



The association between coffee consumption and risk of incident depression and anxiety: Exploring the benefits of moderate intake

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ABSTRACT

Accumulating evidence has reported the associations of coffee consumption with physical conditions and mortality, but the associations with mental disorders were limited. The objective of this study was to examine the associations of coffee consumption with incident depression and anxiety, and to assess whether the associations differed by coffee subtypes (instant, ground, and decaffeinated coffee) or additives (milk, sugar-sweetened, and artificial-sweetened). In this prospective cohort study, we utilized data from the UK Biobank and included a total of 146,566 participants who completed the touchscreen questionnaire at baseline between 2006 and 2010. During the follow-up, incident depression and anxiety were measured in 2016 using the Patient Health Questionnaire (PHQ)-9 and the Generalised Anxiety Disorder Assessment (GAD)-7, respectively. Multivariable-adjusted logistic regression models and restricted cubic splines were used to assess the associations. Approximately 80.7% of participants reported consuming coffee, and most drank 2 to 3 cups per day (41.2%). We found J-shaped associations between coffee consumption and both incident depression and anxiety, with the lowest risk of the mental disorders occurring at around 2–3 cups per day. Results were similar for participants who drank 2–3 cups of ground coffee, milk-coffee, or unsweetened coffee. Our findings highlight that 2–3 cups of coffee consumption could be recommended as part of a healthy lifestyle to improve mental health.

1. Introduction

Mental disorders contribute greatly to the global health burden, with depression and anxiety disorders being the leading causes of disability worldwide ([Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 2022](#)). Numerous evidences have suggested that depression and anxiety were associated with higher risks of physical health conditions and mortality ([Oude Voshaar et al., 2021](#); [Scott et al., 2016](#)). Notably, depression and anxiety often persist as a chronic course, which are more likely to lead to detrimental health conditions and poor life quality ([Satyanarayana et al., 2009](#)). Given the

escalating prevalence and far-reaching consequences of depression and anxiety, identifying the modifiable risk factors that could prevent or alleviate the risk of incident depression and anxiety is a high-priority option.

In view of the high level of coffee consumption, the impact of coffee intake on health outcomes has attracted considerable research attention. Most of the current evidence has demonstrated associations between moderate coffee consumption and the lower risk of type 2 diabetes, chronic liver disease, stroke, cancer, and mortality ([Kositamongkol et al., 2021](#); [Liu et al., 2022](#); [Miranda et al., 2021](#); [Poole et al., 2017](#); [Zhang et al., 2021](#)). A dose-response meta-analysis among the US

Abbreviations: PHQ, Patient Health Questionnaire; GAD, Generalised Anxiety Disorder; TDI, Townsend deprivation index; BMI, body mass index; SD, standard deviation; OR, odd ratio; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease.

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population has also shown that 1 cup of coffee per day was associated with a 9% lower risk of cardiovascular disease (CVD) (Di Maso et al., 2021). Moreover, caffeine is believed to have an impact on mental health. Previous experimental evidence showed that caffeine is a central nervous system stimulant that affects emotions and cognitive function by blocking adenosine receptors and increasing dopamine (van Dam et al., 2020). However, only a few epidemiological studies focused on the associations between coffee consumption and common mental disorders, and reported inconsistent findings, indicating either a positive (Bertasi et al., 2021; Richards and Smith, 2015), a negative (Chan et al., 2018; Iranpour and Sabour, 2019; Kim and Kim, 2018; Ruusunen et al., 2010), or no association (Hintikka et al., 2005) between them. In addition, previous studies have shown different health effects of coffee subtypes. Consumption of unsweetened and sugar-sweetened coffee was associated with a lower risk of all-cause mortality, whereas artificially sweetened coffee has no such benefit (Chieng et al., 2022; Liu et al., 2022). These potential differences in health effects may be attributed to various additives and other compounds in different types of coffee, such as milk, sugar, and artificial-sweeteners. A meta-analysis study has shown that increased consumption of sugar- and artificial-sweetened beverages is associated with a higher risk of chronic diseases and all-cause mortality (Meng et al., 2021). It is largely unknown whether the relationships between coffee consumption and depression or anxiety differ by coffee subtypes or coffee additives.

Using the large-scale prospective cohort in the UK Biobank, the current study aimed to investigate the prospective associations between coffee consumption and incident depression and anxiety. We further explored whether the associations differed by coffee subtypes (instant, ground, and decaffeinated coffee) and coffee additives (milk, sugar-sweetened, and artificial-sweetened).

2. Methods

2.1. Study design and participants

Between April 2006 and December 2010, the UK Biobank recruited 502,411 adults (37–73 years old) from the general population in the UK. Participants attended one of the 22 assessment centers across England, Scotland, and Wales, and completed touchscreen questionnaires, physical examinations, and biological sample collections at baseline. All of the participants have signed the informed consent to be linked to national electronic health records (Fry et al., 2017). In 2016, 157,366 participants were invited to complete online questionnaires, which focused on follow-up information on mental health (Davis et al., 2020).

