# Report on **Coffee** and **Health**

## A LITERATURE REVIEW ON MAJOR AREAS OF EVIDENCE

By Emma Bladyka, SCAA Coffee Science Manager





© 2012 Specialty Coffee Association of America

The Specialty Coffee Association of America (SCAA) is the world's coffee authority and largest coffee trade association with nearly 5,000 members including member companies and their employees. SCAA members are located in more than 40 countries and represent every segment of the specialty coffee industry, including producers, roasters, importers/exporters, retailers, manufacturers, baristas and coffee enthusiasts. SCAA is dedicated to creating a vibrant specialty coffee community, recognizing, developing and promoting specialty coffee by setting and maintaining quality standards for the industry; conducting research on coffee, equipment and perfection of craft; and providing education, training, resources and business services for its members.

Visit www.scaa.org.

Note: No part of this report may be reproduced or published in any form including but not limited to print, photocopy, or electronic form without the written permission of the Specialty Coffee Association of America, 330 Golden Shore #50, Long Beach, CA 90802.

## Table of Contents

Introduction, Important Considerations
Mental Performance3
Neurodegenerative Disorders, Alzeihemer's Disease4
Parkinson's Disease5
Sports Performance5
Type II Diabetes6
Liver Health7
Cancer7
Cardiovascular Health, Cholesterol, Blood Pressure8
Pregnancy, Fetal Health9
Conclusions10
References

Coffee is one of the most commonly consumed beverages around the world, but for many years, its effects on health have been disputed within the medical community. In recent decades, modern research has dispelled most of the myths surrounding coffee's effects on health. This work has also provided insightful information about the possible health benefits of coffee consumption. Most reviews of scientific literature conclude that for adults who consume a moderate amount of coffee (three to four cups per day), there is very little evidence of health risks and even some evidence of health benefits (Higdon and Frei 2006; Floegel and others 2012). A recent, widely publicized study found that drinking coffee is inversely associated with risk of death (Freedman and others 2012). Many other studies address the potential beneficial health effects of drinking coffee. The mechanisms behind these positive health effects have yet to be elucidated, and continue to be an active area of research in the health community. The following health topics are perhaps the most discussed in association with coffee intake.

#### Important Considerations

Confounding factors - which have been historically problematic in coffee studies - have led to several studies attributing coffee to illnesses like cancer. Smoking and caffeine are strongly associated, and heavy smokers consume more caffeine than non-smokers (Zavela and others 1990; Schreiber and others 1988b). At this point, the general population is aware that smoking impacts health negatively and causes cancer, and because of this awareness, there is a stigma against smoking. Therefore, in studies involving humans, people lie about their smoking habits. Self-reporting can also be a problem with other confounding factors, especially with behaviors related to health, such as alcohol consumption, exercise, and diet.

A common problem in many of the studies discussed here is the difficulty in measuring coffee or caffeine 'exposure'. This may be the root of inconclusive results reported by some researchers. A cup of coffee was often assumed to provide 85-100 mg of caffeine (Higdon and Frei 2006). However, we know this amount can vary significantly depending on mug size (Bracken and others 2002; Schreiber and others 1988a), coffee species, cultivar consumed (McCusker and others 2003), and brewing method. Also, we have learned that individuals metabolize coffee at different rates, which stems from individual genetics and undoubtedly results in inconclusive research (Carrillo and Benitez 2000).

#### Mental Performance

There is abundant evidence of the effects of coffee on alertness and attention. From decades of work on this topic we now know that caffeine blocks adenosine, which wards off the tired sensation and can result in increased attention or cognitive performance (Carrillo and Benitez 2000; Ribeiro and Sebastião 2010). This effect has the additional benefit of elevating the mood of coffee drinkers, although some believe this is only a result of the alleviation of withdrawal symptoms (James and Rogers 2005; Addicott and Laurienti 2009). We also know that the extent of these effects is partially mediated by human genetics (Yang and others 2010; Retey and others 2007). Since this is a widely accepted topic, and more related to physiology than health, this report will not elaborate further. Below is an extensive reference list of these topics for further reading.

Improvement in alertness/sleep disruption(Hameleers and others 2000)(Glade 2010)(James 2011)(Lieberman and others 2002)(Lorist and Tops 2003)(Mets and others In Press)(Philip and others 2006)(Quinlan and others 2000)

(Ribeiro and Sebastião 2010) (Roehrs and Roth 2008) Attention/cognitive performance (Adan and Serra-Grabulosa 2010) (Brunyé and others 2010b) (Brunyé and others 2010a) (Glade 2010) (Lieberman et al. 2002) (Ribeiro and Sebastião 2010) (Serra-Grabulosa and others 2010) Positive Mood effects (Addicott and Laurienti 2009) (Cropley and others 2012) (Dawkins and others 2011) (Haskell and others 2005) (Higdon and Frei 2006) (James 2011) (James and Rogers 2005) (Lorist and Tops 2003) (Quinlan and others 1997) (Smith 2009)

#### Neurodegenerative Disorders

There is evidence that certain deteriorative neurological disorders, including age-related cognitive decline, dementia, Alzheimer's and Parkinson's diseases are inversely correlated with coffee consumption. The mechanisms for these are active areas of research, and thought to be related to the adenosine blocking effects of caffeine. Work on Alzheimer's disease suggests that caffeine can limit the specific peptide that accumulates in Alzheimer's patients, and others have speculated that this mechanism can be transferred to other types of cognitive impairment (Santos and others 2010; Abreu and others 2011). More research is needed to provide concrete conclusions.

There is a large amount of evidence to support that drinking coffee can help maintain general cognitive function in older individuals. Generally, people of all ages can benefit from the short-term perks of caffeine consumption (Rees and others 1999). Some research suggests caffeine may be related to the longer-term stalling of cognitive decline in women but not men (Arab and others 2011; Johnson-Kozlow and others 2002), or specifically for those women without dementia (Ritchie and others 2007). Other studies have found a link between coffee drinking and reductions in cognitive decline with men (van Gelder and others 2007). Some research has found that coffee drinkers of both sexes who drank coffee at midlife had a lower risk of dementia later in life than those who did not drink coffee (Eskelinen and others 2009). Other studies point to caffeine as linked to the slowing of dementia progression, including the type of dementia that leads to Alzheimer's disease (Cao and others 2012; Gelber and others 2011). However, not all research has resulted in the same conclusion (Hameleers et al. 2000). Overall, a recent review still urged for more work on this topic, as the mechanisms are unclear, and the gender differences found in many studies are yet to be explained. Like other health topics, issues such as caffeine dosage and self-reporting were likely distorting the results (Santos et al. 2010).

#### Alzheimer's Disease

Alzheimer's disease is one of the most common types of dementia among older people, and is characterized by a progressive decline in cognition, daily functioning, and behavioral alterations, including loss of

<sup>4</sup> SCAA Report: Coffee and Health

short-term memory, language impairment, and disorientation (Santos et al. 2010; Alloul and others 1998). It is estimated that between two and ten percent of Americans and Europeans over 65 years old are affected by this disease (Alloul et al. 1998). In the brain, this has been linked to extracellular plaques containing  $\beta$ -amyloid peptides and neurofibrillary tangles by abnormally broken-up proteins (Arendash and Chuanhai 2010). A large amount of research relates drinking coffee and caffeine consumption with a lower risk of or lessening the progression of the disease (Barranco Quintana and others 2007). Caffeine is shown to reduce these peptides in the brain, and this is the mechanism believed to be causal to this relationship (Arendash and Chuanhai 2010; Arendash and others 2009; Tabaton 2009; Qosa and others 2012; Cao and others 2009; Cao and others 2011; Cao et al. 2012). However, there are other theories as to the specific mechanisms, such as an increased cerebral blood flow, which need to be further investigated (Audenaert and others 2011).

#### Parkinson's Disease

A large number of studies have also reported an inverse relationship between coffee or caffeine ingestion and risk of Parkinson's disease development (Higdon and Frei 2006; James 2011; Costa and others 2010; Hernán and others 2002). Parkinson's disease afflicts about three percent of the over-65 age group in the US, and there is evidence that this number is growing (Ross and others 2000). It is caused by degeneration in certain cells of the brain stem, which causes a continuous loss of dopamine and creates debilitating physical motor disturbance symptoms (Costa et al. 2010). Some studies have noted a dose-dependent effect, where a higher coffee consumption results in a stronger preventative effect (Ross et al. 2000). However, in women, the results are less conclusive (Ascherio and others 2001; Ascherio and others 2003; Palacios and others 2010). Some hypothesize the mechanism may be related to caffeine blocking the adenosine receptors, which increases motor activity (Fenu and Morelli 1998; Chen and others 2001). However, this area is in need of more research. Interestingly, cigarette smoking has also been often associated with a decrease risk of this disease, but some have suggested that coffee drinking is a confounding factor in these cases, as the two are statistically correlated (Hernán et al. 2002).

