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Adipocytokines and their relationship to endometrial cancer risk: a systematic review and meta-analysis

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HIGHLIGHTS

- Participants with reduced adiponectin levels are more likely to develop endometrial cancer regardless of their BMI status, history of hypertension or diabetes.
- When considering participants with high BMI or a history of diabetes, increased leptin levels confer a greater risk of endometrial cancer
- Larger studies are required to establish the role of TNF-α and IL-6 in the development of endometrial cancer

ABSTRACT

Objective

To investigate the association between circulating levels of adipocytokines (adiponectin, leptin, tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6)) and growth factors (insulin-like growth factor I (IGF-I) and II (IGF-II)), and the risk of endometrial cancer.

Methods

Cochrane, CINAHL, Embase, Medline and Web of Science were searched for English-language manuscripts published between January 2000 and August 2018 using the following string of words: cancer and endometrial and (obesity or BMI) and (adiponectin or TNF* or IGF-I or IGF-II or IL-6 or leptin).

Results

Twenty articles were included in this meta-analysis, which corresponded to 18 studies involving 2921 endometrial carcinoma cases and 5302 controls. Fourteen articles reported circulating levels for adiponectin, seven for leptin, three for TNFα, three for IL-6 and one for IGF- I. No article reported values for IGF- II.

Patients with circulating adiponectin levels in the highest tertile had decreased endometrial cancer risk compared to women with levels in the lowest tertile, (summary of odds ratio (SOR) 0.51, 95% CI: 0.38-0.69, $p<0.00001$). Women with circulating leptin concentrations in the highest tertile had increased endometrial cancer risk compared to women with concentrations in the lowest tertile (SOR 2.19, 95% CI: 1.45-3.30, $p=0.0002$). There was no difference in cancer risk between participants with the highest TNFα and IL-6 levels compared to the lowest levels (SOR 1.27, 95% CI: 0.88-1.83, $p=0.20$ and SOR 1.20, 95% CI: 0.89-1.63, $p=0.23$, respectively).

Conclusions

Endometrial cancer risk is inversely affected by adiponectin and leptin levels. There appears to be no relationship between TNF-α and IL- 6 and the overall risk of endometrial cancer.

1. Background

The exact biological mechanism underlying the development of endometrial cancer is still poorly understood. In the UK, endometrial cancer is the 4th most common female cancer; approximately 9000 women were diagnosed with endometrial cancer in 2015 [1]. Worldwide, 320 000 new cases of endometrial cancer were diagnosed in 2012 [2].

Obesity is a well-recognised risk factor for endometrial cancer; however, the relationship between obesity and endometrial cancer is complex and likely to involve multiple biological pathways. Sex steroid and insulin pathways, chronic inflammation and alterations in circulating levels of adipokines have all been suggested as potential mechanisms affecting endometrial cancer risk [3-5]. Whilst elevated levels of endogenous oestrogens cannot justify alone the correlation between obesity and endometrial cancer, experimental studies have shown that adipokines, associated with hyperinsulinemia and insulin resistance, and inflammatory cytokines, associated to increased adiposity, may be also involved in the development of endometrial cancer [6].

Adiponectin, leptin, tumour necrosis factor alpha (TNFα), interleukin 6 (IL-6), insulin-like growth factor I and II (IGF-I and IGF-II), collectively termed adipocytokines, are hormones and cytokines secreted from adipocytes, and potentially key circulating molecules associated to endometrial cancer risk [7, 8].

Adiponectin, the most abundant circulating adipocytokines, plays an important role in regulating insulin and glucose metabolism, by promoting insulin secretion from pancreatic β cells and facilitating insulin up-take in the liver [9-12]. Moreover, adiponectin has anti proliferative properties and, by activating AMP activated protein kinase (AMPK), inhibits cell growth, angiogenesis and promotes apoptosis in malignant cells [13]. Because of its properties and the fact that adiponectin is decreased in obesity, insulin resistance and type 2 diabetes, all

78 independent risk's factors for endometrial cancer, circulating adiponectin levels may be an
79 important factor in endometrial cancer.
80 Leptin affects the activity of several cell types and its main function involves regulating energy
81 intake and expenditure [14]. It has a role in glucose metabolism, as well as in the immune
82 system. Leptin is also secreted by cancer cells and its levels have been reported to be increased
83 in endometrial cancer and hyperplasia compared to controls with normal endometrium [15].
84 TNFα and IL-6 are pro-inflammatory cytokines released by macrophages within adipose tissue
85 and have been implicated in tumourigenesis. TNFα promotes cellular proliferation and prevents
86 apoptosis by activating NFκB, [16], whereas IL-6 initiates tumour development and progression
87 through several pathways [17]. Both cytokines have been reported to be increased in
88 endometrial cancer and their pro-inflammatory actions play a role in cancer growth and
89 metastasis by inducing reactive oxygen species and subsequent DNA damage and DNA repair
90 inhibition [18]. IL-6 was found to be overexpressed in the stroma of endometrial cancer cells
91 and TNFα was associated with poor survival [19, 20]. However, other studies have not reported
92 such an increase and found no difference in the expression of IL-6 in endometrial cancer and at
93 the various clinical stages [21].
94 IGF-I and IGF-II are growth factors involved in growth and development [22]. They are
95 expressed in the normal development of the endometrium and also stimulated by oestrogen in
96 the uterus [23]. Epidemiological, clinical and experimental data have identified IGF-I and II as
97 important players in endometrial cancers. IGFs are thought to play a role in the initiation of
98 endometrial cancer due to oestrogen increasing the synthesis and expression of IGF-I which
99 stimulates cell proliferation thereby initiating endometrial cancer [24]; whereas IGF-II
100 expression was increased in advanced endometrial cancer compared to early stage endometrial
101 cancer [25]. Relative few studies have assessed the correlations between endometrial cancer
102 risk and circulating levels of IGF axis components: however a large degree of variability

between studies and results was reported probably reflecting the complexity of this hormonal system and the involvement of additional (hormonal or other) factors that can either positively or negatively impinge upon IGF axis components.

Although evidences from *in vitro* and *ex-vivo* studies for a causal role of adipocytokines in endometrial cancer are available, results from epidemiological studies are inconsistent. A number of meta-analyses [26-28] have previously summarised epidemiological studies investigating the relationship between circulating adiponectin and leptin concentrations and endometrial cancer risk, however, to date, no meta-analysis has been performed to assess the relationship between circulating levels of the pro-inflammatory cytokines, TNFα and IL-6, or growth factors, IGF-I and IGF-II, and the risk of endometrial cancer. This study further clarifies the association between circulating levels of leptin and adiponectin, and endometrial cancer, and aimed to systematically assess the relationship between cytokines (IL-6 and TNFα) and growth factors (IGF-I and IGF-II) levels with endometrial cancer risk via a meta-analysis of observational studies.

