Current date: August 10th, 2022

Coffee consumption and risk of endometrial cancer: a pooled analysis of individual participant data in the Epidemiology of Endometrial Cancer Consortium (E2C2)

Marta Crous-Bou[1,2*], Mengmeng Du[3], Marc J. Gunter[4], Veronica W. Setiawan[5], Leo J. Schouten[6], Xiao-ou Shu[7], Nicolas Wentzensen[8], Kimberly A. Bertrand[9,10], Linda S. Cook[11,12], Christine M. Friedenreich[13,14], Susan M. Gapstur[15], Marc T. Goodman[16], Torukiri I. Ibiebele[17], Carlo La Vecchia[18], Fabio Levi[19], Linda M. Liao[8], Eva Negri[18,20], Susan E. McCann[21], Kelly O'Connell[3], Julie R. Palmer[9,10], Alpa V. Patel[15], Jeanette Ponte[3], Peggy Reynolds[21], Carlotta Sacerdote[22], Rashmi Sinha[8], Amanda B. Spurdle[23], Britton Trabert[8,24], Piet A. van den Brandt[6], Penelope M. Webb[17], Stacey Petruzella[3], Sara H. Olson[3], Immaculata De Vivo[2,25*]. On behalf of the Epidemiology of Endometrial Cancer Consortium (E2C2)

[1]Unit of Nutrition and Cancer, Cancer Epidemiology Research Program, Catalan Institute of Oncology (ICO) - Bellvitge Biomedical Research Institute (IDIBELL). L'Hospitalet de Llobregat, Barcelona, Spain

[2]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA

[3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[4]Nutrition and Metabolism Branch, International Agency for Research on Cancer, Lyon, France.

[5]University of Southern California, Los Angeles, CA, USA

[6]Department of Epidemiology, GROW – School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands

[7]Division of Epidemiology, Department of Medicine; Vanderbilt Epidemiology Center, Vanderbilt University Medical Center, Nashville, TN, USA

[8]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

[9]Slone Epidemiology Center at Boston University, Boston, Massachusetts, USA

[10]Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, USA

[11]Department of Internal Medicine, NM Health Sciences Center, University of New Mexico, University of New Mexico, Albuquerque, NM, USA

[12]Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[13]Department of Cancer Epidemiology and Prevention Research, Alberta Health Services, Calgary, Alberta, Canada

[14]Departments of Oncology and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[15]American Cancer Society, Department of Population Science, Atlanta, GA, USA

[16]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

[17]Department of Population Health, QIMR Berghofer Medical Research Institute, Brisbane, 4006, QLD, Australia

[18]Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy

[19]Department of Epidemiology and Health Services Research, Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland

[20]Department of Humanities, Pegaso Online University, Naples, Italy

[21]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA

[22]Center for Cancer Prevention (CPO-Peimonte), Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital, Turin, Italy

[23]Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, 4006, QLD, Australia

[24]Department of Obstetrics and Gynecology, University of Utah; Cancer Control and Population Sciences, Huntsman Cancer Institute.

[25]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

***Corresponding Authors:**

Marta Crous-Bou, PhD

Catalan Institute of Oncology. Avda. Gran Via de l'Hospitalet 199-203, 08908 l'Hospitalet de Llobregat. Barcelona, Spain.

Phone: (+34) 93 260 74 01 (ext. 3223)

Email: marta.crous@iconcologia.net

Immaculata De Vivo, PhD

Channing Division of Network Medicine – Harvard Medical School. 181 Longwood Ave, Boston, MA 02115, USA.

Phone: (+1) 617 525 2094

Email: nhidv@channing.harvard.edu

FUNDING

The E2C2 Data Coordinating Center at Memorial Sloan Kettering Cancer Center and multiple authors are supported by the National Cancer institute grant U01 CA250476. The Data Coordinating Center is additionally supported by NCI P30 CA008748.

ALBERTA study was funded by the Canadian Cancer Society. Linda S. Cook held a Canada Research Chair and received career award funding from AHFMR. Christine M. Friedenreich received career awards from the Canadian Institutes of Health Research and the Alberta Heritage Foundation for Medical Research (AHFMR) during the conduct of this study.

The Italian studies were supported by the Associazione Italiana per la Ricerca sul Cancro (AIRC) Foundation.

Swiss data from Vaud had the support of the Swiss National Science Foundation (grant 32.9495.88) and the Swiss National Cancer Research Foundation (grant OCS 1633-02-2008).

Susan E. McCann is supported by Roswell Park Comprehensive Cancer Center and National Cancer Institute (NCI) [Grant number P30CA016056].

The BWHS was supported by the National Cancer Institute – National Institutes of Health (R01 CA058420, UMI CA164974, R03 CA169888). Julie R. Palmer received support from the Karin Grunebaum Cancer Research Foundation.

The NIH-AARP research was supported [in part] by the Intramural Research Program of the NIH, National Cancer Institute.

The Bay Area Women's Health Study (BAWHS) was supported by NIH grant R01 CA74877; controls were collected under NIH grant R01 63446, U.S. Army Medical Research Program DAMD grant 17-96-607, and California Breast Cancer Research Program (CBCRP) grant 4JB-1106.

The Estrogen, Diet, Genetics, and Endometrial Cancer Study (EDGE) was supported by NIH grant R01 CA83918.

The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II (CPS-II) cohort.

Penelope M. Webb and Amanda Spurdle are supported by Fellowships from the National Health and Medical Research Council (NHMRC) [Grant Nos. 1173346, 177524); the ANECS study was funded by NHMRC [Grant No. 339435] and the Cancer Councils of Queensland [Grant No. 4196615] and Tasmania [Grant Nos. 403031, 457636].

The NHS is supported by the National Cancer Institute - National Institutes of Health (UM1 CA186107, P01 CA87969). Immaculata De Vivo is supported by U01 CA250476 grant from NIH.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGEMENTS

BWHS: “Data on endometrial cancer pathology were obtained from several state cancer registries (AZ, CA, CO, CT, DE, DC, FL, GA, IL, IN, KY, LA, MD, MA, MI, NJ, NY, NC, OK, PA, SC, TN, TX, VA). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute, the National Institutes of Health, or the state cancer registries. We thank participants and staff of the BWHS for their contributions.”

