 1.04 [95% CI 1.02–1.06]) and Europe (RR 1.05 [95% CI 1.03–1.06), but not Asia. When stratified by cancer site, a significant increased risk was observed for colon (RR 1.07 [95% CI 1.05–1.09]), proximal colon (RR 1.05 [95% CI 1.03–1.08]), distal colon (RR 1.08 [95% CI 1.04–1.11]) and rectal (RR 1.02 [95% CI 1.01–1.04]) cancer (see CUP colorectal cancer report 2017, Table 39 and CUP colorectal cancer SLR 2016, Figures 522, 523, 528, 533, 536 and 541).

There was evidence of a non-linear dose–response relationship ($p \leq 0.01$; see **Figure 5.13**). Colorectal cancer risk increased with greater BMI throughout the range observed; however, the increased risk appeared to be greater above 27 kg/m^2 (see CUP colorectal cancer report 2017, Table 38 and CUP colorectal cancer SLR 2016, Figure 525).

All studies included in the dose–response meta-analysis accounted or adjusted for age and sex, most adjusted for tobacco smoking and over half adjusted for alcohol consumption and physical activity. For information on the *adjustments* made in individual studies see CUP colorectal cancer SLR 2016, Table 322.

Figure 5.13: CUP non-linear dose–response association of body mass index and the risk of colorectal cancer

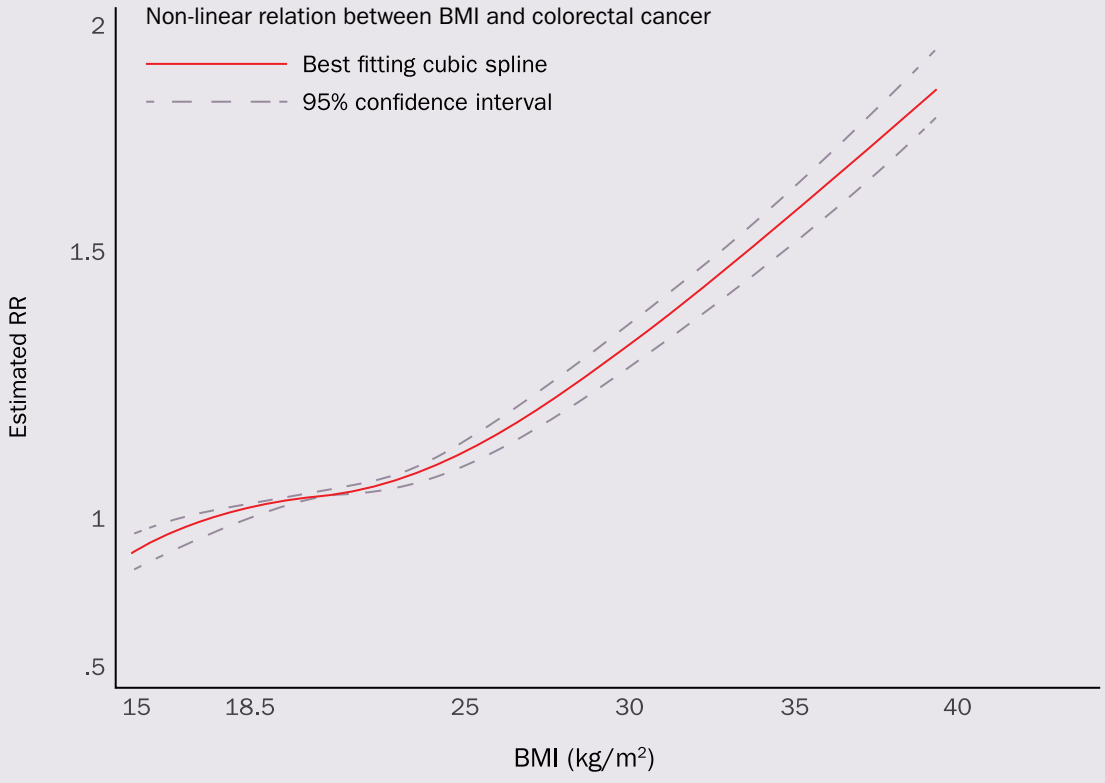
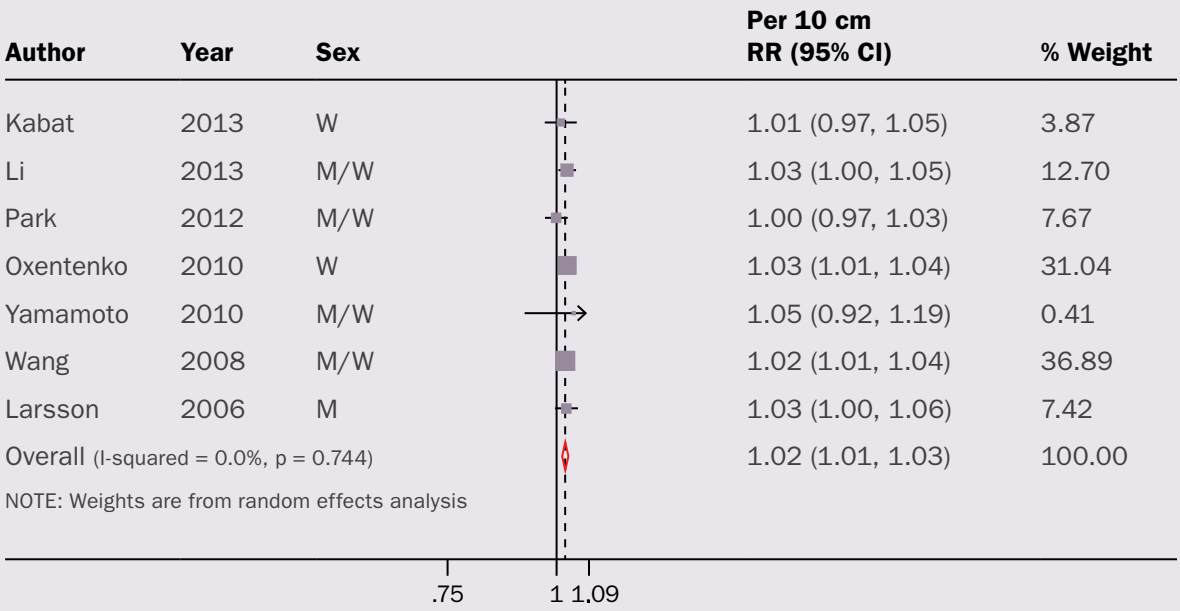


Figure 5.14: CUP dose–response meta-analysis[1,2] for the risk of colorectal cancer, per 10 centimetre increase in waist circumference



Source: Kabat, 2013 [183]; Li, 2013 [206]; Park, 2012 [207]; Oxentenko, 2010 [190]; Yamamoto, 2010 [179]; Wang, 2008 [191]; Larsson, 2006 [193].

5.1.4.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* and one other published meta-analysis on BMI and the risk of colorectal cancer were identified. The published pooled analysis of eight Japanese studies [181] showed a statistically significant increased risk per 1 kg/m^2 in both men and women separately and was included in the CUP dose–response meta-analysis. The published meta-analysis [205] reported a significant increased risk for obese BMI levels compared with normal BMI levels (RR 1.33 [95% CI 1.25–1.42]).

5.1.4.2 Waist circumference

5.1.4.2.1 CUP dose–response meta-analyses

Eight of 13 identified studies were included in the dose–response meta-analysis, which showed a statistically significant two per cent increased risk of colorectal cancer per 10 centimetre increase in waist circumference (RR 1.02 [95% CI 1.01–1.03]; n = 4,301 cases) (see **Figure 5.14**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.45).

Stratified analyses for the risk of colorectal cancer per 10 centimetre increase in waist circumference were conducted for sex, geographic location and cancer site.

When stratified by sex, a statistically significant increased risk was observed in women (RR 1.03 [95% CI 1.02–1.04]), but not men; see CUP colorectal cancer report 2017, Table 40 and CUP colorectal cancer SLR 2016, Figure 550). When stratified by geographic location, a significant increased risk was observed in North America (RR 1.02 [95% CI 1.01–1.03]) and Asia (RR 1.03 [95% CI 1.01–1.05]), but not Europe (see CUP colorectal cancer SLR 2016, Figure 551). When stratified by cancer site, a significant increased risk was observed for colon (RR 1.04 [95% CI 1.02–1.06]), but not

[1] Five studies could not be included in the dose–response meta-analysis; two reported on gene mutations and three did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 333.
[2] A total of eight studies was analysed in the CUP dose–response meta-analysis. Li, 2013 [206] reported the RR for two individual cohorts in a single publication.

rectal cancer (see CUP colorectal cancer report 2017, Table 40 and CUP colorectal cancer SLR 2016, Figures 554 and 561).

There was no evidence of a non-linear dose–response relationship (p = 0.17).

All studies included in the dose–response meta-analysis adjusted or accounted for age, sex and tobacco smoking. All except one [193] adjusted for alcohol consumption and all except one [179] adjusted for physical activity. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 332.

5.1.4.2.2 Published pooled analyses and meta-analyses

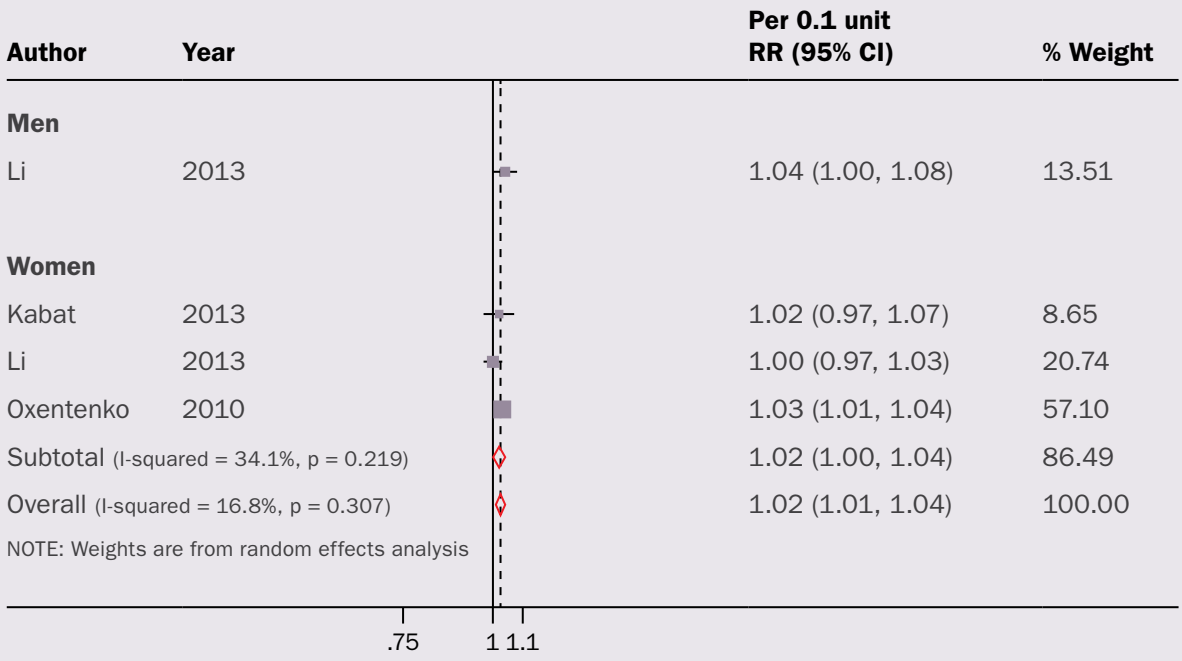
No published pooled analyses were identified. One other published meta-analysis on waist circumference and the risk of colorectal cancer has been identified [205]. It reported a statistically significant increased risk for the highest compared with the lowest measure of waist circumference (RR 1.45 [95% CI 1.33–1.60]).

5.1.4.3 Waist-hip ratio

5.1.4.3.1 CUP dose–response meta-analyses

Four of six identified studies were included in the dose–response meta-analysis, which showed a statistically significant two per cent increased risk of colorectal cancer per 0.1 unit increase in waist-hip ratio (RR 1.02 [95% CI 1.01–1.04]; n = 2,564 cases) (see **Figure 5.15**). Low *heterogeneity* was observed (I^2 = 17%), and there was no evidence of small study bias with *Egger's test* (p = 0.56).

Figure 5.15: CUP dose–response meta-analysis[1,2] for the risk of colorectal cancer, per 0.1 unit increase in waist-hip ratio



Source: Li, 2013 [206]; Kabat, 2013 [183]; Oxentenko, 2010 [190].

[1] Two studies could not be included in the dose–response meta-analysis; one reported on gene mutations and one did not provide sufficient information. For further details, see CUP colorectal cancer SLR 2016, Table 337.

[2] A total of four studies was analysed in the CUP dose–response meta-analysis. Li, 2013 [206] reported the RR for two individual cohorts in a single publication.

A stratified analysis for the risk of colorectal cancer per 0.1 unit increase in waist-hip ratio was conducted by cancer site; a statistically significant increased risk was observed for colon (RR 1.20 [95% CI 1.09–1.32]), but not rectal cancer.

All studies included in the dose–response meta-analysis adjusted or accounted for age, sex, tobacco smoking, alcohol consumption and physical activity. For information on the *adjustments* made in individual studies, see CUP colorectal cancer SLR 2016, Table 336.

5.1.4.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on waist-hip ratio and the risk of colorectal cancer were identified.

5.1.4.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Higher body fatness is associated with changes in hormonal profiles, such as increased levels of *insulin*, which can promote *colon* cancer cell growth and inhibit *apoptosis*. Higher serum concentrations of insulin and IGF-I have been linked to greater risk of colorectal cancer in human [208–210] and experimental studies [211, 212]. Body fatness also stimulates the body's inflammatory response, which can promote colorectal cancer development [213, 214]. Overall, there are convincing mechanistic data supporting a link between body fatness and colorectal cancer.

5.1.4.5 CUP Panel's conclusion

The evidence for colorectal cancer was consistent, with a clear dose–response relationship in the CUP showing a statistically significant increased risk with increased BMI; high *heterogeneity* was observed. There was evidence of a non-linear dose–response relationship, where the risk increase was higher above 27 kg/m^2 for colorectal cancer. The CUP findings for BMI were supported by one published meta-analysis. A significant increased risk was observed for colorectal cancer in the CUP dose–response analysis for waist circumference, supported by one published meta-analysis, and for waist-hip ratio. There is robust evidence for mechanisms in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of colorectal cancer.**

5.1.5 Breast (postmenopause)

(Also see CUP breast cancer report 2017: Section 7.9 and CUP breast cancer SLR 2017: Sections 8.1.1, 8.2.1 and 8.2.3.)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. For evidence on BMI in young adulthood and adult weight gain and postmenopausal breast cancer, see **Sections 5.2.2** and **5.3.1**, respectively. Of the 156 studies identified, 95 were included in the dose–response meta-analyses.

5.1.5.1 Body mass index

5.1.5.1.1 CUP dose–response meta-analyses

Fifty-six of 156 identified studies (including four *pooled analyses*) were included in the dose–response meta-analysis, which showed a statistically significant 12 per cent increased risk of postmenopausal breast cancer per 5 kg/m^2 increase in BMI for all incidence and mortality studies combined (RR 1.12 [95% CI 1.09–1.15]; n = 80,404 cases) (see **Figure 5.16**). High *heterogeneity* was observed (I^2 = 74%), which could be explained partly by geographic locations of the cohorts. There was evidence of small study bias with *Egger's test* (p = 0.03). Inspection of the funnel plot showed that more large-sized studies published an increased risk (see CUP breast cancer SLR 2017, Figure 547).

There was no evidence of a non-linear dose–response relationship (p = 0.08).

Stratified analyses for the risk of postmenopausal breast cancer per 5 kg/m^2 increase in BMI were conducted for geographic location, MHT use and breast cancer subtype. For details of other stratified analyses that have been conducted, see CUP breast cancer SLR 2017, Section 8.1.1.

When stratified by geographic location, a statistically significant increased risk was observed in North America (RR 1.10 [95% CI 1.08–1.12]) and Europe (RR 1.10 [95% CI 1.06–1.15]); a larger significant increased risk was observed in Asia (RR 1.37 [95% CI 1.24–1.50]; see CUP breast cancer report 2017, Table 17 and CUP breast cancer SLR 2017, Figure 548). When stratified by MHT use, a significant increased risk was observed among women who had never used MHT (RR 1.16 [95% CI 1.10–1.23]) and women who had never used or who had previously used MHT (RR 1.20 [95% CI 1.15–1.25]), but not in women who were currently using MHT or those who had ever used MHT (see CUP breast cancer report 2017, Table 17 and CUP breast cancer SLR 2017, Figure 552). When stratified by breast cancer subtype, a significant increased risk was observed with ER-positive (RR 1.17 [95% CI 1.09–1.25]), PR-positive (RR 1.47 [95% CI 1.36–1.60]) and joint ER-positive and PR-positive breast cancer (RR 1.29 [95% CI 1.19–1.40]), but not ER-negative or other joint hormone-receptor-defined breast cancers (see CUP breast cancer report 2017, Table 17 and CUP breast cancer SLR 2017, Figures 554 and 556).

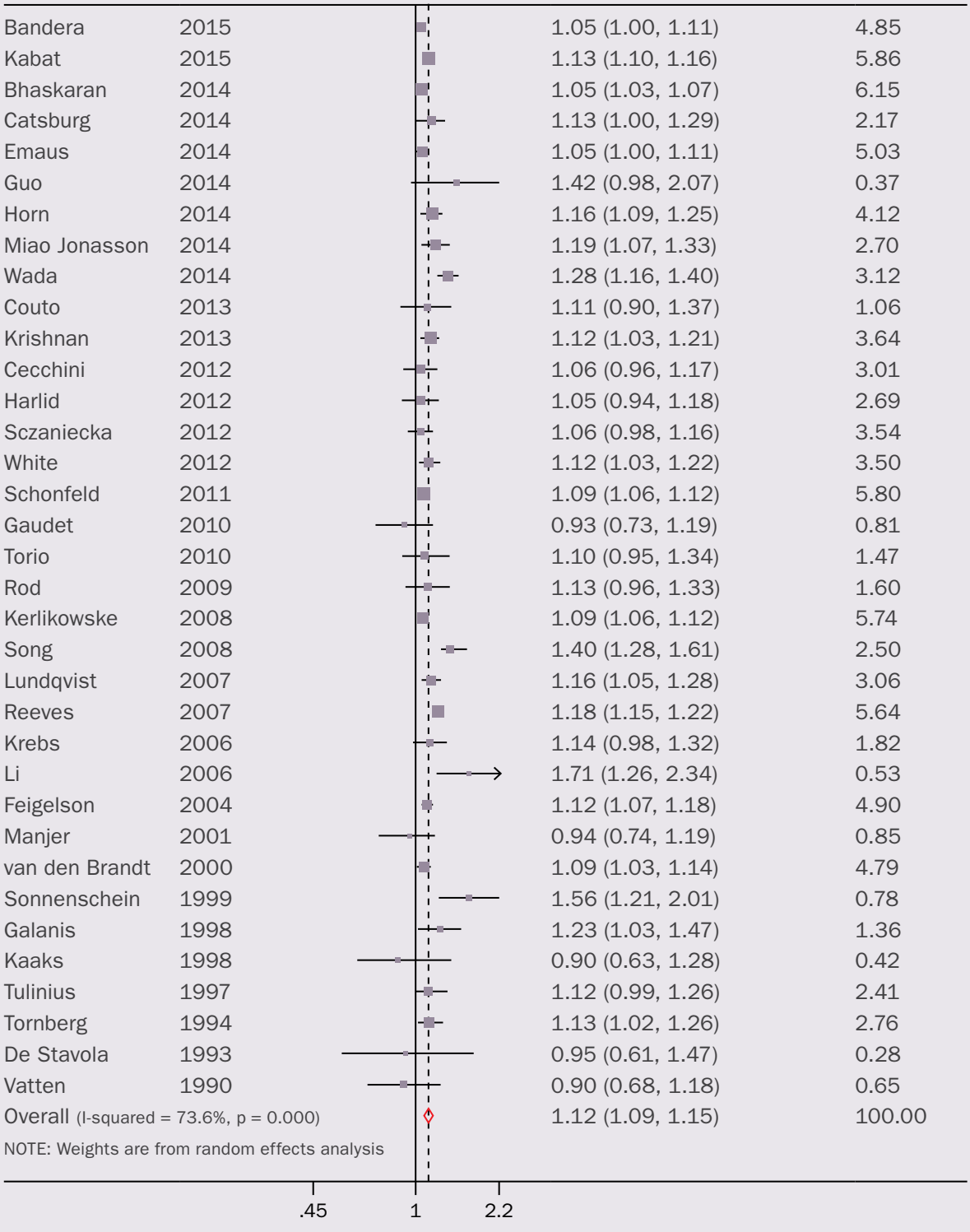
In a separate dose–response meta-analysis of the 38 studies on BMI and postmenopausal breast cancer mortality (including a pooled analysis of 35 studies) (n = 4,131 cases), a statistically significant increased risk of death from postmenopausal breast cancer was also observed (RR 1.20 [95% CI 1.13–1.27]) with evidence of moderate *heterogeneity* (I^2 = 49%; see CUP breast cancer SLR 2017, Figure 561).

About half of the studies included in the dose–response meta-analysis were simultaneously adjusted for age, alcohol intake, reproductive factors and MHT use. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 535.

5.1.5.1.2 Published pooled analyses and meta-analyses

Eight published *pooled analyses* and six other published meta-analyses on BMI and the risk of postmenopausal breast cancer were identified. Five of the pooled analyses were included in the CUP dose–response meta-analyses [163, 215, 222, 229, 240]; three of four pooled analyses showed a statistically significant increased risk per 5 kg/m^2 increase in BMI [222, 229, 240] as did the fifth pooled analysis, which looked only at mortality [163]. Results from the other three published pooled analyses are shown in **Table 5.7**.

Figure 5.16: CUP dose–response meta-analysis[1,2] for the risk of postmenopausal breast cancer, per 5 kg/m² increase in body mass index



Source: Bandera, 2015 [215]; Kabat, 2015 [216]; Bhaskaran, 2014 [217]; Catsburg, 2014 [218]; Emaus, 2014 [219]; Guo, 2014 [180]; Horn, 2014 [220]; Miao Jonasson, 2014 [221]; Wada, 2014 [222]; Couto, 2013 [223]; Krishnan, 2013 [224]; Cecchini, 2012 [225]; Harlid, 2012 [226]; Sczaniecka, 2012 [227]; White, 2012 [228]; Schonfeld, 2011 [229]; Gaudet, 2010 [230]; Torio, 2010 [231]; Rod, 2009 [232]; Kerlikowske, 2008 [233]; Song, 2008 [234]; Lundqvist, 2007 [235]; Reeves, 2007 [103]; Krebs, 2006 [236]; Li, 2006 [237]; Feigelson, 2004 [238]; Manjer, 2001 [239]; van den Brandt, 2000 [240]; Sonnenschein, 1999 [241]; Galanis, 1998 [242]; Kaaks, 1998 [243]; Tulinius, 1997 [177]; Tornberg, 1994 [244]; De Stavola, 1993 [245]; Vatten, 1990 [246].

[1] Sixty-one studies could not be included in any of the dose–response meta-analyses; four reported on an excluded exposure, one reported on a different subtype, 23 did not provide sufficient information and 33 overlapped with other studies included in the meta-analyses; e.g., some pooled analyses were excluded as some studies were common to other pooled analyses. For further details, see CUP breast cancer SLR 2017, Table 536.

[2] The CUP dose–response meta-analysis included four pooled analyses (Bandera, 2015 [215], Wada, 2014 [222], Schonfeld, 2011 [229], van den Brandt, 2000 [240]), which included 23 of the identified studies. For two studies [226, 245] the RR included data for two individual studies.

Table 5.7: Summary of published pooled analyses of body mass index and the risk of postmenopausal breast cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
The Metabolic Syndrome and Cancer Project (Me-Can) [253]	≥ 31.7 vs ≤ 20 kg/m^2		6	
	Incidence	0.87 (0.71–1.07)		1,106 diagnoses
	Mortality	0.92 (0.66–1.27)		219 deaths
Asia-Pacific Cohort Studies Collaboration (APCSC) [145]	Mortality		35	324 deaths
	30–60 vs 18.5–24.9 kg/m^2	1.63 (1.13–2.35)		
	5 kg/m^2	1.19 (1.03–1.38)		
The Australia and New Zealand Diabetes and Cancer Collaboration (ANZDCC) [254]	1 SD	1.06 (1.01–1.12)	10	1,323 diagnoses

Three of the published meta-analyses only included cohort studies and reported a significant increased risk in postmenopausal breast cancer for the highest compared with the lowest measure of BMI (RR 1.13 [95% CI 1.09–1.18], RR 1.12 [95% CI 1.01–1.24] and RR 1.12 [95% CI 1.06–1.18]) [247–249]. The other three meta-analyses included cohort and case-control studies [250–252]. For more information, see CUP breast cancer SLR 2017, Table 534.

A dose–response meta-analysis of the five studies adjusting for BMI (n = 12,022 cases) showed a statistically significant six per cent increased risk of postmenopausal breast cancer per 10 centimetre increase in waist circumference (RR 1.06 [95% CI 1.01–1.12]), with evidence of high *heterogeneity* (I^2 = 72%).

5.1.5.2 Waist circumference

5.1.5.2.1 CUP dose–response meta-analyses

Eleven of 27 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 11 per cent increased risk of postmenopausal breast cancer per 10 centimetre increase in waist circumference (RR 1.11 [95% CI 1.09–1.13]; n = 14,033 cases) (see **Figure 5.17**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.90).

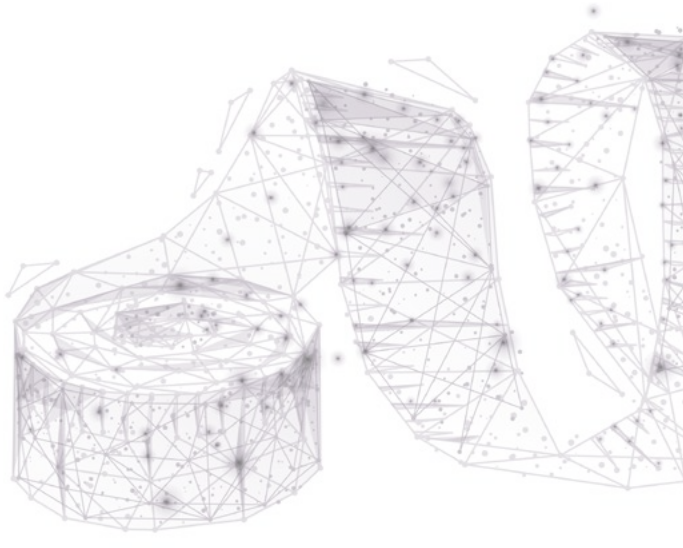
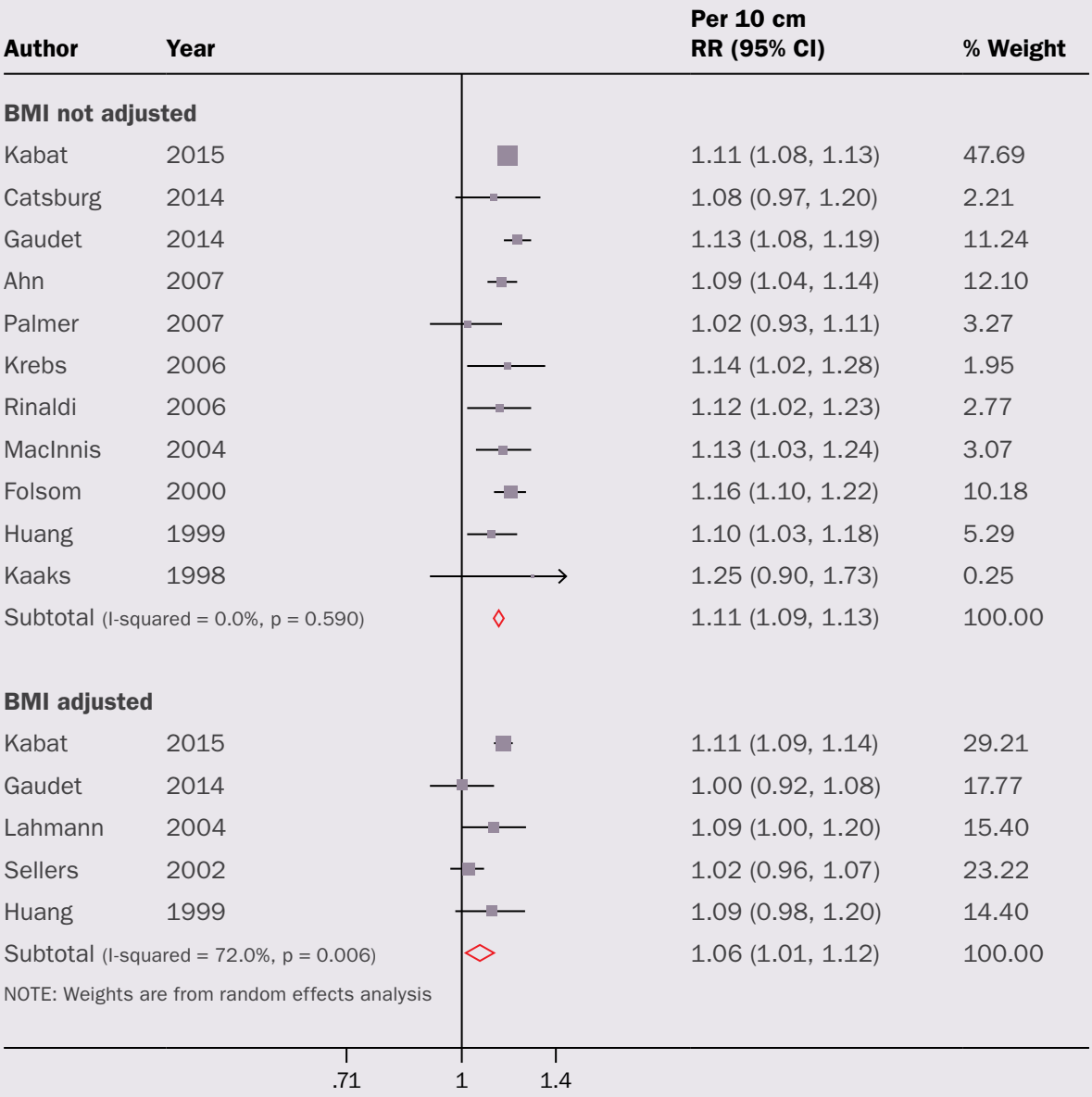


Figure 5.17: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 10 centimetre increase in waist circumference



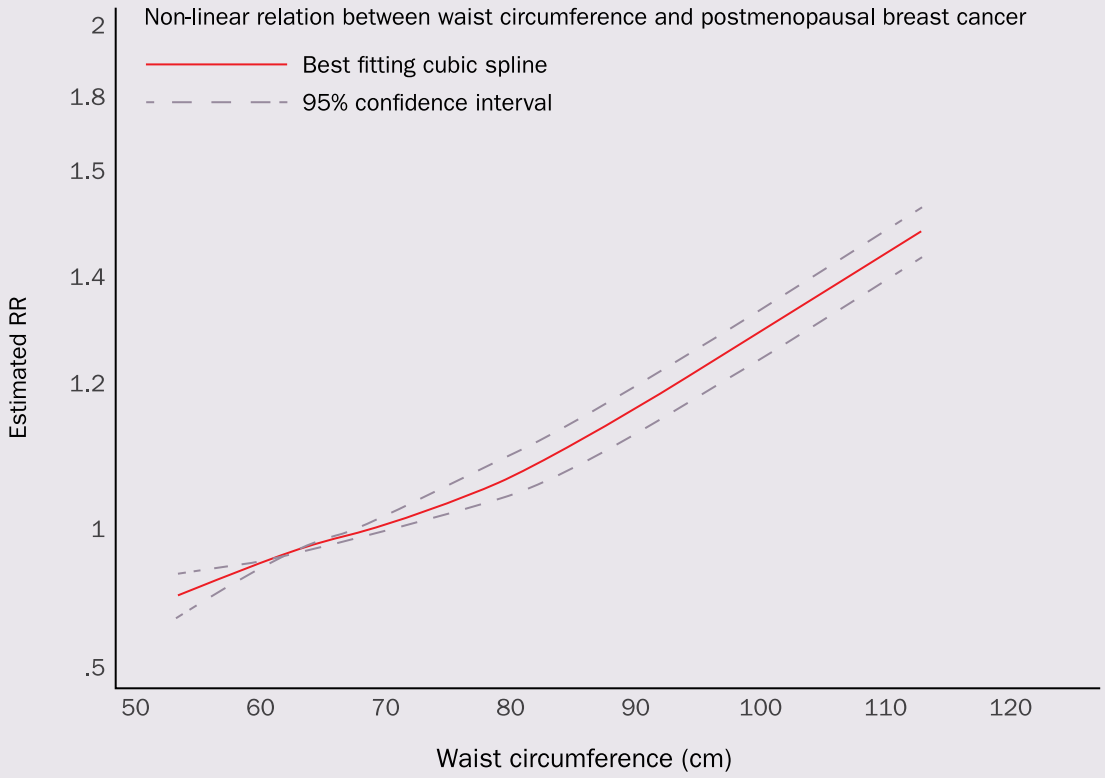
Source: Kabat, 2015 [216]; Catsburg, 2014 [218]; Gaudet, 2014 [255]; Ahn, 2007 [256]; Palmer, 2007 [257]; Krebs, 2006 [236]; Rinaldi, 2006 [258]; MacInnis, 2004 [259]; Folsom, 2000 [260]; Huang, 1999 [261]; Kaaks, 1998 [243]. Lahmann, 2004 [262]; Sellers, 2002 [263].