In the current prospective cohort study, 152,821 participants who responded to the online mental health questionnaires were initially included. We further excluded the participants with depression or anxiety at baseline. Depression at baseline was defined by multiple sources of data: self-reported, the Patient Health Questionnaire (PHQ)–4 (depression items) (Lowe et al., 2010), antidepressants use, and hospital inpatient records. A detailed description of how depression at baseline was measured can be found in previous work (Dregan et al., 2020). Baseline anxiety was also measured using diverse sources: self-reported, the PHQ-4 (anxiety items), and hospital inpatient records. Missing information on coffee intake and covariates were also excluded. Finally, a total of 146,566 participants were included in the analysis of coffee consumption, coffee subtypes, and mental disorders, and a total of 105,656 participants were included in the analysis of coffee additives and mental disorders. All participants provided informed consent, and the UK Biobank study received ethical approval from the North West Multi-Centre Research Ethics Committee (REC reference: 21/NW/0157). The flowchart details of the study design are shown in Supplemental Fig. 1.

2.2. Exposure assessment

Coffee consumption was collected using a touchscreen questionnaire at baseline from 2006 to 2010. Participants were instructed clearly on how to complete the questionnaire, which required them to self-report the precise number of cups of coffee consumed per day. They were asked to confirm if the answer was greater than 10 cups. Next, coffee consumers were asked to select the type of coffee they usually drank, including instant coffee, ground coffee, decaffeinated coffee, and other types of coffee. In the main analysis, we categorized coffee consumption into 7 categories: 0, 1, 2–3, 4–5, 6–7, 8–9, and ≥ 10 cups per day. The category of 0 cups per day was used as the reference group in subsequent analyses. One cup is equal to approximately 250 ml.

A validated web-based 24-hour dietary recall questionnaire was used to collect information on the use of coffee additives (Liu et al., 2011). The questionnaire was first introduced as part of the assessment interview towards the end of recruitment for the last 70,000 participants in 2009 and 2011. Participants who had provided e-mail addresses at baseline were invited to complete the questionnaire online via email on four separate occasions between February 2011 and April 2012. Similarly, participants indicated the number of cups of coffee they had drunk in the previous 24 h in each 24-hour dietary recall questionnaire. For coffee consumers, they could report whether they added milk, sugar, or artificial-sweetener to coffee. In the investigation of the association between coffee additives and the risk of depression and anxiety, our study sample was restricted to participants who successfully completed one or more of the five 24-hour dietary recall questionnaires ($n = 105,656$). Since participants could complete the questionnaire up to 5 times, we calculated an average number of coffee intake across multiple dietary recalls as a habitual intake and we classified the participants into 6 categories: non-coffee consumers, no-milk consumers, milk consumers, unsweetened consumers, sugar-sweetened consumers or artificial-sweetened consumers in each dietary recall. Participants classified in the same category on multiple questionnaires were defined as single consumers. Others, defined as overlapped consumers, were excluded from the subsequent analyses ($n = 1970$) (Supplemental Fig. 1).

2.3. Ascertainment of depression and anxiety

The primary outcomes of interest were incident depression and anxiety, which were ascertained by the PHQ-9 and the GAD-7 questionnaires administered in 2016. The PHQ-9 is a nine-item questionnaire of the depression module, which scores each of the nine DSM-IV criteria for depression from 0 (not at all) to 3 (nearly every day) with a total score ranging from 0–27 (Kroenke et al., 2001). A score of 10 or higher is an indicative of depressive symptoms (Levis et al., 2019), and this was used to create a binary variable for depression outcome. The PHQ-9 has been shown to be a valid and reliable diagnostic tool for possible depression in a variety of populations, exhibiting optimal combined sensitivity (0.88, 95% CI 0.83 to 0.92) and specificity (0.85, 0.82 to 0.88) at a cut-off score of 10 (Levis et al., 2019). The GAD-7 is a seven-item anxiety module questionnaire that asks participants to rate the extent of certain anxiety symptoms over the past two weeks on a scale from 0 (not at all) to 3 (nearly every day), a higher score signifying a worse condition. Total scores range from 0 to 21 and a score of 10 or higher indicates the symptoms of moderate to severe anxiety (Spitzer et al., 2006). The previous study supported the reliability and validity of the GAD-7 as a measure of anxiety (Löwe et al., 2008). Moreover, a study based on standard diagnostic interviews with 965 patients concluded that GAD-7 (cut off ≥ 10) demonstrated a sensitivity of 89% and a specificity of 82% for the diagnosis of generalized anxiety disorder (Spitzer et al., 2006).

2.4. Covariates assessment

A wide range of socio-demographic factors, lifestyle behaviours, and chronic diseases was considered as potential confounders, including sex, age, ethnicity (white or non-white), education (college/university degree or other degrees), Townsend deprivation index (TDI), body mass index (BMI), smoking status (never, former, and current), sleep duration (hours per day), tea intake (cups per day), alcohol intake (grams per day, based on the variable of frequency of alcohol intake and grams of each type of alcohol per one standard drink described in the previous study (Biddinger et al., 2022)), and diet score, history of diabetes (yes or no), history of hypertension (yes or no) obtained from the self-reported questionnaires between 2006 and 2010. TDI is a composite measure of deprivation based on unemployment, non-car ownership, non-cottage ownership, and household overcrowding, with higher values indicating lower socio-economic status. The diet score was constructed to reflect the dietary pattern, including the frequency of consumption of fruit, vegetables, fish, processed meat, unprocessed red meat, whole grains, and refined grains. We assigned 1 point for a healthy level and 0 points for an unhealthy level. The healthy standards for each dietary component were listed: (1) fruit: ≥ 3 servings/day; (2) vegetables: ≥ 3 servings/day; (3) fish: ≥ 2 servings/week; (4) processed meat: ≤ 1 serving/week; (5) unprocessed red meat: ≤ 1.5 servings/week; (6) whole grains: ≥ 3 servings/day; (7) refined grains: ≤ 1.5 servings/day (Mozaffarian, 2016) (Morris et al., 2015). Thus, the diet score was the sum of the points and ranged from 0 to 7, with higher scores indicating a healthier dietary pattern. Diabetes and hypertension were defined as a self-reported history of diabetes and hypertension. In particular, we calculated the time span between the baseline assessment and the mental health follow-up questionnaire as a covariate since the distance of time may affect the strength of the associations.