CPS-II: “The authors express sincere appreciation to all Cancer Prevention Study-II (and/or Cancer Prevention Study-3) participants, and to each member of the study and biospecimen management group. The authors would like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention's National Program of Cancer Registries and cancer registries supported by the National Cancer Institute's Surveillance Epidemiology and End Results Program”.

NIH-AARP: “We are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. We also thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis.” The NIH-AARP study acknowledgement is located here: https://dietandhealth.cancer.gov/acknowledgement.html.

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia. Cancer incidence data from California were collected by the California Cancer Registry, California Department of Public Health’s Cancer Surveillance and Research Branch, Sacramento, California. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program,

Community Health Administration, Lansing, Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (Miami, Florida) under contract with the Florida Department of Health, Tallahassee, Florida. The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, The Rutgers Cancer Institute of New Jersey, New Brunswick, New Jersey. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, North Carolina. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services, Phoenix, Arizona. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Division of Public and Behavioral Health, State of Nevada Department of Health and Human Services, Carson City, Nevada.

The authors would like to acknowledge the Associazione Italiana per la Ricerca sul Cancro (AIRC) Foundation for supporting the Italian data collection.

ANECS: “We thank the many women who participated in this study and the clinicians and institutions that contributed (see www.anecs.org.au for a complete list).”

NHS: “We thank the participants and staff of the Nurses’ Health Study for their valuable contributions, as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. We also thank Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School.”

All authors of this research paper have directly participated in the planning, execution, or analysis of the study. All authors of this paper have read and approved the final version submitted.

Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Declaration of Competing Interest: The authors have no conflict of interest to declare.

Total number of:

Tables: 6

Supplementary Tables: 3

Words, abstract: 264

Words, main text: 3,795

References: 47

Running title: Coffee and endometrial cancer risk

Keywords: coffee consumption; risk factors; endometrial cancer; pooled analysis; epidemiology.

Abbreviations: BMI, body mass index; CI, confidence interval; EC, endometrial cancer; E2C2, Epidemiology of Endometrial Cancer Consortium; FFQ, Food Frequency Questionnaires; OC, oral contraceptive; OR, odds ratio; PMH, post-menopausal hormone; RR, Relative Risk; WCRF, World Cancer Research Fund.

Data described in the manuscript will be made available upon request pending E2C2 Executive Committee approval.

ABSTRACT

Background: Epidemiological studies suggest that coffee consumption may be inversely associated with risk of endometrial cancer (EC), the most common gynecological malignancy in developed countries. Furthermore, coffee consumption may lower circulating levels of estrogen and insulin, hormones implicated in endometrial carcinogenesis. Antioxidants and other chemopreventive compounds in coffee may have anticarcinogenic effects. Based on available meta-analyses, the World Cancer Research Fund concluded that consumption of coffee probably protects against EC.

Objective: Our main aim was to examine the association between coffee consumption and EC risk by combining individual-level data in a pooled analysis. We also sought to evaluate potential effect modification by other risk factors of EC.

Patients and Methods: We combined individual-level data from 19 epidemiologic studies (6 cohort, 13 case-control) of 12,159 endometrial cancer cases and 27,479 controls from the Epidemiology of Endometrial Cancer Consortium (E2C2). Logistic regression was used to calculate odds ratios (OR) and their corresponding 95% confidence intervals (CI). All models were adjusted for potential confounders including age, race, body mass index, smoking status, diabetes status, study design and study site.

Results: Coffee drinkers had a lower risk of EC compared to non-coffee drinkers (multi-adjusted OR=0.87, 95% CI=0.79,0.95). There was a dose-response relationship between higher coffee consumption and lower risk of EC: compared to non-coffee drinkers, the adjusted pooled ORs for those who drank 1, 2-3 and more than 4 cups/day were 0.90 (95% CI=0.82,1.00), 0.86 (95% CI=0.78,0.95), and 0.76 (95% CI=0.66,0.87), respectively (p for trend < 0.001). The inverse association between coffee consumption and EC risk was stronger in participants with body mass index (BMI) over 25 kg/m^2.

Conclusion: The results of the largest analysis to date pooling individual-level data further support the potentially beneficial health effects of coffee consumption in relation to EC, especially among females with higher BMI.

INTRODUCTION

Endometrial cancer (EC) it is the most common gynecological malignancy and the fourth most common cancer among females in developed countries, affecting mainly postmenopausal females. In 2020, over 400,000 females worldwide were diagnosed with EC and over 90,000 died from the disease (1),(2) (https://gco.iarc.fr/ Accessed: August 2021). EC is a hormone-related cancer(3); well-known risk factors include obesity, and factors that elevate circulating levels of estrogen (e.g., estrogen-only postmenopausal hormone therapy, greater number of menstrual cycles, and nulliparity, among others) and insulin (i.e., diabetes). In contrast, smoking and physical activity are inversely associated with EC risk(4,5).

Coffee is among the most widely consumed beverages worldwide (6)(7) . Thus, an inverse association between coffee consumption and EC risk could have substantial implications for public health. Coffee contains a complex mixture of chemicals that have been shown to elicit antimutagenic, anticarcinogenic and antioxidant properties in experimental studies (8). In contrast, coffee (and other dietary components) also contains acrylamide, which is considered to be a carcinogen; however, results on the association between acrylamide and endometrial cancer risk are inconsistent(9). Previous studies have reported an inverse association between coffee consumption and circulating levels of estrogen and C-peptide, a marker of insulin secretion, both of which are involved in endometrial carcinogenesis(10–12). Furthermore, observational studies have shown that increased coffee consumption might be associated with a reduced risk of EC (as well as other chronic diseases) (8,13,14).

Several meta-analyses have been conducted to summarize existing evidence on the association between coffee consumption and the risk of EC(15–19). Most have reported an inverse association between coffee consumption and EC risk. Those associations seem to be stronger in postmenopausal females with higher body mass index (BMI). Based on available data through 2018, the World Cancer Research Fund (WCRF) concluded that consumption of coffee probably protects against EC (5). However, some unanswered questions remain, including the possibility of effect modification by other EC risk factors. Additionally, no pooled analyses combining individual-level data (especially from prospective studies) have been performed to date.

