Rassegna

A systematic review of caffeine-related suicides and an analysis of the controversial role of caffeine consumption in suicidal risk

Rassegna sistematica dei suicidi caffeina-correlati e analisi del controverso ruolo della caffeina nel rischio suicidario

SIMONE CAPPELLETTI[1,2,*], DARIA PIACENTINO[3,4], COSTANTINO CIALLELLA[1]
*E-mail: cappellettisimone@hotmail.com

[1]Department of Anatomical, Histological, Forensic Medicine and Orthopedic Sciences, Sapienza University of Rome, Italy
[2]State Police Health Service Department, Ministry of Interior, Rome, Italy
[3]Department of Psychiatry, Central Hospital, Sanitary Agency of South Tyrol, Bolzano-Bozen, Italy
[4]Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, Division of Intramural Clinical and Basic Research and National Institute on Drug Abuse Intramural Research Program, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, Maryland, USA

SUMMARY. Caffeine is the most widely consumed psychoactive compound worldwide. Its mechanisms of action are dose-dependent and when caffeine overdosing occurs, neurologic, cardiovascular and renal systems are mainly affected. Serious toxicities such as seizure and cardiac arrhythmias, seen with caffeine plasma concentrations of 15 mg/L or higher, have caused poisoning or, rarely, death. Caffeine concentrations of 80-100 mg/L are considered lethal. The aim of this systematic review is to summarize data regarding suicides by caffeine administration and analyze the controversial role of caffeine assumption and suicidal risk. We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) indications in the identification and selection of studies and reviewed a series of fatal cases due intentional intoxication by caffeine. A total of 36 cases have been identified. Our results suggests caffeine seems to be negatively correlated with suicide. Even if some observations suggested that the consumption of caffeine may have beneficial effects against depression, and as a consequence against suicide risk, more in-depth studies are required. Data obtained from our study could support both clinicians and forensic pathologists in identifying possible unrecognized cases.

KEY WORDS: caffeine, caffeine intoxication, suicide.

RIASSUNTO. La caffeina è la sostanza psicoattiva più consumata al mondo. Il suo meccanismo di azione è dose-dipendente e, nei casi di overdose, gli apparati neurologico, cardiovascolare e renale sono quelli principalmente coinvolti. Segni di tossicità quali convulsioni e aritmie cardiache si osservano per concentrazioni plasmatiche maggiori o uguali di 15 mg/L, con rischio, talvolta, di provocare il decesso dell'assuntore. Concentrazioni di caffeina di 80-100 mg/L sono considerate letali. Lo scopo di questa rassegna sistematica è di raccogliere i dati riguardanti l'assunzione di caffeina a scopo suicidario e di analizzare il controverso ruolo della caffeina nel rischio suicidario. Abbiamo, quindi, adottato i criteri PRISMA per l'identificazione e la selezione degli studi esistenti e revisionato i casi letali dovuti ad assunzione volontaria di caffeina. È stato identificato un totale di 36 casi. I nostri risultati suggeriscono che il consumo di caffeina non sia correlato a un rischio suicidario. Anche se alcuni lavori suggeriscono che l'assunzione di tale sostanza possa avere qualche effetto positivo su quadri di depressione e di conseguenza sul rischio suicidario, diminuendolo, ulteriori studi sono necessari per giungere a una più completa analisi. I dati ottenuti dal nostro studio possono, infine, supportare i clinici e i patologi forensi nell'identificare casi di intossicazione o decesso da uso di caffeina che altrimenti potrebbero non essere riconosciuti.

PAROLE CHIAVE: caffeina, intossicazione da caffeina, suicidio.

INTRODUCTION

Several cases of caffeine intoxication, mostly due the easy availability of analgesics, Central Nervous System (CNS) stimulant medicine and dietary supplements at shops, health stores and e-markets have been described in literature in last years. Even though, lethal cases from caffeine intoxications and, more in-depth, lethal cases due to voluntary consumption of caffeine with suicidal intent, are quite uncommon. The first paper about lethal caffeine intoxication was published by Alstott et al. in 1973[1], who describe the suicide of a young woman following oral caffeine pills administration.