#### Sports Performance

For over 100 years, caffeine was known for its capacity to enhance muscular work (Rivers and Webber 1907). Today, scientific evidence has led to the consensus that any sports-related effects of coffee are due to caffeine. We know that caffeine is rapidly absorbed in the body through the gastrointestinal tract and quickly moves through cell membranes to the bloodstream (Harland 2000; Carrillo and Benitez 2000). Later, it is broken down in the liver. Peak caffeine concentrations have been shown to be about an hour post-ingestion (Harland 2000; Lieberman et al. 2002). Much of the scientific research regarding caffeine and exercise has been conducted with caffeine pills rather than coffee, as it is easier to measure caffeine's direct effects when all other biologically active compounds within coffee are not complicating matters.

It has been extensively supported that caffeine can improve intensity and endurance in aerobic sport, measured by time-to-exhaustion tests (Ganio and others 2009; Gant and others 2010). This can be variable, depending on the individual and their genetics, type of caffeine consumed, and other confounding factors. One study found that endurance was enhanced as little as zero percent and as much as 17 percent (Ganio et al. 2009). Others found an average of 27 percent increase in performance time, regardless of medium or high caffeine dosage (200-300 mg) (Pasman and others 1995; Lieberman et al. 2002). Some research has found evidence that caffeine may improve high intensity, short-term exercise (Astorino and Roberson 2010; Stuart and others 2005; Woolf and others 2008; Anselme and others 1992).

There is mixed evidence of improvements in resistance or strength training, including number of repetitions completed (Woolf et al. 2008; Hudson and others 2008; Hoffman and others 2009; Goldstein and others 2010a). However, not all research on this topic has come up with similar results (Beck and others 2006; Astorino and others 2008). Many studies found no difference in resistance capabilities or found

mixed results (Astorino et al. 2008; Green and others 2007; Hudson et al. 2008; Jacobs and others 2003). Therefore, this area is still under research and no conclusions can be drawn.

All of the above effects are likely due to the adenosine blocking effect of caffeine in the brain, making one seem less tired (Graham and Spriet 1991) and feel less pain (Goldstein and others 2010b; Fredholm and others 1999; Davis and Green 2009). Adenosine has been shown not only to induce tiredness but also muscle pain, therefore, blocking it could possibly reduce ones pain threshold during exercise (Sylven and others 1988; Pappagallo and others 1993; Sylven and others 1986; Gliottoni and others 2009). However, not all mechanisms are known, and additional pathways have been suggested, including direct muscle stimulation (Spriet 1995).

#### Type II Diabetes

Type II diabetes is a chronic disease where there are high levels of sugar (glucose) in the blood. This is caused by a problem with how the body produces or uses insulin in the body, which is needed to move blood glucose into cells. Type II diabetes usually forms over time, and those diagnosed are often overweight, as high levels of body fat can interfere with the way the body uses insulin. In the US, diabetes is the seventh leading cause of death for adults (Centers for Disease Control and Prevention 2011). Globally, it is estimated that the total number of people with diabetes will rise from 171 million in 2000 to 366 million by 2030 (Wild and others 2004).

Recently, it's been established that coffee consumption has an inverse association with type II diabetes (Bidel and others 2006; Bidel and others 2008; van Dieren and others 2009; Huxley and others 2009; Natella and Scaccini 2012; Psaltopoulou and others 2010; Floegel et al. 2012). Recent studies have consistently supported the idea that regular, or 'habitual', coffee drinking is associated with reduced risk of type II diabetes (van Dam and Hu 2005; van Dam and Feskens 2002; Oba and others 2010). There are a few proposed mechanisms behind this association, but no consensus has been reached. This consensus is complicated by the fact that some studies have linked caffeine to increased insulin sensitivity (Graham and others 2001; Keijzers and others 2002). This is an active area of research for health professionals as the incidences of type II diabetes are rising rapidly in the United States (Centers for Disease Control and Prevention 2011).

Most research has found that with more coffee consumption, there is less risk of developing type II diabetes, known to the scientific community as 'dose related' (Greenberg and others 2006; van Dieren et al. 2009; van Dam and Hu 2005; Huxley et al. 2009). One study of Dutch citizens found that the risk of getting the disease was cut 50 percent by consuming seven cups of coffee per day (van Dam and Feskens 2002). A very large study found risk reduced by 54 percent for men and 29 percent for women who drank more than six cups per day (Salazar-Martinez and others 2004). These studies are just a few examples of the very robust risk reduction found in studies of risk for type II diabetes and coffee consumption. There are also studies that suggest only moderate, long-term coffee consumption is associated with a lower likelihood of developing diabetes (Panagiotakos and others 2007; Psaltopoulou et al. 2010).

Several studies have found no significant association between drinking coffee and the risk of diabetes (Reunanen and others 2003; van Dam and others 2004; Saremi and others 2003; Hamer and others 2008). It's possible that these populations did not drink enough coffee, or perhaps they drank the 'wrong' type of coffee, or the studies were plagued by self-reporting errors and confounding factors, such as age or lifestyle choices. Or, perhaps all people do not receive the same level of health benefit from coffee, much like caffeine is metabolized differently depending on genetics (Retey et al. 2007; Yang et al. 2010). We will not be able to answer these questions until the specific mechanisms for this association are elucidated.

There are multiple possible mechanisms for the strong inverse relationship found between coffee intake and type II diabetes. Some think it has to do with caffeine (van Dam and Feskens 2002), others not (van Dieren et al. 2009; Oba et al. 2010). There is also evidence of similar preventative effects with decaffeinated coffee (Greenberg et al. 2006; Salazar-Martinez et al. 2004; Wu and others 2005; Greenberg and others 2005; Natella and others 2002). This may be partially explained by chlorogenic acids, which were

found in some studies to inhibit intestinal glucose absorption, therefore slowing the amount of glucose entering the bloodstream (Higdon and Frei 2006; Clifford 2000). Others propose that the additional energy and exercise performance via caffeine ingestion affects weight gain and therefore the risk of diabetes (Greenberg et al. 2006; Natella et al. 2002; Lopez-Garcia and others 2006). Some simply do not attempt to find a mechanism, noting the possible involvement of the thousands of organic compounds in coffee.

Finally, there is new evidence to suggest that drinking coffee after the onset of diabetes could be beneficial. One study found that coffee might have a potentially positive influence on other health complications due to type II diabetes, such as mortality via heart disease (Bidel et al. 2006). This study found a 21 percent decrease in cardiovascular disease mortality risk in those who drank seven or more cups of coffee per day, as compared to patients who drank two cups or less.

#### Liver Health

There is evidence that coffee has beneficial effects on the liver, including reducing the risk of liver cancer (see the cancer section of this report), cirrhosis/fibrosis, and fatty-liver disease (Cadden and others 2007; La Vecchia 2005). Drinking coffee has also been linked by scientific studies to the slowing of the progression of hepatitis C or hepatic fibrosis in the liver (Freedman and others 2009; Modi and others 2010). Chronic injury to the liver can result in an accumulation of a certain extracellular matrix protein in the liver (scar tissue) and this causes hepatic fibrosis/cirrhosis, leading to many complications due to reduced liver function (Gressner 2009). This occurs mainly through hepatitis C or B infections and alcohol abuse. These proteins have been shown to be inversely associated with coffee consumption (Higdon and Frei 2006; Muriel and Arauz 2010; Gressner 2009). There is some evidence that this effect is dose-dependent, as one study showed the number of cups of coffee consumed accounted for >39 percent of the variance seen in severity of liver damage of study participants (Catalano and others 2010). One study went as far as to point out a particular caffeine metabolite, paraxanthine, as the mechanism for breaking up these proteins (Gressner and others 2009). That being said, not all studies have found this inverse relationship between coffee drinking and liver disease (Ong and others 2011). There is some possibility that the disease itself is a confounding factor, as people with cirrhosis tend to decrease their coffee intake because they metabolize caffeine more slowly due to their decreased liver function (Higdon and Frei 2006).