2.5. Statistical analysis

Baseline characteristics of the participants were described as means and standard deviations (SDs) for continuous variables, or numbers and percentages for categorical variables. Multivariable logistic regression models were used to estimate the odds ratio (ORs) and 95% CIs of incident depression and anxiety associated with total coffee consumption, coffee subtypes (instant, ground, and decaffeinated coffee), and additives use (milk, sugar-sweetened, and artificial-sweetened). In the following analyses, two incremental models were constructed. Model 1 was adjusted for age and sex. Model 2 was further adjusted for ethnicity, education, TDI, BMI, smoking status, alcohol intake, tea intake, diet score, sleep duration, history of hypertension, history of diabetes, and time span. Participants with any missing covariates were excluded due to the very small percentage, ranging from 0.04% (coffee consumption) to 4.0% (diet score). Restricted cubic spline models were used to examine the dose-response relationship between coffee consumption and depression and anxiety with adjustment for the above covariates.

Seven sensitivity analyses were carried out to assess the robustness of our results. First, we used hospital inpatient records to determine depression and anxiety, according to the International Classification of Diseases, 10th Revision (ICD-10): F32 and F33 for depression; F40 and F41 for anxiety. Cox proportional hazard models were performed to estimate the time-to-event effect of coffee consumption on the risk of mental disorders to verify the results of the main analysis. Second, we used multiple imputation by chained equations to impute missing data with 10 imputations and repeated the main analysis using the complete data set to test the influence of missing variables. Third, we conducted several subgroup analyses of coffee consumption and mental disorders by age (≤ 60 or > 60 years), sex (female or male), BMI (≤ 25 kg/m² or > 25 kg/m²), and smoking status (never, former, or current) to examine whether the associations varied by these factors. Fourth, we excluded participants with a history of CVD or cancer at or before baseline, as they were more likely to report dietary changes during follow-up. Fifth, we

excluded participants who reported poor or fair self-rated health status. Sixth, we limited our analysis to participants who had completed at least two 24-hour dietary recall questionnaires, as a single 24-hour questionnaire may not be a reliable indicator of typical coffee intake. This approach allowed us to better assess the dynamic associations between coffee additives and depression and anxiety. Seventh, we relied on primary care data rather than hospital inpatient data to confirm depression and anxiety diagnoses, as primary care data could provide a reliable source for depression and anxiety identification. We then repeated the main analysis using this refined data.

All the analyses were conducted using STATA 16 statistical software (Stata Corp LLP, college station, TX) and R software (version 4.1.3). The statistical significance was set as $P < 0.05$ (two-sided test).

3. Results

3.1. Baseline characteristics

146,656 participants (63,860 men and 82,796 women) with a mean age of 55.9 years (SD, 7.7 years) were finally included in our analysis. In total, 118,352 (80.7%) were coffee consumers and 28,304 (19.3%) were non-coffee consumers. Meanwhile, 48,818 (41.2%) participants reported drinking 2 to 3 cups of coffee per day, accounting for the largest proportion, followed by 41,549 (28.3%) participants who reported drinking 1 cup per day (Table 1). In comparison with the participants who were excluded from this study, no obvious differences were observed between the included and excluded cohorts, except for educational attainment (Supplemental Table 1).

3.2. Coffee consumption and common mental disorders

Restricted cubic spline models based on logistic regression showed J-shaped associations between coffee consumption and depression and anxiety, with the lowest risk of depression and anxiety occurring at approximately 3 cups of coffee per day (Fig. 1). Compared with non-coffee consumers, the multivariable-adjusted ORs (95% CIs) for different levels of coffee consumption (1, 2–3, 4–5, 6–7, 8–9, ≥ 10 cups per day) were 0.91 (0.84–0.99), 0.87 (0.81–0.94), 0.86 (0.78–0.95), 1.04 (0.90–1.20), 1.30 (1.03–1.64), and 1.33 (1.02–1.73) for incident depression, and the corresponding estimates were 0.89 (0.82–0.96), 0.90 (0.83–0.97), 0.89 (0.81–0.99), 1.03 (0.89–1.19), 1.19 (0.93–1.52), and 1.48 (1.15–1.92) for incident anxiety (Table 2). Moreover, a trend towards an increased risk of depression and anxiety was found among participants who drank more than 6 cups of coffee per day, although this trend was less significant in some categories.