Stratified analyses for the risk of postmenopausal breast cancer per 10 centimetre increase in waist circumference were conducted for geographic location and simultaneous *adjustment* for age, alcohol intake, reproductive factors and MHT use. For details of other stratified analyses that have been conducted, see CUP breast cancer SLR 2017, Section 8.2.1.

When stratified by geographic location, a statistically significant increased risk was observed in Europe (1.13 [95% CI 1.03–1.24]) and North America (RR 1.11 [95% CI 1.09–1.13]; see CUP breast cancer SLR 2017, Figure 609). A significant increased risk also remained in studies simultaneously adjusted for age, alcohol intake, reproductive factors and MHT use (RR 1.11 [95% CI 1.09–1.13]).

[1] Sixteen studies could not be included in the dose–response meta-analysis; one reported on an excluded exposure, one reported on a different subtype, 10 did not provide sufficient information and four overlapped with other studies included in the meta-analysis. For further details, see CUP breast cancer SLR 2017, Table 581.

Figure 5.18: CUP non-linear dose–response association of waist circumference and the risk of postmenopausal breast cancer



There was evidence of a non-linear dose–response relationship (p = 0.02; see **Figure 5.18**); however, the curve showed an almost linear increase in risk of postmenopausal breast cancer with an increase in waist circumference (see CUP breast cancer SLR 2017, Figure 612 and Table 582).

About half of the studies included in the dose–response meta-analysis simultaneously adjusted for age, alcohol intake, reproductive factors and MHT use. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 580.

5.1.5.2.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.8**) on waist circumference and the risk of postmenopausal breast cancer was identified. No other published meta-analyses have been identified.

Table 5.8: Summary of published pooled analyses of waist circumference and the risk of postmenopausal breast cancer

Publication	Increment	RR (95% CI)	No. of studies	No. of cases
The Australia and New Zealand Diabetes and Cancer Collaboration (ANZDCC) [254]	1 SD	1.06 (1.01–1.12)	10 cohort	1,323 diagnoses

5.1.5.3 Waist-hip ratio

5.1.5.3.1 CUP dose–response meta-analyses

Eighteen of 29 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant 10 per cent increased risk of postmenopausal breast cancer per 0.1 unit increase in waist-hip ratio (RR 1.10 [95% CI 1.05–1.16]; n = 15,643 cases) (see **Figure 5.19**).

High *heterogeneity* was observed (I^2 = 60%), and there was no evidence of small study bias with *Egger's test* (p = 0.42).

A separate dose–response meta-analysis of 10 studies (including one pooled analysis) adjusting for BMI showed no statistically significant association (RR 1.06 [95% CI 0.99–1.15] per 0.1 unit increase in waist-hip ratio; n = 5,700 cases), with moderate heterogeneity observed (I^2 = 41%).

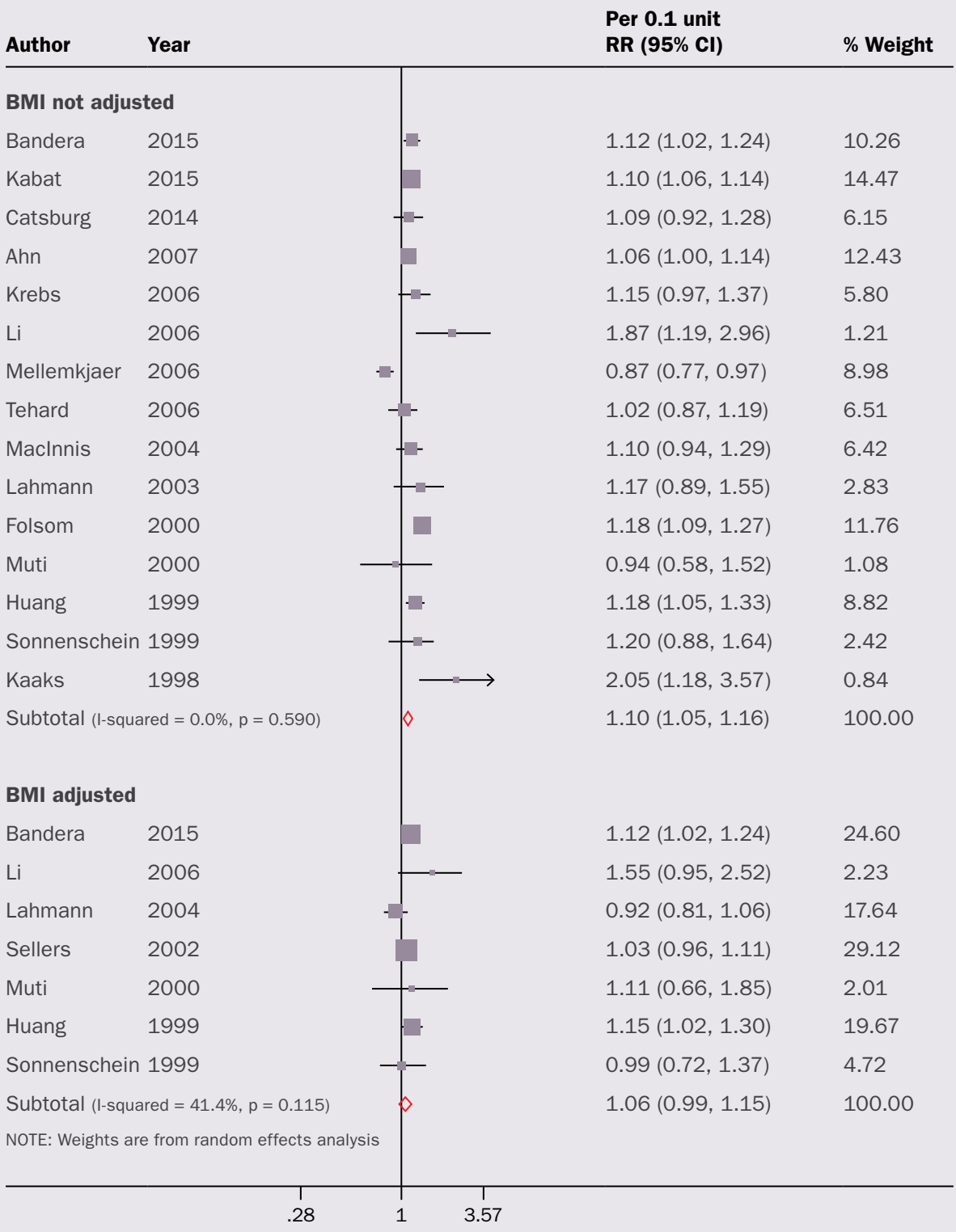
Stratified analyses for the risk of postmenopausal breast cancer per 0.1 unit increase in waist-hip ratio were conducted for geographic location, anthropometric assessment method and simultaneous *adjustment* for age, alcohol intake, reproductive factors and MHT use.

When stratified by geographic location, a statistically significant increased risk was observed in North America (RR 1.08 [95% CI 1.02–1.15] with BMI adjustment and RR 1.11 [95% CI 1.08–1.14] without BMI adjustment) but not in Europe (irrespective of adjustment for BMI). When stratified by anthropometric assessment method, a significant increased risk was observed for self-reported waist and hip measurements (RR 1.09 [95% CI 1.02–1.17] for BMI adjustment and RR 1.12 [95% CI 1.06–1.19] without BMI adjustment), but not measured (irrespective of adjustment for BMI) (see CUP breast cancer report 2017, Table 20 and CUP breast cancer SLR 2017, Figures 623 and 624). When the studies were simultaneously adjusted for age, alcohol intake, reproductive factors and MHT use, a significant increased risk was only observed without the simultaneous adjustment (RR 1.13 [95% CI 1.03–1.23] with BMI adjustment and RR 1.15 [95% CI 1.07–1.23] without BMI adjustment) (see CUP breast cancer report 2017, Table 591).

There was evidence of a non-linear dose–response relationship (p < 0.01; see **Figure 5.20**). The curve showed an increase in risk of postmenopausal breast cancer with an increase in waist-hip ratio, which became steeper after 0.8 units (see CUP breast cancer SLR 2017, Figure 626 and Table 594).

About half the studies included in the dose–response meta-analysis did not adjust for BMI or alcohol intake. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 592.

Figure 5.19: CUP dose–response meta-analysis[1,2] for the risk of postmenopausal breast cancer, per 0.1 unit increase in waist-hip ratio

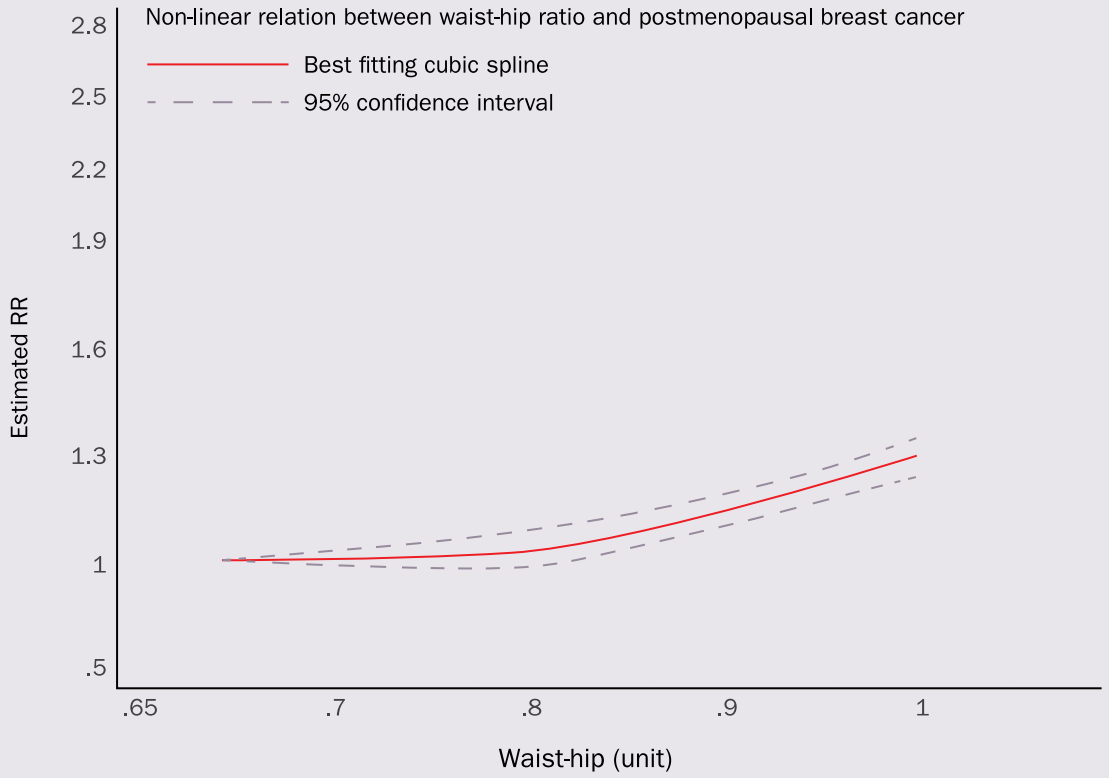


Source: Bandera, 2015 [215]; Kabat, 2015 [216]; Catsburg, 2014 [218]; Ahn, 2007 [256]; Krebs, 2006 [236]; Li, 2006 [237]; Mellemkjaer, 2006 [264]; Tehard, 2006 [265]; MacInnis, 2004 [259]; Lahmann, 2003 [266]; Folsom, 2000 [260]; Muti, 2000 [267]; Huang, 1999 [261]; Sonnenschein, 1999 [241]; Kaaks, 1998 [243]. Lahmann, 2004 [262]; Sellers, 2002 [263].

[1] Ten studies could not be included in any of the dose–response meta-analyses, nine did not provide sufficient information and one overlapped with other studies included in the meta-analyses. For further details, see CUP breast cancer SLR 2017, Table 593.

[2] The CUP dose–response meta-analysis included one pooled analysis, Bandera, 2015 [215], which included four of the identified studies.

Figure 5.20: CUP non-linear dose–response association of waist-hip ratio and the risk of postmenopausal breast cancer



5.1.5.3.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* on waist-hip ratio and the risk of postmenopausal breast cancer were identified. No other published meta-analyses have been identified. The most recent pooled analysis [215] showed a statistically significant increased risk for the highest compared with the lowest measure of waist-hip ratio and was included in the CUP dose–response meta-analysis. The other pooled analysis [254] reported no significant association per 1 SD increase in waist-hip ratio and was not included in the CUP meta-analysis as it reported insufficient data (see **Table 5.9**).

Table 5.9: Summary of published pooled analyses of waist-hip ratio and the risk of postmenopausal breast cancer

Publication	Increment	RR (95% CI)	No. of studies	No. of cases
The Australia and New Zealand Diabetes and Cancer Collaboration (ANZDCC) [254]	1 SD	1.06 (0.95–1.07)	10 cohort	1,323

5.1.5.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Body fatness directly affects levels of several circulating hormones, such as *insulin* and *oestrogens*, creating an environment that promotes *carcinogenesis* and suppresses *apoptosis*. In postmenopausal women, in whom the production of oestrogens from the ovaries has dramatically declined, the main source of oestrogens is from the conversion of androgens within the *adipose tissue*. Consequently, overweight and obese women have higher circulating levels of oestrogens [268], which are well known to be associated with the development of breast cancer [269, 270]. Other sex steroid hormones, including androgens and *progesterone*, are also likely to play a role in the relationship between obesity and breast cancer [271]. Elevated body fatness is also associated with *hyperinsulinemia* and *insulin resistance*, and greater circulating insulin levels have been linked to risk of breast cancer [272]. Insulin could promote the growth of breast tumours directly by binding to its receptor or to the IGF-I (*insulin-like growth factor*-1) receptor or indirectly by inhibiting the synthesis of sex-hormone binding globulin, which sequesters oestrogens in circulation, contributing to higher levels of bioavailable oestrogens [273].

Obesity is also associated with a low-grade *chronic* inflammatory state. Adipose tissue in obese individuals secretes pro-inflammatory *cytokines* and *adipokines*, which can promote development of breast cancer, as shown in experimental studies [274–276] and more recently in epidemiological studies [277, 278].

5.1.5.5 CUP Panel's conclusion

The evidence for BMI was consistent, and the CUP dose–response meta-analyses showed a statistically significant increased risk of postmenopausal breast cancer with increasing BMI in studies on both incidence and mortality. High heterogeneity was observed for BMI, which could be explained in part by the geographic locations of the cohorts. There was no evidence of a non-linear relationship for BMI. Stratification by geographic location showed a significant increased risk with increasing BMI in all groups, with a greater increased risk observed in Asia. The significant increased risk was limited to women who had never used MHT and those who had never used or who had previously used MHT. A significant increased risk was also observed in ER-positive or ER-positive/PR-positive breast cancer and PR-positive breast cancer. Results from eight published pooled analyses overall supported the CUP finding, and five were included in the CUP dose–response meta-analyses.

Most of the other published meta-analyses also supported the CUP finding, reporting a significant increased risk of postmenopausal breast cancer for BMI in highest versus lowest and/or dose–response meta-analyses. The evidence for waist circumference and waist-hip ratio was also consistent, with CUP dose–response meta-analyses showing a significant increased risk, and these associations were generally supported by other published pooled analyses. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

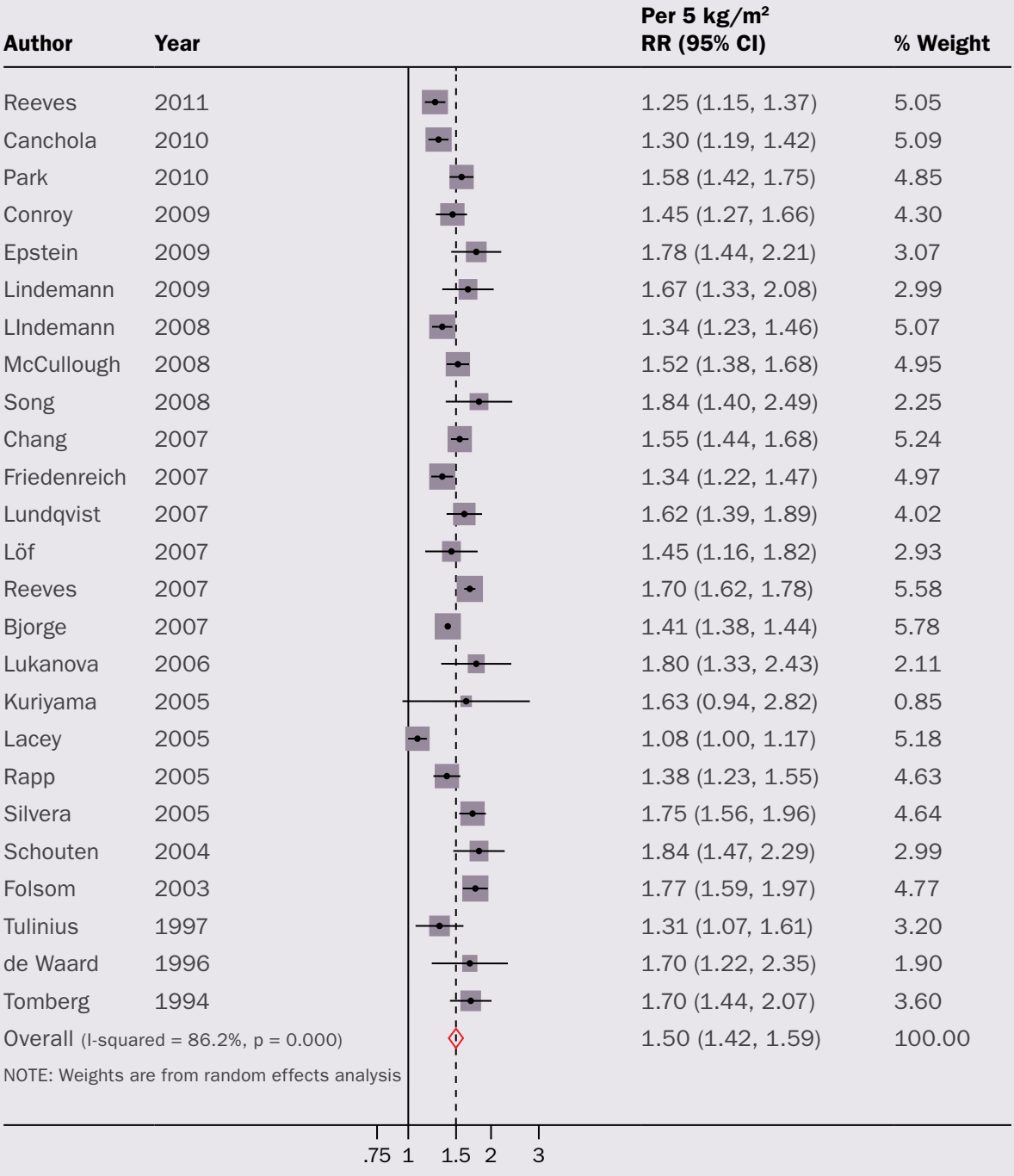
- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of postmenopausal breast cancer.**

5.1.6 Endometrium

(Also see CUP endometrial cancer report 2013: Section 7.5 and CUP endometrial cancer SLR 2012: Sections 8.1.1, 8.1.6, 8.2.1 and 8.2.3)

The evidence for BMI, BMI at age 18 to 25 years, weight gain (including increase in BMI), waist circumference and waist-hip ratio is presented in the following subsections.

Figure 5.21: CUP dose–response meta-analysis[1] for the risk of endometrial cancer, per 5 kg/m² increase in body mass index



Source: Reeves, 2011 [279]; Canchola, 2010 [280]; Park, 2010 [281]; Conroy, 2009 [282]; Epstein, 2009 [283]; Lindemann, 2009 [284]; Lindemann, 2008 [285]; McCullough, 2008 [286]; Song, 2008 [234]; Chang, 2007 [287]; Friedenreich, 2007 [288]; Lundqvist, 2007 [235]; Lof, 2007 [289]; Reeves, 2007 [103]; Bjorge, 2007 [290]; Lukanova, 2006 [194]; Kuriyama, 2005 [127]; Lacey, 2005 [291]; Rapp, 2005 [130]; Silvera, 2005 [292]; Schouten, 2004 [293]; Folsom 2003 [294]; Tulinius, 1997 [177]; de Waard, 1996 [295]; Tornberg, 1994 [244].

[1] The dose–response meta-analysis includes 26 studies; the RR for two individual cohorts was reported in one single publication for Lundqvist, 2007 [235].

5.1.6.1 Body mass index

5.1.6.1.1 CUP dose–response meta-analyses

Twenty-six of 34 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 50 per cent increased risk of endometrial cancer per 5 kg/m^2 increase in BMI (RR 1.50 [95% CI: 1.42–1.59]; n = 18,717 cases) (see **Figure 5.21**).

High *heterogeneity* was observed (I^2 = 86%), but this was due to differences in the size of the effect and not the direction. There was no evidence of small study bias with *Egger's test* (p = 0.21).

Stratified analyses for the risk of endometrial cancer per 5 kg/m^2 increase in BMI were conducted for menopausal status and MHT use.

When stratified by menopausal status, a statistically significant increased risk was observed for both premenopausal (RR 1.41 [95% CI 1.37–1.45]) and postmenopausal women (RR 1.54 [95% CI 1.39–1.71]; see CUP endometrial cancer SLR 2012, Figure 80). When stratified by MHT use, a significant increased risk was observed for both those who had ever used MHT (RR 1.15 [95% CI 1.06–1.25]) and those who had never used MHT (RR 1.73 [95% CI 1.44–2.08]), although the increased risk was larger in those who had never used MHT (see CUP endometrial cancer SLR 2012, Figure 81).

There was evidence of a non-linear dose–response relationship (p < 0.0001; see **Figure 5.22**), with a steeper increase in risk at higher BMI levels.

All studies included in the dose–response meta-analysis adjusted for age, about a half adjusted for tobacco smoking and reproductive factors. Some studies adjusted for alcohol consumption, physical activity and MHT use.

Figure 5.22 CUP non-linear dose–response association of body mass index and the risk of endometrial cancer

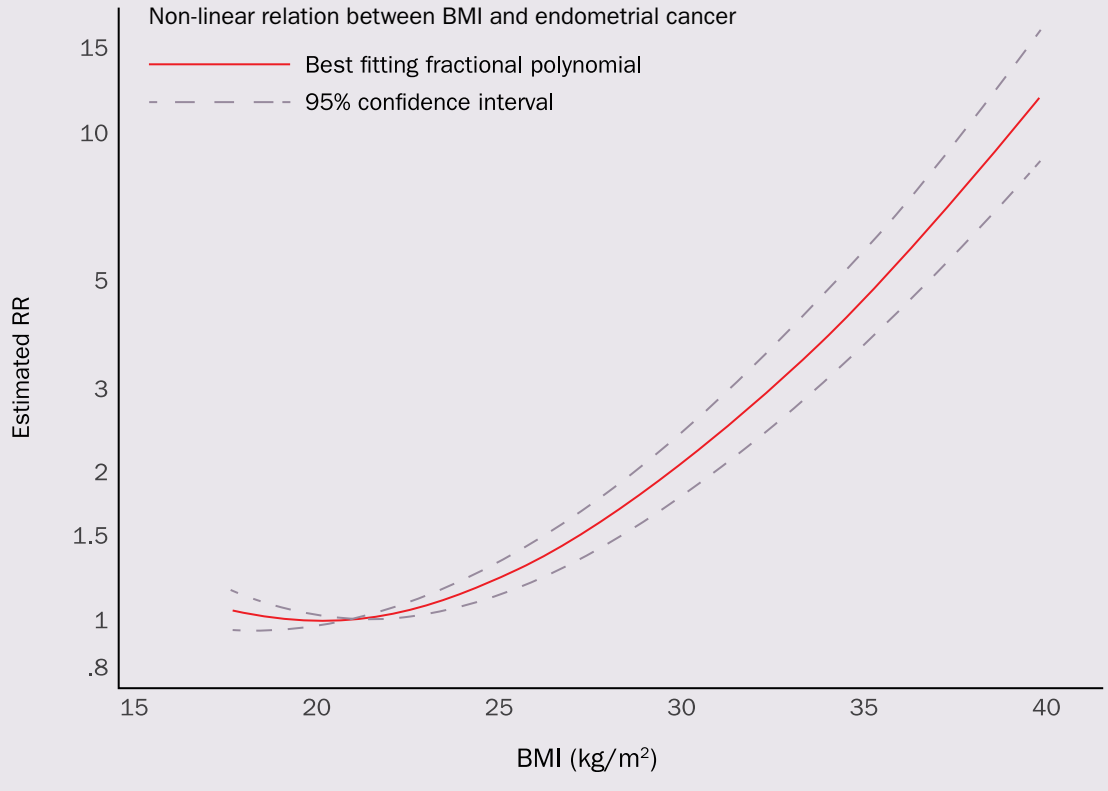
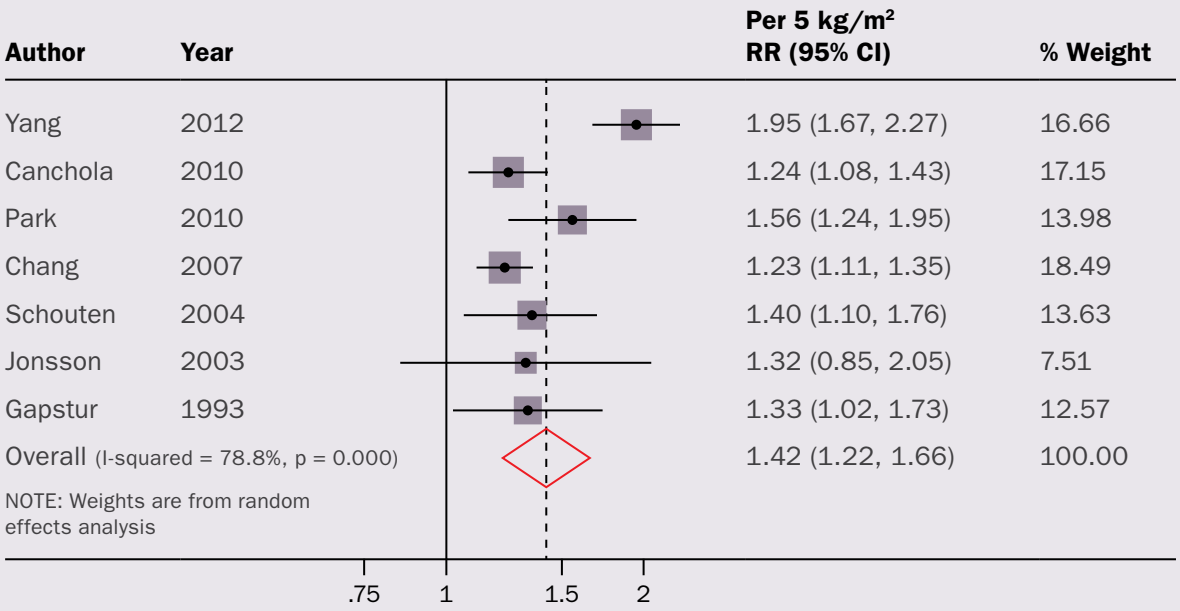


Figure 5.23: CUP dose–response meta-analysis for the risk of endometrial cancer, per 5 kg/m² increase in body mass index at age 18 to 25 years



Source: Yang, 2012 [297]; Canchola, 2010 [280]; Park, 2010 [281]; Chang, 2007 [287]; Schouten, 2004 [293]; Jonsson, 2003 [298]; Gapstur, 1993 [299].

