

Clearing the Smoke on Cannabis

Respiratory and Cardiovascular Effects of Cannabis Smoking

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Key Points

- Cannabis smoke contains many of the same chemicals as tobacco smoke, several of which are known carcinogens.
- Evidence for a link between cannabis smoking and stroke, heart attack and inflammation of the arteries is limited and still unclear. Further studies are required to clarify whether heavy cannabis smoking is a risk factor for the onset of these complications.
- Cannabis smoking has been related to a greater incidence of coughing, wheezing, sore throat, chest tightness and hoarse voice.
- Evidence for a link between cannabis smoking and serious lung conditions such as cancer or chronic obstructive pulmonary disease is unclear. Further research is needed to clarify whether cannabis smoke is a factor for lung cancer.
- There is emerging evidence that quitting cannabis smoking can reverse some of the negative respiratory symptoms associated with its use.
- Further research is needed to investigate the short- and long-term effects of vaping cannabis on both cardiovascular and respiratory systems.
- It is essential for healthcare professionals to be aware of the impact of cannabis smoking on respiratory and cardiovascular health so that they can inform and advise their patients, as well as develop strategies to promote awareness and general cardiovascular and respiratory health.

Background

After alcohol, cannabis (also referred to as marijuana) is the most widely used psychoactive substance in Canada. According to the 2017 Canadian Tobacco, Alcohol and Drugs Survey (CTADS), 15% of Canadians aged 15 years old and older reported using cannabis at least once in the past year (Statistics Canada, 2017), a significant increase from the 12% reported in 2015. The use of cannabis is generally more prevalent among young people, with 19% of youth aged 15 to 19 and 33% of young adults

This is the fourth in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. This report on the respiratory and cardiovascular effects of cannabis smoking provides an update of a previous report with new research findings that validate and extend our current understanding of this issue. Other reports in this series address the effects of regular cannabis use on cognitive functioning, regular cannabis use and mental health, maternal cannabis use during pregnancy, medical use of cannabis and cannabinoids, cannabis use and driving, and edible cannabis products, cannabis extracts and cannabis topicals. This series is intended for a broad audience, including health professionals, policy makers and researchers.



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aged 20 to 24 reporting past-year use. About 33% of Canadians aged 15 and older who used cannabis in the past three months reported that they used it every day or almost every day.

A growing body of evidence suggests that cannabis use may negatively impact several aspects of people's lives, including mental and physical health, cognitive functioning, ability to drive a motor vehicle, and pre- and post-natal development among offspring. This report — the fourth in a series reviewing the effects of cannabis use on various aspects of human functioning and development (see Gabrys & Porath, 2019; Konefal, Gabrys, & Porath, 2019; Porath, Konefal, & Kent, 2018) — provides an update on the cardiovascular and respiratory effects of cannabis smoking. Following a review of the evidence, this report discusses implications for policy and practice.

Comparison of Cannabis and Tobacco Smoke

Cannabis smoke is usually inhaled from compacted and rolled leaves, analogous to a cigarette (a "joint"), from a water pipe ("bong") or by using a vaping device. It is commonly, but wrongly, believed that because cannabis is a natural plant, inhaling smoke from leaves of the plant is safe. Some reports have compared tobacco and cannabis smoke around the well-established respiratory harms of smoking tobacco, such as lung cancer, chronic obstructive pulmonary disease (COPD) and respiratory infections. These reports have shown that both cannabis and tobacco smoke contain many of the same chemicals and fine particles known to have toxic, mutagenic and carcinogenic effects (Moir et al., 2008).

Indeed, although found at lower concentrations than in tobacco smoke, cannabis smoke contains phenolics, heavy metals, aromatic amines, carbonyls and miscellaneous organics (Moir et al., 2008). Strikingly, some analytes, such as nitride oxides (NO, NO_x) and hydrogen cyanide, and some aromatic amines were found in both cannabis mainstream and sidestream smoke¹ at concentrations up to three to five times higher than the levels found in tobacco smoke (Moir et al., 2008). Ammonia was found at levels three times higher in cannabis sidestream smoke and 20 times higher in cannabis mainstream smoke than in tobacco smoke (Moir et al., 2008). Cannabis smoke also contained toxic chemicals called polycyclic aromatic hydrocarbons with levels higher in sidestream cannabis smoke than tobacco sidestream smoke (Moir et al., 2008). Finally, both cannabis and tobacco smoking have the potential to pass unhealthy levels of aluminum into the body

through the lungs, which might contribute to respiratory and other health problems such as neurological conditions (Exley, Begum, Woolley, & Bloor, 2006). The detection of toxic, mutagenic and carcinogenic compounds in cannabis smoke that are known to be implicated in cardiovascular and respiratory diseases and in cardiovascular morbidity and mortality (Brook et al., 2010; Burnett, Krewski, Jgrrett, Shi, & Calle, 2009) is a public health concern that requires further investigation. The health effects of inhaling cannabis sidestream smoke should also be investigated.

