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Caffeine and cardiovascular health

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ABSTRACT

This report evaluates the scientific literature on caffeine with respect to potential cardiovascular outcomes, specifically relative risks of total cardiovascular disease (CVD), coronary heart disease (CHD) and acute myocardial infarction (AMI), effects on arrhythmia, heart failure, sudden cardiac arrest, stroke, blood pressure, hypertension, and other biomarkers of effect, including heart rate, cerebral blood flow, cardiac output, plasma homocysteine levels, serum cholesterol levels, electrocardiogram (EKG) parameters, heart rate variability, endothelial/platelet function and plasma/urine catecholamine levels.

Caffeine intake has been associated with a range of reversible and transient physiological effects broadly and cardiovascular effects specifically. This report attempts to understand where the delineations exist in caffeine intake and corresponding cardiovascular effects among various subpopulations. The available literature suggests that cardiovascular effects experienced by caffeine consumers at levels up to 600 mg/day are in most cases mild, transient, and reversible, with no lasting adverse effect. The point at which caffeine intake may cause harm to the cardiovascular system is not readily identifiable in part because data on the effects of daily intakes greater than 600 mg is limited. However, the evidence considered within this review suggests that typical moderate caffeine intake is not associated with increased risks of total cardiovascular disease; arrhythmia; heart failure; blood pressure changes among regular coffee drinkers; or hypertension in baseline populations.

1. Introduction

Caffeine (1,3,7-trimethylxanthine) is a central nervous system (CNS) stimulant alkaloid that is found in various plants such as coffee and cocoa beans, tea leaves, guarana berries, and the kola nut. It can also be synthetically manufactured for use as a food additive, in dietary supplements, and in over the counter or pharmaceutical preparations where synthetic caffeine is identical to intrinsic or plant-derived caffeine. It has been described as the most frequently ingested pharmacologically active food substance in the world (IOM, 2014). The preponderance of published literature demonstrates that for the general population of healthy adults, moderate caffeine consumption of 400 mg/d is not associated with toxicity, cardiovascular effects, effects on bone status and calcium balance (with consumption of adequate calcium), changes in adult behavior, incidence of cancer, or effects on male fertility (Nawrot et al., 2003). These conclusions are recognized by Health Canada, the U.S. Food and Drug Administration (FDA, 2012), the European Food Safety Authority (2015), and most recently the U.S. Dietary Guidelines for Americans (USDHHS & USDA, 2015).

This report evaluates the scientific literature on caffeine relative to possible cardiovascular effects, specifically, effects on:

a) Total cardiovascular disease (CVD)
b) Coronary heart disease (CHD) and acute myocardial infarction (AMI)
c) Arrhythmia
d) Heart failure
e) Sudden cardiac arrest
f) Stroke
g) Blood pressure
h) Hypertension
i) "Other effects": Heart Rate, Cerebral Blood Flow, Cardiac Output, Plasma Homocysteine, Serum Cholesterol, EKG Parameters, Heart Rate Variability, Endothelial/Platelet Function, Plasma & Urine Catecholamines

An additional area of investigation evaluates possible caffeine tolerance and its effects on some of these endpoints.

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2. Approach and methodology

We identified relevant, high-quality studies – i.e., appropriate design, adequate sample size and appropriate control of potential confounders – in humans from authoritative secondary sources (Bull et al., 2015; Guessous et al., 2014; Kalyoncu et al., 2014; Meltzer et al., 2008; Milanez, 2011; Nawrot et al., 2003; Ali et al., 2015; Sanchis-Gomar et al., 2015; Turagam et al., 2015; Wilson and Bloom, 2016; Zhang et al., 2015; Zulli et al., 2016), as well as through an updated literature search for more recent relevant studies using the PubMed bibliographic database.

The updated literature search included reviews published from May 16, 2014 through May 16, 2016 and studies published in 2015 through September 23, 2016 (to provide adequate overlap with the coverage of other reviews, including those cited above, and EFSA (2015)), and included the following terms:

> ((caffeine) AND (blood pressure OR stroke OR cardiovascular disease OR myocardial infarction OR coronary heart disease OR arrhythmia OR ischemic heart disease OR hypertension OR fibrillation OR homocysteine OR cholesterol)) NOT (mouse OR rat)

Studies for evaluation were identified on the basis of their citation by authoritative bodies, appropriate design, adequate study sample size, and appropriate control of potential confounders. Because observational studies are limited to correlations and cannot address cause-and-effect, particular emphasis was placed on experimental or interventional studies in which exposures could be well-controlled and responses to those exposures carefully measured or monitored. However, reliance on high-quality observational studies was necessary to assist in evaluation of potential effects of prolonged exposure (some 20 years or more) and chronic health effects that cannot be evaluated in an experimental study, since experimental studies were all of relatively short duration (all but one < 14 weeks, and most 4-weeks or less). Observational studies are confounded in that caffeine consumption information was typically assessed at baseline, with follow-up periods up to several years or decades thereafter. This may lead to possible exposure misclassification if consumption habits changed over that time period. Additionally, caffeine consumption in observational studies is typically assessed by daily intake of tea or coffee, which makes it difficult to separate the potential effects of caffeine from other ingredients. Indeed, both coffee and tea contain a variety of other chemicals, particularly polyphenols, which may contribute to the beneficial effects attributed to these beverages (Godos et al., 2014; Gardner et al., 2007), and diterpenes in coffee have been implicated in the effects of coffee intake on serum cholesterol (Bak and Grobbee, 1989; Stensvold et al., 1989; Godos et al., 2014).

Following the identification of potentially relevant studies, these were reviewed in more detail to determine which studies examined the relationship between caffeine dose and relevant cardiovascular effects. Following identification of these studies, we extracted data to assess how the occurrence of these effects varies in incidence/severity with caffeine dose and duration of exposure among subpopulations of interest. More than 300 studies were included in the database of pertinent studies (see supplemental materials).

2.1. Background

A great deal of caffeine intake data are available from both government and academic sources. In recent surveys of caffeine consumption in the US population, results showed that around 85% of the US population consumes at least one caffeinated beverage per day, the mean daily caffeine intake from all beverages was 165 ± 1 mg for all ages combined and, within the aggregated ten-year National Health and Nutrition Examination Survey (NHANES) for 2003 through 2012 dataset, the *per capita* 90th percentile caffeine intake peaks at ~600 mg/day among 56 year olds. (Mitchell et al., 2014; Fulgoni et al., 2015; Tran et al., 2016). The historical trends in caffeine intakes remain steady despite the introduction of new sources of caffeine to the marketplace, supporting the well-established concept of substitution (Somogyi, 2010; Branum et al., 2014; Ahluwalia et al., 2014; Fulgoni et al., 2015; Tran et al., 2016). In other words, with a variety of caffeine choices available, cumulative intake over time has remained relatively constant. Among caffeine consumers, the greatest source of caffeine in the US is coffee, with smaller amounts coming from carbonated soft drinks (e.g., cola), tea, and energy drinks/shots, and very small amounts from cocoa, chocolate, and other minor sources (Mitchell et al., 2014). Information on typical levels of caffeine in a variety of caffeinated beverages is presented by Mitchell et al. (2015) and is included in the USDA National Nutrient Database and other online sources.[1]

At existing levels of intake, caffeine can produce a number of expected reversible and transient cardiovascular physiological effects, such as transitory increases in blood pressure, and many studies have investigated the effect of caffeine consumption on other cardiovascular effects, such as heart rate, cardiac rhythm, and various markers of cardiac disease (Nawrot et al., 2003; ORNL, 2011; Pelchovitz and Goldberger, 2011). Interestingly, a number of studies appear to show beneficial effects of consumption of caffeinated beverages on certain cardiovascular endpoints (Grosso et al., 2016; Tang et al., 2015; Gardner et al., 2007; Godos et al., 2014). Caffeine "bioactivity" has been well-known for over a century and is widely (if not completely) understood by consumers. In these respects, caffeine is unique among common constituents of foods.

Caffeine's effects, like nutraceuticals, vary among individuals. An important contributor to variability relates to the fact that individuals habituate and become tolerant to many of its physiological effects. Non-habitual caffeine consumers do not develop habituation or tolerance thereby typically experiencing the compound's effects at lower levels of dietary intake when consumed. Several genetic polymorphisms that either affect caffeine metabolism or receptor-mediated effects have also been identified as possible contributors to variability of effect.

For all of the aforementioned reasons, a 'bright line' threshold intake level applicable to the general population that would otherwise induce caffeine's effects cannot be determined. Importantly, the ordinary physiological effects of caffeine at current levels of intake are not known to cause any harm to health. The observed physiological effects are transient and reversible and have no known long-term health consequences – they are not adverse.

Establishing so-called "safe" levels of intake based on non-adverse physiological effects of the most sensitive individuals is not meaningful to protecting public health. On the contrary, it would disproportionately deprive the very large number of individuals able to consume higher levels of caffeine who are seeking out caffeine's beneficial effects. Such an approach would be analogous to setting limits on milk intake based on tolerable levels of lactose intake by lactose-intolerant individuals.

Unsafe levels of intake, as noted previously, correspond to excessive levels, e.g., >100 mg/kg bw/day (more than 6000 mg/

[1] USDA National Nutrient Database, https://ndb.nal.usda.gov/ndb/search/list; https://cspinet.org/eating-healthy/ingredients-of-concern/caffeine-chart.

person/day; Boyd et al., 1965) – associated with *bona fide* adverse effects resulting in acute caffeine toxicity. Such levels of caffeine may be achieved with abuse of over-the-counter (OTC) tablets and pure caffeine powder, but are not realistically achievable with consumption of caffeinated foods or beverages. Individuals consuming caffeine at varying levels of intake may experience non-adverse physiological effects that are simultaneously transient and reversible. Most tend to adjust intakes if they perceive those effects as personally undesirable, i.e., they will self-titrate (Soroko et al., 1996; Rétey et al., 2007). Thus, while a single "bright line" between safe and unsafe intakes (as in a traditional "acceptable daily intake" – ADI) cannot be determined and is not appropriate considering wide individual variability, it is clear that among the general population levels up to 600 mg/day – and in some cases as much as 800 mg/day or more – can be and are consumed every day with no ill-effect.

2.2. Definition of an adverse health effect

When evaluating the effects of caffeine consumption, it is important to differentiate between a physiological effect and an adverse (harmful) effect. Caffeine can cause subtle, reversible physiological effects at relatively low doses, such as transient, reversible, minimally elevated blood pressure, that are clearly not adverse. Indeed, many individuals appreciate caffeine's beneficial effects, such as increased alertness or improved concentration, which can be demonstrated experimentally at dose levels at or below 100 mg.

Adverse effects have been defined as follows:

> "the causation, promotion, facilitation and/or exacerbation of a structural and/or functional abnormality, with the implication that the abnormality produced has the potential of lowering the quality of life, contributing to a disabling illness, or leading to a premature death" (Sherwin, 1983)

and:

> "Adverse effects are considered to be functional impairments or pathological lesions that may affect the performance of the whole organism or that reduce an organism's ability to cope with an additional challenge. One of the major problems encountered with this concept is the reporting of 'observed effect levels' as contrasted to 'observed adverse effect levels.' The terms 'adverse' and 'not adverse' are at times satisfactorily defined, but because more subtle responses continue to be identified due to increasingly sophisticated testing protocols, scientific judgment is needed regarding the exact definition of adversity" (USEPA, 1994).

Effects that are transient, reversible, and do not have long-term detrimental health consequences should not be considered adverse.

It is important to note that this report does not address "Adverse Event Reports" (AERs) associated with consumption of caffeine-containing products. The FDA's Center for Food Safety and Applied Nutrition Adverse Event Reporting System (CAERS) is a public database containing information on adverse event and case reports submitted to FDA relative to foods, dietary supplements and cosmetics (81 FR 88244, 2016). Reports submitted to FDA vary in quality and reliability, and reports rarely include necessary data to conduct adequate follow-up or draw conclusions. In medical terminology, an adverse event arises in the context of clinical trials of pharmaceuticals, and is used to refer to any occurrence during a clinical trial that would be considered adverse whether or not it has anything to do with the treatment being studied. For example, if a trial participant fainted during a blood draw, this would be classified as an adverse event despite the fact that it was not related to the treatment itself. AERs may also result from emergency room visits or poison control center calls where the medical staff collects information that may have some bearing on the incident and hopefully correctly codes that information. Regardless, and as recently acknowledged by the FDA (81 FR 88244, 2016), it is not possible to determine cause-and-effect relationships between a particular exposure (such as consumption of a caffeinated beverage) and adverse events.