5.1.6.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses of cohort studies on BMI and the risk of endometrial cancer have been identified, which both reported a statistically significant increased risk per 5 kg/m² increase in BMI (RR 1.59 [95% CI 1.50–1.68] and RR 1.60 [95% CI 1.52–1.68]) [110, 296].

5.1.6.2 Body mass index at age 18 to 25 years

5.1.6.2.1 CUP dose–response meta-analysis

Seven of eight identified studies were included in the dose–response meta-analysis, which showed a statistically significant 42 per cent increased risk of endometrial cancer per 5 kg/m² increase in BMI at age 18 to 25 years (RR 1.42 [95% CI 1.22–1.66]; n = 3,476 cases) (see **Figure 5.23**).

High *heterogeneity* was observed (I^2 = 79%), but this was due to differences in the size of the effect and not the direction. There was no evidence of small study bias with *Egger's test* (p = 0.54).

There was no evidence of a non-linear dose–response relationship (p = 0.07).

All studies included in the dose–response meta-analysis adjusted for age, and over half adjusted for tobacco smoking, physical activity and reproductive factors. Some studies adjusted for alcohol consumption and MHT use.

5.1.6.2.2 Published pooled analyses and meta-analyses

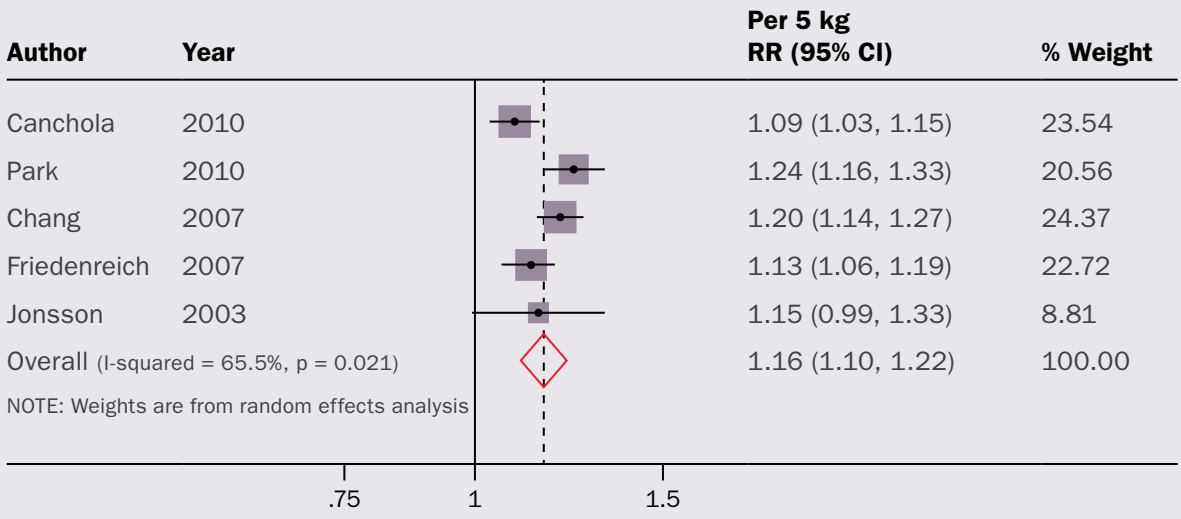
No published pooled analyses and no other published meta-analyses on BMI at age 18 to 25 years and the risk of endometrial cancer were identified.

5.1.6.3 Adult weight gain

5.1.6.3.1 CUP dose–response meta-analysis

All five identified studies were included in the dose–response meta-analysis, which showed a statistically significant 16 per cent increased risk of endometrial cancer per 5 kilograms increase in weight (RR 1.16 [95% CI 1.10–1.22]; n = 1,971 cases) (see **Figure 5.24**).

Figure 5.24: CUP dose–response meta-analysis for the risk of endometrial cancer, per 5 kilograms increase in weight



Source: Canchola, 2010 [280]; Park, 2010 [281]; Chang, 2007 [287]; Friedenreich, 2007 [288]; Jonsson, 2003 [298].

High *heterogeneity* was observed (I^2 = 66%), but this appeared to be due to differences in the size of the effect and not the direction.

All studies included in the dose–response meta-analysis adjusted for age, and over half adjusted for tobacco smoking, physical activity, reproductive factors and MHT use. One study [280] adjusted for alcohol consumption.

5.1.6.3.2 Published pooled analyses and meta-analyses

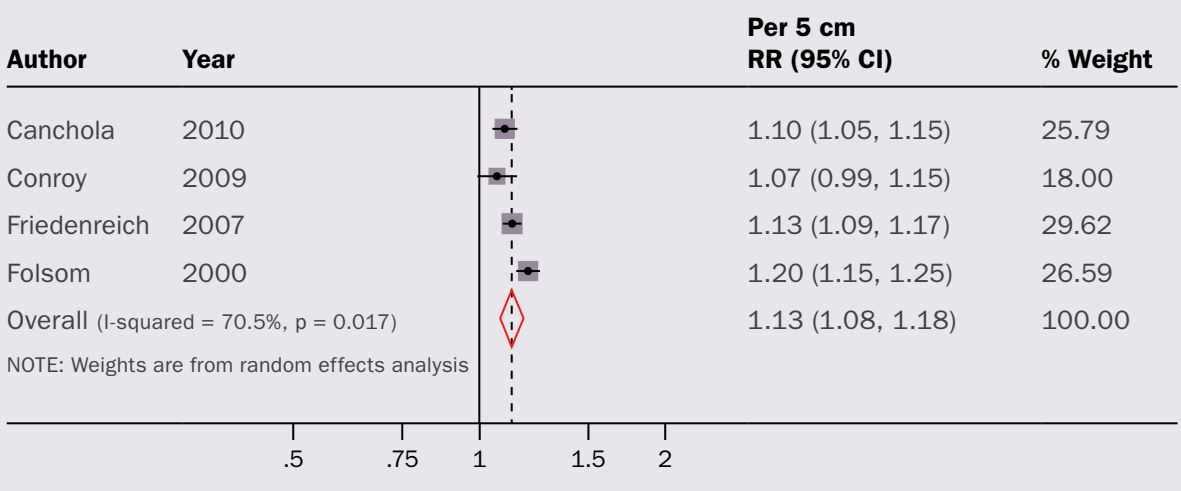
No published pooled analyses and no other published meta-analyses on weight gain and the risk of endometrial cancer were identified.

5.1.6.4 Waist circumference

5.1.6.4.1 CUP dose–response meta-analysis

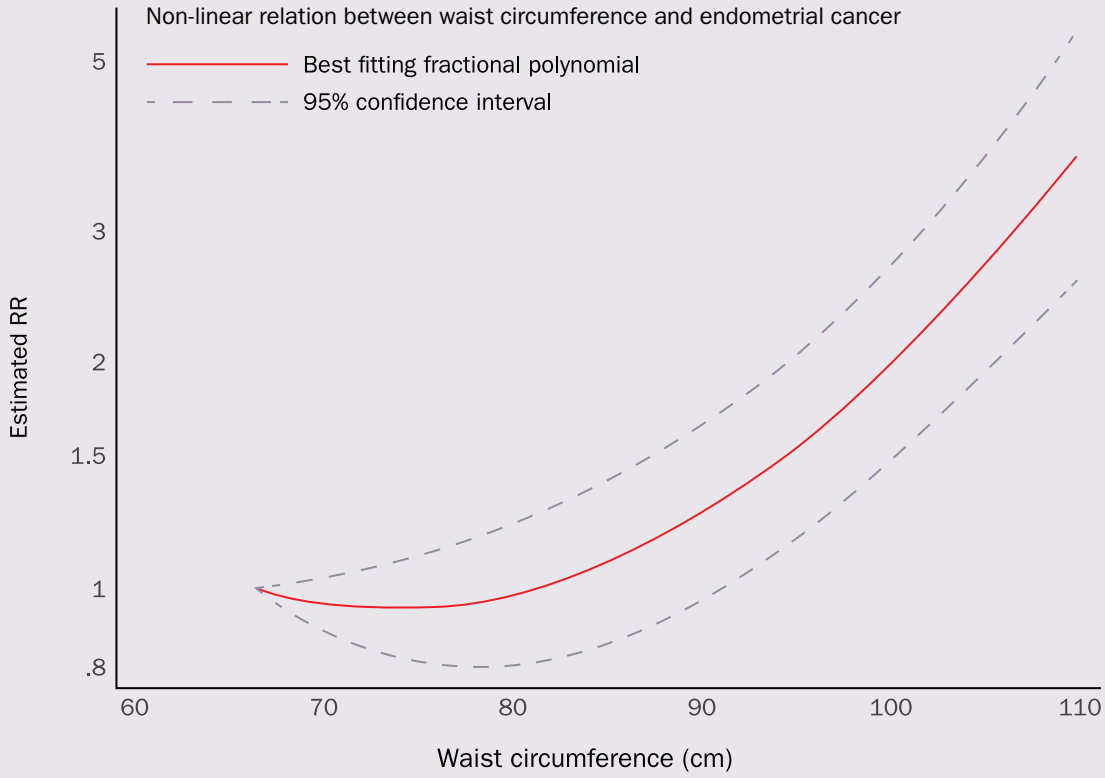
All four identified studies were included in the dose–response meta-analysis, which showed a statistically significant 13 per cent increased risk of endometrial cancer per 5 centimetre increase in waist circumference (RR 1.13 [95% CI 1.08–1.18]; n = 1,641 cases) (see **Figure 5.25**).

Figure 5.25: CUP dose–response meta-analysis for the risk of endometrial cancer, per 5 centimetre increase in waist circumference



Source: Canchola, 2010 [280]; Conroy, 2009 [282]; Friedenreich, 2007 [288]; Folsom, 2000 [260].

Figure 5.26: CUP non-linear dose–response association of waist circumference and the risk of endometrial cancer



High *heterogeneity* was observed (I^2 = 71%) due to differences in the size of the effect but not the direction.

There was evidence of a non-linear dose–response relationship (p < 0.0001; see **Figure 5.26**) with a steeper increase in risk at higher waist circumference, but this was driven by a limited number of observations.

All studies included in the dose–response meta-analysis adjusted for age, at least a half adjusted for tobacco smoking, physical activity, alcohol consumption, reproductive factors and MHT use.

5.1.6.4.2 Published pooled analyses and meta-analyses

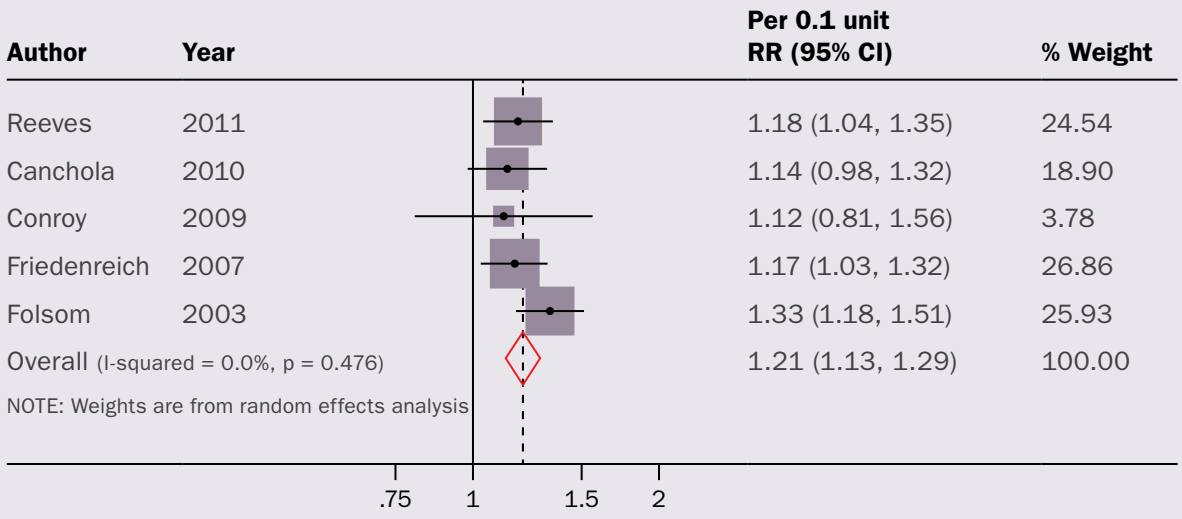
No published pooled analyses and no other published meta-analyses on waist circumference and the risk of endometrial cancer were identified.

5.1.6.5 Waist-hip ratio

5.1.6.5.1 CUP dose–response meta-analysis

All five identified studies were included in the dose–response meta-analysis, which showed a statistically significant 21 per cent increased risk of endometrial cancer per 0.1 unit increase in waist-hip ratio (RR 1.21 [95% CI 1.13–1.29]; n = 2,330 cases) (see **Figure 5.27**). No *heterogeneity* was observed.

Figure 5.27: CUP dose–response meta-analysis for the risk of endometrial cancer, per 0.1 unit increase in waist-hip ratio



Source: Reeves, 2011 [279]; Canchola, 2010 [280]; Conroy, 2009 [282]; Friedenreich, 2007 [288]; Folsom, 2003 [294].

There was no evidence of a non-linear dose–response relationship (p = 0.29).

All studies included in the dose–response meta-analysis adjusted for age, most adjusted for tobacco smoking, physical activity, reproductive factors and MHT use. Some studies adjusted for alcohol consumption.

5.1.6.5.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on waist-hip ratio and the risk of endometrial cancer were identified.

5.1.6.6 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Excess body fatness increases bioavailable *oestrogen* levels, which have been shown, when not counterbalanced by *progesterone*, to increase mitotic activity in endometrial tissue and therefore promote endometrial *carcinogenesis* [269]. Higher *insulin* levels associated with excess body fatness are associated with greater risk of endometrial cancer [300, 301]. Insulin has been to shown to enhance endometrial tumour growth either directly by binding to the insulin or to the IGF-I receptors, or indirectly by inhibiting the synthesis of sex-hormone binding globulin, and thereby increasing oestrogen bioavailability [273]. Obesity-related *chronic inflammation* has also been specifically linked to development of endometrial cancer [302–304].

5.1.6.7 CUP Panel's conclusion

The evidence from the CUP for an association between body fatness (which the CUP Panel interprets to be reflected by BMI [including BMI at age 18 to 25 years], waist circumference, waist-hip ratio and weight gain) and endometrial cancer was consistent, with a dose–response relationship showing significant increased risk. High heterogeneity was observed in most analyses, but this was due to differences in the size of the effect and not the direction. The associations for BMI were supported by other published meta-analyses. Stratification by menopausal status and MHT use showed significant increased risk in all groups. There was evidence of a non-linear relationship for BMI with a steeper increase in risk at higher BMI levels. Fewer studies reported on waist circumference, waist-hip ratio and weight gain than for BMI, but supported the evidence for an association between overall body fatness and endometrial cancer risk. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference, waist-hip ratio and adult weight gain) is a convincing cause of endometrial cancer.**

5.1.7 Kidney

(Also see CUP kidney cancer report 2015: Section 7.3 and CUP kidney cancer SLR 2015: Sections 8.1.1, 8.2.1 and 8.2.3.)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections.

5.1.7.1 Body mass index

5.1.7.1.1 CUP dose–response meta-analyses

Twenty-three of 28 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 30 per cent increased risk of kidney cancer per 5 kg/m^2 increase in BMI (RR 1.30 [95% CI 1.25–1.35]; n = 15,575 cases) (see **Figure 5.28**).

Moderate *heterogeneity* was observed (I^2 = 39%), and there was no evidence of small study bias with *Egger's test* (p = 0.14).

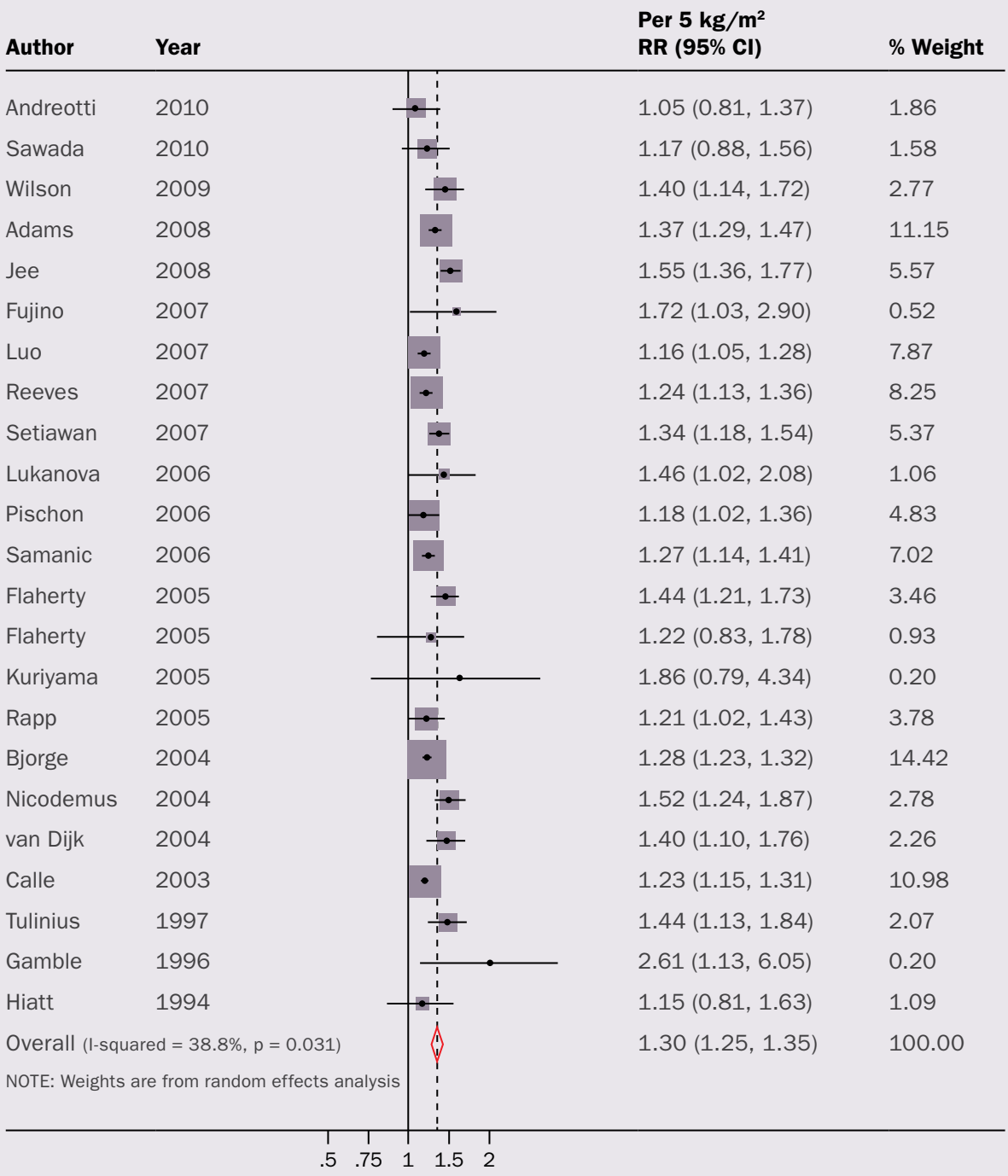
Stratified analyses for the risk of kidney cancer per 5 kg/m^2 increase in BMI were conducted for sex, geographic location and outcome.

When stratified by sex, a statistically significant increased risk was observed for men (RR 1.29 [95% CI 1.23–1.36]) and women (RR 1.28 [95% CI 1.24–1.32]). When stratified by geographic location, a significant increased risk was observed in North America (RR 1.29 [95% CI 1.20–1.39]), Europe (RR 1.27 [95% CI 1.24–1.31]) and Asia (RR 1.47 [95% CI 1.26–1.72]). When stratified by outcome, a significant increased risk was observed for kidney cancer incidence (RR 1.30 [95% CI 1.25–1.36]) and mortality (RR 1.32 [95% CI 1.01–1.71]) (see CUP kidney cancer report 2015, Table 4 and CUP kidney cancer SLR 2015, Figures 119, 120 and 121).

There was no evidence of a non-linear dose–response relationship (p = 0.07).

All studies included in the dose–response meta-analysis adjusted or accounted for age and sex, and all except for three [161, 312, 313] for tobacco smoking. Some studies adjusted for alcohol consumption and physical activity.

Figure 5.28: CUP dose–response meta-analysis[1] for the risk of kidney cancer, per 5 kg/m² increase in BMI



Source: Andreotti, 2010 [116]; Sawada, 2010 [305]; Wilson, 2009 [306]; Adams, 2008 [307]; Jee, 2008 [120]; Fujino, 2007 [161]; Luo, 2007 [308]; Reeves, 2007 [103]; Setiawan, 2007 [309]; Lukanova, 2006 [194]; Pischon, 2006 [310]; Samanic, 2006 [104]; Flaherty, 2005 [311]; Kuriyama, 2005 [127]; Rapp, 2005 [130]; Bjorge, 2004 [312]; Nicodemus, 2004 [313]; van Dijk, 2004 [314]; Calle, 2003 [162]; Tulinius, 1997 [177]; Gamble, 1996 [315]; Hiatt, 1994 [316].

5.1.7.1.2 Published pooled analyses and meta-analyses

Three published *pooled analyses* (see **Table 5.10**) and three other published meta-analyses on BMI and the risk of kidney cancer were identified. Two of the published pooled analyses reported a statistically significant increased risk [163, 317], and the other reported no significant association [145]. All three published meta-analyses reported a significant increased risk for dose–response estimates [110, 318, 319] (see CUP kidney cancer SLR 2015, Section 8.1.1). The CUP included more kidney cancer cases than any of the published pooled analyses.

[1] Flaherty 2005 [311] reported the RR for two individual cohorts in a single publication.

Table 5.10: Summary of published pooled analyses of body mass index and the risk of kidney cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies (cohort)	No. of cases
Asia-Pacific Cohort Studies Collaboration [145]	BMI ≥ 30 vs 18.5–24.9 kg/m^2	1.59 (0.78–3.24)	39	93 deaths
	5 kg/m^2	1.20 (0.86–1.66)		
Metabolic Syndrome and Cancer Project – Me-Can project [317]	BMI 31.7 vs 21.5 kg/m^2 (men)	1.51 (1.13–2.03)	7	592 diagnoses
	BMI 31.7 vs 20.0 kg/m^2 (women)	2.21 (1.32–3.70)	7	263 diagnoses
Prospective Studies Collaboration [163]	5 kg/m^2	1.23 (1.06–1.43)	57	422 deaths

5.1.7.2 Waist circumference

5.1.7.2.1 CUP dose–response meta-analysis

All three identified studies were included in the dose–response meta-analysis, which showed a statistically significant 11 per cent increased risk of kidney cancer per 10 centimetre increase in waist circumference (RR 1.11 [95% CI 1.05–1.19]; n = 751 cases) (see **Figure 5.29**). No *heterogeneity* was observed.

All studies included in the dose–response meta-analysis adjusted or accounted for age, sex and tobacco smoking. One study [310] also adjusted for alcohol consumption and physical activity.

5.1.7.2.2 Published pooled analyses and meta-analyses

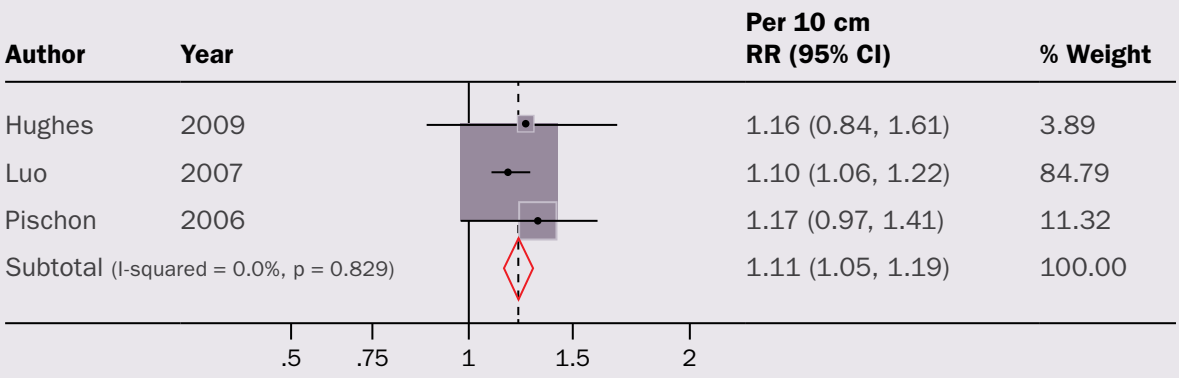
No published pooled analyses and no other published meta-analyses on waist circumference and the risk of kidney cancer were identified.

5.1.7.3 Waist-hip ratio

5.1.7.3.1 CUP dose–response meta-analysis

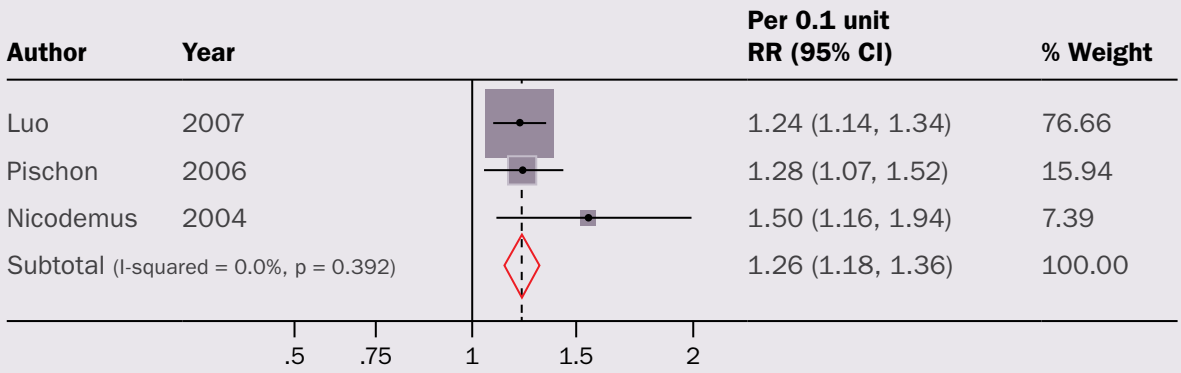
Three of four identified studies were included in the dose–response meta-analysis, which showed a statistically significant 26 per cent increased risk of kidney cancer per 0.1 unit increase in waist-hip ratio (RR 1.26 [95% CI 1.18–1.36]; n = 751 cases) (see **Figure 5.30**). No *heterogeneity* was observed.

Figure 5.29: CUP dose–response meta-analysis for the risk of kidney cancer, per 10 centimetre increase in waist circumference



Source: Hughes, 2009 [320]; Luo, 2007 [308]; Pischon, 2006, [310].

Figure 5.30: CUP dose–response meta-analysis for the risk of kidney cancer, per 0.1 unit increase in waist-hip ratio



Source: Luo, 2007 [308]; Pischon, 2006 [310]; Nicodemus, 2004 [313].

All studies included in the dose–response meta-analysis adjusted or accounted for age and sex, and all except for one adjusted for tobacco smoking [313]. One study [310] also adjusted for alcohol consumption and physical activity.

5.1.7.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on waist-hip ratio and the risk of kidney cancer were identified.

5.1.7.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The vast array of epidemiological studies using diverse measures of obesity, such as weight, BMI or waist-hip ratio, as well as increases in adult weight, all show similar positive associations with the risk of renal cell cancer and likely share common mechanisms. Body fatness is a systemic process that affects host metabolism, as well as many components of the *endocrine* system or microenvironment, which may affect kidney *carcinogenesis*. For example, obesity is associated with raised levels of *mitogenic* and anti-apoptotic growth factors, such as insulin or bioactive IGF-I, which may promote the carcinogenic process [321, 322].

Higher concentrations of *adiponectin*, a protein secreted by *adipose tissue* that is inversely related to body fatness, have been associated with lower risk of kidney cancer [323]. In vitro experimental studies have shown that adiponectin inhibits cellular proliferation and promotes *apoptosis* [324]. Obesity increases the risk of metabolic syndrome, which includes hypertension and obesity, both of which are associated with a greater risk for renal cancer [325]. Obesity is associated with a *chronic* inflammatory state that may alter susceptibility to cancer or promote carcinogenesis [326].

5.1.7.5 CUP Panel's conclusion

Body fatness is reflected by BMI, waist circumference and waist-hip ratio. There was consistent epidemiological evidence of significant increased risk between various measures of body fatness and kidney cancer, with a clear dose–response relationship in the CUP. Moderate or no heterogeneity was observed. For BMI, the statistically significant increased risk was still apparent when stratified by outcome, sex and geographic location. There was no evidence of a non-linear relationship for BMI; analyses were not conducted for the other measures. Results from several published pooled analyses and published meta-analyses were also consistent with the CUP results in the direction of the effect, although not all showed findings that were statistically significant. There is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is a convincing cause of kidney cancer.**

5.1.8 Mouth, pharynx and larynx

(Also see CUP mouth, pharynx and larynx cancer report 2018: Section 7.6 and CUP mouth, pharynx and larynx cancer SLR 2016: Sections 8.1.1, 8.2.1 and 8.2.3)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. Dose-response meta-analyses were not possible for these exposures because of the small number of studies for each cancer subtype.

5.1.8.1 Body mass index

The CUP identified seven studies [104, 217, 327–331] reviewing cancers of the mouth, pharynx and larynx. For more information on these studies, see CUP mouth, pharynx and larynx cancer SLR 2016, Section 8.1.1. Because of the small numbers of studies for each cancer subtype, no meta-analyses were conducted.

5.1.8.1.1 Published pooled analysis

Evidence from a published pooled analysis that was used in place of CUP analyses is described here, and evidence from other pooled analyses is described in the next subsection.

The CUP identified a published *pooled analysis* of 20 cohorts [97] which included three of the seven studies identified in the CUP. A statistically significant increased risk was reported for *head and neck cancer* for people who have never smoked in both highest compared with lowest category of BMI and dose–response analyses (see **Table 5.11** and **Table 5.12**). A significant increased risk was observed for underweight compared with normal weight, but there was no significant association when the analysis was restricted to people who have never smoked, probably reflecting early disease among people who smoke, associated with weight loss. The significant decreased risk with BMI among people who smoke probably reflects *confounding* by smoking tobacco. The analyses included *adjustments* for age, sex, alcohol intake and, where appropriate, tobacco smoking.

