Complex Psychiatry

Research Article

Complex Psychiatry 2025;11:37–49
DOI: 10.1159/000545393

Received: November 1, 2024
Accepted: March 13, 2025
Published online: March 24, 2025

Caffeine Consumption, Psychological Distress, and Insomnia in a Cohort of Individuals with Depression

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Keywords
Caffeine · Psychiatric disorders · Insomnia · *CYP1A1* · *CYP1A2* · *ADORA2A* · *AHR*

Abstract

Introduction: Caffeine is a widely consumed psychoactive compound that can cause anxiety and sleep difficulties, in part due to genetic variation. We investigated the association between caffeine consumption, psychological distress, and sleep difficulties in a genetically informative cohort of individuals with a history of depression. ***Methods:*** Survey data and genetic information were sourced from the Australian Genetics of Depression Study (AGDS [n = 20,689, $\%_{female}$ = 75%, mean age = 43 ± 15 years]). Associations between caffeine consumption and symptoms of distress and sleep disturbance, as well as 9 genetic variants associated with caffeine consumption behaviour, were assessed using linear regression. ***Results:*** The highest consumers of caffeine reported higher psychological distress measured by the Kessler 10 scale (β = 1.21, SE = 0.25, $p = 1.4 \times 10^{-6}$) compared to the lowest consumers. Consumption was associated with 2 genetic variants with effect sizes ~0.35 additional caffeinated drinks/day between opposite homozygotes ($p < 0.005$). A deletion near *MMS22L/POU3F2* was associated with 10% increased odds of reporting caffeine susceptibility (OR = 1.1 per deletion [95% CI: 1.04–1.17], p = 0.002). ***Conclusions:*** Higher rates of caffeine consumption were associated with higher levels of psychological distress, but not insomnia, in individuals with a history of depression. While the direction of causality is unclear, caffeine consumption may be a modifiable factor to reduce distress in

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individuals susceptible to mental health problems. Some of the previous findings of common variant associations with caffeine consumption and susceptibility were replicated.

Plain Language Summary

Caffeine is the world's most popular and available mind-altering drug, commonly found in coffee. Typical caffeine use is generally safe, but caffeine can also cause anxiety and insomnia when consumed in large amounts, or by especially susceptible people. Several genetic variants have been found to change how people react to caffeine. Our study sought to investigate the nature of these relationships. We used data from the Australian Genetics of Depression Study (AGDS), where ~12,000 people with a history of depression were surveyed about their mental health and behaviours like caffeine consumption. A total of ~9,000 AGDS participants provided information on genetic variants of interest. We used linear modelling to see how caffeine consumption correlated with psychological distress, sleep quality, substance use, and genetic variants. People who drank high amounts of caffeine each day were more distressed but did not differ in their sleep. Those who said that caffeine interferes with their sleep drank less caffeine. Participants carrying particular genetic variants tended to have more caffeinated drinks each day, or be more susceptible to caffeine. Our survey data only contain one slice of time, so we cannot say whether caffeine causes distress or whether people use caffeine to alleviate symptoms caused by unrelated distress. Our data do not measure precise dosage, or account for tolerance built over time. These results indicate that changing one's caffeine consumption could help reduce distress in people experiencing depression or similar illnesses.

Introduction

Caffeine, Distress, and Insomnia

Caffeine is the world's most popular psychoactive substance, commonly used as a stimulant to combat fatigue and increase alertness [1, 2]. Caffeine is widely available and lightly regulated and is found in coffee, tea, soft drinks, energy drinks, and other foods (e.g., chocolate) and beverages [3]. Rates of caffeine consumption vary, but moderate levels (e.g., 232 mg or ~1–2 cups of coffee per day in Australian adults) appear safe [3]. In adults, ~75% of caffeine consumption typically comes from coffee [1]. Younger people consume less caffeine and acquire most of their intake from soft drinks and energy drinks [1, 4].

Caffeine users can tailor the magnitude, frequency, and time of their intake based on their perception of its benefits [5]. Individuals may also adjust their caffeine intake based on their sensitivity to caffeine-based sleep disruption or their current sleep needs [5, 6]. Whilst mild consumption of caffeine (e.g., 32 mg) is associated with physical and mental health benefits, higher consumption has been linked to mental distress and insomnia [5, 7–9].

Acute caffeine consumption has been found to increase anxiety in healthy individuals and can cause panic attacks in people with panic disorders [7]. The Diagnosis and Statistical Manual of Mental Disorders-fifth edition (DSM-5) lists caffeine-induced anxiety disorder as a diagnosis [10]. Anxiogenic effects of caffeine have been observed to be sex specific and dosage dependent, with responses to medium doses influenced by genetic variants [11, 12].

Less is known about the relationship between caffeine and depressive disorders. Anxiety and depression are often comorbid: approximately three-quarters of people with an anxiety disorder meet the criteria for major depression, and generalised anxiety disorder and depression have a substantial genetic overlap [13, 14]. However, longitudinal studies have found that typical levels of caffeine consumption are associated with a ~5–15% reduction in the odds of developing depression in non-diagnosed individuals [15–17].