In this report, we discuss both what constitute adverse outcomes (e.g., coronary heart disease) and biomarkers of effect (e.g., blood cholesterol or plasma homocysteine), risk factors for cardiovascular disease.

2.3. Possible variability in response to caffeine

There are a variety of factors that may influence an individual's response to caffeine. Drawing broad conclusions about the effects of various intake levels of caffeine for the general population remains challenging. An individual's response may be influenced by pharmacokinetic factors that affect how rapidly caffeine is absorbed, distributed, metabolized and eliminated (ADME) after being ingested, or by pharmacodynamics factors that influence the interaction between caffeine and its site(s) of action and the effects of that interaction on the body. Some of this variability results from genetic polymorphisms – naturally-occurring mutations in genes either involved in caffeine metabolism (i.e., cytochrome P450 1A2 variants) or in receptor-mediated effects (e.g., adenosine receptors) or non-receptor mediated effects (e.g., low catechol-O-methyltransferase (COMT) activity). Adenosine receptors are a class of purinergic G protein-coupled cell membrane receptors with adenosine as endogenous ligand that are found throughout the body, including the cardiovascular system (Fredholm et al., 2001; Mustafa et al., 2009). Caffeine is a competitive antagonist of adenosine at the A1 and A2A receptors (ADORA1 and ADORA2A), and this antagonistic effect is believed to be responsible for many of the physiological effects of caffeine (Fredholm et al., 2001; Nehlig, 2007; Baraldi et al., 2008). As discussed below, carriers of certain genetic polymorphisms of CYP1A2 show differential effects on the cardiovascular system after caffeine exposure (Palatini et al., 2016). No studies, however, were identified for the influence of adenosine receptor polymorphisms on caffeine's cardiovascular effects.

2.4. ADME differences

Differences in ADME (including delayed gastric emptying which can delay absorption), and metabolism (particularly differences in activity of cytochrome P450 1A2 (CYP1A2)), may lead to differences in plasma caffeine levels and time course from the same dose (Arnaud, 1993). For example, Birkett and Miners (1991) reported an 8-fold range in steady-state plasma caffeine concentration in six adult volunteers given 150 mg caffeine every 8 h for 6 days. Recently, however, salient CYP1A2 polymorphisms which are thought to determine if one is a "slow" or a "fast" 1A2 metabolizer were evaluated among Washington State University college students in a caffeine pharmacokinetic study (White et al., *manuscript in preparation*). Comparison of the subjects in these two groups (slow versus fast) showed that the different polymorphisms were not associated with significant differences in caffeine pharmacokinetics after consumption of 160 mg among the various arms tested, possibly explained by tolerance to caffeine in the corresponding study subjects.

The vast majority of ingested caffeine is metabolized, largely in the liver, prior to excretion. The metabolic pathways are relatively complex (Arnaud, 1993, 2011; see Fig. 1). At least 16 metabolites at levels of 0.1% or more of administered caffeine dose may be found in the urine of humans. In humans, the principal initial step is 3-demethylation of caffeine (1,3,7-trimethylxanthine) to paraxanthine (1,7-dimethylxanthine) - 72–80% of ingested caffeine follows this route - and paraxanthine plasma levels exceed those of caffeine within 8–10 h of ingestion (Bonati et al., 1982; Tang-Liu et al., 1983). 3-Demethylation in humans appears to be catalyzed specifically by cytochrome P450 1A2 (CYP1A2) (Butler et al., 1989; Thorn et al., 2012).

There is substantial inter-individual variability of CYP1A2 activity that influences the disposition of a substrate such as caffeine and these variations may be due to factors such as gender, race, genetic polymorphisms, exposure to enzyme inducers, age, exercise, and pregnancy (Dorne et al., 2001; Vistisen et al., 1990; White et al., *manuscript in preparation*). In particular, at least 6 different polymorphic forms of CYP1A2 (CYP1A2*1A, CYP1A2*1D, CYP1A2*1F, CYP1A2*1L, CYP1A2*1V and CYP1A2*1W) have been reported (Arnaud, 2011; White et al., *manuscript in preparation*). Four other CYP isoforms (CYP1A1, CYP2E1, CYP3A, and CYP2D6-Met) also have minor roles in the metabolism of caffeine (Arnaud, 2011).

Caffeine half-lives of 2.5–4.5 h or slightly more were measured in humans at dose levels of greater than 2 mg/kg body weight (bw) and up to 4 mg/kg body weight (bw) (White et al., 2016; Arnaud, 1993). The ADME profile appears to be age-dependent in rats but not so in humans (Feely et al., 1987; Latini et al., 1980; Blanchard and Sawers, 1983), except in the very young; half-lives of 50–103, 14.4, and 2.6 h have been observed in premature/newborn, 3–5 month and 5–6 month infants, respectively (Gorodischer and Karplus, 1982; Parsons and Neims, 1981; Aldridge et al., 1979; Paire et al., 1988; Pearlman et al., 1989). Thus, caffeine clearance reaches or exceeds adult levels by 5–6 months of age (Aranda et al., 1979, Von Borstel, 1983).

Longer half-lives have been observed in breast-fed than in formula-fed infants (Le Guennec and Billon, 1987), and in women in the last trimester of pregnancy compared with controls (Knutti et al., 1981, 1982). The latter findings contribute to recommendations to limit caffeine intake during pregnancy.

Caffeine half-lives have also been found to be as high as 50–160 h in humans with severe liver diseases (Statland et al., 1976; Statland and Demas, 1980; Desmond et al., 1980; Scott et al., 1988).

2.5. Physiological differences

The other major source of variability in response to caffeine for certain effects is differences in the receptors in the brain that may lead to caffeine's physiological CNS effects (Yang et al., 2010). However, while adenosine receptors play a role in cardiac physiology (Mustafa et al., 2009), we did not identify any studies that examined the role of adenosine receptors, or receptor relevant genetic polymorphisms, in the expression of cardiovascular effects of caffeine.

2.6. Age considerations

Concerns have been raised in some fora that children may be more sensitive than adults to the effects of caffeine which would presumably necessitate restrictions on children's exposure to caffeine. Absent during these discussions is the scientific basis establishing youth as an at-risk population. Other than very young infants, whose metabolic abilities may not be completely developed until they are about six months old, there is little evidence that children and adolescents are inherently any more sensitive than adults when their body weight is taken into consideration (Turnbull et al., 2016; Bruckner, 2000; Scheuplein et al., 2002).

2.7. Habituation/tolerance/withdrawal

Habituation and tolerance to some of the acute effect of caffeine develops with repeated and regular intake. For example, while caffeine may result in a slight increase in the blood pressure of naive individuals, habitual caffeine consumers rapidly develop tolerance and no longer respond to caffeine intake with an increase in blood pressure (Robertson et al., 1981).

Tolerance also develops to increases in tension, anxiety, and jitteriness associated with caffeine administration (Morelli and Simola, 2011; Turnbull et al., 2016). Tolerance to caffeine consumption may be characterized as a desensitization to effects from caffeine among habitual consumers – including genetically susceptible individuals (White et al., *manuscript in preparation*). It appears that chronic exposure to caffeine may override any so-called genetic predisposition - at least at the single nucleotide polymorphisms of CYP1A2 that were previously considered relevant - to metabolic patterns that were thought to modulate caffeine pharmacokinetics.

Abrupt discontinuation of caffeine consumption results in mild and transient withdrawal symptoms starting after 12–24 h of abstinence and peaking 20–48 h later, characterized by headache, fatigue, drowsiness, irritability, depressed mood, and anxiety. Symptoms of caffeine withdrawal vary considerably between different individuals and are usually not harmful, short-term, and self-limiting (Morelli and Simola, 2011). While caffeine withdrawal has been added to the American Psychiatric Association's "*Diagnostic and statistical manual of mental disorders* (*5th edition*)," it does not meet the criteria for "addiction" (e.g. showing compulsive drug seeking behavior and inability to stop).

3. Results

3.1. Overview of literature

Hundreds of studies in humans were identified as potentially relevant, including studies where the exposure of interest was to pure caffeine, coffee, tea, or energy drinks. These included 310 studies that were reviewed in detail. Of these, 158 experimental, and 113 observational studies were included in the final analysis because they included information on caffeine dose and examined the relevant effects. This included 8 studies in children and adolescents (infants to 19 years of age).

All of the studies identified and retrieved are summarized in the associated Excel spreadsheet database, where they are categorized by study type, study population (including age, sex, caffeine consumer type, caffeine sensitivity), endpoint evaluated, study duration, and caffeine dosage studied. These spreadsheet entries go into greater detail on all aspects of the studies and should be consulted for specific information. When detailed caffeine and/or body weight estimates were not available, the following assumptions were made about the caffeine content of coffee, tea, and body weight:

- 95 mg caffeine/cup of coffee[2]
- 45 mg caffeine/cup of tea (approximated based on levels in various types)[3]
- 1 adult = 70 kg

The wealth of studies available on caffeine and cardiovascular endpoints is atypical for a food ingredient, and permits a thorough evaluation of caffeine's possible cardiovascular effects in spite of identified study limitations (e.g., a single or a few repeated administrations – mostly 4-weeks or less). Our understanding of the potential effects of long-term caffeine consumption is informed primarily by the substantial number of observational epidemiological studies that span multiple years – some, 20 years or more. It must be borne in mind, however, that observational studies generally rely on individual dietary recall (typically 1-day recall) at a snapshot in time, so the long-term measure of exposure is often uncertain, thus limiting the conclusions that can be drawn from them and preventing determination of causation in any association that may be identified.

One additional limitation is that while a substantial number of observational studies evaluated higher doses (i.e., >600 mg/day), very few experimental studies examined such doses. Neither examined very high doses (i.e., >1200 mg/day) precluding determination of clear adverse effect levels.

In the following sections, each of the primary cardiovascular endpoints are addressed.

3.2. Total cardiovascular disease (CVD)

Total cardiovascular disease (CVD), also referred to as heart and blood vessel disease, includes numerous heart and blood vessel problems, many of which are related to atherosclerosis, a condition that develops when plaque builds up in the walls of arteries. Some of the major endpoints included within total CVD includes acute myocardial infarction (AMI) or heart attack, stroke, heart failure, arrhythmia, and heart valve problems.[4]

A total of 19 cohort studies (all observational) with a follow up time of approximately 3–28 years evaluated the potential relationship between caffeine intake at various levels (generally reported in cups/day of coffee) and CVD and generally ranged from thousands to hundreds of thousands of participants. Participants in these studies were primarily middle-aged or older adults at study entry with varied caffeine consumption patterns. In a single study of 9484 males enrolled in the Adventist Mortality study, statistically significant 1.2–2.8-fold increased risks (depending on age) of CVD were reported among adults that drank 1, 2 or 3 or more cups of coffee per day (95, 190, or 385 mg caffeine or more) with a mean follow-up time of 15 years, compared to those who consumed less than 1 cup/day (<95 mg caffeine; Lindsted et al., 1992). The authors noted that the associations were weak, and may be “easily cancelled by incomplete control of confounding or through unknown bias.”

Of the remaining 18 studies, four large cohort studies with follow-up periods ranging from 6 to 20 years (3837 to 82,369 participants) demonstrated a statistically significant decreased risk (protective effect) of CVD among participants following consumption of green tea or coffee, or the highest (up to 7 or more cups; ≥665 mg caffeine/day) intake levels studied, compared to a reference group (typically non-consumers or the lowest caffeine consuming group in the study) (Bidel et al., 2006; Kokubo et al., 2013; Kuriyama et al., 2006; Suzuki et al., 2009). One of these studies showed a dose-related reduction in total CVD mortality among patients with Type II *diabetes mellitus*, and a statistically significant protective effect among those who reported consuming 7 or more cups of coffee per day (Bidel et al., 2006). Five additional studies with study populations ranging from 6594 to 402,260 participants, demonstrated a protective effect against CVD among those within the lower (up to 400 mg/day), but not higher (greater than 400 mg/day) caffeine consumption categories during follow-up periods that ranged from approximately 8 to 28 years within the studies. No statistically significant changes (increased or decreased) in CVD risk compared to the relevant comparison group (non-consumers or the lowest caffeine consumption group in the study) were observed among tea, cola or coffee drinkers with caffeine intake between 400 and 600 mg/day during follow-up periods that ranged from approximately 8 to 28 years (Ding et al., 2015; Freedman et al., 2012; Greenberg et al., 2007; Mineharu et al., 2011; Sugiyama et al., 2010). When analyzed separately, the protective effects of coffee consumption tended to be observed more consistently, and at higher intakes, among women than men (Freedman et al., 2012; Kuriyama et al., 2006; Sugiyama et al., 2010; Suzuki et al., 2009).

