The impact of coffee on human health

Article *in* Journal of Education Health and Sport · August 2019

DOI: 10.5281/zenodo.3382360

CITATION
1

READS
208

7 authors, including:

Aleksandra Chałupnik
Medical University of Lublin
17 PUBLICATIONS **48** CITATIONS
SEE PROFILE

Anna Sobstyl
Medical University of Lublin
20 PUBLICATIONS **56** CITATIONS
SEE PROFILE

Zuzanna Chilimoniuk
Medical University of Lublin
31 PUBLICATIONS **126** CITATIONS
SEE PROFILE

Maciej Dobosz
Medical University of Lublin
24 PUBLICATIONS **72** CITATIONS
SEE PROFILE

Chałupnik Aleksandra, Borkowska Aleksandra, Sobstyl Anna, Chilimoniuk Zuzanna, Dobosz Maciej, Sobolewska Paulina, Piecewicz-Szczęsna Halina. The impact of coffee on human health. Journal of Education, Health and Sport. 2019;9(8):563-571. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3382360
http://ojs.ukw.edu.pl/index.php/johs/article/view/7346

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 05.08.2019. Revised: 15.08.2019. Accepted: 31.08.2019.

The impact of coffee on human health

Aleksandra Chałupnik[1], Aleksandra Borkowska[1], Anna Sobstyl[1], Zuzanna Chilimoniuk[1], Maciej Dobosz[1], Paulina Sobolewska[1], Halina Piecewicz-Szczęsna[2]

1. Student Research Circle at the Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin
Supervisor: PhD Halina Piecewicz-Szczęsna[2]
2. Chair and Department of Epidemiology and Clinical Research Methodology, Medical University of Lublin

Corresponding author: Aleksandra Chałupnik, olachalupnik@op.pl

ORICID ID:
Zuzanna Chilimoniuk: https://orcid.org/0000-0001-8261-0192
Aleksandra Borkowska: https://orcid.org/0000-0002-0950-2176
Anna Sobstyl: https://orcid.org/0000-0003-0330-5742
Aleksandra Chałupnik: https://orcid.org/0000-0003-4249-470X
Maciej Dobosz: https://orcid.org/0000-0002-4413-3310
Paulina Sobolewska: https://orcid.org/0000-0001-8010-6013
Halina Piecewicz-Szczęsna: https://orcid.org/0000-0002-0573-7226

ABSTRACT
Introduction: Coffee is one of the most popular beverages in the world. It contains lots of biologically active ingredients. These compounds not only have aromatic properties, but many of them also have antioxidant, hepatoprotective, anti-inflammatory, antimicrobial, antiviral and relaxing smooth muscle properties.
The aim of the study: The purpose of the study is to collect and review scientific publications about the impact of coffee on health.
Material and method: The paper uses standard criteria as the research method. Additionally, during the literature review on PubMed and Google Scholar platforms, keywords such as coffee, caffeine, health, impact were used.
Description of the state of knowledge: Numerous studies suggest that coffee impact on the long-term functioning of the organism is negligible and is associated with the consumption of coffee for a longer period of time. Chlorogenic acid, caffeine and trigoneline are primarily responsible for the positive effect. They have a hypoglycemic, bactericidal and antioxidant effect. Diterpenes, such as kahweol and cafestol may have negative influence on health. Research also suggests that coffee can reduce the risk of Parkinson's disease and type 2 diabetes.
Summary: The results show that coffee ingredients can have both positive and negative effects on health. However, before these observations can be used to create nutritional advice, further research is needed. They will allow a better understanding of the mechanisms of action of the compounds responsible for reduced risk of diabetes mellitus or Parkinson's disease.

Keywords: coffee, caffeine, health, cardiovascular

INTRODUCTION

Coffee is one of the most popular beverages in the world. It contains over 1000 biologically active ingredients. The final content of individual substances in coffee depends on how it is brewed. Bioactive compounds that affect the human body include caffeine, coffee acid, chlorogenic acid, trigonelline, diterpenes and melanoidins [1] These compounds not only have aromatic properties, but many of them also have antioxidant, hepatoprotective, anti-inflammatory, antimicrobial, antiviral and relaxing smooth muscle properties [2].