3.3. Coffee subtypes and common mental disorders

The associations between different coffee subtypes and mental disorders were presented in Table 3. Findings for ground coffee were largely consistent with the total coffee consumption. Compared with no coffee consumption, the multivariable-adjusted ORs (95% CIs) for 2–3 cups of ground coffee per day were 0.79 (0.70–0.89) for depression and 0.79 (0.71–0.89) for anxiety. Moreover, 2–3 cups of instant coffee per day was found to be associated with incident depression (OR = 0.91, 95% CI: 0.83–1.00), but not with incident anxiety (OR = 0.95, 95% CI: 0.85–1.01).

3.4. Coffee additives and common mental disorders

The associations of coffee additives with mental disorders were also examined (Table 4). The multivariable adjusted ORs (95% CIs) for those who drank > 1 –3 cups of milk-coffee per day compared to non-coffee consumers were 0.77 (0.70–0.84) for depression and 0.91 (0.82–1.00) for anxiety; for those who drank > 1 –3 cups of unsweetened-coffee per day, the ORs (95% CIs) were 0.78 (0.71–0.86) for depression and 0.83

Table 1
Baseline characteristics of 146,656 participants by coffee intake in the UK Biobank.

Characteristics	Non-consumers	Coffee intake, cups per day					
		1	2–3	4–5	6–7	8–9	≥10
Total, n	28,304	41,549	48,818	20,037	5624	1373	951
Age, mean (SD)	54.4 (7.8)	56.2 (7.7)	56.5 (7.7)	55.9 (7.6)	55.7 (7.5)	54.3 (7.4)	54.1 (7.8)
Sex, n (%)							
Female	17,654 (62.4)	24,460 (58.9)	26,814 (54.9)	10,101 (50.4)	2774 (49.3)	626 (45.6)	367 (38.6)
Male	10,650 (37.6)	17,089 (41.1)	22,004 (45.1)	9936 (49.6)	2850 (50.7)	747 (54.4)	584 (61.4)
Ethnicity							
White	26,964 (95.3)	40,231 (96.8)	47,895 (98.1)	19,789 (98.8)	5566 (99.0)	1358 (98.9)	935 (98.3)
Non-white	1340 (4.7)	1318 (3.2)	923 (1.9)	248 (1.2)	58 (1.0)	15 (1.1)	16 (1.7)
Education							
College or university	11,494 (40.6)	19,589 (47.1)	24,076 (49.3)	9467 (47.2)	2318 (41.2)	564 (41.1)	391 (41.1)
Other degrees	16,810 (59.4)	21,960 (52.9)	24,742 (50.7)	10,570 (52.8)	3306 (58.8)	809 (58.9)	560 (58.9)
Townsend deprivation index, mean (SD)	−1.5 (2.9)	−1.7 (2.8)	−1.8 (2.8)	−1.9 (2.7)	−1.7 (2.8)	−1.4 (3.0)	−1.0 (3.2)
Smoke status							
Never	17,501 (61.8)	25,018 (60.2)	27,922 (57.2)	10,597 (52.9)	2585 (46.0)	581 (42.3)	329 (34.6)
Former	9125 (32.2)	14,322 (34.5)	17,699 (36.3)	7463 (37.2)	2174 (38.7)	527 (38.4)	346 (36.4)
Current	1678 (5.9)	2209 (5.3)	3197 (6.5)	1977 (9.9)	865 (15.4)	265 (19.3)	276 (29.0)
BMI, mean (SD)	26.7 (4.8)	26.4 (4.5)	26.7 (4.4)	27.4 (4.5)	27.8 (4.7)	28.1 (5.0)	27.9 (4.9)
Diet score, mean (SD)	3.7 (1.5)	3.8 (1.5)	3.8 (1.5)	3.6 (1.5)	3.5 (1.5)	3.4 (1.5)	3.3 (1.6)
Sleep duration, mean (SD)	7.2 (1.0)	7.2 (1.0)	7.2 (0.9)	7.1 (1.0)	7.1 (1.0)	7.0 (1.0)	6.8 (1.2)
Alcohol intake, mean (SD)	14.9 (19.9)	18.1 (19.4)	20.0 (19.9)	20.8 (20.6)	19.6 (22.3)	19.9 (22.6)	19.9 (25.3)
Tea intake, mean (SD)	4.4 (3.1)	4.0 (2.5)	2.9 (2.2)	2.0 (2.2)	1.6 (2.5)	1.5 (2.7)	2.4 (4.9)
Type of coffee							
Decaffeinated coffee	0 (.)	7883 (19.0)	8700 (17.8)	3919 (19.6)	1227 (21.8)	266 (19.4)	175 (18.4)
Instant coffee	0 (.)	18,382 (44.2)	24,396 (50.0)	11,888 (59.3)	3539 (62.9)	924 (67.3)	629 (66.1)
Ground coffee	0 (.)	14,388 (34.6)	15,309 (31.4)	4095 (20.4)	823 (14.6)	173 (12.6)	144 (15.1)
Other types of coffee	0 (.)	896 (2.2)	413 (0.8)	135 (0.7)	35 (0.6)	10 (0.7)	3 (0.3)
Antidepressants use	1927 (6.8)	2207 (5.3)	2482 (5.1)	1134 (5.7)	372 (6.6)	91 (6.6)	96 (10.1)
Time span, mean (SD)	7.6 (0.9)	7.6 (0.9)	7.6 (0.8)	7.6 (0.8)	7.6 (0.8)	7.6 (0.8)	7.6 (0.9)
Hypertension, n (%)	5744 (20.3)	8824 (21.2)	10,226 (20.9)	4168 (20.8)	1182 (21.0)	248 (18.1)	202 (21.2)
Diabetes, n (%)	898 (3.2)	1222 (2.9)	1420 (2.9)	711 (3.5)	218 (3.9)	59 (4.3)	54 (5.7)
Baseline depression, n (%)	3442 (12.2)	4387 (10.6)	4842 (9.9)	2091 (10.4)	662 (11.8)	186 (13.5)	149 (15.7)
Baseline anxiety, n (%)	1402 (5.0)	1916 (4.6)	2109 (4.3)	807 (4.0)	238 (4.2)	68 (5.0)	42 (4.4)

