



Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

Original article

C-reactive protein partially mediates the inverse association between coffee consumption and risk of type 2 diabetes: The UK Biobank and the Rotterdam study cohorts[☆]

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ARTICLE INFO

Article history:

Received 9 September 2022

Accepted 27 February 2023

Keywords:

Diabetes mellitus

Type 2

C-Reactive protein

Coffee

Inflammation

Mediation analysis

Cohort studies

SUMMARY

Background: Coffee is among the most consumed beverages worldwide. Coffee consumption has been associated with lower risk of type 2 diabetes mellitus (T2D), but underlying mechanisms are not well understood. We aimed to study the role of classic and novel-T2D biomarkers with anti- or pro-inflammatory activity in the association between habitual coffee intake and T2D risk. Furthermore, we studied differences by coffee types and smoking status in this association.

Methods: Using two large population-based cohorts, the UK-Biobank (UKB; n = 145,368) and the Rotterdam Study (RS; n = 7111), we investigated associations of habitual coffee consumption with incident T2D and repeated measures of insulin resistance (HOMA-IR), using Cox proportional hazards and mixed effect models, respectively. Additionally, we studied associations between coffee and subclinical inflammation biomarkers including C-reactive protein (CRP) and IL-13, and adipokines, such as adiponectin and leptin, using linear regression models. Next, we performed formal causal mediation analyses to investigate the role of coffee-associated biomarkers in the association of coffee with T2D. Finally, we evaluated effect modification by coffee type and smoking. All models were adjusted for sociodemographic, lifestyle and health-related factors.

Results: During a median follow-up of 13.9 (RS) and 7.4 (UKB) years, 843 and 2290 incident T2D cases occurred, respectively. A 1 cup/day increase in coffee consumption was associated with 4% lower T2D risk (RS, HR = 0.96 [95%CI 0.92; 0.99], p = 0.045; UKB, HR = 0.96 [0.94; 0.98], p < 0.001), with lower HOMA-IR (RS, log-transformed β = -0.017 [-0.024; -0.010], p < 0.001), and with lower CRP (RS, log-transformed β = -0.014 [-0.022; -0.005], p = 0.002; UKB, β = -0.011 [-0.012; -0.009], p < 0.001). We also observed associations of higher coffee consumption with higher serum adiponectin and IL-13 concentrations, and with lower leptin concentrations. Coffee-related CRP levels partially mediated the inverse association of coffee intake with T2D incidence (average mediation effect RS β = 0.105 (0.014; 0.240), p = 0.016; UKB β = 6.484 (4.265; 9.339), p < 0.001), with a proportion mediated by CRP from 3.7%

[☆] Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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[−0.012%; 24.4%] (RS) to 9.8% [5.7%; 25.8%] (UKB). No mediation effect was observed for the other biomarkers. Coffee-T2D and coffee-CRP associations were generally stronger among consumers of ground (filtered or espresso) coffee and among never and former smokers.

Conclusions: Lower subclinical inflammation may partially mediate the beneficial association between coffee consumption and lower T2D risk. Consumers of ground coffee and non-smokers may benefit the most.

Keywords (MeSH terms): coffee consumptions; diabetes mellitus, type 2; inflammation; adipokines; biomarkers; mediation analysis; follow-up studies

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Abbreviations	
CRP	C-Reactive protein
UKB	UK Biobank
RS	Rotterdam study
T2D	Type 2 diabetes
C-3	Complement 3
CFH	Complement component factor H
IL-18	Interleukin 18
IL-17	Interleukin 17
IL-13	Interleukin 13
IL-1RA	Interleukin-1 receptor antagonist
EN-RAGE	Extracellular newly identified receptor for advanced glycation end-products binding protein
TNFR-II	Tumor necrosis factor receptor 2
FFQ	Food frequency questionnaire
GGT	Gamma-glutamyltransferase
HOMA-IR	Homeostatic model assessment-insulin resistance
AME	Average mediation effect

1. Introduction

Coffee is one of the most frequently consumed beverages worldwide [1,2]. It contains several bioactive compounds such as chlorogenic acids, caffeine and polyphenols, although the exact composition depends on the type and preparation process [3]. The beneficial association between higher coffee consumption and lower risk of type 2 diabetes mellitus (T2D) is well-established [4–6]. However, potential mechanisms underlying these associations are not well understood [7].

Diabetes is related to inflammation and a large number of studies have reported altered concentrations of classic subclinical inflammation markers, such as C-reactive protein (CRP); adipokines, such as leptin and adiponectin [8,9]; and novel biomarkers of inflammation such as complement proteins (C3, CFH), interleukins (IL-13 and IL-17), and receptors like EN-RAGE, TNFR-II and IL-1RA [9–11], in insulin resistant and diabetic patients.

Higher coffee intake has been suggested to lead to lower concentrations of pro-inflammatory markers, which may thereby impact the risk of T2D and other cardiometabolic diseases [12]. Efforts to investigate a potential mediating role of inflammatory status and adipokines in the effect of coffee intake on T2D risk are scarce. They show limitations [13] and contradictive results [14], possibly due to differences in follow-up time, amount and type of coffee consumed, different markers of inflammation studied, and the study population's baseline health or lifestyle characteristics. For example, consideration of smoking status may impact observed findings as it has been proposed as a confounder [15–18] or as an effect modifier in coffee and health associations, due to its effects

on body fat distribution and consequent hyperinsulinemia and hypertension [19,20], and by modulating oxidative stress and inflammatory responses [21].

