Annex 1.
WCRF - PUBMED SEARCH STRATEGY

a) Searching for all studies relating to food, nutrition and physical activity:

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]
#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab]
#3 food and beverages[MeSH Terms]
#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR (seeds[tiab] and (diet*[tiab] OR food*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND and (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab]or serum[tiab] or plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR tomato*[tiab]
#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR(ethanol[tiab] and (drink*[tiab] or intake[tiab] or consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]
#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]
#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]
#8 food preservation[MeSH Terms]
#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]
#10 cookery[MeSH Terms]
#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR (microwave[tiab] and (diet*[tiab] or food*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab] OR dietary acrylamide[tiab]
#12 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet*[tiab] or food*[tiab])) OR sweetening agents[MeSH Terms]
#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR ((linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR

aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]
#14 vitamins[MeSH Terms]
#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR (sodium[tiab] AND (diet*[tiab] or food*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet*[tiab] or food*[tiab] or supplement*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND and (diet*[tiab] or food*[tiab] or supplement*[tiab] or deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab] OR lycopene[tiab]
#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]
#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]
#18 body weight [MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms]
#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab] OR body size [MeSH Terms] OR body size [TIAB]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 animal[MeSH Terms] NOT human[MeSH Terms]
#22 #20 NOT #21

b) Searching for all studies relating to endometrial cancer:

#23 endometrial neoplasm [MeSH]
#24 malign* [tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab]
#25 endometr* [tiab] OR corpus uteri [tiab] OR uterine [tiab]
#26 #24 AND #25
#27 #23 OR #26

c) Searching for all studies relating endometrial cancer, and food, nutrition and physical activity:
#28 #22 AND #27

Supplementary text:

Sensitivity analyses excluding one study at a time

BMI

In sensitivity analyses excluding one study at a time, the summary RR in the overall analysis ranged from 1.53 (95% CI: 1.46-1.61) when the Sweden and Finland Co-Twin study by Lundqvist et al (1) was excluded to 1.56 (95% CI: 1.49-1.63) when the Women's HealtInitiative by Reeves et al (2) was excluded.

BMI at age 18-25 years

The summary RR ranged from 1.37 (95% CI: 1.26-1.50) when the Million Women Study by Yang et al (3) was excluded to 1.49 (95% CI: 1.32-1.69) when the NIH-AARP Diet and Health Study by Chang et al (4) was excluded.

Weight

The summary RR ranged from 1.17 (95% CI: 1.13-1.22) when the Iowa Women's Health Study by Folsom et al (5) was excluded to 1.20 (95% CI: 1.16-1.24) when the EPIC study by Friedenreich et al (6) was excluded.

Weight gain

The summary RR ranged from 1.15 (95% CI: 1.11-1.18) when excluding the Multiethnic Cohort Study by Park et al (7) to 1.17 (95% CI: 1.14-1.21) when excluding the California Teacher's Study by Canchola et al (8).

Waist circumference

The summary RR ranged from 1.23 (95% CI: 1.17-1.31) when the Iowa Women's Health Study by Folsom et al (9) was excluded to 1.30 (95% CI: 1.19-1.43) when the Women's Health Study by Conroy et al (10) was excluded.

Waist-to-hip ratio

The summary RR ranged from 1.16 (95% CI: 1.08-1.25) when the Iowa Women's Health Study by Folsom et al (11) was excluded to 1.22 (95% CI: 1.14-1.31) when the California Teacher's Study by Canchola et al (8) was excluded.

Height

The summary RR ranged from 1.13 (95% CI: 1.08-1.18) when the Canadian National Breast Screening Study by Kabat et al (12) was excluded to 1.16 (95% CI: 1.10-1.23) when the EPIC Study by Friedenreich et al (6) was excluded.

Reference List

1. Lundqvist E, Kaprio J, Verkasalo PK et al. Co-twin control and cohort analyses of body mass index and height in relation to breast, prostate, ovarian, corpus uteri, colon and rectal cancer among Swedish and Finnish twins. Int J Cancer 2007;121:810-8.

2. Reeves KW, Carter GC, Rodabough RJ et al. Obesity in relation to endometrial cancer risk and disease characteristics in the Women's Health Initiative. Gynecol Oncol 2011;121:376-82.

3. Yang TY, Cairns BJ, Allen N, Sweetland S, Reeves GK, Beral V. Postmenopausal endometrial cancer risk and body size in early life and middle age: prospective cohort study. Br J Cancer 2012;107:169-75.

4. Chang SC, Lacey JV, Jr., Brinton LA et al. Lifetime weight history and endometrial cancer risk by type of menopausal hormone use in the NIH-AARP diet and health study. Cancer Epidemiol Biomarkers Prev 2007;16:723-30.

5. Folsom AR, Kaye SA, Potter JD, Prineas RJ. Association of incident carcinoma of the endometrium with body weight and fat distribution in older women: early findings of the Iowa Women's Health Study. Cancer Res 1989;49:6828-31.

6. Friedenreich C, Cust A, Lahmann PH et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control 2007;18:399-413.

7. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer 2010;126:490-9.

8. Canchola AJ, Chang ET, Bernstein L et al. Body size and the risk of endometrial cancer by hormone therapy use in postmenopausal women in the California Teachers Study cohort. Cancer Causes Control 2010;21:1407-16.

9. Folsom AR, Kushi LH, Anderson KE et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160:2117-28.

10. Conroy MB, Sattelmair JR, Cook NR, Manson JE, Buring JE, Lee IM. Physical activity, adiposity, and risk of endometrial cancer. Cancer Causes Control 2009;20:1107-15.

11. Folsom AR, Demissie Z, Harnack L. Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa women's health study. Nutr Cancer 2003;46:119-24.

12. Kabat GC, Heo M, Kamensky V, Miller AB, Rohan TE. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer 2013;132:1125-32.

Supplementary Table 1. List of excluded studies and exclusion reasons

BMI change as exposure	(1)
<3 categories of exposure	(2-4)
Duplicates	(5-20)
Endometrial cancer was secondary outcome	(21-24)
Endometrial hyperplasia was the outcome	(25)
No cut-off points for anthropometric measure	(26;27)
No risk estimates	(28)
Obesity diagnosis as exposure	(29;30)
Weight variability as exposure	(31)

Reference List

1. Olson SH, Trevisan M, Marshall JR et al. Body mass index, weight gain, and risk of endometrial cancer. Nutr Cancer 1995;23:141-9.

2. Mack TM, Pike MC, Henderson BE et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med 1976;294:1262-7.

3. Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser M. Detection of endometrial carcinoma and hyperplasia in asymptomatic women. Obstet Gynecol 1984;64:1-11.

4. Parker ED, Folsom AR. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 2003;27:1447-52.

5. Lew EA, Garfinkel L. Variations in mortality by weight among 750,000 men and women. J Chronic Dis 1979;32:563-76.

6. Garfinkel L. Overweight and cancer. Ann Intern Med 1985;103:1034-6.

7. Baanders-van Halewijn EA, Poortman J. A case-control study of endometrial cancer within a cohort. Maturitas 1985;7:69-76.

8. Baanders-van Halewyn EA, Blankenstein MA, Thijssen JH, de Ridder CM, de WF. A comparative study of risk factors for hyperplasia and cancer of the endometrium. Eur J Cancer Prev 1996;5:105-12.

9. Tretli S, Magnus K. Height and weight in relation to uterine corpus cancer morbidity and mortality. A follow-up study of 570,000 women in Norway. Int J Cancer 1990;46:165-72.

10. Olson JE, Sellers TA, Anderson KE, Folsom AR. Does a family history of cancer increase the risk for postmenopausal endometrial carcinoma? A prospective cohort study and a nested case-control family study of older women. Cancer 1999;85:2444-9.

11. Jain MG, Rohan TE, Howe GR, Miller AB. A cohort study of nutritional factors and endometrial cancer. Eur J Epidemiol 2000;16:899-905.

12. Anderson KE, Anderson E, Mink PJ et al. Diabetes and endometrial cancer in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2001;10:611-6.

13. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer 2001;84:975-81.

14. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer 2003;104:669-76.

15. Setiawan VW, Pike MC, Kolonel LN, Nomura AM, Goodman MT, Henderson BE. Racial/ethnic differences in endometrial cancer risk: the multiethnic cohort study. Am J Epidemiol 2007;165:262-70.

16. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer 2008;98:1582-5.

17. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. The impact of BMI on subgroups of uterine cancer. Br J Cancer 2009;101:534-6.

18. Dossus L, Rinaldi S, Becker S et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer 2010;17:1007-19.

19. Yang HP, Wentzensen N, Trabert B et al. Endometrial cancer risk factors by 2 main histologic subtypes: the NIH-AARP Diet and Health Study. Am J Epidemiol 2013;177:142-51.

20. Heo M, Kabat GC, Strickler HD et al. Optimal Cutoffs of Obesity Measures in Relation to Cancer Risk in Postmenopausal Women in the Women's Health Initiative Study. J Womens Health (Larchmt) 2015.

21. Ewertz M, Machado SG, Boice JD, Jr., Jensen OM. Endometrial cancer following treatment for breast cancer: a case-control study in Denmark. Br J Cancer 1984;50:687-92.

22. Bernstein L, Deapen D, Cerhan JR et al. Tamoxifen therapy for breast cancer and endometrial cancer risk. J Natl Cancer Inst 1999;91:1654-62.

23. Pukkala E, Kyyronen P, Sankila R, Holli K. Tamoxifen and toremifene treatment of breast cancer and risk of subsequent endometrial cancer: a population-based case-control study. Int J Cancer 2002;100:337-41.