In comparison to individuals who smoke tobacco, those who smoke cannabis tend to take deeper and longer inhalations, use unfiltered cannabis "joints" and smoke to a shorter butt length and at a higher combustion temperature (Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). These behaviours have been linked to four times the amount of tar inhaled and approximately one-third more tar deposits in the respiratory tract (Benson & Bentley 1995; Tashkin et al., 1991a; Tashkin et al., 1991b).

A pre-clinical study evaluated the function of the rat endothelium or inner lining of heart and blood vessels by measuring arterial flow-mediated vasodilation² (Wang et al., 2016). Endothelium plays a crucial role in regulating and controlling cardiovascular functions such as blood flow, blood vessel tone (vasodilatation and vasoconstriction), blood vessel growth and the control of thrombosis (formation of a blood clot in a blood vessel). Researchers have shown that, like the effects of sidestream tobacco smoke, one minute of exposure of rats to sidestream cannabis smoke was able to prevent the endothelium from functioning normally. This harmful effect persisted for 90 minutes, which is a longer effect compared to the endothelium dysfunction caused by sidestream tobacco smoke (Wang et al., 2016). This effect on endothelium function was not induced by Δ9-tetrahydrocannabinol (THC) because it occurred even when the cannabis used lacked cannabinoids (Wang et al., 2016). Impaired endothelium function is known to be associated with increased risks of myocardial infarction, atherosclerosis³ and other heart problems (Celermajer et al., 1992; Flammer et al., 2012; Widlansky, Gokce, Keaney, & Vita, 2003).

These findings strongly suggest that smoke from cannabis can induce adverse cardiovascular effects. More studies and information about the chemistry of cannabis smoke are required to evaluate the potential health risks associated with cannabis smoke exposure. People who use cannabis for medical purposes also need to evaluate the risk/benefit health ratio associated with their medical consumption of cannabis cigarettes.

¹ Mainstream smoke is the smoke exhaled by the person who is smoking, while sidestream smoke is the smoke emitted from the burning tip of the cigarette or joint.

² Arterial flow-mediated vasodilation is a technique to assess endothelium function. It consists in measuring artery dilatation in response to increased blood flow in the artery.

³ Atherosclerosis is the process of progressive formation of plaque in arteries due to fat deposits. Plaque hardens and narrows arteries, resulting in restricted blood flow.

Endocannabinoid System and the Cardiovascular and Respiratory Systems

The brain produces natural compounds called endocannabinoids that act like THC. Endocannabinoids, which include anandamide and 2-arachidonoylglycerol, exert their effects by binding to cannabinoid (CB1 and CB2) receptors. Endocannabinoids, CB1 and CB2 receptors, and the enzymes involved in endocannabinoid degradation make up the endocannabinoid system. CB1 receptors are the most abundant G-protein-coupled receptors in the mammalian brain, where they are responsible for the THC-induced psychoactive effects. Both CB1 and CB2 receptors are also expressed in the cardiovascular and respiratory systems.

Studies in humans and rodents showed that CB1 receptors are expressed in many cells and tissues of the cardiovascular system, including the myocardium, aorta smooth muscle cells, vascular endothelium and blood cells. CB2 receptors are mainly expressed in vascular cells and in immune cells, such as macrophages, eosinophils, monocytes and leucocytes (Turcotte, Chouinard, Lefebvre, & Flamand, 2015). Endocannabinoid synthesis has been identified in vascular cells, cardiac cells, monocytes, lymphocytes, dendritic cells and platelets. Endocannabinoids can have complex effects on cardiovascular functions, ranging from the regulation of vascular activity to controlling and influencing the ability of the heart muscle to contract, the development of new blood vessels and inflammation of blood vessels.

In the respiratory system, CB1 and CB2 receptors are found in the lungs and the bronchial tissue with levels of CB1 receptors higher than those of CB2 receptors (Galiègue et al., 1995). They are also found in the lung alveolar macrophages, where CB2 receptor levels are higher than CB1 receptor levels (Staiano et al., 2016). Given their high expression levels and function in the cardiovascular and respiratory systems, it is not surprising that acute or chronic cannabis use has been linked with severe effects on cardiovascular and respiratory functions, including stroke, heart attack, chronic bronchitis, arrhythmias and blood pressure dysregulations. The cardiovascular and respiratory effects associated with the use of cannabis are discussed in the next sections.