To help understand biological pathways connecting coffee to inflammatory processes and T2D development, we aimed, firstly, to determine longitudinal associations of long-term habitual coffee consumption with insulin resistance and T2D. Secondly, to investigate to what extent classic and novel T2D-related markers of inflammation and adipokines mediate these associations through formal mediation analysis [17]. Thirdly, to study potential effect modification by coffee type and smoking status.

For this, we used data from two large population-based prospective studies with a wide distribution of coffee intake: the UK Biobank (UKB) [22] and the Rotterdam Study (RS) [23]. These data benefit from large sample sizes and long follow-up time, supplemented with comprehensive data on classic and novel biomarkers in the RS cohort and coffee types in UKB.

2. Research design and methods

2.1. Study design

This study involved prospective and cross-sectional analyses, embedded in two large population-based cohorts: UKB in the United Kingdom and RS in the Netherlands. UKB [24–26] is a prospective cohort that recruited 502,536 individuals aged 37–73 years, across England, Scotland and Wales, between April 2006 and December 2010 [24–26]. At the time of conducting the analysis, follow-up data were available up to September 27th, 2017.

RS [23] is an ongoing prospective cohort in Rotterdam, the Netherlands. It started with the first sub-cohort (RS-I) of 7983 participants aged >55 years, in 1990. The second sub-cohort (RS-II) recruited 3011 new participants aged >55 years in 2000 and the third sub-cohort (RS-III) added 3932 individuals aged >45 years, in 2006, resulting in a total number of 14,929 participants at baseline. We used data from RS-I, RS-II and RS-III for the current analyses. At the time of conducting the analyses, follow-up data were available up to January 1st, 2015.

2.2. Coffee consumption

In UKB, data on habitual coffee consumption and food groups were collected at the baseline visit to the recruitment centre, through a self-administrated touch-screen food-frequency questionnaire (FFQ) of 29 questions about diet and 18 about alcohol [27]. Questions on coffee included the average number of cups of coffee usually consumed per day, and the most frequent coffee type consumed (decaffeinated, instant, or ground (filtered or espresso)). In RS, data were collected on average number of cups of coffee consumed during the past month. Among participants of sub-cohorts RS-I and RS-II, data were obtained during home interviews by trained interviewers. They also completed a 170-item

FFQ to self-report intake of food groups during the past month. Participants of sub-cohort RS-III reported their coffee and food groups consumption during the last month through an updated 389-item FFQ [28].

2.3. T2D and insulin resistance

In UKB, follow-up data on T2D diagnosis were derived from linkage to primary care data, covering 45% of the initial cohort ($n = 228,495$) up to 2017. Incident T2D was defined as diagnosis of ICD-10 code E11. Linkage procedures of UKB are available at http://biobank.ndph.ox.ac.uk/showcase/showcase/docs/primary_care_data.pdf.

In RS, follow-up data on T2D diagnosis were ascertained through access to general practitioners' records and hospital discharge letters. Data on glucose-lowering medication use was obtained from pharmacy dispensing records and home interviews. Blood glucose and insulin measurements were obtained from baseline and follow-up visits at the research centre. T2D was defined according to the WHO guidelines: fasting blood glucose ≥ 7.0 mmol/L, non-fasting blood glucose ≥ 11.1 mmol/L and/or use of blood glucose-lowering medication (RS). Two study physicians independently adjudicated all potential incident cases of T2D. In case of disagreement, a consensus was reached by consulting an endocrinologist. Glucose was measured in blood samples at baseline and follow-up visits every 3–5 years using the glucose hexokinase method within one week of sampling [29]. Insulin levels were determined through electrochemiluminescence immunoassay technology, using a Modular Analytics E170 analyser (Roche Diagnostics GmbH, Germany). Homeostatic model assessment–insulin resistance (HOMA-IR) was calculated as: fasting glucose (nmol/L)*fasting insulin (uU/L)/22.5.

2.4. Inflammatory markers and adipokines

Fasting blood samples were collected at the research centres at the time of recruitment for both studies and immediately put on ice and stored at -80°C . Plasma high-sensitive C-reactive protein (CRP, ug/mL) concentrations were assessed using an immunoturbidimetric assay (Beckman Coulter AU5800) in UKB, and rate near-infrared particle immunoassay for high-sensitivity CRP (IMMAGE Immunochemistry System, Beckman Coulter) in RS. Citrate plasma samples (200UI) from a random subset of $n = 856$ participants (RS) were sent to Rules-Based Medicine, Austin, Texas (www.myriadrbm.com) to measure specific inflammation biomarkers and adipokines using a multiplex immunoassay. The luminex-100 instrument was used and the resulting data were interpreted using proprietary software (<https://myriadrbm.com/scientific-media/quality-control-systems-white-paper/>). Details are described elsewhere [30]. The following inflammation biomarkers, recently linked to T2D and/or insulin resistance [9–11], were included in the current study: extracellular newly identified receptors for advanced glycation end-products binding protein (EN-RAGE, ng/mL), interleukin-13 (IL-13, pg/mL), IL-17 (pg/mL), IL-18 (pg/mL), IL-1 receptor antagonist (IL1ra, pg/mL), complement factor-H (CFH, ug/mL), complement-3 (C3, mg/mL), tumor necrosis factor receptor-2 (TNFR2, ng/mL), adiponectin (ug/mL) and leptin (ng/mL).