As reported in previous papers[2], the pharmacological effects of caffeine usually occurs at plasma concentrations of

15 mg/L or higher and include central nervous system and cardiac stimulation.

Life-threatening caffeine overdoses entail the ingestion of caffeine-containing medications, rather than caffeinated foods or beverages[3], and have been associated with blood concentrations in excess of 60-80 mg/l[4].

Common features of caffeine intoxication include anxiety, agitation, restlessness, insomnia, gastrointestinal disturbances, tremors, psychomotor agitation, and, in some cases, death. Symptoms of caffeine intoxication can mimic those of anxiety and other affective disorders. The cardiovascular effects include supraventricular and ventricular tachyarrhythmia. The direct cause of death is often described as ventricular fibrillation.

The aim of this systematic review is to summarize data regarding suicides by caffeine administration and analyze the controversial role of caffeine assumption and suicidal risk; data obtained from our study could support both clinicians and forensic pathologists in identifying possible unrecognized cases.

METHODS

Eligibility criteria

The present systematic review was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) standards[5]. Studies examining caffeine-related suicides using caffeine were included. Study designs comprised case reports, case series, retrospective and prospective studies, letters to the editors, and reviews. The latter were downloaded to search their reference lists similarly to other papers, but yielded no other potentially eligible paper. The search was limited to human studies.

Search criteria and critical appraisal

A systematic literature search and a critical appraisal of the collected studies were conducted. An electronic search of PubMed, ScienceDirect Scopus, and Excerpta Medica Database (EMBASE) from the inception of these databases to the 01st of October 2021 was performed.

Search terms were ("caffeine" OR "coffee") AND ("toxicology" OR "death" OR "decease" OR "fatal intoxication") AND ("suicide") in title, abstract, and keywords. Cases in which death has been related to consume of energy drinks or caffeinated drinks were excluded because they do not represent "pure" caffeine-related deaths as they are the results of a combinations of more substances.

The bibliographies of all located papers were examined and cross-referenced for further relevant literature.

Methodological appraisal of each study was conducted according to the PRISMA standards, including evaluation of bias. Data collection entailed study selection and data extraction. Two researchers (D.P., S.C.) independently examined those papers whose title or abstract appeared to be relevant and selected the ones that analyzed deaths due to caffeine intoxication. Disagreements concerning eligibility between the researchers were resolved by consensus process. No unpublished or gray literature was searched. Data extraction was performed by one investigator (C.C.) and verified by another investigator (D.P.). This study was exempt from institutional review board approval as it did not involve human subjects.

RESULTS

Search results and included studies

An appraisal based on titles and abstracts as well as a hand search of reference lists was carried out. The reference lists of all located articles were reviewed to detect still unidentified literature. Figure 1 illustrate our search strategy.

A total of 21 studies fulfilled the inclusion criteria, producing a pooled data set of 36 individuals. The reviewed studies involved a sample size ranging from 1 (i.e., case reports) to 12 individuals (i.e., a retrospective study), with a mean of 1.89 and a median of 1, indicating skewness towards smaller samples.

Study characteristics

The following data were extracted from the included studies: study source; age and sex of participants in the study; toxicological data (if reported); way of administration. An exhaustive summary of the literature, including extracted data, is shown in Table 1[6-25].

Risk of bias

This systematic review has a number of strengths that include the amount and breadth of the studies, which span the globe, the hand search and scan of reference lists for the identification of all relevant studies, and a flowchart that describe in detail the study selection process. It must be noted that this review includes studies that were published in a time frame of 58 years, thus, despite our efforts to fairly evaluate the existing literature, study results should be interpreted taking into account that the accuracy of the toxicological analyses, where reported, has changed over the years.

CAFFEINE-RELATED SUICIDES

Our study permitted us to identify 38 cases of suicide. Route of administration of caffeine was: oral (pills, powder, liquid) in 25 cases and not reported in the remaining 13 cases.