Insomnia, fatigue, and lack of motivation are common symptoms of depression and there is evidence to suggest that individuals with depression may self-medicate with caffeine to combat such experiences [18, 19]. Caffeine consumption is higher in clinical mental health populations compared to the general population, with highest consumption amongst those who have experienced depressive symptoms [18, 20]. A previous study found that young people with depression consumed between 3 and 4 more servings of caffeine per day than controls [19]. While caffeine may alleviate symptoms of poor sleep in the short-term, excess caffeine consumption can lead to worsened sleep in the following days [21, 22], thus potentially increasing the likelihood of depressive symptoms.

Caffeine consumption is influenced by genetic variation, with heritability estimates between 0.3 and 0.6 [23]. A systematic review by Low et al. [6] of 1,851,428 individuals identified several variants linked to caffeine consumption with effect sizes ranging from 3% to 32% (in

Table 1. Caffeine-related genetic variants

rsID	Alleles	Effect	*p* value	Nearest gene(s)	Reference
rs5751876	C/T	Conflicting		*ADORA2A*	[6]
rs762551	A/C	−0.19	<0.0002	*CYP1A2*	[6]
rs2472297	C/T	+0.08	3.6×10^{-65}	*CYP1A1, CYP1A2*	[38]
rs4410790	C/T	−0.06	5.2×10^{-55}	*AGR3, AHR*	[38]
rs114711388*	A/G	−0.10	1.8×10^{-10}	*ADORA2A, UPB1*	[38]
rs34645063	D/I CA/C	−0.02	3.3×10^{-9}	*MMS22L, POU3F2*	[38]
rs7270745*	G/C	−0.02	1.1×10^{-8}	*PCMTD2*	[38]
rs117824460	A/G	−0.06	1.7×10^{-8}	*CTC-490E21.12*	[38]

SNPs marked "*" were unavailable in the AGDS dataset, so LD proxies were found using the Ensemble Genome Browser LD calculator [39]. The original SNP rsIDs are *ADORA2A, UPB1* rs199612805 D/I ($r^2 = 1.0$, D′ = 1.0), and *PCMTD2* rs11474881 D/I ($r^2 = 0.98$, D′ = 1.0). Effect size refers to the reported number of caffeinated coffee items consumed each day.

number of cups per day per allele). Two single-nucleotide polymorphisms (SNPs) that have been consistently associated with caffeine response are rs5751876 in the adenosine A2A receptor gene (*ADORA2A*; 1976 C/T) and rs762551 upstream of the cytochrome P450 1A2 gene (*CYP1A2*; −163 C/A) [6, 24].

Genetic Variants Related to Caffeine Consumption/ Response

Interventional and observational data have uncovered genetic variants involved in caffeine consumption and response. Adenosine receptors, coded for by the ADORA gene family, are the main target of caffeine's action in the nervous system, where it acts as a sleep inhibitor [23–26]. *ADORA2A* rs5751876 has been experimentally implicated in caffeine consumption [27], as well as caffeine-induced anxiety [12, 24, 28, 29] and insomnia [30–33].

Cytochrome p450 (CYP) genes encode enzymes responsible for 95% of caffeine metabolism [34]. *CYP1A2* rs762551 has been associated with caffeine metabolism and coffee consumption [31, 35–37].

A recent genome-wide association study including 130,153 23andMe participants by Thorpe et al. [38] identified numerous loci associated with coffee intake. Many of these variants replicate previous GWAS results for caffeine consumption or are located nearby genes independently linked to caffeine consumption or response (e.g., *ADORA2A*, *CYP1A1* and *CYP1A2*, and *AHR*) [6, 24, 38]. The list of SNPs used in this study are presented in Table 1.

Given caffeine's anxiogenic and sleep-inhibiting properties, high caffeine consumption may lead to psychological distress, particularly in at-risk individuals with a history of mental health problems. Furthermore, these effects may be influenced by genetic variants involved in caffeine consumption or response. Here, we sought to investigate the association between recent (past-month) psychological distress and typical caffeine consumption in a genetically informative cohort of individuals diagnosed with or treated for depression at some point in their lifetime. This provided us the opportunity to also investigate the relationship between caffeine-related genetic variants and caffeine consumption and susceptibility.

Methods

The Australian Genetics of Depression Study

The Australian Genetics of Depression Study (AGDS, 2020 freeze) was established to explore genetic and environmental risk factors for depression. The AGDS is a cohort of individuals diagnosed with depression aged 18–89 (n = 20,689, 74% female; mean age = 43 ± 15 years) [40]. Participants were assessed via questionnaires on their history of mental health problems and optional modules assessed their caffeine intake, sleep, and recent psychological distress relating to anxiety and depression [41]. Overall, 15,807 participants (76%) provided a DNA sample.