BMI = body mass index; SD = standard deviation.

The time span was calculated by the duration time between the baseline assessment and the mental health follow-up questionnaire.

The diet score ranging from 0 to 7 was constructed to reflect the diet pattern including the frequency of consumption of fruits, vegetables, fish, processed meat, unprocessed red meat, whole grains, and refined grains. Baseline depression was assessed by multiple sources: self-report, the PHQ-4, baseline anti-depressants use, and hospital inpatient records. Baseline anxiety was assessed by self-report, the PHQ-4, and hospital inpatient records.

(0.75–0.91) for anxiety. However, this pattern was not found for the no-milk coffee (OR = 0.97, 95% CI = 0.85–1.10 for depression; OR = 0.88, 95% CI = 0.77–1.01 for anxiety), sugar-sweetened coffee (OR = 1.04, 95% CI: 0.90–1.20 for anxiety) and artificial-sweetened coffee (OR = 0.95, 95% CI: 0.78–1.15 for depression; OR = 1.11, 95% CI: 0.92–1.35 for anxiety).

3.5. Sensitivity analyses

We examined the time-to-event effect of coffee consumption on common mental disorders, the results were not materially varied from the main analysis. The multivariable-adjusted hazard ratios (HRs) and 95% CIs for 2–3 cups of coffee per day compared with non-coffee consumers were 0.87 (0.83–0.92) for incident depression and 0.81 (0.69–0.95) for incident anxiety. (Supplemental Tables 2, 3 and Supplemental Fig. 2). Furthermore, we found that the lowest risk of both incident depression and anxiety arose at a level of 2–3 cups of ground coffee per day. Subgroup analyses showed that the inverse associations of 2–3 cups of coffee per day with incident anxiety were stronger among participants aged > 60 years old (OR = 0.79, 95% CI: 0.66–0.93) than those aged ≤ 60 years (OR = 0.87, 95% CI: 0.80–0.95; Supplemental Table 4). The associations between coffee consumption and risk of common mental disorders were not modified by sex, BMI, and smoking status, with all *P* values for interaction > 0.05. (Supplemental Tables 5–7). The results were largely consistent with the main analysis when we used the complete data set (Supplemental Tables 8, 9, and Supplemental Fig. 3), excluded participants with CVD or cancer at or before baseline (Supplemental Tables 10–12), excluded participants

with poor or fair self-rated health status (Supplemental Tables 13–15), restricted our analysis to participants who had completed at least two 24-hour dietary recall questionnaires (Supplemental Table 16), and used primary care data to confirm depression and anxiety (Supplemental Tables 17 and 18).

4. Discussion

In this large prospective cohort study in the UK, we found J-shaped associations between coffee consumption and risk of incident depression and anxiety, with the lowest risk for both depression and anxiety at around 2–3 cups of coffee per day. Furthermore, coffee subtypes including 2–3 cups of ground coffee, milk-coffee, and unsweetened coffee were significantly associated with similar risk reductions for depression and anxiety. Nevertheless, the associations of no-milk, sugar-sweetened, and artificial-sweetened coffee with the mental disorders were inconsistent. These associations were independent of potential confounders, including socio-demographic factors, lifestyle behaviours, dietary patterns, and comorbid conditions.

Previous studies have examined the association between coffee consumption and mental health, but the results have been inconsistent. Two studies of meta-analyses showed a protective effect of coffee on the risk of depression, one found a non-linear J-shaped association between coffee consumption and depression (Grosso et al., 2016), while another found an inverse linear association (Wang et al., 2016). In a prospective study of 9576 adults from the Korean population, frequent coffee drinkers (≥ 2 cups/day) had a 32% lower prevalence of depression than non-coffee drinkers (Kim and Kim, 2018). Another prospective study of