2. Methods

2.1. Literature search

Meta-analysis was performed and reported by adopting the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines [29]. English-language manuscripts published between January 2000 and August 2018 were searched from the databases: Cochrane, CINAHL, Embase, Medline and Web of Science. The following string of words was used for searches in all databases – cancer and endometrial and (obesity or BMI) and (adiponectin or TNF* or IGF-I or IGF-II or IL-6 or leptin).

2.2. Selection of studies and exclusion criteria

Published studies were included if they met the following criteria: the study i) used an epidemiologic study design (e.g. case–control, case-cohort, nested case-control and cohort study); ii) provided information on circulating adiponectin, leptin, TNFα, IL-6, IGF-I, IGF-II concentrations as exposure of interest; iii) reported endometrial cancer as the outcome of interest; and iv) reported usable risk estimates (e.g. odds ratio, risk ratio or relative risk with 95% confidence intervals between circulating adipocytokines levels and endometrial cancer risk). In addition, if more than one study was conducted in the same population, the most recent report or the report with the most applicable estimates was selected for analysis.

Published studies were excluded by the following exclusion criteria: i) non epidemiological studies, reviews without original data, ecological studies, editorials and case reports; ii) the study reported the risk estimates that could not be summarized (i.e. reported the risk estimates without 95% CIs); and iii) the study reported exclusively on endometrial cancer mortality. All study selection and exclusion procedures were carried out by two independent investigators (PEE and GB). If there was discordance, a third independent reviewer, GAB would make the final decision.

2.3. Data Extraction

The following key data were extracted from each included study: first author's name, publication year, study country, study design, number, ages and BMI of cases/controls, assay methods, risk estimates, and matched or adjusted factors including age, body mass index (BMI), menopausal status, whether they have had diabetes mellitus (DM) or hypertension, hormone replacement therapy (HRT) usage, parity or whether they smoked.

2.4. Statistical analysis

Review Manager software, Version 5.3, was used to perform the meta-analysis: inverse variance, odds ratio and random effect were chosen as statistical method, effect measure and analysis model, respectively. The risk estimates were analysed as an estimation of odds ratio (OR) or relative risk (RR) for simplicity. People with the levels of exposure in the top tertile were compared with those in the bottom tertile. If the highest tertile (T3) and the lowest tertile (T1) were not available from the individual studies [30-37], a scaling method similar to Danesh *et al*. [38] and used by Gong *et al*. [26] was applied: a scaling factor of 2.18 divided by 2.54 times the log OR for comparison of the top and bottom quartiles, or a scaling factor of 2.18 times the log OR for 1 standard deviation difference in the baseline levels of adiponectin or leptin. In addition, some of the studies [6, 39] used the highest category of adiponectin rather than the lower category as comparison: an effective count method described by Hamling and colleagues [40], was therefore used to transform the comparison to the lowest tertile (T1). To assess the relationship between circulating adipocytokines and the risk of endometrial cancer, the summary of odds ratio (SOR) with 95% CI was estimated. This was performed using a random effect model of analysis. Chi-Squared test was used to assess the variation across the studies, which was included in the forest plots. Heterogeneity across the studies was analysed using the I^2 statistics [41] and results were defined as heterogenous for an $I^2 > 50\%$. All statistical tests were two-sided. $p < 0.05$ were considered to be statistically significant.

Sensitivity analysis was performed to assess the influence of individual studies on the pooled OR and 95% CI by excluding each study in turn.

Heterogeneity of the study results were explored by using stratified analyses and subgroup analyses. These analyses included design of the study, fasting status for the collection of the blood samples and the type of assay method used. Subgroup analyses to identify potential confounders included BMI, hypertension, diabetes and menopausal status. A variable was

considered confounding if they were found to be significantly associated with endometrial cancer $p < 0.05$ on the univariate analysis.

3. Results

3.1. Search Results and publication characteristics

The database searches identified 473 publications. A total of 427 studies were excluded on title and abstract review as they did not meet the inclusion criteria as shown in Figure 1. The remaining 46 studies were reviewed for further details and full text retrieved. Twenty-six studies were excluded for not containing OR values, risk ratio or relative risk with 95% CI. Therefore, a total of 20 articles were included in this meta-analysis, which corresponded to 18 studies involving 2921 endometrial carcinoma cases and 5302 controls. Fourteen articles reported circulating levels for adiponectin [6, 8, 31, 36, 37, 39, 42-49], 7 for leptin [8, 30, 36, 43, 44, 47, 48] 3 for TNFα [34, 35, 50], 3 for IL-6 [33, 35, 50] and 1 for IGF-I [51]. No article reported values for IGF-II. The characteristics of these studies, all published between 2002 and 2015, are presented in Table 1.

3.2. Adiponectin and its relationship to endometrial cancer risk

In this current meta-analysis, fourteen studies evaluated adiponectin and its relationship to endometrial cancer [6, 8, 31, 36, 37, 39, 42-49]. Two thousand and twenty-four endometrial cancer cases and 3,593 controls were assessed in 9 retrospective studies (8 case control studies [6, 31, 36, 37, 42-45] and 1 cross sectional-controlled study [39]) and 5 prospective studies (nested case control studies) [8, 46-49] (Table 1). Combined data showed a significant difference between the risks of developing endometrial cancer in women with the highest adiponectin levels compared to the lowest levels. Women with adiponectin concentrations in the highest tertile had a reduced risk (~0.5 times) of endometrial cancer compared to women

with adiponectin concentration levels in the lowest tertile (SOR 0.51, 95% CI: 0.38-0.69 p<0.00001). There was significant heterogeneity, I^2=77% p<0.00001 (Figure 2).

Sensitivity analysis was performed to determine whether any particular study had a greater degree of influence between the association of adiponectin's levels and the risk of endometrial cancer. Omitting each study one at a time and analysing the SOR of the rest of the studies, the SOR ranged from 0.48 (95% CI: 0.35-0.66, I^2=79%, p<0.00001) when omitting Soliman *et al*., (2011) [46] study to 0.58 (95% CI: 0.45-0.75, I^2=67% p=0.0002) when omitting Soliman *et al*., (2006) [6]. No single study had a larger influence over the other studies when assessing the association between adiponectin and endometrial cancer risk.

Stratifying by study design revealed a SOR of 0.64 (95% CI: 0.41-0.99, p=0.05) for prospective studies [8, 46-49] and a SOR of 0.45 (95% CI: 0.29-0.68, p=0.0001) for the retrospective studies (Table 2) [6, 31, 36, 37, 39, 42-45]. The heterogeneity was lower for the prospective studies (56%, p=0.06) compared to the retrospective studies (83%, p<0.00001). There were variations in the type of blood samples used as well as the method used to measure the concentration of adiponectin. Eight studies [8, 31, 36, 37, 39, 43, 44, 47] used fasting samples to measure adiponectin and in the other six [6, 42, 45, 46, 48, 49], it was not clear whether the blood samples were fasted or postprandial. The point estimate for studies using fasting samples was 0.51 (95% CI: 0.34-0.76, p=0.0009) and for the non-fasting studies, it was 0.51 (95% CI: 0.32-0.81, p=0.004). Eleven studies used an ELISA to measure adiponectin concentrations [6, 8, 36, 37, 39, 42, 43, 44, 46, 47, 49] and 3 studies used RIA/IMRA [31, 45, 48]. The point estimate of SOR in the studies using the ELISA method was similar to the studies using RIA/IMRA (SOR 0.53 vs 0.45). Within prospective studies, there was no significant heterogeneity (I^2=56% p=0.06), whereas there was within retrospective studies (I^2=83% p<0.00001). Within studies using fasting or non-fasting blood samples, there was significant heterogeneity (p=0.04 and p<0.00001, respectively). The studies using ELISA demonstrated statistically significant

heterogeneity (79% p<0.00001) whereas the one using RIA/IMRA did not (p=0.45). However there was no evidence of significant heterogeneity between subgroups detected by meta-regression analyses (Table 2).