Before outlining the evidence related to the cardiovascular and respiratory effects of cannabis use, it must be acknowledged that a number of issues have made it difficult to identify the consequences of smoking cannabis. First, many individuals who smoke cannabis also smoke tobacco, making it challenging to tease apart the effect of cannabis smoke alone (Rooke, Norberg, Copeland,

& Swift, 2013). Second, the variety, amount and strength of cannabis in a joint can dramatically differ among subjects (Cascini, Aiello, & Di Tanna, 2012; Potter, Clark, & Brown, 2008). Third, studies that rely on self-reported cannabis use might be subject to the under-reporting of consumption (Hashibe et al., 2005). Fourth, many studies have been of participants who are younger and have not had sufficient exposure to cannabis smoke for symptoms of illness to emerge (Mehra et al., 2006). Finally, as will be discussed, the risk of respiratory and cardiovascular effects from cannabis smoke seems to be most prevalent among those who use cannabis daily or almost daily for many years and the sample size of individuals who fall within this category is often quite small (Hashibe et al., 2005).

Cardiovascular Effects of Cannabis Smoking

Heart Attack or Acute Myocardial Infarction

The acute physiological effects of THC in healthy volunteers include cardiovascular effects such as increases in blood pressure and heart rate (Aronow & Cassidy, 1974; Fant, Heishman, Bunker, & Pickworth, 1998; Johnson & Domino, 1971; Roth, Tinklenberg, Kopell, & Hollister, 1973), with the maximal effect on heart rate occurring within 10 to 30 minutes after inhaling cannabis (Benowitz & Jones, 1975; Johnson & Domino, 1971). Orthostatic hypotension (head rush or dizziness on standing up) may also occur as a response to a decrease in vascular resistance, possibly raising the risk of fainting and falling (Benowitz & Jones, 1975; Mathew, Wilson, Humphreys, Lowe, & Wiethe, 1992; Merritta, Cook, & Davis, 1982). Tolerance to some cardiovascular effects induced by cannabis often develops with repeated THC exposure (Benowitz & Jones, 1981; Sidney, 2002). Consequently, long-term use of cannabis tends to decrease blood pressure, heart rate, the ability of the heart to contract and circulatory responses to exercise, and increase blood volume. THC can also cause sinus tachycardia, premature ventricular beats, arrhythmias and thrombosis, and can precipitate angina (Drummer, Gerostamoulos, & Woodford, 2019). The acute and chronic effects of cannabis on heart rate and blood pressure are confirmed by numerous case reports and studies that have demonstrated there might be an association between cannabis smoking and increased risk for acute myocardial infarction or heart attack.

A growing body of evidence shows that in healthy individuals with normal coronary arteries or minimal atherosclerosis cannabis smoking can increase the risk of a heart attack. A study conducted in a cohort of 3,882 patients hospitalized for acute myocardial infarction found that patients who smoked cannabis had a 4.8 times higher risk for developing

an acute myocardial infarction during the hour following cannabis use (Mittleman, Lewis, Maclure, Sherwood, & Muller, 2001). The average age of patients who smoked cannabis was 44 years old compared to 62 years old for patients who did not smoke cannabis. Different results were found in a retrospective cohort study conducted on 62,012 individuals aged between 15 and 49 years old (mean age 33 years old) that assessed the risk for both stroke and acute myocardial infarction associated with cannabis use. The study concluded that cannabis use (both present and previous) were not associated with an increased risk of acute myocardial infarction (Sidney, 2002). The major limitations of this latter study were that it relied on self-reported use of cannabis and that the age of the individual in the study were younger and therefore not typical of the older age range in which acute myocardial infarction often happens. However, several case reports have demonstrated that recent cannabis use was associated with an increased risk of myocardial infarction in healthy young adults (median age 29 years old) (Arora, Goyal, Aggarwal, & Kukar, 2012; Kotsalou et al., 2007; Pearl & Choi, 1992; Safaa, Markham, & Jayasinghe, 2012; Yurtdaş & Aydın, 2012). Finally, a study assessing the serious adverse events related to cannabis use showed that in young and overall healthy individuals who use cannabis hospital admission for severe cardiovascular problems, such as myocardial infarctions, thromboses and cerebral strokes, were associated with recent use of cannabis (Jouanjus, Leymarie, Tubery, & Lapeyre-Mestre, 2011).