Table 5.11: Summary of published pooled analysis [97] of body mass index and the risk of head and neck cancer

Publication	No. of cases	HR (95% CI) Obese (≥30.0) vs. 21 to <23 kg/m²	HR (95% CI) Underweight (15.0 to 20.9) vs. 21.0 to <23 kg/m²	HR (95% CI) per 5 kg/m²	P_{trend}
All	3,760	0.85 (0.76–0.96)	1.28 (1.11–1.46)	0.94 (0.90–0.98)	0.003
People who have never smoked	796	1.40 (1.08–1.81)	1.17 (0.85–1.61)	1.15 (1.06–1.24)	0.0006
People who smoke	1,508	0.58 (0.47–0.72)	1.30 (1.08–1.57)	0.76 (0.71–0.82)	<0.0001
People who used to smoke	1,367	0.96 (0.79–1.18)	1.24 (0.94–1.63)	0.99 (0.93–1.06)	0.79

5.1.8.1.2 Other published pooled analyses and meta-analyses

Two other published *pooled analyses* (see **Table 5.13**) but no published meta-analyses on BMI and the risk of cancers of the mouth, pharynx and larynx were identified.

A pooled analysis of 39 cohort studies [145] reported a statistically significant decreased risk for oropharyngolaryngeal and upper aerodigestive tract mortality. No significant associations were observed for highest BMI or underweight categories compared to healthy weight category [145], see CUP mouth, pharynx and larynx cancer SLR 2016, Tables 30 and 32.

Another pooled analysis of 15 *case-control studies* [332] reported a decreased risk (many significant) for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancer when comparing high with low BMI. When comparing underweight (BMI < 18.5 kg/m²) with normal BMI, an increased risk was observed for oral cavity, oropharyngeal, hypopharyngeal and laryngeal cancer.

Table 5.12: Summary of published pooled analysis [97] of body mass index and the risk of cancers of the mouth, pharynx and larynx in people who have never smoked

Cancer site	Increment	No. of cases	HR (95% CI)	P_{trend}
Oral cavity	per 5 kg/m² BMI in people who have never smoked	298	1.10 (0.97–1.25)	0.14
Oral cavity and pharyngeal (not otherwise specified) combined		93	1.36 (1.11–1.66)	0.003
Oropharyngeal		241	0.98 (0.84–1.14)	0.77
Hypopharyngeal		22	0.96 (0.55–1.67)	0.88
Laryngeal		142	1.42 (1.19–1.70)	0.0001

Table 5.13: Summary of other pooled analyses of body mass index and the risk of mouth, pharynx, larynx cancer

Publication		Increment/contrast	RR (95% CI)	P_{trend}	No. of cases	No. of cases
Asia-Pacific Cohort Studies Collaboration [145]	Oropharyngeal and laryngeal combined, mortality	5 kg/m^2	0.66 (0.46–0.95)[1]	–	39 cohort	159 deaths
	Upper aerodigestive tract, mortality	5 kg/m^2	0.78 (0.62–0.98)[1]	–		388 deaths
International Head and Neck Cancer Epidemiology (INHANCE) Consortium [332]	Oral cavity	BMI ≥ 35 kg/m^2 vs BMI 18.5–24.9 kg/m^2			15 case-control	
		Men	0.65 (0.40–1.10)[2]	<0.01		1,516
		Women	0.92 (0.50–1.60)[2]	<0.01		935 diagnoses
	Oropharyngeal	BMI ≥ 35 kg/m^2 vs BMI 18.5–24.9 kg/m^2				
		Men	0.48 (0.30–0.70)[2]	<0.01		1,733
		Women	0.35 (0.20–0.70)[2]	<0.01		564 diagnoses
	Hypopharyngeal	BMI 30.0–34.9 kg/m^2 vs BMI < 18.5 kg/m^2				
		Men	0.24 (0.10–0.50)[2]	0.10		412
		Women	0.24 (0.10–0.80)[2]	<0.01		96 diagnoses
	Laryngeal	BMI ≥ 35 kg/m^2 vs BMI 18.5–24.9 kg/m^2				
		Men	0.77 (0.40–1.40)[2]	<0.01		1,503
		Women	0.27 (0.10–0.80)[2]	<0.01		237 diagnoses

5.1.8.2 Waist circumference

One study was identified on waist circumference and the risk of cancers of the mouth, pharynx and larynx [329]. It reported a statistically significant increased risk in highest compared with lowest category of waist circumference for oral cavity (RR 2.00 [95% CI 1.24–3.23]), and head and neck cancer (RR 1.42 [95% CI 1.04–1.93]). No significant associations were reported for oro- and hypopharyngeal cancers combined, or laryngeal cancer. This study was adjusted for age, sex, alcohol and tobacco smoking.

5.1.8.2.1 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.14**) on waist circumference and the risk of cancers of the mouth, pharynx and larynx was identified. No published meta-analyses have

[1] Hazard ratios
[2] *Odds ratios.*

Table 5.14: Summary of published pooled analysis [97] of waist circumference and the risk of head and neck cancer

Publication	No. of cases	HR (95% CI) Highest vs lowest	RR (95% CI) per 5 cm)[1]	P_{trend}
All	1,931	1.08 (0.93–1.25)	1.04 (1.03–1.05)	< 0.0001
People who have never smoked	441	1.51 (1.09–2.08)	1.07 (1.01–1.14)	0.022
People who smoke	706	0.80 (0.62–1.04)	1.04 (1.02–1.05)	< 0.0001
People who used to smoke	745	1.21 (0.94–1.55)	1.06 (1.01–1.11)	0.01

been identified. The pooled analysis contained 20 cohorts [97] and included the one study identified in the CUP. A statistically significant increased risk was observed in people who have never smoked, for both the highest compared with lowest category for waist circumference and dose–response analyses, for head and neck cancer, as well as in the dose–response analyses in people who have never smoked, for oral cavity cancer, but were not significant for other specific cancers (see CUP mouth, pharynx and larynx SLR 2016, Table 33). The analyses included *adjustments* for age, sex, alcohol intake and, where appropriate, tobacco smoking.

5.1.8.3 Waist-hip ratio

One study was identified on waist-hip ratio and the risk of cancers of the mouth, pharynx and larynx [329]. This study reported a statistically significant increased risk in highest compared with lowest category of waist-hip ratio for oral cavity cancer (RR 1.58 [95% CI 1.10–2.28]). No significant association was reported for oro- and hypopharyngeal cancers combined, laryngeal cancer, and head and neck cancer. This study was adjusted for tobacco smoking.

5.1.8.3.1 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.15**) on waist-hip ratio and the risk of cancers of the mouth, pharynx and larynx was identified. No other published meta-analyses have been identified.

Table 5.15: Summary of published pooled analysis [97] of waist-hip ratio and the risk of head and neck cancer

Publication	No. of cases	HR (95% CI) Highest vs lowest	RR (95% CI) per 0.1 unit)[1]	P_{trend}
All	1,677	1.30 (1.12–1.50)	1.07 (1.05–1.09)	< 0.0001
People who have never smoked	382	1.23 (0.89–1.69)	1.06 (0.93–1.11)	0.2013
People who smoke	577	1.38 (1.09–1.75)	1.08 (1.04–1.12)	0.0017
People who used to smoke	685	1.25 (0.98–1.59)	1.10 (1.01–1.21)	0.0351

[1] Controlling for BMI.

The pooled analysis contained 20 cohorts [97] and included the study identified in the CUP. For head and neck cancer, a statistically significant increased risk was observed in both the highest compared with lowest category of waist-hip ratio and dose–response analyses, but statistical significance was lost when the analyses were restricted to people who have never smoked. For dose–response analyses in people who have never smoked, a significant increased risk for oral cavity cancer and a significant decreased risk for oropharyngeal cancer were reported, but not were not significant for other specific cancers (see CUP mouth, pharynx and larynx SLR 2016, Table 35). The analyses included *adjustments* for age, sex, alcohol intake and, where appropriate, tobacco smoking.

5.1.8.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Specific mechanisms to support the relationship between body fatness and mouth, pharynx and larynx cancers have not been proposed to date. However, greater body fatness is associated with metabolic and *endocrine* abnormalities such as *hyperinsulinemia* and elevated levels of bioavailable *oestrogen*, and in other tissues, *insulin* and oestrogen have been shown to stimulate mitogenesis [333] and inhibit *apoptosis* [321, 322], leading to enhanced cellular proliferation. Obesity has also been shown to stimulate the inflammatory response, which may also promote *tumorigenesis* [326].

Further research on the mechanisms underlying the link between obesity and cancers of the mouth, pharynx and larynx is needed.

5.1.8.5 CUP Panel's conclusion

For BMI and waist circumference, one pooled analysis of 20 cohort studies reported a statistically significant increased risk for head and neck cancer for people who have never smoked in both highest compared with lowest category and dose–response analyses. The increased risk observed for underweight compared with normal weight may be due to pre-existing disease. There were few individual cohort studies published reviewing each cancer, so no meta-analyses were possible. Two other published pooled analyses were identified that showed significant decreased risk; however, they did not stratify by smoking status. There is evidence of plausible mechanisms.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is probably a cause of cancers of the mouth, pharynx and larynx.**

5.1.9 Stomach (cardia)

(Also see CUP stomach cancer report 2016: Section 7.7 and CUP stomach cancer SLR 2015: Sections 8.1.1.)

The evidence for BMI and *cardia stomach cancer* is presented in the following subsection. For information on BMI in young adulthood, waist circumference and waist-hip ratio and stomach cancer, see CUP stomach cancer SLR 2015: Sections 8.1.1, 8.2.1 and 8.2.3, respectively. Also, for information on the risk of *non-cardia stomach cancer*, see the relevant sections from the CUP stomach cancer report 2016 and the CUP stomach cancer SLR 2015.

5.1.9.1 Body mass index

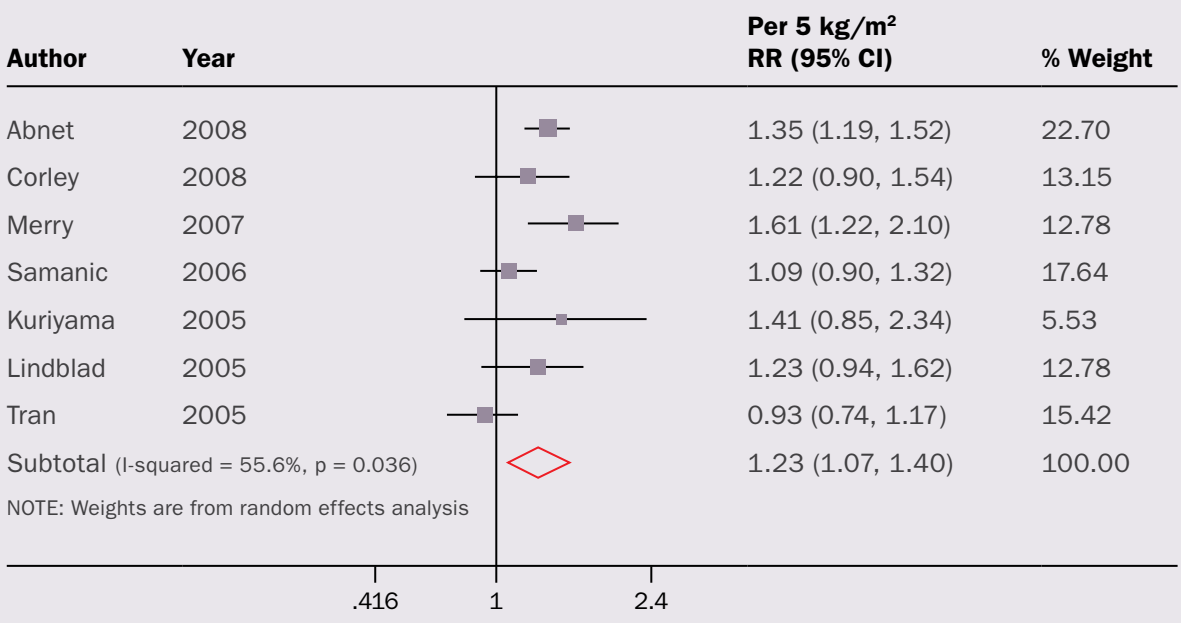
5.1.9.1.1 CUP dose–response meta-analyses

Seven of ten identified studies were included in the dose–response meta-analysis, which showed a statistically significant 23 per cent increased risk of cardia stomach cancer per 5 kg/m^2 increase in BMI (RR 1.23 [95% CI 1.07–1.40]; n = 2,050 cases) (see **Figure 5.31**). High *heterogeneity* was observed (I^2 = 56%). There was no evidence of small study bias with *Egger's test* (p = 0.29).

Stratified analyses for the risk of cardia stomach cancer per 5 kg/m^2 increase in BMI were conducted for geographic location and method of reporting height and weight. For details of other stratified analyses that have been conducted, see CUP stomach cancer SLR 2015, Section 8.1.1.

When stratified by geographic location, a statistically significant increased risk was observed in Europe (RR 1.27 [95% CI 1.01–1.60]) and North America (RR 1.32 [95% CI 1.18–1.48]), but not Asia. A significant increased risk was also observed for self-reported height and weight (RR 1.39 [95% CI 1.25–1.55]), but not measured height and weight.

Figure 5.31: CUP dose–response meta-analysis[1] for the risk of cardia stomach cancer, per 5 kg/m^2 increase in body mass index



Source: Abnet, 2008 [100]; Corley, 2008 [101]; Merry, 2007 [102]; Samanic, 2006 [104]; Kuriyama, 2005 [127]; Lindblad, 2005 [105]; Tran, 2005 [334].

[1] Three studies could not be included in the dose–response meta-analysis: one reported on patients who were obese, one reported on an exclude outcome and one did not provide sufficient information. For further details, see CUP stomach cancer SLR 2015, Table 177.

One published study that was included in the CUP dose–response meta-analysis [100] reported a significant increased risk of cardia stomach cancer in both people who smoke and those who do not smoke (see CUP stomach cancer report 2016, Table 7 and CUP stomach cancer SLR 2015, Table 176).

There was evidence of a non-linear dose–response relationship ($p < 0.001$; see **Figure 5.32**); with a significant increased risk of cardia stomach cancer at higher BMI levels (26 kg/m^2 and above; see CUP stomach cancer report 2016, Table 8 and CUP stomach cancer SLR 2015, Figure 201).

All studies included in the dose–response meta-analysis were adjusted for age, sex and tobacco smoking. No study was adjusted for *Helicobacter pylori* status. For information on the *adjustments* made in individual studies, see CUP stomach cancer SLR 2015, Table 176.

5.1.9.1.2 Published pooled analyses and meta-analyses

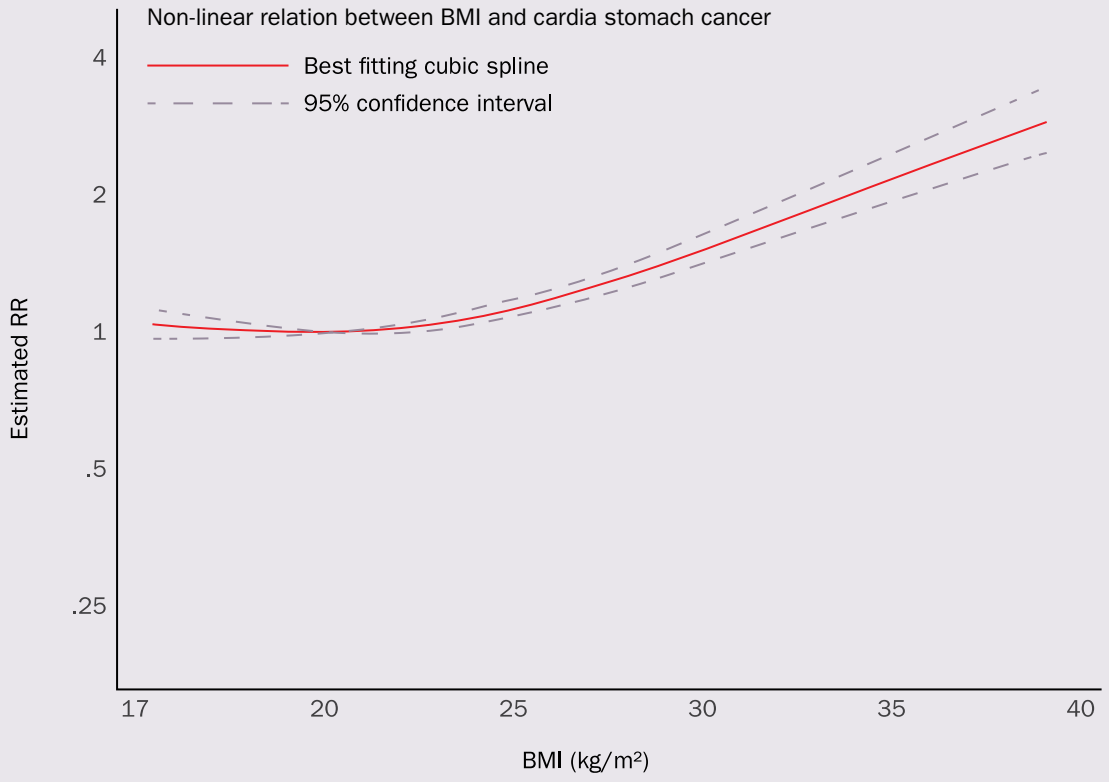
No published pooled analyses were identified. One other published meta-analysis of cohort studies on BMI and the risk of cardia stomach cancer was identified, which reported a statistically significant increased risk per 5 kg/m^2 increase in BMI (RR 1.32 [95% CI 1.07–1.64]) [335].

5.1.9.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Figure 5.32: CUP non-linear dose–response association of body mass index and the risk of cardia stomach cancer



Greater body fat promotes the development of *chronic* gastroesophageal reflux disease or *inflammation* of the oesophagus and the potential transition to Barrett's oesophagus, and increases the risk of developing *cardia stomach cancer*. Being overweight and obese is also associated with higher levels of *insulin*, which can act as a mitogen and has anti-apoptotic properties [321, 322] and therefore may represent a mechanism, though there are limited data to support this hypothesis to date. Obesity has also been shown to stimulate the inflammatory response, which may promote *tumorigenesis* [326].

5.1.9.3 CUP Panel's conclusion

The evidence for stomach cardia cancer was generally consistent. The dose–response meta-analysis showed a statistically significant increased risk, although with high *heterogeneity*, which may partially be explained by the size of the effect. A significant increased risk was also observed in some analyses stratified by geographic area (Europe and North America) and by tobacco smoking status. There was evidence of a non-linear relationship, with results becoming statistically significant at a BMI of approximately 26 kg/m^2 and above. Results were supported by one published meta-analysis. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI) is probably a cause of cardia cancer.**

5.1.10 Gallbladder

(Also see CUP gallbladder cancer report 2015: Section 7.1 and CUP gallbladder cancer SLR 2014: Section 8.1.1.)

The evidence for BMI is presented in the following subsection.

5.1.10.1 Body mass index

5.1.10.1.1 CUP dose–response meta-analyses

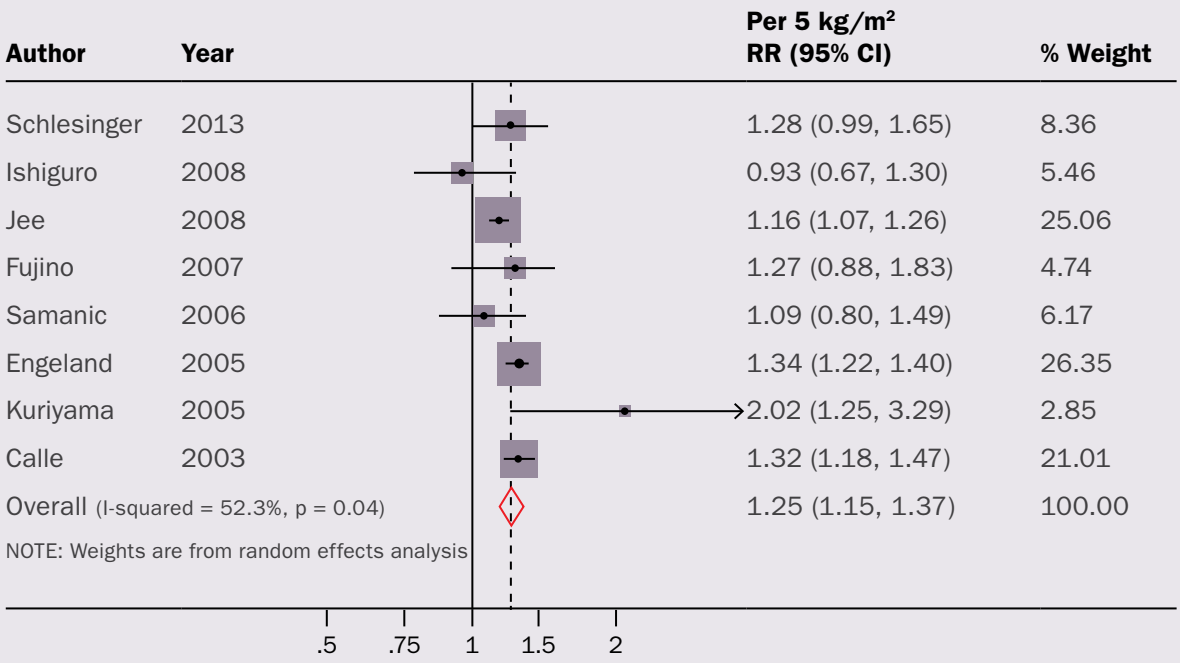
Eight of 11 identified studies were included in the dose–response meta-analysis, which showed a statistically significant 25 per cent increased risk of gallbladder cancer per 5 kg/m^2 of BMI (RR 1.25 [95% CI 1.15–1.37; n = 6,004 cases) (see **Figure 5.33**). Moderate *heterogeneity* was observed (I^2 = 52%), which appeared to be mainly due to the size of the effect. There was no evidence of small study bias with *Egger's test* (p = 0.89).

Stratified analyses for the risk of gallbladder cancer per 5 kg/m^2 increase in BMI were conducted for sex, geographic location and outcome.

When stratified by sex, a statistically significant increased risk was observed for both men (RR 1.23 [95% CI 1.13–1.33]) and women (RR 1.25 [95% CI 1.07–1.46]). When stratified by geographic location, a significant increased risk was observed in Europe (RR 1.32 [95% CI 1.24–1.41]), but not Asia. When stratified by outcome, a significant increased risk was observed for both gallbladder cancer incidence (RR 1.23 [95% CI 1.10–1.39]) and mortality (RR 1.31 [95% CI 1.18–1.46]) (see CUP gallbladder cancer report 2015, Table 1 and CUP gallbladder cancer SLR 2014, Figures 9, 10 and 11).

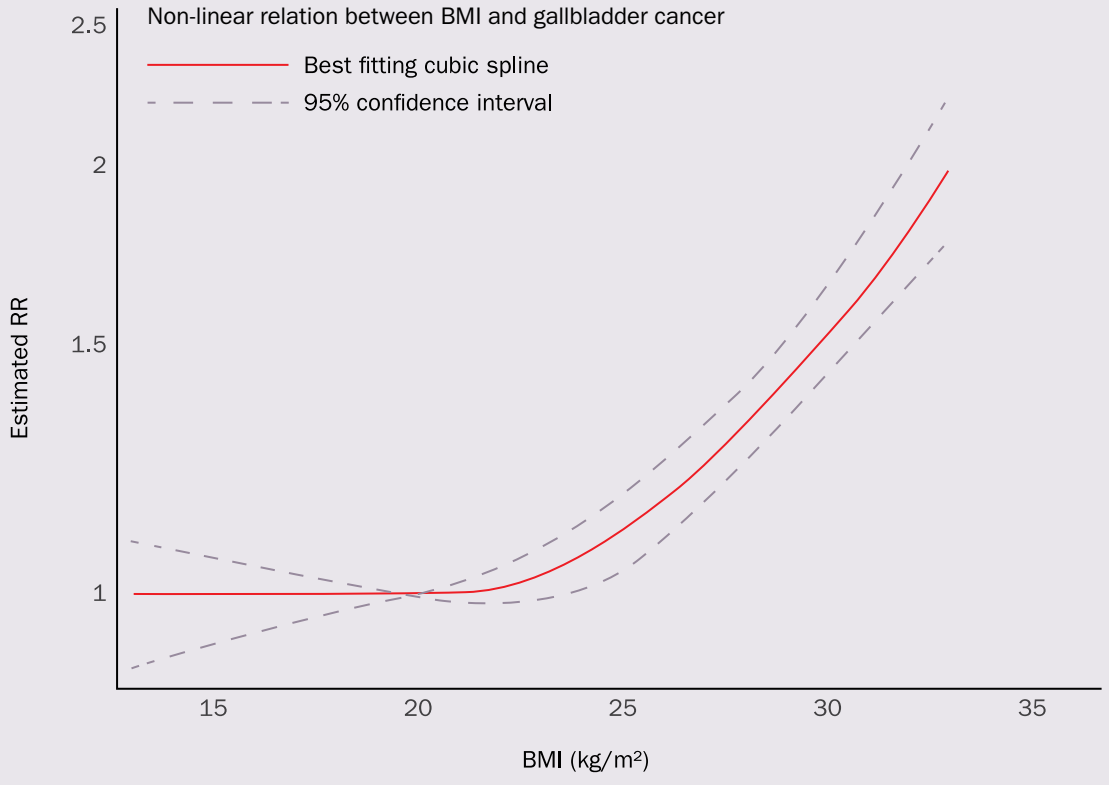
There was evidence of a non-linear dose–response relationship (p < 0.01; see **Figure 5.34**), with an increased risk at BMI of approximately 24 kg/m^2 or greater (see CUP gallbladder cancer SLR 2014, Figures 14 and 15, and Table 14).

Figure 5.33: CUP dose–response meta-analysis[1] for the risk of gallbladder cancer, per 5 kg/m² increase in body mass index



Source: Schlesinger, 2013 [156]; Ishiguro, 2008 [336]; Jee, 2008 [120]; Fujino, 2007 [161]; Samanic, 2006 [104]; Engeland, 2005 [196]; Kuriyama, 2005 [127]; Calle, 2003 [162].

Figure 5.34: CUP non-linear dose–response association of body mass index and the risk of gallbladder cancer



[1] Three studies could not be included in the dose–response meta-analysis as they did not provide sufficient information. For further details, see CUP gallbladder cancer SLR 2014, Table 13.

All studies included in the dose–response meta-analysis accounted for or adjusted for age and sex, about a half adjusted for tobacco smoking and alcohol consumption. One study [162] adjusted for physical activity.

5.1.10.2 Published pooled analyses and meta-analyses

One published *pooled analysis* (see **Table 5.16**) and two other published meta-analyses on BMI and the risk of gallbladder cancer were identified. One of the published meta-analyses of cohort studies reported a statistically significant increased risk per 5 kg/m^2 increase in BMI for women (RR 1.59 [95% CI 1.02–2.47]), but not for men [110]. The other published meta-analysis of eight cohort studies reported a significant increased risk when comparing obese (BMI > 30 kg/m^2) with normal weight (BMI < 25 kg/m^2) categories (RR 1.69 [95% CI 1.48–1.92] [337]).

5.1.10.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

The mechanisms underlying the positive association of body fatness with gallbladder cancer development are likely to be similar to those proposed for other anatomical sites, namely development of metabolic syndrome and its components, such as hyperglycemia, dyslipidemia, *hyperinsulinemia* and hypertension. *Chronic inflammation*, production of growth factors and increased levels of pro-inflammatory *cytokines* are also possible cancer-promoting consequences of increased body fatness [149]. Interestingly, body fatness and metabolic syndrome appear to be associated with increased risk of gallstones [338, 339], which has been observed as a major risk factor for gallbladder cancer development in various populations [340, 341], likely through promotion of increased chronic inflammation at this site [149]. The stronger association of body fatness with gallbladder cancer in women than in men may in part be due to adverse effects of female sex hormones on hepatic *bile* secretion and gallbladder function [342].

5.1.10.4 CUP Panel's conclusion

The evidence for BMI and gallbladder cancer was generally consistent, and the dose–response relationship in the CUP showed a statistically significant increased risk. Moderate heterogeneity was observed. This significant increased risk was still apparent when stratified by outcome and sex, but was only significant in European studies when stratified by geographic location. Non-linear analysis in the CUP showed an increased risk with higher BMI.

Table 5.16: Summary of published pooled analyses of body mass index and the risk of gallbladder cancer

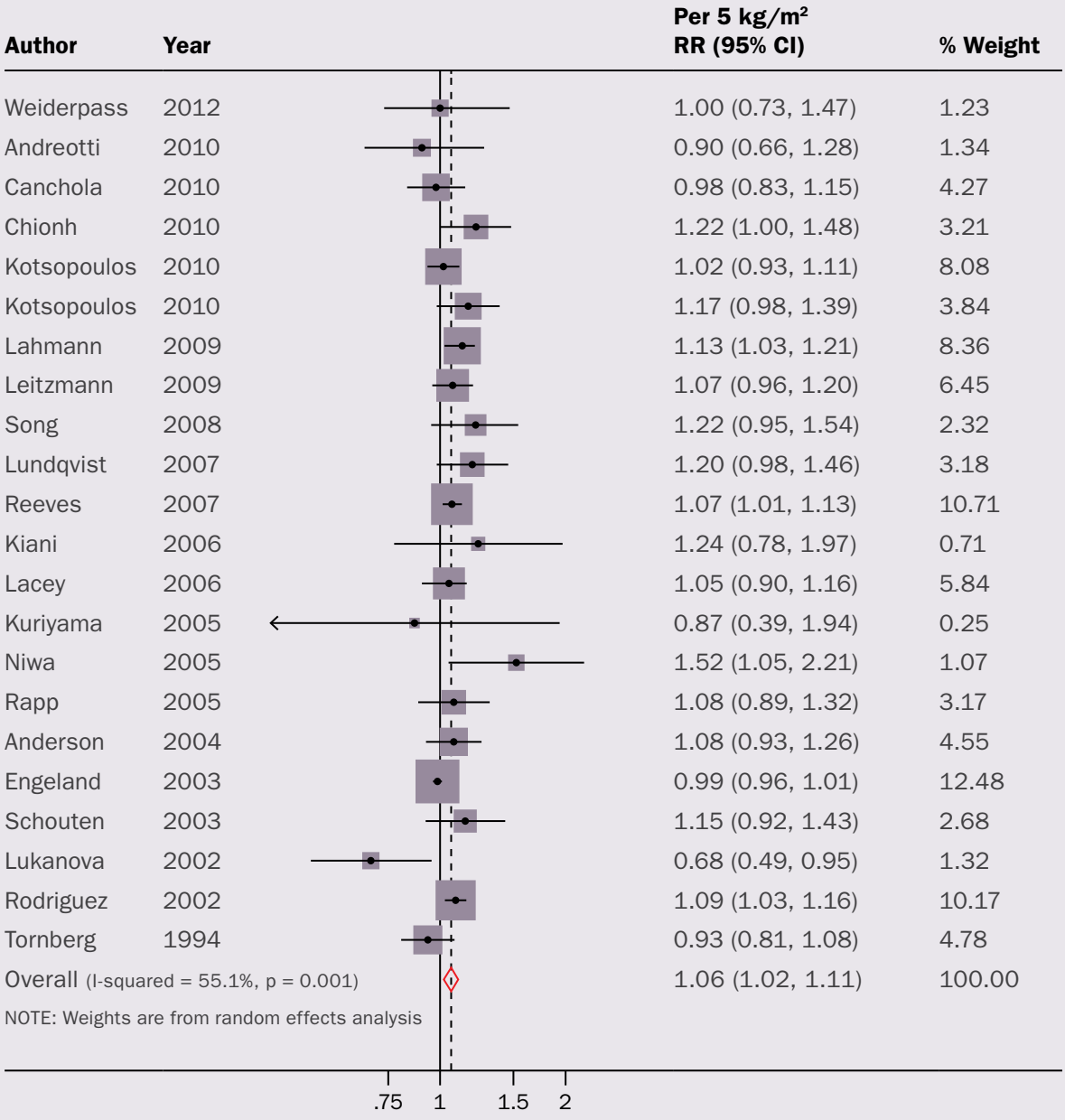
Publication	Increment	RR (95% CI)	No. of studies	No. of cases
Prospective Studies Collaboration [163]	5 kg/m^2	1.12 (0.90–1.38)	57 cohort	222 deaths

Results from one published pooled analysis and two published meta-analyses were also consistent with the CUP in the direction of the effect, although not all showed findings that were statistically significant. There is also evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI) probably causes gallbladder cancer.**

Figure 5.35: CUP dose–response meta-analysis[1] for the risk of ovarian cancer, per 5 kg/m² increase in body mass index



Source: Weiderpass, 2012 [343]; Andreotti, 2010 [116]; Canchola, 2010 [344]; Chionh, 2010 [345]; Kotsopoulos, 2010 [346]; Lahmann, 2009 [347]; Leitzmann, 2009 [348]; Song, 2008 [234]; Lundqvist, 2007 [235]; Reeves, 2007 [103]; Kiani, 2006 [349]; Lacey, 2006 [350]; Kuriyama, 2005 [127]; Niwa, 2005 [351]; Rapp, 2005 [130]; Anderson, 2004 [352]; Engeland, 2003 [353]; Schouten, 2003 [354]; Lukanova, 2002 [355]; Rodriguez, 2002 [356]; Tornberg, 1994 [244].