#### Cancer

There is a bit of an unfortunate history of flawed associations between coffee and cancer due to common confounding factors like smoking and alcohol use. These factors lead to a confusing lack of consistency in the scientific literature on this topic. For example, a review of studies concluded that there was a correlation between coffee drinking and lung cancer, but admitted in the discussion that confounding effects of smoking may still exist (Tang and others 2010). Today, we know that there is no real relationship between coffee and cancer risk in the majority of body sites. There is now ample evidence that coffee consumption is not related to the risk of cancers of the stomach (Arab 2010; Botelho and others 2006), breast (Fagherazzi and others 2011; Bhoo Pathy and others 2010; Arab 2010; Larsson and others 2009), kidney or renal cell (Bravi and others 2007a; Lee and others 2007), prostate (Park and others 2010; Jain and others 1998; Hsing and others 1990), esophagus (Tverdal and others 2011; Yu and others 2011), and ovaries (Larsson and Wolk 2005; Steevens and others 2007). There are also a growing number studies that have found coffee drinking associated with a reduced risk of certain cancers (list below), although the exact mechanisms for these are still unknown (Yu et al. 2011; Arab 2010). The mechanisms behind these relationships may or may not differ, depending on the particular cancer site. Anti-oxidant and anti-microbial activity (Ferrazzano and others 2009) may all play roles. However, there is still some research that links coffee consumption with specific types of cancer. These are most notably lung and bladder cancer (Arab 2010; Tang et al. 2010; Zeegers and others 2001; Villanueva and others 2006). However, these studies are in the definite minority as research improves and confounding factors are removed more thoroughly from study groups.

ivor	<b>0</b>
iver	(Browi and others 2007b)
	(Cadden et al. 2007)
	(Gressner 2009)
	(Inoue and others 2005)
	(La Vecchia 2005)
	(Larsson and Wolk 2007)
	(Muriel and Arauz 2010)
	(Nkondjock 2009)
Indoi	<u>metrium (uterine)</u>
	(Bravi and others 2009)
	(Hirose and others 2007)
	(Koizumi and others 2008)
	(McCann and others 2009)
	(Shimazu and others 2008)
Colon	and rectum
	(Arab 2010)
	(Galeone and others 2010)
	(Nikondiack 2000)
	(Okondjock 2009)
	$(\bigcirc Da and others 2000)$
	(Tavani and La Vecchia 2004)

#### Cardiovascular Health

Most studies have found no statistically significant association between coffee and cardiovascular diseases, including coronary heart disease (Sofi and others 2007; Wu and others 2009; Andersen and others 2006). Over the past thirty years, research has been conducted on the effects of coffee and caffeine on cardio-vascular health, with mixed results. Some studies have found evidence that links drinking coffee to heart disease and cardiac events (Nilsson and others 2010). Overall it is likely that coffee does contribute a small amount to human cholesterol levels (Wu et al. 2009). This has left health professionals and the public concerned. There are likely confounding factors at play that make it difficult to analyze this complex topic.

#### Cholesterol

There is evidence that drinking unfiltered coffee can lead to a very small increase in LDL-cholesterol (Jee and others 2001; Grubben and others 2000). Coffee diterpenes (cafestol and kahweol) have been found in certain studies to raise the cholesterol of humans (Gross and others 1997; Ranheim and Halvorsen 2005; Urgert and Katan 1996). One study found that five cups per day could elevate cholesterol by 8-10 mg/dL. However, they also found that filtered coffee retained negligible traces of these cholesterol-raising compounds (Urgert and others 1995; Ranheim and Halvorsen 2005). Other studies have found no relationship between coffee and increasing cholesterol, possibly due to the difficulty of separating coffee brewing methods (Thelle and others 1987; Grubben et al. 2000).

#### Blood Pressure

There is some confusion about the effect of coffee on blood pressure; a major concern for some coffee drinkers, as blood pressure is a serious risk factor for developing heart disease, stroke, and heart failure. Some research has linked coffee drinking to hypertension (Zhang and others 2011b; Zhang and others 2011a; Jee and others 1999). Other studies have found that this increase is negligible for coffee drinkers (Noordzij and others 2005; Geleijnse 2008). There is a possibility that this research is also confounded by

smoking or physical inactivity (Jee et al. 1999; Wu et al. 2009). However, recent reviews have made clear that drinking filtered coffee has no effect on blood pressure, and may even reduce the risk of hypertension in women (Geleijnse 2008).

#### Pregnancy

There are as many conflicting opinions as there are scientific studies on the effects of coffee and caffeine on pregnancy outcomes. The lack of clear evidence has made it very difficult for health professionals to advise pregnant women on safe levels of coffee consumption. This is a case where confounding factors are impossible to separate from the consumption of coffee. For example, pregnancy outcomes are dependent on the effects on the body of the pregnancy itself, which are individual and vary greatly over different populations. Pregnant women are also a group which tend to have unreliable self-reporting about smoking, alcohol use, or other 'risky' behaviors (Peck and others 2010). On top of this, due to the difficulty of adequately measuring caffeine ingestion, exposure level within studies is inconsistent and difficult to compare between studies (Bracken et al. 2002). We do know that caffeine metabolism slows during pregnancy, which makes it last longer in the blood. Some authors conclude that caffeine is harmful to the fetus, others that it has no effect. Recent reviews of many studies have concluded that there is still insufficient evidence to link caffeine with adverse fetal, neonatal, or maternal outcomes (Peck et al. 2010; Jahanfar and Sharifah 2009; Brent and others 2011). Most concerns and evidence fall into two categories, spontaneous abortion and fetal health. There are certainly other concerns, none of which have a large amount of evidence behind them and therefore they are not covered in this review.

#### "Reverse Causation"

Some think that a natural aversion to coffee and therefore caffeine in early pregnancy is a signal of a healthy pregnancy. Therefore, over time reduced caffeine consumption is found to be associated with a healthy pregnancy, which has caused a 'reverse causation' in the literature. This term is used to describe such errors in causation. The cause of this natural aversion to caffeine is attributed to stronger pregnancy hormones in viable pregnancies that are naturally likely to last longer and to be healthier than pregnancies with less strong hormones (Lawson and others 2002). In the literature this is called 'pregnancy signal'. One study found a 59 percent decrease in caffeine intake in women 4-6 weeks pregnant, which occurred concurrently with morning sickness (Lawson and others 2004).

#### Preterm Labor, Stillbirth, Miscarriage, and/or Spontaneous Abortion

There are insufficient numbers of comparable studies without confounding factors to conclude a clear link between spontaneous abortions and caffeine intake. Individual research studies have concluded a relationship in specific instances (Greenwood and others 2010), some having inadequate sample sizes (Weng and others 2008; Mongraw-Chaffin and others 2008). Studies that found no increase of risk due to caffeine ingestion (Pollack and others 2010; Zhang and others 2010; Jarosz and others 2012; Savitz and others 2008; Kuczkowski 2009; Browne and others 2007). When the body of research is evaluated; there is not enough of a consensus to draw conclusions (Signorello and McLaughlin 2004; Peck et al. 2010; Brent et al. 2011). Some still recommend moderate consumption during pregnancy, just to be 'safe' (Kuczkowski 2009).

#### Fetal Health

Although there have been large studies devoted to understanding the relationship between caffeine intake and fetal health, including risk of birth defects and birth weight, there is little evidence of causation via caffeine. For birth defects, estimating early exposure levels would be particularly important, as defects often are formed very early in the first trimester. Due to erroneous self-reporting of exposure, adequate estimation of caffeine ingestion is all but impossible. Also, defects are most commonly documented and measured at birth, therefore defects that result in miscarriage are not included in these types of studies (Peck et al. 2010). This leads to a whole set of literature that is unintentionally biased. Birth weight can also be

......

easily confounded by factors such as smoking (Balat and others 2003; Klebanoff and others 2002), which makes many studies void the possibility of certainty in their own results.

That being said, some studies have concluded that caffeine ingestion is correlated with low birth weight or birth defects (Orskou and others 2003), but they often present with a very small sample size (Miller and others 2009; Balat et al. 2003) or statistically insignificant conclusions (Schmidt and others 2010). Other studies have found no links to either affliction (Collier and others 2009; Jarosz et al. 2012; Torfs and Christianson 2000; Grosso and others 2001), and most reviews conclude that there is inadequate evidence to draw a conclusion about this relationship (Peck et al. 2010; Brent et al. 2011). However, the association between caffeine intake and birth defects has been null in the majority of recent studies (Peck et al. 2010). It is possible that it's simply difficult to measure the effect of caffeine on fetal health, but it is also possible that the level of caffeine humans consume would never cause these problems. As there are moral obligations to forcing pregnant women to consume semi-toxic levels of caffeine throughout their gestation period, we will probably never know conclusively.