Raised BMI, hypertension, diabetes and menopause are all risk factors for endometrial cancer. Sub-analyses were performed to assess for potential confounding factors. When considering BMI [6, 8, 31, 37, 39, 42-46, 49], the association between adiponectin levels and endometrial cancer risk is maintained (SOR 0.46, 95% CI: 0.31-0.69, p=0.0002, I^2=81%, p<0.00001). When considering hypertension [6, 36, 37, 42, 44, 47], diabetes [6, 37, 42, 44, 46-48], or menopause status [8, 31, 36, 37, 39, 42, 44, 47, 48], a statistically significant association with endometrial cancers was maintained in the groups with hypertension (SOR 0.57, 95% CI: 0.36-0.91, p=0.02, I^2=81% p<0.0001), diabetes (SOR 0.6, 95% CI: 0.38-0.94, p=0.03, I^2=79% p<0.001) and post menopause (SOR 0.56, 95% CI: 0.40-0.80, p=0.001, I^2=70% p=0.0007). This association was not lost in those without these conditions (Table 2).

3.3. Leptin and its relationship to endometrial cancer risk

A total of seven studies [8, 30, 36, 43, 44, 47, 48]; four retrospective [30, 36, 43, 44] and three prospective [8, 47, 48], assessed the association between circulating leptin concentrations and the risk of endometrial cancer. Three studies were nested case controls [8, 47, 48], and four were case control studies [30, 36, 43, 44]. One thousand, one hundred and ninety-nine endometrial cancers cases and 2076 control participants were assessed in the seven studies. The forest plot of the combined data (Figure 3) demonstrated a summary of OR of 2.19 (95% CI: 1.45-3.30, p=0.0002). These results suggest a significant difference between the risk of developing endometrial cancer in individuals with the highest leptin levels versus the lowest levels. Women with leptin concentrations in the highest tertile had 2.19 times increased risk of

endometrial cancer compared to women with leptin concentrations in the lowest tertile. There was variation between the studies, with significant heterogeneity, I^2 =64%, p=0.01.

Sensitivity analysis was performed to determine whether any particular study had a greater degree of influence between the association of leptin and the risk of endometrial cancer. Omitting one study at a time and analysing the SOR of the rest of the studies, the SOR ranged from 1.99 (95% CI: 1.37-2.91 p=0.0003, I^2=58%, p=0.03) when omitting Wu *et al*., (2014) [8] to 2.50 (95% CI: 1.84-3.40 p<0.00001, I^2=13% p=0.330) when omitting Friedenreich *et al*., (2012) [36]. No single study had a larger influence over the other studies when assessing the association between leptin and endometrial cancer risk.

When stratifying by study design (Table 2), the prospective studies [8, 47, 48] had a higher SOR of 3.32 (95% CI: 1.98-5.56 p<0.00001, I^2=15%, p=0.31) compared to the retrospective studies' SOR of 1.67 (95% CI: 1.09-2.57 p=0.02, I^2=56%, p=0.08) [30, 36, 43, 44]. There were variations between the type of samples used and the measurement of leptin concentration; 6 studies used fasting blood samples [8, 30, 36, 43, 44, 47] and 1 used a post prandial sample [48]. When comparing the type of samples, the point estimate of SOR for studies using non fasting blood samples was higher than the SOR for studies using fasting blood samples (2.77 vs 2.10). The concentration of leptin was either measured using an ELISA [8, 36, 43, 47] or RIA [44, 48], in 4 and 2 studies, respectively. In a further study, leptin was measured using an IMRA [30]. The point estimate of SOR for studies using ELISA was 2.27 (95% CI: 1.16-4.42 p=0.02, I^2=75%, p=0.007) and for the studies using RIA/IMRA was 2.45 (95% CI: 1.67-3.59 p<0.00001, I^2=0%, p=0.45). Within prospective or retrospective studies there was no significant heterogeneity (I^2=15% p=0.31, I^2=56% p=0.08, respectively), however there was evidence of significant heterogeneity (p=0.04) between subgroups detected by meta-regression analyses (Table 2). Within studies using fasting blood samples [8, 30, 36, 43, 44, 47] and measuring leptin levels by ELISA [8, 36, 43, 47], there was significant heterogeneity (I^2=65% p=0.01 and

I^2=75% p=0.007, respectively), whereas the one using non-fasting blood samples and RIA/IMRA did not (n/a and p=0.45). There was no evidence of significant heterogeneity between the two subgroups detected by meta-regression analyses (Table 2).

Both pre and post-menopausal women were included in these studies. Other factors that were matched/adjusted included BMI (n=4) [8, 30, 43, 44], hypertension (n=3) [36, 44, 47], a history of diabetes (n=3) [44, 47, 48] and post-menopausal status (n=5) [8, 30, 44, 47, 48]. When BMI is not considered [36, 47, 48], the overall association between leptin levels and the risk of developing endometrial cancer is reduced to borderline levels, p=0.05 (SOR 2.05, 95% CI 0.99-4.25, I^2=80% p=0.007). When considering patients with hypertension [36, 44, 47], the overall association between leptin levels and the risk of endometrial cancer is borderline (p=0.06, SOR 1.99, 95% CI 0.98-4.04) whereas the overall association is increased when considering patients with diabetes [44, 47, 48], (p<0.00001, SOR 2.80, 95% CI 1.93-4.05). When post-menopausal status is not considered [36, 43], the overall association between leptin levels and the risk of developing endometrial cancer is lost, p=0.18 (SOR 1.49, 95% CI: 0.83-2.70). There was significant heterogeneity (I^2=76%, p=0.02) in those studies that recorded hypertension compared to those studies that did not (I^2=42%, p=0.16). For those studies that did not adjust for the presence of diabetes in its participants, the heterogeneity was higher (I^2=68%, p=0.02) compared to those studies that consider diabetes as confounding factor (I^2=0%, p=0.91). Similarly, for those studies that did not adjust for post-menopausal status, the heterogeneity was higher (I^2=73%, p=0.05) compared to those studies that consider it as confounding factor (I^2=16%, p=0.31). No evidence of significant heterogeneity between BMI, hypertension, diabetes and post-menopausal status subgroups was detected by meta-regression analyses (Table 2).