The remaining 9 studies, with study populations ranging from 817 to 41,836 participants, demonstrated no statistically significant changes in CVD risk with caffeine or coffee consumption at the highest intake levels studied – ranging from 100 to 400 mg in three studies, 400–600 mg in four studies, and greater than 600 mg in two studies – compared to non-consumers or the lowest caffeine consumption group in the study with approximately 3–27 years of follow-up (Andersen et al., 2006; Happonen et al., 2008; Jacobsen et al., 1986; Jazbec et al., 2003; Lopez-Garcia et al., 2008; Martin et al., 1988; Paganini-Hill, 2011; Siletta et al., 2007; Wilson et al., 1989).

Based on the available evidence, caffeine consumption at a variety of intake levels, primarily in the form of tea or coffee, is generally associated with either a statistically significant decreased risk of CVD (in almost half of the available studies) or no statistically significant relationship at all, even at intakes above 600 mg of caffeine per day. Among studies reporting a protective effect with caffeine consumption, intakes generally ranged from 100 to 400 mg per day, with the exception of one study with intakes over 600 mg of caffeine per day. Study authors consistently controlled for a variety of potentially important lifestyle (e.g., diet, smoking status) and health (e.g., hypertension) factors in multivariate analyses. With the exception of one study showing an increased risk of CVD, evidence from many more, well-conducted studies suggest that caffeine consumption is not associated with an increased risk of CVD, and may even be protective against CVD. Observational studies of CVD do not include “pure” caffeine exposures, thus the potential harmful or protective effects of other components within caffeine-containing beverages such as coffee or tea cannot be ruled out. These findings likewise do not necessarily rule out any potential association with specific cardiovascular diseases within the total CVD category, which will be explored further in this review.

3.3. Coronary heart disease (CHD) and acute myocardial infarction (AMI)

Acute myocardial infarction (AMI) also referred to as a “heart attack,” occurs if the flow of oxygen-rich blood to a section of heart muscle suddenly becomes blocked, leading to death of the heart muscle if blood flow is not quickly restored. Most heart attacks

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[2] USDA National Nutrient Database, https://ndb.nal.usda.gov/ndb/foods/show/4277?fgcd=&manu=&lfacet=&format=&count=&max=50&offset=&sort=default&order=asc&qlookup=14209&ds=.

[3] USDA National Nutrient Database, https://ndb.nal.usda.gov/ndb/search/list.

[4] American Heart Association, http://www.heart.org/HEARTORG/Caregiver/Resources/WhatisCardiovascularDisease/What-is-Cardiovascular-Disease_UCM_301852_Article.jsp#.

occur as a result of coronary heart disease (CHD), a condition in which a waxy substance called plaque builds up inside of the coronary arteries (atherosclerosis) which supply oxygen-rich blood to the heart. The resultant narrowing of the arteries leads to less blood and oxygen being available for the heart muscle, also referred to as ischemic heart disease (IHD).[5] Due to the interrelatedness of these outcomes, CHD and AMI events are evaluated together in this review.

A total of 50 observational (40 cohort and 10 case-control) studies evaluated the potential relationship between caffeine intake at various levels (generally reported in cups/day of coffee or tea) and CHD/AMI relative risk, and typically ranged in size from thousands to tens of thousands of participants with mean follow-up periods of approximately 3–32 years. Most of the participants in these studies were middle-aged adults at baseline with varied caffeine consumption patterns.

Thirteen of the 50 studies, with follow-up periods ranging from 3 to 35 years, reported a statistically significant increased risk of CHD or AMI (with relative risks generally ranging from 1.1 to <3.0) at or above the following caffeine intake categories, primarily from coffee: <100 mg/day: 3 studies (1–2 cups/day); 100-<400 mg/day: 6 studies; 400–600 mg/day: 2 studies (only among those in the highest intake groups); >600 mg/day: 2 studies (only among those in the highest intake groups) (Cornelis et al., 2006; Hammar et al., 2003; Happonen et al., 2004, 2006; Kabagambe et al., 2007; Klag et al., 1994; LaCroix et al., 1986; LeGrady et al., 1987; Lindsted et al., 1992; Marchioli et al., 1996; Notara et al., 2015; Stensvold and Tverdal, 1995; Tavani et al., 2001). In several of these studies, increased risks of CHD or AMI were reported only for specific subanalyses, further explained as follows. One study reported a U-shaped dose-response relationship for risk of CHD events, where statistically significant increased risks were reported at the lowest (204 mg/day) and highest (722 mg/day) caffeine intake categories, but not at moderate intake (446 mg/day) (Happonen et al., 2004). Another study reported an increased risk only among normotensive, but not hypertensive patients. Another study reported higher risks of CHD/AMI among those who drank boiled coffee compared to filtered (Hammar et al., 2003), a preparation method that has been reported by some researchers to result in higher blood cholesterol levels among consumers (Bak and Grobbee, 1989; Stensvold et al., 1989). Two additional studies reported an increased risk of CHD or AMI only among individuals with a genotype associated with slow caffeine metabolism (CYP1A2*1F instead of CYP1A2*1A) when analyzed separately (Cornelis et al., 2006), or low COMT activity genotype (low catecholamine metabolism) (Happonen et al., 2006) compared to non- or low-consumption of coffee. In another study, risk of CHD or AMI was increased among men, but not women (Stensvold and Tverdal, 1995).

Most of the available studies (37 of 50) demonstrated no statistically significant increased risk (at least at the highest caffeine intake level investigated) or a significantly decreased risk (protective effect) of CHD or AMI with caffeine consumption compared to non- or low-consumption. Of these 37 studies that do not suggest an increased risk of CHD or AMI following caffeine consumption, 21 studies with mean follow-up periods ranging from 6 to 21 years reported no statistically significant change in risk at any daily intake level investigated compared to non- or low-consumption (100-<400 mg: 5 studies; 400–600 mg: 10 studies; >600 mg: 6 studies) (Floegel et al., 2012; Grobbee et al., 1990; Gyntelberg et al., 1995; Hart and Smith, 1997; Jacobsen et al., 1986; Klatsky et al., 2008; Kokubo et al., 2013; Kuriyama et al., 2006; Loomba et al., 2016; Lopez-Garcia et al., 2006a; Mineharu et al., 2011; Rosengren and Wilhelmsen, 1991; Rosner et al., 2007; Sesso et al., 2003; Stensvold et al., 1996; Tverdal et al., 1990; Willett et al., 1996; Woodward and Tunstall-Pedoe, 1999; Yano et al., 1977; Zhang et al., 2009a, 2009b). An additional 7 of the 37 studies, with mean follow-up periods of approximately 7–13 years, reported a statistically significant protective effect against CHD or AMI among coffee or tea drinkers at the highest intake level investigated in the study compared to non- or low-consumers (100-<400 mg: 3 studies; >600 mg: 4 studies) (Azevedo and Barros, 2006; Freedman et al., 2012; Larsson et al., 2008; Mukamal et al., 2009; Murray et al., 1981; Rautiainen et al., 2012; Loftfield et al., 2015). Five studies, with follow-up periods ranging from approximately 4 to 28 years, reported a statistically significant increased risk of CHD or AMI among lower caffeine consumption groups and a null effect among higher intake groups (up to 10 cups of coffee/day – 950 mg caffeine/day – in one study, Palmer et al., 1995) compared to non- or very low consumption groups (Baylin et al., 2006; Ding et al., 2015; Klatsky et al., 1990; Kleemola et al., 2000; Palmer et al., 1995). The four remaining studies of the 37, with follow-up periods ranging from 5 to 13 years, reported a statistically significant protective effect against CHD or AMI among different caffeine intake (e.g., low intake level, tea vs. coffee) and gender groups compared to non- or low-consumption of caffeine (de Koning Gans et al., 2010; Leurs et al., 2010; Miller et al., 2016; Sesso et al., 1999). Protective effects against CHD or AMI were typically reported among tea drinkers and lower caffeine intake groups (<100 mg/day or 100-<400 mg/day), with null results typically reported among coffee drinkers or higher caffeine intake groups (generally in the 100–600 mg/day range).

The majority of the evidence indicates that caffeine intake does not increase the risk of CHD or AMI. Some evidence suggests that some sensitive subgroups, including those with a specific genotype (e.g., CYP1A2 or COMT variants) may be more susceptible to the potential CVD effects of caffeine (or coffee specifically). Of the 13 studies that reported statistically significant increased risks of CHD or AMI at least at the highest intake category studied among coffee drinkers, all involved consumption of coffee as the primary exposure. The various components in coffee other than caffeine may confound these results and cannot be dismissed. Of those studies that suggest that caffeine consumption is not associated with an increased risk of CHD or AMI (i.e., 35 of 50 studies), 11 studies reported statistically significant decreased risks of CHD or AMI following caffeine consumption at a variety of intake levels ranging from <100 to >600 mg/day. Of the nine studies of tea drinkers with caffeine intakes of up to more than 225 mg/day, none reported a statistically significant increased risk of CHD or AMI, with some reporting statistically significant protective effects against CHD or AMI compared to a reference group (typically non-consumers or the lowest caffeine consuming group in the study) (de Koning Gans et al., 2010; Klatsky et al., 1990; Kokubo et al., 2013; Kuriyama et al., 2006; Leurs et al., 2010; Miller et al., 2016; Sesso et al., 1999, 2003; Woodward and Tunstall-Pedoe, 1999). Overall, the majority of the studies do not suggest that increasing caffeine consumption is associated with an increased risk of CHD or AMI.

3.4. Arrhythmia

Arrhythmia involves any change from the normal sequence of electrical impulses that controls the beating of the heart. These impulses can happen too fast, too slowly, or erratically – causing fluctuations in the normal heart beat. When the heart doesn't beat

[5] American Heart Association, http://www.heart.org/HEARTORG/Conditions/HeartAttack/TreatmentofaHeartAttack/Silent-Ischemia-and-Ischemic-Heart-Disease_UCM_434092_Article.jsp#.WEnTs2lrLRZ. National Institutes of Health, https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0062989/.

properly, it can't pump blood effectively. There are a variety of different types of arrhythmias, with some types more severe than others. The following is a list of major types of arrhythmias[6]:

- Atrial fibrillation: upper heart chambers contract irregularly
- Bradycardia: slow heart rate
- Conduction disorders: heart does not beat normally
- Premature contraction: early heart beat
- Tachycardia: very fast heart rate
- Ventricular fibrillation: disorganized contraction of the lower chambers of the heart
- Atrial flutter: rapidly firing signals that cause the muscles in the atria to contract quickly

A total of 13 studies (4 experimental, 9 observational) evaluated the potential relationship between caffeine intake at various levels and arrhythmia. The type of arrhythmia investigated differed from study to study, some of which investigated the effects of caffeine consumption on a variety of arrhythmia subtypes. Among the four experimental studies (Dobmeyer et al., 1983; Lemery et al., 2015; Newby et al., 1996; Zuchinali et al., 2016), arrhythmias were reported following caffeine ingestion in only the older intervention study (Dobmeyer et al., 1983). Tachycardia and atrial flutter-fibrillation were reported in some mitral valve patients and normal controls following acute intake of 200 mg of caffeine. The study was small ($n = 14$), and the authors of a larger, more recent study stated that interpretation of this, and other earlier studies that investigated the effects of caffeine on electrophysiological changes, are limited by a lack of randomization, and a small number of patients (Lemery et al., 2015). More recent experimental studies are not suggestive of a relationship between acute caffeine intake at levels ranging from 227 to 500 mg, and induction of arrhythmias including supraventricular tachycardia (SVT), palpitation, and premature beats (Lemery et al., 2015; Newby et al., 1996; Zuchinali et al., 2016). The study conducted by Lemery et al. (2015) involved 80 patients with SVT, and although SVT was induced in all but three patients, there was no statistically significant difference between groups receiving placebo or caffeine on inducibility, or the cycle length of induced tachycardias. Caffeine was also not associated with any other electrophysiological effects in the study. Zuchinali et al. (2016) conducted a study of 51 patients with pre-existing heart failure, and reported no statistically significant differences in the number of premature beats, or episodes of tachycardia between those who consumed 500 mg of caffeine, or ingested a placebo lactose pill. The authors concluded that "[t]o date, there is no solid evidence to support the common recommendation to limit moderate caffeine consumption in patients at risk for arrhythmias."