In addition to the exclusion criteria of the AGDS, participants were removed based on incomplete responses to the satellite modules regarding caffeine consumption, distress, and sleep [42]. A total of 11,030 participants (n [female] = 8,217; 74.5%) remained after exclusion, of whom 8,711 (n [female] = 6,476; 74.3%) also

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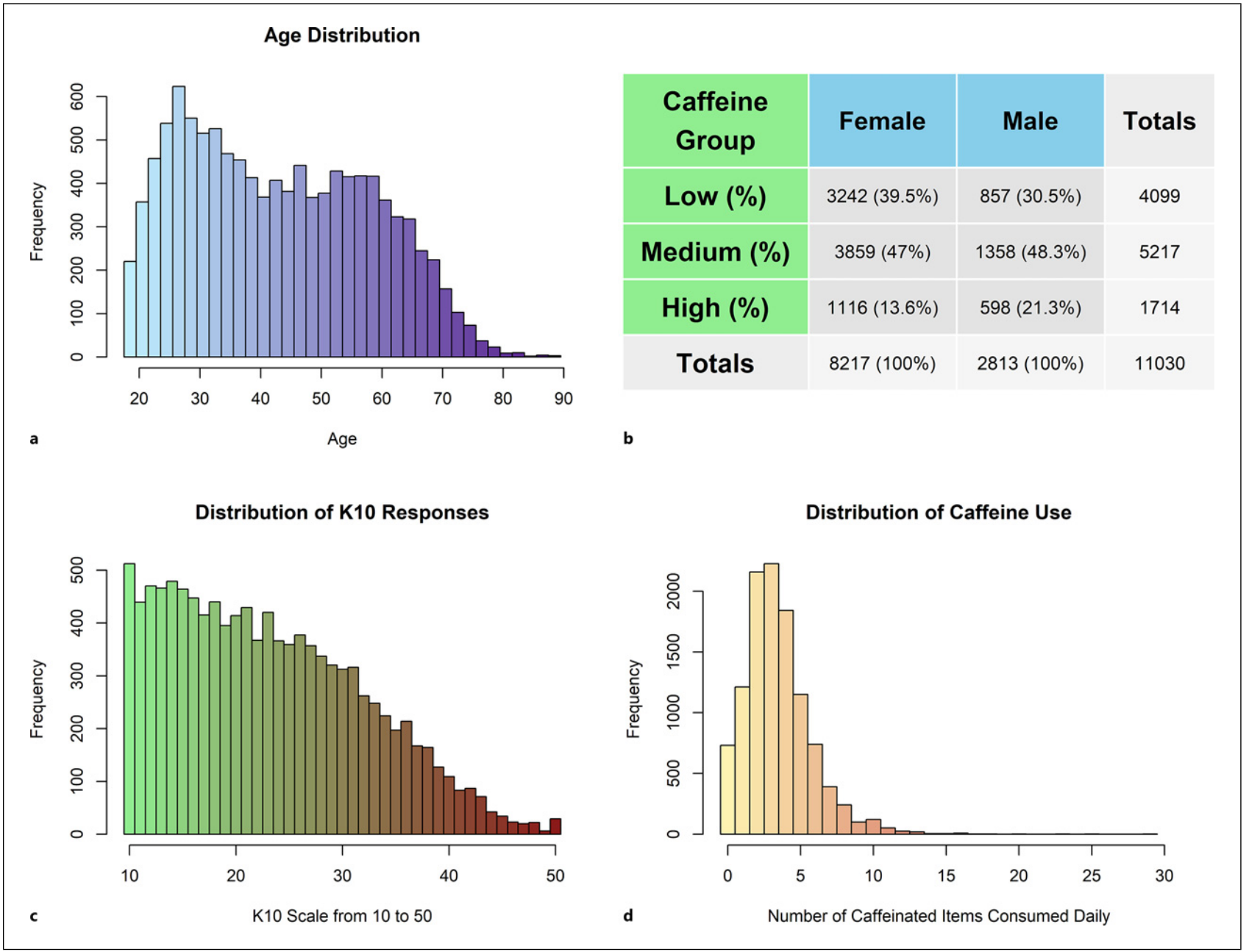

Caffeine Group	Female	Male	Totals
Low (%)	3242 (39.5%)	857 (30.5%)	4099
Medium (%)	3859 (47%)	1358 (48.3%)	5217
High (%)	1116 (13.6%)	598 (21.3%)	1714
Totals	8217 (100%)	2813 (100%)	11030

Fig. 1. Cohort variable distributions. **a** Frequency histogram of participant ages. **b** Cross-tabulation of caffeine consumption group by sex. **c** Frequency histogram of participant K10 scores. **d** Frequency distribution of participants' daily caffeine use (as a count of drinks).

Table 2. Cohort summary statistics (numeric variables)

	Mean	SD	Median	IQR	Range
Age	42.9	15.2	42	25	18–89
K10 score	23	9.1	22	14	10–50
Summed caffeine consumption, drinks/day	3.5	2.3	3	3	0–29
BMI	28.4	6.8	27.1	8.6	14–55
Binge drinking events, *n*	6.7	16.3	0	5	0–92

provided genetic data. Cohort information regarding key variables and covariates is displayed in Figure 1 and Tables 2, 3.