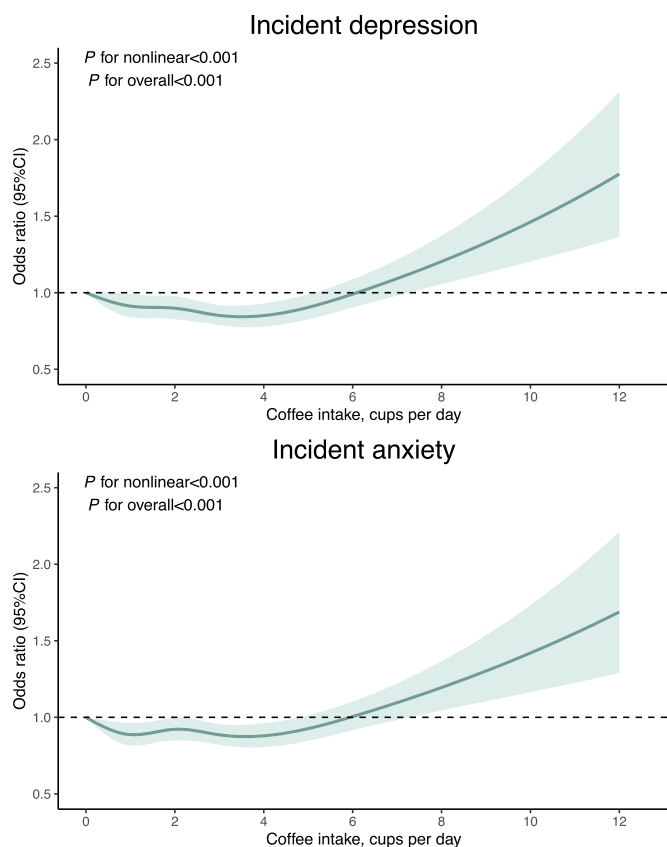


Fig. 1. Dose-response associations between coffee consumption and depression and anxiety.

The odds ratio was adjusted for age; sex; ethnicity (white or non-white); education (university or other); Townsend deprivation index; BMI (kg/m²); smoke status (never, former or current); alcohol intake (grams per day); tea intake (cups per day); diet score; sleep duration (hours per day); hypertension (yes or no) and diabetes (yes or no) and the distance of time between the baseline assessment and the mental health follow-up questionnaire.

50,739 women in the United States (mean age, 63 years) with a follow-up 10 years revealed that compared with consuming 1 or fewer cups of coffee per week, consuming 2 to 3 cups per day was associated with a 15% lower risk of depression (Lucas et al., 2011). In a prospective study of 14,413 Spanish university graduates, those consuming ≥4 cups of coffee daily exhibited a significantly reduced depression risk (HR: 0.37, 95% CI: 0.15–0.95) compared to those consuming <1 cup/day (Navarro et al., 2018). However, some studies revealed positive or no associations between coffee consumption and mental disorders. Two cross-sectional studies based on the student populations found a positive

association between caffeine intake and the symptoms of depression and anxiety (Bertasi et al., 2021; Richards and Smith, 2015). A Finnish study including 2011 participants showed that coffee drinking had no risk reduction of being depressed (Hintikka et al., 2005), in accordance with a cross-sectional study among Japanese auto factory workers reporting no significant association between coffee consumption and psychological well-being (Kawada, 2021). The reasons for these inconsistent findings could result from the differential study design (prospective vs. cross-sectional), ethnic background (European vs. America vs. Asian), sample size (ranging from 2011 to 50,739), classification of coffee consumption, and measurement of depression and anxiety. In the current study, we found robust results indicating that moderate coffee consumption was associated with a lower risk of both depression and anxiety, and these associations still existed regardless of coffee subtypes, including ground coffee, milk-coffee, and unsweetened coffee. Compared to previous research, our study was conducted based on the UK Biobank database, allowing us to draw the convincing findings as a larger sample size and more information on coffee subtypes and additives. The findings expanded our understanding of the prevention of mental disorders by coffee consumption.

Some potential biological mechanisms may explain the findings of our present study. Coffee generally contains more than a thousand biologically active substances, such as phenolic compounds, alkaloids, and melanin (Saeed et al., 2019). These substances, especially phenolic compounds such as chlorogenic acid, play important anti-inflammatory and antioxidant roles in the body (Dias et al., 2012; Kolb et al., 2020), which are involved in the pathogenesis of antidepressants and anxiolytics (Kiecolt-Glaser et al., 2015; Vaváková et al., 2015), resulting in a benefit in reducing the risk of mental disorders. In addition, caffeine is the dominant physiologically active compound in coffee that performs biological functions mainly through adenosine receptors in the central nervous system (Huang and Sperlágh, 2021). Adenosine receptors, including A_{2A} and A₁, play a vital part in emotional and spiritual adjustment. Activation of A_{2A} receptors is associated with increased depression-like symptoms, while increased A₁ receptor signaling elicits rapid antidepressant effects (van Calker et al., 2019). Caffeine exerts mainly antagonistic effects on A_{2A} and agonistic A₁ receptors after being consumed and therefore can produce antidepressant and anxiolytic effects in humans (Huang and Sperlágh, 2021; van Calker et al., 2019). Significant risk reductions for depression and anxiety were only observed in the caffeinated subtypes (instant and ground coffee) in our study might be explained by this mechanism. Moreover, it has been suggested that a high intake of polyphenols can produce cytotoxic effects (Murakami, 2014), and a high intake of caffeine may increase serum cholesterol and cortisol stress (Butt and Sultan, 2011; Lane et al., 1990), which are detrimental to human health. Moreover, we found that compared to non-coffee consumers, those who drank >10 cups of coffee per day were more likely to smoke (Table 1; 29.0% vs. 5.9%), drink (19.9 g/day vs. 14.9 g/day), use antidepressants (10.1% vs. 6.8%), and have a higher prevalence of diabetes (5.7% vs. 3.2%) and hypertension

Table 2
Odds ratio (95% CIs) for depression and anxiety by coffee intake in the UK Biobank*.