THE CHEMISTRY OF COFFEE

Caffeine

Caffeine is a purine alkaloid present in the form of a white crystalline powder with a bitter taste [3]. The caffeine content of coffee depends on the method of its preparation, the preferred strength of the drink, the brand of the product and the type of coffee. Caffeine is a non-selective adenosine receptor antagonist. It blocks the action of this compound through the receptors A1, A2A, A2B and A3. This is done by: mobilization of intracellular calcium, inhibition of phosphodiesterase (PDEs), modulation of benzodiazepine receptor (GABAA) activity and inhibition of cAMP transporters and increase of catecholamine levels [4]. At low doses it blocks A1 and A2 receptors and increases the activity of the central nervous system [5]. By stimulating adenyl cyclase, it increases the concentration of cAMP in the cell Inhibition of adenosine A1 receptors is associated with the release of acetylcholine, noradrenaline and dopamine. The increased concentration of neurotransmitters results in accelerated heart rate, vasodilatation, increased lipolysis and relaxation of the mesangium cells [6]. The inhibition of A2 receptor causes the opposite effect because it leads to a lower cAMP level in the cell [7]. The toxic effect of caffeine occurs at a concentration of 129 μmol / L (25 mg / kg body weight). After drinking 2-3 cups of coffee, level of caffeine in the plasma

reaches 20-40 μmol / L. Therefore, normal coffee consumption does not carry the risk of overdosing [8].

Caffeic acid

Caffeic acid is a representative of hydroxycinnamic acids, which are a subgroup of phenolic acids. It is synthesized in plants as a product of the shikimic acid pathway. Its precursor are amino acids: tyrosine or phenylalanine. Thanks to having hydroxyl groups, the acid has an antioxidant effect. It can also play an important role in inhibiting the peroxidation of various lipids. Thanks to its properties, it has a beneficial effect on the human body [9].

Chlorogenic acid

Chlorogenic acid is the ester formed between caffeic acid and the 3-hydroxyl of L-quinic acid. According to research, this acid as a component of coffee reduces the level of gamma-glutamyl transpeptidase, which is a biomarker of the early phase of oxidative stress [9]. It is recently believed that these acids as potential modulators of cell pathways can be involved in the pathogenesis of neurodegenerative diseases and possess anti-tumor activity [8].

Diterpenes

Diterpenes are a class of chemical compounds composed of two terpenic units. They consist of four isoprene subunits. Diterpenes are fat-soluble compounds, including cafestol and kahweol. They show antibacterial, anti-inflammatory and anti-cancer effect [10]. According to research, diterpenes contained in coffee may be associated with elevated levels of cholesterol and triglycerides in plasma cells [11].

THE IMPACT OF COFFEE ON HEALTH

Cardiovascular system

Some studies suggest that coffee consumption may have an effect on blood pressure, arrhythmia or coronary heart disease. Several studies have assessed the effect of large amounts of caffeine on heart rate. The results were inconclusive. They showed a significant decrease in heart rate after consuming 100 mg or 200 mg of caffeine in ordinary consumers [12,13]. Caffeine can mediate the atrial fibrillation through neurohormonal stimulation and sympathetic activation. The effects can be increased in people who do not drink coffee every day [14]. Caffeine toxicity may cause supraventricular tachycardia, atrial fibrillation and ventricular fibrillation [15]. The effect of coffee on the health of people with stable coronary artery disease is not fully understood. However, the results of most studies indicate that consumption of more than five cups of coffee can cause disease progression [16, 17]. A dose of caffeine corresponding to 2-3 cups of coffee may increase systolic blood pressure by 3-14 mmHg and diastolic blood pressure by 4-13 mmHg in people with normotension. In people with hypertension, this effect may be greater. The habitual consumption of coffee can lead to the formation of tolerance to caffeine, making its effect on pressure less visible [18].

Cancers

Some epidemiological studies show correlations between the consumption of caffeinated coffee and cancer risk. The results of studies conducted in 2019 show that caffeic acid present in coffee may play an important role in the treatment of hepatocellular carcinoma (HCC). This compound has anti-HCC activity, preventing excessive formation of oxygen radicals and thus helping to kill cancer cells through DNA oxidation [19]. In 2019, research was conducted on the influence of coffee on the development of brain cancer. The results suggest that higher coffee consumption may contribute to a lower risk of brain cancer development in the Asian population [20]. It is believed that coffee can reduce the incidence of esophageal cancer