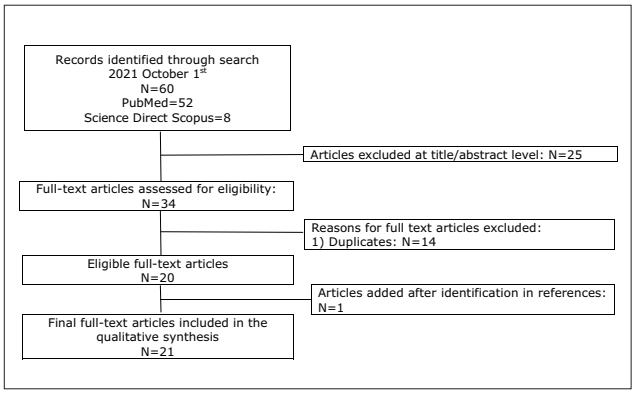

Figure 1.

Table 1. Caffeine-related suicides.

Author[reference]	Caffeine blood level	Age	Route of administration (source)
Alstott et al.[1]	-	27 M	Oral (pills)
Bryant[6]	113.5 mg/L	42 F	Oral (pills)
Chaturvedi et al.[7]	62 mg/L	21 M	Oral (pills)
Garriott et al.[8]	129.9 mg/L	19 F	Oral (pills)
	147 mg/L	21 M	Oral (pills)
	343.9 mg/L	21 M	Oral (pills)
	251 mg/L	21 F	Oral (pills)
Winek et al.[9]	240 mg/L	21 F	Oral (pills)
Hanzlick et al.[10]	264 mg/L	44 F	Oral (pills)
Takayasu et al.[11]	177.0 g/g	20 F	Oral (pills)
Riesselmann et al.[12]	220 mg/L	19 F	Oral (pills)
	190 mg/L	81 F	Not reported
Watson et al.[13]	-	17	Oral (pills)
Holmgren et al.[14]	210 mg/L	21 M	Oral (pills)
	153 mg/L	31 M	Oral (pills)
Rudolph et al.[15]	-	21 F	Oral (pills)
Thelander et al.[16]	105 mg/L	53 M	Not reported
	210 mg/L	25 F	Not reported
	210 mg/L	21 M	Not reported
	153 mg/L	31 M	Not reported
	180 mg/L	18 F	Not reported
	166 mg/L	20 F	Not reported
	140 mg/L	72 F	Not reported
	80 mg/L	24 M	Not reported
	160 mg/L	46 F	Not reported
	190 mg/L	84 M	Not reported
	192 mg/L	79 F	Not reported
	310 mg/L	33 F	Not reported
Jantos et al.[17]	141 mg/L	25 F	Oral (pills)
Poussel et al.[18]	190 mg/L	44 M	Oral (powder)
Bonsignore et al.[19]	170 mg/L	31 M	Oral (pills)
Banerjee et al.[20]	320 mg/L	43 F	Oral (pills)
	220 mg/L	57 M	Oral (pills)
Ishikawa et al.[21]	Blood 154.2 mg/L Bile 852.3 mg/L Stomach 197.5 mg/L	20 F	Oral (pills)
Yamamoto et al.[22]	290 mg/L	18 F	Oral (pills)
Aknouche et al.[23]	401 mg/L	48 M	Oral (pills)
Sidlo et al.[24]	Blood 362 mg/L Urine 187 mg/L	26 M	Oral (powder)
Usui et al.[25]	Blood 391 mg/L	Teenage M	Oral (pills)

Among the cases of deaths due to caffeine intoxications reported in a previous paper[26], use of caffeine for suicidal purposes has been recognized as particularly prevalent among psychiatric population.

Table 2 show the main the main drugs that were detected simultaneously in toxicological investigations carried out in lethal cases. These drugs were divided into three categories: ingredients of over the counter products, psychotropic drugs and drugs of abuse.

Psychiatric patients

Eighteen cases (50%) with a history of a psychiatric disorder have been identified; among the psychiatric disorders, depression is undoubtedly the most frequent (Table 3). The age ranged from 21 to 84 years-old. Many of these individuals have a history of past suicide attempts.