The aim of the present study was to assess the association between coffee consumption and EC risk by combining individual-level data of 12,159 endometrial cancer cases and 27,479 controls from 19 epidemiologic studies (6 cohort, 13 case-control) from the Epidemiology of Endometrial Cancer Consortium (E2C2). Additionally, we sought to assess whether this association is modified by other risk factors for the disease. This will be the largest analysis to date pooling individual-level data to address the coffee-endometrial cancer relationship and with the ability to stratify by key EC risk factors.

SUBJECTS AND METHODS

Participating Studies

A total of 19 epidemiological studies (6 cohort, 13 case-control) from the Epidemiology of Endometrial Cancer Consortium (E2C2) that collected information on coffee consumption were included in the pooled analysis with a total of almost 40,000 individuals (12,159 endometrial cancer cases and 27,479 controls) (see **Supplementary Table 1** for the full list of participating studies and their characteristics; note that five of the included studies have previously published on coffee consumption (20–24)).

The E2C2 is an international consortium established in 2006 to provide a collaborative environment to study EC by pooling resources and data from many EC studies, in an effort to increase statistical power to identify genetic and environmental risk factors for EC(25). Cohort studies were included as nested case-control studies, with up to 4 controls selected per case from females with an intact uterus at the time of study participation and without EC before the diagnosis of the index case. In each study, controls were frequency-matched to cases based on year of birth and race/ethnicity.

Out of 39,638 individuals from all participating studies, a total of 37,091 individuals had complete information on coffee consumption, thus were included in the present analysis: 11,109 EC cases and 25,982 controls (see **Supplementary Figure 1** for a flowchart of the participants included in the present study). Controls were frequency matched with EC cases by age. For most studies, the majority of participants were self-reported non-Hispanic whites. The number of EC cases in each study ranged from 132 to 1,850. Informed consent was obtained from all study participants as part of the original studies and in accordance with each study's Institutional Review Board.

Data collection

De-identified individual-level data from participating studies were sent to the E2C2 coordinating center at Memorial Sloan Kettering Cancer Center for initial data harmonization and cleaning. Data sets were checked for inconsistencies and completeness and queries were sent to the investigators to resolve any data issues. Questions regarding data or missing variables were referred to the site study coordinator and/or principal investigator. Each study also provided information regarding age at diagnosis (cases), age at interview or reference date (controls), interview year, tumor characteristics (cases), demographic variables, anthropometric measures, and known/potential risk factors for EC and covariates. These variables were defined and uniformly recoded in accordance with the E2C2 data dictionary (available upon request).

Incident cases of EC were included in the present analysis (primary site codes ICD-O-3: C54 and C55.9). EC diagnosis was confirmed by medical records, or by linkage with state tumor registries.

All included studies provided information on the main exposure variables (related to coffee consumption). Information on coffee consumption was obtained from food frequency questionnaires (FFQ). Variables related to the frequency (times per month/week/day), amount (cups/day; mg/day), type (caffeinated vs decaffeinated), and duration (years) of coffee consumption were requested for each individual study. After reviewing the questionnaires from each individual study, exposure variables provided were recoded into the following uniform variables: coffee drinking (yes/no); cups of coffee per day; type of coffee (caffeinated vs decaffeinated) when available. Regarding the latest, only the studies that provided information on coffee type were included in the corresponding analysis.

Additionally, individuals who reported drinking both caffeinated and decaffeinated coffee were excluded from this particular analysis.

Statistical methods

We analyzed the complete individual data using a pooled analysis. Logistic regression models were used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals (CI). Unmatched logistic regression models were performed, thus matching factors (i.e., age) were included in the model as potential confounders. Stratified analyses by study design, BMI, smoking status and diabetes status were also performed. Tests of interaction were calculated using log-likelihood test statistics comparing models with and without an interaction term. Tests for linear trend were calculated from linear models including the exposures as continuous variables.

Given the potential that females with endometrial cancer in case-control studies may have changed their diet in response to early unrecognized symptoms, or potential recall bias in these studies, analyses including cases and controls from prospective cohort studies only were also performed. Heterogeneity across studies and by study design was also examined by means of the I^2 statistic (26).

The following covariates were considered potential confounders: age (matching factor; years), study design (case-control versus cohort studies); study site (each individual study); ethnicity/race (white/black/Asian/Hispanic/mixed/other); BMI (kg/m^2); smoking (pack-years of smoking); alcohol (grams/day); energy intake (kcal/day); parity (number of children); post-menopausal hormone (PMH) therapy use (yes/no); oral contraceptive (OC) use (yes/no); diabetes status (yes/no); hypertension (yes/no). Models were adjusted for each potential confounder and variables were included in the final model if they were associated with the outcomes and exposures in the bivariate data analysis (p-value < 0.05), or caused a change in

the model estimate for coffee [beta] ≥10%). Variables included in the final models were: age, race, BMI, smoking, energy intake, study design and study site. Most of those variables have already been described as potential confounders according to previous literature. Additional analyses including other potential confounders (e.g. reproductive-related variables) were also performed. Not all studies had complete information available for all covariables included in the present analysis (e.g., energy intake, OC use, PMH use), especially some case-control studies. Complete-case analyses, which exclude participants with only partially available data on the variables of interest, were performed for the main pooled analysis (sample size for each particular model, and the covariables included in each analysis, are specified in the corresponding tables). Sensitivity analysis using the missing-indicator method (i.e., using a dummy variable in the statistical model to indicate whether the value for that variable is missing, with all missing values set to the same value) were also performed. Additional analyses excluding confounders with missing information (such as energy intake) were also performed.

All reported *p* values are two sided, and an α level of 0.05 was used to define statistical significance. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R software version 3.6.3 (R Foundation, Vienna, Austria).