#### Conclusions

It is important to remember that none of the research conducted on the health effects of coffee have discriminated as to 'specialty' or any other categories of coffee. While we would like to think that specialty coffee is more 'healthful' than other coffees, there is no evidence to support this yet. Some scientists investigating diabetes have addressed coffee brewing methods, and there is some consensus that filtered versus unfiltered coffees have differing levels of cholesterol. Unfortunately, most studies did not report this type of information, probably due to the difficulty on data collection (and perhaps, because they did not know to differentiate). In American studies, one review stated that most studies reflect consumption of drip-filtered coffee (van Dam and Hu 2005). Another article brought up the potential confounding factor of coffee additives, "for example, the ardent coffee enthusiast who drinks seven cups of black coffee without sugar compared with the social coffee drinker who adds full-fat cream and two lumps of sugar to his daily cup." (Tan 2003). However, most studies have not accounted for such additives. The preponderance of research to date has focused on trying to accurately estimate caffeine content. Since this is such a difficult task on its own, research has not gone further into the more specific type of coffee. Perhaps one day the industry can push research in a new direction, one where health professionals are more educated about the products they are investigating. Until then, there is some evidence that drinking coffee is related to health benefits.

### **REFERENCES:**

- Abreu RV, Silva-Oliveira EM, Moraes MF, Pereira GS & Moraes-Santos T. 2011. Chronic coffee and caffeine ingestion effects on the cognitive function and antioxidant system of rat brains. Pharmacology, biochemistry, and behavior 99(4):659-664.
- Adan A & Serra-Grabulosa JM. 2010. Effects of caffeine and glucose, alone and combined, on cognitive performance. Human Psychopharmacology: Clinical & Experimental 25(4):310-317.
- Addicott M & Laurienti P. 2009. A comparison of the effects of caffeine following abstinence and normal caffeine use. Psychopharmacology 207(3):423-431.
- Alloul K, Sauriol L, Kennedy W, Laurier C, Tessier G, Novosel S & Contandriopoulos A. 1998. Alzheimer's disease: a review of the disease, its epidemiology and economic impact. Archives of Gerontology and Geriatrics 27(3):189-221.
- Andersen LF, Jacobs DR, Carlsen MH & Blomhoff R. 2006. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. The American Journal of Clinical Nutrition 83(5):1039-1046.
- Anselme F, Collomp K, Mercier B, Ahmaïdi S & Prefaut C. 1992. Caffeine increases maximal anaerobic power and blood lactate concentration. European Journal of Applied Physiology and Occupational Physiology 65(2):188-191.
- Arab L. 2010. Epidemiologic Evidence on Coffee and Cancer. Nutrition & Cancer 62(3):271-283.
- Arab L, Biggs ML, O'Meara ES, Longstreth WT, Crane PK & Fitzpatrick AL. 2011. Gender Differences in Tea, Coffee, and Cognitive Decline in the Elderly: The Cardiovascular Health Study. Journal of Alzheimer's Disease 27(3):553-566.
- Arendash GW & Chuanhai C. 2010. Caffeine and Coffee as Therapeutics Against Alzheimer's Disease. Journal of Alzheimer's Disease 20:117-126.
- Arendash GW, Moric T, Chuanhai C, Mamcarz M, Runfeldt M, Dickson A, Rezai-Zadeh K, Tan J, Citron BA, Xiaoyang L, Echeverria V & Potter H. 2009. Caffeine Reverses Cognitive Impairment and Decreases Brain Amyloid- Levels in Aged Alzheimer's Disease Mice. Journal of Alzheimer's Disease 17(3):661-680.
- Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA & Speizer FE. 2003. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology 60(5):790-795.
- Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE & Willett WC. 2001. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Annals of Neurology 50(1):56-63.
- Astorino TA & Roberson DW. 2010. Efficacy of acute caffeine ingestion for short-term high-intensity exercise performance: a systematic review. Journal of Strength and Conditioning Research 24(1):257-265.
- Astorino TA, Rohmann RL & Firth K. 2008. Effect of caffeine ingestion on one-repetition maximum muscular strength. Eur J Appl Physiol 102(2):127-132.
- Audenaert K, De Deyn PP, Van Dam D & Wostyn P. 2011. Increased cerebrospinal fluid production as a possible mechanism underlying caffeine's protective effect against Alzheimer's disease. International Journal of Alzheimer's Disease.
- Balat O, Balat A, Ugur MG & Pence S. 2003. The effect of smoking and caffeine on the fetus and placenta in pregnancy. Clinical and experimental obstetrics & gynecology 30(1):57-59.
- Barranco Quintana JL, Allam MF, Serrano Del Castillo A & Fernandez-Crehuet Navajas R. 2007. Alzheimer's disease and coffee: a quantitative review. Neurological research 29(1):91-95.
- Beck TW, Housh TJ, Schmidt RJ, Johnson GO, Housh DJ, Coburn JW & Malek MH. 2006. The acute effects of a caffeine-containing supplement on strength, muscular endurance, and anaerobic capabilities. Journal of strength and conditioning research / National Strength & Conditioning Association 20(3):506-510.
- Bhoo Pathy N, Peeters P, van Gils C, Beulens J, van der Graaf Y, Bueno-de-Mesquita B, Bulgiba A & Uiterwaal C. 2010. Coffee and tea intake and risk of breast cancer. Breast Cancer Research and Treatment 121(2):461-467.

- Bidel S, Hu G, Qiao Q, Jousilahti P, Antikainen R & Tuomilehto J. 2006. Coffee consumption and risk of total and cardiovascular mortality among patients with type 2 diabetes. Diabetologia 49(11):2618-2626.
- Bidel S, Hu G & Tuomilehto J. 2008. Coffee consumption and type 2 diabetes An extensive review. Central European Journal of Medicine 3(1):9-19.
- Botelho F, Lunet N & Barros H. 2006. Coffee and gastric cancer: systematic review and meta-analysis. Cadernos de saude publica / Ministerio da Saude, Fundacao Oswaldo Cruz, Escola Nacional de Saude Publica 22(5):889-900.
- Bracken MB, Triche E, Grosso L, Hellenbrand K, Belanger K & Leaderer BP. 2002. Heterogeneity in Assessing Self-Reports of Caffeine Exposure: Implications for Studies of Health Effects. Epidemiology 13(2):165-171.
- Bravi F, Bosetti C, Scotti L, Talamini R, Montella M, Ramazzotti V, Negri E, Franceschi S & La Vecchia C. 2007a. Food groups and renal cell carcinoma: a case-control study from Italy. International journal of cancer. Journal international du cancer 120(3):681-685.
- Bravi F, Bosetti C, Tavani A, Bagnardi V, Gallus S, Negri E, Franceschi S & La Vecchia C. 2007b. Coffee drinking and hepatocellular carcinoma risk: A meta-analysis. Hepatology 46(2):430-435.
- Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C & Tavani A. 2009. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol 200(2):130-135.
- Brent RL, Christian MS & Diener RM. 2011. Evaluation of the reproductive and developmental risks of caffeine. Birth Defects Research Part B: Developmental and Reproductive Toxicology 92(2):152-187.
- Browne ML, Bell EM, Druschel CM, Gensburg LJ, Mitchell AA, Lin AE, Romitti PA & Correa A. 2007. Maternal caffeine consumption and risk of cardiovascular malformations. Birth Defects Res A Clin Mol Teratol 79(7):533-543.
- Brunyé TT, Mahoney CR, Lieberman HR, Giles GE & Taylor HA. 2010a. Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain and Cognition 74(3):186-192.
- Brunyé TT, Mahoney CR, Lieberman HR & Taylor HA. 2010b. Caffeine modulates attention network function. Brain and Cognition 72(2):181-188.
- Cadden IS, Partovi N & Yoshida EM. 2007. Review article: possible beneficial effects of coffee on liver disease and function. Alimentary pharmacology & therapeutics 26(1):1-8.
- Cao C, Cirrito JR, Lin X, Wang L, Verges DK, Dickson A, Mamcarz M, Zhang C, Mori T, Arendash GW, Holtzman DM & Potter H. 2009. Caffeine suppresses amyloid-beta levels in plasma and brain of Alzheimer's disease transgenic mice. Journal of Alzheimer's disease : JAD 17(3):681-697.
- Cao C, Loewenstein DA, Lin X, Zhang C, Wang L, Duara R, Wu Y, Giannini A, Bai G, Cai J, Greig M, Schofield E, Ashok R, Small B, Potter H & Arendash GW. 2012. High Blood Caffeine Levels in MCI Linked to Lack of Progression to Dementia. Journal of Alzheimer's Disease.
- Cao C, Wang L, Lin X, Mamcarz M, Zhang C, Bai G, Nong J, Sussman S & Arendash G. 2011. Caffeine Synergizes with Another Coffee Component to Increase Plasma GCSF: Linkage to Cognitive Benefits in Alzheimer's Mice. Journal of Alzheimer's Disease 25(2):323-335.
- Carrillo JA & Benitez J. 2000. Clinically Significant Pharmacokinetic Interactions Between Dietary Caffeine and Medications. Clinical Pharmacokinetics 39(2):127-153.
- Catalano D, Martines G, Tonzuso A, Pirri C, Trovato F & Trovato G. 2010. Protective Role of Coffee in Non-alcoholic Fatty Liver Disease (NAFLD). Digestive Diseases and Sciences 55(11):3200-3206.
- Centers for Disease Control and Prevention. 2011. National Diabetes Fact Sheet: national estimates and general information on diabetes and prediabetes in the United States. NIH Publication No. 11-3892. Atlanta, GA: U.S. Department of Health and Human Services Centers for Disease Control and Prevention.
- Chen J-F, Xu K, Petzer JP, Staal R, Xu Y-H, Beilstein M, Sonsalla PK, Castagnoli K, Castagnoli N & Schwarzschild MA. 2001. Neuroprotection by Caffeine and A2A Adenosine Receptor Inactivation in a Model of Parkinson's Disease. The Journal of Neuroscience 21(10):RC143.
- Clifford MN. 2000. Chlorogenic acids and other cinnamates nature, occurrence, dietary burden, absorption and metabolism. Journal of the Science of Food and Agriculture 80(7):1033-1043.