24. Yamazawa K, Miyazawa Y, Suzuki M et al. Tamoxifen and the risk of endometrial cancer in Japanese women with breast cancer. Surg Today 2006;36:41-6.

25. Anastasiadis PG, Skaphida PG, Koutlaki NG, Galazios GC, Tsikouras PN, Liberis VA. Descriptive epidemiology of endometrial hyperplasia in patients with abnormal uterine bleeding. Eur J Gynaecol Oncol 2000;21:131-4.

26. Le Marchand L, Wilkens LR, Mi MP. Early-age body size, adult weight gain and endometrial cancer risk. Int J Cancer 1991;48:807-11.

27. Kabat GC, Xue X, Kamensky V et al. Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. Cancer Causes Control 2015;26:219-29.

28. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril 2004;82:145-8, quiz.

29. Moller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer 1994;30A:344-50.

30. Wolk A, Gridley G, Svensson M et al. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 2001;12:13-21.

31. French SA, Folsom AR, Jeffery RW, Zheng W, Mink PJ, Baxter JE. Weight variability and incident disease in older women: the Iowa Women's Health Study. Int J Obes Relat Metab Disord 1997;21:217-23.

Supplementary Table 2: Prospective studies of body fatness measures and endometrial cancer risk

Author, publication year, country/ region	Study name	Follow-up period	Study size, gender, age, number of cases	Assessment of weight and height	Exposure and subgroup	Description of quantiles or categories	RR (95% CI)	Adjustment for confounders
Dougan MM et al, 2015, USA	Nurses' Health Study Nurses' Health Study 2	NHS: 1988-2010, 22 years follow-up NHS2: 1989-2009, 20 years follow-up	47289 pre-& postm. women, age 42-67 years and 105386 women, age 25-42 years: 757 cases	Self-reported	BMI at age 18 years Recent BMI Weight change since age 18	≤19.9 20-21.4 21.5-22.9 ≥23.0 ≤24.9 25.0-29.9 30.0-34.9 ≥35.0 -2 kg -2 to +2 +2 to <5 +5 to <10 +10 to <15 +15 to <20 +20 to <25 +≥25	1.00 1.08 (0.88-1.31) 1.15 (0.93-1.44) 1.58 (1.30-1.92) 1.00 1.22 (1.00-1.47) 2.08 (1.68-2.58) 4.05 (3.24-5.07) 0.76 (0.48-1.21) 1.00 1.10 (0.73-1.65) 1.16 (0.81-1.67) 1.11 (0.77-1.60) 1.40 (0.97-2.02) 1.42 (0.96-2.09) 2.52 (1.78-3.55)	Age, smoking status, OC use, HRT use, age at menopause, FH – colon/rectal cancer, FH – EC, height, parity, age at last birth, physical activity, weight change
Alford SH et al, 2015, USA	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial	1993-2001-NA, 2.8 years follow-up	23485 postm. women, age 55-74 years: 77 cases	Self-reported	BMI	<18.5 18.5-24.9 25.0-29.9 ≥30.0	1.02 (0.14-7.55) 1.00 1.05 (0.62-1.79) 2.25 (1.37-3.70)	Age, race, HRT use, smoking
Bhaskaran K et al, 2014, United Kingdom	UK Clinical Practice Research Datalink	1987-2012, 7.5 years follow-up	2864658 pre- & postm. women, age ≥16 years: 2758 cases	Measured	BMI BMI BMI, never smokers	<18.5 18.5-24.9 25.0-29.9 30.0-34.9 ≥35.0 Per 5 units Per 5 units	0.93 (0.58-1.50) 1.00 1.52 (1.33-1.74) 2.65 (2.29-3.06) 5.86 (5.08-6.76) 1.62 (1.56-1.69) 1.63 (1.55-1.71)	Age Age, diabetes, smoking, alcohol, socioeconomic status, calendar year

Wu MM et al, 2014, Taiwan	Community-Based Cancer Screening Program	1991-1993 – 2011, 19.9 years follow-up	11258 pre- & postm. women, age 30-65 years: 38 cases	Measured	BMI Waist circumference WHR	<23 23-26 ≥27 <80 cm ≥80 <0.82 ≥0.82	1.00 0.81 (0.39-1.69) 1.12 (0.47-2.64) 1.00 1.24 (0.56-2.72) 1.00 0.98 (0.47-2.01)	Age, birth cohort
Weiderpass E et al, 2014, Sweden	Women's Lifestyle and Health Study	1991-1992 – 2009, 17 years follow-up	42270 pre-& postm. women, age 30-49 years: 144 cases	Self-reported	BMI Weight	Per 5 units Per 5 kg	1.42 (1.22-1.66) 1.15 (0.97-1.35)	Age, education, duration of OC use, parity, duration of breastfeeding, smoking status, number of cigarettes per day, menopausal status, diabetes mellitus
Han X et al, 2014, USA	Atherosclerosis Risk in Communities Study	1987-1989 – 2006, ~18 years follow-up	7569 pre-& postm. women, age 45-64 years: 78 cases	Self-reported (weight at age 25), baseline weight and height was measured	BMI at age 25 BMI at age 25 Weight change Weight change	<18.5 18.5-24.9 ≥25.0 Per 5 units <18.5 18.5-24.9 ≥25.0 Per 5 units <-3 % -3 to <3% 3 to <10% 10+ % Per 5% <-3 % -3 to <3% 3 to <10% 10+ % Per 5%	1.14 (0.45-2.89) 1.00 2.79 (1.67-4.68) 1.69 (1.40-2.03) 1.15 (0.46-2.93) 1.00 2.87 (1.70-4.84) 1.83 (1.47-2.26) 0.59 (0.15-2.38) 1.00 0.85 (0.31-2.34) 0.69 (0.30-1.62) 1.07 (1.03-1.13) 0.43 (0.11-1.77) 1.00 0.90 (0.33-2.48) 0.75 (0.32-1.76) 1.09 (1.04-1.14)	Age, race-center, education, height, smoking status at age 25, age at menarche, cigarette smoking status, alcohol, physical activity at baseline + further adjusted for weight change
Wang TYO et al, 2012, United Kingdom	Million Women Study	1996/2001 – 2009, 7.3 years follow-up	249791 postm. women (never users of hormonal therapy), mean age 60.5 years:	Self-reported	BMI at age 20 BMI	Per 5 units Per 5 units	1.95 (1.67-2.27) 1.87 (1.77-1.96)	Year of birth, region, socioeconomic status, height, age at menarche, parity, age at menopause, use of hormone contraceptives, alcohol, smoking, strenous exercise

			1410 cases					
Reeves KW et al, 2011, USA	Women's Health Initiative	1993/1998 – NA, 7.8 years follow-up	86937 postm. women, age 50-79 years: 806 cases	Measured	BMI WHR	≥30 vs. <25 ≥0.8530 vs. <0.7554	1.76 (1.41-2.19) 1.33 (1.04-1.70)	Age, race/ethnicity, income, education, physical activity, smoking, total energy, intake of fat, fiber, fruit and vegetables and grains, DM, hypertension, age at menarche, age at menopause, tried getting pregnant for >1 year, age at last term pregnancy, duration of hormone use, duration of OC use, NSAID use, FH – EC/OC, study component
Clark SL et al, 2010, USA	Multiethnic Cohort Study	1993/1996 – 2004, 10.3 years follow-up	50376 pre- & postm. women, age 45-75 years: 463 cases	Self-reported	Weight BMI at age 21 BMI Body weight change, African American Body weight change, Japanese American Body weight change, Latina Body weight change, White	≥74.8 vs. <55.7 kg ≥21.897 vs. <18.840 ≥30 vs. <25 Tertile 3 vs. 1 Tertile 3 vs. 1 Tertile 3 vs. 1 Tertile 3 vs. 1	3.43 (2.50-4.72) 1.71 (1.31-2.25) 3.54 (2.70-4.63) 3.47 (1.81-6.67) 2.02 (1.25-3.26) 3.08 (1.66-5.71) 1.83 (1.17-2.86)	Age, ethnicity, education, age at menarche, menopausal status, age at menopause, duration and type of HRT, OC use, parity, smoking history, DM, hypertension
Canchola AJ et al, 2010, USA	California Teacher's Study	1995/1996 -2006, 11.1 years follow-up	28418 postm. women, median age 61 years: 395 cases	Self-reported	BMI, never used HT BMI at age 18 Waist circumference WHR Weight change BMI, ever estrogen alone BMI at age 18	≥30 vs. <25 Per unit ≥25 vs. <25 Per unit ≥35 vs. <35 inches Per inch ≥0.80 vs. <0.80 Per 0.1 unit Gain 40 lb vs. stable Per 1 lb increase ≥30 vs. <25 Per unit ≥25 vs. <25 Per unit	3.5 (2.2-5.5) 1.07 (1.04-1.09) 1.8 (1.1-2.9) 1.07 (1.03-1.12) 2.7 (1.5-4.8) 1.09 (1.05-1.13) 2.7 (1.3-5.6) 1.31 (1.02-1.68) 3.7 (2.0-7.1) 1.10 (1.05-1.14) 1.6 (0.88-2.8) 1.04 (1.00-1.08) 1.2 (0.64-2.3) 1.03 (0.97-1.09)	Age, age at menarche, parity, age at 1st full-term pregnancy, OC use and duration, physical activity, height and hypertension and its interaction with time-dependent age