RESULTS

All studies included in the present analysis are part of the Epidemiology of Endometrial Cancer Consortium (E2C2) and are presented in **Supplementary Table 1** (more details in Olson et al., 2009 (25)). Characteristics of the cases and controls included in the present analysis are shown in **Table 1**. EC cases tended to have higher BMI, smoke less, drink less alcohol, have higher energy intake, exercise less, use more PMH therapy and less OC, and drink less coffee. The proportion of white participants was also higher among cases, as well as the proportion of nulliparous females, females with diabetes and with hypertension. Mean age at diagnosis for EC was 63.5 years (SD=8.9). Characteristics of control participants by coffee consumption categories are shown in **Table 2**. Participants who drank more coffee had lower BMI, smoked more, drank less alcohol, had higher energy intake, and exercised more compared to participants who did not drink coffee. A higher proportion of participants who drank more coffee were Caucasian, while a higher proportion of those who did not drink coffee were nulliparous.

Table 3 shows the results from the pooled analysis regarding the association between coffee consumption and EC risk. In multivariable analysis, coffee consumption was inversely associated with EC. The pooled age- and race-adjusted OR for coffee drinkers versus non-drinkers was 0.92 (95% CI=0.85,0.98); pooled multivariable OR was 0.87 (95% CI=0.79,0.95). Coffee consumption was linearly associated with a lower risk of EC: the higher the coffee consumption, the stronger the inverse association (p for trend <0.001). The inverse association between coffee consumption and EC risk was limited to caffeinated coffee consumption (**Table 4**). The proportion of participants who only drank decaffeinated coffee (28% of coffee drinkers) was lower than that for caffeinated coffee (72% of coffee drinkers).

When all studies (cohort and case-control) were included to assess the association between coffee consumption and EC risk, heterogeneity across studies was observed (p=0.026). **Table 5** presents the results from the pooled analysis on the association between coffee and EC risk, stratified by study design. The inverse association between coffee consumption and EC was slightly stronger when limited to prospective studies (total number of participants: 20,290: 15,693 controls; 4,597 cases). Compared to non-coffee drinkers, ever coffee drinkers had a 13% lower odds of EC in cohort studies (pooled multivariable OR=0.87; 95% CI=0.78,0.96), with no significant heterogeneity observed across studies (p=0.10). Compared to non-coffee drinkers, the pooled ORs for those who drank more than 1 cup of coffee per day, 2-3 cups/day and more than 4 cups/day were 0.90 (95% CI=0.81,1.00), 0.87 (95% CI=0.77,0.97), and 0.74 (95% CI=0.63,0.87), respectively (p for trend = 3.26×10^{-4}) in cohort studies. Although an inverse association between coffee consumption and EC was also suggested in case-control studies, the effect sizes were smaller and the confidence intervals wider.

The inverse association between coffee consumption and EC risk was stronger in participants with higher BMI (**Table 6**). Among females with BMI >=25 kg/m^2, coffee drinkers had a 21% lower odds of EC (OR=0.79; 95% CI=0.71,0.89) compared to an 8% smaller odds in females with BMI less than 25 kg/m^2 (OR=0.92; 95% CI=0.79,1.07). There was an interaction between coffee consumption and BMI on EC risk ($p_{interaction}$ <0.001). Among females with a BMI <25 kg/m^2, only the highest level of coffee consumption (>4 cups/day) was negatively associated with EC (OR=0.72; 95% CI=0.57,0.92). Additional analyses stratified by smoking and diabetes status, have been conducted. Even though a lower odds of EC associated with coffee drinking was observed mainly in never smokers, no interactions were found between those EC risk factors and coffee consumption. Specifically, among participants who never smoked, coffee drinkers had a 14% lower odds of EC (95% CI=0.77,0.95) compared to a 10% lower odds in ever smokers (95% CI=0.79,1.16). However,

there was no differential effect of coffee consumption on EC risk by smoking status ($p_{interaction}$ =0.58). No differences regarding diabetes status subgroups were observed (**Supplementary Tables 2 and 3**, respectively).

DISCUSSION

In the present study, we performed a pooled analysis of individual level data from almost 40,000 females to evaluate the association between coffee consumption and EC risk. Our results suggest that, after adjusting for potential confounders, coffee drinkers have at least a 10% lower risk of EC compared to non-coffee drinkers, an association that was even stronger when restricting the analysis to prospective studies. Moreover, we observed an inverse dose-response relationship between coffee consumption and EC risk. Results of the pooled analysis also showed that the inverse association between coffee consumption and EC risk was especially stronger in females with higher BMI.

Several meta-analyses have summarized existing evidence on the association between coffee consumption and the risk of EC. In 2015, Yang et al(27) meta-analyzed 7 prospective and 4 retrospective studies (10,545 cases) and reported a weak inverse association between coffee consumption and EC (OR= 0.96, 95% CI=0.95,0.98 for retrospective studies; OR=0.91; 95% CI=0.87,0.95) for retrospective studies. Wang et al.(18) included 12 prospective studies (6,033 cases) and reported an inverse association for endometrial cancer (relative risk, RR, of the highest vs. the lowest coffee consumption category was 0.73; 95% CI=0.67,0.81) and confirmed that the strongest protective effect was found in females with BMI over 25 kg/m^2. However, there was no evidence of a linear association between coffee consumption and EC risk. In another dose-response meta-analysis of 12 studies (10,548 cases) published in 2017 by Lafranconi et al.(17), authors showed an association between coffee consumption and a

decreased risk of postmenopausal EC with a RR of 0.79 (95% CI: 0.73,0.87) of EC for the highest versus the lowest category of coffee consumption. In a sub-analysis including only 4 of the 12 studies, these authors analyzed the associations by coffee type (caffeinated versus decaffeinated coffee) and reported inverse associations with both types of coffee but heterogeneity among studies was present. In the most recent publication by Lukic and colleagues(16), including 12 cohort studies and 8 case-control studies (2,746 EC cases and 11,663 controls), the authors found an inverse association. After combining the results from cohort and case control studies, which showed a moderate level of heterogeneity, they reported a protective effect of highest versus lowest coffee consumption on EC risk. Among the studies that provided sufficient information, these authors performed a dose-response analysis and reported that one-cup increment per day was associated with 3% risk reduction in cohort studies and 12% in case-control studies. After a meta-analysis of the results from cohort studies, the association remained significant only among participants with obesity (BMI over 30kg/m^2) but not among overweight (BMI 25 to 30 kg/m^2) or participants with BMI<25 kg/m^2. Most recently, another cohort study of 3,185 Canadian females also showed that total coffee and caffeinated coffee consumption and caffeine intake were inversely associated with EC risk, while no associations were observed in relation to breast or ovarian cancer(28).