- Collier SA, Browne ML, Rasmussen SA & Honein MA. 2009. Maternal caffeine intake during pregnancy and orofacial clefts. Birth Defects Research Part A: Clinical and Molecular Teratology 85(10):842-849.
- Costa J, Lunet N, Santos C, Santos J & Vaz-Carneiro A. 2010. Caffeine Exposure and the Risk of Parkinson's Disease: A Systematic Review and Meta-Analysis of Observational Studiess. Journal of Alzheimer's Disease 20:221-238.
- Cropley V, Croft R, Silber B, Neale C, Scholey A, Stough C & Schmitt J. 2012. Does coffee enriched with chlorogenic acids improve mood and cognition after acute administration in healthy elderly? A pilot study. Psychopharmacology 219(3):737-749.
- Davis JK & Green JM. 2009. Caffeine and Anaerobic Performance. Sports Medicine 39(10):813-832.
- Dawkins L, Shahzad F-Z, Ahmed SS & Edmonds CJ. 2011. Expectation of having consumed caffeine can improve performance and mood. Appetite 57(3):597-600.
- Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H & Kivipelto M. 2009. Midlife Coffee and Tea Drinking and the Risk of Late-Life Dementia: A Population-Based CAIDE Study. Journal of Alzheimer's Disease 16(1):85-91.
- Fagherazzi G, Touillaud MS, Boutron-Ruault M-C, Clavel-Chapelon F & Romieu I. 2011. No association between coffee, tea or caffeine consumption and breast cancer risk in a prospective cohort study. Public Health Nutrition 14(07):1315-1320.
- Fenu S & Morelli M. 1998. Motor stimulant effects of caffeine in 6-hydroxydopamine-lesioned rats are dependent on previous stimulation of dopamine receptors: a different role of D1 and D2 receptors. European Journal of Neuroscience 10(5):1878-1884.
- Ferrazzano GF, Amato I, Ingenito A, De Natale A & Pollio A. 2009. Anti-cariogenic effects of polyphenols from plant stimulant beverages (cocoa, coffee, tea). Fitoterapia 80(5):255-262.
- Floegel A, Pischon T, Bergmann MM, Teucher B, Kaaks R & Boeing H. 2012. Coffee consumption and risk of chronic disease in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Germany study. The American Journal of Clinical Nutrition 95(4):901-908.
- Fredholm BB, Bättig K, Holmén J, Nehlig A & Zvartau EE. 1999. Actions of Caffeine in the Brain with Special Reference to Factors That Contribute to Its Widespread Use. Pharmacological Reviews 51(1):83-133.
- Freedman ND, Everhart JE, Lindsay KL, Ghany MG, Curto TM, Shiffman ML, Lee WM, Lok AS, Di Bisceglie AM, Bonkovsky HL, Hoefs JC, Dienstag JL, Morishima C, Abnet CC, Sinha R & Group H-CT. 2009. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. Hepatology 50(5):1360-1369.
- Freedman ND, Park Y, Abnet CC, Hollenbeck AR & Sinha R. 2012. Association of Coffee Drinking with Total and Cause-Specific Mortality. New England Journal of Medicine 366(20):1891-1904.
- Galeone C, Turati F, La Vecchia C & Tavani A. 2010. Coffee consumption and risk of colorectal cancer: a metaanalysis of case-control studies. Cancer Causes and Control 21(11):1949-1959.
- Ganio MS, Klau JF, Casa DJ, Armstrong LE & Maresh CM. 2009. Effect of Caffeine on Sport-Specific Endurance Performance: A Systematic Review. The Journal of Strength & Conditioning Research 23(1):315-324 310.1519/JSC.1510b1013e31818b31979a.
- Gant N, Ali A & Foskett A. 2010. The influence of caffeine and carbohydrate coingestion on simulated soccer performance. International journal of sport nutrition and exercise metabolism 20(3):191-197.
- Gelber RP, Petrovitch H, Masaki KH, Ross GW & White LR. 2011. Coffee Intake in Midlife and Risk of Dementia and its Neuropathologic Correlates. Journal of Alzheimer's Disease 23(4):607-615.
- Geleijnse JM. 2008. Habitual coffee consumption and blood pressure: an epidemiological perspective. Vascular health and risk management 4(5):963-970.
- Glade MJ. 2010. Caffeine-Not just a stimulant. Nutrition 26(10):932-938.
- Gliottoni RC, Meyers JR, Arngrimsson SA, Broglio SP & Motl RW. 2009. Effect of caffeine on quadriceps muscle pain during acute cycling exercise in low versus high caffeine consumers. International journal of sport nutrition and exercise metabolism 19(2):150-161.
- Goldstein E, Jacobs P, Whitehurst M, Penhollow T & Antonio J. 2010a. Caffeine enhances upper body strength in resistance-trained women. Journal of the International Society of Sports Nutrition 7(1):18.

- Goldstein ER, Ziegenfuss T, Kalman D, Kreider R, Campbell B, Wilborn C, Taylor L, Willoughby D, Stout J, Graves BS, Wildman R, Ivy JL, Spano M, Smith AE & Antonio J. 2010b. International society of sports nutrition position stand: caffeine and performance Journal of the International Society of Sports Nutrition 7:5.
- Graham TE, Sathasivam P, Rowland M, Marko N, Greer F & Battram D. 2001. Caffeine ingestion elevates plasma insulin response in humans during an oral glucose tolerance test. Canadian journal of physiology and pharmacology 79(7):559-565.
- Graham TE & Spriet LL. 1991. Performance and metabolic responses to a high caffeine dose during prolonged exercise. Journal of applied physiology (Bethesda, Md. : 1985) 71(6):2292-2298.
- Green JM, Wickwire PJ, McLester JR, Gendle S, Hudson G, Pritchett RC & Laurent CM. 2007. Effects of caffeine on repetitions to failure and ratings of perceived exertion during resistance training. International journal of sports physiology and performance 2(3):250-259.
- Greenberg JA, Axen KV, Schnoll R & Boozer CN. 2005. Coffee, tea and diabetes: the role of weight loss and caffeine. International journal of obesity (2005) 29(9):1121-1129.
- Greenberg JA, Boozer CN & Geliebter A. 2006. Coffee, diabetes, and weight control. The American Journal of Clinical Nutrition 84(4):682-693.
- Greenwood D, Alwan N, Boylan S, Cade J, Charvill J, Chipps K, Cooke M, Dolby V, Hay A, Kassam S, Kirk S, Konje J, Potdar N, Shires S, Simpson N, Taub N, Thomas J, Walker J, White K & Wild C. 2010. Caffeine intake during pregnancy, late miscarriage and stillbirth. European Journal of Epidemiology 25(4):275-280.
- Gressner OA. 2009. Less Smad2 is good for you! A scientific update on coffee's liver benefits. Hepatology 50(3):970-978.
- Gressner OA, Lahme B, Siluschek M & Gressner AM. 2009. Identification of paraxanthine as the most potent caffeine-derived inhibitor of connective tissue growth factor expression in liver parenchymal cells. Liver International 29(6):886-897.
- Gross G, Jaccaud E & Huggett AC. 1997. Analysis of the content of the diterpenes cafestol and kahweol in coffee brews. Food and Chemical Toxicology 35(6):547-554.
- Grosso LM, Rosenberg KD, Belanger K, Saftlas AF, Leaderer B & Bracken MB. 2001. Maternal caffeine intake and intrauterine growth retardation. Epidemiology 12(4):447-455.
- Grubben MJ, Boers GH, Blom HJ, Broekhuizen R, de Jong R, van Rijt L, de Ruijter E, Swinkels DW, Nagengast FM & Katan MB. 2000. Unfiltered coffee increases plasma homocysteine concentrations in healthy volunteers: a randomized trial. The American Journal of Clinical Nutrition 71(2):480-484.
- Hameleers PAHM, Van Boxtel MPJ, Hogervorst E, Riedel WJ, Houx PJ, Buntinx F & Jolles J. 2000. Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. Human Psychopharmacology: Clinical & Experimental 15(8):573-581.
- Hamer M, Witte DR, Mosdøl A, Marmot MG & Brunner EJ. 2008. Prospective study of coffee and tea consumption in relation to risk of type 2 diabetes mellitus among men and women: The Whitehall II study. British Journal of Nutrition 100(05):1046-1053.
- Harland BF. 2000. Caffeine and nutrition. Nutrition 16(7-8):522-526.
- Haskell CF, Kennedy DO, Wesnes KA & Scholey AB. 2005. Cognitive and mood improvements of caffeine in habitual consumers and habitual non-consumers of caffeine. Psychopharmacology 179(4):813-825.
- Hernán MA, Takkouche B, Caamaño-Isorna F & Gestal-Otero JJ. 2002. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Annals of Neurology 52(3):276-284.
- Higdon JV & Frei B. 2006. Coffee and Health: A Review of Recent Human Research. Critical Reviews in Food Science and Nutrition 46(2):101-123.
- Hirose K, Niwa Y, Wakai K, Matsuo K, Nakanishi T & Tajima K. 2007. Coffee consumption and the risk of endometrial cancer: Evidence from a case-control study of female hormone-related cancers in Japan. Cancer science 98(3):411-415.
- Hoffman JR, Kang J, Ratamess NA, Hoffman MW, Tranchina CP & Faigenbaum AD. 2009. Examination of a preexercise, high energy supplement on exercise performance. J Int Soc Sports Nutr 6:2.