2.5. Covariate assessment

We collected data on demographic factors (age, sex, ethnicity (UKB only)) and measures of socioeconomic status (self-reported education attainment (RS) or Townsend deprivation index [31] (UKB)); lifestyle factors (smoking, diet, physical activity, and

alcohol and tea intake); and cardiovascular risk factors (hypertension, blood lipids, and body mass index (BMI)) at baseline. Further details on measurements can be found elsewhere [22,32]. Ethnicity was self-reported and classified into five categories (white, mixed, south Asian, black, Chinese).

Lifestyle factors were self-reported through questionnaires. Smoking was categorised into never, former or current smoking. Physical activity was assessed using the validated International Physical Activity Questionnaire (UKB) [33], and Zutphen [34] (RS-I and RS-II) and LASA [35] (RS-III) questionnaires, and expressed in Metabolic Equivalent (MET) -hours/week.

In both cohorts, habitual alcohol and food consumption were collected through the FFQs mentioned above. In UKB, alcohol consumption was expressed as weekly frequency. Food data were used to build a cumulative dietary score [36] based on the UK Eatwell Guide recommendations [37], the Food-Based Dietary Guidelines from the European Food Safety Authority [38], or the median intake. In RS data on alcohol consumption were expressed in glasses/day and were log-transformed to approach normality. A score reflecting adherence to Dutch dietary guidelines was calculated [28]. In each cohort, tea consumption (cups/day), was assessed in the same manner as coffee intake.

Physical measures and blood sample collection were performed at the research centres. BMI was calculated (kg/m^2). Fasting total serum cholesterol (total-C) and high-density lipoprotein cholesterol (HDL-C) were measured using the cholesterol oxidase-peroxidase (CHO-POD) enzymatic reaction and enzyme immune-inhibition methods (AU5800 chemistry analyser, Beckman Coulter), respectively. Blood pressure was the mean of two consecutive measurements. Data on medication use was obtained from pharmacy dispensing records and home interviews. Presence of hypertension (yes/no) was defined as blood pressure $>140/90$ mmHg or the use of anti-hypertensive medication. Disease information was collected by linkage to primary care and general practitioner records [22,32].

2.6. Population for analyses

Participants with missing data on coffee intake, T2D incidence or CRP concentrations were excluded, as well as prevalent cases of T2D and CVD at baseline [18]. In addition, participants declaring a recent change in dietary patterns (UKB) and those reporting implausible daily energy intake of <500 kcal or >5000 kcal per day (UKB and RS) were excluded. The final analytical samples were $n = 145,368$ (UKB) and $n = 7111$ (RS). For analyses on specific inflammation markers we used a subset of $n = 722$ (RS) participants and for analyses of coffee types, $n = 111,159$ (UKB) participants. Supplementary Fig. S-1 displays the study sample.

2.7. Ethical considerations

UK Biobank has approval from the Northwest Multi-centre Research Ethics Committee, which covers the UK; the National Information Governance Board for Health & Social Care; the Community Health Index Advisory Group; and the National Research Ethics Service and UK Biobank's governing Research Ethics Committee.

The Rotterdam Study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and

the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictip/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and obtain their information from treating physicians.

2.8. Statistical analyses

Longitudinal and cross-sectional analyses were performed separately in both cohorts. Coffee intake was analysed continuously (i.e. per 1 cup/day) and in categories: non-consumers (0 cups/day, reference group), >0–2, 3–4, and ≥ 5 cups/day. Two models were constructed. Model 1 was adjusted for age, sex, sub-cohort (RS), education attainment (RS) or deprivation index (UKB), smoking, physical activity, diet quality score, alcohol consumption, and tea intake. Model 2 was additionally adjusted for baseline BMI, hypertension, and serum total/HDL cholesterol ratio. Covariates were included based on prior studies and recent causal evidence showing that residual confounding by smoking and baseline cardiovascular health may confound associations between coffee consumption and health outcomes in observational studies [18], due to the correlation between coffee intake and smoking, and because those with baseline cardiovascular risk factors tend to moderate their coffee consumption [17,18,39].

Using Cox proportional hazards regression, we investigated associations between coffee intake and incident T2D. Results are reported as hazard ratios (HR) with corresponding 95% confidence intervals (CIs). The timescale was follow-up time in years from baseline examination until incident T2D, death, withdrawal from the study, or censoring date, whichever came first. Linear mixed-effect models were used to study associations between coffee intake and repeated measures of HOMA-IR in RS participants with at least two available HOMA-IR measurements. We modelled random intercepts (participants) and random slopes (time). Results are presented as coefficients β , 95% CIs. Linear regressions were performed to examine cross-sectional associations between coffee and inflammation biomarkers and adipokines, which were transformed to the natural logarithmic scale to approximate normal distribution. Results are reported as coefficients β , 95% CIs. Non-linear associations were explored using penalised smoothing splines. All the analyses above were repeated among habitual consumers of decaffeinated, filtered/ground, and instant coffee, separately and effect modification by smoking status was tested by performing subgroup analyses among current smokers, former smokers and never smokers.

Analyses were performed using R v.4.0.1 (R Foundation for Statistical Computing, Austria).