Outcomes	Non-consumers	Coffee intake, cups per day					
		1	2–3	4–5	6–7	8–9	≥10
Incident depression (n = 130, 897)							
Events, n	1299	1490	1641	723	268	88	69
Age and sex-adjusted	1.00 (Reference)	0.84 (0.78–0.91)	0.80 (0.74–0.87)	0.86 (0.78–0.94)	1.16 (1.01–1.33)	1.52 (1.21–1.90)	1.82 (1.41–2.35)
Multivariable-adjusted *	1.00 (Reference)	0.91 (0.84–0.99)	0.87 (0.81–0.94)	0.86 (0.78–0.95)	1.04 (0.90–1.20)	1.30 (1.03–1.64)	1.33 (1.02–1.73)
Incident anxiety (n = 140, 074)							
Events, n	1321	1491	1676	708	244	73	70
Age and sex-adjusted	1.00 (Reference)	0.83 (0.77–0.90)	0.82 (0.76–0.88)	0.84 (0.76–0.92)	1.04 (0.90–1.20)	1.24 (0.97–1.58)	1.80 (1.40–2.32)
Multivariable-adjusted *	1.00 (Reference)	0.89 (0.82–0.96)	0.90 (0.83–0.97)	0.89 (0.81–0.99)	1.03 (0.89–1.19)	1.19 (0.93–1.52)	1.48 (1.15–1.92)

* Estimates are odds ratio (95% CIs) from binary logistic regression models adjusted for age; sex; ethnicity (white or non-white); education (university or other); Townsend deprivation index; BMI (kg/m²); smoke status (never, former or current); alcohol intake (grams per day); tea intake (cups per day); diet score; sleep duration (hours per day); hypertension (yes or no), diabetes (yes or no) and the distance of time between the baseline assessment and the mental health follow-up questionnaire.

Table 3
Odds ratio (95% CIs) for depression and anxiety by coffee subtypes in the UK Biobank *.

Coffee subtypes	Non-consumers	Coffee intake, cups per day					
		1	2-3	4-5	6-7	8-9	≥10
Incident depression (n = 130, 897)							
Decaffeinated coffee	1.00 (Reference)	1.07 (0.94-1.22)	0.88 (0.76-1.00)	0.84 (0.70-1.02)	1.11 (0.84-1.47)	2.07 (1.33-3.22)	1.59 (0.89-2.82)
Instant coffee	1.00 (Reference)	0.91 (0.82-1.00)	0.91 (0.83-1.00)	0.86 (0.76-0.97)	1.00 (0.84-1.20)	1.26 (0.95-1.67)	1.23 (0.89-1.70)
Ground coffee	1.00 (Reference)	0.81 (0.72-0.91)	0.79 (0.70-0.89)	0.86 (0.71-1.03)	1.07 (0.76-1.50)	0.35 (0.11-1.10)	1.19 (0.58-2.43)
Incident anxiety (n = 140, 074)							
Decaffeinated coffee	1.00 (Reference)	0.96 (0.84-1.09)	0.87 (0.76-0.99)	0.83 (0.69-1.00)	0.78 (0.57-1.07)	1.13 (0.65-1.95)	1.16 (0.61-2.23)
Instant coffee	1.00 (Reference)	0.87 (0.79-0.96)	0.93 (0.85-1.01)	0.87 (0.77-0.98)	1.11 (0.93-1.31)	1.22 (0.91-1.63)	1.52 (1.12-2.06)
Ground coffee	1.00 (Reference)	0.80 (0.71-0.89)	0.79 (0.71-0.89)	0.91 (0.76-1.10)	0.84 (0.57-1.24)	0.96 (0.44-2.06)	1.49 (0.77-2.89)

* Estimates are odds ratio (95% CIs) from binary logistic regression models adjusted for age; sex; ethnicity (white or non-white); education (university or other); Townsend deprivation index; BMI (kg/m²); smoke status (never, former or current); alcohol intake (grams per day); tea intake (cups per day); diet score; sleep duration (hours per day); hypertension (yes or no), diabetes (yes or no) and the distance of time between the baseline assessment and the mental health follow-up questionnaire.

Table 4
Odds ratio (95% CIs) for depression and anxiety stratified by coffee additives in the UK Biobank *.