[1] The dose–response meta-analysis includes 24 studies and 22 data points, as Lukanova, 2002 [355], included three studies. One publication (Kotsopoulos, 2010 [346]) included results of two studies.

5.1.11 Ovary

(Also see CUP ovarian cancer report 2014: Section 7.2 and CUP ovarian cancer SLR 2013: Sections 8.1.1)

The evidence for BMI is presented in the following subsection. For information on waist circumference and waist-hip ratio, see CUP ovarian cancer SLR 2013: Sections 8.2.1 and 8.2.3, respectively.

5.1.11.1 Body mass index

5.1.11.1.1 CUP dose–response meta-analyses

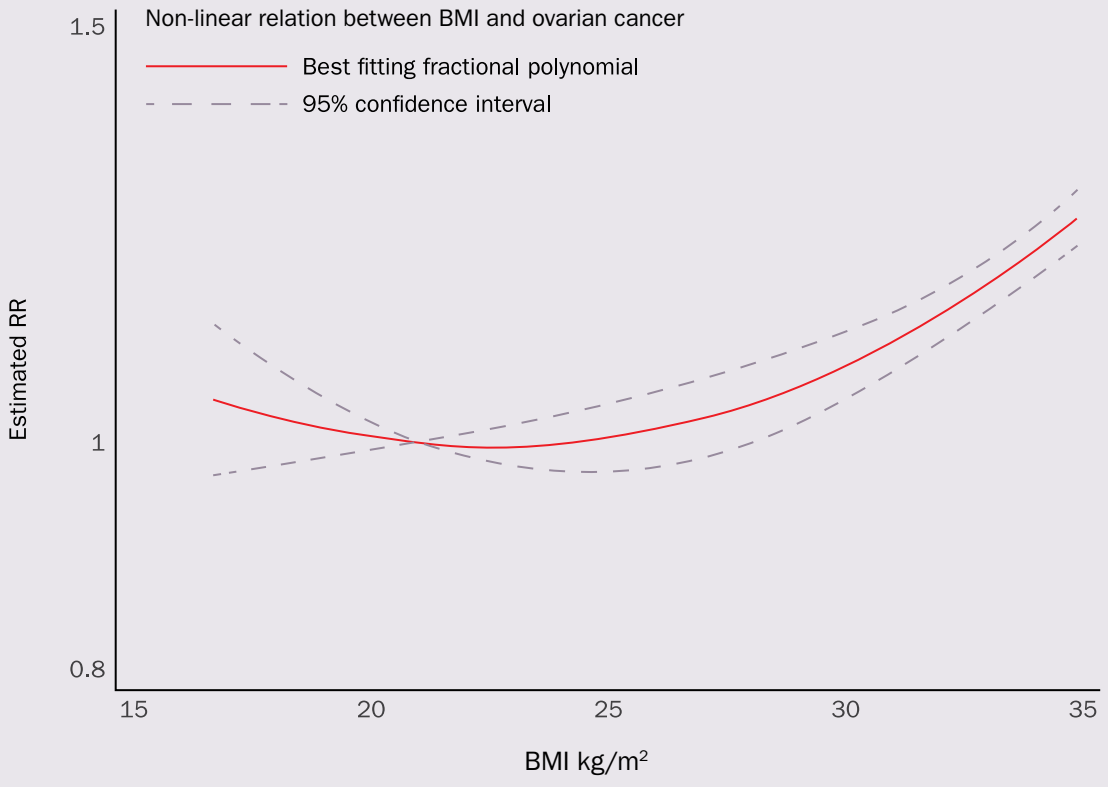
Twenty-four of 25 identified studies were included in the dose–response meta-analysis, which showed a statistically significant six per cent increased risk of ovarian cancer per 5 kg/m^2 increase in BMI (RR 1.06 [95% CI 1.02–1.11]; n = 15,899 cases) (see **Figure 5.35**).

High *heterogeneity* was observed (I^2 = 55%), largely due to the size of the effect. There was no evidence of small study bias with *Egger's test* (p = 0.05).

There was evidence of a non-linear dose–response relationship (p < 0.0001; see **Figure 5.36**), with a significant increase in risk of ovarian cancer for BMI greater than 28.4 kg/m^2.

All studies included in the dose–response meta-analysis adjusted for age, most adjusted reproductive factors and tobacco smoking and MHT use. Some studies adjusted for alcohol consumption and physical activity.

Figure 5.36: CUP non-linear dose–response association of body mass index and the risk of ovarian cancer



5.1.11.1.2 Published pooled analyses and meta-analyses

Two published *pooled analyses* (see **Table 5.17**) and two other published meta-analyses on BMI and the risk of ovarian cancer were identified. One pooled analysis reported no significant association in both highest versus lowest and dose–response analyses of cohort studies [357]. The second pooled study conducted a dose–response analysis and reported no significant association [358].

The two published meta-analyses of cohort studies also reported no significant association between BMI and the risk of ovarian cancer [110, 359] (see CUP ovarian cancer SLR 2013, Section 8.1.1).

An additional CUP analysis that included the Collaborative Group on Epidemiological Studies of Ovarian Cancer [358] combined with non-overlapping studies from the CUP also reported no significant association between BMI and the risk of ovarian cancer [116, 127, 130, 194, 234, 235, 244, 343–346, 348–350, 355].

The Collaborative Group on Epidemiological Studies of Ovarian Cancer *pooled analysis* found a significant increased risk of ovarian cancer in women who had never used MHT (RR 1.10 [95% CI 1.07–1.13]) per 5 kg/m^2 increase in BMI, but not in those who had ever used MHT [358]. Similarly, the 2013 Ovarian Cancer Association Consortium pooled analysis of *case-control studies* observed a significant increased risk among women who had never used MHT (RR 1.10 [95% CI 1.07–1.14]) per 5 kg/m^2, but not in those who had used MHT [75]. Furthermore, markedly different patterns of association between BMI and the risk of ovarian cancer were observed when considering pre and postmenopausal women and the different histological subtypes separately [75].

5.1.11.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Greater body fatness is associated with higher circulating levels of *endogenous oestrogens* and androgens, and these hormones are associated, albeit inconsistently, with a higher risk of ovarian cancer [360]. Adipose tissue is also a source of *adipokines* and inflammatory *cytokines* that promote a low-grade inflammatory milieu, and both local and systemic pro-inflammatory factors are associated with development of ovarian cancer [361–365].

Table 5.17: Summary of published pooled analyses of body mass index and the risk of ovarian cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies	No. of cases
Pooling Project of Prospective Studies of Diet and Cancer [357]	BMI ≥ 30 vs 18.5–23	1.03 (0.86–1.22)	12 cohort	2,036
	4 kg/m^2	1.01 (0.95–1.07)		2,036
Collaborative Group on Epidemiological Studies of Ovarian Cancer [358]	5 kg/m^2	1.03 (1.00–1.06)	17 cohort	10,643

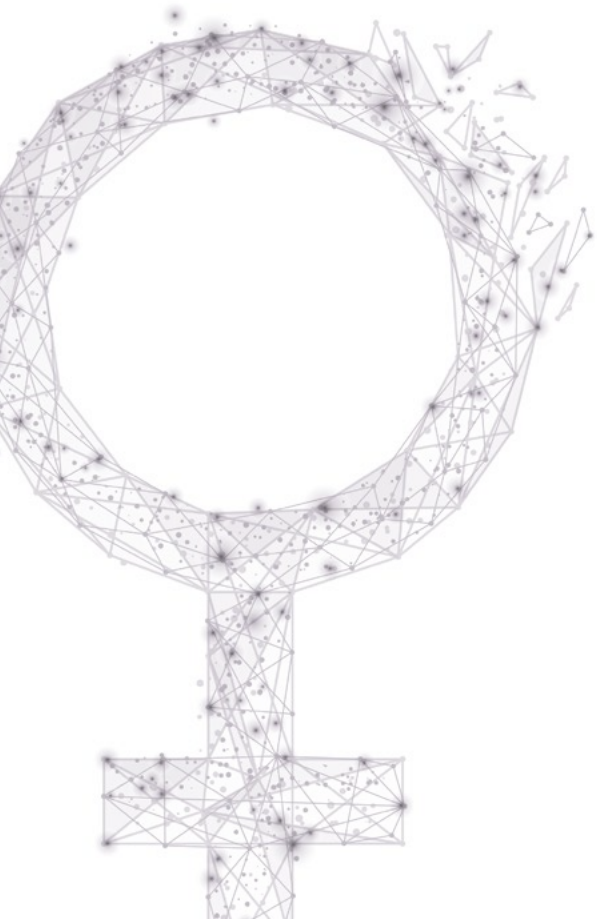
5.1.11.3 CUP Panel's conclusion

Overall the evidence from the CUP was supportive of an association between body fatness (which the CUP Panel interprets to be marked by BMI) and ovarian cancer. High heterogeneity was observed. Results from published pooled analyses identified several possible sources of *heterogeneity* including MHT use, menopausal status and histologic type. There was evidence of a non-linear dose–response relationship, with a significant increase in risk of ovarian cancer for BMI greater than 28.4 kg/m^2.

Considering results from both the CUP analysis and published pooled analyses, the Panel concluded there was evidence of an association between overall body fatness and ovarian cancer risk. There is evidence for plausible mechanisms that operate in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI) is probably a cause of ovarian cancer.**



5.1.12 Prostate (advanced)

(Also see CUP prostate cancer report 2014: Section 7.6 and CUP prostate cancer SLR 2014: Sections 8.1.1, 8.2.1 and 8.2.3.)

The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. For information on BMI at age 18 to 21, see CUP prostate cancer SLR 2014: Section 8.1.1. For information on the risk of non-advanced prostate cancer, also see the relevant sections from the CUP prostate cancer report 2014 and the CUP prostate cancer SLR 2014.

For the CUP analyses studies on advanced prostate cancer, studies with the following outcomes were included: fatal, advanced, aggressive or high-grade prostate cancer.

5.1.12.1 Body mass index

5.1.12.1.1 CUP dose–response meta-analysis

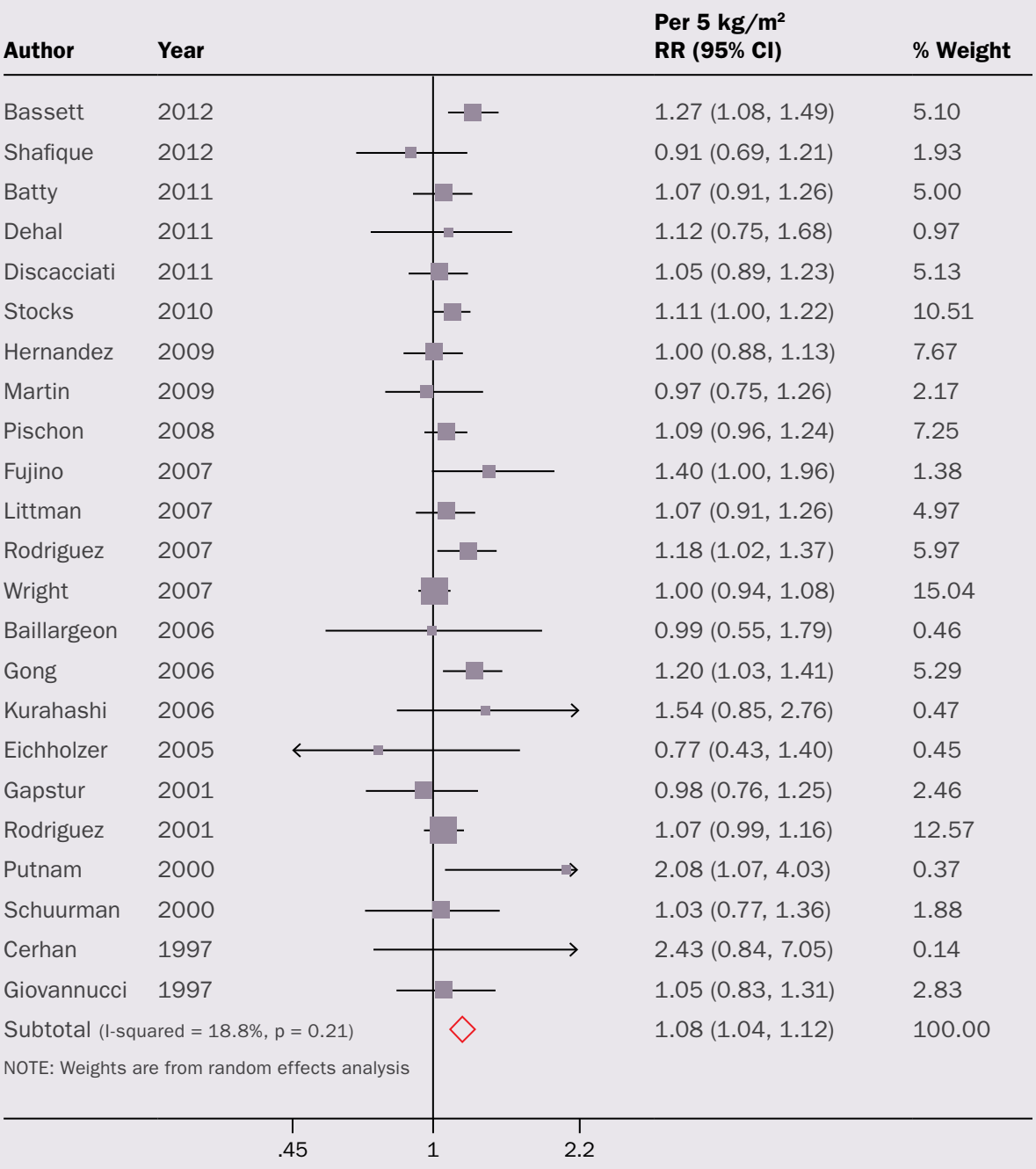
Twenty-three of 24 identified studies were included in the dose–response meta-analysis, which showed a statistically significant eight per cent increased risk of advanced prostate cancer per 5 kg/m^2 increase in BMI (RR 1.08 [95% CI 1.04–1.12]; n = 11,149 cases) (see **Figure 5.37**).

Low *heterogeneity* was observed (I^2 = 19%). There was no evidence of a non-linear dose–response relationship (p = 0.75).

Five of the studies on advanced prostate cancer investigated the influence of PSA tests, and no studies identified a modification of the association. Three of the studies reported a lower proportion of screening or PSA testing in obese men.

All studies included in the dose–response meta-analysis adjusted for age, about a half for tobacco smoking and some for alcohol consumption and physical activity.

Figure 5.37: CUP dose–response meta-analysis for the risk of advanced prostate cancer, per 5 kg/m² increase in BMI



Source: Bassett, 2012 [366]; Shafique, 2012 [367]; Batty, 2011 [368]; Dehal, 2011 [369]; Discacciati, 2011 [370]; Stocks, 2010 [371]; Hernandez, 2009 [372]; Martin, 2009 [373]; Pischon, 2008 [374]; Fujino, 2007 [161]; Littman, 2007 [375]; Rodriguez, 2007 [376]; Wright, 2007 [377]; Baillargeon, 2006 [378]; Gong, 2006 [379]; Kurahashi, 2006 [380]; Eichholzer, 2005 [381]; Gapstur, 2001 [382]; Rodriguez, 2001 [383]; Putnam, 2000 [384]; Schuurman, 2000 [385]; Cerhan, 1997 [386]; Giovannucci, 1997 [387].

5.1.12.1.2 Published pooled analyses and meta-analyses

Two published pooled analyses were identified (**Table 5.18**) and two other published meta-analyses on BMI and the risk of advanced or fatal prostate cancer were identified. One pooled analysis [163] reported a statistically significant increased risk, and the other reported no significant association [145]. One meta-analysis included 13 cohort studies and reported a statistically significant increased risk per 5 kg/m² increase in BMI (RR 1.09 [95% CI 1.02–1.16]) [388]. The other meta-analysis of six cohort studies on prostate cancer mortality also reported a significant increased risk (RR 1.15 [95% CI 1.06–1.25]) [389].

Table 5.18: Summary of published pooled analyses of body mass index and the risk of fatal prostate cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies (cohort)	No. of deaths
Prospective Studies Collaboration [163]	5 kg/m^2	1.13 (1.02–1.24)	57	1,243
Asia-Pacific Cohort Studies Collaboration [145]	30–60 vs 18.5–24.9 kg/m^2	1.45 (0.97–2.19)	39	278
	5 kg/m^2	1.18 (0.96–1.44)		

5.1.12.2 Waist circumference

5.1.12.2.1 CUP dose–response meta-analysis

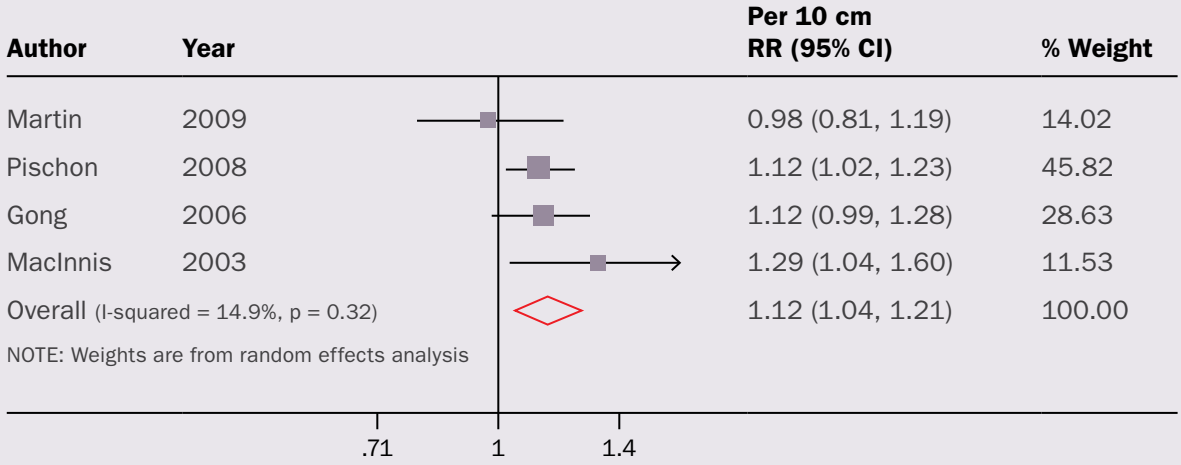
Four of five identified studies were included in the dose–response meta-analysis, which showed a statistically significant 12 per cent increased risk of advanced prostate cancer per 10 centimetre increase in waist circumference (RR 1.12 [95% CI 1.04–1.21]; n = 1,781 cases) (see **Figure 5.38**). Low *heterogeneity* was observed (I^2 = 15%).

All studies included in the dose–response meta-analysis adjusted for age, a half for tobacco smoking and physical activity and some for alcohol consumption.

5.1.12.2.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on waist circumference and the risk of advanced prostate cancer were identified.

Figure 5.38: CUP dose–response meta-analysis for the risk of advanced prostate cancer, per 10 centimetre increase in waist circumference



Source: Martin, 2009 [373]; Pischon, 2008 [374]; Gong, 2006 [379]; MacInnis, 2003 [390].

5.1.12.3 Waist-hip ratio

5.1.12.3.1 CUP dose–response meta-analysis

All four identified studies were included in the dose–response meta-analysis, which showed a statistically significant 15 per cent increased risk of advanced prostate cancer per 0.1 unit increase in waist-hip ratio (RR 1.15 [95% CI 1.03–1.28]; n = 1,781) (see **Figure 5.39**). No *heterogeneity* was observed.

All studies included in the dose–response meta-analysis adjusted for age, about a half for tobacco smoking and some for alcohol consumption and physical activity.

5.1.12.3.2 Published pooled analyses and meta-analyses

No published pooled analyses and no other published meta-analyses on waist-hip ratio and the risk of advanced prostate cancer were identified.

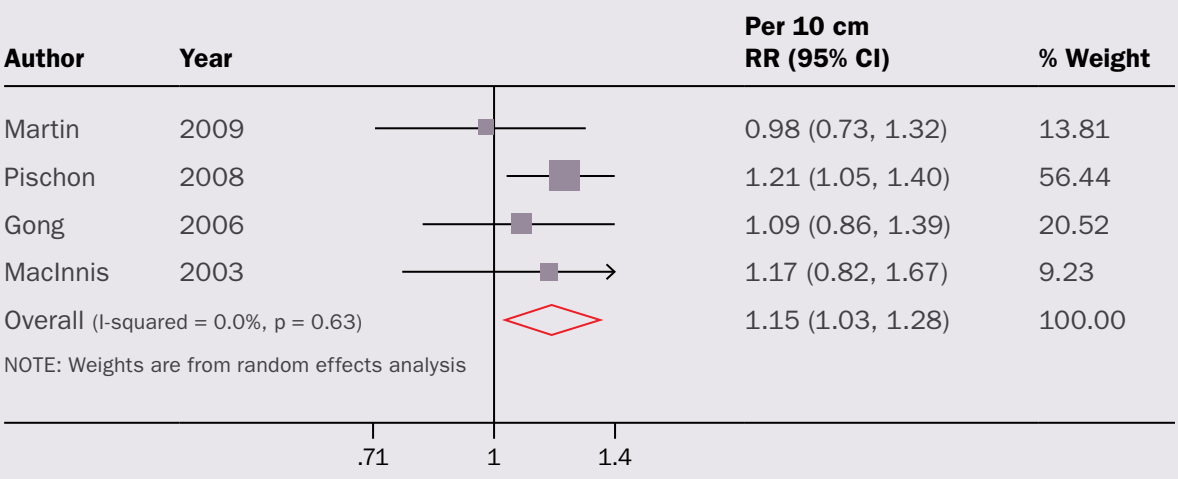
5.1.12.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Greater body fatness is associated with higher risk of advanced prostate cancer. Several biological mechanisms have been proposed that link *adiposity* to cancer, including dysregulated sex steroid metabolism, *hyperinsulinemia* and elevated levels of proinflammatory *cytokines*; however, the evidence linking these pathways specifically to prostate cancer is limited.

Figure 5.39: CUP dose–response meta-analysis for the risk of advanced prostate cancer, per 0.1 unit increase in waist-hip ratio



Source: Martin, 2009 [373]; Pischon, 2008 [374]; Gong, 2006 [379]; MacInnis, 2003 [390].

Androgens such as testosterone play critical roles in the development and function of the prostate gland. It has been hypothesised that a hypoandrogenic environment promotes the development of higher-grade prostate tumours, and at least two prospective studies have reported inverse relationships between serum testosterone levels and higher grade prostate cancer [391, 392]. Testosterone levels tend to be lower in obese males compared with those of normal weight and therefore may represent a potential mediator of the relationship between body fatness and advanced prostate cancer.

Hyperinsulinemia has been shown to accelerate tumour growth in prostate cancer xenograft models, and human prostate tumours commonly express the *insulin* receptor, suggesting that insulin may stimulate prostate cancer growth [393–395]. However, data in human studies generally do not support a relationship between hyperinsulinemia and development of prostate cancer. Similarly, proinflammatory cytokines and *adipokines* such as *leptin* have been shown to exert a *mitogenic* effect in prostate cancer *cell lines* that are human *androgen*-independent, inducing proliferation and inhibiting *apoptosis*, while epidemiologic data generally do not support an association between inflammatory cytokines and prostate cancer development. Overall, further research is needed to advance knowledge on the mechanisms that potentially underlie the association of body fatness with advanced prostate cancer.

5.1.12.5 CUP Panel's conclusion

The evidence was consistent for a dose–response relationship for advanced prostate cancer. There was a statistically significant increased risk for BMI, waist circumference and waist-hip ratio with low heterogeneity observed in the dose–response meta-analyses. There was no evidence of a non-linear relationship for BMI, and no analyses were conducted for waist circumference and waist-hip ratio. The results were supported by two pooled analyses (one of which was statistically significant) and one other published meta-analysis for BMI. There is evidence for plausible mechanisms that operate in humans.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) is probably a cause of advanced prostate cancer.**

5.1.13 Breast (premenopause)

(Also see CUP breast cancer report 2017: Section 7.9 and CUP breast cancer SLR 2017: Sections 8.1.1, 8.2.1 and 8.2.3.)

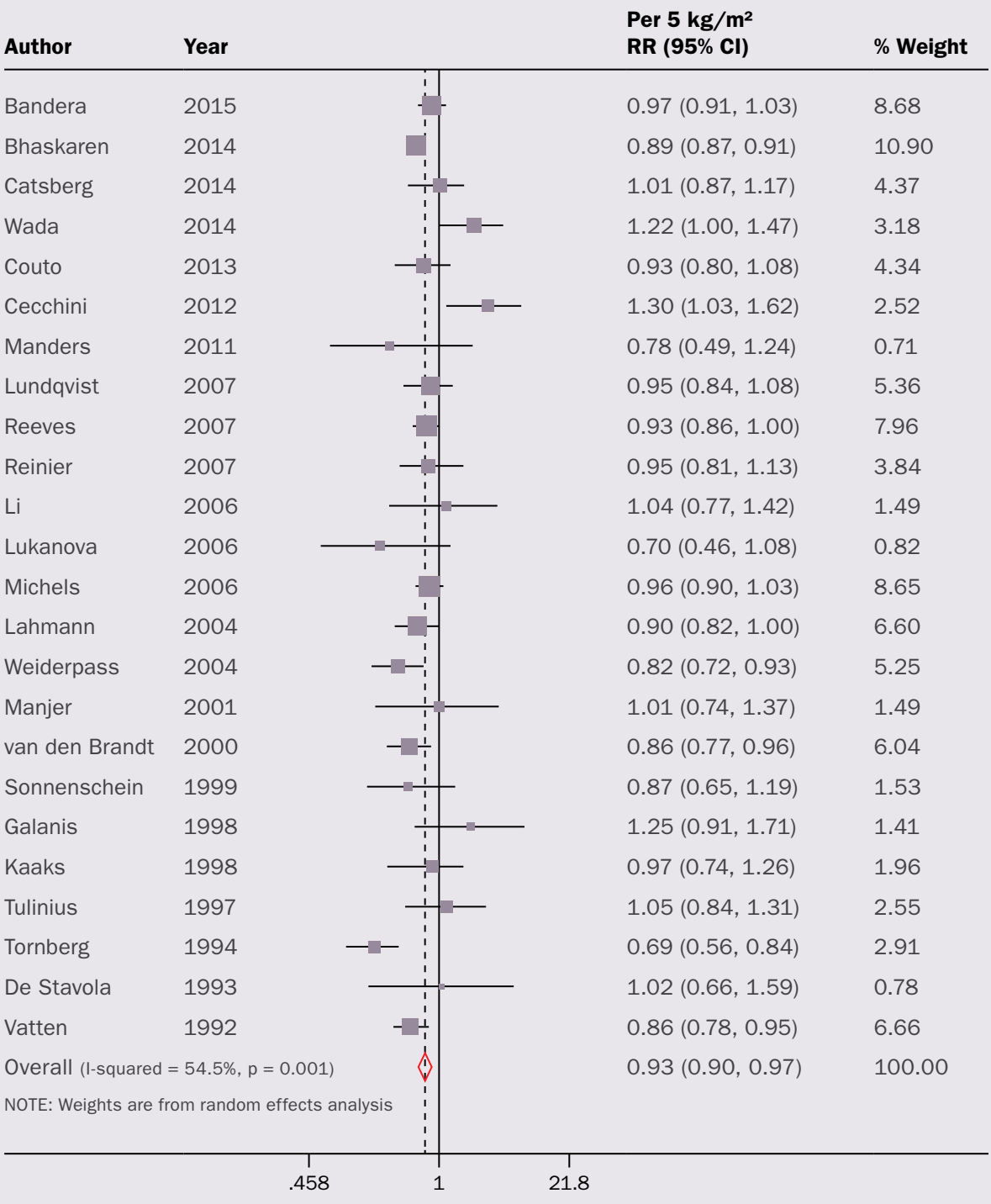
The evidence for BMI, waist circumference and waist-hip ratio is presented in the following subsections. For evidence for BMI in young adulthood and premenopausal breast cancer, see **Section 5.2.1**. For information on weight change, weight gain and BMI change, see CUP breast cancer SLR 2017: Section 8.1.6.