					Waist circumference WHR Weight change BMI, used E+P BMI at age 18 Waist circumference WHR Weight change	≥35 vs. <35 inches Per inch ≥0.80 vs. <0.80 Per 0.1 unit Gain 40 lb vs. stable Per 1 lb increase ≥30 vs. <25 Per unit ≥25 vs. <25 Per unit ≥35 vs. <35 inches Per inch ≥0.80 vs. <0.80 Per 0.1 unit Gain 40 lb vs. stable Per 1 lb increase	1.3 (0.78-2.2) 1.02 (0.97-1.08) 1.5 (0.83-2.67) 1.10 (0.85-1.43) 0.85 (0.50-1.40) 1.05 (0.98-1.13) 1.0 (0.63-1.7) 1.03 (0.99-1.06) 1.4 (0.89-2.3) 1.02 (0.97-1.07) 1.3 (0.85-2.0) 1.02 (0.98-1.06) 1.1 (0.70-1.6) 1.01 (0.78-1.31) 1.50 (0.93-2.30) 1.04 (0.99-1.10)	
Lopstein E et al, 2009, Sweden	Lund University Study	1990/1992 – 2007, 15.5 years follow-up	17822 postm. women, age <65 years: 166 cases	Self-reported	BMI	>29 vs. <25	3.5 (2.2-5.4)	Age
Conroy MB et al, 2009, USA	Women's Health Study	1992-95 – 2004, 8.8 years	32642 pre- & postm. women, age ≥45 years: 264 cases	Self-reported	Baseline BMI Waist circumference Hip circumference WHR	≥30.0 vs. <22.5 ≥39.0 vs. <31.0 inches ≥44.5 vs. <39.0 inches ≥0.87 vs. <0.78	2.49 (1.73-3.59) 1.61 (0.91-2.83) 1.84 (1.05-3.22) 1.34 (0.75-2.37)	Age, physical activity, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, and menopausal status
Lindemann K et al, 2009, Norway	The HUNT-2 Study	1995-1997 - 2005, 9 years follow-up	31473 pre- & postm. women, mean age 48.8 years: 100 cases	Measured	BMI	≥40 vs. <25	8.59 (3.29-22.44)	Age
McCullough ML et al, 2008, USA	Cancer Prevention Study 2 Nutrition Cohort	1992/1993 -2003, 11 years follow-up	33436 postm. women, age 50-74 yrs: 318 cases	Self-reported	BMI BMI, never HT use BMI, ever E+P use	≥35.0 vs. 22.5-<25.0 ≥35.0 vs. 22.5-<25.0 30.0-<35.0 vs. 22.5-<25.0	4.70 (3.12-7.07) 4.41 (2.70-7.20) 1.49 (0.68-3.28)	Age, age at menarche, age at menopause, parity, age at 1st birth, HT use, smoking history, exercise METs, OC use

Song YM et al, 2008, Korea	Korea Medical Insurance Corporation Study	1993/1994 – 2003, 8.75 years follow-up	152772 postm. women, age 40-64 years: 112 cases	Measured	BMI	≥30 vs. 21-22.9 Per 1 unit	2.95 (1.20-7.24) 1.13 (1.07-1.20)	Age, height, smoking status, alcohol, physical exercise, pay level
Chang SC et al, 2007, USA	NIH-AARP Diet and Health Study	1995/96 – 2000, 4.6 years follow-up	103729 postm. women, age 50-71 years: 677 cases	Self-reported	BMI, baseline population BMI at age 18, age-adj. BMI at age 18, MV-adj. Weight change	≥30 vs. <25 ≥30 vs. <25 ≥30 vs. <25 ≥20 vs. -5 to +4.9 kg	3.03 (2.50-3.68) 1.98 (1.09-3.62) 0.94 (0.50-1.76) 2.75 (1.96-3.86)	Age, physical activity, personal history of diabetes, menopausal hormone therapy, age at menarche, parity, age at menopause, history of OC use, smoking, race BMI at age 18 years was also adjusted for baseline BMI in the multivariate model Weight change also adjusted for weight at age 18 years
Reeves GK et al, 2007, UK	Million Women Study	1996/2001 – 2003/2004, 5.4 years follow-up	1222630 pre- & postm. women, age 50-64 years: 2657 cases 236 deaths	Self-reported	BMI, incidence BMI, mortality	≥30 vs. 22.5-24.9 Per 10 units ≥30 vs. 22.5-24.9 Per 10 units	2.73 (2.55-2.92) 2.89 (2.62-3.18) 2.28 (1.81-2.87) 2.46 (1.78-3.39)	Age, geographical region, socioeconomic status, age at 1st birth, parity, smoking status, alcohol intake, physical activity
Friedenreich CM et al, 2007, Europe	The European Prospective Investigation into Cancer and Nutrition	1992/2000 – 1999/2004, 6.4 years follow-up	223008 pre- & postm. women, age mainly 35-70 years: 567 cases Weight change: 106536 women: 264 cases	Measured	Weight BMI Waist circumference Hip circumference WHR Weight change	>72.4 vs. ≤58.0 kg Per 5 kg ≥40 vs. <25 Per 5 units ≥88 vs. <80 cm Per 5 cm ≥106.0 vs. ≤94.5 cm Per 5 cm >0.831 vs. ≤0.742 Per 0.1 unit 20 vs. -3 to <3 kg Per 5 kg	1.74 (1.35-2.23) 1.11 (1.08-1.15) 3.02 (1.66-5.52) 1.06 (1.04-1.08) 1.76 (1.42-2.19) 1.13 (1.09-1.17) 1.51 (1.17-1.94) 1.15 (1.10-1.21) 1.58 (1.19-2.10) 1.17 (1.03-1.32) 1.75 (1.11-2.77) 1.13 (1.06-1.19)	Age, center, total physical activity, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of OC, ever use of HRT, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, energy intake

Lundqvist E et al, 2007, Sweden & Finland	Swedish and Finish Twin Cohorts	Sweden: 1961/1973 – 2002 Finland: 1975/1976 – 2004 Total follow-up: 26.3 years	36490 pre- & postm. women, age 18-96 years: 214 cases	Self-reported	BMI, older subjects BMI, younger subjects	30 vs. 18.5-<25.0 Per 1 unit 30 vs. 18.5-<25.0 Per 1 unit	3.2 (2.1-4.8) 1.11 (1.06-1.15) 2.9 (1.4-5.9) 1.09 (1.04-1.14)	Age, country, smoking, leisure-time physical activity, educational level, diabetes, parity
Löf M et al, 2007, Sweden	Women's Lifestyle and Health Study	1991 – 2003, 12 years follow-up	38566 pre- & postm. women, mean age 39 years: 73 cases	Self-reported	BMI	30 vs. <25	3.05 (1.60-5.82)	Age, parity, age at 1st birth, total months of breastfeeding, FH - BC
Bjørge T et al, 2007, Norway	Norwegian Health Surveys	1963-2001, 25 years follow-up	1036877 pre- & postm. women, age 20-74 years: 9227 cases	Measured	BMI	≥30.0 vs. 18.5-24.9	2.51 (2.38-2.66)	Age, birth cohort, height and weight mutually adjusted
Khan MMH et al, 2006, Japan	Japan Collaborative Cohort Study	1988-90 – 2003, 13.3 years follow-up	63541 pre- and postm. women, age 40-79 years: 22 deaths	Self-reported	BMI	≥25.0 vs. <18.5	0.65 (0.06-7.31)	Age
Lukanova A et al, 2006, Sweden	Northern Sweden Health and Disease Cohort	1985-2003, 8.2 years follow-up	35362 pre-& postm. women, age 29-61 years: 118 cases	Measured	BMI	≥27.1 vs. 18.5-22.1	3.53 (1.86-7.43)	Age, calendar year, smoking
Rapp K et al, 2005, Austria	The Vorarlberg Health Monitoring and Promotion Program	1985/2001 – 2002, 9.9 years follow-up	78484 pre- & postm. women, 35-54 years: 175 cases	Measured	BMI	≥30 vs. 18.5-24.9	3.93 (2.35-6.56)	Age, smoking status, occupational group

Kuriyama S et al, 2005, Japan	Miyagi Prefecture Cohort Study	1984 – 1992, 7.6 years follow-up	15054 pre- & postm. women, age ≥40 years: 22 cases	Self-reported	BMI	≥30 vs. 18.5-24.9	4.04 (1.14-14.36)	Age, smoking status, alcohol drinking, meat, fish, fruits, green or yellow vegetables, bean-paste soup, type of health insurance
Lacey JV et al, 2005, USA	Breast Cancer Detection Demonstration Project	1979 – 1998, 13.0 years follow-up	30379 postm. women, mean age 57.2 years: 541 cases	Measured	BMI	≥35 vs. 18.5-24.9	2.5 (0.7-3.7)	Age, calendar time
Silvera SAN et al, 2005, Canada	Canadian National Breast Screening Study	1980/1985 - 1998/2000, 16.4 years follow-up	49613 pre- & postm. women, age 40-59 years: 426 cases	Measured	BMI	>30 vs. <25	3.40 (2.68-4.33)	Age
Schouten LJ et al, 2004, Netherlands	Netherlands Cohort Study	1986-1995, 9.3 years follow-up	2589 postm. women, age 55-69 years: 226 cases	Self-reported	Weight BMI BMI at age 20 years	≥80 vs. <65 kg Per 10 kg ≥30 vs. 20-22.9 Per 1 unit ≥25 vs. 20-22.9 Per 1 unit	3.29 (2.17-4.99) 1.57 (1.35-1.82) 4.50 (2.62-7.72) 1.13 (1.08-1.18) 1.33 (0.77-2.30) 1.07 (1.02-1.12)	Age, age at menarche, OC use, age at menopause, parity, cigarette smoking, non-occupational physical activity
Jonsson F et al, 2003, Sweden	Swedish Twin Cohort Study	1961/1969 – 1997, 26 years follow-up	11598 pre- & postm. women, age 44-83 years: 172 cases	Self-reported	BMI at age 25 Weight change	≥25.00 vs 18.5-24.99 ≥21 kg vs. 0-5 kg	1.9 (1.2-3.0) 2.5 (1.1-5.4)	Age, BMI at baseline Age, weight at age 25 years, baseline BMI
Calle E et al, 2003, USA	Cancer Prevention Study 2	1982-1998, 16 years follow-up	495477 pre- & postm. women, age ≥30 years: 704 deaths	Self-reported	BMI	≥40 vs. 18.5-24.9	6.25 (3.75-10.42)	Age, education, smoking status, number of cigarettes smoked, physical activity, alcohol, marital status, aspirin use, estrogen replacement therapy, fat consumption, vegetable consumption
Folsom AR et al, 2003, USA	Iowa Women's Health Study	1986-2000, 15 years follow-up	23335 postm. women, age 55-69 years:	Self-reported	BMI WHR	≥30.30 vs. <22.73 ≥0.91 vs. <0.76	3.36 (2.51-4.58) 1.96 (1.43-2.71)	Age