through the influence of its anticancer components such as polyphenols and diterpenes. However, these assumptions are uncertain due to inconsistencies in the results of cohort and case-control studies conducted in previous years [21]. The results of research conducted in 2017 by scientists from the Medicine and Oral Surgery Department and Institute of Research and Advanced Training in Health Sciences and Technologies showed an inverse relationship between coffee consumption and oral cancer. The probability of developing the above-mentioned cancer may be even 1.45 lower in people consuming larger amounts of coffee than in the case of people consuming small amounts of coffee or not drinking it at all [22]. Research conducted in 2018 suggests that coffee consumption is not associated with an increased risk of lung cancer [23]. So far, various meta-analyzes have been conducted on the relationship between coffee consumption and the endometrial cancer risk. Caffeine has been positively associated with sex hormone binding globulin (SHBG) in postmenopausal women. SHBG is the main carrier of estrogens and testosterone, thus reducing free hormone levels. Another mechanism that can cause lower estrogen levels in the blood after coffee is inhibition of the enzyme that converts androgens into estrogens. It is called CYP19. Low estrogen levels are considered as a protective factor against endometrial cancers by reducing its proliferation. Thus, increased coffee consumption may be associated with a reduced risk of endometrial cancer, especially in obese postmenopausal women [24].

Osteoporosis

Caffeine contained in coffee can lead to a slight negative calcium balance. This is due to impaired calcium absorption [25]. Most studies investigating the effect of coffee on bone mineral density(BMD) showed no correlation between caffeine and BMD. However, one study indicates that daily caffeine intake of more than 300 mg of caffeine may have been associated with accelerated BMD loss [26]. Another study, found that caffeine may have an impact on faster BMD loss only in women whose daily calcium intake was less than 744 mg [27].

Depression

Coffee is one of the most consumed drinks in the world, while depression is considered to be a major contributor to the overall global burden of disease. A 2019 study found that those who consumed at least four cups of coffee a day were at a lower risk of depression than those who drank less than one cup of coffee a day [28]. The mechanism underlying the link between coffee and depression is not fully understood. There are two main hypotheses that can explain it. First, coffee has a high concentration of polyphenols such as chlorogenic acid and trigoneline, which have anti-inflammatory and antioxidant effects [29]. In this way, coffee can protect against inflammation and oxidation which are involved in the pathogenesis of depression [30]. Secondly, caffeine, being a non-selective adenosine A1 and A2 receptor antagonist, stimulates the central nervous system and modulates dopaminergic activity. A moderate amount of caffeine can have a beneficial effect by improving psychomotor activity and alertness, as well as by the feeling of having more energy [31].

Parkinson disease

Epidemiological evidence suggests that coffee drinkers have a lower risk of Parkinson's disease (PD). According to one hypothesis, PD patients exhibit special personality traits such as caution and lack of search for novelty even before movement symptoms occur. This has led to the suggestion that people who later develop PD are less likely to feel the need for stimulation provided by coffee. Another possible explanation is that caffeine contained in coffee has a neuroprotective effect [32]. Research on the effect of coffee on the development of Parkinson's disease has been going on since the second half of the 20th century. Ascherio

et al. found that men who drank at least 1 cup of coffee per day were less likely to die from PD compared to men who did not drink coffee [33]. Similar results were obtained in the male study population by Ross et al. According to them, men who did not drink coffee had a 3-5 times higher risk of developing PD compared to men who drank at least 800 ml of coffee per day [34]. According to a meta-analysis from 2014, the most positive effect of caffeine was observed for the daily consumption of 3 cups of coffee [35]. Studies by Nurse's Health Study have shown that coffee consumption is inversely correlated with the risk of Parkinson's disease in women who have not undergone postmenopausal estrogen therapy. However, a significant increase in the risk of PD has been observed in postmenopausal women on estrogen therapy who have consumed at least 6 cups of coffee a day [36]. It is not entirely clear how estrogen modifies the effects of caffeine. Caffeine is mainly metabolised by the liver's CYP1A2 enzyme. Estrogens used in hormone replacement therapy inhibit this enzyme, resulting in reduced caffeine metabolism [37]. In the study of Popata et al. the positive correlation between coffee consumption and Parkinson's disease was stronger in subjects with slow caffeine metabolism.[38] Caffeine is thought to have neuroprotective effects by blocking adenosine receptors, leading to increased serotonin and acetylcholine levels [39]. The use of adenosine receptor antagonists may alleviate the symptoms of the disease [40]. Clinical studies on animal models have shown that caffeine stabilizes the integrity of the blood-brain barrier that participates in the maintenance of brain hemostasis. The disruption of brain haemostasis is involved in PD pathogenesis [41]. The positive effect of coffee can also be associated with the polyphenols having antioxidant properties which is very important because oxidative stress is considered as a factor promoting PD [42]. There is also a hypothesis that coffee consumption changes the composition of the intestinal microflora in a way that alleviates enteritis. This would lead to a reduction in the incorrect folding of the alpha-synuclein protein in the intestinal nerves [43]. According to the research, α-synuclein in the intestinal nerves can act in a prion way, leading to the propagation of neuropathological changes through autonomous connections with the central nervous system. It is believed that a reduced amount of this abnormal protein may reduce the risk of PD [44].