2.9. Mediation by inflammation biomarkers

To investigate the role of biomarkers linking coffee consumption and T2D, we performed a formal mediation analysis [40] using the *mediation* R package [41] with incident T2D as main outcome. For this, a regression for a parametric survival model with Weibull distribution [42] was fitted using the *survival* R package [43]. The mediation analysis aims to dissect the total effect of the exposure (coffee intake) on the outcome (risk of T2D) into direct and indirect effects [40]. The indirect effect represents the portion of the effect that is mediated by the studied inflammatory biomarkers. The direct effect represents the portion of the effect that goes directly or is mediated by variables other than the studied inflammatory markers. The proportion of the effect mediated is quantified, assuming observed confounding. A graphic representation of the mediation analysis is shown in [Supplementary Fig. S-2](#). Briefly, we modelled habitual coffee consumption (cups/day) during the

month previous to the blood collection (t_0) as the main exposure. Inflammation biomarkers assessed at recruitment at time t_0 were modelled as mediators, and the outcome corresponds to incident T2D during follow-up (t_1). As described in the previous step (represented as arrow *a*, [Fig. S-2](#)), associations between coffee consumption and each biomarker were firstly estimated. Further, associations of each significant biomarker with T2D were tested, adjusting for coffee intake (*b*); and of coffee intake with T2D, adjusting for each biomarker (*c*). Finally, we determined the proportion of the total effect (*c*) of coffee on T2D that is mediated by coffee-related changes in the biomarkers' concentrations. And the Average Mediation Effect (AME) was computed. AME estimate is obtained under the simulated scenario that the exposure (coffee consumption) is held constant, and resolves the potential difference in the outcome (incident T2D) when the mediator (inflammation biomarker) is set to values under the exposure level. We would like to note that the word 'effect' as notation in mediation analyses [40,41] must not be interpreted as a causal effect, given the observational nature of the study. Mediation analysis works under the sequential ignorability assumption, which assumes no unmeasured confounding. Quasi-Bayesian confidence intervals were constructed for the estimated effects with 10,000 simulations. Results are expressed as proportion mediated in percentage and as AME estimates with their respective 95% CIs.

To account for potential reverse causation, the associations coffee-T2D were repeated excluding cases of incident T2D that occurred during the first 2 years of follow-up in UKB and RS.

Ten-fold multiple imputations were used to address missing data on covariates. We report pooled results of the imputed datasets of each cohort separately. A two-sided *p*-value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

RS participants (*n* = 7111) had a mean age of 65.1 (SD = 9.4) years and 59.8% (*n* = 4249) were women. In UKB (*n* = 145,368), the mean age was 55.2 (SD = 8.10) years and 58.0% (*n* = 84,342) were women. During a median follow-up of 13.9 (RS, IQR = 7.6; 8; 15.7) and 7.44 (UKB, IQR = 6.81; 8.34) years, 843 and 2290 incident T2D cases occurred, respectively. [Table 1](#) and [Supplementary Tables S-1 and S-2](#) show details of the participants' characteristics.

3.2. Coffee consumption, insulin resistance and incident T2D

After adjustment for sociodemographic, dietary and health status covariates (model 2), higher habitual coffee intake was associated with lower T2D risk in both RS (HR = 0.96 per cup/day increase [95%CI = 0.92; 0.99], *p* = 0.045) and UKB (HR = 0.96 [0.94; 0.98], *p* < 0.001). Among RS participants, we further observed an association between higher coffee consumption and a longitudinal decrease in HOMA-IR levels (β = −0.017 log-HOMA-IR per cup/day increase [−0.024; −0.010], *p* < 0.001). An inverse linear trend was observed across coffee consumption categories ([Table 2](#)).

3.3. Coffee consumption and markers of inflammation

Higher habitual coffee intake was cross-sectionally associated with lower circulating levels of CRP in both RS (β = −0.014 log-ug/mL CRP per 1 cup/day (95%CI = −0.022; −0.005), *p* = 0.002) and UKB (β = −0.011 [−0.012; −0.009], *p* < 0.001) ([Table 3](#)). Among participants with data on specific inflammatory markers, we observed that higher coffee intake was also associated with higher adiponectin concentrations (β = 0.023 log-ug/mL per 1 cup/day

Table 1

Summary of baseline characteristics of the Rotterdam Study and UK Biobank participants, stratified by coffee consumption categories.