Measures

Recent (past-month) levels of psychological distress were assessed using the 10-item Kessler Psychological Distress Scale (K10) [41, 43]. Sleep satisfaction was measured using question 4 of the Insomnia Severity Index (ISI), which asks respondents to rate their satisfaction with their current sleep pattern on a scale from 1 (very satisfied) to 5 (very dissatisfied). Caffeine consumption was assessed by asking participants how many cups of caffeinated coffee, tea, soft drinks/soda, and energy drinks they consume daily. The total number of cups of caffeinated drinks consumed per day was calculated. Caffeine consumption was grouped into low (0–2 drinks per day), medium (2–5 drinks per day), and high consumption (6 or more drinks per day) [6, 44]. Susceptibility to caffeine-related sleep disturbance was assessed by asking if drinking coffee in the evening would prevent participants from getting to sleep (yes/no). This was used as a proxy measure of general caffeine susceptibility.

Participants reported their weight in kilograms and height in centimetres, which was used to calculate BMI using weight (kg)/height $(m)^2$. Various measures of substance use were recorded, including the number of days within the past 3 months where participants consumed 5 or more standard alcoholic drinks. Additionally, participants reported the frequency of use of nicotine (tobacco products, e-cigarettes), stimulants (cocaine, amphetamines, ketamine, and others), sedatives (opioids, sleeping pills, Valium, Rohypnol, and others), cannabis, and painkillers (prescription or over the counter). For each substance grouping, "use" was defined as (daily or weekly) use of one or more of the individual substances, referred to as "frequent use" in the results. The rate of incomplete responses is shown in Table 3.

Participants who provided DNA were genotyped using the Illumina Global Screening Array v2. Further details on genotyping, quality control, and imputation are provided elsewhere [45]. Genotypes for SNPs that have previously been associated with coffee consumption and with caffeine-related sleep disturbance were extracted using PLINK [46]. Two SNPs identified by Thorpe et al. [38], *ADORA2A/UPB1* rs199612805 and *PMCTD2* rs11474881, were not available in the AGDS dataset, so proxy SNPs in high linkage disequilibrium were identified using Ensembl, then similarly extracted (LD ≥0.98, $D' = 1.0$) (Table 1) [39].

Statistical Analysis

Associations between variables were evaluated using linear regression in R version 4.4.0 [47]. Raw counts of daily consumption of each type of caffeinated beverage were summed, then binned, to create numeric and grouped measures of caffeine consumption used in analyses. These measures were used a proxy for caffeine consumption.

Age, sex, BMI, and substance use variables were included as covariates in all models. Caffeine consumption was evaluated both as a summed continuous variable and as a grouped categorical variable in separate analyses.

First, we investigated whether psychological distress (K10 score) and sleep satisfaction were associated with caffeine consumption. Then, we assessed the association between caffeine consumption, caffeine susceptibility, and genetic variants.

Bonferroni correction was used to adjust for multiple testing [48]. In total, there were 9 predictors of interest: caffeine consumption and the 8 genetic variants. The corrected significance threshold is 0.05/9 = 0.0055.

Results

Descriptive statistics for the variables of interest and covariates are shown in Figure 1 and Tables 2 and 3.

Descriptive Statistics

Patterns of caffeine consumption by sex, age, and psychological distress are shown in online supplementary Figures 1–3 (for all online suppl. material, see https://doi.org/10.1159/000545393).

Caffeine Consumption, Psychological Distress (K10 Score), and Sleep Satisfaction

Complete results for the regressions for Caffeine consumption, psychological distress, and sleep satisfaction are shown in Table 4.

Psychological Distress (K10 Score) and Caffeine Consumption

Psychological distress had a positive association with participants' caffeine consumption at high levels of consumption. Participants in the "medium" caffeine group did not differ in their K10 score compared to the "low" group ($p = 0.1$), while participants in the "high" group had a mean K10 score ~1.2 points higher ($\beta = 1.21$, SE = 0.25, $p = 1.4 \times 10^{-6}$) than the low group. When the total number of caffeinated beverages was evaluated as the predictor variable, drinking 1 additional caffeinated item each day was associated with a 0.2-point higher K10 score ($\beta = 0.2$, SE = 0.036, $p = 5.2 \times 10^{-8}$).

Sleep Satisfaction

Participants with high consumption reported sleep satisfaction 0.07 points lower on the 1–5 scale compared to those with low consumption (SE = 0.035, $p = 0.039$). An additional caffeinated drink per day was associated with slightly worse sleep satisfaction ($\beta = -0.01$ points per drink, SE = 0.0052, $p = 0.02$). After Bonferroni correction, no predictors of interest were associated with sleep satisfaction.

Caffeine Consumption, Sleep Satisfaction, Caffeine Susceptibility, and Caffeine-Related Genetic Variants

Complete results for models including genetic variants are shown in Table 5.

Caffeine Consumption

AGR3/AHR rs4410790 CC individuals consumed 0.3 more caffeinated drinks each day than TT individuals ($\beta = 0.15$/allele, SE = 0.034, $p = 9.6 \times 10^{-6}$). *CYP1A1/CYP1A2* rs2472297 CC individuals consumed ~0.4 fewer caffeinated drinks compared to TT individuals ($\beta = -0.19$/allele, SE = 0.04, $p = 1.3 \times 10^{-6}$).