The meta-analyses published to date are not completely independent since there is some overlap in relation to the included studies. By combining individual participant data from 19 epidemiologic studies (some of them also included in the previously mentioned studies), our pooled analysis of nearly 40,000 participants is the largest available to date. Our results support the inverse association between coffee intake and EC risk found in previous meta-analyses, with a clear dose-response effect, which confirms a protective association between coffee consumption and EC risk. This inverse association is especially strong in females with

higher BMI, and within the lowest and intermediate categories of coffee consumption. No effect modification by other EC risk factors has been observed in previous meta-analyses. Even though several meta-analyses were available with consistent results regarding the association between coffee intake and EC risk, some questions remain regarding effect modification by other EC risk factors and coffee type. As the first pooled analysis, our study was able to overcome some of the limitations of meta-analyses including differences in study design, methods and analysis that could influence the combined results. More reliable results can be expected if individual data are available for a pooled analysis, since more consistent control for confounding is possible, although some heterogeneity still remains(29).

Several studies have reported that coffee constituents may have anti-carcinogenic properties; thus, coffee could reduce EC risk through several biological mechanisms such as oxidative damage, DNA methylation, induction of angiogenesis, loss of apoptosis, oncogene activation or tumor suppressor gene inactivation, among others(13). Active coffee compounds include not only caffeine, but also other bioactive agents with antioxidant properties such as polyphenols, lipids in the form of diterpenes, melanoidins and trigonelle(30,31). In particular, it has been reported that among all beverages, coffee has the highest concentration of polyphenols[26], which have been associated with decreased mortality and cancer risk, and may be the mediators of the potential effects of coffee on cancer prevention(32). Polyphenols in coffee might counteract carcinogenesis by improving insulin sensitivity and suppressing the production of free radicals, therefore minimizing oxidative stress, DNA damage, and other potentially carcinogenic processes (15,33–36).

Caffeine and other compounds in coffee have been shown to increase clearance of estradiol and inhibit estradiol-mediated carcinogenesis in endometrial cells(37). Additionally, coffee might have a role in reducing circulating estrogens, which is a well-established risk factor for EC, through different mechanisms: coffee and caffeine consumption/intake have been

positively associated to sex hormone-binding globulin in post-menopausal females, which is the major carrier of estrogens and testosterone, thus lowering the circulating levels of free hormones; enzymes converting androgens into estrogens have been shown to be inhibited after coffee consumption(38–40). Additional effects of coffee consumption on hormonal functions may be related to improved insulin sensitivity; thus, coffee could have a protective effect against diabetes, which is another known risk factor for EC(41,42). Even though an interaction with diabetes was biologically plausible, our analysis might be underpowered to detect such association.

The stronger association observed in participants within the higher BMI categories could be explained through the impaired metabolism of females with obesity and the higher levels of circulating estrogens in females with obesity, especially post-menopausal. Higher BMI and obesity have been associated with cancer risk through several mechanisms such as chronic inflammation, oxidative stress, obesity-induced hypoxia, cross-talk between tumor cells and surrounding adipocytes, among others. Additionally, metabolic risk factors such as obesity, impaired glucose tolerance or dyslipidemia have been associated with elevated systemic inflammation and oxidative stress. Thus, impaired metabolism may induce oxidative stress and inflammation which, in turn, may lead to carcinogenesis(43–45).

Our study had limitations that needed to be considered. Potential residual confounding is possible since we had missing data for some confounding factors, specifically those related to dietary factors, that were not available for the present study (e.g., energy intake, which was available for 15 out of the 19 studies). We performed a “complete-case” analysis, which included only those participants without missing observations on the variables of interest and found similar results. Even though this method is the most widely used technique in epidemiology to handle missing data, this approach may result in biased estimates of the associations between covariates and outcomes, in addition to reducing statistical power(46).

However, the percentage of missing data (18.4%), was mainly regarding for the case-control, not cohort studies; and complete-case analysis included a large number of participants. Additional analyses excluding such confounders (i.e., energy intake) have been performed with no change in results. Furthermore, sensitivity analyses using the missing-indicator method were also performed and results did not change. Furthermore, it is worth mentioning that missing data was an issue for the case-control analyses, but not for prospective cohort studies (e.g., individuals excluded because of missing information on energy intake were from case-control studies). Higher missing rates in case-control studies might partially explain the weaker associations found in those studies. In relation to the results on type of coffee, it is worth mentioning that the proportion of participants who drank only decaffeinated coffee was lower compared with those who drank only caffeinated coffee. Additionally, not all the studies provided information on coffee type so the sample size for that analysis was smaller and the results on decaffeinated coffee might be underpowered compared to caffeinated coffee (number of EC cases are 1480 and 4137, respectively). Finally, it is worth mentioning that, as in all observational studies, residual confounding cannot be ruled out. Several potential confounders could not be included in the present analysis since were not available for most of the included studies (e.g., income, overall dietary patterns). However, the most relevant predictors of EC risk and coffee consumption have been considered, including menopausal status, BMI, smoking habits and energy intake, among others.

Potential measurement error in coffee intake might also be possible(47). We are aware that coffee consumption (mostly reported as cups/day) is a heterogeneous measure due to numerous preparation methods and cup sizes, which might lead to misclassification. Heterogeneity in exposure assessment in how each study asked about certain exposures is a general limitation of pooled analyses. However, we expect this type of error to bias our

results towards the null (especially when including prospective studies). Furthermore, the risks reported in our pooled study are consistent with findings from other studies. Additionally, since differential misclassification is most likely related to case-control designs, we performed sensitivity analysis only including prospective cohort studies, and the observed inverse associations are even stronger.

To the best of our knowledge, this study is the largest and most comprehensive analysis to date, combining nearly 40,000 participants from 19 epidemiologic studies (6 cohort, 13 case-control studies). Because of the potential that participants with endometrial cancer in case-control studies changed their diet in response to early unrecognized symptoms, or potential recall bias in these studies, analyses including only prospective cohort studies were performed as well (total number of participants: 20,290: 15,693 controls; 4,597 cases), and the inverse association between coffee intake and EC risk was even stronger.