	Non-coffee drinkers	0.5–2 cups/day	3–4 cups/day	5 or more cups/day	Total
The Rotterdam Study					
n, (%)	542 (7.6)	1594 (22.2)	2883 (40.2)	2053 (28.6)	7111
Age, mean (SD), years	62.1 (9.8)	68.4 (10.1)	65.8 (9.2)	62.3 (7.8)	65.1 (9.4)
Sex, (%) women	373 (68.8)	1064 (66.8)	1844 (61.8)	1002 (48.8)	4245 (59.7)
Smoking status					
Never smoker	252 (46.5)	652 (40.9)	994 (33.3)	453 (22.1)	2351 (32.8)
Former smoker	209 (38.6)	730 (45.8)	1939 (66.8)	839 (40.9)	3174 (44.3)
Current smoker	81 (14.9)	212 (13.3)	593 (19.9)	761 (37.0)	1647 (22.9)
Physical activity, median (IQR), MET-hours/week	61.9 (68.4)	71.3 (60.9)	60.8 (60.8)	70.5 (67.6)	72.0 (63.4)
BMI, mean (SD), kg/m ²	26.8 (4.7)	26.7 (4.0)	26.9 (3.8)	27.1 (4.0)	26.9 (4.0)
CRP, median (IQR), ug/mL	1.40 (2.80)	1.27 (2.9)	1.50 (2.70)	1.36 (2.47)	1.5 (2.7)
Incident T2D cases, n (%)	52 (9.6)	171 (10.7)	276 (9.6)	187 (9.1)	843 (9.6)
The UK Biobank					
n, (%)	31,773 (21.9)	66,152 (45.5)	30,439 (20.9)	17,004 (11.7)	145,368
Age, mean (SD), years	53.9 (8.09)	55.8 (8.10)	55.5 (8.03)	54.5 (7.94)	55.2 (8.10)
Sex, (%) women	19,818 (62.4)	39,087 (59.1)	16,715 (54.9)	8722 (51.3)	84,342 (58.0)
Smoking status, n (%)					
Never smoker	19,661 (61.9)	39,537 (59.8)	16,636 (54.6)	7562 (44.4)	83,396 (57.4)
Former smoker	9071 (28.6)	21,334 (32.3)	10,318 (33.9)	5708 (33.6)	46,431 (32.0)
Current smoker	3041 (9.6)	5281 (8.0)	3485 (11.5)	3734 (22.0)	15,541 (10.7)
Physical activity, median (IQR), MET-hours/week	48.1 (46.8)	45.8 (43.7)	45.0 (43.3)	47.3 (45.9)	46.3 (44.4)
BMI, mean (SD), kg/m ²	26.2 (4.4)	25.9 (4.0)	26.6 (4.2)	27.1 (4.3)	26.3 (4.20)
CRP, median (IQR), ug/mL	1.15 (1.84)	1.03 (1.57)	1.08 (1.65)	1.76 (1.19)	1.08 (1.67)
Incident T2D cases, n (%)	205 (1.6)	298 (1.2)	147 (1.1)	95 (1.4)	2290 (1.3)

Table 2

Associations of coffee consumption with longitudinal measures of HOMA-IR and incident T2D in the Rotterdam Study and with incident T2D in the UK Biobank.

Total Coffee cups/day	The Rotterdam Study				The UK Biobank	
	HOMA-IR ^a (n = 4138)		Incident T2D (n = 7111)		Incident T2D (n = 145,368)	
	β (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
MODEL 1						
Per cup increase	−0.011 (−0.020; −0.002)	0.013	0.97 (0.93; 1.00)	0.099	0.98 (0.95; 0.99)	0.043
0	ref		ref		ref	
0.5–2	0.044 (−0.021; 0.109)	0.187	0.84 (0.61; 1.15)	0.268	0.90 (0.81; 0.99)	0.004
3–4	−0.005 (−0.065; 0.054)	0.856	0.73 (0.54; 0.99)	0.046	0.84 (0.74; 0.96)	0.012
≥5	−0.028 (−0.089; 0.033)	0.376	0.72 (0.53; 0.99)	0.048	0.86 (0.73; 0.99)	0.046
p-trend		0.028		0.033		0.015
MODEL 2						
Per cup increase	−0.017 (−0.024; −0.010)	<0.001	0.96 (0.92; 0.99)	0.045	0.96 (0.94; 0.98)	<0.001
0	ref		ref		ref	
0.5–2	0.020 (−0.033; 0.073)	0.465	0.80 (0.59; 1.10)	0.147	0.92 (0.83; 1.02)	0.127
3–4	−0.022 (−0.071; 0.026)	0.366	0.70 (0.52; 0.96)	0.004	0.82 (0.72; 0.94)	0.004
≥5	−0.064 (−0.114; −0.014)	0.012	0.69 (0.50; 0.95)	0.004	0.79 (0.68; 0.92)	0.002
P-trend		<0.001		0.022		<0.001

Estimates are regression coefficients (β) from linear mixed models and hazard ratios (HR) from proportional hazards regression models, with corresponding 95% confidence intervals (CI).

Model 1: adjusted for age, sex, Rotterdam Study cohort (RS only), level of education (RS only), deprivation index (UKB only), ethnicity (UKB only), tea consumption, alcohol consumption, smoking status, physical activity, and diet quality score; Model 2: additionally adjusted for body mass index, hypertension, ratio serum total cholesterol/HDL. Cases of incident T2D in the Rotterdam Study n = 843 and in the UK Biobank n = 2290.

Bold text indicates statistically significant associations (p < 0.05).

^a Natural logarithm-transformed.

[0.005; 0.040], p = 0.012) and with higher IL-13 (β = 0.011 log-ug/mL [−0.0004; −0.021], p = 0.042). No significant associations were observed for the other biomarkers. Results for the specific inflammatory markers did not change after additional adjustment for CRP, except for the inverse association with leptin, which became statistically significant (β = −0.024 [−0.047; −0.001], p = 0.004).

3.4. Stratification by coffee types

Consumers of ground (filtered or espresso) coffee showed stronger associations of coffee with CRP (β = −0.026 [−0.030; −0.023], p < 0.001), as compared with those drinking instant coffee or decaffeinated coffee. Similarly, stronger longitudinal associations were observed among ground coffee drinkers for

incident T2D (HR = 0.88 [0.83; 0.93], p < 0.001), in comparison with consumers of the other coffee types (Table 4).

3.5. Mediation analyses

The biomarkers associated with coffee intake (CRP, adiponectin and IL-13) were modelled as potential mediators in the coffee-T2D association. Significant evidence for mediation was observed for CRP in both cohorts as presented in Fig. 1 and Supplementary Tables S–3. Briefly, after estimating the aforementioned coffee-CRP association (a_{CRP-RS} : β = −0.014, [−0.022; −0.005], p = 0.002 and $a_{CRP-UKB}$: β = −0.011 [−0.012; −0.009], p < 0.001), the observed association between coffee and T2D was additionally adjusted by CRP. In UKB the association remained significant while in RS this

Table 3

Associations between coffee intake and type 2 diabetes-related inflammatory markers and adipokines in UKB and RS, with and without additional adjustment for CRP.