Pregnancy

The results of numerous epidemiological studies that focused on the relationship between coffee consumption by a pregnant woman and the risk of miscarriage were contradictory. Some studies suggest that large amounts of caffeine (350-699 mg / day) increase the risk of pregnancy loss by 40% [45]. There is also a large number of studies with no significant relationship between caffeine intake and pregnancy loss [46,47]. However, caffeine increases the level of cyclic adenosine monophosphate in cells by inhibiting phosphodiesterase, which can affect fetal growth and development [48]. In addition, the caffeine structure is similar to adenine and guanine, so it can be incorporated into DNA during mitosis causing chromosomal anomalies [49]. Similarly to the problem of pregnancy loss, the results of the studies on the influence of caffeine on fetal birth weight are contradictory. Numerous studies indicate that coffee consumption within the range of 200-400 mg / day may result in a reduction of fetal birth weight by about 100 g [50]. Coffee consumption during pregnancy may also be associated with fetal retardation [51]. Prenatal exposure to caffeine has long-term behavioral effects in rats [52]. Unfortunately the effects in humans have been poorly studied so far. Caffeine and its metabolites, including paraxanthin and theophylline are non-selective adenosine antagonists. They affect the activity of the nervous system by blocking adenosine receptors, whose correct modulation influences the formation of axons [53]. One study showed that intensive consumption of caffeine by the mother during pregnancy was associated with increased nighttime awakening of a 3 months baby [54]. Another study found a small relationship between the consumption of coffee during pregnancy and the increased

activity of the 18-month-old child [55]. However, the results of most studies suggest that coffee consumption in the correct amounts does not have a negative effect on pregnancy [56].

Diabetes mellitus

Coffee is the main source of caffeine, which according to research reduces insulin sensitivity and impairs glucose tolerance [57]. It is also a source of a large amount of phenolic compounds, with a total content in the range from 200 mg to 550 mg per cup [58]. The main phenolic compound in coffee is chlorogenic acid, which most likely inhibits the glucose-6-phosphatase system. Hydrolysis of glucose-6-phosphate to glucose and phosphate is the final step in glucose production pathways during gluconeogenesis and glycogenolysis. Hydrolysis of glucose-6-phosphate requires proper operation of a translocase, whose competitive inhibitor in rats liver microsomes is chlorogenic acid [59]. Additionally, studies have shown that chlorogenic acid weakens sodium-dependent glucose transport in brush border membrane vesicles isolated from rat small intestine [60]. The first epidemiological report suggesting a link between coffee consumption and type 2 diabetes appeared in 2002. Since then, the number of studies has been steadily increasing. A study in the Dutch population found that the risk of developing type 2 diabetes was half as high in men and women who drink at least seven cups of coffee compared to people who drink no more than two cups of coffee a day [61]. In Finland, however, research showed that men who drank at least 10 cups of coffee a day had a 55% lower risk of developing 2DM than men who drink a maximum of 2 cups per day [62]. Studies on the impact of coffee on the development of type 1 diabetes are significantly less numerous. This is mainly due to the age of people suffering from this type of diabetes. Usually these are children or young adults with lower coffee consumption.

SUMMARY

Coffee is one of the most popular drinks in the world, which is why it is so important to study its impact on health. Numerous studies suggest that its impact on the long-term functioning of the organism is negligible and is associated with the consumption of coffee for a longer period of time. The results show that its ingredients can have both positive and negative effects on health. Chlorogenic acid, caffeine and trigoneline are primarily responsible for the positive effect. They have a hypoglycemic, bactericidal and antioxidant effect. They also have neuroprotective properties. Diterpenes, such as kahweol and cafestol, which cause an increase in blood cholesterol levels, may have a negative influence on health. However, these compounds also have advantages, they act chemoprotectively. Research suggests that coffee can reduce the risk of Parkinson's disease and type 2 diabetes. However, before these observations can be used to create nutritional advice, further research is needed. They will allow a better understanding of the mechanisms of action of the compounds responsible for the above-mentioned effects.