A total of nine observational (6 cohort, 2 cross-sectional, and 1 case-control) studies evaluated the potential relationship between caffeine intake and arrhythmia (Conen et al., 2010; Dixit et al., 2016; Frost and Vestergaard, 2005; Klatsky et al., 2011; Larsson et al., 2015; Mattioli et al., 2005, 2011; Mostofsky et al., 2016; Wilhelmsen et al., 2001b). Among the three cohort studies that evaluated the effects of daily caffeine intakes (based on food frequency questionnaires) greater than 600 mg/day (with mean/median caffeine intakes ranging from 656 to 1137 mg/day), none reported an increased risk of atrial fibrillation or flutter (Conen et al., 2010; Frost and Vestergaard, 2005; Mostofsky et al., 2016). Conen et al. (2010) also reported a statistically significant decreased (protective) risk of atrial fibrillation among women with caffeine consumption ranging from 217 to 326 mg/day. Median follow-up time ranged from 5.7 to 14.4 years, and the study populations ranged in size from 33,638 to 57,053 participants.

Three other cohort studies that evaluated the effects of daily caffeine intakes between 400 and 600 mg reported either a protective effect against any arrhythmia (Klatsky et al., 2011: ≥6 cups of coffee (>570 mg caffeine)/day), or a null effect between coffee consumption (≥475 mg of caffeine) and atrial fibrillation (Larsson et al., 2015; Wilhelmsen et al., 2001b: ≥5 cups/day) compared to those with no or low consumption (<2 cups/day; <190 mg caffeine/day). These intakes were the highest reported in these studies of approximately 7500 to 130,000 participants, who were followed for 12–25 years. A large proportion of the participants from the Wilhelmsen et al. (2001b) study had a history of CVD. Klatsky et al. (2011) also reported statistically significant protective effects against SVT, atrial fibrillation, ventricular fibrillation/flutter/cardiac arrest, and other arrhythmia among participants that reported intakes of ≥4 cups of coffee/day (≥390 mg of caffeine/day) compared to those with no reported coffee consumption. However, Klatsky et al. (2011), did report a statistically significant increased risk of premature beats among participants that reported drinking less than one cup of coffee/day, though when analyzed as a continuous variable, a protective effect was observed, and no increased risk was observed among those reporting intakes ≥4 cups/day (≥380 mg caffeine/day). The authors of a cross-sectional study did not report an increased risk of premature beats among participants who drank low levels of coffee or tea (<100 mg of caffeine/day) (Dixit et al., 2016).

In addition to the two studies discussed previously that evaluated the effects of daily consumption of 100 to <400 mg of caffeine (Conen et al., 2010; Klatsky et al., 2011), Mattioli et al. (2005, 2011) investigated the probability of the resolution of atrial fibrillation through conversion to sinus rhythm (return to normal heart rhythm) within 48 h from the onset of symptoms. In a small case-control study of 116 patients that experienced atrial fibrillation, Mattioli et al. (2005) reported an increased risk of atrial fibrillation, and a decreased probability of conversion to sinus rhythm among participants in the highest intake group (>3 cups of coffee/day; >285 mg caffeine/day) compared to never coffee drinkers. In a small cross-sectional study of 600 patients that experienced their first known episode of atrial fibrillation, moderate coffee drinking (2 cups/day; 190 mg caffeine/day) was associated with 1.13 times lower odds of conversion of atrial fibrillation to sinus rhythm among 247 of the patients that were hypertensive compared to non-habitual coffee drinkers (Mattioli et al., 2011). No statistically significant associations were observed between the other coffee intake categories (low: 1 cup/day − 95 mg caffeine/day or heavy: >3 cups/day − >285 mg caffeine/day) among the hypertensive patients. Normotensive, non-habitual and low coffee consumers had the highest probability of conversion to sinus rhythm within 48 h from the onset of symptoms.

Overall, the evidence suggests that caffeine (from coffee) consumption is not associated with an increased risk of incident arrhythmia of varying types. While reports of a lower probability of atrial fibrillation resolution has been observed in two small observational studies and an effect on conversion to sinus rhythm following an arrhythmia cannot be excluded, the authors of recent experimental and large prospective studies have concluded that moderate to high intakes of caffeine does not increase the risk of incident arrhythmias and are safe even for those with a history of arrhythmia. Several large prospective cohort studies involving caffeine intakes up to more than 600 mg/day did not report an increased risk of arrhythmia, including a report of a protective effect in one study among participants that drank six or more cups of coffee/day.

[6] American Heart Association, http://www.heart.org/HEARTORG/Conditions/Arrhythmia/AboutArrhythmia/About-Arrhythmia_UCM_002010_Article.jsp#.WEnUgWIrLRZ.

3.5. Heart failure

Heart failure, sometimes referred to as congestive heart failure, indicates that the heart isn't pumping blood as well as it should, and the weakened heart can't supply the body's cells with enough blood and oxygen.[7] The most common conditions that can lead to heart failure are CHD, high blood pressure, and previous AMI.[8]

A total of five cohort studies (all observational) evaluated the potential relationship between caffeine intake at various levels (generally in the form of coffee cups/day) and heart failure, and ranged in size from approximately 8000 to 59,000 participants with approximately 9–25 years of follow-up (Ahmed et al., 2009; Levitan et al., 2011; Loomba et al., 2016; Wang et al., 2011; Wilhelmsen et al., 2001a). Participants in these studies were primarily middle-aged or older adults at baseline. In a single study of 7495 Swedish men with a mean follow up of 25.2 years, a 17% increased risk of heart failure was reported among those who drank 5 or more cups of coffee per day (≥475 mg caffeine/day) compared to no intake (OR = 1.17, 95% CI: 1.05, 1.30) after adjustment for age, AMI in brothers or sisters, diabetes, chest pain, smoking, alcohol abuse, high blood pressure, and BMI (Wilhelmsen et al., 2001a). No increased risks were reported among those who drank 1 to 4 cups per day (95–380 mg caffeine/day). The study analyses, interpretations, and conclusions are suspect due to the fact that coffee consumption was recorded only in 1974 through 1977, with follow-up taking place through 1996.

Of the four remaining cohort studies (8608 to 59,490 participants) with approximately 9–19 years of follow-up, no statistically significant increased risks were reported among participants who generally drank five or more cups of coffee per day (400–600 mg caffeine) compared to no or the lowest intake category (Ahmed et al., 2009; Levitan et al., 2011; Loomba et al., 2016; Wang et al., 2011). Wang et al. (2011), who conducted a cohort study in 59,490 Finnish adults, reported a protective effect in women who drank up to 6 cups of coffee per day, while non-statistically significant decreased risks were observed among women who reported 10 or more cups per day. No statistically significant associations were observed for men with consumption up to 10 or more cups of coffee (≥950 mg caffeine) per day, or with tea consumption up to 3 or more cups (≥135 mg caffeine) per day in men or women.

Overall, the available evidence suggests that caffeine intake (primarily from coffee) is not associated with an increased risk of heart failure. Additionally, the largest cohort study available that investigated this relationship reported a protective effect against heart failure among some study participants.

3.6. Sudden cardiac arrest

Sudden cardiac arrest or death (SCA/SCD) is a condition in which the heart suddenly and unexpectedly stops beating, which results in a stoppage of blood flow to the brain and other vital organs. SCA is triggered by an electrical malfunction in the heart that causes an irregular heartbeat (arrhythmia). Heart attacks increase the risk of SCA, but other conditions can disrupt the heart's rhythm and lead to SCA, such as cardiomyopathy (thickening of the heart muscle), heart failure, arrhythmias (particularly ventricular fibrillation), and long Q-T syndrome (AHA 2016 – SCA; NIH 2016).[9]

A total of three observational studies (1 cohort, 2 case-control) evaluated the potential relationship between caffeine intake by adult participants at various levels (generally in the form of coffee cups/day) and SCA or SCD (Bertoia et al., 2013; de Vreede-Swagemakers et al., 1999; Weinmann et al., 1997). In a cohort study of 93,676 postmenopausal women followed-up for 11–16 years (age 50 to 79 at baseline) conducted by Bertoia et al. (2013), no statistically significant relationship was reported between caffeine intake from coffee or tea up to the highest consumption group (mean of 368 mg/day in the fifth quintile compared to 19 mg/day in the first quintile) and SCD. Analyses were adjusted for age, total energy intake, race, income, smoking status, physical activity, waist-to-hip ratio, BMI, atrial fibrillation, coronary artery disease, heart failure, diabetes, high cholesterol, and hypertension.

In contrast, two small case-control studies generated mixed findings depending on coffee intake level and/or smoking status (de Vreede-Swagemakers et al., 1999; Weinmann et al., 1997). de Vreede-Swagemakers et al. (1999) reported a statistically significant increased risk of SCA among 117 SCA patients (all of whom had CHD) who consumed 10 or more cups of coffee per day (approximately 950 mg of caffeine) compared to no coffee intake, i.e., 144 controls with CHD (age 20–75). Confidence intervals for this risk estimate were extremely wide (OR = 55.7, 95%CI: 6.4, 482.8). No statistically significant increased risk was reported for any of the other intake groups ranging from 1 to 10 cups of coffee (95–950 mg caffeine) per day, and no apparent dose-response relationship was observed. The authors noted that "independent effects of smoking and of alcohol and coffee consumption on the risk of SCA are difficult to disentangle because these factors were strongly related to one another."

In the second case-control study of 362 primary cardiac arrest patients, and 581 matched controls (age 25–74), no statistically significant increased risk of SCA was observed with any level of daily coffee consumption compared to those who drank less than 1 cup (95 mg caffeine) per week following a multivariate-adjusted analysis that included smoking history. When stratified by smoking status (and excluding smoking history from the model) statistically significant increased risks of SCA were reported among current smokers and never smokers (but not former smokers) who consumed 5 or more cups of coffee (≥475 mg caffeine) per day. No increased risks were observed among never-smoking individuals in lower coffee intake categories. The latter simply underscores the importance of conducting a multivariate-adjusted analysis in these types of case-control studies to account for potential confounders. No statistically significant increased risk of SCA was observed when the appropriate statistical analyses were performed.

Though some of the available evidence is somewhat limited and mixed (among subjects consuming more than 10 cups of coffee – ≥950 mg caffeine – per day), the results of a large cohort study of women age 50–79 at baseline suggest that intake of 368 mg of caffeine per day is not associated with SCD (Bertoia et al., 2013). In addition, further support of a lack of an association between caffeine intake and SCA comes from results discussed previously, that the risk of development of ventricular fibrillation, one of the leading forms of arrhythmia that can lead to SCA, is statistically significantly decreased among adults who consume 4 or more cups of coffee (≥380 mg caffeine) per day (Klatsky et al., 2011). Some statistically significant increased risks were reported in some sub-

7 American Heart Association, http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/About-Heart-Failure_UCM_002044_Article.jsp#.WEnVDWIrLRZ.

8 American Heart Association, http://www.heart.org/HEARTORG/Conditions/HeartFailure/CausesAndRisksForHeartFailure/Causes-and-Risks-for-Heart-Failure_UCM_002046_Article.jsp#.WEnU9mIrLRZ.

9 American Heart Association, http://www.heart.org/HEARTORG/Conditions/More/MyHeartandStrokeNews/Heart-Attack-or-Sudden-Cardiac-Arrest-How-Are-They-Different_UCM_440804_Article.jsp#.WEnV-2IrLRZ. National Institutes of Health, https://www.nhlbi.nih.gov/health/health-topics/topics/scda.

analyses, including coffee intake of 10 or more cups (≥950 mg caffeine) per day, but these results should be interpreted cautiously given the studies' limitations (de Vreede-Swagemakers et al., 1999; Weinmann et al., 1997).