			415 cases					
Folsom AR et al, 2000, USA	Iowa Women's Health Study	1986 - 1996, 11-12 yrs follow-up	31702 postm. women, age 55-69 years: 298 cases	Self-reported	Waist circumference	≥96.0 vs. <74.3 cm	3.3 (2.3-4.8)	Age, education, physical activity, alcohol, smoking status, age at 1st live birth, estrogen use, vitamin use, energy, whole grain, fruit and vegetables, fish, red meat, Keys score, high blood pressure
Berry et al, 1999, Sweden	Swedish Twin Registry	1967-1992, 20.4 years follow-up	11659 pre-& postm. women, mean age 56.2 years: 133 cases	Self-reported	Weight at enrollment	≥71 vs. ≤57 kg	2.4 (1.4-3.8)	Age
Tulinius H et al, 1997, Iceland	Icelandic Cardiovascular Risk Factor Study	1967/1991 – 1995, 4-27 years follow-up	11580 pre-& postm. women, mean age 50.5 years: 98 cases	Measured	Weight BMI	Per kg Per unit	1.023 (1.008-1.038) 1.056 (1.024-1.130)	Age
de Waard F et al, 1996, Netherlands	The DOM Breast Cancer Detection Project	1975/1984 – 1993, up to 18 years follow-up	900 pre- & postm. women, age 40-64 years: 147 cases	Measured	Weight, prem. Quetelet index Weight, postm. Quetelet index	≥80 vs. <60 kg ≥29 vs. <25 ≥80 vs. <60 kg ≥29 vs. <25	1.2 1.6 4.0 1.9	Not available
Tornberg & Carstensen, 1994, Sweden	NA	1963-1987, ~20 years follow-up	47003 pre-& postm, women, age <75 years: 412 cases	Measured	BMI, age <55 years BMI, age 55+ years BMI	≥28 vs. <22 Per unit ≥28 vs. <22 Per unit ≥28 vs. <22 Per unit	1.64 1.08 (0.92-1.27) 3.16 1.29 (1.19-1.40) 2.55 1.24 (1.16-1.34)	Age, period of follow-up
Gapstur SM et al, 1993, USA	Iowa Women's Health Study	1986-1990, 4 years follow-up	25170 postm. women, age 55-69 years: 167 cases	Self-reported	BMI at age 18	≥24.60 vs. ≤19.34	1.6 (1.0-2.6)	Age
Folsom AR et al, 1989,	Iowa Women's Health Study	1986-1987, 2 years	63 cases 1274	Self-reported	Weight	>73 vs. <62 kg	3.34 (1.83-6.29)	Age

USA		follow-up	controls postm. women, age 55-69 years					

Supplementary Table 3: Prospective studies of height and endometrial cancer

Author, publication year, country/ region	Study name	Follow-up period	Study size, gender, age, number of cases	Assessment of weight and height	Exposure and subgroup	Description of quantiles or categories	RR (95% CI)	Adjustment for confounders
Weiderpass E et al, 2014, Sweden	Women's Lifestyle and Health Study	1991-1992 – 2009, 17 years follow-up	42270 women, age 30-49 years: 144 cases	Self-reported	Height	Per 10 cm	1.31 (0.98-1.74)	Age, education, duration of OC use, parity, duration of breastfeeding, smoking status, number of cigarettes per day, menopausal status, diabetes mellitus
Kabat GC et al, 2014, USA	NIH-AARP Diet and Health Study	1995-1996 – 2006, 10.5 years follow-up	192514 women, age 50-71 years: 1534 cases	Self-reported	Height	Per 10 cm	1.11 (1.03-1.20)	Age, education, race, smoking status, BMI, age at menarche, menopausal status, age at 1st birth, parity, HRT, alcohol, physical activity
Kabat GC et al, 2013, USA	Women's Health Initiative	1993-1998 – 2012, 12 years follow-up	144701 women, age 50-79 years: 1109 cases	Measured	Height	Per 10 cm	1.19 (1.08-1.31)	Age, alcohol, pack-years, HRT, parity, OC use, education, ethnicity, randomization status, BMI
Kabat GC et al, 2013, Canada	Canadian National Breast Screening Study	1980/1985 – 1998/2000, 16.2 years follow-up	88256 pre- & postm. women, age 40-59 years: 780 cases	Measured	Height	Per 10 cm	1.36 (1.22-1.52)	Age, menopausal status, years of education, pack-years of smoking, age at menarche, parity, OC use, HRT
Green J et al, 2011, United Kingdom	Million Women Study	1996/2001 – 2008, 9.4 years follow-up	1297124 pre- & postm. women, mean age 56 years: 5810 cases	Self-reported	Height	Per 10 cm	1.19 (1.12-1.26)	Age, region, SES, smoking, alcohol, BMI, strenous exercise, age at menarche, parity, age at first birth

Park SL et al, 2010, USA	Multiethnic Cohort Study	1993/1996 – 2004, 10.3 years follow-up	50376 pre- & postm. women, age 45-75 years: 463 cases	Self-reported	Height	≥165.1 vs. <157 cm	0.97 (0.72-1.32)	Age, ethnicity, education, age at menarche, menopausal status, age at menopause, duration and type of HRT, OC use, parity, smoking history, DM, hypertension
Sung J et al, 2009, Korea	Korea Medical Insurance Corporation Study	1993/1994 – 2003, 8.72 years follow-up	339575 pre- & postm. women, age 40-64 years: 298 cases	Measured	Height	>158.0 vs. ≤151.0 cm Per 5 cm	1.11 (0.70-1.73) 1.04 (0.88-1.22)	Age, BMI, cigarette smoking, alcohol, regular exercise, monthly salary, occupation, area of residence, age at menarche, duration of breastfeeding, age at 1st childbirth, menopausal status, estrogen replacement, OC use
Friedenreich CM et al, 2007, Europe	The European Prospective Investigation into Cancer and Nutrition	1992/2000 – 1999/2004, 6.4 years follow-up	223008 pre- & postm. women, age mainly 35-70 years: 567 cases	Measured	Height	>166.5 vs. ≤157.0 cm Per 5 cm	1.09 (0.83-1.42) 1.01 (0.94-1.09)	Age, center, total physical activity, age at menarche, menopausal status, age at menopause, number of full-term pregnancies, age at birth of last child, ever use of OC, ever use of HRT, education, smoking status, hypertension, diabetes, fruit and vegetable intake, fiber intake, carbohydrate intake, energy intake
Bjørge T et al, 2007, Norway	Norwegian Health Surveys	1963-2001, 25 years follow-up	1036877 pre- & postm. women, age 20-74 years: 9227 cases	Measured	Height	≥170 vs. 160-169 cm	1.11 (1.04-1.19)	Age, birth cohort, height and weight mutually adjusted
Lundqvist E et al, 2007, Sweden & Finland	Swedish and Finish Twin Cohorts	Sweden: 1961/1973 – 2002 Finland: 1975/1976 – 2004 Total follow-up: 26.3 years	36490 pre- & postm. women, age 18-96 years: 214 cases	Self-reported	Height	Quartile 4 vs. 1	0.9 (0.6-1.2)	Age, country, smoking, leisure-time physical activity, educational level, diabetes, parity

Schouten LJ et al, 2004, Netherlands	Netherlands Cohort Study	1986-1995, 9.3 years follow-up	2589 postm. women, age 55-69 years: 226 cases	Self-reported	Height	≥175 vs. <160 cm Per 5 cm	2.57 (1.32-4.99) 1.26 (0.98-1.62)	Age, age at menarche, OC use, age at menopause, parity, cigarette smoking, non-occupational physical activity
de Waard F et al, 1996, Netherlands	The DOM Breast Cancer Detection Project	1975/1984 – 1993, up to 18 years follow-up	900 pre- & postm. women, age 40-64 years: 147 cases	Measured	Height, prem. Height, postm.	≥170 vs. <160 cm ≥170 vs. <160 cm	0.8 2.5	CHECK!!