299 *3.4. TNFα, IL-6 and IGF-I and their relationship to endometrial cancer risk*

300 The paucity of studies analysing TNFα, IL-6 and IGF-I and their association with the risk of
301 endometrial cancer is evident (Table 1) [33, 34, 35, 50, 51]. Two studies (one prospective [35]
302 and one retrospective [50]) assessed both TNFα and IL-6 in a single cohort and a further 2
303 studies (both prospective) assessed TNF-α [34] and IL-6 [33] only. There was only one study
304 (prospective) investigating the role of IGF-I [51] and the risk of endometrial cancer. The total
305 number of endometrial cancer and control cases for TNF-α was 940 and 1781 respectively, and
306 for IL-6, it was 975 and 1837, respectively. The prospective study assessing IGF-I and its
307 correlation with endometrial cancer risk had 166 cases and 315 controls.

308 From the meta-analyses, there appeared to be no association between circulating levels of TNFα
309 or IL-6 and overall risk of developing endometrial cancer (SOR=1.27, 95% CI: 0.88-1.83
310 p=0.20, SOR=1.20, 95% CI: 0.89-1.63, p=0.23, respectively) (Figures 4 A and B).
311 Heterogeneity was not present for either TNFα studies or IL-6 studies (I^2=65% p=0.06 for
312 TNFα, and I^2= 42% p=0.18 for IL-6).

313 Sensitivity analysis was performed to determine whether any single study had a greater degree
314 of influence between the association of TNFα and the risk of endometrial cancer. When Wang
315 *et al*., (2011) [35] was excluded, the SOR was 1.22 (95% CI: 0.77-1.93 p=0.39, I^2 =78%
316 p=0.030); excluding the study performed by Freidenreich *et al*., (2013) [50], the SOR was 1.58
317 (95% CI: 1.13-2.22 p=0.007, I^2=0%, p=0.92) and finally excluding the study performed by
318 Dossus *et al*., (2011) [34], the SOR was 1.10 (95% CI: 0.77-1.56 p=0.59, I^2 =36%, p=0.21).
319 There are differences between the 3 studies which could explain the change in SOR; the Wang
320 study [35] was a prospective study and the studies by Friedenreich *et al.*, (2013) [50] and Dossus
321 *et al*., (2011) [34] were retrospective and prospective studies, respectively. The participants in
322 the Wang *et al*., (2011) [35] study were postmenopausal women who were not using any

hormone treatments. Both pre- and post–menopausal women were included in the other 2 studies and some participants in these 2 studies were also noted to be using hormones.

Sensitivity analysis was also performed to determine whether any single study had a greater degree of influence between the association of IL-6 and endometrial cancer risk. The SOR ranged from 1.06 (95% CI: 0.76-1.49 p=0.72, I^2=18%, p=0.27), when omitting the Dossus *et al*, (2010) [33] to a SOR of 1.29 (95% CI: 0.97-1.70 p=0.08, I^2=37% p=0.21, when excluding the Wang *et al*., (2011) [35] study. Excluding the Friedenreich *et al*., (2013) [50] study, the SOR was 1.15 (95% CI: 0.56-2.34 p=0.71, I^2= 66%, p=0.09).

Only one prospective study [51] investigated the association of pre-diagnostic blood concentrations of IGF-I and other factors associated to hyperinsulinemia with endometrial cancer risk. While increased circulating C-peptide levels were associated with increased endometrial cancer risk, the risk was unrelated to IGF-I levels (OR 0.90, 95% CI 0.44-1.82, p =0.54) when case-control pairs were matched for study cohort, age at recruitment into the study, menopausal status, and adjusted for BMI and HRT use.

4. Discussion

Inflammation, an important factor in the development and progression of cancer, has been implicated in the link between obesity and cancer [52, 53]. Adiponectin, leptin, TNF-α, IL-6 and IGF-I are biological factors that are involved in different stages of the inflammatory pathway. To the best of our knowledge, this study is the most updated meta-analysis examining the relationship between circulating levels of adiponectin and leptin, and endometrial cancer; and the first one to assess the association between TNFα, IL-6, IGF-I and IGF-II and endometrial cancer risk. Our findings indicated that decreased circulating levels of adiponectin and increased levels of leptin are associated with increased endometrial cancer risk, whereas no

difference in cancer risk were observed between participants with the highest TNFα and IL-6 levels.

The paucity of studies reported in the literature investigating the link between the adipocytokines and endometrial cancer is evident; between 2000 and 2018, only 20 publications were found in the literature that met the inclusion criteria set. Undertaking a systematic review and meta-analysis increased population size enhancing the accuracy and precision of the findings from the various studies and allowing a greater understanding of the association between adipocytokines and endometrial cancer risk. Our analyses concurred with other reported studies [43, 48] on the association between adiponectin and leptin concentration levels and endometrial cancer risk: increased adiponectin serum levels and decreased leptin levels are associated with an overall decreased risk of endometrial cancer. It was found that women with higher levels of adiponectin had the risk of developing endometrial cancer decreased by half compared to those women with lower levels of adiponectin. Women with high levels of leptin had a two-fold increased risk of developing endometrial cancer compared to women with low levels of leptin. Similarly to the findings in this meta-analysis, low serum adiponectin levels and high serum leptin levels have been associated to increased risk of other types of cancer (e.g. colon and breast cancer) [54, 55]. In colorectal cancer patients, the association between TNFα, adiponectin and leptin has also been assessed concluding that leptin levels correlated with TNFα levels and that TNFα levels were an independent predictor of increased leptin levels [54]. Such association may be present in endometrial cancer, and leptin and TNFα may act synergistically to promote the development of endometrial cancer due to evidence that leptin promotes low grade inflammation by elevating levels of TNFα [56].

The studies reported by Dallal *et al.,* (2013) [47] and Soliman *et al*., (2011) [46] did not find an association between adiponectin serum levels and endometrial cancer risk, possibly due to the limited numbers of cases and controls Moreover, both studies were prospective, and slight

differences between the prospective and retrospective studies were highlighted by the sub analyses carried out (Table 2). For adiponectin, the SOR was 0.64 for prospective studies compared to 0.45 for retrospective with statistical difference for retrospective studies ($p=0.0001$) and for leptin, the SOR for prospective studies was 3.32 ($p<0.00001$) compared to 1.67 ($p=0.02$) for retrospective studies.