5.1.13.1 Body mass index

5.1.13.1.1 CUP dose–response meta-analyses

Of 128 studies identified, 37 (including studies from three *pooled analyses*) were included in the dose–response meta-analysis, which showed a statistically significant seven per cent decreased risk of premenopausal breast cancer per 5 kg/m^2 increase in BMI for all incidence and mortality studies combined (RR 0.93 [95% CI 0.90–0.97]; n = 16,371 cases) (see **Figure 5.40**). High *heterogeneity* was observed (I^2 = 55%), which could be explained in part by the geographic locations of the cohorts. There was no evidence of small study bias with *Egger's test* (p = 0.13).

Figure 5.40: CUP dose–response meta-analysis[1,2] for the risk of premenopausal breast cancer, per 5 kg/m² increase in body mass index



Source: Bandera, 2015 [215]; Bhaskaran, 2014 [217]; Catsburg, 2014 [218]; Wada, 2014 [222]; Couto, 2013 [223]; Cecchini, 2012 [225]; Manders, 2011 [396]; Lundqvist, 2007 [235]; Reeves, 2007 [103]; Reinier, 2007 [397]; Li, 2006 [237]; Lukanova, 2006 [194]; Michels, 2006 [398]; Lahmann, 2004 [262]; Weiderpass, 2004 [399]; Manjer, 2001 [239]; van den Brandt, 2000 [240]; Sonnenschein, 1999 [241]; Galanis, 1998 [242]; Kaaks, 1998 [243]; Tulinius, 1997 [177]; Tornberg, 1994 [244]; De Stavola, 1993 [245]; Vatten, 1992 [400].

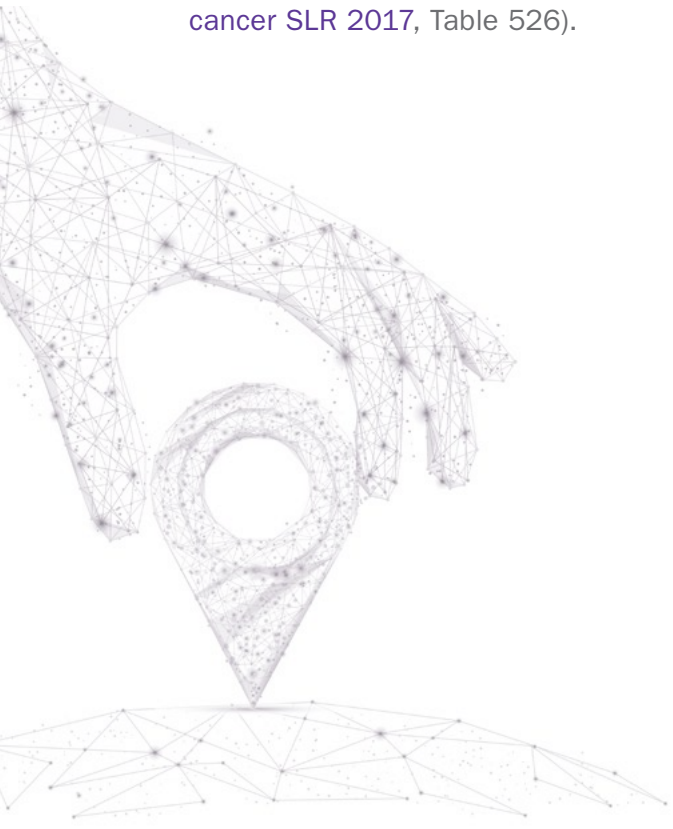
[1] Fifty-seven studies could not be included in any of the dose–response meta-analyses; two reported on an excluded exposure, one reported on a different subtype, 18 did not provide sufficient information and 36 overlapped with other studies included in the meta-analyses; e.g. some pooled analyses were excluded as some studies were common to other pooled analyses. For further details, see CUP breast cancer SLR 2017, Table 529.

[2] The CUP dose–response meta-analysis included three pooled analyses (Bandera, 2015 [215], Wada, 2014 [222], van den Brandt, 2000 [240]), which included 14 of the identified studies. For two studies [235, 245], the RR included data for two individual studies.

There was no evidence of a non-linear dose–response relationship (p = 0.78).

Stratified analyses for the risk of premenopausal breast cancer per 5 kg/m^2 increase in BMI were conducted for geographic location and using the anthropometric assessment method.

When stratified by geographic location, a statistically significant decreased risk was observed in Europe (RR 0.89 [95% CI 0.86–0.92]), but not North America or Asia (see CUP breast cancer report 2017, Table 15 and CUP breast cancer SLR 2017, Figure 537). When stratified by the anthropometric assessment method, a significant decreased risk was observed in studies that measured participants' height and weight (RR 0.92 [95% CI 0.86–0.98]; see CUP breast cancer SLR 2017, Figure 538), but not those that were based on self-reported measurements. There was no significant association when analyses were restricted to only invasive breast cancer, studies that involved breast or mammography screening, and studies that adjusted for *confounders* (age, alcohol intake and reproductive factors) (see CUP breast cancer SLR 2017, Table 525). When stratified by *hormone receptor* type, no significant association was observed (see CUP breast cancer SLR 2017, Table 526).



Fifteen of the studies in the dose–response meta-analysis (including studies from two pooled analyses) [103, 218, 222, 223, 240, 262] simultaneously adjusted for age, alcohol intake and reproductive factors. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 528.

In a separate meta-analysis of the 36 studies on premenopausal breast cancer mortality (including a pooled analysis of 35 studies [163]) (n = 545 cases), no significant association was observed (RR 1.00 [95% CI 0.73–1.38]) with evidence of high *heterogeneity* (I^2 = 75%) (see CUP breast cancer SLR 2017, Figure 543).

5.1.13.1.2 Published pooled analyses and meta-analyses

Seven published *pooled analyses* and six other published meta-analyses on BMI and the risk of premenopausal breast cancer were identified. Four of the pooled analyses [163, 215, 222, 240] were included in the CUP dose–response meta-analyses. Two of these reported no significant association per 5 kg/m^2 increase in BMI [215, 222], one reported a significant decreased risk [240] and one showed a significant increased risk for mortality per 5 kg/m^2 increase in BMI [163]. Results from the other three published pooled analyses are shown in **Table 5.19**.

Two of the published meta-analyses reported a significant decreased risk of premenopausal breast cancer (RR 0.72 [95% CI 0.55–0.94] for the highest compared with the lowest level of BMI and RR 0.95 [95% CI 0.94–0.97] per 5 kg/m^2 increase in BMI) [247, 401], and two reported a significant decreased risk for joint ER-positive and PR-positive premenopausal breast cancer (RR 0.90 [95% CI 0.82–0.99] per 5 kg/m^2 increase in BMI and RR 0.78 95% CI [0.67–0.92] for the highest compared with the lowest BMI) [247, 252] (see CUP breast cancer SLR 2017, Table 527).

Table 5.19: Summary of published pooled analyses of body mass index and the risk of premenopausal breast cancer

Publication	Increment/contrast	RR (95% CI)	No. of studies	No. of cases
Breast Cancer Association Consortium Studies (BCAC) [402]	≥ 30 vs ≤ 25 kg/m^2 Invasive breast cancer		12 cohort and population-based case control	
	Oestrogen-receptor-positive	0.81 (0.69–0.95)		10,900 diagnoses
	Oestrogen-receptor-negative	1.10 (0.92–1.30)		3,895 diagnoses
The Metabolic Syndrome and Cancer Project (Me-Can) [253]	≥ 31.7 vs ≤ 20 kg/m^2		6 cohort	
	Incidence	0.70 (0.57–0.85)		3,043 diagnoses
	Mortality	1.22 (0.64–2.31)		414 deaths
Asia-Pacific Cohort Studies Collaboration (APCSC) [145]	30–60 vs 18.5–24.9 kg/m^2	0.93 (0.42–2.09)	35 cohort	324 deaths (breast cancer unspecified)
	Per 5 kg/m^2	1.13 (0.97–1.33)	35 cohort	

5.1.13.2 Waist circumference

5.1.13.2.1 CUP dose–response meta-analyses

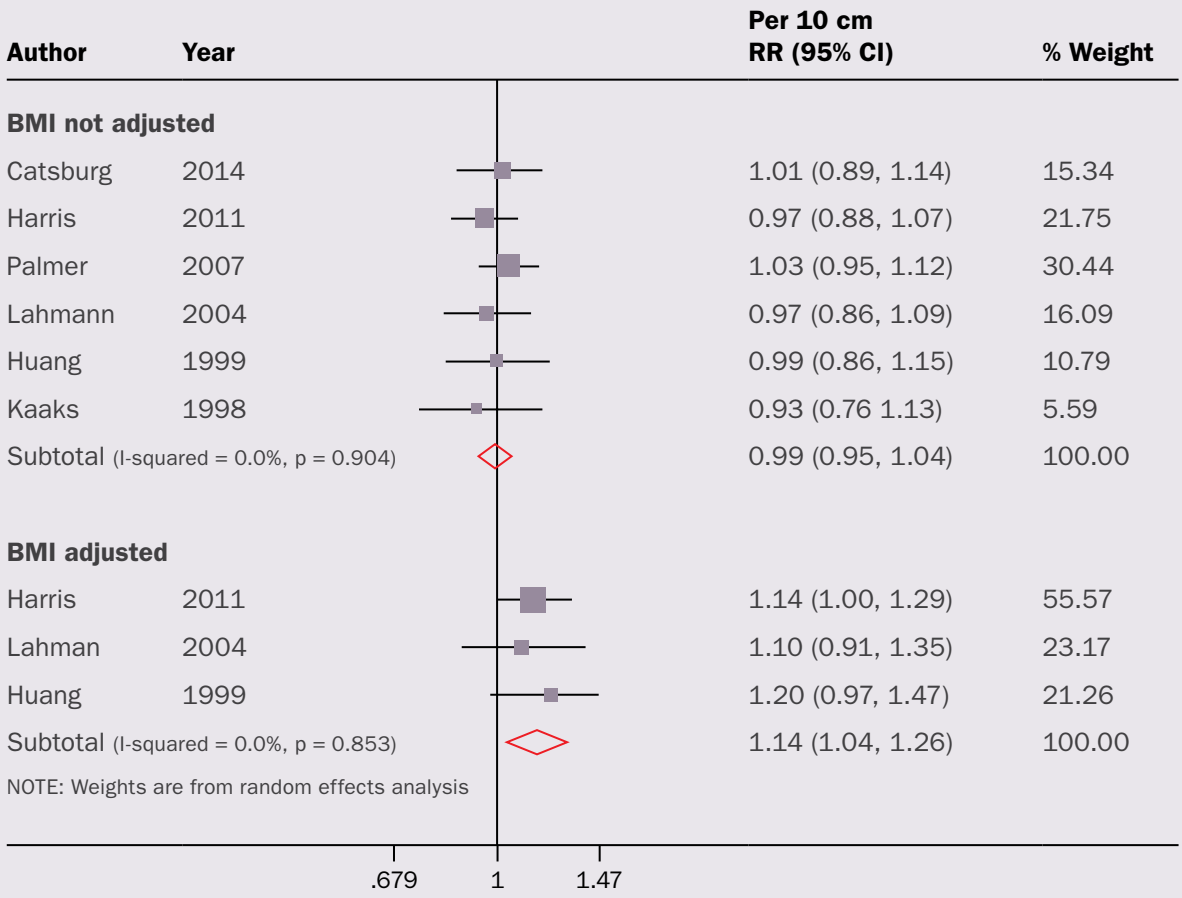
All six identified studies were included in the dose–response meta-analysis, which showed no significant association between the risk of premenopausal breast cancer and waist circumference (RR 0.99 [95% CI 0.95–1.04]; per 10 centimetre increase in waist circumference; n = 2,423 cases) (see **Figure 5.41**). No *heterogeneity* was observed, and there was no evidence of small study bias with *Egger's test* (p = 0.17).

In a separate dose–response meta-analysis of the three studies adjusting for BMI (n = 1,291 cases), a statistically significant 14 per cent increased risk of premenopausal breast cancer was observed per 10 centimetre increase in waist circumference (RR 1.14 [95% CI 1.04–1.26]), with no evidence of *heterogeneity* (see **Figure 5.41**).

There was evidence of a non-linear dose–response relationship (p < 0.01; see **Figure 5.42**). The curve showed an initial increase in the risk of premenopausal breast cancer with an increase in waist circumference that began to decrease after 80 centimetres (see CUP breast cancer SLR 2017, Figure 604 and Table 577).

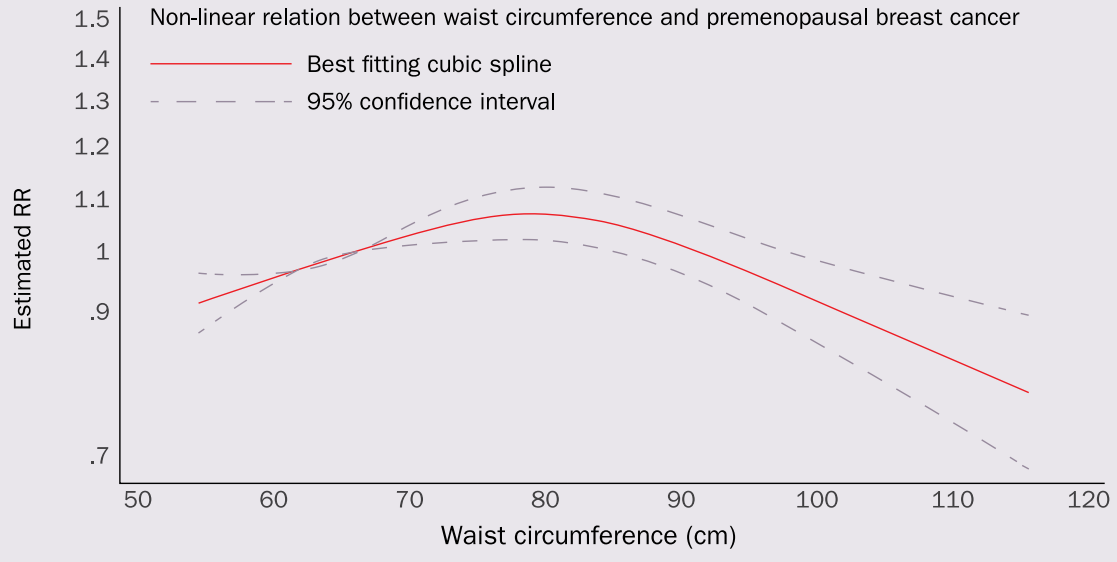
Most studies included in the dose–response meta-analysis adjusted for age, alcohol intake and reproductive factors. Three studies [243, 257, 261] did not adjust for alcohol intake. Not all studies reported results with and without BMI adjustment. For information on the *adjustments* made in individual studies, see CUP breast cancer SLR 2017, Table 575.

Figure 5.41: CUP dose–response meta-analysis for the risk of premenopausal breast cancer, per 10 centimetre increase in waist circumference



Source: Catsburg, 2014 [218]; Harris, 2011 [403]; Palmer, 2007 [257]; Lahmann, 2004 [262]; Huang, 1999 [261]; Kaaks, 1998 [243].

Figure 5.42: CUP non-linear dose–response association of waist circumference and the risk of premenopausal breast cancer[1]



[1] Studies for which BMI was not adjusted.

5.1.13.2.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. One other published meta-analysis on waist circumference and the risk of premenopausal breast cancer was identified, which showed no significant association per 10 centimetre increase in waist circumference [401].

5.1.13.3 Waist-hip ratio

5.1.13.3.1 CUP dose–response meta-analyses

All 11 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed no significant association between the risk of premenopausal breast cancer and waist-hip ratio (RR 1.06 [95% CI 0.98–1.16]; per 0.1 unit increase in waist-hip ratio; n = 3,465 cases) (see **Figure 5.43**). Low *heterogeneity* was observed (I^2 = 27%), and there was no evidence of small study bias with *Egger's test* (p = 0.40).

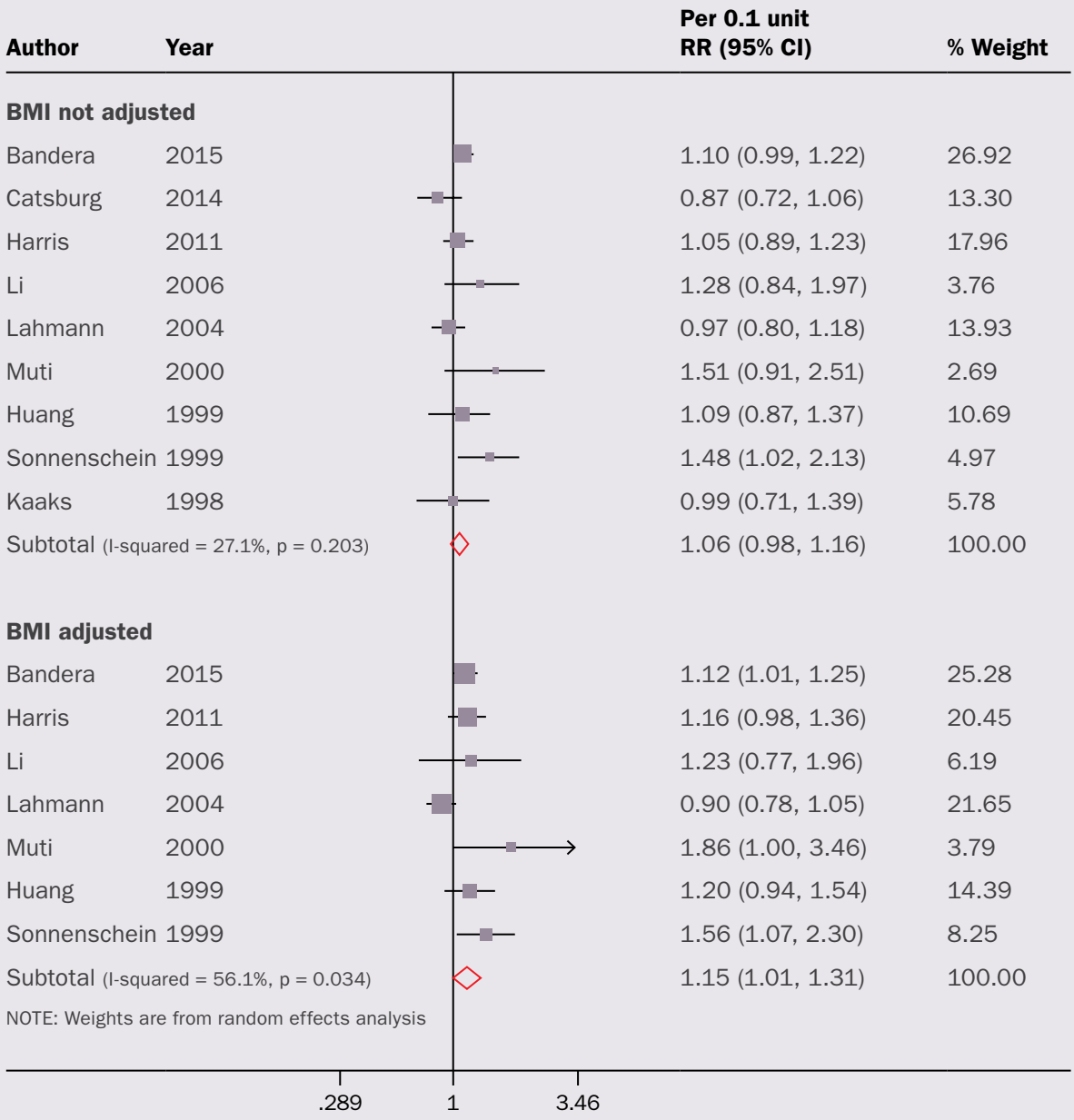
However, the association became statistically significant (RR 1.09 [95% CI 1.02–1.17]) in the sensitivity analysis when one study (13% weight) [218] was excluded from the dose–response meta-analysis. A dose–response meta-analysis of the nine studies (including one pooled analysis [215]) adjusting for BMI (n = 2,722 cases) showed a statistically significant 15 per cent increased risk of premenopausal breast cancer per 0.1 unit increase in waist-hip ratio (RR 1.15 [95% CI 1.01–1.31]), with high *heterogeneity* (I^2 = 56%); see **Figure 5.43**.

Stratified analyses for the risk of premenopausal breast cancer per 0.1 unit increase in waist-hip ratio were conducted for geographic location and using the anthropometric assessment method.

When stratified by geographic location, a statistically significant increased risk was observed for BMI-adjusted studies in North America (RR 1.16 [95% CI 1.07–1.26]), but not Europe. No significant association was observed in North America and Europe in studies that did not adjust for BMI (see CUP breast cancer SLR 2017, Figure 617). When stratified by anthropometric assessment method, a significant increased risk was observed with self-reported waist and hip measurement (RR 1.14 [95% CI 1.05–1.24]), but not in studies where waist and hip measurements were measured (see CUP breast cancer SLR 2017, Figure 618). A significant increased risk was also observed without *adjustment* for *confounding factors* (age, alcohol intake and reproductive factors) in BMI-adjusted (RR 1.28 [95% CI 1.04–1.59]) and unadjusted (RR 1.15 [95% CI 1.02–1.29]) studies.

All studies included in the dose–response meta-analysis adjusted for most major confounding factors, but most studies did not adjust for alcohol consumption. Two studies did not adjust for BMI [218, 243]. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 588.

Figure 5.43: CUP dose–response meta-analysis[1] for the risk of premenopausal breast cancer, per 0.1 unit increase in waist-hip ratio



Source: Bandera, 2015 [215]; Catsburg, 2014 [218]; Harris, 2011 [403]; Li, 2006 [237]; Lahmann, 2004 [262]; Muti, 2000 [267]; Huang, 1999 [261]; Sonnenschein, 1999 [241]; Kaaks, 1998 [243].

5.1.13.3.2 Published pooled analyses and meta-analyses

One published *pooled analysis* and one other published meta-analysis on waist-hip ratio and the risk of premenopausal breast cancer were identified. The published pooled analysis reported no significant association for the highest compared with the lowest measurement of waist-hip ratio and was included in the CUP dose–response analysis [215]. The published meta-analysis showed a statistically significant increased risk per 0.1 unit increase in waist-hip ratio (RR 1.08 [95% CI 1.01–1.16]) [401].

[1] The CUP dose–response meta-analysis included one pooled analysis (Bandera, 2015 [215]), which included three of the identified studies.

5.1.13.4 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

There is no single well-established mechanism though which body fatness could prevent premenopausal breast cancer. One possible mechanism relates to anovulation, which is commonly associated with obesity and results in abnormal hormone profiles, characterised by lower *endogenous* levels of *progesterone* [404, 405]. Although the mechanisms of the potential protective effect of obesity on premenopausal breast cancer have not been fully elucidated, they appear to be related to fat distribution, as a higher waist circumference seems to be more strongly associated with an increased risk of premenopausal breast cancer after accounting for BMI. Mechanisms specifically related to abdominal *adiposity* measured by waist circumference include a strong relationship to *chronic inflammation* and *insulin resistance* [406].

5.1.13.5 CUP Panel's conclusion

The evidence for BMI was generally consistent and the CUP dose–response meta-analysis showed a statistically significant decreased risk with increasing BMI. No effect was observed for BMI and mortality. Four pooled analyses identified by the CUP on BMI were included in the dose–response meta-analysis. High heterogeneity was observed for BMI; however, this could be due to the geographic locations of cohorts, and low or no heterogeneity was observed for waist circumference and waist-hip ratio. There was no evidence of a non-linear relationship for BMI. No significant association was observed for waist circumference and waist-hip ratio, although a significant increased risk was observed after adjusting for BMI. There was evidence of a non-linear relationship for waist circumference. There is evidence of plausible mechanisms operating in humans. Although overall the evidence for body fatness indicates a decreased risk of premenopausal breast cancer, the Panel notes that breast cancer diagnosed after menopause is much more common and that the decreased risk of premenopausal breast cancer would be outweighed by an increased risk of postmenopausal breast cancer.

The CUP Panel concluded:

- **Greater adult body fatness (marked by BMI, waist circumference and waist-hip ratio) probably protects against premenopausal breast cancer.**

5.2 Body fatness in young adulthood

Table 5.20 summarises the main findings from the CUP dose–response meta-analyses of cohort studies on body fatness in young adulthood and the risk of breast cancer. Separate conclusions for body fatness in young adulthood (18 to 30 years of age) are made for breast cancer owing to the well-established *effect modification* by menopausal status. For the evidence on adult body fatness and pre and postmenopausal breast cancer, see **Sections 5.1.13** and **5.1.5** respectively. For cancer of the endometrium, the evidence for BMI at age 18 to 25 years is summarised under adult body fatness (see **Section 5.1.6.2**).

Table 5.20: Summary of CUP dose–response meta-analyses of body fatness in young adulthood[1] and the risk of breast cancer

Cancer	Measure-ment	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion[2]	Date of CUP cancer report[3]
Breast (pre-menopause)	BMI	12	12	4,953	0.82 (0.76–0.89)	5 kg/m^2	15	**Probable: Decreases risk**	2017
Breast (post-menopause)	BMI	21	18	10,229	0.82 (0.76–0.88)	5 kg/m^2	44	**Probable: Decreases risk**	2017

1 Evidence for body fatness in young adulthood and breast cancer (pre and postmenopause) comes from women aged about 18 to 30 years and includes evidence marked by BMI.

2 See Definitions of WCRF/AICR grading criteria (**Section 1**: Body fatness and weight gain and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'probable'.

3 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

Evidence for endometrial cancer (2013) is included under adult body fatness (see **Section 5.1.6.2**). Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[1]: stomach (2016), pancreas (2012), prostate (2014) and skin (2017).

The strong evidence for the effects of body fatness in young adulthood on the risk of cancer is described in the following subsections. This strong evidence includes analyses performed in the CUP and other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the following subsections and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

5.2.1 Breast (premenopause)

(Also see CUP breast cancer report 2017: Section 7.8 and CUP breast cancer SLR 2017: Section 8.1.1.)

The evidence for BMI of women aged about 18 to 30 years is presented in the following subsection. For evidence on adult body fatness and premenopausal breast cancer, see **Section 5.1.13**.

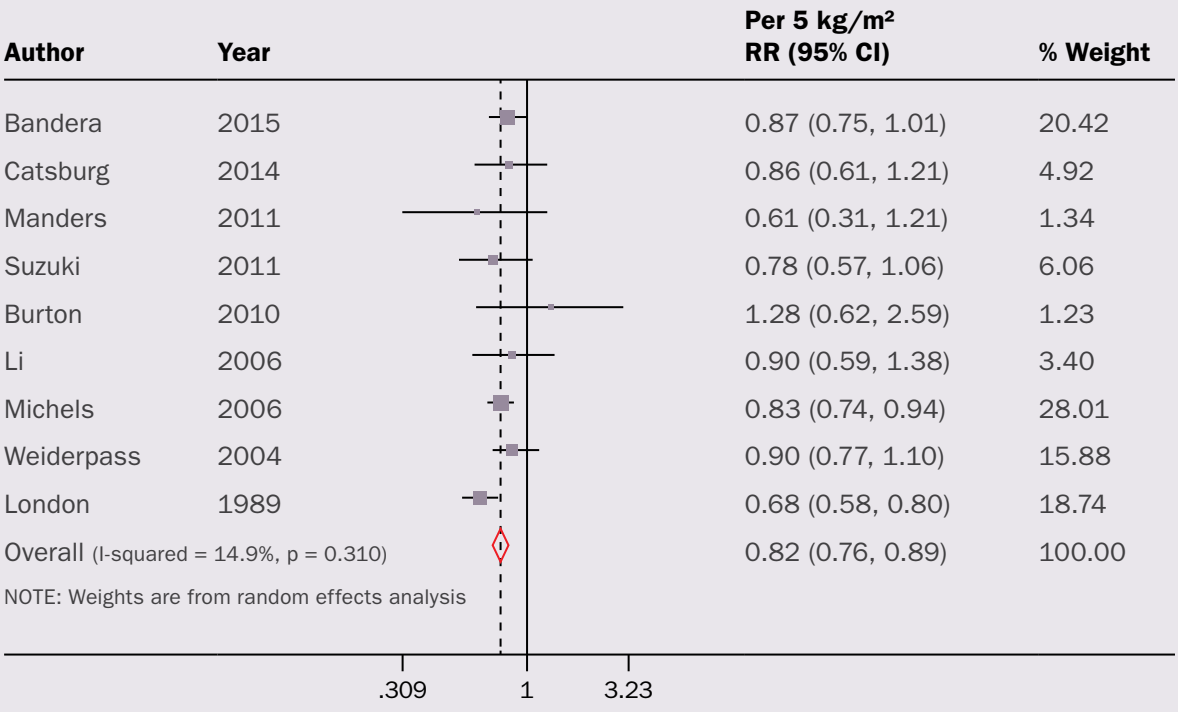
5.2.1.1 Body mass index

5.2.1.1.1 CUP dose–response meta-analyses

All 12 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant 18 per cent decreased risk of premenopausal breast cancer per 5 kg/m^2 increase in BMI in young adulthood (RR 0.82 [95% CI 0.76–0.89]; n = 4,953 cases) (see **Figure 5.44**). Low *heterogeneity* was observed (I^2 = 15%), and there was no evidence of small study bias with *Egger's test* (p = 0.75).

[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

Figure 5.44: CUP dose–response meta-analysis[1] for the risk of premenopausal breast cancer, per 5 kg/m² increase in body mass index in young adulthood



Source: Bandera, 2015 [215]; Catsburg, 2014 [218]; Manders, 2011 [396]; Suzuki, 2011 [407]; Burton, 2010 [408]; Li, 2006 [237]; Michels, 2006 [398]; Weiderpass, 2004 [399]; London, 1989 [409].

Stratified analyses for the risk of premenopausal breast cancer per 5 kg/m² increase in BMI in young adulthood were conducted for geographic location; simultaneous adjustment for age, alcohol intake and reproductive factors; and after adjustment for weight change or adult BMI and/or waist-hip ratio.

When stratified by geographic location, a statistically significant decreased risk was observed in North America (RR 0.80 [95% CI 0.71–0.90]), but not Asia or Europe (see CUP breast cancer SLR 2017, Figure 571). The significant decreased risk remained in studies simultaneously adjusted for age, alcohol intake and reproductive factors (RR 0.77 [95% CI 0.70–0.85]), as well as studies adjusted for weight change or adult BMI or waist-hip ratio (RR 0.85 [95% CI 0.79–0.92]) (see CUP breast cancer SLR 2017, Table 543).

There was no evidence of a non-linear dose–response relationship (p = 0.09).

All studies included in the dose–response meta-analysis adjusted for age and most adjusted for reproductive factors; some studies adjusted for alcohol consumption and physical activity. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 544.

5.2.1.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* on BMI in young adulthood and the risk of premenopausal breast cancer was identified. No other published meta-analyses have been identified. The pooled analysis was included in the CUP dose–response meta-analysis and reported no significant association for the highest compared with the lowest measure of BMI in young adulthood [215].