References:

1. Bułdak RJ, Hejmo T, Osowski M, Bułdak Ł, Kukla M, Polaniak R, Birkner E. The Impact of Coffee and Its Selected Bioactive Compounds on the Development and Progression of Colorectal Cancer In Vivo and In Vitro. Molecules 2018, 23(12), 3309.
2. A. Cano-Marquina, J.J. Tarin, A. Cano. The impact of coffee on health. Maturitas 2013, 75(1):7-21.
3. Farmakopea Polska VIII tom I. Polskie Towarzystwo Farmaceutyczne, Warszawa 2008:1412.
4. A.Oñatibia-Astibia, R. Franco, E. Martínez-Pinilla. Health benefits of methylxanthines in neurodegenerative diseases, Mol Nutr Food Res. 2017 Jun;61.

5. Tieges Z, Snel J, Kok A, et al. Caffeine does not modulate inhibitory control. Brain Cogn 2009, 69: 316-327.
6. Temple JL. Caffeine use in children: What we know, what we have left to learn, and why we should worry. Neurosci and Biobehav Rev 2009, 33: 793-806.
7. Tanda G, Goldberg SR. Alternation of the Behavioral Effects of Nicotine by Chronic Caffeine Exposure. Pharmacol Biochem Behav 2000, 66(1): 47-64.
8. I.A. Ludwig, M.N. Clifford, M.E. Lean i wsp., Coffee: biochemistry and potential impact on health. Food Funct. 2014;5(8):1695-717.
9. Kołodziejczyk-Czepas J, Szejk M, Pawlak A, Żbikowska HM. Właściwości przeciwutleniające kwasu kawowego i jego pochodnych. ŻYWNOŚĆ. Nauka. Technologia. Jakość, 2015, 3 (100), 5-17.
10. C. Cavin, D. Holzhaeuser, G. Scharf, A. Constable, W. W. Huber and B. Schilter, Cafestol and kahweol, two coffee specific diterpenes with anticarcinogenic activity. Food Chem. Toxicol., 2002, 40, 1155–1163.
11. R. Urgert and M. B. Katan, The cholesterol-raising factor from coffeebeans, Annu. Rev. Nutr., 1997, 17, 305–324.
12. Sondermeijer HP, van Marle AG, Kamen P, Krum H. Acute effects of caffeine on heart rate variability. Am J Cardiol. 2002 Oct 15; 90(8):906-7.
13. Rauh R, Burkert M, Siepmann M, Mueck-Weymann M. Acute effects of caffeine on heart rate variability in habitual caffeine consumers. Clin Physiol Funct Imaging. 2006 May; 26(3):163-6.
14. Strubelt O, Diederich KW. Experimental treatment of the acute cardiovascular toxicity of caffeine. J Toxicol Clin Toxicol. 1999;37(1):29-33.
15. Zimmerman PM, Pulliam J, Schwengels J, MacDonald SE. Caffeine intoxication: a near fatality. Ann Emerg Med. 1985 Dec; 14(12):1227-9.
16. I. Stensvold, A. Tverdal, and B. K. Jacobsen. Cohort study of coffee intake and death from coronary heart disease over 12 years. 1996, BMJ., 312:544–545.
17. de Vreede-Swagemakers, J.J., Gorgels, A.P., Weijenberg, M.P. et al. Risk indicators for out-of-hospital cardiac arrest in patients with coronary artery disease. 1999, J. Clin Epidemiol., 52:601–607.
18. Nurminen, M.L., Niittynen, L., Korpela, R., and Vapaatalo, H. Coffee, caffeine and blood pressure: a critical review. 1999, Eur. J. Clin. Nutr., 53:831–839.
19. Espíndola KMM, Ferreira RG, Narvaez LEM, Silva Rosario ACR, da Silva AHM, Silva AGB, Vieira APO, Monteiro MC. Chemical and Pharmacological Aspects of Caffeic Acid and Its Activity in Hepatocarcinoma, Front Oncol. 2019; 9: 541.
20. Song Y, Wang Z, Jin Y, Guo J. Association between tea and coffee consumption and brain cancer risk: an updated meta-analysis. World J Surg Oncol. 2019; 17: 51.
21. Zhang J, Zhou B, Hao C. Coffee consumption and risk of esophageal cancer incidence. 2018 Apr; 97(17): e0514.
22. Miranda J, Monteiro L, Albuquerque R, Pacheco JJ. Coffee is protective against oral and pharyngeal cancer: A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2017 Sep; 22(5): e554–e561.
23. Narita S, Saito E, Sawada N, Shimazu T, Yamaji T, Iwasaki M, Sasazuki S, Noda M, Inoue M, Tsugane S. Coffee Consumption and Lung Cancer Risk: The Japan Public Health Center-Based Prospective Study. J Epidemiol. 2018; 28(4): 207–213.
24. Lafranconi A, Micek A, Galvano F, Rossetti S, Del Pup L, Berretta M, Facchini G. Coffee Decreases the Risk of Endometrial Cancer: A Dose–Response Meta-Analysis of Prospective Cohort Studies. Nutrients. 2017 Nov; 9(11): 1223.
25. Lloyd T, Rollings NJ., Kieselhorst K, et al. Dietary caffeine intake is not correlated with adolescent bone gain. 1998, J. Am. Coll Nutr.,17:454–457