There have been limited studies assessing TNF-α and IL-6 and its risk with endometrial cancer. TNF-α and IL-6 play an important role in promoting carcinogenesis through the activation of various transcription factors and multiple oncogenic pathways. However, no significant associations between these two markers and risk of cancers were observed in the current meta-analysis. Despite the limited number of studies, the number of endometrial cancer cases and controls were relatively high; 940 vs 1781 and 975 vs 1837 cases vs controls, respectively. When assessing the individual studies, Wang *et al*., 2011 [35] and Friedenreich *et al*., 2013 [50] did not find an association between TNFα and IL-6 which is in contrast to the studies conducted by Dossus *et al*., 2010, 2011 [33, 34]. The risk of endometrial cancer appears not to be initiated by TNFα and IL-6, but may develop through other inflammatory pathways, such as genetic aberrations in PTEN or NFκB genes and the increased production of other mediators of inflammation [57]. Similar results related to the association of increased risk of endometrial cancer with TNF-α and IL-6 were also found in a recent systematic review and meta-analysis on circulating adipokines and their risk to obesity related cancers including breast, colorectal, kidney pancreatic, prostate, endometrial, and multiple myeloma cancers [58].

The only study considering the association of circulating levels of IGF-I with endometrial cancer, showed no association, in agreement with a study by Petridou et al., [59] which showed that endometrial cancer was positively associated with IGF-II and inversely with IGF-I. This study adds to the gradually developing consensus that components of the IGF system play a central role in human carcinogenesis, and that IGF-II, rather than IGF-I, may be closely linked

to the aetiology of endometrial cancer, one of the types of cancer most strongly associated with obesity.

Different study populations have differing characteristics, including BMI levels and presence of hypertension and diagnosis of diabetes. Further sub-analyses were performed to identify any other factors that could affect the risk of endometrial cancer. Tables 2 summarises the OR of the association between circulating adiponectin, leptin and endometrial cancer stratified by study characteristics. BMI appeared to affect the association between circulating leptin levels and endometrial cancer risk, but not with circulating adiponectin levels and endometrial cancer risk. Hypertension and diabetes appear to affect the association between circulating leptin levels but not between adiponectin levels and increased endometrial cancer risk. Adiponectin and leptin may act synergistically and increase the risk of endometrial cancer. This is not the case for TNF-α and IL-6.

The strength of our research is that this study presents a relatively comprehensive review of the existing evidence on the association of various adipocytokines and endometrial cancer. In particular, stratified analysis using a variety of selected variables has strengthened our results against the influence of confounding. There were also limitations to the meta-analysis; the number of cases in each study was relatively small, however the overall number of endometrial cancer cases in the meta-analysis was high, 2921. Retrospective studies were included and therefore, there is always a risk of potential bias in the form of recall bias.

This meta-analysis is the first to assess multiple adipocytokines in relation to endometrial cancer risk. Larger prospective studies assessing a variety of adipocytokines in the same cohort of patients are required to investigate further the association between adipocytokines and endometrial cancer, especially studies considering circulating levels of TNF-α, IL-6 and IGF I and II. This would allow elucidating in more details, the exact mechanisms underlying the link between adipocytokines and endometrial cancer.

Ethics approval and consent to participate

In this meta-analysis, we used only previously published data. Because no unpublished data were used, we did not seek ethics committee approval. The study is in accordance with the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Data availability

Not applicable.

Authors' contributions

PEE, GAB, and GB conceptualized this study, developed the protocol, and wrote the manuscript. PEE and GB selected articles for full-text review, extracted data from the included studies, and performed all statistical analyses.

Declaration of competing interest

None.

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Table 1

Characteristics of included articles (n=20)

First author, Year, Study Country	Study design	No. of case/control	Age of case/control	BMI of case/control	Biomarkers (assay method)	Risk Estimates (95% CI) Exposure categories	Adjusted factors
Retrospective studies							
Zhang, 2015 China	Case control	88/90	64.7±10.1a 58.7±8.6b	n/a	Adiponectin (ELISA)	OR 0.822 (0.759-0.889) Not specified in text	Age, BMI, WHR, diabetes, hypertension
Ohbuchi, 2014 Japan	Case control	43/62	61.2±9.8a 58.1±8.3b	26.1±4.5a 23.3±3.8b	Adiponectin (ELISA)	OR 1.987 (0.290-13.617) Q1 vs Q2	Age, BMI, diabetes, hypertension
Erodogan, 2013 Turkey	Cross sectional controlled study	60/70	56.57±9.05a 49.7±7.59b	31.12±4.18a 27.49±3.22b	Adiponectin (ELISA)	OR 10.64 (3.61-31.40) T1 vs T3	Age, BMI, HOMA-IR, QUICKI
Friedenreich, 2013 Canada	Case control	519/964	58.7 58.3	32.3 28.1	TNF-α (ELISA) IL-6 (ELISA)	OR 1.00 (0.84-1.18) OR 1.15 (0.89-1.48) Not specified in text	Age, BMI, nulliparity, physical activity, hypertension, alcohol consumption, hormone usage
Ma, 2013 China	Case control	206/310	53.2 (26-81)b 53.3 (27-82)b	n/a	Adiponectin (ELISA) Leptin (ELISA)	OR 0.52 (0.32-0.83) OR 2.05 (1.28-3.29) T3 vs T1	Age, BMI, glucose, cholesterol, triglycerides, HDL cholesterol, insulin, adiponectin (for leptin), leptin (for adiponectin)

Friedenreich, 2012 Canada	Case control	514/961	59 (53, 65)c 59 (52, 66)c	31.0 (26.4,36.8)c 27.2 (24.1, 30.9)c	Adiponectin (ELISA) Leptin (ELISA)	OR 0.55 (0.37-0.80) OR 1.14 (0.73-1.77) Q4 vs Q1	Age, weight, waist to hip ratio, nulliparity, HRT, hypertension, glucose, insulin, adiponectin (for leptin), leptin (for adiponectin)
Ashizawa, 2010 Japan	Case control	146/150	59.9±8.9a 57.5±7.4a	23.7±4.5a 22± 3.3a	Adiponectin (ELISA) Leptin (RIA)	OR 0.6 (0.3-1.2) OR 2.6 (1.4-4.9) T3 vs T1	Age, BMI, hypertension, diabetes
Soliman, 2006 USA	Case control	117/238	66.6 (25-88)b 61.2 (50-80)b	33.2 28.0	Adiponectin (ELISA)	OR 10.5 (4.18-26.35) T1 vs T3	Age, BMI, diabetes, hypertension,
Dal Maso, 2004 Italy	Case control	87/132	62 (34-78)d 61 (29-72)d	27.8 (25.4-32)e 25.1 (22.3-27.9)e	Adiponectin (RIA)	0.30 (0.14-0.68) T3 vs T1	Age, BMI, parity, education, HRT use, smoking status
Petridou, 2003 Greece	Case control	84/84	n/a	n/a	Adiponectin (RIA)	OR 0.78 (0.56-1.10) 1SD increment	Age, BMI, height, education, age at menarche, pregnancy, IGF-I, IGF-II, IGFBP-3 and leptin
Petridou, 2002 Greece	Case control	84/84	63.3±9.69a 62.6±11.3a	29.2±5.72a 26.5±3.43a	Leptin (IRMA)	OR 1.13 (0.70-1.81) 1SD increment	Age, education, height, age at menarche, menopausal status, history of pregnancy by outcome, alcohol and coffee consumption, smoking status
Prospective studies							
Wu, 2014 Taiwan	Nested case control	20/120	44.3±8.5a 46.6±9.8a	n/a	Adiponectin (ELISA) Leptin (ELISA)	OR 0.07 (0.01-0.62) OR 10.68 (2.09-54.67) T3 vs T1	Age, BMI, years of estrogen exposure
Soliman, 2011 USA	Nested case control	146/377	57 (47-67)b 57 (47-67)b	27.2 25.5	Adiponectin (ELISA)	OR 0.98 (0.57-1.68) T3vs T1	Age, BMI, parity, diabetes
Dallal, 2013 USA	Nested case control study	62/124	67.4±5.5a 67.5±5.1a	29.5±6.9a 26.8±4.7a	Adiponectin (ELISA) Leptin (ELISA)	OR 0.87 (0.39-1.94) OR 3.29 (1.41-7.69) T3 vs T1	Age, estradiol, C-peptide and BMI, diabetes