Supplementary Table 4: Body mass index and endometrial cancer incidence, nonlinear dose-response

BMI	RR (95% CI)
15	1.14 (1.00-1.29)
17.5	1.03 (0.97-1.09)
20	1.00
22.5	1.05 (1.00-1.11)
25	1.20 (1.08-1.33)
27.5	1.47 (1.27-1.71)
30	1.97 (1.62-2.39)
32.5	2.82 (2.23-3.56)
35	4.40 (3.33-5.81)
37.5	7.35 (5.31-10.17)
40	13.41 (9.18-19.60)

Supplementary Table 5: Body mass index and endometrial cancer mortality, nonlinear dose-response

BMI	RR (95% CI)
17.5	1.15 (0.95-1.39)
20	1.00
22.5	1.06 (0.97-1.16)
25	1.25 (1.12-1.40)
27.5	1.55 (1.41-1.72)
30	2.00 (1.85-2.15)
32.5	2.60 (2.48-2.71)
35	3.37 (3.29-3.45)
37.5	4.38 (4.28-4.48)
40	5.63 (5.39-5.89)

Supplementary Table 6: Body mass index at age 18-25 and endometrial cancer, nonlinear dose-response

BMI	RR (95% CI)
13	1.04 (0.55-1.97)
15	0.91 (0.66-1.25)
17.5	0.90 (0.81-0.99)
20	1.00
22.5	1.21 (1.17-1.26)
25	1.56 (1.50-1.62)
27.5	2.07 (2.00-2.15)
30	2.86 (2.70-3.02)
32.5	4.03 (3.61-4.50)
35	5.79 (4.69-7.16)
37.5	8.46 (5.93-12.06)
40	12.43 (7.33-21.09)

Supplementary Table 7: Weight and endometrial cancer, nonlinear dose-response

Weight (kg)	RR (95% CI)
46.85	1.00
50	0.99 (0.93-1.05)
55	1.01 (0.88-1.15)
60	1.07 (0.88-1.31)
65	1.21 (0.95-1.53)
70	1.43 (1.10-1.85)
75	1.78 (1.36-2.33)
80	2.36 (1.81-3.08)
85	3.23 (2.53-4.36)
90	5.03 (3.72-6.80)

Supplementary Table 8: Weight gain and endometrial cancer, nonlinear dose-response

Weight gain (kg)	RR (95% CI)
+1	1.00
+5	0.98 (0.85-1.12)
+10	1.18 (0.99-1.41)
+15	1.45 (1.18-1.77)
+20	1.75 (1.39-2.20)
+25	2.10 (1.61-2.73)
+30	2.49 (1.85-3.34)

Supplementary Table 9: Waist circumference and endometrial cancer, nonlinear dose-response

Waist circumference	RR (95% CI)
66.17	1.00
70	0.95 (0.88-1.03)
75	0.94 (0.80-1.11)
80	0.99 (0.79-1.23)
85	1.09 (0.84-1.40)
90	1.27 (0.97-1.66)
95	1.55 (1.18-2.06)
100	2.01 (1.50-2.69)
105	2.72 (1.97-3.76)
110	3.84 (2.61-5.65)

Supplementary Table 10: Waist-to-hip ratio and endometrial cancer, nonlinear dose-response

WHR	RR (95% CI)
0.7035	1.00
0.7508	1.10 (0.99-1.21)
0.8009	1.22 (1.05-1.42)
0.8501	1.37 (1.16-1.60)
0.9002	1.55 (1.32-1.83)
0.9503	1.79 (1.47-2.18)
1.0004	2.09 (1.54-2.84)

Supplementary Table 11: Height and endometrial cancer, nonlinear dose-response

Height (cm)	RR (95% CI)
150	1.00
155	1.03 (0.98-1.07)
160	1.06 (0.99-1.14)
165	1.13 (1.03-1.22)
170	1.19 (1.09-1.29)
175	1.28 (1.16-1.40)
180	1.39 (1.23-1.56)

Supplementary Table 12: Anthropometric factors and endometrial cancer

Anthropometric factor	Increment	N	RR (95% CI)	I^2 (%)	$p_{nonlinearity}$
BMI	Per 5 units	28	1.54 (1.47-1.61)	81	<0.0001
BMI, further adjusted for waist-to-hip ratio	Per 5 units	2	1.28 (1.17-1.40)	46	NC
BMI in young adulthood	Per 5 units	9	1.45 (1.28-1.64)	76	0.09
BMI in young adulthood, further adjusted for BMI in middle age (baseline)	Per 5 units	3	1.00 (0.92-1.08)	0	NC
Weight	Per 5 kg	8	1.18 (1.14-1.23)	68	0.004
Weight gain	Per 5 kg	7	1.16 (1.12-1.20)	51	0.02
Weight gain, further adjusted for BMI/weight in young adulthood	Per 5 kg	4	1.18 (1.15-1.21)	0	NC
Waist circumference	Per 10 cm	4	1.27 (1.17-1.39)	70	<0.0001
Waist circumference, further adjusted for BMI	Per 10 cm	2	1.26 (1.18-1.34)	70	NC
Waist-to-hip ratio	Per 0.1 unit	5	1.21 (1.13-1.29)	0	0.29
Waist-to-hip ratio, further adjusted for BMI	Per 0.1 unit	3	1.07 (0.97-1.17)	0	NC
Hips circumference	Per 10 cm	2	1.30 (1.19-1.41)	0	NC
Height	Per 10 cm	12	1.15 (1.09-1.22)	61	0.39

NC, Not calculated

Continuous update of the WCRF-AICR report on diet and cancer

Protocol

Continuous update of the epidemiological evidence on food, nutrition, physical activity and the risk of endometrial and ovarian cancers

Prepared by: CUP team, Imperial College London

WCRF/AICR has been the global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The first and second expert reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update project, in collaboration with Imperial College London (ICL).

The Continuous Update will provide the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It will also provide an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Second Expert Report.

WCRF/AICR has convened a panel of experts (the Continuous Update Panel) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who will consider the evidence produced by the systematic literature review and meta-analysis, and will consider the results and draw conclusions before making recommendations.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the continuous update will systematically review all of the science as it is published. The ongoing systematic literature review will be conducted by a team of scientists at ICL in liaison with the SLR centres where possible.

The current protocol for the continuous update of endometrial and ovarian cancers should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used in the literature reviews[1] for the Second Expert Report.

The starting point for this protocol are:

- The convention for conducting systematic reviews[1] developed by WCRF International for the Second Expert Report.
- The protocols developed by the SLR groups for the Second Expert Report for:
    - Endometrial cancer (Kaiser Permanente) [2]
    - Ovarian cancer (National Cancer Institute, Milan, Italy) [3]

The peer-reviewed protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Background

Endometrial cancer

The majority of cancers that occur in the *corpus uteri* are endometrial cancers, mostly adenocarcinomas.

Endometrial cancer is the fifth most commonly diagnosed cancer in women worldwide. It is more frequent in high-income countries, where age standardised incidence rates were estimated as 12.9 per 100, 000 females in 2008, compared to less developed areas where incidence rate was estimated at 5.9[4] .Around three quarters of women with this cancer survive for 5 years.

Risk increases with age, with most diagnoses made post menopause. Nulliparous women are at increased risk of cancer of the endometrium. There is also substantial evidence that, as with breast and ovarian cancer, late natural menopause increases the risk of endometrial cancer. Oral contraceptives protect against this cancer. Oestrogen-only hormone replacement therapy and tamoxifen are both associated with an increased risk of this cancer. Polycystic ovary syndrome and insulin sensitivity, which are both components of metabolic syndrome, may play a role in the pathogenesis of endometrial cancer, perhaps through hormonal disruption[5].

In the judgment of the Panel of the WCRF-AICR Second Expert Report [5], the factors listed below modify the risk of cancers of the endometrium.

CANCER OF ENDOMETRIUM		
	DECREASES RISK	INCREASES RISK
Convincing	No factor identified	Body fatness
Probable	Physical activity	Abdominal fatness
Limited –suggestive	Non-starchy vegetables	Red meat Adult attained height
Limited –no conclusion	Cereals (grains) and their products; dietary fibre ; fruits; pulses (legumes); soya and soya products; poultry; fish; eggs; milk and dairy products; total fat; animal fat; saturated fatty acids; cholesterol; coffee; alcohol; carbohydrates; protein; retinol; vitamin C; vitamin E; beta-carotene; lactation; energy intake	
Substantial effect on risk unlikely	No factor identified	

Ovarian cancer

Ovarian cancer is the third most common female gynaecological cancer worldwide and the second in developed countries after endometrial cancer. Worldwide there were 225,500 new cases of ovarian cancer estimated in 2008, accounting for around 4% of all cancers diagnosed in women[4].Ovarian cancer rates are nearly three times higher in high than in middle- to low-income countries. Risk increases with age, with most ovarian cancers occurring after menopause. Ovarian cancer is diagnosed often in advanced stages and survival rates are poor.

The etiology of epithelial ovarian cancer remains poorly understood. Most ovarian cancers occur spontaneously, although up to 10 per cent of cases develop due to a genetic predisposition (i.e., BRCA1, BRCA2, MLH1, MSH2)[6].

Use of oral contraceptives, parity, tubal ligation, and hysterectomy have been associated with decreased risk, while use of hormone replacement therapy, a family history of ovarian cancer and infertility have been associated with increased risk of ovarian cancer. Early menarche and late menopause have also been associated with an increased risk of ovarian cancer likely due to increased ovulation[6].

In the judgment of the Panel of the WCRF-AICR Second Expert Report [5], the factors listed below modify the risk of ovarian cancer.

CANCER OF THE OVARY		
	DECREASES RISK	INCREASES RISK
Convincing	No factor identified	No factor identified
Probable	No factor identified	Adult attained height
Limited –suggestive	Non-starchy vegetables Lactation	No factor identified
Limited –no conclusion	Dietary fibre; fruit; pulses/legumes; meat; poultry; fish; eggs; milk and dairy products; total fat; cholesterol; coffee; tea; alcohol; carbohydrate; lactose; protein; vitamin A; folate; vitamin C; vitamin E; recreational activity; body fatness; abdominal fatness; weight change; energy intake	
Substantial effect on risk unlikely	No factor identified	

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of endometrial cancer and ovarian cancers.