Cohort/biomarker	Multivariable adjusted (Model 2)		Model 2 additionally adjusted for CRP	
	β (95% CI)	P	β (95% CI)	P
UK Biobank				
CRP (ug/mL)	−0.011 (−0.012; −0.009)	<0.001	—	
The Rotterdam Study				
CRP (ug/mL)	−0.014 (−0.022; −0.005)	0.002	—	
Adiponectin (ug/mL)	0.023 (0.005; 0.040)	0.012	0.024 (0.007; 0.041)	0.007
Leptin (ng/mL)	−0.022 (−0.045; 0.002)	0.068	−0.024 (−0.047; −0.001)	0.004
ENRAGE (ng/mL)	0.010 (−0.013; 0.033)	0.379	0.005 (−0.017; 0.027)	0.648
C3 (mg/mL)	−0.005 (−0.012; 0.002)	0.194	−0.006 (−0.013; 0.0005)	0.069
IL-17 (pg/mL)	−0.004 (−0.021; 0.013)	0.064	−0.003 (−0.020; 0.014)	0.740
IL-1RA (pg/mL)	−0.001 (−0.027; 0.025)	0.954	−0.005 (−0.030; 0.021)	0.717
CFH (ug/mL)	0.011 (−0.007; 0.030)	0.227	0.010 (−0.008; 0.028)	0.280
IL-18 (pg/mL)	0.002 (−0.016; 0.021)	0.814	−0.0001 (−0.019; 0.019)	0.985
IL-13 (pg/mL)	0.011 (0.0004; 0.021)	0.042	0.011 (0.0001; 0.022)	0.047
TNFR II (ng/mL)	0.0003 (−0.012; 0.012)	0.959	−0.002 (−0.014; 0.001)	0.717

Model 1: adjusted for age, sex, Rotterdam Study cohort (RS only), level of education (RS only), deprivation index (UKB only), ethnicity (UKB only), tea consumption, alcohol consumption, smoking status, physical activity, and diet quality score, body mass index, hypertension, ratio serum total cholesterol/HDL.

Bold text indicates statistically significant associations ($p < 0.05$).

Table 4

Associations of specific types of coffee consumption with type 2 diabetes incidence and CRP in UKB.

	Decaffeinated coffee ^a		Instant coffee ^b		Ground coffee ^c	
Type 2 diabetes	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
	0.97 (0.93; 1.01)	0.147	0.96 (0.93; 0.99)	0.003	0.88 (0.83; 0.93)	<0.001
CRP ^d	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
	−0.015 (−0.018; −0.012)	<0.001	−0.012 (−0.012; −0.008)	<0.001	−0.026 (−0.030; −0.023)	<0.001

Model: adjusted for age, sex, deprivation index, ethnicity, tea consumption, alcohol consumption, smoking status, physical activity, diet quality score, hypertension and ratio serum total cholesterol/HDL. Sample of noncoffee drinkers $n = 31,773$.

^a Total sample $n = 53,253$ of whom $n = 21,480$ were decaffeinated-coffee drinkers.

^b Total sample $n = 95,119$ of whom $n = 63,346$ were instant-coffee drinkers.

^c Total sample $n = 58,106$ of whom $n = 26,333$ were ground (filtered or espresso)-coffee drinkers.

^d Naturally logarithm transformed variable.