Luhn, 2013 USA	Nested case control	167/327	66.4±5.7a n/a	n/a	Adiponectin (RIA) Leptin (RIA)	OR 0.48 (0.29-0.80) OR 2.77 (1.60-4.79) T3 vs T1	Age, HRT, current smoking status, family history of breast and endometrial cancer, education, parity, diabetes, oral contraception use
Dossus, 2011 Europe	Nested case control	270/518	57.0 (6.9)a 57.0 (6.9)a	28.1 (5.9)a 26.3 (4.5)a	TNFα (ELISA)	OR 1.73 (1.09-2.73) Q4 vs Q1	Age, BMI, nulliparity, age at menopause, HRT use
Wang, 2011 USA	Case cohort	151/299	65.2 (7.1)a 63.5 (7.5)a	29.7 (7.8)a 27.5 (5.8)a	IL-6 (ELISA) TNFα (multiplex assay)	OR 0.70 (0.29-1.68) OR 1.65 (0.77 - 3.54) Q4 vs Q1	Age, BMI, Free IGF-I, estradiol, insulin
Dossus, 2010 Europe	Nested case control	305/574	56.9 (7.3)a 57.1 (7.4)a	27.5 (5.5)a 26.0 (4.3)a	IL-6 (ELISA)	OR 1.66 (1.08-2.54) Q4 vs Q1	BMI, C-peptide, estrone
Cust, 2007 Europe	Nested case control	284/548	56.9 (45.4-67.9)f 56.9 (45.0-68.0)f	28.1 (20.9-37.60)f 26.5 (20.2-34.8)f	Adiponectin (ELISA)	OR 0.63 (0.36-1.10) Q4 vs Q1	Age, BMI, C-peptide, IGFBP-1, IGFBP-2, SHBG, estrone, free testosterone
Lukanova, 2004 USA, Sweden, Italy	Case control	166/315	61 ±7.8a n/a	27.3 (26.5-28.0)g 25.3 (24.7-25.9)g	IGF-1 (RIA)	OR 0.90 (0.44-1.82) Q5 vs Q1	Age, menopausal status, day of menstrual cycle for pre-menopausal women

BMI, body mass index; WHR, waist-to-hip-ratio; ELISA ,enzyme linked immunosorbent assay; HOMA-IR, homeostasis model assessment of insulin resistance; QUICKI, quantitative insulin sensitivity check index; IGF, insulin like growth factor; IGFBP, insulin like growth factor binding protein; SHBG, sex hormone binding globulin; HRT, hormone replacement therapy; OR , odds ratio; RIA, radio-immuno assay.

a: mean ± SD; b: mean (range); c: median (25^{th}, 75^{th} percentile); d: median (range); e: median (interquartile range); f: mean (5^{th}-95^{th} percentiles); g: mean (95% confidence interval); n/a: not available

624 **Table 2**

625 Summary of OR of the relationship between adiponectin or leptin and possible risk factors for endometrial cancer

	Adiponectin						Leptin					
No of study		**SOR**	**95% CI**	**I^2**	**[1]p value**	**[2]p value**	**No of study**	**SOR**	**95% CI**	**I^2**	**[1]p value**	**[2]p value**
Study design												
Prospective	5	0.64	0.41-0.99	56%	p=0.06	p=0.27	3	3.32	1.98-5.56	15%	p=0.31	p=0.04
Retrospective	9	0.45	0.29-0.68	83%	P<0.00001		4	1.67	1.09-2.57	56%	p=0.08	
Fasting blood samples												
Yes	8	0.51	0.34-0.76	52%	p=0.04	p=1	6	2.10	1.31-3.38	65%	p=0.01	n/a
No	6	0.51	0.32-0.81	85%	p<0.00001		1	2.77	1.60-4.80	n/a	n/a	
Assay method												
ELISA	11	0.53	0.38-0.75	79%	p<0.00001	p=0.52	4	2.27	1.16-4.42	75%	p=0.007	p=0.85
RIA/IMRA	3	0.45	0.31-0.65	0%	p=0.45		3	2.45	1.67-3.59	0%	p=0.45	
BMI												
Yes	11	0.46	0.31-0.69	81%	P<0.00001	p=0.31	4	2.35	1.43-3.88	39%	p=0.18	p=0.76
No	3	0.59	0.45-0.76	0%	p=0.46		3	2.05	0.99-4.25	80%	p=0.007	
Hypertension												
Yes	6	0.57	0.36-0.91	81%	P<0.0001	p=0.54	3	1.99	0.98-4.04	76%	p=0.02	p=0.66
No	8	0.47	0.31-0.70	64%	p=0.007		4	2.42	1.47-3.97	42%	p=0.16	
Diabetes												
Yes	7	0.6	0.38-0.94	79%	P<0.001	p=0.31	3	2.80	1.93-4.05	0%	p=0.91	p=0.23
No	7	0.44	0.30-0.65	60%	P=0.02		4	1.80	0.97-3.35	68%	p=0.02	

Menopausal status												
Yes	9	0.56	0.40-0.80	70%	p=0.0007	p=0.47	5	2.75	1.87-4.05	16%	p=0.31	P=0.09
No	5	0.44	0.25-0.81	81%	p=0.0004		2	1.49	0.83-2.70	73%	P=0.05	

[1] p value for heterogeneity within each subgroup; [2]p values for heterogeneity between subgroups with meta-regression analysis