Table 2. Other drugs than caffeine detected simultaneously in toxicological investigations in decreasing order of appearance.

Psychotropic drugs*	Drugs contained in over-the-counter *	Other drugs*
Diazepam	Acetaminophen	Ethanol
Phenobarbital	Ephedrine	Phenyl-propanolamine
Venlafaxine	Acetylsalicylic acid	paracetamol
Citalopram	Theophylline	
Nortriptyline		
Clonazepam		
Levomepromazine		
Mirtazapine		
Olanzapine		
Zopiclone		
Flunitrazepam		
Aripripazole		
Nordiazepam		
Biperiden		

*More than one drug may have been identified for each case.

Table 3. Psychiatric disorders diagnosed before death.

Disease*	Number
Depression	17
Alcohol dependence	6
Sleep disorders	4
Drug dependence	2
Not specified	2
Schizophrenia	1

*More than one disease may have been identified for each case.

DISCUSSION

The correlation between caffeine and suicidal risk has been examined in some important studies[27-31].

These papers shown that caffeine could have an antidepressant effect. The hypothesis, supported by epidemiological studies, that risk of depression[32,33] and suicide[29,34] is lower in a dose-dependent manner with increasing consumption of caffeinated coffee was supported by many authors. Only few authors described a different statistical distribution, with a positive association, between coffee and suicide risk where the highest suicide rate was in individuals consuming 7 or more cups of coffee daily[34-36].

In particular, a recent paper by Kim et al.[36] tried to analyze the relationship between caffeinated-drink consumption, depression and suicide ideation on 53,312 young patients (12-18 years-old) suggesting that caffeine overdose can increase the rate of suicide by affecting the individual's perception of stress through modulation of cortisol response.

This study indicates that caffeinated-drink consumption increases depressive mood and suicide ideation in adolescents population.

Lucas et al.[28] accessed data from three large cohorts in which consumption of caffeinated and non-caffeinated beverages was assessed to investigate coffee and caffeine consumption and suicide risk. In these three large prospective cohorts of US men and women, they observed that suicide risk decreased in a dose-dependent manner with increasing consumption of coffee. As compared with non-coffee drinkers, the relative risk of suicide was 45% lower among individuals who consumed 2-3 cups of coffee per day, and 53% lower among individual consuming 4 cups of coffee per day. Authors also analyzed, showing a negative association, the relation between decaffeinated coffee and suicide risk, suggesting that caffeine, rather than other coffee components, contributes to caffeinated coffee/suicide risk association.

Before last years, only three important cohort studies have examined the association between caffeine consumption and suicide. Klatsky et al.[29], in 1993, carried out a longitudinal investigation of over 128,000 individuals who were followed for an average of 8 years. Use of caffeinated beverages was related to a lower risk of suicide, progressively lower at higher coffee intake (relative risk per cup of coffee per day= 0.87, 95% confidence interval= 0.77-0.98).

Similarly, Kawachi et al.[34], examined prospectively the relationship of coffee and caffeine intake to risk of death from suicide among a group of over 85,000 individuals who were followed for an average of 10 years. The data suggested an inverse association between coffee intake and risk of suicide. Suicide risk was 72% lower among individuals in the group who drank 4 cups of caffeinated coffee per day as compared to non-drinkers.

Finally, Tanskanen et al.[30] conducted two studies on over 43,000 and 36,000 individuals, to evaluate the risk of suicide among coffee drinkers. A positive association was noted between daily coffee drinking and suicide risk. Compared to those drinking 1 cup of coffee daily, suicide risk was lower for moderate coffee consumption (2-3 cups/day up to 6-7 cups/day), but increased with higher consumption (8-10 cups/day). The increased suicide risk among heavy coffee drinkers was significant even after adjusted for potential risk factors for suicide. Similarly, Baethge et al.[35], in a study conducted on bipolar disorder patients, found a positive association between caffeine intake and suicide risk.