3.7. Stroke

Stroke occurs when blood flow to an individual's brain is interrupted, causing cell death within the brain due to a lack of proper oxygenation. A stroke may manifest in two primary ways: via blockage of a blood vessel supplying the brain (ischemic stroke), or via bleeding into and around the brain (hemorrhagic stroke). Stroke symptoms include sudden numbness or weakness, sudden confusion, trouble speaking or understanding speech, sudden issues related to balance, and/or sudden severe headache with no known cause.[10]

Overall, 31 total studies evaluated the relationship between caffeine consumption and stroke incidence and/or mortality (Bidel et al., 2006; de Koning Gans et al., 2010; Ding et al., 2015; Floegel et al., 2012; Freedman et al., 2012; Greenberg et al., 2007; Grobbee et al., 1990; Hakim et al., 1998; Jacobsen et al., 1986; Kokubo et al., 2013; Kuriyama et al., 2006; Larsson et al., 2008, 2011, 2013; Leurs et al., 2010; Loomba et al., 2016; Lopez-Garcia et al., 2009; Marchioli et al., 1996; Martin et al., 1988; Mineharu et al., 2011; Mostofsky et al., 2010; Mukamal et al., 2009; Saito et al., 2015; Sesso et al., 2003; Silletta et al., 2007; Sugiyama et al., 2010; Tanabe et al., 2008; Zhang et al., 2009a, 2009b; Liebeskind et al., 2015; Loftfield et al., 2015). All of these observational studies assessed correlations between stroke and self-reported coffee and/or tea consumption. Ten of the 31 stroke-related studies evaluated stroke risk by subtype (Hakim et al., 1998; Kokubo et al., 2013, Kuriyama et al., 2006;Larsson et al., 2008, 2011, 2013; Lopez-Garcia et al., 2009; Mostofsky et al., 2010; Sugiyama et al., 2010; Tanabe et al., 2008; Liebeskind et al., 2015; Loftfield et al., 2015).

There was no statistically significant relationship between coffee and/or tea consumption at any level of consumption investigated and risk of stroke in 19 of 31 the studies (Bidel et al., 2006; de Koning Gans et al., 2010; Ding et al., 2015; Floegel et al., 2012; Greenberg et al., 2007; Grobbee et al., 1990; Jacobsen et al., 1986; Larsson et al., 2008; Leurs et al., 2010; Loomba et al., 2016; Lopez-Garcia et al., 2009; Martin et al., 1988; Mukamal et al., 2009; Sesso et al., 2003; Silletta et al., 2007; Sugiyama et al., 2010; Zhang et al., 2009a, 2009b; Liebeskind et al., 2015). The majority of studies in this group were longitudinal in design except for one large cross-sectional study (n = 12,959 subjects). All observational studies included approximately 3500 to 200,000 participants, reported a mean follow-up period ranging from approximately 2 to 30 years and considered coffee and tea consumption levels varying from 95 to ≥760 mg/caffeine a day.

Nine out of 31 studies reported statistically significant decreased risks of stroke in some coffee and tea consumers, though these decreases in risk were not always consistent across consumption groups, study sub-populations or stroke subtype within individual studies (Freedman et al., 2012; Kokubo et al., 2013; Kuriyama et al., 2006; Larsson et al. 2011, 2013; Mineharu et al., 2011; Saito et al., 2015; Tanabe et al., 2008; Loftfield et al., 2015). Again, these studies were large cohort studies including several thousand participants (ranging from approximately 6400 to 402,000 in number), with mean follow-up periods ranging from approximately 5 to 19 years and with a wide variation of coffee and tea consumption levels (<45 to ≥475 mg/caffeine a day). Within these nine studies, the levels of consumption at which investigators reported decreased risks varied, ranging from 190 to ≥475 mg/day of caffeine from coffee and 180–225 mg/day of caffeine from tea.

Four of these nine studies considering stroke subtypes reported decreased relative risks in the combined stroke categories (i.e., all stroke sub-types combined), but these decreases disappeared when further parsing the population by stroke sub-type (Kokubo et al., 2013; Kuriyama et al., 2006; Larsson et al. 2011, 2013).

Of particular note is one study of 6358 Japanese adults without a history of stroke or heart disease; this study reported that green tea drinkers drinking more than several cups of tea every two to three days were at decreased relative risk of developing cerebral hemorrhage compared to individuals who drank several cups of green tea per week or less (Tanabe et al., 2008). These results were only statistically significant in green tea drinkers; no relationship between tea consumption and stroke was reported among roasted tea drinkers, suggesting that the results may be more related to green tea as a beverage than caffeine as an ingredient.

Three studies out of the 31 total stroke-related studies reported an increased relative risk of stroke associated with some level of coffee consumption (Hakim et al., 1998; Marchioli et al., 1996; Mostofsky et al., 2010). The first study, a cohort study of 499 hypertensive older and middle-aged Hawaiian men followed for 25 years, reported a statistically significant association between consumption of at least 5 cups of coffee per day (≥475 mg caffeine) and thromboembolic (i.e., ischemic) stroke (RR = 2.3, 95% CI: 1.4, 4.0) (Hakim et al., 1998). This particular analysis excluded men with diabetes, and adjusted for age, blood pressure, total cholesterol, triglycerides, alcohol use, and physical activity. This study also excluded past and current smokers from all analyses, and did not identify a statistically significant association for hemorrhagic stroke in any coffee consumption category. The second study, a case-control study of 237 patients at an Italian hospital who have experienced ischemic stroke, reported an increased risk among those reporting at least 5 cups of coffee per day (≥475 mg caffeine, OR = 15.3, 95% CI: 2.4, 97.5) (Marchioli et al., 1996). However, this estimate is limited because of the small number of cases within this consumption category (n = 16), and even smaller number of matched controls (n = 2); the model used for this estimate adjusted for social class, education, alcohol consumption, smoking, *diabetes mellitus*, hypertension, cholesterol, BMI, physical activity and family history of AMI and stroke. Associations were not statistically significant in the other consumption categories. The third study, a case-control study of 390 individuals, mean age 68–70, interviewed shortly after experiencing acute ischemic stroke (median follow-up: 3 days), reported that the risk of experiencing a stroke within one hour of coffee consumption was higher compared to the risk of experiencing a stroke during periods of coffee non-consumption (RR = 2.0, 95% CI: 0.4, 2.4) (Mostofsky et al., 2010). When further considering daily intake of caffeinated coffee in the previous week, the investigators noted that the increased risk of stroke in the hour after consuming coffee was only elevated among those consuming 1 or fewer cups per day (≤95 mg caffeine/day). Those who consumed coffee more regularly were not at increased risk of stroke in the hour after consuming coffee. The statistical significance of these results were retained after sensitivity analyses accounted for coffee consumption at certain times of day and select stroke triggers (i.e., physical activity, anger, alcohol consumption, cigarette smoking).

Overall, the weight of evidence (28 out of 31 studies) suggests that there is no statistically significant association between caffeine consumption (in the form of coffee and/or tea) and the relative risk of stroke.

[10] National Institutes of Health, https://medlineplus.gov/stroke.html.

3.8. Blood pressure

"Blood pressure" is the force of blood pushing against the walls of the arteries as the heart pumps blood. Blood pressure is expressed as a ratio of two measures: systolic blood pressure (SBP), or blood pressure while pumping blood, to diastolic blood pressure (DBP), or blood pressure while the heart rests, in between heartbeats (SBP/DBP).[11] There exist "normal" and "high" thresholds for blood pressure; a normal range encompasses an SBP<120 and DBP<80 mmHg, while "high" blood pressure (also called hypertension) encompasses an SBP>140 and/or a DBP >90 mmHg.[12]

Overall, 130 studies – primarily experimental studies – evaluated the relationship between caffeine consumption and blood pressure changes. Most studies considered exposures ranging from approximately 100 to 400 mg per day (or exposure/dose period).

3.8.1. Controlled exposure (experimental) studies

There were 111 controlled-exposure studies with fixed dose(s) of caffeine administered often via a pill or suspension to subjects, followed by the monitoring of blood pressure changes over the course of a few hours or one day (Addicott et al., 2009; Ammar et al., 2001; Ammon et al., 1983; Arciero et al., 1998, Arciero and Ormsbee, 2009; Astorino et al., 2007; Astorino et al., 2013; Awaad et al., 2011; Bak and Grobbee, 1990, 1991; Barry et al., 2005; Benowitz et al., 1995; Berry et al., 2003; Blaha et al., 2007; Burr et al., 1989; Buscemi et al. 2009, 2010; Cavalcante et al., 2000; Chen and Parrrish, 2009; Childs and de Wit, 2006; Daniels et al., 1998; Del Cosco et al., 2012; Eggertsen et al., 1993; Engels et al., 1999; Farag et al. 2005a, 2005b, 2006, 2010; Fernandez-Elias et al., 2015; Franks et al., 2012; Funatsu et al., 2005; Grasser et al., 2014, 2015; Hamer et al., 2006; Hartley et al., 2000, 2004; Hodgson et al., 1999; Hodgson et al., 2005; Hoffman et al., 2006; Humayun et al., 1997; James, 1994a, 1994b; James and Gregg, 2004; Kaminsky et al., 1998; Karatzis et al., 2005; Kennedy et al., 2008; Kurtz et al., 2013; Lane et al., 1998, 2002; Lemery et al., 2015; Lovallo et al., 1996, 2004; Mahmud and Feely, 2001; Miles-Chan et al., 2015; Mosqueda-Garcia et al., 1990; Noguchi et al., 2015; Notarius et al., 2006a, 2006b; Nussberger et al., 1990; Papaioannou et al., 2006; Papamichael et al., 2005; Passmore et al., 1987; Phan and Shah, 2014; Pincomb et al., 1996; Rachima-Maoz et al., 1998; Ragab et al., 2004; Ragsdale et al., 2010; Rakic et al., 1999; Rashti et al., 2009; Roberts et al., 2005; Robertson et al., 1978, 1981, 1984; Savoca et al., 2004, 2005; Shepard et al., 2000; Sondermeijer et al., 2002; Souza et al., 2014; Steinke et al., 2009; Strandhagen and Thelle, 2003; Stubbs and Macdonald, 1995; Sudano et al., 2005; Sung et al. 1994, 1995; Swampillai et al., 2006; Temple et al., 2010; Terai et al., 2012; Tse et al., 2009; Turley and Gerst, 2006; Turley et al., 2007, 2008; Ulanovsky et al., 2014; Umemura et al., 2006; van Dusseldorp et al., 1991; van Dusseldorp et al., 1989; Vlachopoulos et al., 2003b; Waring et al., 2003; Watson et al., 2000, 2002; Zimmermann-Viehoff et al., 2016; Agudelo-Ochoa et al., 2016; Brothers et al., 2016; Doerner et al., 2015; Domotor et al., 2015; Garcia et al., 2016; Hajsadeghi et al., 2016; Molnar and Somberg, 2015a; Papakonstantinou et al., 2016; Peveler et al., 2016; Shah et al., 2016; Teng et al., 2016). In 19 observational studies, individuals' blood pressures were measured after ascertaining their average daily coffee and/or tea intake (Bakker et al., 2011; Bertrand et al., 1978; Chen et al., 2010; Giggey et al., 2011; Guessous et al., 2012; Hart and Smith, 1997; Larsson et al., 2008; Palatini et al., 1996; Reis et al., 2010; Stensvold et al., 1989; Vlachopoulos et al. 2005, 2007; Wakabayashi et al., 1998; Wang et al., 2011; Wilhelmsen et al., 1977; Wilson et al., 1989; Lopez-Garcia et al., 2016; Palatini et al., 2016; Rhee et al., 2016). Some experimental studies considered special populations – 19 studies measured blood pressure changes in individuals with some form of hypertension (e.g., prehypertension or mild, moderate or established hypertension) (Astorino et al., 2013; Awaad et al., 2011; Eggertsen et al., 1993; Funatsu et al., 2005; Giggey et al., 2011; Hartley et al., 2000; Lovallo et al., 1996; Palatini et al., 1996; Pincomb et al., 1996; Rachima-Maoz et al., 1998; Rakic et al., 1999; Robertson et al., 1984; Shepard et al., 2000; Sung et al. 1994, 1995; Vlachopoulos et al., 2007; Vlachopoulos et al., 2003b; Lopez-Garcia et al., 2016; Palatini et al., 2016), while 7 controlled-exposure studies measured blood pressure changes in adolescents (Savoca et al., 2004, 2005; Temple et al., 2010), children (Turley and Gerst, 2006; Turley et al., 2007, 2008), and infants (Ulanovsky et al., 2014).