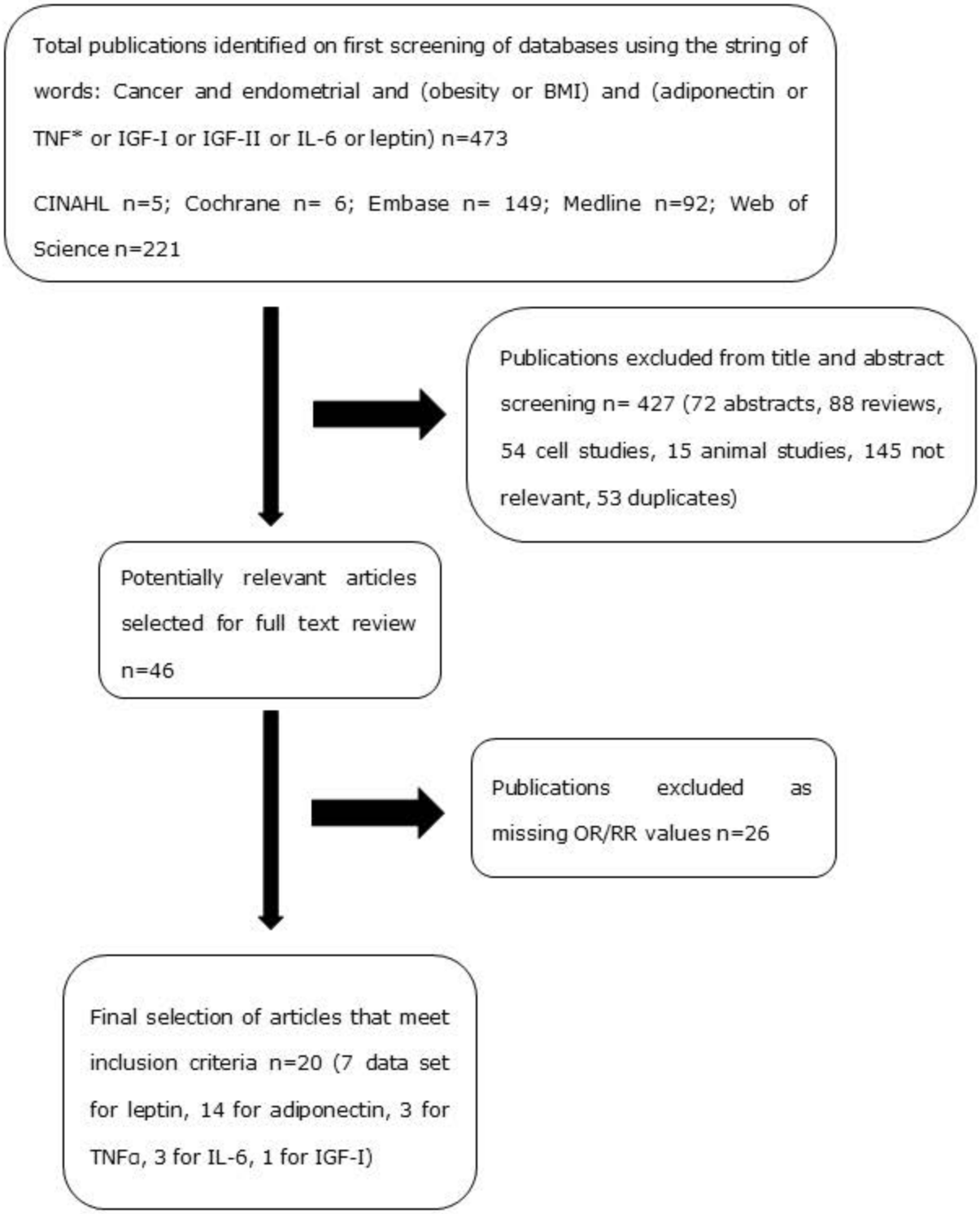
627 **Figure legends**

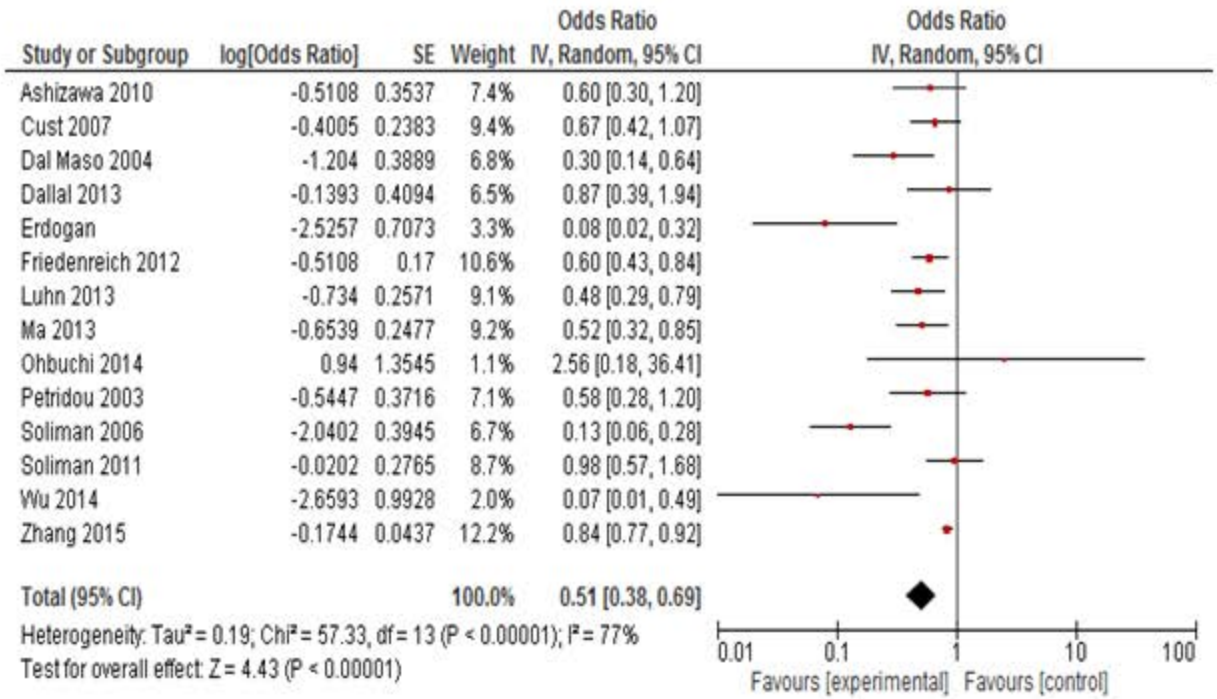
628 **Figure 1:** Flow diagram of screened, excluded and analysed publications

629 **Figure 2:** Forest plots representing the association between circulating levels of adiponectin
630 and the risk of endometrial cancer risk. The red squares represent the OR of the individual
631 studies and the horizontal lines through the boxes represent the 95% coefficient interval. The
632 overall treatment effect is represented by the black diamond.

633 **Figure 3:** Forest plots representing the association between circulating levels of leptin and the
634 risk of endometrial cancer risk. Red squares represent the OR of the individual studies and the
635 horizontal lines through the boxes represent the 95% coefficient interval. The overall treatment
636 effect is represented by the black diamond.

637 **Figure 4:** Forest plots representing the association between circulating levels of TNFα (A) or
638 IL-6 (B) and the risk of endometrial cancer risk. The red squares represent the OR of the
639 individual studies and the horizontal lines through the boxes represent the 95% coefficient
640 interval. The overall treatment effect is represented by the black diamond.