These discrepant results might be associated (a) with the proportions of individuals in each study who consumed large quantities of coffee, (b) with the involvement of a psychiatric population. Furthermore, the above-mentioned studies shown limited ability to distinguish the association between caffeine and other components of coffee and suicide. For this reason, these results should be interpreted with caution.

Because of the observational design, these investigations cannot prove that caffeine reduces suicide risk, and it remains possible that individuals with high intake of caffeine have lower suicide risk for reasons other than caffeine consumption, such as a different prevalence of chronic diseases or severe psychiatric disorders.

Furthermore, the association between anxiety-related manifestations and caffeine, in predisposed individuals, has already been described[37,38], and thus persons with panic attacks and panic disorder often avoid caffeine. Because anxiety is a risk factor for attempted suicide, and possibly for completed suicide, the lower suicide risk among coffee drinkers may be due to a lower prevalence of anxiety disorders in this group[39,40].

On the contrary, a possible protective effect of caffeine is biologically plausible and deserves serious consideration. Indeed, caffeine has complex effects in the central nervous system, largely mediated by antagonism of adenosine A2a and A1 receptors, including an increased turnover of several monoamine transmitters, such as serotonin, dopamine, and noradrenaline[2]. A deficiency of central monoamines is one of the features of depression[41], and several antidepressant drugs are designed to increase monoaminergic transmission. Central deficiency of monoamines may be improved by caffeine, which enhances dopaminergic neurotransmission[42,43]. These pharmacological effects suggest that caffeine could also act as a mild antidepressant, a hypothesis that could explain the lower risk of depression among coffee drinkers in epidemiological studies[33].

With regard to the antidepressant effect of coffee, several studies have examined this association, most were cross-sectional which complicates data interpretation[44-48]. Few prospective studies have been published. Among these, in 2011 Lucas et al.[32] conducted the first large-scale study of coffee consumption to evaluate depression on over 50,000 individuals. This study found that depression risk decreases with increasing caffeinated coffee consumption. A recent study from Guo et al.[48] prospectively evaluated the consumption of caffeinated beverages in relation to self-reported depression diagnosis among over 260,000 individuals, showing a lower risk for depression among coffee drinkers.

Even if previous observations suggested that the consumption of caffeine may have beneficial effects against depression, and as a consequence against suicide risk, more in-depth studies are required.

In conclusion, none of the articles address the question of the motivations that lead to the suicide act with use of caffeine. Furthermore, except for one particular study[35], no evaluation was carried out with consideration of the presence of mental disorders associated with suicide. It is possible that, in some cases, caffeine played a direct role in the suicide attempt. In other cases, it appears to function in an indi-

rect way through combination with other substances. It is not always clear whether the individual consumed caffeine with the real intention of ending their life or whether this consumption was an impulsive act without a relation to the desire of killing themselves[27].

Caffeine seems to be negatively correlated with suicide according to most of studies. But it is uncertain yet the direct effects of caffeine on depressive symptoms such as suicide.

Although further studies are needed to better understand the motivational factors involved in the use of caffeine in attempted suicide. A better understanding of how caffeine may be linked to suicide is crucial for its prevention. In addition, the understanding of the patients knowledge regarding the toxicity of caffeine is also necessary to confirm which cases are real suicide attempts and not accidents.

Conflict of interest: the authors have no conflict of interests to declare.

Funding: the authors received no specific funding for this work.