In conclusion, we found that increased coffee consumption is associated with a lower risk of EC. The inverse association between coffee consumption and EC risk was especially strong among females who were overweight or obese. No effect modification by other EC risk factors was observed. Our results further support the potential beneficial health effects of coffee consumption in relation to EC. Further research to assess the potential causality of such association as well as a better understanding of the underlying biological mechanisms is warranted.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I. Global Cancer Statistics 2018 : GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. 2018;394–424.
2. American Cancer Society. Cancer Facts & Figures 2019. 2019.
3. Key TJA, Pike MC. The dose-effect relationship between ' unopposed ' oestrogens and endometrial mitotic rate : Its central role in explaining and predicting endometrial cancer risk. British Journal of Cancer 1988;57:205–12.

4. Crous-Bou M, Lagiou P, De Vivo I. Endometrial Cancer. In: Textbook of cancer epidemiology. Third. Adami H-O, Hunter DJ, Lagiou P, Mucci L, editors. Oxford University Press; 2018.

5. World Cancer Research Fund AI for CR. Diet, nutrition, physical activity and endometrial cancer. Continuous Update Project Expert Report. 2018.

6. Özen AE, Bibiloni MDM, Pons A, Tur JA. Fluid intake from beverages across age groups: a systematic review. J Hum Nutr Diet England; 2015;28:417–42.

7. FAOSTAT [Internet]. [cited 2022 Aug 6]. Available from: https://www.fao.org/faostat/en/#home

8. Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Mattock H, Straif K. Carcinogenicity of drinking coffee, mate, and very hot beverages. The Lancet Oncology. 2016.

9. Pelucchi C, Bosetti C, Galeone C, La Vecchia C. Dietary acrylamide and cancer risk: An updated meta-analysis. International Journal of Cancer Wiley-Liss Inc.; 2015;136:2912–22.

10. Lukanova A, Zeleniuch-Jacquotte A, Lundin E, Micheli A, Arslan AA, Rinaldi S, Muti P, Lenner P, Koenig KL, Biessy C, et al. Prediagnostic levels of C-peptide, IGF-I, IGFBP -1, -2 and -3 and risk of endometrial cancer. International Journal of Cancer 2004;108:262–8.

11. Cust AE, Allen NE, Rinaldi S, Dossus L, Friedenreich C, Olsen A, Tjønneland A, Overvad K, Clavel-Chapelon F, Boutron-Ruault M-C, et al. Serum levels of C-peptide, IGFBP-1 and IGFBP-2 and endometrial cancer risk; results from the European prospective investigation into cancer and nutrition. International journal of cancer 2007;120:2656–64.

12. Wu T, Willett WC, Hankinson SE, Giovannucci E. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes care 2005;28:1390–6.

13. Bøhn SK, Blomhoff R, Paur I. Coffee and cancer risk, epidemiological evidence, and molecular mechanisms. Molecular Nutrition and Food Research. 2014.

14. Poole R, Kennedy OJ, Roderick P, Fallowfield JA, Hayes PC, Parkes J. Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. BMJ 2017;359:j5024.

15. Je Y, Giovannucci E. Coffee consumption and risk of endometrial cancer: Findings from a large up-to-date meta-analysis. International Journal of Cancer 2012;131:1700–10.

16. Lukic M, Guha N, Licaj I, van den Brandt PA, Stayner LT, Tavani A, Weiderpass E. Coffee Drinking and the Risk of Endometrial Cancer: An Updated Meta-Analysis of Observational Studies. Nutrition and Cancer Taylor & Francis; 2018;70:513–28.

17. Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L, Berretta M, Facchini G. Coffee Decreases the Risk of Endometrial Cancer: A Dose–Response Meta-Analysis of Prospective Cohort Studies. Nutrients 2017;9:1223.

18. Wang A, Wang S, Zhu C, Huang H, Wu L, Wan X, Yang X, Zhang H, Miao R, He L, et al. Coffee and cancer risk: A meta-analysis of prospective observational studies. Scientific Reports Nature Publishing Group; 2016;6:33711.

19. Merritt MA, Tzoulaki I, Tworoger SS, De Vivo I, Hankinson SE, Fernandes J, Tsilidis KK, Weiderpass E, Tjønneland A, Petersen KEN, et al. Investigation of dietary factors and endometrial cancer risk using a nutrient-wide association study approach in the EPIC and Nurses' Health Study (NHS) and NHSII. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2015;24:466–71.

20. Je Y, Hankinson SE, Tworoger SS, De Vivo I, Giovannucci E. A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2011;20:2487–95.

21. Park S-Y, Freedman ND, Haiman CA, Le Marchand L, Wilkens LR, Setiawan VW. Prospective Study of Coffee Consumption and Cancer Incidence in Non-White Populations. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2018;27:928–35.

22. Gunter MJ, Schaub JA, Xue X, Freedman ND, Gaudet MM, Rohan TE, Hollenbeck AR, Sinha R. A prospective investigation of coffee drinking and endometrial cancer incidence. International journal of cancer 2012;131:E530-6.

23. Bandera E V, Williams-King MG, Sima C, Bayuga-Miller S, Pulick K, Wilcox H, Zauber AG, Olson SH. Coffee and tea consumption and endometrial cancer risk in a population-based study in New Jersey. Cancer causes & control : CCC NIH Public Access; 2010;21:1467–73.

24. McCann SE, Yeh M, Rodabaugh K, Moysich KB. Higher regular coffee and tea consumption is associated with reduced endometrial cancer risk. International Journal of Cancer 2009;124:1650–3.

25. Olson SH, Chen C, De Vivo I, Doherty JA, Hartmuller V, Horn-Ross PL, Lacey J V., Lynch SM, Sansbury L, Setiawan VW, et al. Maximizing resources to study an uncommon cancer: E2C2-Epidemiology of Endometrial Cancer Consortium. Cancer Causes and Control 2009;

26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

27. Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V. Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. The American journal of clinical nutrition 2015;101:570–8.