Two SNPs near the ADORA2A gene were nominally significantly associated with caffeine consumption. *ADORA2A* rs5751876 CC participants consumed 0.14 additional caffeinated drinks per day compared to TT individuals; the association had a large standard error ($\beta = 0.07$, SE = 0.034, $p = 0.046$). *ADORA2A/UPB1* rs114711388 AA individuals consumed ~0.6 additional caffeinated drinks than GG individuals ($\beta = 0.31$/allele, SE = 0.15, $p = 0.038$). rs114711388 is an LD proxy for rs199612805. These results did not survive Bonferroni correction for multiple testing.

Other genetic variants were not associated with either measure of caffeine consumption.

Table 3. Cohort summary statistics (categorical variables)

Category	*n*	%
Sex		
Female	8,217	74.5
Male	2,813	25.5
Caffeine consumption group		
Low (0–2)	4,099	37.2
Medium (3–5)	5,217	47.3
High (6+)	1,714	15.5
Sleep satisfaction		
Very dissatisfied	2,006	18.2
Dissatisfied	3,390	30.7
Moderately satisfied	3,444	31.2
Satisfied	1,818	16.5
Very satisfied	372	3.4
Caffeine susceptibility		
No	5,100	46.2
Yes	5,930	53.8
Nicotine use		
No	5,290	48
Yes	1,720	15.6
Missing	4,020	36.4
Stimulant use		
No	4,583	41.6
Yes	203	1.8
Missing	6,244	56.6
Sedative use		
No	3,943	35.7
Yes	499	4.5
Missing	6,588	59.7
Cannabis use		
No	5,662	51.3
Yes	473	4.3
Missing	4,895	44.4
Painkiller use		
No	5,088	46.1
Yes	1,014	9.2
Missing	4,928	44.7

Caffeine consumption and binge drinking were reported across the last 3 months. BMI was calculated using weight (kg)/height $(cm)^2$.

Table 4. Non-genetic model results

Dependent variable	Predictor	Estimate (β)	SE	*p* value
K10 score (summed caffeine consumption)	Number of caffeinated drinks/day	0.2	0.036	5.2×10^{-8}
	Age	−0.17	0.0058	$<1.0 \times 10^{-10}$
	Sex (male)	0.36	0.19	0.057
	BMI (kg/m^2)	0.17	0.012	$<1.0 \times 10^{-10}$
	Alcohol bingeing (count of recent events)	0.02	0.0051	3.5×10^{-4}
	Nicotine use	2.5	0.25	$<1.0 \times 10^{-10}$
	Stimulant use	2.44	0.61	6.5×10^{-5}
	Sedative use	4.64	0.41	$<1.0 \times 10^{-10}$
	Cannabis use	1.39	0.42	8.8×10^{-4}
	Painkiller use	1.91	0.3	1.6×10^{-10}
K10 score (grouped caffeine consumption)	Medium caffeine consumption versus low	−0.3	0.18	0.1
	High caffeine consumption versus low	1.21	0.25	1.7×10^{-6}
	Age	−0.17	0.0058	$<1.0 \times 10^{-10}$
	Sex (male)	0.36	0.19	0.058
	BMI (kg/m^2)	0.17	0.012	$<1.0 \times 10^{-10}$
	Alcohol bingeing (count of recent events)	0.02	0.0051	3.3×10^{-4}
	Nicotine use	2.54	0.25	$<1.0 \times 10^{-10}$
	Stimulant use	2.44	0.61	6.6×10^{-5}
	Sedative use	4.63	0.41	$<1.0 \times 10^{-10}$
	Cannabis use	1.38	0.42	9.6×10^{-4}
	Painkiller use	1.91	0.3	1.5×10^{-10}
Sleep satisfaction (5 levels, least to most satisfied) (summed caffeine consumption)	Number of caffeinated drinks/day	−0.01	0.0052	0.022
	Age	0.01	0.00081	$<1.0 \times 10^{-10}$
	Sex (male)	0.03	0.027	0.2
	BMI (kg/m^2)	−0.02	0.0017	$<1.0 \times 10^{-10}$
	Number of alcohol bingeing events	0	0.00071	0.020
	Nicotine use	−0.16	0.036	$<1.0 \times 10^{-10}$
	Stimulant use	−0.16	0.087	0.060
	Sedative use	−0.38	0.057	$<1.0 \times 10^{-10}$
	Cannabis use	0.14	0.06	0.017
	Painkiller use	−0.21	0.041	4.8×10^{-7}

K10 scores range from 10 to 50. Higher scores indicate increased psychological distress. Substance use indicates daily or weekly use compared to less-frequent use. Significance threshold adjusted for multiple comparisons across 9 variables of interest using Bonferroni correction: $p < 0.0055$.