REFERENCES

1. Alstott RL, Miller AJ, Forney RB. Report of a human fatality due to caffeine. J Forensic Sci 1973; 18: 135-7.
2. Cappelletti S, Piacentino D, Sani G, Aromatario M. Caffeine: Cognitive and Physical Performance Enhancer or Psychoactive Drug? Curr Neuropharmacol 2015; 13: 71-88.
3. Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M. Effects of caffeine on human health. Food Addit Contam 2003; 20: 1-30.
4. Higdon JV, Frei B. Coffee and health: a review of recent human research. Crit Rev Food Sci Nutr 2006; 46: 101-23.
5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009; 62: 1006-212.
6. Bryant J. Suicide by ingestion of caffeine. Arch Pathol Lab Med 1981; 105: 685-6.
7. Chaturvedi AK, Rao NG, McCoy FE. A multi-chemical death involving caffeine, nicotine and malathion. Forensic Sci Int 1983; 23: 265-75.
8. Garriott JC, Simmons LM, Poklis A, Mackell MA. Five cases of fatal overdose from caffeine-containing "look-alike" drugs. J Anal Toxicol 1985; 9: 141-3.
9. Winek CL, Wahba W, Williams K, Blenko J, Janssen J. Caffeine fatality: a case report. Forensic Sci Int 1985; 29: 207-11.
10. Hanzlick R, Gowitt GT, Wall W. Deaths due to caffeine in "look-alike drugs". J Anal Toxicol 1986; 10: 126.
11. Takayasu T, Nishigami J, Ohshima T, et al. A fatal case due to intoxication with seven drugs detected by GC-MS and TDx methods. Nihon Hoigaku Zasshi 1993; 47: 63-71.
12. Riesselmann B, Rosenbaum F, Roscher S, Schneider V. Fatal caffeine intoxication. Forensic Sci Int 1999; 103: 49-52.
13. Watson WA, Litovitz TL, Klein-Schwartz W, et al. 2003 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004; 22: 335-404.
14. Holmgren P, Nordén-Pettersson L, Ahlner J. Caffeine fatalities. Four case reports. Forensic Sci Int 2004; 139: 71-3.
15. Rudolph T, Knudsen K. A case of fatal caffeine poisoning. Acta Anaesthesiol Scand 2010; 54: 521-3.
16. Thelander G, Jönsson AK, Personne M, Forsberg GS, Lundqvist KM, Ahlner J. Caffeine fatalities: do sales restrictions prevent intentional intoxications? Clin Toxicol (Phila) 2010; 48: 354-8.
17. Jantos R, Stein KM, Flechtenmacher C, Skopp G. A fatal case involving a caffeine-containing fat burner. Drug Test Anal 2013; 5: 773-6.
18. Poussel M, Kimmoun A, Levy B, et al. Fatal cardiac arrhythmia following voluntary caffeine overdose in an amateur body-builder athlete. Int J Cardiol 2013; 166: e41-2.
19. Bonsignore A, Sblano S, Pozzi F, Ventura F, Dell'Erba A, Palmiere C. A case of suicide by ingestion of caffeine. Forensic Sci Med Pathol 2014; 10: 448-51.
20. Banerjee P, Ali Z, Levine B, Fowler DR. Fatal caffeine intoxication: a series of eight cases from 1999 to 2009. J Forensic Sci 2014; 59: 865-8.
21. Ishikawa T, Yuasa I, Endoh M. Non specific drug distribution in an autopsy case report of fatal caffeine intoxication. Leg Med (Tokyo) 2015; 17: 535-8.
22. Yamamoto T, Yoshizawa K, Kubo S, et al. Autopsy report for a caffeine intoxication case and review of the current literature. J Toxicol Pathol 2015; 28: 33-6.
23. Aknouche F, Guibert E, Tessier A, Eibel A, Kintz P. Suicide by ingestion of caffeine. Egypt J Forensic Sci 2017; 7: 6.
24. Sidlo J, Sikuta J, Sidlova H, Niznansky L. Suicides by ingestion of pure caffeine powder. New challenge for public health? Neuro Endocrinol Lett 2019; 40 (Suppl 1): 11-6.
25. Usui K, Fujita Y, Kamijo Y, Igari Y, Funayama M. LC-MS/MS method for rapid and accurate detection of caffeine in a suspected overdose case. J Pharmacol Toxicol Methods 2021; 107: 106946.
26. Cappelletti S, Piacentino D, Fineschi V, Frati P, Cipolloni L, Aromatario M. Caffeine-related deaths: manner of deaths and categories at risk. Nutrients 2018; 10: 611.
27. Silva AC, de Oliveira Ribeiro NP, de Mello Schier AR, et al. Caffeine and suicide: a systematic review. CNS Neurol Disord Drug Targets 2014; 13: 937-44.
28. Lucas M, O'Reilly EJ, Pan A, et al. Coffee, caffeine, and risk of completed suicide: results from three prospective cohorts of American adults. World J Biol Psychiatry 2014; 15: 377-86.
29. Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. Ann Epidemiol 1993; 3: 375-81.
30. Tanskanen A, Tuomilehto J, Viinamäki H, Vartiainen E, Lehtonen J, Puska P. Heavy coffee drinking and the risk of suicide. Eur J Epidemiol 2000; 16: 789-91.
31. Cho MS. Use of alcohol, tobacco, and caffeine and suicide attempts: findings from a nationally representative cross-sectional study. J Prim Care Community Health 2020; 11: 2150132720913720.
32. Lucas M, Mirzaei F, Pan A, et al. Coffee, caffeine, and risk of depression among women. Arch Intern Med 2011; 171: 1571-8.
33. Ruusunen A, Lehto SM, Tolmunen T, Mursu J, Kaplan GA, Voutilainen S. Coffee, tea and caffeine intake and the risk of severe depression in middle-aged Finnish men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Public Health Nutr 2010; 13: 1215-20.
34. Kawachi I, Willett WC, Colditz GA, Stampfer MJ, Speizer FE. A prospective study of coffee drinking and suicide in women. Arch Intern Med 1996; 156: 521-5.
35. Baethge C, Tondo L, Lepri B, Baldessarini RJ. Coffee and cigarette use: association with suicidal acts in 352 Sardinian bipolar disorder patients. Bipolar Disord 2009; 11: 494-503.
36. Kim H, Park J, Lee S, Lee SA, Park EC. Association between energy drink consumption, depression and suicide ideation in Korean adolescents. Int J Soc Psychiatry 2020; 66: 335-43.
37. Nardi AE, Lopes FL, Valença AM, et al. Caffeine challenge test in panic disorder and depression with panic attacks. Compr Psychiatry 2007; 48: 257-63.