28. Arthur R, Kirsh VA, Rohan TE. Associations of coffee, tea and caffeine intake with risk of breast, endometrial and ovarian cancer among Canadian women. Cancer Epidemiology Elsevier; 2018;56:75–82.

29. Blettner M. Traditional reviews, meta-analyses and pooled analyses in epidemiology. International Journal of Epidemiology Oxford Academic; 1999;28:1–9.

30. Niseteo T, Komes D, Belščak-Cvitanović A, Horžić D, Budeč M. Bioactive composition and antioxidant potential of different commonly consumed coffee brews affected by their preparation technique and milk addition. Food Chemistry 2012;

31. Liang N, Kitts DD. Antioxidant property of coffee components: assessment of methods that define mechanisms of action. Molecules (Basel, Switzerland) 2014;19:19180–208.

32. Grosso G, Micek A, Godos J, Pajak A, Sciacca S, Galvano F, Giovannucci EL. Dietary Flavonoid and Lignan Intake and Mortality in Prospective Cohort Studies: Systematic Review and Dose-Response Meta-Analysis. American journal of epidemiology 2017;185:1304–16.

33. Godos J, Pluchinotta FR, Marventano S, Buscemi S, Volti GL, Galvano F, Grosso G. Coffee components and cardiovascular risk: Beneficial and detrimental effects. International Journal of Food Sciences and Nutrition. 2014.

34. Caprioli G, Cortese M, Sagratini G, Vittori S. The influence of different types of preparation (espresso and brew) on coffee aroma and main bioactive constituents. International journal of food sciences and nutrition 2015;66:505–13.

35. Asaad NA, Zeng ZC, Guan J, Thacker J, Iliakis G. Homologous recombination as a potential target for caffeine radiosensitization in mammalian cells: reduced caffeine radiosensitization in XRCC2 and XRCC3 mutants. Oncogene 2000;19:5788–800.

36. Joerges C, Kuntze I, Herzinger T, Herzinge T. Induction of a caffeine-sensitive S-phase cell cycle checkpoint by psoralen plus ultraviolet A radiation. Oncogene 2003;22:6119–28.

37. Fotsis T, Zhang Y, Pepper MS, Adlercreutz H, Montesano R, Nawroth PP, Schweigerer L. The endogenous oestrogen metabolite 2-methoxyoestradiol inhibits angiogenesis and suppresses tumour growth. Nature 1994;368:237–9.

38. Kotsopoulos J, Eliassen AH, Missmer SA, Hankinson SE, Tworoger SS. Relationship between caffeine intake and plasma sex hormone concentrations in premenopausal and postmenopausal women. Cancer 2009;115:2765–74.

39. Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. Nutrition and cancer 1998;30:21–4.

40. Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. American journal of epidemiology 1996;144:642–4.

41. Akash MSH, Rehman K, Chen S. Effects of coffee on type 2 diabetes mellitus. Nutrition (Burbank, Los Angeles County, Calif) 2014;30:755–63.

42. Lees B, Leath CA. The Impact of Diabetes on Gynecologic Cancer: Current Status and Future Directions. Current obstetrics and gynecology reports 2015;4:234–9.

43. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet (London, England) 2008;371:569–78.

44. De Pergola G, Silvestris F. Obesity as a major risk factor for cancer. Journal of obesity 2013;2013:291546.

45. Grosso G, Stepaniak U, Micek A, Topor-Mądry R, Pikhart H, Szafraniec K, Pająk A. Association of daily coffee and tea consumption and metabolic syndrome: results from the Polish arm of the HAPIEE study. European Journal of Nutrition 2015;54:1129–37.

46. Pedersen AB, Mikkelsen EM, Cronin-Fenton D, Kristensen NR, Pham TM, Pedersen L, Petersen I. Missing data and multiple imputation in clinical epidemiological research. Clinical Epidemiology Dove Medical Press Ltd; 2017;9:157–66.

47. Hu FB, Satija A, Rimm EB, Spiegelman D, Sampson L, Rosner B, Camargo CA, Stampfer M, Willett WC. Diet Assessment Methods in the Nurses' Health Studies and Contribution to Evidence-Based Nutritional Policies and Guidelines. American journal of public health 2016;106:1567–72.

Table 1. Characteristics of endometrial cancer (EC) cases and controls from E2C2.

Characteristic	Controls (N=27,479)	EC Cases (N=12,159)
BMI (mean, SD)	26.1 (5.4)	29.1 (7.4)
Smoking (N, %)		
never	17,281 (63)	7,527 (65)
former	6,405 (23)	2,826 (24)
current	3,713 (14)	1,165 (11)
Pack-years (mean, SD)[1]	10.7 (16.4)	9.7 (17.1)
Race (N, %)		
Caucasian	21,757 (83)	9,467 (87)
African-American	1,694 (6)	500 (5)
Asian	1,429 (5)	519 (5)
Hawaiian	503 (2)	162 (2)
Mixed	53 (0)	38 (0)
Other	848 (3)	240 (2)
Alcohol, grams/week (mean, SD)[2]	100.8 (250.5)	81.5 (229.6)
Energy, kcal/day (mean, SD)	1663 (742)	1772 (719)
Parity, % nulliparity (N, %)	3,832 (14)	2,090 (17)
Menopausal hormone therapy use (N, %)		
no	15,027 (64)	5,844 (61)
yes	8,615 (36)	3,672 (39)
Oral contraceptive use (N, %)		
no	11,520 (62)	5,393 (64)
yes	6,974(38)	3,023 (36)
Diabetes (N, %)		
no	15,163 (86)	6,462 (80)
yes	2,500 (14)	1,585 (20)
Hypertension (N, %)		
no	13,698 (66)	4,558 (56)
yes	7,165 (34)	3,579 (44)
Coffee consumption (N, %)		
never	3,895 (15)	1,939 (18)
ever	22,087 (85)	9,170 (83)
Coffee cups/day (mean, SD)[3]	1.9 (1.8)	1.7 (1.7)

[1]Among ever smokers; [2]Among alcohol drinkers; [3]Among coffee drinkers.

Table 2. Characteristics of E2C2 participants by coffee consumption (controls-only).