26. Rapuri PB, Gallagher JC, Kinyamu HK., and Ryschon KL. Caffeine intake increases the rate of bone loss in elderly women and interacts with vitamin D receptor genotypes. 2001, Am. J. Clin. Nutr., 74:694–700.
27. Harris SS and Dawson-Hughes B. Caffeine and bone loss in healthy postmenopausal women. 1994, Am. J. Clin. Nutr., 60:573–578.
28. Navarro AM, Abasheva D, Martínez-González MA, Ruiz-Estigarribia L, Martín-Calvo N, Sánchez-Villegas A and Toledo E. Coffee Consumption and the Risk of Depression in a Middle-Aged Cohort: The SUN Project. Nutrients. 2018 Sep; 10(9): 1333.
29. Godos J, Pluchinotta FR, Marventano S, Buscemi S, Volti GL, Galvano F, Grosso G. Coffee components and cardiovascular risk: Beneficial and detrimental effects. Int. J. Food Sci. Nutr. 2014;65:925–936.
30. Sanchez-Villegas A., Martinez-González M.A. Diet, a new target to prevent depression? BMC Med. 2013;11:3.
31. Adan A, Prat G, Fabbri M, Sanchez-Turet M. Early effects of caffeinated and decaffeinated coffee on subjective state and gender differences. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008;32:1698–1703.
32. Evans AH, Lawrence AD, Potts J, MacGregor L, Katzenschlager R, Shaw K, Zijlmans J, Lees AJ. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. J Neurol Neurosurg Psychiatry. 2006 Mar;77(3):317-21.
33. Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, Thun MJ. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen. Am J Epidemiol. 2004 Nov 15; 160(10):977-84.
34. Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, Tanner CM, Masaki KH, Blanchette PL, Curb JD, Popper JS, White LR. Association of coffee and caffeine intake with the risk of Parkinson disease. JAMA. 2000 May 24-31; 283(20):2674-9.
35. Qi H, Li S. Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease. Geriatra Gerontol Int. 2014 Apr; 14(2):430-9.
36. Ascherio A, Chen, H., Schwarzschild, M.A. et al. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology. 2003, 60:790–795.
37. Pollock BG, Wylie M, Stack JA. et al. Inhibition of caffeinene metabolism by estrogen replacement therapy in postmenopausal women. J. Clin. Pharmacol. 1999, 39:936–940.
38. Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, Mayeux R, Ritz B, Ross GW, Petrovitch H, Topol B, McGuire V, Costello S, Manthripragada AD, Southwick A, Myers RM, Nelson LM. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. Eur J Neurol. 2011 May; 18(5):756-65.
39. Schwarzschild MA. Caffeine in Parkinson disease: better for cruise control than snooze patrol? Neurology. 2012 Aug 14; 79(7):616-8.
40. Bara-Jimenez W, Sherzai A, Dimitrova T, Favit A, Bibbiani F, Gillespie M, Morris MJ, Mouradian MM, Chase TN. Adenosine A(2A) receptor antagonist treatment of Parkinson's disease. Neurology. 2003 Aug 12; 61(3):293-6.
41. Chen X, Lan X, Roche I, Liu R, Geiger JD. Caffeine protects against MPTP-induced blood-brain barrier dysfunction in mouse striatum. J Neurochem. 2008 Nov; 107(4):1147-57.
42. Sääksjärvi K, Knekt P, Rissanen H, Laaksonen MA, Reunanen A, Männistö S. Prospective study of coffee consumption and risk of Parkinson's disease. Eur J Clin Nutr. 2008 Jul; 62(7):908-15.
43. Derkinderen P, Shannon KM, Brundin P. Gut feelings about smoking and coffee in Parkinson's Disease. Mov Disord. 2014 Jul; 29(8): 976–979.