[1] The CUP dose–response meta-analysis included one pooled analysis (Bandera, 2015 [215]), which included three of the identified studies, and one study (Suzuki, 2011 [407]) that included two cohorts.

5.2.1.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Body fatness in childhood and adolescence is inversely related to the risk of premenopausal breast cancer as well as postmenopausal breast cancer, suggesting a long-term effect of body fatness at young age on breast cancer risk later in life. These findings contrast with the higher risk of breast cancer among postmenopausal women with greater body fatness in adulthood. Early life, including childhood and adolescence, is hypothesised to be a critical window for breast *carcinogenesis*. This is a period of rapid growth and development of breast tissue, with higher rates of mammary gland tissue proliferation during puberty, which may increase susceptibility to molecular damage and may explain why particular exposures may be important for breast cancer risk later in life.

Body fatness during childhood has been associated with slower adolescent growth and development; however, peak height growth velocity as a measure of adolescent development is associated with an increased risk of breast cancer [410]. Higher circulating levels of IGF-I, the main mediator of growth hormone activity, is an established positive risk factor for breast cancer [411] but may be lower among women who had greater body fatness in childhood and adolescence [412]. Sex hormones may also partly explain the inverse relation between *adiposity* in early life and risk of breast cancer. Adipose tissue-derived *oestrogen* in overweight adolescents may induce early breast differentiation and render the breast tissue less susceptible to carcinogenesis, as has been demonstrated in animal models [413]. Obese young women are also more likely to experience anovulation and therefore lower levels of ovarian hormones such as *progesterone* and lower peaking of oestradiol [404]. However, body fatness in pre-adolescent and adolescent girls is related to higher *insulin* [414] and *androgen* levels and lower sex hormone binding globulin concentrations [415], which would be hypothesised to increase breast cancer risk. Overall, the mechanisms underlying the inverse association of body fatness in early life and risk of breast cancer are complex, likely multiple and not well-delineated.

5.2.1.3 CUP Panel's conclusion

The evidence for body fatness in young adulthood and premenopausal breast cancer was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant decreased risk with increasing BMI in young adulthood. Low *heterogeneity* was observed. Significant findings were observed in North American studies, and the decreased risk remained significant when adjusted for age, alcohol intake and reproductive factors, and when adjusted for weight change or adult BMI or waist-hip ratio. There was no evidence of a non-linear relationship. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Greater body fatness (marked by BMI) in young adulthood (aged about 18 to 30 years) probably protects against premenopausal breast cancer.**

5.2.2 Breast (postmenopause)

(Also see CUP breast cancer report 2017: Section 7.8 and CUP breast cancer SLR 2017: Section 8.1.1.)

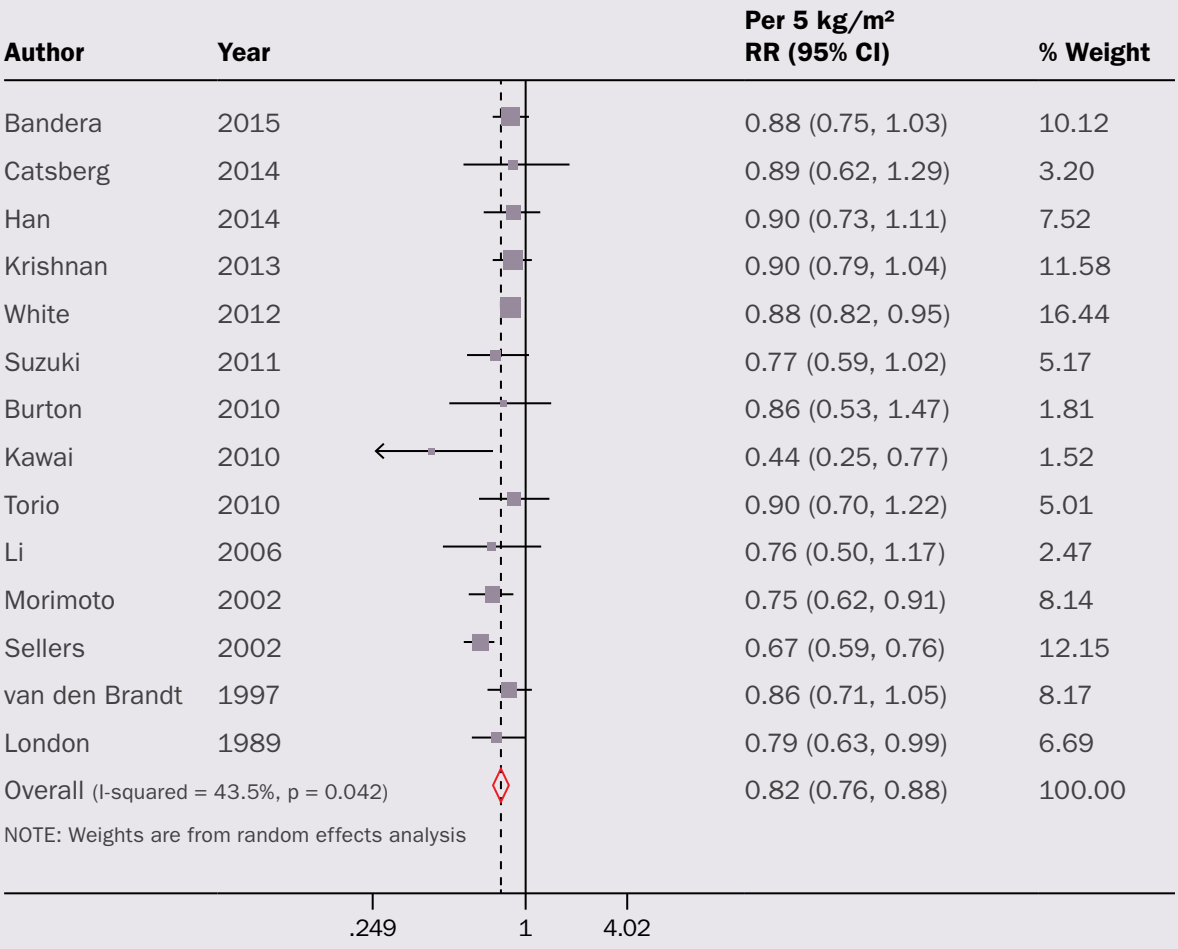
The evidence for BMI of women aged about 18 to 30 years is presented in the following subsection. For evidence on adult body fatness and adult weight gain and postmenopausal breast cancer, see **Sections 5.1.5** and **5.3.1** respectively.

5.2.2.1 Body mass index

5.2.2.1.1 CUP dose–response meta-analyses

Eighteen of 22 identified studies (including one *pooled analysis*) were included in the dose–response meta-analysis, which showed a statistically significant 18 per cent decreased risk of postmenopausal breast cancer per 5 kg/m^2 increase in BMI in young adulthood (RR 0.82 [95% CI 0.76–0.88]; n = 10,229 cases) (see **Figure 5.45**). Moderate *heterogeneity* was observed (I^2 = 44%), and there was no evidence of small study bias with *Egger's test* (p = 0.28).

Figure 5.45: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 5 kg/m^2 increase in body mass index in young adulthood



Source: Bandera, 2015 [215]; Catsburg, 2014 [218]; Han, 2014 [416]; Krishnan, 2013 [224]; White, 2012 [228]; Suzuki, 2011 [407]; Burton, 2010 [408]; Kawai, 2010 [417]; Torio, 2010 [231]; Li, 2006 [237]; Morimoto, 2002 [418]; Sellers, 2002 [263]; van den Brandt, 1997 [419]; London, 1989 [409].

[1] The CUP dose–response meta-analysis included one pooled analysis (Bandera, 2015 [215]), which included four of the identified studies, and one study (Suzuki, 2011 [407]) that included two cohorts.

Stratified analyses for the risk of postmenopausal breast cancer per 5 kg/m^2 increase in BMI in young adulthood were conducted for geographic location; simultaneous *adjustment* for age, alcohol intake and reproductive factors; and after adjustment for weight change or adult BMI and/or waist-hip ratio.

When stratified by geographic location, a statistically significant decreased risk was observed in North America (RR 0.82 [95% CI 0.75–0.90]) and Asia (RR 0.68 [95% CI 0.51–0.92]), but not Europe (see CUP breast cancer SLR 2017, Figure 576). The significant decreased risk remained in studies simultaneously adjusted for age, alcohol intake and reproductive factors (RR 0.81 [95% CI 0.74–0.88]), and in studies adjusted for weight change or adult BMI and/or waist-hip ratio (RR 0.76 [95% CI 0.64–0.91]).

There was no evidence of a non-linear dose–response relationship (p = 0.07).

All studies included in the dose–response meta-analysis adjusted for age and most adjusted for reproductive factors, about a half of studies adjusted for alcohol consumption, smoking and physical activity and some adjusted for MHT use. For information on the adjustments made in individual studies, see CUP breast cancer SLR 2017, Table 548.

5.2.2.1.2 Published pooled analyses and meta-analyses

One published *pooled analysis* on BMI in young adulthood and the risk of postmenopausal breast cancer was identified. No other published meta-analyses have been identified. The pooled analysis was included in the CUP and reported no significant association for the highest compared with the lowest measure of BMI in young adulthood [215].

5.2.2.2 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

For further information on general processes involved in the development of cancer, see The cancer process.

Body fatness in childhood and adolescence is inversely related to the risk of premenopausal breast cancer as well as postmenopausal breast cancer, suggesting a long-term effect of body fatness at a young age on breast cancer risk later in life. These findings contrast with the higher risk of breast cancer among postmenopausal women who had greater body fatness in adulthood. Early life, including childhood and adolescence, is hypothesised to be a critical window for breast *carcinogenesis*. This is a period of rapid growth and development of breast tissue, with higher rates of mammary gland tissue proliferation during puberty, which may increase susceptibility to molecular damage and may explain why particular exposures may be important for breast cancer risk later in life.

Body fatness during childhood has been associated with slower adolescent growth and development; however, peak height growth velocity as a measure of adolescent development is associated with an increased risk of breast cancer [410]. Higher circulating levels of IGF-I, the main mediator of growth hormone activity, is an established positive risk factor for breast cancer [411] but may be lower among women who had greater body fatness in childhood and adolescence [412]. Sex hormones may also partly explain the inverse relation between early life *adiposity* and breast cancer risk. Adipose-tissue-derived *oestrogen* in overweight adolescents may induce early breast differentiation and render the breast tissue less susceptible to

carcinogenesis, as has been demonstrated in animal models [413]. Obese young women are also more likely to experience anovulation and therefore lower levels of ovarian hormones such as *progesterone* and lower peaking of oestradiol [404]. However, body fatness in pre-adolescent and adolescent girls is related to higher *insulin* [414] and *androgen* levels and lower sex-hormone binding globulin concentrations [415], which would be hypothesised to increase breast cancer risk. Overall, the mechanisms underlying the inverse association of early life body fatness and breast cancer risk are complex, likely multiple and not well-delineated.

5.2.2.3 CUP Panel's conclusion

The evidence for body fatness in young adulthood and postmenopausal breast cancer was generally consistent, and the CUP dose–response meta-analysis showed a statistically significant decreased risk with increasing BMI in young adulthood. Moderate *heterogeneity* was observed. Significant findings were observed in North American studies and Asian studies. The decreased risk remained significant when adjusted for age, alcohol intake and reproductive factors, and when adjusted for weight change or adult BMI or waist-hip ratio. There was no evidence of a non-linear relationship. There is evidence of plausible mechanisms operating in humans.

The CUP Panel concluded:

- **Greater body fatness (marked by BMI) in young adulthood (aged about 18 to 30 years) probably protects against postmenopausal breast cancer.**

5.3 Adult weight gain

Separate conclusions for adult weight gain are made for breast cancer because of the well-established *effect modification* by menopausal status (for the evidence on adult body fatness and pre and postmenopausal breast cancer, see **Sections 5.1.13** and **5.1.5** respectively). For cancer of the endometrium, the evidence for adult weight gain is summarised under adult body fatness (see **Section 5.1.6.3**).

Table 5.21 summarises the main findings from the CUP dose–response meta-analysis of cohort studies on adult weight gain and the risk of postmenopausal breast cancer.

Table 5.21: CUP dose–response meta-analysis of adult weight gain and the risk of postmenopausal breast cancer

Cancer	Total no. of studies	No. of studies in meta-analysis	No. of cases	Risk estimate (95% CI)	Increment	I^2 (%)	Conclusion[1]	Date of CUP cancer report[2]
Breast (postmenopause)	22	15	16,660	1.06 (1.05–1.08)	5 kg	38	**Convincing: Increases risk**	2017

1 See Definitions of WCRF/AICR grading criteria (**Section 1**: Body fatness and weight gain and the risk of cancer: a summary matrix) for explanations of what the Panel means by 'convincing'.

2 Throughout this Third Expert Report, the year given for each cancer site is the year the CUP cancer report was published, apart from for nasopharynx, cervix and skin, where the year given is the year the SLR was last reviewed. Updated CUP cancer reports for nasopharynx and skin will be published in the future.

Evidence for cancers of the endometrium is included under body fatness (**Section 5.1.6.3**). Evidence for cancers of the following types was discussed in the CUP but was too limited to draw a conclusion[1]: pancreas (2012), breast (premenopause, 2017) and skin (2017).

The strong evidence on the effects of adult weight gain on the risk of cancer is described in the following subsection. This strong evidence includes analyses performed in the CUP and other published analyses, and information on mechanisms that could plausibly influence the risk of cancer.

Please note that the information on mechanisms included in the following subsection and in the appendix (see **Appendix 2**) supersedes that in CUP cancer reports published before this Third Expert Report.

5.3.1 Breast (postmenopause)

(Also see CUP breast cancer report 2017: Section 7.10 and CUP breast cancer SLR 2017: Section 8.1.6.)

The evidence for adult weight gain presented in the following subsections. For evidence on adult body fatness and body fatness in young adulthood and postmenopausal breast cancer, see **Sections 5.1.5** and **5.2.2** respectively. For information on BMI change, see CUP breast cancer SLR 2017: Section 8.1.6.

5.3.1.1 CUP dose–response meta-analyses

Fifteen of 22 identified studies were included in the dose–response meta-analysis, which showed a statistically significant six per cent increased risk of postmenopausal breast cancer per 5 kilograms increase in adult weight (RR 1.06 [95% CI 1.05–1.08]; n = 16,600 cases) (see **Figure 5.46**).

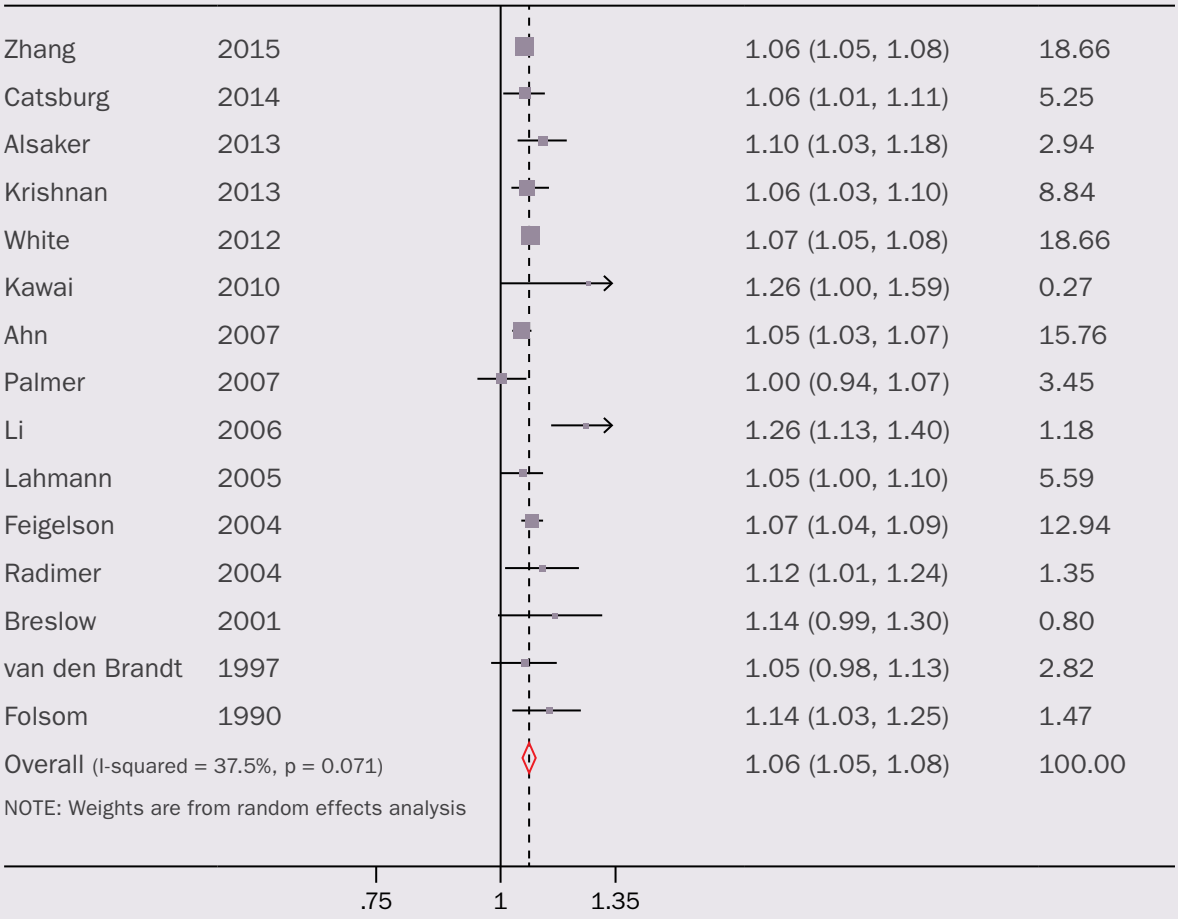
Moderate *heterogeneity* was observed (I^2 = 38%), and there was no evidence of small study bias with *Egger's test* (p = 0.10).

Stratified analyses for the risk of postmenopausal breast cancer per 5 kilograms increase in adult weight were conducted for geographic location, joint *hormone receptor* status, MHT use and simultaneous *adjustment* for age, alcohol intake and reproductive factors. For details of other stratified analyses that have been conducted, see CUP breast cancer SLR 2017, Section 8.1.6.

When stratified by geographic location, a statistically significant increased risk was observed in North America (RR 1.06 [95%CI 1.05–1.07]) and Europe (RR 1.06 [95% CI 1.03–1.10]); a larger significant increased risk was observed in Asia (RR 1.26 [95% CI 1.14–1.39]; see CUP breast cancer report 2017, Table 22 and CUP breast cancer SLR 2017, Figure 589). When stratified by joint hormone receptor status, a significant increased risk was observed for ER-positive and PR-positive breast cancer (RR 1.13 [95% CI 1.04–1.22]), but not joint ER-positive and PR-negative or joint ER-negative and PR-negative breast cancers. When stratified by MHT use, a significant increased risk was observed among women who had never used MHT (RR 1.06 [95% CI 1.03–1.09]) and those who had never or previously used MHT (RR 1.09 [95% CI 1.07–1.12]), but not in women who were currently using MHT or had ever used MHT; see CUP breast cancer report 2017, Table 22). The significant increased risk also remained in studies that simultaneously adjusted for age, alcohol intake and reproductive factors (RR 1.08 [95% CI 1.03–1.13]), see CUP breast cancer SLR 2017, Table 559.

[1] **'Limited – no conclusion'**: There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these.

Figure 5.46: CUP dose–response meta-analysis[1] for the risk of postmenopausal breast cancer, per 5 kilograms increase in adult weight



Source: Zhang, 2015 [420]; Catsburg, 2014 [218]; Alsker, 2013 [421]; Krishnan, 2013 [224]; White, 2012 [228]; Kawai, 2010 [417]; Ahn, 2007 [256]; Palmer, 2007 [257]; Li, 2006 [237]; Lahnmann, 2005 [422]; Feigelson, 2004 [238]; Radimer, 2004 [423]; Breslow, 2001 [424]; van den Brandt, 1997 [419]; Folsom, 1990 [425].

There was evidence of a non-linear dose–response relationship (p = 0.04; see **Figure 5.47**), although postmenopausal breast cancer risk appeared to increase linearly with increasing weight gain.

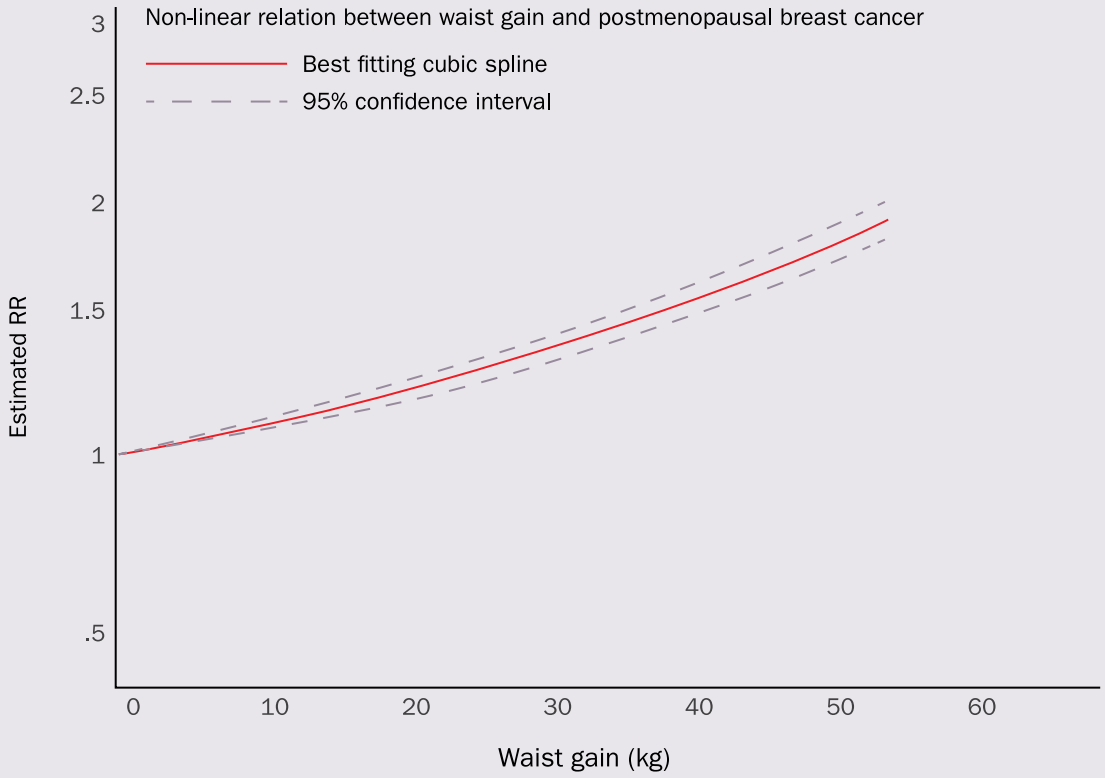
All studies included in the dose–response meta-analysis adjusted for age and most adjusted for alcohol consumption, physical activity, reproductive factors and MHT use, about a half of studies adjusted for tobacco smoking, see CUP breast cancer SLR 2017, Table 555.

5.3.1.2 Published pooled analyses and meta-analyses

No published pooled analyses were identified. Two other published meta-analyses on adult weight gain and the risk of postmenopausal breast cancer have been identified. The most recent meta-analysis of cohort studies [24] reported a statistically significant increased risk for women who had not used MHT (RR 1.11 [95% CI 1.08–1.13]) and for those with limited exposure or no exposure to MHT (RR 1.11 [95% CI 1.08–1.13]) per 5 kilograms increase in adult weight; no significant association was observed for women who

[1] Seven studies could not be included in the dose–response meta-analysis, three reported on excluded exposures and four as did not provide sufficient information. For further details, see CUP breast cancer SLR 2016, Table 564.

Figure 5.47: CUP non-linear dose–response association of adult weight gain and the risk of postmenopausal breast cancer



had used MHT. The other published meta-analysis of mainly *case-control studies* [426] reported a significant increased risk of postmenopausal breast cancer that were joint *hormone receptor* types – ER-positive and PR-positive (RR 2.33 [95% CI 2.05–2.60]) and ER-negative and PR-negative (RR 1.34 [95% CI 1.06–1.63]) – for the highest compared with the lowest level of adult weight gain.

For further information on general processes involved in the development of cancer, see The cancer process.

For further information on the relationship between adult body fatness and the risk of postmenopausal breast cancer, see **Section 5.1.5.4**.

5.3.1.3 Mechanisms

The information on mechanisms is based on both human and animal studies, with a preference for human studies whenever possible. This section covers the primary hypotheses that are currently prevailing and is not based on a systematic or exhaustive search of the literature.

5.3.1.4 CUP Panel's conclusion

The evidence was consistent and the CUP dose–response meta-analysis showed a statistically significant increased risk of postmenopausal breast cancer with increasing adult weight gain. Moderate *heterogeneity* was observed. Further analysis showed evidence of non-linearity, although the risk appeared to increase linearly with increasing weight gain. The significant increased risk remained in women who had never used MHT and those who had never or previously used MHT, and joint ER-positive and PR-positive postmenopausal breast cancer subtypes. The significant increased risk also remained when stratified by geographic location and when simultaneously adjusted for age, alcohol intake and reproductive factors. For adult body fatness there is robust evidence for mechanisms operating in humans.

The CUP Panel concluded:

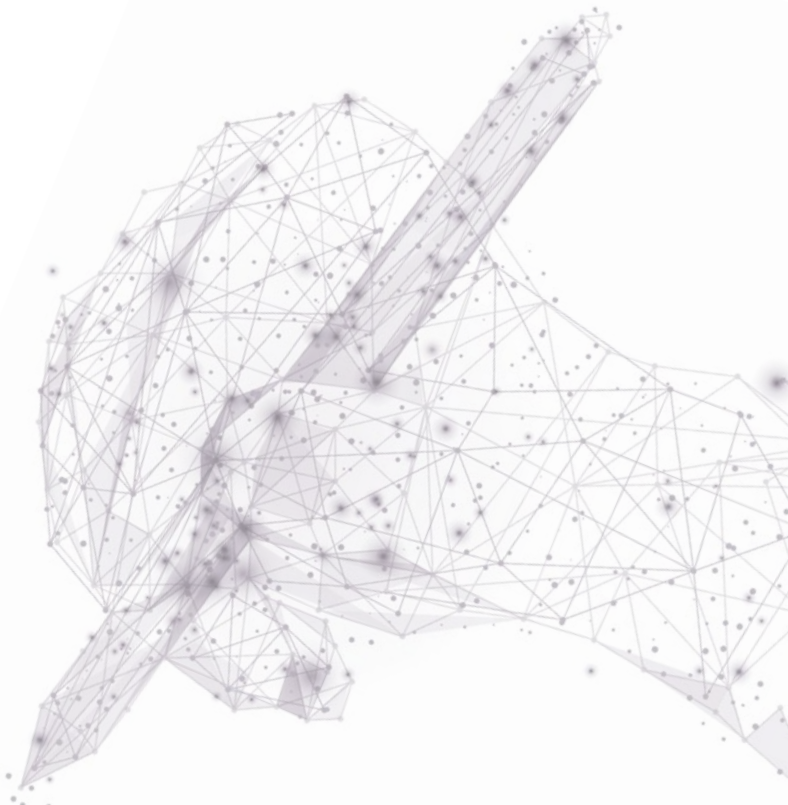
- **Adult weight gain is a convincing cause of postmenopausal breast cancer.**

6. Comparison with the 2007 Second Expert Report

In 2007, there was strong evidence that adult body fatness is a cause of seven cancers (oesophageal *adenocarcinoma*, pancreatic, gallbladder, colorectal, postmenopausal breast, endometrial and kidney). There was also strong evidence that adult body fatness has a protective effect against breast cancer in premenopausal women. The evidence for all of those cancers has remained strong. In this Third Expert Report, there is new strong evidence that adult body fatness is a cause of cancers of the mouth, pharynx, larynx; cardia stomach; liver; ovary; and advanced prostate. There is now strong evidence for adult body fatness and 12 cancers.

The strong evidence from 2007 that adult weight gain is a cause of breast cancer in postmenopausal women was also upheld.

In this Third Expert Report, body fatness in young adulthood and the risk of breast cancer could be assessed for the first time, and there was strong evidence that it has a protective effect in both pre and postmenopausal women.