The majority of studies (n = 89), of which 85 were controlled-exposure studies, report an increase in blood pressure shortly following caffeine consumption. These 89 studies note increases in either a general measure of blood pressure (i.e., SBP and DBP measures are not independently reported) (n = 10), both SBP and DBP (n = 52), SBP only (n = 24), or DBP only (n = 3). In 32 studies, of which 21 were controlled-exposure studies, no statistically significant association was reported between caffeine consumption and blood pressure changes at any level of consumption; most of these studies considered caffeine consumption ranging from 100 to 400 mg per day. Relative to blood pressure decreases, four observational studies reported decreased blood pressure with increased caffeine consumption at various levels (Larsson et al., 2008; Reis et al., 2010; Stensvold et al., 1989; Wakabayashi et al., 1998), suggestive of caffeine tolerance among regular caffeine consumers. Further, nine controlled-exposure studies recorded "decreases" in blood pressure at some point during the study (Awaad et al., 2011; Bak and Grobbee, 1990; Berry et al., 2003; Funatsu et al., 2005; Notarius et al., 2006b; Passmore et al., 1987; Phan and Shah, 2014; van Dusseldorp et al., 1989; Papakonstantinou et al., 2016). Most of the decreases within these controlled-exposure studies were in response to specific circumstances, e.g., decline in blood pressure following an initial increase in blood pressure, or following a period of coffee abstinence or decaffeinated coffee consumption in habitual caffeine consumers.

3.8.2. Observational studies

Most observational cohort studies (n = 13) identified no statistically significant association between daily coffee consumption at various levels and blood pressure changes (Bakker et al., 2011; Bertrand et al., 1978; Chen et al., 2010; Giggey et al., 2011; Hart and Smith, 1997; Larsson et al., 2008; Palatini et al., 1996; Reis et al., 2010; Wang et al., 2011; Wilhelmsen et al., 1977; Wilson et al., 1989; Palatini et al., 2016; Rhee et al., 2016). One study, rather, identified a protective effect of ≥8 cups (760 mg) of coffee per day among male smokers (age 50–69), compared to male smokers who drink <2 cups (190 mg) of coffee per day (Larsson et al., 2008). The weight of evidence suggests that chronic caffeine consumption at different levels is not associated with sustained changes in blood pressure.

3.8.3. Populations at risk for hypertension or with hypertension

Increases in blood pressure following caffeine consumption (i.e., 100 to <400 mg) were reported in 19 studies of prehypertensive and hypertensive individuals (Astorino et al., 2013; Awaad et al., 2011; Eggertsen et al., 1993; Funatsu et al., 2005; Giggey et al., 2011; Hartley et al., 2000; Lovallo et al., 1996; Palatini et al., 1996;

[11] American Heart Association, http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/AboutHighBloodPressure/About-High-Blood-Pressure_UCM_002050_Article.jsp#.V5uZzvkrJhE.

[12] National Institutes of Health, http://www.nhlbi.nih.gov/health/health-topics/topics/hbp.

Pincomb et al., 1996; Rachima-Maoz et al., 1998; Rakic et al., 1999; Robertson et al., 1984; Shepard et al., 2000; Sung et al. 1994, 1995; Vlachopoulos et al., 2007; Vlachopoulos et al., 2003b; Lopez-Garcia et al., 2016; Palatini et al., 2016). These increases were for SBP only, or SBP and DBP together; DBP alone was not increased in any study. In studies investigating both hypertensive and normotensive individuals, the increases in blood pressure in pre/hypertensive individuals were sometimes stronger in magnitude and sustained for longer periods of time. Accordingly, individuals at risk for hypertension or who already have hypertension may be more sensitive to acute blood-pressure related effects of caffeine compared to normotensive individuals.

3.8.4. Adolescents, children, and infants

As stated previously, seven controlled-exposure studies evaluated blood pressure changes in adolescents, children, and infants (Savoca et al., 2004, 2005; Temple et al., 2010; Turley and Gerst, 2006; Turley et al., 2007, 2008; Ulanovsky et al., 2014). Three studies of adolescents (ages 12–19) reported dose-response increases in SBP and DBP following the consumption of 0–50 mg (0–0.79 mg/kg BW) of caffeine per day, >50–100 mg per day (>0.79–1.6 mg/kg BW), >100 mg (>1.6 mg/kg BW) per day, and up to 200 mg (3.2 mg/kg BW) per day (Savoca et al., 2004, 2005; Temple et al., 2010).

Three studies of children (ages 7–9) consuming caffeine before exercising had disparate findings (Turley and Gerst, 2006; Turley et al., 2007, 2008). One study of children administered approximately 30–160 mg (1.1–5.7 mg/kg BW) caffeine prior to cycling reported statistically significant increases in 1) DBP at all doses while at rest, and 2) SBP at rest only after consuming 160 mg; there was no change in either blood pressure measurement during exercise (Turley et al., 2008). A second study of children administered approximately 160 mg (5.7 mg/kg BW) of caffeine prior to cycling reported statistically significant increases in DBP for boys and girls at rest, and during exercise (Turley and Gerst, 2006). Similar increases were reported in SBP for boys and girls at rest, although SBP was only increased for boys during exercise. The third study, of only boys, administered approximately 160 mg of caffeine prior to cycling reported no statistically significant blood pressure association related to caffeine (Turley et al., 2007).

Finally, a study of 36 premature infants administered a single intravenous dose of 21–28 mg of caffeine (15–20 mg/kg bw) reported no changes in blood pressure within 2 h of administration (Ulanvsky et al., 2014).

Overall, the blood-pressure related effects in adolescents and children appear to be transient and not sustained, and also do not appear to differ substantially from the effects seen in adults.

3.9. Hypertension

Hypertension, also known as “high blood pressure,” occurs when an individual's SBP and/or DBP are consistently elevated (i.e., SBP>140 and/or DBP>90 mmHg).[13] Hypertension is typically diagnosed following multiple observations of high blood pressure in a clinical setting. “Prehypertension,” a criteria used to identify individuals at risk for hypertension, is a classification given to those with an SBP ranging from 120 to 139 mmHg, and/or a DBP ranging from 80 to 89 mmHg. Treatment for hypertension typically includes healthy lifestyle changes and medication such as beta blockers, angiotensin-converting-enzyme inhibitors, diuretics, etc.[14]

The 13 observational studies considered for this section evaluated the correlation between caffeine consumption – based on coffee, tea, and/or caffeinated beverages – and the risk of developing or having hypertension in adults (Bakker et al., 2011; Guessous et al., 2012; Gyntelberg et al., 1995; Hu et al., 2007; Klag et al., 2002; Larsson et al., 2011; Lopez-Garcia et al., 2009; Palatini et al., 2007, 2009, 2016; Rhee et al., 2016; Uiterwaal et al., 2007; Winkelmayer et al., 2005). Studies investigating acute blood pressure changes in hypertensive populations are discussed in Section 3.8 above.

3.9.1. Healthy populations at baseline

Of the 13 total studies, nine studies investigated the relationship between caffeinated-beverage consumption and the risk of hypertension development in adults without hypertension at study initiation (Bakker et al., 2011; Guessous et al., 2012; Hu et al., 2007; Klag et al., 2002; Larsson et al., 2011; Lopez-Garcia et al., 2009; Uiterwaal et al., 2007; Rhee et al., 2016; Winkelmayer et al., 2005). These studies included approximately 6000 to 83,000 participants followed for mean periods of between 9 months and 33 years. Six of these studies with self-reported caffeine intakes up to and exceeding 800 mg/day did not identify a statistically significant increased relative risk of hypertension in any subset of coffee drinkers (Bakker et al., 2011; Guessous et al., 2012; Larsson et al., 2011; Lopez-Garcia et al., 2009; Rhee et al., 2016; Winkelmayer et al., 2005).

Three studies had equivocal findings in that certain subsets of caffeinated-beverage consumers were at increased risk of developing hypertension while others not (Hu et al., 2007; Klag et al., 2002; Uiterwaal et al., 2007). The first, a study of 24,710 Finnish men and women followed for an average of 13.2 years starting from a baseline age of 25–64, identified an increased risk of using antihypertensive treatment (used as a measure for hypertension risk) in individuals drinking 2–7 cups of coffee (190–665 mg caffeine) per day, compared to those drinking ≤1 cup of coffee (≤95 mg caffeine) per day (Hu et al., 2007). However, this relationship was not significant in the ≥760 mg caffeine per day coffee category, and the possibility of reverse causality (use of caffeine to counteract the antihypertensive treatment on their blood pressure) cannot be ruled out.

In a study of 1017 male college graduates (mean age 26 at baseline), those reporting baseline coffee consumption of 3–4 cups (285–380 mg caffeine) per day had a significantly increased risk of developing hypertension compared to those who were non-consumers at baseline (Klag et al., 2002). However, this association was not statistically significant in either the highest (≥5 cups coffee; ≥475 mg caffeine per day) or lowest intake group (1–2 cups coffee; 95–190 mg caffeine per day) compared to coffee abstainers, a similar pattern as reported in the Finnish study. In a study of 6368 Dutch adults (mean age 40 at baseline), the risk of hypertension in women drinking greater than 6 cups of coffee a day (855 mg caffeine) was decreased compared to women drinking 3 cups of coffee or less (0–285 mg caffeine) per day (OR = 0.67, 95% CI: 0.46, 0.98) (Uiterwaal et al., 2007). No statistically significant relationship was observed among men, but in the total population considering both men and women, coffee abstainers were at decreased risk compared to coffee consumers reporting intakes up to 3 cups/day or 285 mg caffeine/d (OR = 0.54, 95% CI: 0.31, 0.92).

Overall, these studies generally suggest no association between caffeine consumption and hypertension development in a baseline healthy population. The three exceptions, noted above, yield inconsistent results.

[13] National Institutes of Health, http://www.nhlbi.nih.gov/health/health-topics/topics/hbp/diagnosis.

[14] National Institutes of Health, http://www.nhlbi.nih.gov/health/health-topics/topics/hbp/treatment.

3.9.2. Hypertensive populations at baseline

Four of the 12 total studies included individuals who were screened for hypertension at the study's initiation and either followed for a period of time or included in a cross-sectional evaluation (Gyntelberg et al., 1995; Palatini et al., 2007, 2009, 2016).

Two studies, using the same Italian cohort of approximately 1000 individuals (age 18–45 at baseline) screened for hypertension and followed for a median of 12.6 years (as of the most recent publication), report similar results with inconsistent statistical significance (Palatini et al., 2007, 2016). In the earlier analysis, those consuming approximately 100–300 mg caffeine (from coffee) per day had an increased risk of sustained hypertension compared to coffee abstainers (HR = 1.27, 95% CI: 1.04, 1.56) (Palatini et al., 2007). Though similar in magnitude, risks were not statistically significant in those consuming >400 mg caffeine per day (HR = 1.24, 95% CI: 0.94, 1.66). In the most recent report of this cohort, only those drinking >300 mg caffeine/day experienced a statistically significant increased risk of sustained hypertension (HR = 1.5, 95% CI: 1.1, 1.9) (Palatini et al., 2016). Results were not statistically significant in those reporting consumption of 100–300 mg caffeine/day (HR = 1.2, 95% CI: 0.99, 1.4). Finally, a study of approximately 3000 Danish men (age 53–74 at baseline) followed for IHD over six years reported no statistically significant correlation between coffee consumption (up to and exceeding intake of 855 mg caffeine/day) and hypertension at baseline (Gyntelberg et al., 1995).

Palatini and colleagues evaluated the influence of CYP1A2 gene variants (*1F and *1A) in approximately 550 men (age 18–45 at baseline) screened for hypertension followed for a median time of 8.2 years (Palatini et al., 2009). Those with the "slow" metabolism allele (CYP1A2*1F) who also drank 100–300, or ≥400 mg caffeine (from coffee)/d were at increased risk of having sustained hypertension compared to their non-consumer counterparts with the same CYP1A2*1F allele variant. In contrast, those with the "fast" metabolism allele (*1A) who also drink ≥400 mg caffeine per day in coffee were at significantly decreased risk of having sustained hypertension compared to their non-coffee consumers counterpart with the same CYP1A2 variant. The decrease in risk was not significant in the 10–300 mg caffeine/d consumers among "fast" metabolizers.