Coffee additives	Non-consumers	Coffee intake, cups per day					
		>0-1	>1-3	>3-5	>5-7	>7-9	>9
Incident depression (n = 94, 886)							
No milk	1.00 (Reference)	0.99 (0.85-1.15)	0.97 (0.85-1.10)	0.92 (0.77-1.10)	1.02 (0.75-1.37)	1.51 (0.87-2.61)	0.69 (0.16-2.92)
Milk	1.00 (Reference)	0.85 (0.75-0.97)	0.77 (0.70-0.84)	0.88 (0.79-0.99)	0.94 (0.79-1.13)	0.82 (0.53-1.27)	1.84 (1.04-3.27)
Unsweetened	1.00 (Reference)	0.84 (0.74-0.95)	0.78 (0.71-0.86)	0.83 (0.74-0.94)	0.92 (0.77-1.11)	0.87 (0.57-1.32)	1.48 (0.80-2.72)
Sugar-sweetened	1.00 (Reference)	1.06 (0.89-1.26)	0.85 (0.73-0.98)	1.05 (0.86-1.29)	0.84 (0.58-1.23)	1.25 (0.59-2.66)	2.72 (0.78-9.51)
Artificial-sweetened	1.00 (Reference)	0.87 (0.64-1.18)	0.95 (0.78-1.15)	0.95 (0.73-1.23)	1.22 (0.83-1.81)	1.66 (0.64-4.25)	0.64 (0.08-5.22)
Incident anxiety (n = 101, 173)							
No milk	1.00 (Reference)	0.93 (0.80-1.09)	0.88 (0.77-1.01)	0.93 (0.78-1.12)	1.08 (0.80-1.47)	0.55 (0.22-1.35)	1.22 (0.37-3.98)
Milk	1.00 (Reference)	0.96 (0.85-1.09)	0.91 (0.82-1.00)	0.86 (0.77-0.97)	1.09 (0.91-1.30)	0.65 (0.39-1.08)	1.63 (0.87-3.06)
Unsweetened	1.00 (Reference)	0.86 (0.76-0.97)	0.83 (0.75-0.91)	0.82 (0.72-0.92)	1.08 (0.91-1.30)	0.52 (0.30-0.90)	1.17 (0.57-2.41)
Sugar-sweetened	1.00 (Reference)	1.20 (1.02-1.42)	1.04 (0.90-1.20)	1.13 (0.92-1.39)	0.86 (0.57-1.28)	0.92 (0.37-2.28)	2.49 (0.71-8.81)
Artificial-sweetened	1.00 (Reference)	0.99 (0.74-1.33)	1.11 (0.92-1.35)	0.92 (0.70-1.22)	1.37 (0.92-2.04)	1.00 (0.31-3.21)	2.89 (0.81-10.27)

* Estimates are odds ratio (95% CIs) from binary logistic regression models adjusted for age; sex; ethnicity (white or non-white); education (university or other); Townsend deprivation index; BMI (kg/m²); smoke status (never, former or current); alcohol intake (grams per day); tea intake (cups per day); diet score; sleep duration (hours per day); hypertension (yes or no), diabetes (yes or no) and the distance of time between the baseline assessment and the mental health follow-up questionnaire.

(21.2% vs. 20.3%) at baseline. That is, the high-risk behaviors and physical conditions of individuals were associated with a higher risk of incident depression and anxiety, yielding a J-shaped association. Therefore, confounding factors seems to be a plausible explanation for these associations.

4.1. Strength and limitations

The current study has several strengths, including the prospective design, the large sample size, and the wide range kinds of coffee consumption data. Moreover, we adjusted for numerous potential confounders, particularly for the dietary score constructed.

Several limitations still need to be considered. First, information on coffee consumption was self-reported by participants at baseline, which may lead to biases. Therefore, we cannot entirely exclude the possibility of misreporting. To mitigate the constraint of self-reported data, future research could employ more accurate measurement methods to enhance the reliability of the data on coffee consumption. Besides, it does not seem rigorous to define participants as one type of coffee consumer since participants may be consumers of multiple coffee types over time. A high degree of reproducibility for assessing nutrient intake over time has been demonstrated in a previous study (Yuan et al., 2017), suggesting that our assumption of coffee subtypes was harmless. Second, although the PHQ-9 and the GAD-7 questionnaires have been shown to be valid for screening mental disorders, the diagnosis of depression and anxiety still requires clinician assessment (Kroenke, 2021). The results of the secondary analysis with depression and anxiety ascertained by hospital inpatient records and primary care data confirmed our main findings, which reduced the bias in the identification of mental disorders by the PHQ-9 and the GAD-7. Third, similar to any observational study,

although a series of potential confounders have been adjusted for, the reverse causality or unmeasured confounders could not be completely excluded. Fourth, participants enrolled in the UK Biobank tilt to be white British, live in less socioeconomically deprived areas, and have healthier lifestyles than the general population (Fry et al., 2017). Hence, it should be cautious to generalize these results to other populations.

5. Conclusion

In this large prospective cohort study, we found that moderate daily coffee consumption, especially at 2-3 cups of ground coffee, milk-coffee, or unsweetened coffee, was associated with a lower risk of incident depression and anxiety. Our findings support the recommendation that moderate coffee consumption could be part of a healthy lifestyle to prevent and manage depression and anxiety in the general population.

Disclosures

None of the funders had any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; and the preparation, review, or approval of the manuscript.

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CRediT authorship contribution statement

Jiahao Min: Conceptualization, Methodology, Software, Formal analysis, Investigation, Visualization, Writing – original draft. **Zhi Cao:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Software, Validation, Visualization, Writing – original draft. **Linlin Cui:** Conceptualization, Writing – review & editing. **Feimeng Li:** Writing – review & editing. **Zuolin Lu:** Writing – review & editing. **Yabing Hou:** Writing – review & editing. **Hongxi Yang:** Writing – review & editing. **Xiaohe Wang:** Conceptualization, Project administration, Resources, Supervision, Writing – review & editing. **Chenjie Xu:** Project administration, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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