2. Review team

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Rui Vieira	Data manager	Responsible of the data management, the design and architecture of the database
Doris Chan	Research Assistant	Nutritional epidemiologist, supervisor of data entry, analyst
Ana Rita Vieira	Research Assistant	Nutritional epidemiologist, reviewer
Deborah Navarro	Research Assistant	Nutritional epidemiologist, reviewer

Review coordinator, WCRF: Rachel Thomson

Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

3. Timeline.

The SLR's for the Second Expert Report ended in December 30th 2005. A pre-publication update extended the search to June 30th 2006 for exposures and cancer sites with suggestive, probable, convincing associations with the exposures of interest.

In order to ensure the completeness of the database, the ICL team will repeat the search conducted for the pre-publication update. Therefore, the continuous update will include the articles added to Medline from January 1st 2006. The reviewers will verify that there are not duplicities in the database. With that purpose, a module for article search has been implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on endometrial and ovarian cancers:

Task	Deadline
Start Medline search of relevant articles published from January 2006	1st April, 2011
Review abstracts and citations identified in initial electronic search. Select papers for complete review	Monthly
Review relevant papers. Select papers for data extraction	Monthly
Data extraction	Monthly
Start quantitative analysis	January 2012*
End of quantitative analysis	March 2012
Send report to WCRF-AICR	May 2012
Transfer Endnote files to WCRF	May 2012

*Search will end in December 31st 2011

4. Search strategy

The search will be conducted in Medline using PubMed as interface. An automatic system for monthly searches has been implemented by the review team. The search for one cancer site will be conducted independently of the search for the other cancer sites.

The Continuous update team will use the search strategy established in the SLR Guidelines with the modifications implemented by the SLR centres (Kaiser Permanente, for endometrial cancer [2] and National Cancer Institute, Milan, Italy for cancers of and ovary[3]) for the WCRF-AICR Second Expert Report.

The search will not be limited to "human studies" as it can't be guaranteed that all studies on PubMed have been coded as human. The full search strategy for each cancer site is in Annex 1.

5. Selection of articles

Only articles that match the inclusion criteria (see 5.1) will be updated in the database. Pooled analysis and meta-analysis will be identified in the search, but they will not be included in the database. The results of these studies will be used as support document in the preparation of the report. The inclusion of a pooling project as a single study in the Continuous Update may decrease the heterogeneity, if included as a single study. However, if study-specific results are shown in the manuscript of a pooling project, these results will be extracted and included separately in meta-analyses In the Continuous Update project.

5.1 Inclusion criteria

The articles to be included in the review:

- Have to be included in Medline from January 1st 2006 (closure date of the database for the Second Expert Report[5]).
- Have to present results from an epidemiologic study of one of the following types[+]:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)
    - Prospective cohort study
    - Nested case-control study
    - Case-cohort study
    - Historical cohort study
- Must have as outcome of interest cancer incidence or mortality of:
    - Endometrial cancer, or
    - Ovarian cancer

- Have to present results on the relevant exposures

† *Only trials and cohort studies will be included in the review because they are considered to be less prone to bias than case-control studies. Filters for study design will not be implemented in the search strategy.*

Note on articles published in languages other than English:
The relevance of articles in languages other than English will be assessed by inspection of the title and if available in English, the abstract. If the same study is published in English and in another language, only the data of the article in English will be extracted.

5.2 Exclusion criteria

The articles to be excluded from the review:

- Are out of the research topic
- Do not report measure of association between the exposure and the risk of any of the cancers investigated (endometrial, ovary).
- Cohort studies in which the measure of the relationship between exposure and outcome is only the mean difference of exposure as this is not adjusted by main confounders.
- Are supplement to the main manuscript (e.g. Authors' Reply).

6. Exposures

The continuous update will use the labels and exposure codes listed in the SLR Guidelines[1] for the Second Expert Report. Additional codes for sub-exposures were added during the SLRs for the Second Expert Report and tin the continuous update of prostate, colorectal, breast and pancreatic cancers at Imperial College.

The original SLR code list of exposures and the additional sub-exposure codes has been updated by the ICL review team to ensure the identity of codes and labels for all cancer sites. The codes defined in the SLR Guidelines remained the same.

The updated list of selected codes for exposures is in Annex 2. The exposures listed represent the minimum list of exposures to be examined. These exposures are programmed in the interface for data entry generated at Imperial College with the purpose of facilitating data entry.

6.1 Biomarkers of exposure

In the SLR for the Second Expert Report[5], biomarkers of exposure were included under the heading and with the code of the corresponding exposure. Some review centres decided to include only biomarkers for which there was some evidence on reliability or validity, while other centres included in the database results on all the biomarkers retrieved in the search, independently of their validity. During the process of evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

The SLR centre on prostate cancer (Bristol) prepared a list of biomarkers that should not be included in the review, based on data of studies on validity and repeatability of the biomarkers. A table with included and excluded biomarkers and the reasons for exclusion are in Annex 3.

Study results on "new" biomarkers whose validity has not yet been fully documented will be extracted in the database of the continuous update.

The excluded biomarkers are:

Vit D: 1.25 $(OH)_2D$, Alkaline phosphatase activity (serum)

Iron (serum, hair, nails)

Copper (plasma, serum, hair)

Glutathione peroxidase (plasma, serum, erythrocytes, blood)

Zinc, metallotein levels (any)

Lipids: total fats (any)

Cholesterol, LDL (any)

Lipoprotein levels (serum)

Monounsaturated fatty acids (oleic acid) (plasma, adipose tissue)

Saturated fatty acids (palmitic acid, stearic acids) (plasma)

Protein (any)

Biomarkers of effect and biomarkers of cancer are not included in this review.

7. Outcome

The outcomes of interest are endometrial and ovarian cancers, encompassing incidence and mortality.

8. Search databases

Only the Medline database will be initially searched used PubMed as platform. Data provided from the Second Expert Report[2, 3] indicates that most articles included in the review have been retrieved from the Medline database.

9. Hand searching for cited references

For feasibility reasons, it was decided that full hand search will not be done. However, we will conduct to test for potential missing articles:

- The references of reviews and meta-analyses identified during the search will be hand searched.
- The references of the articles relevant to the review and published in 2010 and 2011 (last two years before the preparation of the report) will be hand searched.

If the hand searching shows that articles have been missed by PubMed, the Imperial College team will consider other strategies, such as modifying the search strategy and looking into other databases.

10. Selecting articles

The results of the PubMed searches will be downloaded monthly into the Reference Manager Databases. The articles of ovarian and endometrial cancer will be downloaded into two separated databases, one for each cancer site.

Initially a further electronic search will be undertaken within Reference Manager to identify and remove irrelevant records. This will be achieved by generating a list of stop words. The list of stop words was developed and tested by the SLR Leeds during the preparation of the WCRF-AICR second expert report. The list of stop words (Annex 4) was compiled from terms that describe surgical, diagnostic or oncology procedures. Also included in the stop word are terms referring to animal studies and in vitro studies. These terms will be used to identify non human studies. All references that include any of these stop words in the title of the citation will be excluded and stored in a separate Reference Manager database.

In a second step the remaining articles downloaded from PubMed will be inspected by a reviewer, who will indicate which articles are potentially relevant, articles to be excluded and articles that cannot be classified upon reading the title and abstracts.

The complete article of potentially relevant references and of references that cannot be excluded upon reading the title and abstracts will be retrieved. A second assessment will be done after review of the complete papers.

The assessment of papers will be checked by a second reviewer.

11. Labelling of references

For consistency, the Imperial College team will use the same labelling of articles employed during the SLR process for the Second Expert Report[1]: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: OVA for ovary and END for endometrial cancer, followed by a 5-digit number that will be allocated in sequence.

12. Reference Manager Files

Reference Manager files containing the references retrieved on the initial search are generated in the continuous update. The variables contained in the Reference manager files are those generated using the filter Medline for importing data. Additionally, customized fields will be implemented.

Three Reference Manager Files will be created:

.

1) A file containing the results of the initial search. The study identifier should be entered under a customized field titled ‘label’. Another customised field named ‘inclusion’ should be marked ‘in’ or ‘out’ for each paper, thereby indicating which papers were deemed potentially relevant based on an assessment of the title and abstract.

2) A file containing the excluded papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named 'reasons' should include the reason for exclusion for each paper. This file will be named Endometrium- (or Ovary-) excluded.
3) A file containing the included papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named "study design" should include a letter (A-Q) representing the study design of each paper, allocated using the study design algorithm in Annex 5. This file will be named Endometrium- (or Ovary-) included.

The Reference Management databases will be converted to EndNote and sent once per year to the WCRF Secretariat.

13. Data extraction

The IC team will update the database using the interface created at Imperial College for this purpose. The interface allows the update of all the information included in the Access databases generated during the SLRs for the Second Expert Report. This includes information on study design, characteristics of study population, methods of exposure assessment, study results, analytical methods, adjustment variables, matching variables, and whether methods for correction of measurement error were used.

The study design algorithm devised for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers (Annex 5). In some cases it will be appropriate to assign more than one design to a particular paper (e.g. analyses in the entire cohort and nested case-control).

13.1 Quality control

Data extraction will not be performed in duplicate. This will require important resources. Instead, all the data extracted during the first year of the continuous update will be checked by a second reviewer at Imperial College. In the second year, a random sample of 10% of the data extracted will be assessed by a second reviewer. If there are no errors, no more articles will be reviewed for that year. If there are errors, another 10% will be assessed by a second reviewer. The process will be continued in this way to guarantee the quality of the data extracted.