44. Forsyth CB, Shannon KM, Kordower JH, Voigt RM, Shaikh M, Jaglin JA, Estes JD, Dodiya HB, Keshavarzian A. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. PLoS One. 2011;6(12):e28032.
45. Chen LW, Wu Y, Neelakantan N, Chong MF, Pan A, van Dam RM. Maternal caffeine intake during pregnancy and risk of pregnancy loss: a categorical and dose–response meta-analysis of prospective studies. Public Health Nutr. 2016 May;19(7):1233-44.
46. Bracken MB, Triche E, Grosso L et al. Heterogeneity in assessing self-reports of caffeine exposure: Implications for studies of health effects. Epidemiology. 2002, 13:165–171.
47. Leviton A, and Cowan L. A review of the literature relating caffeine consumption by women to their risk of reproductive hazards. Food Chem Toxicol. 2002, 40:1271–1310.
48. Grosso LM, Bracken MB. Caffeine metabolism, genetics, and perinatal outcomes: a review of exposure assessment considerations during pregnancy. Ann Epidemiol. 2005;15(6):460–6.
49. Ebrahimi A, Habibi-Khorassani M, Akher FB, Farrokhzadeh A, Karimi P. Caffeine as base analogue of adenine or guanine: a theoretical study. J Mol Graph Model 2013;42:81–91.
50. Martin TR and Bracken MB. The association between low birth weight and caffeine consumption during pregnancy. Am. J. Epidemiol. 1987,126:813–821.
51. McDonald AD, Armstrong BG and Sloan M.. Cigarette, alcohol, and coffee consumption and prematurity. Am. J. Public Health. 1992, 82:87–90.
52. Grimm VE, Frieder B. Prenatal caffeine causes long lasting behavioral and neurochemical changes. Int J Neurosci . 1988;41(1-2):15–28.
53. Rivkees SA, Zhao Z, Porter G, Turner C. Influences of adenosine on the fetus and newborn. Mol Genet Metab 2001; 74: 160–171.
54. Santos IS, Matijasevich A, Domingues MR. Maternal caffeine consumption and infant nighttime waking: prospective cohort study. Pediatrics. 2012;1295:860–868.
55. Bekkhus M, Skjøthaug T, Nordhagen Ret al. Intrauterine exposure to caffeine and inattention/overactivity in children. Acta Paediatr . 2010;996:925–928.
56. Linn S, Schoenbaum SC, Monson RR, Rosner B, Stubblefield PG, Ryan KJ. No Association between Coffee Consumption and Adverse Outcomes of Pregnancy. N Engl J Med 1982; 306:141-145.
57. Keijzers GB, De Galan BE, Tack CJ, Smits P. Caffeine can decrease insulin sensitivity in humans. Diabetes Care. 2002 Feb;25(2):364-9.
58. Bravo L. Polyphenols: chemistry, dietary sources, metabolism, and nutritional significance. Nutr Rev. 1998;56:317–333.
59. Arion WJ, Canfield WK, Ramos FC et al. Chlorogenic acid and hydroxynitrobenzaldehyde: New inhibitors of hepatic glucose 6-phosphatase. Arch. Biochem Biophys. 1997, 339:315–322.
60. Welsch CA, Lachance PA and Wasserman BP. Dietary phenolic compounds: Inhibition of Na+-dependent D-glucose uptake in rat intestinal brush border membrane vesicles. J. Nutr. 1989, 119:1698–1704.
61. van Dam RM, Feskens EJ. Coffee consumption and risk of type 2 diabetes mellitus. Lancet. 2002;360:1477–1478.
62. Tuomilehto J, Hu G and Bidel S. Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. JAMA. 2004, 291:1213–1219.