- Hsing AW, McLaughlin JK, Schuman LM, Bjelke E, Gridley G, Wacholder S, Chien HT & Blot WJ. 1990. Diet, tobacco use, and fatal prostate cancer: results from the Lutheran Brotherhood Cohort Study. Cancer research 50(21):6836-6840.
- Hudson GM, Green JM, Bishop PA & Richardson MT. 2008. Effects of caffeine and aspirin on light resistance training performance, perceived exertion, and pain perception. Journal of strength and conditioning research / National Strength & Conditioning Association 22(6):1950-1957.
- Huxley RD, Lee CMP, Barzi FP, Timmermeister L, Czernichow SMDP, Perkovic VMDP, Grobbee DEMDP, Batty DP & Woodward MP. 2009. Coffee, Decaffeinated Coffee, and Tea Consumption in Relation to Incident Type 2 Diabetes Mellitus: A Systematic Review With Meta-analysis. Archives of Internal Medicine 169(22):2053-2063.
- Inoue M, Yoshimi I, Sobue T, Tsugane S & Group JS. 2005. Influence of coffee drinking on subsequent risk of hepatocellular carcinoma: a prospective study in Japan. Journal of the National Cancer Institute 97(4):293-300.
- Jacobs I, Pasternak H & Bell DG. 2003. Effects of ephedrine, caffeine, and their combination on muscular endurance. Medicine and science in sports and exercise 35(6):987-994.
- Jahanfar S & Sharifah H. 2009. Effects of Restricted Caffeine Intake by Mother on Fetal, Neonatal, and Pregnancy Outcome. Obstetrics & Gynecology 114(1):161-162 110.1097/AOG.1090b1013e3181acbda1095.
- Jain MG, Hislop GT, Howe GR, Burch JD & Ghadirian P. 1998. Alcohol and other beverage use and prostate cancer risk among Canadian men. International journal of cancer. Journal international du cancer 78(6):707-711.
- James J & Rogers P. 2005. Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation. Psychopharmacology 182(1):1-8.

James JE. 2011. Caffeine

- Addiction Medicine. In: Johnson, B. A., editor). Springer New York. p. 551-583.
- Jarosz M, Wierzejska R & Siuba M. 2012. Maternal caffeine intake and its effect on pregnancy outcomes. European Journal of Obstetrics & amp; Gynecology and Reproductive Biology 160(2):156-160.
- Jee SH, He J, Appel LJ, Whelton PK, Suh I & Klag MJ. 2001. Coffee Consumption and Serum Lipids: A Meta-Analysis of Randomized Controlled Clinical Trials. American Journal of Epidemiology 153(4):353-362.
- Jee SH, He J, Whelton PK, Suh I & Klag MJ. 1999. The effect of chronic coffee drinking on blood pressure: a metaanalysis of controlled clinical trials. Hypertension 33(2):647-652.
- Johnson-Kozlow M, Kritz-Silverstein D, Barrett-Connor E & Morton D. 2002. Coffee Consumption and Cognitive Function among Older Adults. American Journal of Epidemiology 156(9):842-850.
- Keijzers GB, De Galan BE, Tack CJ & Smits P. 2002. Caffeine can decrease insulin sensitivity in humans. Diabetes Care 25(2):364-369.
- Klebanoff MA, Levine RJ, Clemens JD & Wilkins DG. 2002. Maternal Serum Caffeine Metabolites and Small-for-Gestational Age Birth. American Journal of Epidemiology 155(1):32-37.
- Koizumi T, Nakaya N, Okamura C, Sato Y, Shimazu T, Nagase S, Niikura H, Kuriyama S, Tase T, Ito K, Tsubono Y, Okamura K, Yaegashi N & Tsuji I. 2008. Case-control study of coffee consumption and the risk of endometrial endometrioid adenocarcinoma. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 17(4):358-363.
- Kuczkowski K. 2009. Caffeine in pregnancy. Archives of Gynecology and Obstetrics 280(5):695-698.
- La Vecchia C. 2005. Coffee, liver enzymes, cirrhosis and liver cancer. Journal of hepatology 42(4):444-446.
- Larsson SC, Bergkvist L & Wolk A. 2009. Coffee and black tea consumption and risk of breast cancer by estrogen and progesterone receptor status in a Swedish cohort. Cancer causes & control : CCC 20(10):2039-2044.
- Larsson SC & Wolk A. 2005. Coffee consumption is not associated with ovarian cancer incidence. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 14(9):2273-2274.
- Larsson SC & Wolk A. 2007. Coffee Consumption and Risk of Liver Cancer: A Meta-Analysis. Gastroenterology 132(5):1740-1745.