38. Pfeiffer PN, Ganoczy D, Ilgen M, Zivin K, Valenstein M. Comorbid anxiety as a suicide risk factor among depressed veterans. Depress Anxiety 2009; 26: 752-7.
39. Sareen J, Houlahan T, Cox BJ, Asmundson GJ. Anxiety disorders associated with suicidal ideation and suicide attempts in the National Comorbidity Survey. J Nerv Ment Dis 2005; 193: 450-4.
40. Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008; 358: 55-68.
41. Ferre S, Ciruela F, Borycz J, et al. Adenosine A1-A2A receptor heteromers: new targets for caffeine in the brain. Front Biosci 2008; 13: 2391-9.
42. Ferré S. An update on the mechanisms of the psychostimulant effects of caffeine. J Neurochem 2008; 105: 1067-79.
43. Pham NM, Nanri A, Kurotani K, et al. Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. Public Health Nutr 2014; 17: 625-33.
44. Greden JF, Fontaine P, Lubetsky M, Chamberlin K. Anxiety and depression associated with caffeinism among psychiatric inpatients. Am J Psychiatry 1978; 135: 963-6.
45. Leibenluft E, Fiero PL, Bartko JJ, Moul DE, Rosenthal NE. Depressive symptoms and the self-reported use of alcohol, caffeine, and carbohydrates in normal volunteers and four groups of psychiatric outpatients. Am J Psychiatry 1993; 150: 294-301.
46. Whalen DJ, Silk JS, Semel M, et al. Caffeine consumption, sleep, and affect in the natural environments of depressed youth and healthy controls. J Pediatr Psychol 2008; 33: 358-67.
47. Benko CR, Farias AC, Farias LG, Pereira EF, Louzada FM, Cordeiro ML. Potential link between caffeine consumption and pediatric depression: A case-control study. BMC Pediatr 2011; 11: 73.
48. Guo X, Park Y, Freedman ND, et al. Sweetened beverages, coffee, and tea and depression risk among older US adults. PLoS One 2014; 9: e94715.