Table 5. Genetic model results

Dependent variable	Predictor	Estimate	SE	Low CI	High CI	*p* value
Linear models: estimate = beta						
Summed caffeine consumption [17] (drinks per day)	rs5751876 C	0.07	0.034			0.046
	rs114711388* A	0.31	0.15			0.038
	rs4410790 C	0.15	0.034			9.6×10^{-6}
	rs117824460 A	0.11	0.1			0.3
	rs2472297 C	−0.19	0.04			1.3×10^{-6}
	rs762551 A	0.02	0.039			0.7
	rs34645063 C	0.03	0.032			0.4
	rs7270745* C	−0.02	0.033			0.6
	Age	0.03	0.0016			$<1.0 \times 10^{-10}$
	Sex (male)	0.35	0.055			$<1.0 \times 10^{-10}$
	BMI (kg/m^2)	0.02	0.0034			9.3×10^{-10}
	Number of alcohol bingeing events	−0.01	0.0015			4.0×10^{-4}
	Nicotine use	1.02	0.073			$<1.0 \times 10^{-10}$
	Stimulant use	0.26	0.18			0.2
	Sedative use	−0.18	0.12			0.1
	Cannabis use	0.19	0.12			0.1
	Painkiller use	0.14	0.085			0.1
Sleep satisfaction (5 levels, least to most satisfied) (summed caffeine consumption)	Number of caffeinated drinks/day	−0.01	0.0052			0.022
	Age	0.01	0.00081			$<1.0 \times 10^{-10}$
	Sex (male)	0.03	0.027			0.2
	BMI (kg/m^2)	−0.02	0.0017			$<1.0 \times 10^{-10}$
	Number of alcohol bingeing events	0	0.00071			0.020
	Nicotine use	−0.16	0.036			$<1.0 \times 10^{-10}$
	Stimulant use	−0.16	0.087			0.060
	Sedative use	−0.38	0.057			$<1.0 \times 10^{-10}$
	Cannabis use	0.14	0.06			0.017
	Painkiller use	−0.21	0.041			4.8×10^{-7}
Logistic model: estimate = odds ratio						
Reported caffeine susceptibility (no/yes) (summed caffeine consumption)	rs5751876 C	1.1	0.033	0.995	1.13	0.072
	rs114711388* A	1.1	0.14	0.813	1.43	0.6
	rs4410790 C	0.99	0.033	0.931	1.06	0.8
	rs117824460 A	1.2	0.1	0.947	1.4	0.2
	rs2472297 C	1	0.039	0.924	1.07	0.9
	rs762551 A	1	0.037	0.939	1.09	0.8
	rs34645063 C	1.1	0.031	1.04	1.17	0.002
	rs7270745*C	1	0.032	0.977	1.11	0.2
	Number of caffeinated drinks/day	0.84	0.011	0.821	0.857	$<1.0 \times 10^{-10}$
	Age	1.01	0.0016	1.009	1.016	$<1.0 \times 10^{-10}$

Table 5 (continued)

Dependent variable	Predictor	Estimate	SE	Low CI	High CI	*p* value
	Sex (male)	0.79	0.053	0.711	0.875	6.8×10^{-6}
	BMI (kg/m^2)	0.97	0.0033	0.966	0.979	$<1.0 \times 10^{-10}$
	Number of alcohol bingeing events	1	0.0014	0.997	1	0.9
	Nicotine use	0.7	0.071	0.607	0.803	4.4×10^{-7}
	Stimulant use	0.56	0.18	0.398	0.797	0.001
	Sedative use	1.2	0.11	0.949	1.49	0.1
	Cannabis use	1	0.12	0.815	1.31	0.8
	Painkiller use	0.93	0.082	0.793	1.09	0.4

SNPs marked "*" were unavailable in the AGDS dataset, so LD proxies were found using the Ensemble Genome Browser LD calculator. rs114711388 is a proxy for *ADORA2A, UPB1* rs199612805 ($r^2 = 1.0$, $D' = 1.0$). rs7270745 is a proxy for *PCMTD2* rs11474881 ($r^2 = 0.98$, $D' = 1.0$). Significance threshold adjusted for multiple comparisons across 9 variables of interest using Bonferroni correction: $p < 0.0055$.

Caffeine Susceptibility

Participants with medium caffeine consumption were ~40% less likely to report caffeine susceptibility compared to those with low consumption (OR = 0.61 [95% CI: 0.56–0.68], $p < 1.0 \times 10^{-10}$). Those with high caffeine consumption were ~65% less likely to report susceptibility (OR = 0.34 [95% CI: 0.30–0.40], $p < 1.0 \times 10^{-10}$) than those with low consumption. Each additional caffeinated drink/day was associated with 16% lower odds of reporting caffeine susceptibility (OR = 0.84 [95% CI: 0.82–0.86], $p < 1.0 \times 10^{-10}$).

Participants carrying two copies of the deletion at rs34645063 CC (double deletion) near the MMS22L/*POU3F2* genes were 20% more likely to report caffeine susceptibility than those without (OR = 1.1 per copy of the deletion [95% CI: 1.04–1.17], $p = 0.002$).

Discussion

We investigated the relationship between caffeine and recent psychological distress in a cohort of individuals with lived experience of depression. Higher caffeine consumption was associated with higher psychological distress, and being less likely to report caffeine sensitivity, but not poorer sleep, after adjusting for confounders such as substance use. We also explored the effects of previously identified genetic variants and replicated the association with two genetic variants for caffeine consumption. Moreover, participants with a deletion near *MMS22L* and *POU3F2* had a higher likelihood of reporting caffeine susceptibility.