- Lawson CC, LeMasters GK, Levin LS & Liu JH. 2002. Pregnancy Hormone Metabolite Patterns, Pregnancy Symptoms, and Coffee Consumption. American Journal of Epidemiology 156(5):428-437.
- Lawson CC, LeMasters GK & Wilson KA. 2004. Changes in caffeine consumption as a signal of pregnancy. Reproductive Toxicology 18(5):625-633.
- Lee JE, Hunter DJ, Spiegelman D, Adami HO, Bernstein L, van den Brandt PA, Buring JE, Cho E, English D, Folsom AR, Freudenheim JL, Gile GG, Giovannucci E, Horn-Ross PL, Leitzmann M, Marshall JR, Mannisto S, McCullough ML, Miller AB, Parker AS, Pietinen P, Rodriguez C, Rohan TE, Schatzkin A, Schouten LJ, Willett WC, Wolk A, Zhang SM & Smith-Warner SA. 2007. Intakes of coffee, tea, milk, soda and juice and renal cell cancer in a pooled analysis of 13 prospective studies. International journal of cancer. Journal international du cancer 121(10):2246-2253.
- Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL & Tulley R. 2002. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Sea-Air-Land. Psychopharma-cology (Berl) 164(3):250-261.
- Lopez-Garcia E, van Dam RM, Rajpathak S, Willett WC, Manson JE & Hu FB. 2006. Changes in caffeine intake and long-term weight change in men and women. The American Journal of Clinical Nutrition 83(3):674-680.
- Lorist MM & Tops M. 2003. Caffeine, fatigue, and cognition. Brain and Cognition 53(1):82-94.
- McCann SE, Yeh M, Rodabaugh K & Moysich KB. 2009. Higher regular coffee and tea consumption is associated with reduced endometrial cancer risk. International Journal of Cancer 124(7):1650-1653.
- McCusker RR, Goldberger BA & Cone EJ. 2003. TECHNICAL NOTE: Caffeine Content of Specialty Coffees. Journal of Analytical Toxicology 27(7):520-522.
- Mets M, Baas D, van Boven I, Olivier B & Verster J. In Press. Effects of coffee on driving performance during prolonged simulated highway driving. Psychopharmacology (2012) doi 10.1007/s00213-012-2647-7.
- Miller EA, Manning SE, Rasmussen SA, Reefhuis J, Honein MA & the National Birth Defects Prevention S. 2009. Maternal exposure to tobacco smoke, alcohol and caffeine, and risk of anorectal atresia: National Birth Defects Prevention Study 1997–2003. Paediatric and Perinatal Epidemiology 23(1):9-17.
- Modi AA, Feld JJ, Park Y, Kleiner DE, Everhart JE, Liang TJ & Hoofnagle JH. 2010. Increased caffeine consumption is associated with reduced hepatic fibrosis. Hepatology 51(1):201-209.
- Mongraw-Chaffin ML, Cohn BA, Cohen RD & Christianson RE. 2008. Maternal smoking, alcohol consumption, and caffeine consumption during pregnancy in relation to a son's risk of persistent cryptorchidism: a prospective study in the Child Health and Development Studies cohort, 1959-1967. Am J Epidemiol 167(3):257-261.
- Muriel P & Arauz J. 2010. Coffee and liver diseases. Fitoterapia 81(5):297-305.
- Natella F, Nardini M, Giannetti I, Dattilo C & Scaccini C. 2002. Coffee Drinking Influences Plasma Antioxidant Capacity in Humans. Journal of Agricultural and Food Chemistry 50(21):6211-6216.
- Natella F & Scaccini C. 2012. Role of coffee in modulation of diabetes risk. Nutrition Reviews 70(4):207-217.
- Nilsson LM, Wennberg M, Lindahl B, Eliasson M, Jansson JH & Van Guelpen B. 2010. Consumption of filtered and boiled coffee and the risk of first acute myocardial infarction; a nested case/referent study. Nutrition, Metabolism and Cardiovascular Diseases 20(7):527-535.
- Nkondjock A. 2009. Coffee consumption and the risk of cancer: An overview. Cancer Letters 277(2):121-125.
- Noordzij M, Uiterwaal CS, Arends LR, Kok FJ, Grobbee DE & Geleijnse JM. 2005. Blood pressure response to chronic intake of coffee and caffeine: a meta-analysis of randomized controlled trials. Journal of hypertension 23(5):921-928.
- Oba S, Nagata C, Nakamura K, Fujii K, Kawachi T, Takatsuka N & Shimizu H. 2010. Consumption of coffee, green tea, oolong tea, black tea, chocolate snacks and the caffeine content in relation to risk of diabetes in Japanese men and women. British Journal of Nutrition 103(03):453-459.
- Oba S, Shimizu N, Nagata C, Shimizu H, Kametani M, Takeyama N, Ohnuma T & Matsushita S. 2006. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. Cancer Lett 244(2):260-267.

- Ong A, Wong VW, Wong GL & Chan HL. 2011. The effect of caffeine and alcohol consumption on liver fibrosis a study of 1045 Asian hepatitis B patients using transient elastography. Liver international : official journal of the International Association for the Study of the Liver 31(7):1047-1053.
- Orskou J, Henriksen TB, Kesmodel U & Secher NJ. 2003. Maternal characteristics and lifestyle factors and the risk of delivering high birth weight infants. Obstetrics and gynecology 102(1):115-120.
- Palacios N, Weisskopf M, Simon K, Gao X, Schwarzschild M & Ascherio A. 2010. Polymorphisms of caffeine metabolism and estrogen receptor genes and risk of Parkinson's disease in men and women. Parkinsonism & related disorders 16(6):370-375.
- Panagiotakos DB, Lionis C, Zeimbekis A, Makri K, Bountziouka V, Economou M, Vlachou I, Micheli M, Tsakountakis N, Metallinos G & Polychronopoulos E. 2007. Long-term, moderate coffee consumption is associated with lower prevalence of diabetes mellitus among elderly non-tea drinkers from the Mediterranean Islands (MEDIS Study). The review of diabetic studies : RDS 4(2):105-111.
- Pappagallo M, Gaspardone A, Tomai F, Iamele M, Crea F & Gioffre PA. 1993. Analgesic effect of bamiphylline on pain induced by intradermal injection of adenosine. Pain 53(2):199-204.
- Park C-H, Myung S-K, Kim T-Y, Seo HG, Jeon Y-J, Kim Y & Korean Meta-Analysis Study G. 2010. Coffee consumption and risk of prostate cancer: a meta-analysis of epidemiological studies. BJU International 106(6):762-769.
- Pasman WJ, van Baak MA, Jeukendrup AE & de Haan A. 1995. The effect of different dosages of caffeine on endurance performance time. International journal of sports medicine 16(4):225-230.
- Peck JD, Leviton A & Cowan LD. 2010. A review of the epidemiologic evidence concerning the reproductive health effects of caffeine consumption: A 2000-2009 update. Food and Chemical Toxicology 48(10):2549-2576.
- Philip P, Taillard J, Moore N, Delord S, Valtat C, Sagaspe P & Bioulac B. 2006. The Effects of Coffee and Napping on Nighttime Highway Driving: A Randomized Trial. Annals of Internal Medicine 144(11):785-W188.
- Pollack AZ, Buck Louis GM, Sundaram R & Lum KJ. 2010. Caffeine consumption and miscarriage: a prospective cohort study. Fertility and sterility 93(1):304-306.
- Psaltopoulou T, Ilias I & Alevizaki M. 2010. The role of diet and lifestyle in primary, secondary, and tertiary diabetes prevention: a review of meta-analyses. The review of diabetic studies : RDS 7(1):26-35.
- Qosa H, Abuznait AH, Hill RA & Kaddoumi A. 2012. Enhanced Brain Amyloid-beta Clearance by Rifampicin and Caffeine as a Possible Protective Mechanism against Alzheimer's Disease. Journal of Alzheimer's disease : JAD.
- Quinlan P, Lane J & Aspinall L. 1997. Effects of hot tea, coffee and water ingestion on physiological responses and mood: the role of caffeine, water and beverage type. Psychopharmacology 134(2):164-173.
- Quinlan PT, Lane J, Moore KL, Aspen J, Rycroft JA & O'Brien DC. 2000. The Acute Physiological and Mood Effects of Tea and Coffee: The Role of Caffeine Level. Pharmacology Biochemistry and Behavior 66(1):19-28.
- Ranheim T & Halvorsen B. 2005. Coffee consumption and human health--beneficial or detrimental?--Mechanisms for effects of coffee consumption on different risk factors for cardiovascular disease and type 2 diabetes mellitus. Molecular nutrition & food research 49(3):274-284.
- Rees K, Allen D & Lader M. 1999. The influences of age and caffeine on psychomotor and cognitive function. Psychopharmacology 145(2):181.
- Retey JV, Adam M, Khatami R, Luhmann UFO, Jung HH, Berger W & Landolt HP. 2007. A Genetic Variation in the Adenosine A2A Receptor Gene (ADORA2A) Contributes to Individual Sensitivity to Caffeine Effects on Sleep. Clin Pharmacol Ther 81(5):692-698.
- Reunanen A, Heliövaara M & Aho K. 2003. Coffee consumption and risk of type 2 diabetes mellitus. The Lancet 361(9358):702-703.
- Ribeiro JA & Sebastião AM. 2010. Caffeine and Adenosine. Journal of Alzheimer's Disease 20(0):3-15.
- Ritchie K, Carrière I, de Mendonça A, Portet F, Dartigues JF, Rouaud O, Barberger-Gateau P & Ancelin ML. 2007. The neuroprotective effects of caffeine. Neurology 69(6):536-545.