Overall, the results of these studies suggest an association between caffeine consumption among "slow" metabolizers with hypertension at baseline and sustained hypertension, though the magnitude of effect remains small. These findings should be replicated for these subpopulations due to the limited number of available cohort studies.

3.10. Other effects

3.10.1. Heart rate

A total of 101 experimental and 2 observational studies were identified that examined the effect of caffeine intake on heart rate. In the two observational studies, there was no correlation between heart rate and daily coffee consumption in normotensive or hypertensive adults (Vlachopoulos et al., 2005, 2007). Among the 101 experimental studies, the majority involved a single exposure to caffeine among adults and monitoring heart rate at various times thereafter. Among those, 15 reported an increase in heart rate following ingestion of a single dose (130–560 mg) of caffeine (Astorino et al., 2013; Bunsawat et al., 2015; Buscemi et al., 2009, 2011; Del Coso et al., 2012; Grasser et al., 2014, 2015; Lane et al., 1998, 2002; Miles-Chan et al., 2015; Passmore et al., 1987; Peveler et al., 2016; Stadheim et al., 2013; Steinke et al., 2009; Stubbs and Macdonald, 1995), 19 reported a decrease after 80–350 mg (Addicott et al., 2009; Arciero and Ormsbee, 2009; Awaad et al., 2011; Berry et al., 2003; Domotor et al., 2015; Hajsadeghi et al., 2016; Hartley et al., 2004; Lovallo et al., 1996; Molnar and Somberg, 2015a; Papaioannou et al., 2006; Pincomb et al., 1996; Sung et al., 1994, 1995; Temple et al., 2010; Turley and Gerst, 2006; Turley et al., 2007, 2008; Vlachopoulos et al., 2003a; Waring et al., 2003) - including all four studies that involved children (Temple et al., 2010; Turley and Gerst, 2006; Turley et al., 2007, 2008) - while the majority (55) reported no significant change in heart rate after 250–570 mg (Ammar et al., 2001; Ammon et al., 1983; Arciero et al., 1998; Astorino et al., 2013; Bak and Grobbee, 1991; Barry et al., 2005; Baum and Weiss, 2001; Blaha et al., 2007; Bonnet et al., 2005; Bortolotti et al., 2014; Brothers et al., 2016; Burr et al., 1989; Buscemi et al., 2010; Chen and Parrish, 2009; Childs and de Wit, 2006; Daniels et al., 1998; Doerner et al., 2015; Donnerstein et al., 1998; Duncan et al., 2013; Engels et al., 1999; Fernandez-Elias et al., 2015; Garcia et al., 2016; Giacomin et al., 2008; Hajsadeghi et al., 2016; Hodgson et al., 1999; Hoffman et al., 2006; Humayun et al., 1997; Kennedy et al., 2008; Kurtz et al., 2013; Lemery et al., 2015; Miles-Chan et al., 2015; Molnar and Somberg, 2015a,b; Mosqueda-Garcia et al., 1990; Nash et al., 2002; Noguchi et al., 2015; Nussberger et al., 1990; Paton et al., 2015; Pettersen et al., 2014; Peveler et al., 2016; Phan and Shah, 2014; Ragsdale et al., 2010; Rashti et al., 2009; Scott et al., 2015; Shah et al., 2016; Shechter et al., 2011; Sondermeijer et al., 2002; Souza et al., 2014; Sudano et al., 2005; Tse et al., 2009; Turley et al., 2007; Umemura et al., 2006; Vlachopoulos et al., 2003b, 2006; Yeragani et al., 2005; Zimmermann-Viehoff et al., 2016). In some cases, the effect on heart rate from caffeine consumption at similar levels may have appeared to be administration-dependent (i.e., pure caffeine; coffee (filtered, boiled, or espresso); energy drink) but it was not consistent. For example, Passmore et al. (1987) reported no effect on heart rate in men following a dose of 45, 90, or 180 mg, but an <u>increase</u> at a higher dose (360 mg). Conversely, Turley et al. (2008), while also reporting no effect at a low dose (1 mg/kg body weight (b.w.)), reported a decrease in heart rate at higher doses (3 and 5 mg/kg b.w.) in boys (age 7–9). No effect was reported in men at 5 mg/kg b.w. (Turley et al., 2007). Among healthy adults, the effects noted on heart rate from sugar-sweetened energy drink consumption were inconsistent (Peveler et al., 2016; Miles-Chan et al., 2015). Interestingly, no effect on heart rate was observed when the same amount of caffeine was consumed from the sugar-free version of an energy drink or from capsule form (Miles-Chan et al., 2015).

There were 22 studies involving healthy adults with repeated exposures to caffeinated-beverages (6 days–14 weeks duration). Of those, two reported an increase in heart rate following exposure to daily doses of caffeine ranging between 200 and 560 mg (Hamer et al., 2006; Steinke et al., 2009), four reported a decrease with daily doses between 350 and 445 mg (Berry et al., 2003; James, 1994a; James and Gregg, 2004; van Dusseldorp et al., 1989) and 16 reported no significant effect of caffeine consumption on heart rate with daily doses between 250 and 600 mg (Ammon et al.,1983; Bak and Grobbee, 1990, 1991; Burr et al., 1989; Debrah et al., 1995; Eggersten et al., 1993; Farag et al., 2005b, 2006, 2010; Hodgson et al., 1999; James, 1994b; Mosqueda-Garcia et al., 1990; Shah et al., 2016; Strandhagen and Thelle, 2003; van Dusseldorp et al., 1991; Watson et al., 2000).

Overall, caffeine's effect on heart rate remains ambiguous. The majority of studies reported no effect on heart rate, while smaller numbers (about the same in each direction) reported increases or decreases following ingestion of caffeine. While some reported consistent outcomes (Grasser et al., 2014, 2015; Lane et al., 1998, 2002; Sung et al., 1994, 1995; Turley and Gerst, 2006; Turley et al., 2007, 2008), others reported conflicting outcomes (Arciero et al., 1998; Arciero and Ormsbee, 2009; Astorino et al., 2007, 2013; Bak and Grobbee, 1990, 1991; Buscemi et al., 2009, 2010, 2011; James, 1994a,b; James and Gregg, 2004; van Dusseldorp et al., 1989, 1991; Vlachopoulos et al., 2003a,b, 2006).

3.10.2. Cerebral blood flow

The brain requires a substantial and reliable flow of blood to deliver oxygen, glucose, and other nutrients, and remove carbon dioxide, lactic acid, and other metabolic products. This cerebral blood flow (about 50 mL/min/100 g brain tissue, but with considerable regional variation between white and grey matter, and among different portions of grey matter) represents about 15% of the total resting cardiac output, and is tightly regulated by autoregulation to maintain a constant level (Andreoli et al., 2001; De Girolami et al., 1999). Caffeine's effect (45–400 mg) on cerebral blood flow in adults was assessed in 17 experimental studies. Those 13 studies that evaluated intake levels of 175 mg or more reported statistically significant decreases in cerebral blood flow in all subjects (Addicott et al., 2009; Bendlin et al., 2007; Blaha et al., 2007; Chen and Parrish, 2009; Debrah et al., 1995; Field et al., 2003; Lunt et al., 2004; Perthen et al., 2008; Rack-Gomer et al., 2009; Ragab et al., 2004; Sedlacik et al., 2008; Watson et al., 2000, 2002). In line with the 175 mg or higher treatments, two studies of caffeine-naïve or low-caffeine consumers administered a lower dose (114 mg of caffeine from energy drinks) reported significant decreases in cerebral blood flow velocity (Grasser et al., 2014, 2015). One study of 75 mg caffeine intake reported a statistically significant decrease in cerebral blood flow in caffeine-naïve subjects, but no change in habitual consumers (Kennedy and Haskell, 2011). One study investigating effects from 45 mg to 117 mg caffeine among habitual consumers (no caffeine-naïve subjects) found no effect with the lower dose but a slight decrease (though not statistically significant) with the higher dose (Perod et al., 2000). Collectively, these studies suggest a dose-response relationship between caffeine and cerebral blood flow, with greater sensitivity among caffeine-naïve subjects compared to habitual consumers. Caffeine's observed effect on cerebral blood flow may explain its efficacy as an adjuvant for headache relief, as some types of headache are associated with localized increased cerebral blood flow (Sawynok, 1995).

3.10.3. Plasma homocysteine

Based in part on the observation of early onset of cardiovascular disease in patients with homocysteinuria (a congential metabolic disorder), elevated plasma homocysteine has been identified as a risk factor for occlusive cardiovascular disease (Ueland et al., 2000).

Six experimental studies (Christensen et al., 2001; Grubben et al., 2000; Hodgson et al., 2007; Strandhagen et al., 2004; Urgert et al., 2000; Verhoef et al., 2002) and five observational studies (Carlsen et al., 2005; Jacques et al., 2001; Nygard et al., 1997; Panagiotakos et al., 2004; Stolzenberg-Solomon et al., 1999) evaluated the relationship between caffeine intake in adults and blood homocysteine levels. In five experimental studies, coffee consumption for 2–6 weeks (~380–600 mg caffeine/d) resulted in a statistically significant increase in blood homocysteine levels (Christensen et al., 2001; Grubben et al., 2000; Strandhagen et al., 2004; Urgert et al., 2000; Verhoef et al., 2002). In another experimental study, consumption of three cups of tea (~150 mg caffeine) within 3 h similarly increased homocysteine levels (Hodgson et al., 2007). One study (Verhoef et al., 2002) reported a greater effect on plasma homocysteine with 6 cups of coffee containing 870 mg caffeine/day than with the same amount of pure caffeine in 6 capsules/day. The observational studies also showed a more or less consistent relationship between caffeine intake and plasma homocysteine, with evidence of a dose-response relationship: >89 mg caffeine (from coffee)/day in one study (Jacques et al., 2001); ≥63 mg caffeine (from coffee)/day among men and ≥126 mg caffeine (from coffee)/day among women (Panagiotakos et al., 2004). However, there was a weak, but statistically significant inverse relationship between tea consumption and plasma homocysteine level despite an increase in caffeine intake with increasing tea intake (Jacques et al., 2001). The latter suggests that perhaps confounding factors other than beverage caffeine content may be important in modulating plasma homocysteine levels.

It should be noted that while plasma homocysteine has been identified as a risk factor for heart disease (Wald et al., 2002), intervention studies do not show a reduction in heart disease resulting from treatments that reduce plasma homocysteine (Martí-Carvajal et al., 2015). It is therefore unclear if the observed correlation between caffeine intake, and plasma homocysteine level has any meaningful implication for cardiovascular disease risk, particularly in light of the generally negative, or even protective, associations seen between caffeine intake and overall cardiovascular disease risk (see Sections 3.2–4.7).

3.10.4. Serum cholesterol

High serum cholesterol is also recognized as a risk factor for heart disease.[15] Six experimental and six observational studies were identified that evaluated the relationship between caffeine consumption and serum cholesterol in adults. Among the experimental studies, two reported that unfiltered/boiled coffee increased serum cholesterol (Bak and Grobbee, 1989; Stensvold et al., 1989) while three reported that filtered coffee did not (Bak and Grobbee, 1989; Grubben et al., 2000; Agudelo-Ochoa et al., 2016). Two other studies, however, reported that when habitual consumers of filtered coffee abstain from coffee for 3 or 6 weeks their serum cholesterol decreased over the 3 or 6-week period of abstention (Christensen et al., 2001; Strandhagen and Thelle, 2003) and returned to a higher level when they switched to consuming four cups of filtered coffee/day for 4 weeks (Strandhagen and Thelle, 2003). The increase observed in serum cholesterol with unfiltered/boiled coffee has been attributed to the diterpenes (kahweol and cafestol) that are absent in filtered coffee.

Among the observational studies, four reported no statistically significant association between coffee consumption and serum cholesterol (Hart and Smith, 1997; Lopez-Garcia et al., 2009; Reis et al., 2010; Wilson et al., 1989), while two – both from Norway where a high proportion of the population drinks unfiltered boiled coffee – reported a positive association between coffee consumption and serum cholesterol levels (Stensvold et al., 1989; Tverdal et al., 1990). The study by Stensvold et al. (1989) specifically noted that the association between coffee consumption and serum cholesterol was strongest for those who drank boiled unfiltered coffee; for drinkers of filtered coffee, the association was statistically significant only for women. Overall, the results from both experimental and observational studies are mixed. Should there be an association between coffee consumption and serum cholesterol, this is likely due to components in coffee other than caffeine. One study among young adults, found no association between caffeine consumption – administered as pure caffeine with filtered decaffeinated coffee – and serum cholesterol as compared to the control arm, i.e., filtered decaffeinated coffee (Bak and Grobbee, 1991).