The effect size of the association between distress and caffeine consumption when comparing high consumers to low consumers is small, corresponding to approximately one seventh of a standard deviation for K10 score (β = ~1.2 points, SD = 9.1). Medium consumers did not have significantly different distress than low consumers, in line with existing knowledge that caffeine's anxiogenic properties are dose dependent [5, 7]. These effects were estimated after accounting for relevant confounders, including substance use, age, sex, and BMI.

The benefits and harms of caffeine to a consumer depends on their physiological susceptibility and their level of consumption, which are related. Their level of consumption is influenced by their perception of caffeine's effect on their health. We found no significant association between caffeine use and lower sleep satisfaction. Additionally, we found that participants who reported a susceptibility to caffeine-related insomnia were ~40% less likely to consume 3–5 caffeinated drinks per day versus 0–2 ($p < 1.0 \times 10^{-10}$), and ~70% less likely to consume 6+ drinks per day compared to 0–2 ($p < 1.0 \times 10^{-10}$) (Table 5). The negative correlation between consumption and sensitivity supports the idea that caffeine's effect on insomnia and psychological distress could be limited by negative feedback, particularly in caffeine-susceptible individuals.

Despite people's ability to alter their caffeine intake in response to interrupted sleep, caffeine is still associated with psychological distress. This could be explained due to differences in perception of caffeine's health effects – it

may be easier for an individual to detect caffeine-related insomnia than a general anxiogenic effect of caffeine. Another non-exclusive explanation is that caffeine is used in response to stress to alleviate secondary symptoms such as fatigue. Education regarding a healthy relationship with caffeine may be valuable to public health, particularly considering the widespread use of caffeine and the high prevalence of mental health problems.

Longitudinal studies of previously non-depressed individuals have described a protective effect of caffeine against developing depression [16, 17]. Our data cannot directly address long-term effects or causation, but it produces some implications. In our cohort of depressed individuals, caffeine use was associated with poorer mental health, contrasting with longitudinal findings. This could indicate that individuals experiencing psychological distress may be more susceptible to caffeine's negative effects, or more likely to use caffeine to self-medicate the symptoms of distress.

rs2472297 C near *CYP1A1/CYP1A2* was associated with lower caffeine consumption compared to the T allele ($\beta = -0.19$ drinks/day, SE = 0.04, $p = 1.3 \times 10^{-6}$), corroborating findings that the T allele is associated with consuming +0.2 caffeinated drinks per day [49]. This SNP is related to a promoter for the two CYP genes involved in the rate of caffeine metabolism [6]. People who metabolise caffeine more quickly may seek higher consumption to receive the same beneficial effects, explaining the association [6]. *CYP1A2* rs762551 A alleles were not associated with higher caffeine consumption ($p = 0.7$) (Table 5), failing to replicate previous findings in other populations [35]. However, our genetic analysis fit all SNPs in the same model. In univariate analysis without including rs2472297 near *CYP1A1/CYP1A2*, *CYP1A2* rs762551 A was associated with caffeine consumption ($\beta = 0.019$, $p = 0.02$) replicating previous effects [24]. In our cohort, rs2472297 C had a far more significant effect ($\beta = -0.19$, $p = 1.3 \times 10^{-6}$), which implies it may be more closely tagging the causal variant at this locus.

rs4410790 C near *AGR3/AHR* was associated with participants consuming 0.15 more caffeinated drinks each day than the T allele (SE = 0.034, $p = 9.6 \times 10^{-6}$), supporting similar findings in the GWAS of 23andMe data by Thorpe et al. ($\beta = +0.06$ coffee servings/day, $p < 1.0 \times 10^{-50}$) [38].

rs34645063 CA->C deletions near *MMS22L/POU3F2* were associated with a 10% increased likelihood to report caffeine susceptibility (OR = 1.1 per deletion [95% CI: 1.04–1.17], $p = 0.002$). Thorpe et al.'s [38] GWAS found that this deletion was associated with lower caffeine consumption ($\beta = -0.02$ coffee servings/day, $p = 3.3 \times 10^{-9}$) [38]. This is consistent with our finding that increased caffeine consumption was negatively associated with susceptibility. This deletion is proximal to *MMS22L* and *POU3F2*, but further work is required to determine the mechanism of action [6].

ADORA2A rs5751876 C alleles had a nominally significant association with increased caffeine consumption ($\beta = 0.07$/allele, SE = 0.034, $p = 0.046$) and an increased likelihood of reported caffeine susceptibility (OR: 1.1 per allele [95% CI: 0.995–1.13], $p = 0.076$) (Table 5). These associations did not survive Bonferroni correction. Literature has reported C or T alleles at the SNP having conflicting associations with consumption, attributed to differences in allele frequencies in study populations [6, 27, 50]. The nominal association with susceptibility is consistent with previous findings that *ADORA2A* rs5751876 C alleles are associated with caffeine's anxiogenic and wake-promoting effects [27].

ADORA2A/UPB1 rs114711388*, *PCMTD2* rs7270745*, and *CTC-490E21.12* rs117824460 were not associated with caffeine consumption after correcting for multiple tests ($p > 0.005$), failing to replace results from Thorpe et al. [6]. *These are LD proxies, as described in Table 1.