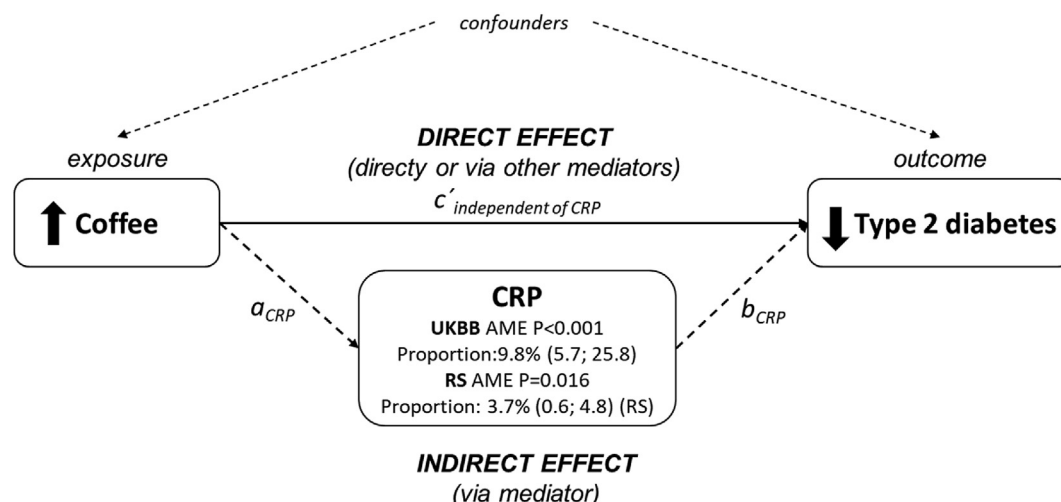


Fig. 1. Mediation analyses results. 'a' refers to the effect of coffee intake on the corresponding inflammation marker. 'b' refers to the effect of the coffee-related levels of the biomarkers in CRP and adiponectin on incident T2D, independent of coffee. RS b_{CRP} : HR = 1.17 (1.04; 1.31); UKB b_{CRP} : HR = 1.45 (1.37; 1.54); and $b_{adiponectin}$: HR = 0.58 (0.32; 0.83). c' refers to coffee' effect on T2D going directly or via others mediators. UKB $c'_{independent\ of\ CRP}$: HR = 0.96 (0.94; 0.99); RS $c'_{independent\ of\ CRP}$: HR = 0.94 (0.90; 0.99); and RS $c'_{independent\ of\ CRP + adiponectin}$: HR = 0.90 (0.80; 1.01). Coffee-related changes in CRP may partially explain the beneficial link between coffee and T2D, with an average mediation effect (AME) of $\beta = 6.484$ (4.265; 9.339), P value < 0.001 in UKB, and $\beta = 0.105$ (0.014; 0.240), P value = 0.016. Regarding the proportion mediates, it was found that coffee-related differences in CRP mediated a 9.8% (5.7; 25.8, UKB) and 3.7% (−1.2; 26.7, RS) of the association coffee-T2D. Note that, despite the notation in the mediation analysis uses the words 'effect' (Imai, K. et al., 2010; Tingley, D. et al., 2014), this must not be interpreted as a causal effect, given the observational nature of the study.

was borderline significant ($c'_{independent\ of\ CRP-RS}$: HR = 0.96 [0.93; 1.00], $p = 0.069$; and $c'_{independent\ of\ CRP-UKB}$: HR = 0.96 [0.94; 0.99], $p < 0.001$). Moreover, the association CRP-T2D remained significant after adjustment for coffee intake (b_{CRP-RS} : HR = 1.17 [1.04; 1.31],

$p = 0.028$; and $b_{CRP-UKB}$: HR = 1.45 [1.37; 1.54], $p < 0.001$). We found significant results for mediation by CRP (UKB AME $\beta = 6.484$ [4.265; 9.339], $p < 0.001$; RS AME $\beta = 0.105$ [0.014; 0.240], $p = 0.016$) (Supplementary Tables S-3) with a statistically significant

proportion mediated by coffee-related changes in CRP in UKB (9.8% [5.7%; 25.8%], $p < 0.001$), and borderline significant in RS (3.7% [−1.2%; 26.7%], $p = 0.059$). Adiponectin and IL-13 were also tested as mediators in RS, with no significant findings (Supplementary Tables S-3).

3.6. Additional analyses and stratification by smoking status

After excluding T2D incident cases that occurred during the first 2 years of follow-up (RS $n = 86$; UKB $n = 547$), no meaningful differences were observed in the effect estimates for the associations coffee-T2D (Supplementary Tables S-4).

For the association coffee-CRP, we observed a statistically significant effect modification by smoking (p -interaction < 0.05) in both cohorts and for coffee-T2D, we observed a borderline significant modification effect in UKB (p -interaction 0.054). In smoking-stratified analyses, coffee-CRP and coffee-T2D associations were generally more robust and remained statistically significant only among never and former smokers in both cohorts (Supplementary Tables S-5).

4. Discussion

In two large population-based cohorts, we observed longitudinal associations between higher habitual coffee consumption and lower risk of T2D and insulin resistance. Our evidence also suggests that higher coffee consumption was associated with lower CRP and leptin, and higher adiponectin and IL-13 concentrations. Further, we observed that coffee-related CRP concentrations might partially mediate the association between coffee and T2D.

A previous study by Jacobs et al. (2014) [13] investigated the role of CRP and adiponectin in the association between coffee consumption and T2D. They used a similar design as ours, with cross-sectional analyses between coffee and biomarkers, and longitudinal assessment of T2D, but was limited by a smaller sample ($n = 1610$), shorter follow-up (7 years), no exploration of coffee types and no formal mediation test [13]. In line with our results, they reported an inverse association between coffee intake and CRP concentrations but no association with adiponectin, likely due to their sample size restrictions. Based on comparing of effect estimates with and without adjustment for CRP, the authors concluded that CRP partly explained the inverse association between coffee and T2D, but only for those drinking > 4 coffee cups/day.

Our findings confirm previous observational and interventional findings showing the beneficial effects of coffee consumption on T2D risk [4,5], and we contributed with further evidence on differences across coffee types and smoking status. Also, we strengthened the available knowledge by implementing formal mediation tests [40,41], which suggest that modulation of sub-clinical inflammation might explain part of the protective effect of coffee on T2D. Nevertheless, additional studies with experimental design or causal inference methods are needed to draw firm conclusions about long-term coffee consumption's effect on the inflammatory response.

Using mediation analyses, we also provided a quantitative estimation of the proportion potentially mediated by CRP differences in the association coffee-T2D, resulting in a modest proportion of 3.7% (RS, AME $P = 0.016$) and 9.8% (UKB, AME $P < 0.001$). This modest effect may be indicative of a complex interplay of metabolic and inflammatory markers implicated in T2D development, and coffee intake may be associated with a broader range of biomarkers beyond CRP, for which our analyses were underpowered or that we did not evaluate [44]. CRP is produced in response to increases in pro-inflammatory cytokines IL-6, IL-1 and IL-17, IL-18, as shown in experimental studies [45,46]. Thus, CRP constitutes a downstream

marker reflecting intracellular damage, which promotes interleukin production [47]. Therefore, CRP is preferred in clinical practice as biomarker for treatment monitoring, while interleukins mainly serve research purposes [47]. Limited epidemiological studies have assessed the potential causal effect of CRP on T2D. Although one Mendelian Randomization (MR) study suggested a non-causal association that could reflect a causal inflammation pathway via upstream effectors [48], recent MR evidence supports CRP's causal role in increasing T2D risk [49]. Further studies are warranted to disentangle the causal nature of the CRP-T2D association.