Characteristic	**No coffee** N=3,985	**1 cup coffee/day** N=8,711	**2-3 cups coffee/day** N=8,703	**>4 cups coffee/day** N=3,779
Diagnostic age, cases only (mean, SD)	61.8 (10.3)	63.8 (9.3)	62.9 (9.5)	61.4 (9.6)
BMI (mean, SD)	27.0 (6.9)	27.2 (6.4)	26.7 (6.0)	26.3 (5.6)
Pack-years (mean, SD)[1]	8.7 (15.0)	8.2 (14.6)	11.3 (17.8)	14.8 (19.7)
Race (%)				
Caucasian	84	81	90	90
African-American	6	6	2	2
Asian	5	7	4	5
Hawaiian	3	2	1	1
Other	2	4	3	2
Alcohol, grams/week (mean, SD)[2]	119.6 (290.4)	126.0 (286.1)	73.7 (196.3)	59.7 (171.7)
Energy, kcal/day (mean, SD)	1668 (742)	1661 (725)	1685 (709)	1775 (748)
Parity, % nulliparity (%)	18.8	15.6	15.8	15.5
Menopausal hormone therapy use (%)				
No	65	60	63	65
Yes	35	40	37	35
Oral contraceptive use (%)				
no	65	64	65	64
yes	35	36	35	36
Diabetes (%)				
no	87	87	85	72
yes	13	13	15	28
Hypertension (%)				
no	62	62	67	64
yes	38	38	33	36

[1]Among ever smokers; [2]Among alcohol drinkers

Table 3. Association between coffee consumption and endometrial cancer risk

Coffee Exposure	Controls	Cases	OR[1]	95% CI	p-value	OR[2]	95% CI	p-value
	N=25,982	N=11,109						
Coffee consumption								
no	3,895	1,939	1.00	REF	0.016	1.00	REF	0.0028
yes	22,087	9,170	0.92	0.85,0.98		0.87	0.79,0.95	
	N=25,088	N=10,734						
Coffee cups/day								
no coffee	3,895	1,939	1.00	REF	$1.76x10^{-5}$	1.00	REF	$9.21x10^{-5}$
1 cup/day	8,711	3,821	0.96	0.88,1.03		0.90	0.82,1.00	
2-3 cups/day	8,703	3,678	0.93	0.85,1.00		0.86	0.78,0.95	
>4 cups/day	3,779	1,296	0.78	0.70,0.86		0.76	0.66,0.87	

[1]ORs adjusted for age and race

[2]ORs adjusted for age, race, BMI, pack-years of smoking, energy intake, study design and study site

Note: reported sample sizes correspond to model 1 (adjusting for age and race only). For the multi-adjusted model 2, the sample size for the complete-case analysis was: 21,389 controls and 8,873 cases.

Table 4. Association between type of coffee consumed and endometrial cancer risk

Type of coffee	**Controls** N=16,440	**Cases** N=6,915	**OR**	**95% CI**	**p-value**
Type of coffee					
no coffee	2,607	1,298	1.00	REF	
caffeinated only	9,794	4,137	0.83	0.75,0.92	$5.11x10^{-4}$
decaffeinated only	4,039	1,480	0.93	0.82,1.05	0.23

ORs adjusted by age, race, BMI, pack-years of smoking, energy intake, study design and study site

Note: Studies that did not ask about coffee type and individuals who reported drinking both caffeinated and decaffeinated coffee were excluded from the present analysis.

Table 5. Association between coffee consumption and endometrial cancer risk, stratified by study design

COHORT STUDIES (6)	**Controls**	**Cases**	**OR**	**95% CI**	**p-value**
Coffee consumption	N=15,693	N=4597			
no	2,271	908	1.00	REF	4.01×10^{-3}
yes	13,422	3,689	0.87	0.78,0.96	
Coffee cups/day	N=14,845	N=4,405			
no coffee	2,271	908	1.00	REF	3.26×10^{-4}
1 cup/day	5,452	1,581	0.90	0.81,1.00	
2-3 cups/day	5,044	1,374	0.87	0.77,0.97	
>4 cups/day	2,078	542	0.74	0.63,0.87	

CASE-CONTROL STUDIES (13)	**Controls**	**Cases**	**OR**	**95% CI**	**p-value**
Coffee consumption	N=10,289	N=6,512			
no	1,624	1,031	1.00	REF	0.31
yes	8,665	5,481	0.89	0.71,1.11	
Coffee cups/day	N=10,224	N=6489			
no coffee	1,625	1,031	1.00	REF	0.10
1 cup/day	3,259	2,240	0.94	0.74,1.20	
2-3 cups/day	3,659	2,304	0.85	0.63,1.09	
>4 cups/day	1,701	914	0.82	0.60,1.12	

ORs adjusted by age, race, BMI, pack-years of smoking, energy intake and study site.

Table 6. Association between coffee consumption and endometrial cancer risk, stratified by BMI

BMI <=25	**Controls**	**Cases**	**OR**	**95% CI**	**p-value**
Coffee consumption	N=12,681	N=3,746			
no	1,878	590	1.00	REF	0.30
yes	10,803	3,156	0.92	0.79,1.07	
Coffee cups/day	N=12,362	N=3,695			
no coffee	1,878	590	1.00	REF	0.031
1 cup/day	4,105	1,266	0.95	0.81,1.22	
2-3 cups/day	4,396	1,309	0.94	0.79,1.12	
>4 cups/day	1,983	530	0.72	0.57,0.92	

BMI >25	**Controls**	**Cases**	**OR**	**95% CI**	**p-value**
Coffee consumption	N=12,782	N=7,158			
no	1,932	1,301	1.00	REF	3.91×10^{-5}
yes	10,850	5,857	0.79	0.71,0.89	
Coffee cups/day	N=12,216	N=6,996			
no coffee	1,932	1,301	1.00	REF	8.83×10^{-7}
1 cup/day	4,419	2,473	0.84	0.75,0.95	
2-3 cups/day	4,140	2,314	0.76	0.67,0.86	
>4 cups/day	1,725	908	0.69	0.58,0.82	

ORs adjusted by age, race, pack-years of smoking, energy intake, study design and study site.
p for interaction < 0.001