Acknowledgements

Panel Members

CHAIR – **Alan Jackson** CBE MD FRCP FRCPath FRCPCH FAfN
University of Southampton
Southampton, UK

DEPUTY CHAIR – **Hilary Powers** PhD RNutr
University of Sheffield
Sheffield, UK

Elisa Bandera MD PhD
Rutgers Cancer Institute of New Jersey
New Brunswick, NJ, USA

Steven Clinton MD PhD
The Ohio State University
Columbus, OH, USA

Edward Giovannucci MD ScD
Harvard T H Chan School of Public Health
Boston, MA, USA

Stephen Hursting PhD MPH
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Michael Leitzmann MD DrPH
Regensburg University
Regensburg, Germany

Anne McTiernan MD PhD
Fred Hutchinson Cancer Research Center
Seattle, WA, USA

Inger Thune MD PhD
Oslo University Hospital and
University of Tromsø
Oslo and Tromsø, Norway

Ricardo Uauy MD PhD
Instituto de Nutrición y Tecnología
de los Alimentos
Santiago, Chile

David Forman PhD
(2007 to 2009)
University of Leeds
Leeds, UK

David Hunter PhD
(2007 to 2012)
Harvard University
Boston, MA, USA

Arthur Schatzkin
(2007 to 2011, *d. 2011*)
National Cancer Institute
Rockville, MD, USA

Steven Zeisel MD PhD
(2007 to 2011)
University of North Carolina at Chapel Hill
Chapel Hill, NC, USA

Observers

Marc Gunter PhD
International Agency for Research on Cancer
Lyon, France

Elio Riboli MD ScM MPH
Imperial College London
London, UK

Isabelle Romieu MD MPH ScD
(2013 to 2016)
International Agency for Research on Cancer
Lyon, France

Advisor

John Milner PhD
(2012, *d. 2013*)
National Cancer Institute
Rockville, MD, USA

Imperial College London Research Team

Teresa Norat PhD
Principal Investigator

Leila Abar MSc
Research Associate

Louise Abela
(2016 to 2017)
Research Associate

Dagfinn Aune PhD
(2010 to 2016)
Research Associate

Margarita Cariolou MSc
Research Assistant

Doris Chan PhD
Research Fellow

Rosa Lau MSc
(2008 to 2010)
Research Associate

Neesha Nanu MSc
Research Assistant

Deborah Navarro-Rosenblatt MSc
(2011 to 2015)
Research Associate

Elli Polemiti MSc
(2015 to 2016)
Research Associate

Jakub Sobiecki MSc
Research Associate

Ana Rita Vieira MSc
(2011 to 2016)
Research Associate

Snieguole Vingeliene MSc
(2012 to 2017)
Research Associate

Christophe Stevens
(2013 to 2017)
Database Manager

Rui Viera
(2007 to 2011)
Data Manager

Statistical Adviser

Darren Greenwood PhD
Senior Lecturer in Biostatistics
University of Leeds
Leeds, UK

Visiting trainees, researchers, scientists

Renate Heine-Bröring PhD
(2010, PhD training)
Wageningen University
Wageningen, The Netherlands

Dirce Maria Lobo Marchioni PhD
(2012 to 2013, visiting scientist)
University of São Paulo
São Paulo, Brazil

Yahya Mahamat Saleh MSc
(2016, Masters training)
Bordeaux University
Bordeaux, France

Sabrina Schlesinger PhD
(2016, Postdoctoral researcher)
German Diabetes Center
Düsseldorf, Germany

Mathilde Touvier PhD
(2009, Postdoctoral researcher)
Nutritional Epidemiology Unit (UREN)
Bobigny, France

WCRF Network Executive

Marilyn Gentry
President
WCRF International

Kelly Browning
Executive Vice President
AICR

Kate Allen PhD
Executive Director
Science and Public Affairs
WCRF International

Deirdre McGinley-Gieser
Senior Vice President for Programs
and Strategic Planning
AICR

Stephenie Lowe
Executive Director
International Financial Services
WCRF Network

Rachael Gormley
Executive Director
Network Operations
WCRF International

Nadia Ameyah
Director
Wereld Kanker Onderzoek Fonds

Secretariat

HEAD – **Rachel Thompson** PhD RNutr
Head of Research Interpretation
WCRF International

Kate Allen PhD
Executive Director
Science and Public Affairs
WCRF International

Emily Almond
Research Interpretation Assistant
WCRF International

Isobel Bandurek MSc RD
Science Programme Manager
(Research Interpretation)
WCRF International

Nigel Brockton PhD
Director of Research
AICR

Susannah Brown MSc
Senior Science Programme Manager
(Research Evidence)
WCRF International

Stephanie Fay PhD
(2015 to 2016)
Science Programme Manager
(Research Interpretation)
WCRF International

Susan Higginbotham PhD RD
(2007 to 2017)
Vice President of Research
AICR

Mariano Kälfors
CUP Project Manager
WCRF International

Rachel Marklew MSc RNutr
(2012 to 2015)
Science Programme Manager
(Communications)
WCRF International

Deirdre McGinley-Gieser
Senior Vice President for Programs
and Strategic Planning
AICR

Giota Mitrou PhD
Director of Research Funding
and Science External Relations
WCRF International

Amy Mullee PhD
(2014 to 2015)
Science Programme Manager
(Research Interpretation)
WCRF International

Prescilla Perera
(2011 to 2012)
Science Programme Manager
WCRF International

Malvina Rossi
(2016)
CUP Project Manager
WCRF International

Martin Wiseman FRCP FRCPath FAfN
Medical and Scientific Adviser
WCRF International

Mechanisms authors

LEAD – **Marc Gunter** PhD
Section of Nutrition and Metabolism
International Agency for Research on Cancer
Lyon, France

Laure Dossus PhD
Section of Nutrition and Metabolism
International Agency for Research on Cancer
Lyon, France

Mazda Jenab PhD
Section of Nutrition and Metabolism
International Agency for Research on Cancer
Lyon, France

Neil Murphy PhD
Section of Nutrition and Metabolism
International Agency for Research on Cancer
Lyon, France

Scientific consultants

Kirsty Beck MSc

Louise Coghlin MBiochem

Kate Crawford PhD

Elizabeth Jones PhD

Rachel Marklew MSc RNutr

Peer reviewers

For the full list of CUP peer reviewers please visit wcrf.org/acknowledgements

Abbreviations

AICR	American Institute for Cancer Research
BMI	Body mass index
CI	Confidence interval
CUP	Continuous Update Project
ER-negative	Oestrogen-receptor-negative
ER-positive	Oestrogen-receptor-positive
H. pylori	*Helicobacter pylori*
hEGF	Human epidermal growth factor
HPV	Human papilloma virus
NAFLD	Non-alcoholic fatty liver disease
IGF-I	Insulin-like growth factor 1
MHT	Menopausal hormone therapy
PR-negative	Progesterone-receptor-negative
PR-positive	Progesterone-receptor-positive
PSA	Prostate-specific antigen
RR	Relative risk
SLR	Systematic literature review
WCRF	World Cancer Research Fund

Glossary

Adenocarcinoma
Cancer of glandular epithelial cells.

Adenosquamous carcinoma
A type of cancer that contains two types of cells: squamous cells (thin, flat cells that line certain organs) and gland-like cells.

Adipokines
Cytokines (cell signalling proteins) secreted by adipose tissue.

Adiponectin
A protein secreted by adipose tissue that is inversely related to body fatness. High concentrations have been associated with a lower risk of kidney cancer.

Adipose tissue
Body fat. Tissue comprising mainly cells containing triglyceride (adipocytes). It acts as an energy reserve, provides insulation and protection, and secretes metabolically active hormones.

Adiposity
Degree of body fatness; can be measured indirectly in a variety of ways including body mass index (see **body mass index**) and percentage body fat.

Adjustment
A statistical tool for taking into account the effect of known confounders (see **confounder**).

Androgen
Any masculinising sex hormone, such as testosterone.

Anthropometric measures
Measures of body dimensions.

Apoptosis
The death of cells that occurs as a normal and controlled part of the cell cycle.

Bile
A greenish-yellow fluid secreted by the liver and stored in the gallbladder. Bile plays an important role in the intestinal absorption of fats. Bile contains cholesterol, bile salts and waste products such as bilirubin.

Biomarker
A naturally occurring molecule, gene or characteristic by which a particular pathological or physiological process can be identified.

Body mass index (BMI)
Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m^2). Provides an indirect measure of body fatness.

Caecum
A pouch connected to the junction of the small and large intestines.

Carcinogen
Any substance or agent capable of causing cancer.

Carcinogenesis
The process by which a malignant tumour is formed.

Carcinoma
Malignant tumour derived from epithelial cells, usually with the ability to spread into the surrounding tissue (invasion) and produce secondary tumours (metastases).

Cardia stomach cancer
A sub-type of stomach cancer that occurs in the cardia, near the gastro-oesophageal junction

Case-control study
An epidemiological study in which the participants are chosen on the basis of their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as tobacco smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

Cell line
A cell culture developed from a single cell and therefore consisting of cells with a uniform genetic make-up.

Cholangiocarcinoma
A malignant tumour in the ducts that carry bile from the liver to the small intestine.

Cholesterol
The principal sterol in animal tissues, synthesised in the body; an essential component of cell membranes and the precursor of the steroid hormones and vitamin D.

Chronic
Describing a condition or disease that is persistent or long lasting.

Cirrhosis
A condition in which normal liver tissue is replaced by scar tissue (fibrosis), with nodules of regenerative liver tissue.

Clear cell renal cell carcinoma (CCRCC)
The most common type of kidney cancer in adults, characterised by malignant epithelial cells with clear cytoplasm.

Cohort study
A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes later) and followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, tobacco smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

Colon
Part of the large intestine extending from the caecum to the rectum.

Confidence interval (CI)
A measure of the uncertainty in an estimate, usually reported as 95% confidence interval (CI), which is the range of values within which there is a 95% chance that the true value lies. For example, the association of tobacco smoking and relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95% chance that the true value lies between 5 and 15.

Confounder/confounding factors
A variable that is associated with both an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that tobacco smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

Cytokines
Cell-signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells toward sites of inflammation, infection and trauma.

Diet, nutrition and physical activity
In the CUP, these three exposures are taken to mean the following: **diet**, the food and drink people habitually consume, including dietary patterns and individual constituent nutrients as well as other constituents, which may or may not have physiological bioactivity in humans; **nutrition**, the process by which organisms obtain energy and nutrients (in the form of food and drink) for growth, maintenance and repair, often marked by nutritional biomarkers and body composition (encompassing body fatness); and **physical activity**, any body movement produced by skeletal muscles that requires energy expenditure.

Dose–response
A term derived from pharmacology that describes the degree to which an association or effect changes as the level of an exposure changes, for instance, intake of a drug or food.

Effect modification
Effect modification (or effect-measure modification) occurs when the effect of an exposure differs according to levels of another variable (the modifier).

Egger's test
A statistical test for small study effects such as publication bias.

Endocrine
Referring to organs or glands that secrete hormones into the blood.

Endogenous
Substances or processes that originate from within an organism, tissue or cell.

Energy
Energy, measured as calories or joules, is required for all metabolic processes. Fats, carbohydrates, proteins and alcohol from foods and drinks release energy when they are metabolised in the body.

Epithelial (see **epithelium**)

Epithelium
The layer of cells covering internal and external surfaces of the body, including the skin and mucous membranes lining body cavities such as the lung, gut and urinary tract.

Exocrine
Relating to or denoting glands that secrete their products through ducts opening on to an epithelium rather than directly into the blood.

Exposure
A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

Familial
Relating to or occurring in a family or its members.

Fatty acid
A carboxylic acid with a carbon chain of varying length, which may be saturated (no double bonds) or unsaturated (one or more double bonds). Three fatty acids attached to a glycerol backbone make up a triglyceride, the usual form of fat in food and adipose tissue.

Germ cells
The cells that develop into eggs and sperm, through which genetic information is passed from generation to generation.

Head and neck cancer
Includes cancers of the oral cavity, pharynx and larynx, nasal cavity and salivary glands.

Helicobacter pylori (H. pylori)
A gram-negative bacterium that lives in the human stomach. It colonises the gastric mucosa and elicits both inflammatory and lifelong immune responses.

Hepatitis
Inflammation of the liver, which can occur as the result of a viral infection or autoimmune disease, or because the liver is exposed to harmful substances, such as alcohol.

Hepatocellular carcinoma
Primary malignant tumour of the liver.

Hepatocytes
The main cells of the liver.

Heterogeneity
A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the I^2 test.

High-income countries
As defined by the World Bank, countries with an average annual gross national income per capita of US$12,236 or more in 2016. This term is more precise than and used in preference to 'economically developed countries'.

Hormone
A substance secreted by specialised cells that affects the structure and/or function of cells or tissues in another part of the body.

Hormone receptor status
Hormone receptors are proteins found in and on breast or other cells that respond to circulating hormones and influence cell structure or function. A cancer is called oestrogen-receptor-positive (ER+) if it has receptors for oestrogen, and oestrogen-receptor-negative (ER-) if it does not have the receptors for oestrogen.

Hyperinsulinemia
High blood concentrations of insulin.

Hyperplasia
An increase in the number of cells in a tissue.

Incidence
Frequency of occurrence of new cases of a disease in a particular population during a specified period.

Inflammation
The immunologic response of tissues to injury or infection. Inflammation is characterised by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling. Inflammation may be acute (such as in response to infection or injury) or chronic (as part of several conditions, including obesity).

Insulin
A protein hormone secreted by the pancreas that promotes the uptake and utilisation of glucose, particularly in the liver and muscles. Inadequate secretion of, or tissue response to, insulin leads to diabetes mellitus.

Insulin-like growth factor (IGF)
Polypeptides with high sequence similarity to insulin that are part of a complex system that cells use to communicate with their physiologic environment. IGF-I is the main mediator of growth hormone activity.

Insulin resistance
A pathological condition in which cells fail to respond normally to the hormone insulin.

Lactation
The production and secretion of milk by the mammary glands.

Leptin
A hormone secreted by adipose cells that helps to regulate energy balance by inhibiting hunger.

Low- and middle-income countries
As defined by the World Bank, low-income countries are countries with an average annual gross national income per capita of US$1,005 or less in 2016. Middle-income countries, are countries with an average annual gross national income per capita of between US$1,006 and US$12,235 in 2016. These terms are more precise than and used in preference to 'economically developing countries'.

Malignancy
A tumour with the capacity to spread to surrounding tissue or to other sites in the body.

Menarche
The start of menstruation.

Mendelian randomisation
A method of using natural variation in genes of known function to mimic a potential causal effect of a modifiable exposure on disease. The design helps to avoid problems from reverse causation and confounding.

Menopausal hormone therapy (MHT)
Treatment with oestrogens and progesterones with the aim of alleviating menopausal symptoms or osteoporosis. Also known as hormone replacement therapy.

Menopause
The cessation of menstruation.

Meta-analysis
The process of using statistical methods to combine the results of different studies.

Metastasis/metastatic spread
The spread of malignant cancer cells to distant locations around the body from the original site.

Mitogenic
Referring to a chemical substance that encourages a cell to divide, by triggering mitosis. Mitogens are usually proteins. Mitogenesis is the induction (triggering) of mitosis, typically through a mitogen.

Mucinous carcinoma
A type of cancer that begins in cells that line certain internal organs and produce mucin (the main component of mucus).

Mutation
A permanent change in the nucleotide sequence of the genome (an organism's complete set of DNA).

Non-cardia stomach cancer
A subtype of stomach cancer that occurs in the lower portion of the stomach.

Non-communicable diseases (NCDs)
Diseases which are not transmissible from person to person. The most common NCDs are cancer, cardiovascular disease, chronic respiratory diseases, and diabetes.

Non-linear analysis
A non-linear dose–response meta-analysis does not assume a linear dose–response relationship between exposure and outcome. It is useful for identifying whether there is a threshold or plateau.

Odds ratio
A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

Oestrogen
The female sex hormones, produced mainly by the ovaries during reproductive life and also by adipose tissue.

Papillary renal cell carcinoma
A type of cancer that forms inside the lining of the kidney tubules.

Pathogenesis
The origin and development of disease. The mechanisms by which causal factors increase the risk of disease.

Phenotype
The observable characteristics displayed by an organism; depends on both the genotype (the genetic makeup of a cell) and environmental factors.

Polymorphisms
Common variations (in more than one per cent of the population) in the DNA sequence of a gene.

Pooled analysis
In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

Progesterone
Female sex hormone, produced mainly by the ovaries during reproductive life and by the placenta during pregnancy.

Reactive oxygen species (ROS)
Oxygen-containing radical species or reactive ions that can oxidise DNA (remove electrons), for example, hydroxyl radical (OH–), hydrogen peroxide (H_2O_2) or superoxide radical (O^2–).

Rectum
The final section of the large intestine, terminating at the anus.

Relative risk (RR)
The ratio of the rate of an outcome (for example, disease (incidence) or death (mortality)) among people exposed to a factor, to the rate among the unexposed, usually used in cohort studies.

Selection bias
Bias arising from the procedures used to select study participants and from factors influencing participation.

Squamous cell carcinoma
A malignant cancer derived from squamous epithelial cells.

Statistical power
The power of any test of statistical significance, defined as the probability that it will reject a false null hypothesis.

Systematic literature review (SLR)
A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods.

Transitional cell carcinomas
Cancer that develops in the lining of the renal pelvis, ureter or bladder.

Tumorigenesis
The process of tumour development.

Upper aerodigestive tract cancer
Cancers of the upper aerodigestive tract (UADT) include head and neck cancers and oesophageal cancers.

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Appendix 1: Criteria for grading evidence for cancer prevention

Adapted from Chapter 3 of the 2007 Second Expert Report [1]. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent *cohort studies*.
- No substantial unexplained *heterogeneity* within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including *confounding*, measurement error and *selection bias*.
- Presence of a plausible biological gradient ('*dose–response*') in the association. Such a gradient need not be linear or even in the same direction across the different levels of *exposure*, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five *case-control studies*.
- No substantial unexplained *heterogeneity* between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and *selection bias*.
- Evidence for biological plausibility.

LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of *adjustment* for known *confounders*) or by any combination of these factors.

When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (dietandcancerreport.org). However, such evidence is usually not included in the summaries.

SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose–response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate *statistical power*. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- Presence of a plausible biological gradient ('dose–response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for *confounders*.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

Appendix 2: Mechanisms

The evidence on mechanisms has been based on human and animal studies. Though not a systematic or exhaustive search, the expert reviews represent the range of currently prevailing hypotheses.

Adult body fatness

Oesophagus (*adenocarcinoma*)

Increased body fatness may promote *chronic* gastroesophageal reflux disease or *inflammation* of the oesophagus; this may lead to the development of Barrett's oesophagus which has been shown to increase the risk of developing oesophageal adenocarcinoma [115]. Greater body fatness is also associated with higher circulating *insulin* levels and inflammation, both of which have been proposed as plausible mechanisms linking body fatness to cancers in other sites. However, to date there are limited data supporting a direct link between elevated insulin or inflammation and oesophageal adenocarcinoma. Further research is needed to better understand the biological mechanisms that underlie the association of body fatness with oesophageal adenocarcinoma.

Pancreas

Body fatness may influence the development of pancreatic cancer through similar and diverse mechanisms purported to underlie its cancer-promotive role at other anatomical sites. Elevated *chronic inflammation* with activation of NF-kappaB signaling, increased production of pro-inflammatory *cytokines* and pancreatic infiltration of immunosuppressive cells have all been proposed as possible mechanisms [149–151]. In addition, higher body fatness has been associated with increased levels of *hormones* such as *insulin*, which can promote cell growth and inhibit *apoptosis*, and hence could be cancer promotive [152, 153]. A recent Mendelian randomisation analysis performed in a study of more than 7,000 pancreatic cancer cases and 7,000 controls found robust evidence for a strong association between genetic variants that determine higher body fatness and circulating insulin levels and pancreatic cancer risk, suggesting a causal role for body fatness in pancreatic cancer development [154].

Liver

Although the exact mechanisms linking obesity and liver cancer development are still unclear, recent evidence supports a role for greater body fatness in the development of non-alcoholic fatty liver disease (NAFLD), which is strongly linked to metabolic syndrome and which can lead to a complex dysregulation of hepatic lipid metabolism. In its more aggressive forms, NAFLD can drive *inflammation* and hepatic tissue damage by increasing endoplasmic reticulum stress, elevating production of *reactive oxygen species* (increased oxidative stress), and higher inflammation [169, 170].

Body fatness is associated with host *chronic* inflammation and *insulin resistance* [171, 172] and may contribute to the hepatic dysfunction underlying this relationship. Obesity is associated with increased levels of pro-inflammatory *cytokines* (for example, TNF-alpha and IL-6) and *insulin*, which can promote *hepatocyte* growth and malignant transformation through activation of the oncogenic transcription factor Signal Transducer and Activator of Transcription-3 [173]. The resulting chronic liver injury due to chronic inflammatory processes can promote compensatory hepatocyte injury, death, tissue

remodeling and regeneration, which has been shown in animal models to be a necessary factor for liver cancer development [174, 175]. Animal studies also suggest that gut bacterial dysbiosis within the context of NAFLD may also propagate liver injury [176].

Colorectum

Higher body fatness is associated with changes in hormonal profiles, such as increased levels of *insulin*, which can promote the growth of *colon* cancer cells and inhibit *apoptosis*. Higher serum concentrations of insulin and IGF-I have been linked to greater risk of colorectal cancer in human [208–210] and experimental studies [211, 212]. Body fatness also stimulates the body's inflammatory response, which can promote development of colorectal cancer [213, 214]. Overall, there are convincing mechanistic data supporting a link between body fatness and colorectal cancer.

Breast (postmenopause)

Body fatness directly affects levels of several circulating *hormones*, such as *insulin* and *oestrogens*, creating an environment that promotes *carcinogenesis* and suppresses *apoptosis*. In postmenopausal women, when the production of oestrogens from the ovaries has dramatically declined, the main source of oestrogens is from the conversion of *androgens* within the *adipose tissue*. Consequently, overweight and obese women have higher circulating levels of oestrogens [268], which are well known to be associated with the development of breast cancer [269, 270]. Other sex steroid hormones, including androgens and *progesterone*, are also likely to play a role in the relationship between obesity and breast cancer [271]. Elevated body fatness is also associated with *hyperinsulinemia* and insulin resistance, and greater circulating insulin levels have been linked to breast cancer risk [272]. Insulin could promote breast tumor growth directly by binding to its receptor or to the IGF-I (*insulin-like growth factor*-I) receptor or indirectly by inhibiting the synthesis of sex-hormone binding globulin, which sequesters oestrogens in circulation, contributing to higher levels of bioavailable oestrogens [273].

Obesity is also associated with a low-grade *chronic* inflammatory state. Adipose tissue in obese individuals secretes pro-inflammatory *cytokines* and *adipokines*, which can promote development of breast cancer, as shown in experimental studies [274–276] and more recently in epidemiological studies [277, 278].

Endometrium

Excess body fatness increases bioavailable *oestrogen* levels that have been shown, when not counterbalanced by *progesterone*, to increase endometrial tissue mitotic activity and therefore promote endometrial *carcinogenesis* [269]. Higher *insulin* levels associated with excess body fatness are associated with greater risk of endometrial cancer [300, 301]. Insulin has been shown to enhance endometrial tumour growth either directly by binding to the insulin or to the IGF-I receptors or indirectly by inhibiting the synthesis of sex hormone binding globulin and thereby increasing oestrogen bioavailability [273]. Obesity-related *chronic inflammation* has also been specifically linked to development of endometrial cancer [302–304].

Kidney

The vast array of epidemiological studies using diverse measures of obesity, such as weight, BMI or waist-hip ratio as well as increases in adult weight, all show similar positive associations with the risk of renal cell cancer and likely share common mechanisms. Body fatness is a systemic process affecting host metabolism, as well as many components of the *endocrine* system or microenvironment, that may affect kidney *carcinogenesis*. For example, obesity is associated with raised levels of *mitogenic* and anti-apoptotic growth factors such as *insulin* or bioactive IGF-I that may promote the carcinogenic process [321, 322].

Higher concentrations of *adiponectin*, a protein secreted by *adipose tissue* that is inversely related to body fatness, have been associated with lower risk of kidney cancer [323]. In vitro experimental studies have shown that adiponectin inhibits cellular proliferation and promotes *apoptosis* [324]. Obesity increases the risk of metabolic syndrome, which includes hypertension and obesity, both of which are associated with a greater risk for renal cancer [325]. Obesity is associated with a *chronic* inflammatory state that may alter susceptibility to cancer or promote carcinogenesis [326].

Mouth, pharynx and larynx

Specific mechanisms to support the relationship between body fatness and mouth, pharynx and larynx cancers have not been proposed to date. However, greater body fatness is associated with metabolic and *endocrine* abnormalities such as *hyperinsulinemia* and elevated levels of bioavailable *oestrogen*, and in other tissues, *insulin* and oestrogen have been shown to stimulate mitogenesis [333] and inhibit *apoptosis* [321, 322], leading to enhanced cellular proliferation. Obesity has also been shown to stimulate the inflammatory response, which may also promote *tumorigenesis* [326]. Further research on the mechanisms underlying the link between obesity and cancers of the mouth, pharynx and larynx is needed.

Stomach (cardia)

Greater body fat promotes the development of *chronic* gastroesophageal reflux disease or *inflammation* of the oesophagus, the potential transition to Barrett's oesophagus, and increases the risk of developing *cardia stomach cancer*. Being overweight and obese is also associated with higher levels of *insulin*, which can act as a mitogen and has anti-apoptotic properties [321, 322] and therefore may represent a mechanism, though there are limited data to support this hypothesis to date. Obesity has also been shown to stimulate the inflammatory response, which may promote *tumorigenesis* [326].

Gallbladder

The mechanisms underlying the positive association of body fatness with gallbladder cancer development are likely to be similar to those proposed for other anatomical sites, namely development of metabolic syndrome and its components, such as hyperglycemia, dyslipidemia, *hyperinsulinemia* and hypertension. *Chronic inflammation*, production of growth factors and increased levels of pro-inflammatory *cytokines* are also possible cancer-promoting consequences of increased body fatness [149]. Interestingly, body fatness and metabolic syndrome appear to be associated with increased risk of gallstones [338, 339], which has been observed as a major risk factor for gallbladder cancer development in various populations [340, 341], likely through promotion of increased chronic inflammation at this site [149]. The stronger association of body fatness with gallbladder cancer in women than in men may in part be due to adverse effects of female sex *hormones* on hepatic *bile* secretion and gallbladder function [342].

Ovary

Greater body fatness is associated with higher circulating levels of *endogenous oestrogens* and *androgens*, and these *hormones* are associated, albeit inconsistently, with higher risk of ovarian cancer [360]. Adipose tissue is also a source of *adipokines* and inflammatory *cytokines* that promote a low-grade inflammatory milieu, and both local and systemic pro-inflammatory factors are associated with development of ovarian cancer [361–365].

Prostate (advanced)

Greater body fatness is associated with higher risk of advanced prostate cancer. Several biological mechanisms have been proposed that link *adiposity* to cancer, including dysregulated sex steroid metabolism, *hyperinsulinemia* and elevated levels of proinflammatory *cytokines*; however, the evidence linking these pathways specifically to prostate cancer is limited. Androgens such as testosterone play critical roles in the development and function of the prostate gland. It has been hypothesised that a hypoandrogenic environment promotes the development of higher-grade prostate tumours, and at least two prospective studies have reported inverse relationships between serum testosterone levels and higher-grade prostate cancer [391, 392]. Testosterone levels tend to be lower in obese males than in those of normal weight and therefore may represent a potential mediator of the body fatness-advanced prostate cancer relationship. Hyperinsulinemia has been shown to accelerate tumour growth in prostate cancer xenograft models, and human prostate tumours commonly express the *insulin* receptor, suggesting that insulin may stimulate prostate cancer growth [393–395]. However, data in human studies generally do not support a relationship between hyperinsulinemia and prostate cancer development. Similarly, proinflammatory cytokines and *adipokines* such as *leptin* have been shown to exert a *mitogenic* effect in prostate cancer *cell lines* that are human *androgen*-independent, inducing proliferation and inhibiting *apoptosis*, while epidemiologic data generally do not support an association between inflammatory cytokines and development of prostate cancer. Overall, further research is needed to advance knowledge on the mechanisms that potentially underlie the association of body fatness with advanced prostate cancer.

Cervix (BMI ≥ 29)

Specific biological mechanisms underlying the association between body fatness and cervical cancer are not well understood, but may be similar to the mechanisms proposed for other cancers. Experimental models of cervical cancer are poorly developed, and few have been employed in studies of diet and nutrition. A major cause of cervical cancer is infection by human papilloma virus (HPV), and it is plausible that certain hormonal and metabolic changes that are common in obesity could act as co-factors in HPV-related *carcinogenesis*. For example, higher circulating *oestrogen* and *androgen* levels are common in obese women and in mouse models of HPV-induced cervical cancer, and oestradiol has been shown to synergise with HPV oncogenes to promote the development of cervical cancer [427–429]. However, this would not represent a plausible mechanism in younger women (in whom the majority of cervical cancers occur) as obese premenopausal women do not generally have raised oestrogen levels. Other possible biological mechanisms include obesity-induced changes in immune function that could affect clearance of HPV infection and elevated levels of *inflammation*; however, direct evidence for a link between these pathways and cervical cancer is only beginning to be examined.

Breast (premenopause)

There is no single well-established mechanism through which body fatness could prevent premenopausal breast cancer. One possible mechanism relates to anovulation, which is commonly associated with obesity and results in abnormal *hormone* profiles characterised by lower *endogenous* levels of *progesterone* [404, 405]. Although the mechanisms of the potential protective effect of obesity on premenopausal breast cancer have not been fully elucidated, it appears to be related to fat distribution, as a higher waist circumference seems to be more strongly associated with an increased risk of premenopausal breast cancer after accounting for BMI. Mechanisms specifically related to abdominal *adiposity* measured by waist circumference include a strong relationship to *chronic inflammation* and *insulin resistance* [406].

Body fatness in young adulthood

Breast (pre and postmenopause)

Body fatness in childhood and adolescence is inversely related to the risk of premenopausal breast cancer as well as postmenopausal breast cancer, suggesting a long-term effect of body fatness at young age on breast cancer risk later in life. These findings contrast with the higher risk of breast cancer among postmenopausal women who have greater body fatness in adulthood. Early life, including childhood and adolescence, is hypothesised to be a critical window for breast *carcinogenesis*. This is a period of rapid growth and development of breast tissue, with higher rates of mammary gland tissue proliferation during puberty, which may increase susceptibility to molecular damage and may explain why particular *exposures* may be important for breast cancer risk later in life.

Body fatness during childhood has been associated with slower adolescent growth and development; however, peak height growth velocity as a measure of adolescent development is associated with an increased risk of breast cancer [410]. Higher circulating levels of IGF-I, the main mediator of growth hormone activity, is an established positive risk factor for breast cancer [411] but may be lower among women who had greater body fatness in childhood and adolescence [412]. Sex *hormones* may also partly explain the inverse relation between

adiposity in early life and risk of breast cancer. Adipose-tissue-derived *oestrogen* in overweight adolescents may induce early breast differentiation and render the breast tissue less susceptible to carcinogenesis, as has been demonstrated in animal models [413]. Obese young women are also more likely to experience anovulation and therefore lower levels of ovarian hormones such as *progesterone* and lower peaking of oestradiol [404]. However, body fatness in pre-adolescent and adolescent girls is related to higher *insulin* [414] and *androgen* levels and lower sex hormone binding globulin concentrations [415], which would be hypothesised to increase breast cancer risk. Overall, the mechanisms underlying the inverse association of early life body fatness and breast cancer risk are complex, likely multiple and not well-delineated.

Adult weight gain

Breast (postmenopause)

No specific mechanisms have been identified through which adult weight gain may increase the risk of postmenopausal breast cancer. For further information on the relationship between adult body fatness and the risk of postmenopausal breast cancer, see above).

Our Cancer Prevention Recommendations

Be a healthy weight
Keep your weight within the healthy range and avoid weight gain in adult life

Be physically active
Be physically active as part of everyday life – walk more and sit less

Eat a diet rich in wholegrains, vegetables, fruit and beans
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars
Limiting these foods helps control calorie intake and maintain a healthy weight

Limit consumption of red and processed meat
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

Limit consumption of sugar sweetened drinks
Drink mostly water and unsweetened drinks

Limit alcohol consumption
For cancer prevention, it's best not to drink alcohol

Do not use supplements for cancer prevention
Aim to meet nutritional needs through diet alone

For mothers: breastfeed your baby, if you can
Breastfeeding is good for both mother and baby

After a cancer diagnosis: follow our Recommendations, if you can
Check with your health professional what is right for you

Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.

Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.

Managed and produced by:

World Cancer Research Fund International

ISBN (pdf): 978-1-912259-26-7

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