Total publications identified on first screening of databases using the string of words: Cancer and endometrial and (obesity or BMI) and (adiponectin or TNF* or IGF-I or IGF-II or IL-6 or leptin) n=473
CINAHL n=5; Cochrane n= 6; Embase n= 149; Medline n=92; Web of Science n=221
Publications excluded from title and abstract screening n= 427 (72 abstracts, 88 reviews, 54 cell studies, 15 animal studies, 145 not relevant, 53 duplicates)
Potentially relevant articles selected for full text review n=46
Publications excluded as missing OR/RR values n=26
Final selection of articles that meet inclusion criteria n=20 (7 data set for leptin, 14 for adiponectin, 3 for TNFα, 3 for IL-6, 1 for IGF-I)


Study or Subgroup
log[Odds Ratio]
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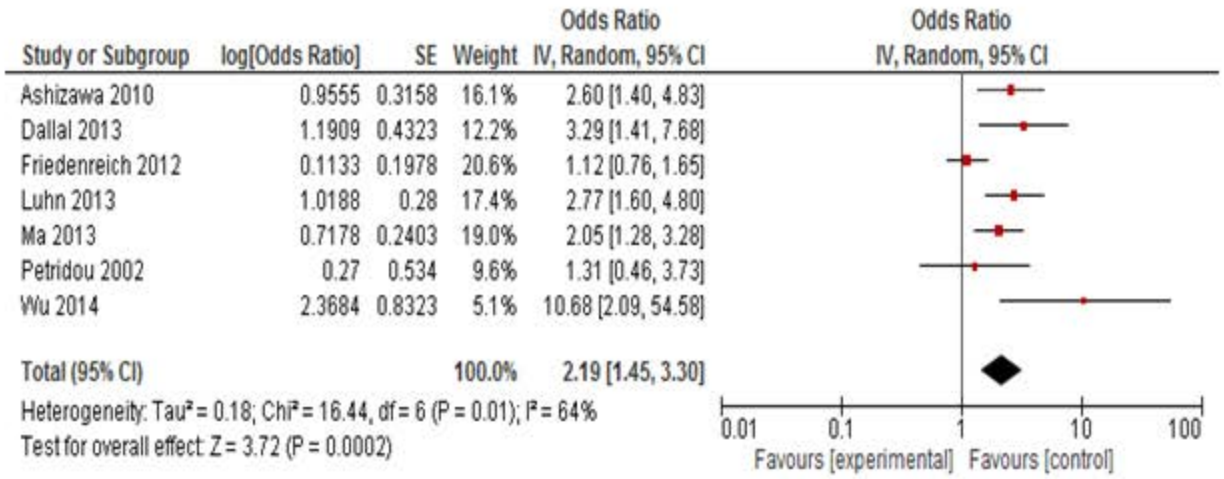
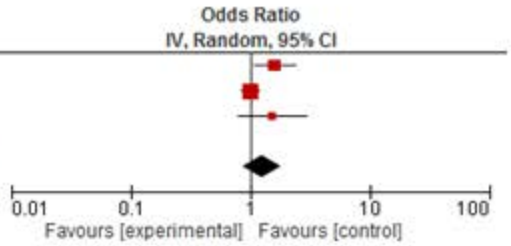
Odds Ratio
IV, Random, 95% CI
Odds Ratio
IV, Random, 95% CI
Ashizawa 2010 -0.5108 0.3537 7.4% 0.60 [0.30, 1.20]
Cust 2007 -0.4005 0.2383 9.4% 0.67 [0.42, 1.07]
Dal Maso 2004 -1.204 0.3889 6.8% 0.30 [0.14, 0.64]
Dallal 2013 -0.1393 0.4094 6.5% 0.87 [0.39, 1.94]
Erdogan -2.5257 0.7073 3.3% 0.08 [0.02, 0.32]
Friedenreich 2012 -0.5108 0.17 10.6% 0.60 [0.43, 0.84]
Luhn 2013 -0.734 0.2571 9.1% 0.48 [0.29, 0.79]
Ma 2013 -0.6539 0.2477 9.2% 0.52 [0.32, 0.85]
Ohbuchi 2014 0.94 1.3545 1.1% 2.56 [0.18, 36.41]
Petridou 2003 -0.5447 0.3716 7.1% 0.58 [0.28, 1.20]
Soliman 2006 -2.0402 0.3945 6.7% 0.13 [0.06, 0.28]
Soliman 2011 -0.0202 0.2765 8.7% 0.98 [0.57, 1.68]
Wu 2014 -2.6593 0.9928 2.0% 0.07 [0.01, 0.49]
Zhang 2015 -0.1744 0.0437 12.2% 0.84 [0.77, 0.92]
Total (95% CI) 100.0% 0.51 [0.38, 0.69]
Heterogeneity: Tau² = 0.19; Chi² = 57.33, df = 13 (P < 0.00001); I² = 77%
Test for overall effect: Z = 4.43 (P < 0.00001)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]


Study or Subgroup
log[Odds Ratio]
SE
Weight
Odds Ratio
IV, Random, 95% CI
Odds Ratio
IV, Random, 95% CI
Ashizawa 2010 0.9555 0.3158 16.1% 2.60 [1.40, 4.83]
Dallal 2013 1.1909 0.4323 12.2% 3.29 [1.41, 7.68]
Friedenreich 2012 0.1133 0.1978 20.6% 1.12 [0.76, 1.65]
Luhn 2013 1.0188 0.28 17.4% 2.77 [1.60, 4.80]
Ma 2013 0.7178 0.2403 19.0% 2.05 [1.28, 3.28]
Petridou 2002 0.27 0.534 9.6% 1.31 [0.46, 3.73]
Wu 2014 2.3684 0.8323 5.1% 10.68 [2.09, 54.58]
Total (95% CI) 100.0% 2.19 [1.45, 3.30]
Heterogeneity: Tau² = 0.18; Chi² = 16.44, df = 6 (P = 0.01); I² = 64%
Test for overall effect: Z = 3.72 (P = 0.0002)
0.01
0.1
1
10
100
Favours [experimental]
Favours [control]

A)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dossus 2011	0.47	0.2005	32.9%	1.60 [1.08, 2.37]
Friedenreich 2013	0	0.089	47.5%	1.00 [0.84, 1.19]
Wang 2011	0.4318	0.3342	19.6%	1.54 [0.80, 2.96]
Total (95% CI)			**100.0%**	**1.27 [0.88, 1.83]**

Heterogeneity: Tau² = 0.07; Chi² = 5.65, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 1.29 (P = 0.20)



B)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Dossus 2010	0.4318	0.1906	36.1%	1.54 [1.06, 2.24]
Friedenreich 2013	0.1398	0.1308	50.7%	1.15 [0.89, 1.49]
Wang 2011	-0.3147	0.3899	13.2%	0.73 [0.34, 1.57]
Total (95% CI)			**100.0%**	**1.20 [0.89, 1.63]**

Heterogeneity: Tau² = 0.03; Chi² = 3.43, df = 2 (P = 0.18); I² = 42%
Test for overall effect: Z = 1.19 (P = 0.23)