3.10.5. Cardiac output

Eleven experimental studies examined the effect of caffeine on cardiac output (the amount of blood the heart pumps in 1 min) in adults (nine in healthy adults; two in mildly hypertensive adults).

[15] National Heart, Lung, and Blood Institute. What are the risk factors for heart disease? https://www.nhlbi.nih.gov/health/educational/hearttruth/lower-risk/risk-factors.htm.

Three studies from the same laboratory (Grasser et al., 2014, 2015; Miles-Chan et al., 2015) reported increased cardiac output in subjects administered 355 mL of a particular energy drink brand containing about 120 mg caffeine. However, Miles-Chan et al. (2015) found no effect on cardiac output when the same amount of caffeine was administered in water or in a sugar-free version of the same energy drink, suggesting a role for sugar in cardiac output. Eight other studies, including two among hypertensive individuals (Sung et al., 1994, 1995), reported no increase in cardiac output when caffeine (~190–393 mg) was administered in unsweetened grapefruit juice (Hartley et al., 2004; Pincomb et al., 1996; Sung et al., 1994, 1995), in capsules (James and Gregg, 2004; Souza et al., 2014), in coffee (Stubbs and Macdonald, 1995) or added to caffeine-free diet cola (Engels et al., 1999).

Overall, there was no evidence of an effect of caffeine *per se* on cardiac output.

3.10.6. Electrocardiogram (EKG) parameters

Thirteen experimental studies, all in healthy adults, were identified that examined the influence of caffeine consumption (in the form of pure caffeine, energy drinks, or coffee) on various EKG parameters. Ten studies reported QTc (QT interval corrected for heart rate): seven reported no effect (Ammar et al., 2001; Brothers et al., 2016; Buscemi et al., 2011; Hajsadeghi et al., 2016; Shah et al., 2016; Steinke et al., 2009; Wiklund et al., 2009), one of which reported an increase in uncorrected QT interval following ingestion of 200–400 mg caffeine (Buscemi et al., 2011); one study reported increased QTc following caffeine intake of 400 mg, but that study involved treadmill exercise to exhaustion (Bunsawat et al., 2015); one reported a shortening of QTc following ingestion of 120 or 240 mg caffeine (from coffee) (Molnar and Somberg, 2015a); and, one reported a shortening of QTc with one type of energy drink, but no effect with two other types, all with similar amounts of caffeine, 147–155 mg (Garcia et al., 2016).

Bonnet et al. (2005) reported only uncorrected QT interval, and found no effect prior to falling asleep, or during non-REM or REM sleep after ingestion of 400 mg caffeine by capsule, consumed 30 min before retiring. Wiklund et al. (2009) reported an increase in PQ interval, but no effect on QRS interval following ingestion of 240 mg caffeine (from an energy drink), while Donnerstein et al. (1998) reported prolonged QRS duration following ingestion of 5 mg/kg bw caffeine (from fruit punch). Caron et al. (2001) and Donnerstein et al. (1998) reported no change in P-wave duration following pure caffeine ingestion (400 mg or 5 mg/kg b.w. [~375 mg]). Shah et al. (2016), in addition to reporting no effect on QTc, also reported no effect on PR, QRS, or QT (uncorrected) interval following a single ingestion of 200 mg caffeine from an energy shot, or twice/day for seven days.

Overall, the evidence of adverse effects on EKG parameters from caffeine consumption is equivocal.

3.10.7. Endothelial/platelet function

One observational and ten experimental studies examined the effect of caffeine consumption on aspects of endothelial or platelet function in adults, mostly healthy, but two studies included subjects with a history of coronary artery disease (Hodgson et al., 2005; Shechter et al., 2011). The single observational study reported no relationship between coffee consumption (ranging from <1 cup (<95 mg caffeine)/month to ≥2 cups (≥190 mg caffeine)/day) and markers of inflammation and endothelial dysfunction (soluble intercellular adhesion molecule 1 [sICAM-1], E-selectin, soluble tumor necrosis factor alpha receptor 2 [sTNF-R2], and high-sensitivity C-reactive protein [CRP]) in healthy adults (Lopez-Garcia et al., 2006b).

Seven experimental studies examined the effect of acute caffeine consumption from coffee (80–240 mg caffeine), black tea (150 mg), energy drink (80–230 mg) or capsule (200 mg) on flow mediated dilation (FMD) of the brachial artery or reactive hyperemia. Two coffee studies reported a decrease in FMD in response to consumption of coffee containing either 80 or 130 mg caffeine (Buscemi et al., 2010; Papamichael et al., 2005), one reported an increase following 54.5 mg caffeine from instant coffee (Noguchi et al., 2015), while two reported no change with 120–240 mg caffeine from regular coffee (Agudelo-Ochoa et al., 2016; Molnar and Somberg, 2015b); the tea study (Hodgson et al., 2005) reported no change in adults with a history of coronary artery disease, while the energy drink study (Molnar and Somberg, 2015b) and the capsule study (Shechter et al., 2011) reported an increase in FMD, particularly in patients with coronary artery disease (Shechter et al., 2011).

Two experimental studies examined the effect of caffeine consumption on *ex vivo* platelet aggregation. One study reported no effect of caffeine ingestion on platelet aggregation in response to ADP, collagen, or adrenaline in blood samples taken from healthy young adults receiving 250 mg of pure caffeine, three times/day for seven days. Platelet aggregation was measured after the first caffeine exposure and after seven days of exposure (Cavalcante at al. 2000). Worthley et al. (2010) reported enhanced platelet aggregation in response to ADP 60 min after consumption of a sugar-free energy drink containing 80 mg caffeine.

Overall, the results of these studies are ambiguous, with no clear relationship between caffeine intake and endothelial or platelet function.

3.10.8. Heart rate variability

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. It is measured by the variation in the beat-to-beat interval. Nine experimental studies evaluated HRV in response to exposure to caffeine. Two studies examined intravenous administration of 4 mg/kg b.w. (~280 mg) in adult chronic heart failure patients (Notarius and Floras, 2012), and 15–20 mg/kg b.w. in premature infants (~21–28 mg) (Ulanovsky et al., 2014). The others, all in healthy adults, involved oral administration of 100 mg or 200 mg caffeine from capsules (Rauh et al., 2006), 100 or 200 mg caffeine added to honey (Sondermeijer et al., 2002), 240 mg caffeine from a particular energy drink brand (Wiklund et al., 2009), 5 mg/kg b.w. caffeine added to caffeine-free diet cola (Yeragani et al., 2005), three times 100 mg caffeine from gum (Thomas et al., 2016), 5 mg/kg b.w. caffeine added to decaffeinated coffee (Domotor et al., 2015), or 257 mg from regular espresso (Zimmermann-Viehoff et al., 2016). Of the oral studies, one reported a decrease in HRV with 100 mg pure caffeine (Sondermeijer et al., 2002) and two reported an increase in HRV with 5 mg/kg (~350 mg) pure caffeine (Domotor et al., 2015; Yeragani et al., 2005) while the other six reported no effect on HRV.

Overall, as with heart rate itself, there was no consistent effect from caffeine intake on heart rate variability.

3.10.9. Plasma and urine catecholamines

The natural catecholamines (epinephrine and/or norepinephrine) act in the body predominantly by stimulating adrenergic receptors. Among other effects, catecholamines can increase blood pressure and heart rate (Landsberg and Young, 1998), with excessive levels of epinephrine potentially triggering arrhythmia (Lüllmann et al., 2000).

Five studies (one observational and four experimental) were identified that examined urinary and/or plasma catecholamines levels upon caffeine consumption in adults. In the observational study, urinary epinephrine was reported to be higher in “heavy” coffee drinkers (>3 cups/day; >285 mg caffeine/day) than in the two other groups (0 or 1–3 cups/day; 95–285 mg caffeine/day) but the differences were not statistically significant (Palatini et al., 1996). All four experimental studies reported increased plasma and/or urinary catecholamines following a single dose of 250 mg caffeine (Debrah et al., 1995; Rachima-Maoz et al., 1998; Robertson et al., 1978, 1981). However, two of these studies also examined repeated exposures (6–7 days, 250 mg/day) and found smaller increases, if any, in plasma and/or urinary catecholamines following ingestion of 250 mg caffeine after multi-day exposure (Debrah et al., 1995; Robertson et al., 1981). The latter may suggest caffeine tolerance. It is, therefore, unclear whether normal exposure to typical levels of caffeine has sufficient effect on catecholamine levels to affect cardiovascular health, though this phenomenon may in part explain the acute effect of caffeine consumption on blood pressure and the tolerance to that effect that develops with repeated exposure (see section 3.8). One possible exception may be in the case of individuals who are homozygous for a low-activity form of the enzyme, catechol-O-methyltransferase (COMT). Such “low COMT-activity” individuals who are also above-average coffee drinkers (≥814 mL/day) appear to show an elevated risk of acute coronary events compared to their “high COMT-activity” homozygous or heterozygous counterparts (Happonen et al., 2006). Interestingly, among individuals homozygous or heterozygous for the high-activity form of the enzyme, those who were above-average coffee drinkers appeared to be at slightly lower risk of acute coronary events than those who drank less coffee.

4. Summary and conclusions

The relationship between caffeine consumption and various cardiovascular health-related outputs has been extensively studied. A simple search for “caffeine AND cardiovascular” in PubMed returns approximately 4000 results of publications. Keeping the vast universe of cardiovascular-related caffeine research in mind, this review aimed to summarize a focused subset of this literature gleaned from high-quality secondary sources and targeted literature searches. A total of 310 relevant articles evaluated a number of cardiovascular disorders, events, and markers of disease. Much of the observational studies considered caffeine via self-reported coffee and/or tea intake, while controlled-exposure studies involved the administration of fixed caffeine doses via pill, suspension, or controlled amounts of coffee, tea, diet cola, energy drinks (regular or diet) or energy shots.

The existing literature suggests moderate (400–600 mg/d) caffeine intake is not associated with increased risks of total cardiovascular disease; arrhythmia; heart failure; blood pressure changes among regular caffeine consumers; and hypertension in baseline healthy populations. On the contrary, consumption of moderate amounts of caffeine is associated with a reduced risk of CVD and may even be protective against CVD. Additionally, caffeine is not consistently associated with changes in heart rate, cardiac output, EKG parameters, or heart rate variability. Evidence is equivocal relative to a relationship between caffeine intake and increased risk of CHD/AMI; sudden cardiac arrest; stroke; elevated serum cholesterol; changes in endothelial/platelet function; and, changes in plasma/urine catecholamines that if present at sufficient levels might otherwise affect cardiovascular health.

Populations at risk for hypertension, or already with hypertension, may be more sensitive to some effects of caffeine; for example, pre/hypertensive populations experienced acute increases in blood pressure following caffeine consumption ranging from 100 to <400 mg per day compared to their normotensive counterparts. Additionally, a small increased relative risk of sustained hypertension related to caffeinated-beverage consumption was observed in pre/hypertensive populations.

The reviewed studies consistently demonstrate a clear relationship between caffeine consumption and decreased cerebral blood flow, with an indication of a dose-response relationship and a tendency for greater sensitivity among caffeine-naïve subjects. Furthermore, while both controlled-exposure and observational studies suggest a correlation between caffeine consumption and plasma homocysteine, it is not clear whether this effect results in increased occlusive cardiovascular disease as interventional studies aimed at lowering plasma homocysteine levels did not result in a concomitant decreased risk.

This review also confirmed observed acute blood pressure changes in response to caffeine consumption. Short-term, transient, and reversible – that is not sustained – increases in blood pressure were observed in almost all controlled-exposure studies evaluating blood pressure changes in response to caffeine administration, with similar effects for a particular dose of caffeine whatever the form of delivery (i.e., powder, tea, coffee, energy drink). However, in most cases, these short-term increases later normalized or did not persist over the course of several days of repeated exposure supporting the concept of caffeine tolerance. Importantly, observational cohort studies (n = 13) identified no statistically significant association between daily caffeine consumption at various levels and blood pressure.

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Appendix A. Supplementary data

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Transparency document

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