- Rivers WH & Webber HN. 1907. The action of caffeine on the capacity for muscular work. The Journal of physiology 36(1):33-47.
- Roehrs T & Roth T. 2008. Caffeine: Sleep and daytime sleepiness. Sleep Medicine Reviews 12(2):153-162.
- Ross GW, Abbott RD, Petrovitch H, Morens DM, Grandinetti A, Tung KH, Tanner CM, Masaki KH, Blanchette PL, Curb JD, Popper JS & White LR. 2000. Association of coffee and caffeine intake with the risk of Parkinson disease. JAMA : the journal of the American Medical Association 283(20):2674-2679.
- Salazar-Martinez E, Willett WC, Ascherio A, Manson JE, Leitzmann MF, Stampfer MJ & Hu FB. 2004. Coffee consumption and risk for type 2 diabetes mellitus. Annals of Internal Medicine 140(1):1-8.
- Santos C, Costa J, Santos J, Vaz-Carneiro A & Lunet N. 2010. Caffeine Intake and Dementia: Systematic Review and Meta-Analysis. Journal of Alzheimer's Disease 20:187-204.
- Saremi A, Tulloch-Reid M & Knowler WC. 2003. Coffee consumption and the incidence of type 2 diabetes. Diabetes Care 26(7):2211-2212.
- Savitz DA, Chan RL, Herring AH, Howards PP & Hartmann KE. 2008. Caffeine and Miscarriage Risk. Epidemiology 19(1):55-62 10.1097/EDE.1090b1013e31815c31809b31819.
- Schmidt RJ, Romitti PA, Burns TL, Murray JC, Browne ML, Druschel CM & Olney RS. 2010. Caffeine, selected metabolic gene variants, and risk for neural tube defects. Birth Defects Research Part A: Clinical and Molecular Teratology 88(7):560-569.
- Schreiber GB, Maffeo CE, Robins M, Masters MN & Bond AP. 1988a. Measurement of coffee and caffeine intake: Implications for epidemiologic research. Preventive Medicine 17(3):280-294.
- Schreiber GB, Robins M, Maffeo CE, Masters MN, Bond AP & Morganstein D. 1988b. Confounders contributing to the reported associations of coffee or caffeine with disease. Preventive Medicine 17(3):295-309.
- Serra-Grabulosa JM, Adan A, Falcón C & Bargalló N. 2010. Glucose and caffeine effects on sustained attention: an exploratory fMRI study. Human Psychopharmacology: Clinical & Experimental 25(7/8):543-552.
- Shimazu T, Inoue M, Sasazuki S, Iwasaki M, Kurahashi N, Yamaji T, Tsugane S & Study JSGMotJPHC-bP. 2008. Coffee consumption and risk of endometrial cancer: a prospective study in Japan. International journal of cancer. Journal international du cancer 123(10):2406-2410.
- Signorello LB & McLaughlin JK. 2004. Maternal Caffeine Consumption and Spontaneous Abortion: A Review of the Epidemiologic Evidence. Epidemiology 15(2):229-239.
- Smith AP. 2009. Caffeine, cognitive failures and health in a non-working community sample. Human Psychopharmacology: Clinical & Experimental 24(1):29-34.
- Sofi F, Conti AA, Gori AM, Eliana Luisi ML, Casini A, Abbate R & Gensini GF. 2007. Coffee consumption and risk of coronary heart disease: A meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases 17(3):209-223.
- Spriet LL. 1995. Caffeine and performance. International journal of sport nutrition 5 Suppl:S84-99.
- Steevens J, Schouten LJ, Verhage BA, Goldbohm RA & van den Brandt PA. 2007. Tea and coffee drinking and ovarian cancer risk: results from the Netherlands Cohort Study and a meta-analysis. British journal of cancer 97(9):1291-1294.
- Stuart GR, Hopkins WG, Cook C & Cairns SP. 2005. Multiple effects of caffeine on simulated high-intensity teamsport performance. Medicine and science in sports and exercise 37(11):1998-2005.
- Sylven C, Beermann B, Jonzon B & Brandt R. 1986. Angina pectoris-like pain provoked by intravenous adenosine in healthy volunteers. British medical journal (Clinical research ed.) 293(6541):227-230.
- Sylven C, Jonzon B, Fredholm BB & Kaijser L. 1988. Adenosine injection into the brachial artery produces ischaemia like pain or discomfort in the forearm. Cardiovascular research 22(9):674-678.
- Tabaton M. 2009. Coffee "Breaks" Alzheimer's Disease. Journal of Alzheimer's Disease 17(3):699-700.
- Tan DSW. 2003. Coffee consumption and risk of type 2 diabetes mellitus. The Lancet 361(9358):702.
- Tang N, Wu Y, Ma J, Wang B & Yu R. 2010. Coffee consumption and risk of lung cancer: A meta-analysis. Lung Cancer 67(1):17-22.

- Tavani A & La Vecchia C. 2004. Coffee, decaffeinated coffee, tea and cancer of the colon and rectum: a review of epidemiological studies, 1990-2003. Cancer causes & control : CCC 15(8):743-757.
- Thelle DS, Heyden S & Fodor JG. 1987. Coffee and cholesterol in epidemiological and experimental studies. Atherosclerosis 67(2-3):97-103.
- Torfs CP & Christianson RE. 2000. Effect of Maternal Smoking and Coffee Consumption on the Risk of Having a Recognized Down Syndrome Pregnancy. American Journal of Epidemiology 152(12):1185-1191.
- Tverdal A, Hjellvik V & Selmer R. 2011. Coffee intake and oral-oesophageal cancer: follow-up of 389,624 Norwegian men and women 40-45 years. British journal of cancer 105(1):157-161.
- Urgert R & Katan MB. 1996. The cholesterol-raising factor from coffee beans. Journal of the Royal Society of Medicine 89(11):618-623.
- Urgert R, van der Weg G, Kosmeijer-Schuil TG, van de Bovenkamp P, Hovenier R & Katan MB. 1995. Levels of the Cholesterol-Elevating Diterpenes Cafestol and Kahweol in Various Coffee Brews. Journal of Agricultural and Food Chemistry 43(8):2167-2172.
- van Dam R & Hu F. 2005. Coffee consumption and risk of type 2 diabetes: a systematic review. (1538-3598 (Electronic)).
- van Dam RM, Dekker JM, Nijpels G, Stehouwer CD, Bouter LM, Heine RJ & Hoorn s. 2004. Coffee consumption and incidence of impaired fasting glucose, impaired glucose tolerance, and type 2 diabetes: the Hoorn Study. Diabetologia 47(12):2152-2159.
- van Dam RM & Feskens EJM. 2002. Coffee consumption and risk of type 2 diabetes mellitus. The Lancet 360(9344):1477-1478.
- van Dieren S, Uiterwaal C, van der Schouw Y, van der A D, Boer J, Spijkerman A, Grobbee D & Beulens J. 2009. Coffee and tea consumption and risk of type 2 diabetes. Diabetologia 52(12):2561-2569.
- van Gelder BM, Buijsse B, Tijhuis M, Kalmijn S, Giampaoli S, Nissinen A & Kromhout D. 2007. Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. European Journal of Clinical Nutrition 61(2):226-232.
- Villanueva CM, Cantor KP, King WD, Jaakkola JJ, Cordier S, Lynch CF, Porru S & Kogevinas M. 2006. Total and specific fluid consumption as determinants of bladder cancer risk. International journal of cancer. Journal international du cancer 118(8):2040-2047.
- Weng X, Odouli R & Li D-K. 2008. Maternal caffeine consumption during pregnancy and the risk of miscarriage: a prospective cohort study. American journal of obstetrics and gynecology 198(3):279.e271-279.e278.
- Wild S, Roglic G, Green A, Sicree R & King H. 2004. Global Prevalence of Diabetes. Diabetes Care 27(5):1047-1053.
- Woolf K, Bidwell WK & Carlson AG. 2008. The effect of caffeine as an ergogenic aid in anaerobic exercise. International journal of sport nutrition and exercise metabolism 18(4):412-429.
- Wu J-n, Ho SC, Zhou C, Ling W-h, Chen W-q, Wang C-l & Chen Y-m. 2009. Coffee consumption and risk of coronary heart diseases: A meta-analysis of 21 prospective cohort studies. International Journal of Cardiology 137(3):216-225.
- Wu T, Willett WC, Hankinson SE & Giovannucci E. 2005. Caffeinated coffee, decaffeinated coffee, and caffeine in relation to plasma C-peptide levels, a marker of insulin secretion, in U.S. women. Diabetes Care 28(6):1390-1396.
- Yang A, Palmer A & de Wit H. 2010. Genetics of caffeine consumption and responses to caffeine. Psychopharmacology 211(3):245-257.
- Yu X, Bao Z, Zou J & Dong J. 2011. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer 11(1):96-106.
- Zavela KJ, Barnett JE, Smedi KJ, Istvan JA & Matarazzo JD. 1990. Concurrent Use of Cigarettes, Alcohol, and Coffee. Journal of Applied Social Psychology 20(10):835-845.
- Zeegers MP, Tan FE, Goldbohm RA & van den Brandt PA. 2001. Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis. International Journal of Epidemiology 30(2):353-362.

- Zhang B-Y, Wei Y-S, Niu J-M, Li Y, Miao Z-L & Wang Z-N. 2010. Risk factors for unexplained recurrent spontaneous abortion in a population from southern China. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 108(2):135-138.
- Zhang Y, Lee ET, Cowan LD, Fabsitz RR & Howard BV. 2011a. Coffee consumption and the incidence of type 2 diabetes in men and women with normal glucose tolerance: The Strong Heart Study. Nutrition, Metabolism and Cardiovascular Diseases 21(6):418-423.
- Zhang Z, Hu G, Caballero B, Appel L & Chen L. 2011b. Habitual coffee consumption and risk of hypertension: a systematic review and meta-analysis of prospective observational studies. The American Journal of Clinical Nutrition 93(6):1212-1219.