Findings of *CYP1A2* and *AHR* involvement in caffeine metabolism were found to be the most consistently replicated in a meta-analysis by Low et al. [6], with involvement found in 15 and 11 studies, respectively. SNPs near these genes had an association with caffeine consumption in our cohort, which remained significant in our findings after adjusting for confounders and Bonferroni correction. By comparison, *ADORA2A* was the next most commonly replicated gene across only 5 studies [6]. Findings regarding *ADORA2A*/*CYP* genetic variants have not always been replicated: Jessel et al. [51] found that caffeine was associated with lower sleep quality, but *ADORA2A* and *CYP1A2* variants were not associated with sleep quality, duration, or caffeine dose. Previous findings may not have been replicated due to differences in cohort characteristics, imprecise measurement of caffeine, or the relationship between high caffeine consumption and developed tolerance [6, 44].

These results should be interpreted with respect to limitations of the data. The cross-sectional data do not account for an individual's past caffeine consumption or current tolerance. The current size or timing of dosage was not reported, only the recent typical number of drinks per day as a proxy for caffeine consumption. We considered weighting caffeine measures by drink type to address ambiguity in the measurement. There is considerable variation in the caffeine content of a given beverage within and between the categories of tea (20–80 mg), coffee (259–564 mg), energy drinks (17–224 mg), and soft drinks (30–70 mg), and considering that terms such as "coffee"

could include both espresso or filtered coffee [52–57]. We therefore decided to use number of caffeinated drinks.

Our caffeine measure had a strong negative association with reporting that caffeine interferes with sleep, indicating that it is capturing part of the true variation in caffeine consumption. Future studies would benefit from more specific measures of caffeine intake, specifying the size or specific type of the beverage. However, there is a trade-off between detail of measurement and sample size as it would not have been possible to obtain detailed measurements such a large sample.

The strength of the study is the large cohort of participants with lived experience of depression and genetic data. Our dataset is powered to detect very small effects and allows controlling of many confounders, which had large effects. Conversely, analyses of this cohort may be less generalisable to the general population.

In a cohort of depressed individuals, higher levels of caffeine consumption were associated with reporting recent psychological distress. In addition, associations with genetic variants in the *AG3R/AHR CYP1A1/CYP1A2* loci were replicated and caffeine sensitivity was associated with an insertion/deletion at the*MMS22L/POU3F2* locus. These associations highlight potential interactions between an individual's physiological sensitivity to caffeine, their psychological response to caffeine, and their consumption choices. Our analyses support previous associations between consuming caffeine, distress (anxiety) and genetic variation but not associations of caffeine and insomnia. Differences between cohort attributes and measurement accuracy/timescale may explain these differences. Our results suggest that insomnia is not the key mechanism by which caffeine and mental distress interact.

The findings of the study are consistent with the hypothesis that individuals experiencing psychological distress use more caffeine, perhaps to self-medicate. However, the extent to which self-medication is effective or exacerbates psychological distress is not clear.

Caffeine use may be a modifiable risk factor for mental distress, particularly people susceptible to caffeine or anxiety/distress more generally. Given caffeine's popularity, public awareness of its adverse effects is of high importance, especially for individuals predisposed to (or already suffering from) insomnia or mental health disorders.

Acknowledgments

We are indebted to all the participants for giving their time to contribute to this study. We thank all the people who helped in the conception, implementation, beta testing, media campaign, and data cleaning.

Statement of Ethics

The AGDS was approved by the QIMR Berghofer Human and Research Ethics Committee under project number P1218. Written informed consent was provided at each level of participation of the AGDS [40]. This study was approved by the University of Queensland Human Research Ethics Committee under the project number 2023/HE001180.

Conflict of Interest Statement

IBH has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, and AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 3.2% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the AUD 30M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental health services internationally using innovative technologies. Dr. Enda M. Byrne was a member of the journal's Editorial Board at the time of submission.

Funding Sources

E.M.B. received funding from PRE-EMPT National Health and Medical Research Council Centre for Research Excellence and from the University of Queensland Health Research Accelerator Program. J.J.C. is supported by a NHMRC Emerging Leadership grant (2008196). I.B.H. is supported by a NHMRC Leadership (L3) grant (2016346). The AGDS was primarily funded by National Health and Medical Research Council (NHMRC) of Australia grant (1086683). This work was further supported by NHMRC grants (1145645, 1078901, and 1087889).

Author Contributions

Harry McIntosh was responsible for data analysis and writing the paper. Aleah Borgas contributed to data analysis. Dr. Enda Byrne was involved in data access and transfer, drafting the paper, and general supervision including statistical analysis. Dr. Christel Middeldorp, Nisreen Aouira, Brittany L. Mitchell, Jacob J. Crouse PhD, Sarah E. Medland PhD, Ian B. Hickie MD, Naomi R. Wray PhD, Nicholas G. Martin PhD, and Enda M. Byrne PhD were involved in data collection, interpretation of results, and drafting the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy requirements. Interested researchers should contact Professor Nicholas Martin (nick.martin@qimrberghofer.edu.au) for data access.

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