The extracted data will be also checked automatically by the data manager, who will prepare monthly reports of the errors identified for its correction by the reviewer. Examples of automatic checks are checking if the confidence interval contains the effect estimate and if it is symmetrical, checking that the sum of cases and non case individuals by categories of exposure add up to the total number of cases and non case individuals.

13.2 Choice of Result

There could be several results for a particular exposure within a study according to the number of models presented in the article (unadjusted, minimally, maximally) and the

number of subgroup or stratified analyses conducted (by gender, race, outcome type, etc.)

The results obtained using all the models reported in the paper and all the subgroup or stratified analysis should be extracted by the reviewer.

The reviewer should label the results as not adjusted, minimally adjusted, intermediately adjusted and maximally adjusted. In addition, the IC reviewer should indicate results obtained with a "best model". This serves the dual purpose of marking that result to be exported to the reports and also flagging it as the best model for potential inclusion in a meta-analysis.

The identification of "best model" will be undertaken firstly on the appropriateness of adjustment.

Minimally adjusted models should have been adjusted for age, and in dietary analyses, for energy intake.

"Best" adjusted models in analyses of ovarian cancer should have been adjusted for menopausal status, oral contraceptive use, hormone replacement therapy use among postmenopausal women and parity.

"Best" adjusted models in analyses of endometrial cancer should have been adjusted for BMI, menopausal status, oral contraceptive use, hormone replacement therapy use among postmenopausal women and parity.

Where there is more than one model adjusting for the main potential confounders, the most adjusted one will be considered to be the best model. Exception to this criterion will be "mechanistic" models, adjusting for variables likely to be in the causal pathway. When such results (over adjusted results) are reported, the most adjusted results that are not over adjusted will be extracted.

Sometimes, potential risk factors are not kept in the model because their inclusion does not modify the risk estimates. If this is specified in the article text, this model should also be considered the "best model".

In addition to adjustment, other subsidiary criteria to consider for identifying the 'best model' for meta-analysis are the number of cases (highest), and in certain circumstances the completeness of the data (e.g. where quantile ranges are provided over where missing).

13.3 Effect modification and interaction

The IC team should report whether interaction or heterogeneity tests were conducted and extract the results of these tests. The results will be summarized in Tables and when possible, meta-analyses will be conducted. These should be considered cautiously as often only statistically significant results of subgroup analyses are reported in the publications and therefore, they can be subject to selective publication bias.

In the SLR for the 2nd Expert Report, the results of stratified analyses were included in the database generally as subgroup analyses. Results of interaction analyses were

extracted using the same module of data entry by creating new "double entry" sub-exposures (e.g. Body mass index and physical activity).

In the continuous update, the results of stratified analyses will be extracted using the module "Subgroup analysis". To avoid the creation of new "double entry" exposures, the IC team has developed a new module for data entry of results of interaction analysis. The module 'interaction' allows the use of existing headings of single exposures during data entry that will be automatically linked in the database. The reviewer will not need to create new sub-exposures codes.

13.4 Gene and hormone interactions with dietary exposures, physical activity or measures of adiposity.

No attempt was made to critically appraise or analyse the studies that reported gene and endogenous or exogenous hormone interactions with dietary exposures, physical activity or measures of adiposity in the Second Expert Report.

The search strategy will not include gene or hormone related terms; however, when literature on gene and hormone interactions with dietary exposures, physical activity or measures of adiposity will arise, they will be also retrieved and reviewed, but we will not include these studies in the meta-analyses.

The results of these studies will be described in the narrative review under the relevant exposures. Dose-response meta-analyses will be conducted if there is available data from at least three studies.

13.5 Multiple articles

Different updates of a specific analysis from the same study are published. Occasionally, the same study results are published in more than one paper. The data of all relevant papers should be extracted, even if there is more than one paper from the same study reporting the same results.
The most appropriate data set will be selected during the reporting and data analysis process to ensure there is no duplication of data from the same study in an analysis. Multiple reports from the same study will be identified using first the study name. Study names are assigned automatically from a list include in the interface for data entry created by the IC team. In other occasions the selection of the best dataset will be made by visual inspection during data analysis using the criteria for inclusion in meta-analysis (in 14.2).

If needed, the IC team should contact the authors for clarification. If the matter remains unresolved the review coordinator of the continuous update will discuss the issue with the WCRF Secretariat and the CUP, if necessary.

14. Data analysis

The meta-analyses of studies on endometrial and ovarian cancers will be conducted separately for each cancer site.

Studies with incidence as outcome will be analysed separately from those with mortality as outcome. However, because survival from ovarian cancer is low, the IC

team will also do analyses combining studies on ovarian cancer incidence and mortality, and explore if the outcome explains potential heterogeneity.

When possible, the analyses will be stratified by menopausal status and histological subtype. Sensitivity analyses will be conducted excluding results that are not "best" adjusted models.

Scoring of study quality will not be used as it is unclear which of the many published scales is better. During the analyses, when the number of studies makes it possible, the IC team will conduct sensitivity analyses using as criteria, those included in the Newcastle –Ottawa quality assessment scale[7]. For clinical trials –if any is identified in the search- the CU team will use The Cochrane Collaboration's tool for assessing risk of bias[8].

Meta-analytic and narrative aspects of the data analysis will complement each other. The meta-analyses will examine the evidence for dose-response effects.

Information will be collected on whether individual studies investigated non-linearity, the methods used, and whether there was any evidence of non-linearity.

Non-linear dose-response meta-analysis will be conducted if the data suggest a non-linear shape.

STATA version 10.0 (College Station, TX, USA) will be used to analyse the data.

14.1 When to do a meta-analysis

A meta-analysis for a particular exposure and outcome will be conducted when 3 or more trials or cohort studies has been published in the period reviewed, and if the total number of studies in the database totalise to more than 3 trials or 5 cohort studies with enough information to conduct a dose-response meta-analysis or providing data to calculate the required information.

The study results extracted during the SLR and the studies identified in the Continuous update will be included in the meta-analysis. Special care will be taken to avoid including more than once the results of the same study (see 14.2).

14.2 Selection of results for meta-analyses and reporting.

The following guidelines for inclusion of studies in the meta-analysis will be applied:

1. Where more than one paper was published from the same study, the paper using the larger number of cases for analysis will be selected. This is often the most recent paper.

2. Where the same exposure was analysed in more than one way with different levels of adjustment, the best model will be the one with the most appropriate adjustment for confounding. This is often the maximally adjusted analysis (except mechanistic models).

3. Where an exposure was presented for all study participants, and by subgroup, the analysis of all study participants will be used.

4. Where an exposure was presented only by subgroup, the subgroups will be pooled first and then included in the meta-analysis. This is essentially equivalent to including the overall estimate and will provide a better estimate of heterogeneity across studies.

5. Where a paper presented results from two separate studies and included a pooled analysis of different studies (e.g. the Nurses' Health Study and the New York University- Women's Health Study), then the studies will be included separately and the pooled result will not be included. This maintains the independence of observations included and permits to look at heterogeneity across study results. The results of the pooled analysis will be mentioned in the narrative review.

14.3 Statistical Methods

To enable comparison of different studies, the relative risk estimates per unit of intake increase (with its standard error) provided by the studies or computed by us from the categorical data will be pooledusing the methods of Greenland & Longnecker[9] (the pool last approach) and Chêne and Thompson[10]. Means or medians of the intake categories will be used if reported in the articles. Zero consumption was used as boundary when the lowest category was open-ended. When the highest category was open-ended, we used the amplitude of the lower nearest category.The same methods were used to do the linear dose-response meta-analyses in the SLRs for the Second Expert Report. The advantage of the method proposed by Greenland & Longnecker is that it provides dose-response estimates that take account of the correlation induced by using the same reference group. The relative risk estimates for each unit of increase of the exposure will be derived with the method of DerSimonian and Laird[11] using the assumption of a random effects model that incorporates between-study variability. The unit of increment will be kept as the same unit used in the SLR. We will use the "best" (most adjusted risk estimate) from each study and if no model is considered the "best", we will use the most adjusted model that is not mechanistic model. Sensitivity tests will be conducted, limiting the analyses to the "best" models.

14.4 Derivation of data required for meta-analyses.

The information required for data to be usable for meta-analysis, for each type of result is:

Dose-response data (regression coefficients)

-Estimated odds, risk, or hazard ratio per unit increase in exposure with confidence interval (or standard error of log ratio or p value)
-Unit of measurement

Quantile-based or category data

-No. of cases and non cases (or person-time denominator for cohort studies) in each group; or total number of cases and non cases (or study size) plus explicitly defined equal-sized groups (for quantile-based data)
-Estimated odds, risk, or hazard ratios with confidence intervals (or standard error of log ratio or p value) compared with the baseline group, for each non baseline group (if these are not reported, unadjusted odds ratios can be calculated from the numbers of cases and controls)
-Range, mean, or median of exposure in each group
-Unit of measurement

The data needed to estimate the dose-response associations are often incompletely reported, which may result in exclusion of results from meta-analyses. Failure to include all available evidence will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations.

A number of approaches have to be taken in order to derive the information required. These will be applied in the following order of priority:

1. Where the exposure was measured as a continuous variable and the dose-response slope given, this will be used directly.

2. Where the slope (and its standard error or confidence interval) was not given in the text, these will be estimated applying the methods of Greenland & Longnecker[9] and using the mean exposure in each category given in the paper. No additional assumptions are required.

3. Greenland & Longnecker's method[9] requires the total numbers of cases and controls to be known, and starting estimates for the number of cases in each category. Where these were not presented, values will be estimated based on the categorisation into quantiles or on the information contained in each category estimated from the width of the confidence intervals.