Our study also found a cross-sectional association between coffee intake and higher adiponectin concentrations. This adipokine, secreted by adipocytes, has anti-inflammatory and insulin-sensitising effects [50], and decreased concentrations have been associated with adiposity, T2D and CVD [50]. Several intervention studies have also reported increased adiponectin concentrations after coffee consumption [51–53]. While our findings confirm a dose-response association between coffee intake and adiponectin levels, previous observational studies are inconsistent [13,44]. Evidence on a causal effect of adiponectin on T2D onset is limited [54,55]. This topic merits further research in well-powered studies.

Finally, we found a positive association between coffee and plasma IL-13, but not with the other biomarkers, most of which had not been previously investigated concerning coffee. Our null finding for IL1ra agrees with reports from coffee intervention trials [56]. Contrarily, our null findings for TNRII contrast with a recent observational study reporting an inverse trend with coffee intake [44].

Regarding coffee types, our study in UKB showed that ground coffee including filtered coffee or espresso preparations, had the strongest beneficial association with lower T2D risk and CRP concentrations. How coffee is prepared may impact its health effects, reflected in e.g. coffee's differential effects on serum lipids. Unfiltered coffee is known to raise cholesterol levels [57], attributed to coffee oils like cafestol, which can be removed from the coffee extract using a filter [57]. In espresso preparations, hot water is in contact with the coffee for a short time, allowing the extraction of mainly hydrophilic compounds, resulting in low concentrations of coffee oils in the prepared coffee. We observed somewhat smaller associations for decaffeinated coffee, which may be due to an actual difference in effect for caffeinated coffee, but could also be explained by the low consumption and lower statistical power for decaffeinated coffee in our analysis. A recent systematic review of clinical trials on caffeine's effect on inflammatory markers suggested that the available evidence is inconclusive [14]. Further research is needed to determine caffeine's role in the inflammatory response and glycaemic control.

We observed disparities in the strength of the associations of coffee with T2D and CRP across smoking statuses, with generally stronger associations among non-smokers. Other studies [16,58] suggested that observed null or unfavourable associations of coffee intake with health outcomes without smoking stratification suffered from residual confounding by smoking and were unlikely to be causal [16,58]. Our results add to this and recommend consideration of smoking habits in coffee-health studies.

Our findings were generally consistent between RS and UKB, although there were some differences in the two populations' characteristics. RS participants had higher average coffee consumption (modal consumption 3–4 cups) and were around 10 years younger than UKB participants (0.5–2 cups/day). Analyses were performed separately to account for these differences between populations, including tea consumption and age as confounders.

Strengths of this study are the large sample size from two prospective studies with long follow-ups and different coffee consumption patterns, finding similar results. Furthermore, we had extensive data on repeated measures of HOMA-IR, a comprehensive set of classic and novel T2D-related inflammation markers and covariates. We also included a thorough assessment of confounders, including sociodemographic and health-related factors, smoking, diet, tea and alcohol consumption. Furthermore, we investigated potential modifiers and stratified analyses by coffee type and smoking, providing insights into how the association between coffee-T2D may differ across sub-groups.

Our study also has some limitations that should be acknowledged. Although we performed causal mediation analyses, the observational nature of our study, similar to previously published evidence, warrants caution in deriving conclusions about the causality of the observed associations. Replication and explanation on potential underlying mechanisms merit further research. The subset of specific inflammatory markers and adipokines were analysed in a subset of participants, resulting in a possible lack of statistical power. Furthermore, we did not consider genetic predisposition for coffee consumption, which has been suggested to modify associations of coffee and (pre)diabetes risk [59]. Finally, our results might not be generalisable to populations with other coffee consumption habits or ethnicities.

5. Conclusion

Our findings from two large population-based cohorts emphasise the association between higher habitual coffee consumption and lower T2D risk, especially among drinkers of ground (filtered or espresso) coffee and among non-smokers. We also showed that coffee-related CRP concentration differences might mediate, to a modest extent, the beneficial effect of coffee on T2D. Future well-powered studies with extended follow-up and detailed data on inflammation biomarkers and coffee subtypes are needed to confirm our findings and infer causal conclusions.

Authors' responsibilities

COR and TV designed the study. TV and CACM allowed access to the data. COR analysed the data. NVDS, KB, FKH, FPR, CACM and TV gave advisory on the statistical analyses and data use. COR, CACM and TV interpreted the results. COR, NVDS and TV wrote the manuscript. All co-authors provided critical comments on the manuscript. COR and TV had primary responsibility for the final content.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgements

We thank all UKB and RS participants and staff. Carolina Ochoa-Rosales received funding from the National Agency for Research and Development (ANID)/Scholarship Program Doctorado Becas Chile/2016–72170524; and from the Albert Renold Travel Fellowship Programme by the European Foundation for the Study of Diabetes (EFSD), Germany. The RS part of this research project was funded by a grant from the Institute for Scientific Information on Coffee (ISIC). The funders did not have a role in the design of this study, execution, analyses or interpretation of the data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.clnu.2023.02.024>.

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