4. Mean exposure for each category is rarely given. The midpoints will be used instead.

5. For open-ended categories, the methods of Chêne & Thompson[10] will be used to estimate the means. This approach made the assumption of a normally distributed exposure, or a distribution that could be transformed to normality. If the method can't be applied, the midpoint will be calculated using the amplitude of the adjacent category.

6. Where no confidence intervals were given in the paper, but approximate standard errors can be obtained from the cell counts, these will be used to derive approximate confidence intervals for the adjusted relative risks. Greenland & Longnecker's method[9] will then be applied using means given in the paper or estimated assuming normality, based on these derived confidence intervals.

7. Where there is a category representing a zero exposure, such as "non-drinker" or "not consumed", this will be treated separately for the purposes of estimating means in each category. Such "never" categories often lead to a peak in the distribution at zero, and the data will not follow neither a normal nor a lognormal distribution. By using a mean of zero for the "never" category and estimating means for the other categories separately, distributional assumptions could be made and more studies could be included in the meta-analysis.

8. The decision whether to log-transform will be made on an exposure by exposure basis. This will based on whether log-transformation were used in the articles to be included in the meta-analyses and in the experience of the SLR on endometrial [2] and ovarian [3] cancers for the Second Expert Report.

14.4 Missing values.

Insufficient detail in reporting of results of observational studies can lead to exclusion of these results from meta-analyses and is an important threat to the validity of systematic reviews of such research. It has been reported that only 64% of the results of cohort studies provide enough data to be included in dose-response meta-analysis[11]. Moreover, results that showed evidence of an association were more likely to be usable in dose-response meta-analysis than results that found no such evidence.

The most frequently occurring problems in reporting and the suggested solutions to make results usable in a dose-response meta-analysis are [12] :

Type of data	Problem	Assumptions
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR Prostate (Annex 6)
	Standard error missing	The p value (either exact or the upper bound) or the confidence interval is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Confidence interval is missing	Standard error and hence confidence interval were calculated from raw numbers (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chêne and Thompson [10] with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (see 14.3)
Category data	Numbers of cases and controls (or the denominator in cohort studies) is missing	These numbers may be inferred based on numbers of cases and the reported odds ratio (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

14. 5 Analysis of heterogeneity and potential bias

Heterogeneity between studies will be assessed with the I^2 statistic as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 30% and 50% correspond to cut-off points for mild, moderate, and strong heterogeneity [13].

Meta-regression will be performed to investigate sources of heterogeneity if there are enough studies to do it. The variables that will be examined as sources of heterogeneity are menopausal status, level of adjustment (best model, not best model), geographic area (North-America –Non black population, North-America –Black population, Europe, Asia, Other), length of follow-up, whether the dose-response slope was reported in the article or derived by the CUP team from categorical data.

Other variables that may be considered as source of heterogeneity are characterisation of the exposure (FFQ, recall, diary, anthropometry etc.) and exposure range (including correction for measurement error, length of intervention).

The interpretation of the exploration of heterogeneity should be cautious. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations between the study characteristics and the size of associations.

Small study bias (e.g. publication bias) was explored through visual examination of funnel plots and through Egger's test.

Influence-analyses where each individual study will be omitted in turn will be done to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies [14] .

14.6 Non linear trends in meta-analysis.

Non-linear meta-analysis will be applied when the data suggest that the dose-response curve is non-linear and when detecting a threshold of exposure might be of interest.

Considering a non-linear dose-response curve using the Greenland and Longnecker's pool-last approach is not possible. However a non-linear dose-response can be examined if means and covariances of the individual studies are pooled before estimating the slope (pool first approach).

Non-linear dose-response meta-analysis will be conducted using the pool first approach method implemented within Stata by Darren Greenwood (personal communication). The studies that only provide linear dose-response estimates per unit of increase will be excluded from the non-linear meta-analysis. The best fitting nonlinear dose-response curve from a family of fractional polynomials will be selected. The best model will be the one that gives the most improvement (decrease) in deviance compared to the linear model.

15. Reports

An update of the report will be produced in 2012 by the IC team. The report will include the following elements:

15.1 Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described. This information will be summarised in a flowchart.

15. 2 Description of studies identified in the continuous update

Number of studies by study design and publication year

Number of studies by population characteristics (gender, geographic area, others)

Number of studies by exposure (main heading and selected subheadings) and publication year

Number of studies by exposure and outcome subtype

15.3 Summary of number of studies by exposure and study type in the database, separated on new (studies identified in the continuous update).

Example of table of summary study numbers:

Exposure Code	Exposure Name	Outcome	Number of controlled trials			Number of cohort studies		
			Total	SLR	Continuous update	Total	SLR	Continuous update

15.4 Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) of the relevant studies will be summarised in tables using the same format as for the SLR for the Second Expert Report[1].
Within this table the studies should be ordered according to design (trials, cohort studies).

Example of table of study characteristics (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	OR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

Where
A: Age
B: Oral contraceptive use, parity, hormone replacement therapy use
C: Smoking
D: Anthropometry: height, BMI, others
E: Physical activity
F: Energy intake, other dietary factors
G: Others, e.g. Family history of the cancer, marital status, race, socioeconomic status

15. 5 Graphic presentation

Tabular presentation may be complemented with graphic displays when the elevated number of studies justifies it. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ‘‘high versus low’’ comparisons for each study. No summary effect estimate of high versus low comparison will be calculated. Studies will be ordered chronologically.
Dose-response graphs are given for individual studies in which the information is available.

15.6 Results of meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.
The results of meta-analysis will be presented in tables and forest plots, as well as the results of the exploration of heterogeneity and sensitivity analyses.
Studies already included in a meta-analysis during the SLR for the Second Expert Report will be identified with a star (*).

15.7 Future reports

After 2012, the CUP team at Imperial College will produce annual reports with tables summarising number of studies identified in the CUP and total number of studies by exposure. An updated report with meta-analyses will be produced upon recommendation of the WCRF Secretariat and the CUP Panel of Experts.

References

1. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. ***The SLR Specification Manual*** In : Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007

2. World Cancer Research Fund/ American Institute for Cancer Research. Kaiser Permanente SLR Team: Systematic Literature Review. ***The associations between food, nutrition and physical activity and the risk of endometrial cancer and underlying mechanisms.*** In: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007

3. World Cancer Research Fund/ American Institute for Cancer Research. National Cancer Institute Milan, Italy SLR Team: Systematic Literature Review. ***The associations between food, nutrition and physical activity and the risk of ovarian cancer and underlying mechanisms.*** In: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007

4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr

5. World Cancer Research Fund/ American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective.page 305 Washington DC: AICR , 2007

6. Schorge JO, Modesitt SC, Coleman RL, Cohn DE, Kauff ND, Duska LR, Herzog TJ.SGO White Paper on ovarian cancer: etiology, screening and surveillance. Gynecol Oncol. 2010 Oct; 119(1):7-17.

7. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European Journal of Epidemiology 25 (9): 603-605, DOI: 10.1007/s10654-010-9491-z.

8. Cochrane Handbook for Systematic Reviews of Interventions [Internet] Available from http://www.cochrane.org/training/cochrane-handbook.

9. N Orsini, R Bellocco and S Greenland, Generalized least squares for trend estimation of summarized dose-response data, Stata *J* 6 (2006), pp. 40–57.

10. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form.Am J Epidemiol. 1996; 144(6):610-21.

11. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

12. Bekkering GE et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol (2008); 167(9):1017-26.

13. JP Higgins and SG Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med 21 (2002), pp. 1539–1558.

14. A Tobias. Assessing the influence of a single study in meta-analysis, Stata Tech Bull 47 (1999), pp. 15–17.

Moose checklist_anthropometry and endometrial cancer

Reporting of background should include	Page
Problem definition	4
Hypothesis statement	4
Description of study outcome(s)	4, 5
Type of exposure or intervention used	5
Type of study designs used	5
Study population	Supplementary Table 2, 3
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	6
Search strategy, including time period included in the synthesis and keywords	5, Supplement (search terms)
Effort to include all available studies, including contact with authors	No contact with authors
Databases and registries searched	5
Search software used, name and version, including special features used (eg, explosion)	5, Supplement
Use of hand searching (eg, reference lists of obtained articles)	5
List of citations located and those excluded, including justification	6, Supplementary Table 1
Method of addressing articles published in languages other than English	Non-english articles were not identified
Method of handling abstracts and unpublished studies	Not included
Description of any contact with authors	No contact with authors
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5,6
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	6

Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	Supplemental Table 2, 3
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Indicators of study quality, such as duration of follow-up, number of cases, adjustment for confounding factors were investigated in subgroup analyses in Table 1 and 2
Assessment of heterogeneity	7-8
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	7-8
Provision of appropriate tables and graphics	Figure 1-6, Table 1-2, Supplemental Table 1-12
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	9-13, Figure 1-6,
Table giving descriptive information for each study included	Supplementary Table 1 and 2
Results of sensitivity testing (eg, subgroup analysis)	13, Table 1-2
Indication of statistical uncertainty of findings	9-13, Figure 1-6
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	9-13 (under each exposure)
Justification for exclusion (eg, exclusion of non–English-language citations)	17 (included only prospective studies to reduce potential recall or selection bias), non-English citations were not excluded, but were also not identified.
Assessment of quality of included studies	Subgroup analyses by study quality scores are provided in Table 1 and 2

Reporting of conclusions should include	
Consideration of alternative explanations for observed results	17-18
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	18-19
Guidelines for future research	17, 19
Disclosure of funding source	19