In patients with coronary artery disease, the use of cannabis can aggravate coronary ischemia and increase the risk of onset of myocardial infarction (Gaziano, 2008; Lindsay, Foale, Warren, & Henry, 2005). The mortality risk is significantly higher for people with a history of myocardial infarction who use cannabis than in the general population (Frost, Mostofsky, Rosenbloom, Mukamal, & Mittleman, 2013; Mukamal, Maclure, Muller, & Mittleman, 2008). In a study conducted on 1,913 adults hospitalized for myocardial infarction, the researchers found that the risk for mortality was 4.2 times higher in individuals who frequently use cannabis compared with those who do not use cannabis (Mukamal et al., 2008). In contrast, a study of over 2.45 million patients hospitalized for acute myocardial infarction in the United States did not show an increased mortality associated with recent use of cannabis, but did show an increased risk for acute myocardial infarction and other cardiovascular complications such as respiratory failure, cardiac shock⁴ and abnormal heart rhythm (Desai et al., 2017).

Although studies and case reports describe cardiac complications and deaths after recent cannabis use, it must be kept in mind that cannabis is often smoked in combination with tobacco, which makes it difficult to clearly dissociate the effects of the two substances. As well, most of the patients included in the studies were also using other illicit drugs, which prevents a direct conclusion about the specific role of cannabis in the reported cardiovascular disorders and the causality between recent use of cannabis and deaths. However, several case reports have confirmed the relationship between recent use of cannabis and sudden death in young adults (median age 37) with coronary atherosclerosis or other cardiovascular pathology (Bachs & Mørland, 2001; Casier, Vanduyndhoven, Haine, Vrints, & Jorens, 2014; Dines et al., 2015; Hartung, Kauferstein, Ritz-Timme, & Daldrup, 2014; Orsini et al., 2016; Tormey, 2012). The authors of these case reports believed that cannabis use contributed to the deaths as toxicologic studies only revealed the presence of THC in the urine and blood (ranging from two to 22 ng/ml) and no other substances or drugs were detected.

The hypothesis that cannabis is a risk factor for acute myocardial infarction is still controversial and more scientific studies are needed to establish its validity. According to the National Academies of Sciences, Engineering, and Medicine, there is no strong evidence yet for a link between chronic cannabis use and the increased risk of heart attack (National Academies of Sciences, Engineering, and Medicine, 2017), but caution should be taken until more scientific evidence becomes available. Patients who suffer from, or are at high risk of developing, heart disease should be advised that cannabis use might precipitate severe cardiovascular events. Further studies and information about the relationship between cannabis use and acute myocardial infarction are needed to better evaluate the risks on health heart associated with cannabis use.

Strokes and Other Cerebrovascular Events

According to Heart and Stroke Foundation of Canada, strokes represent one of the principal causes of death in Canada with more than 62,000 strokes occurring each year (2018). A stroke is defined as the death of brain cells in a part of the brain due to a disruption of the blood supply in that part of the brain. Strokes can be ischemic (not enough blood or oxygen supply to the brain) or hemorrhagic (bleeding into the brain). Several studies have analyzed the cerebrovascular effects of cannabis use and have demonstrated that in adults it might be an important risk factor for negative cerebrovascular events such as stroke.

⁴ Cardiac shock occurs when the heart is not able to pump enough blood and oxygen to vital organs.

For example, one study found that non-medical cannabis use in patients aged between 15 and 54 years old with a primary diagnosis of acute ischemic stroke increased by 17% the risk for acute ischaemic stroke and by 18% the risk of aneurysmal subarachnoid haemorrhage⁵ (Rumalla, Reddy, & Mittal, 2016a, 2016b). A general population survey conducted on 7,455 Australians showed that 153 cases of stroke or transient ischemic attacks were potentially associated with heavy use of cannabis (Hemachandra, McKetin, Cherbuin, & Anstey, 2016). Indeed, after adjustment for covariates related to stroke, including tobacco smoking, the risk of non-fatal stroke or transient ischemic attack events was 2.3 times higher in individuals who used cannabis regularly (weekly or more often) compared with individuals who did not use cannabis (Hemachandra et al., 2016). In a cross-sectional analysis conducted on adults aged between 18 and 44 years old, results showed that cannabis use was associated with an increased risk of ischemic stroke, but not associated with an increased risk of hemorrhagic stroke (Westover, McBride, & Haley, 2007). Different results were found in a retrospective cohort study of 62,012 individuals aged between 15 and 49 years old (mean age 33 years old) that assessed the risk for both stroke and acute myocardial infarction associated with cannabis use. This study concluded that cannabis use (present and previous) was not associated with an increased risk for stroke (Sidney, 2002).

Other findings from numerous case reports have demonstrated an important relationship between cannabis use and the onset of strokes (ischemic or transient ischemic attacks) (Duchene et al., 2010; Geller, Loftis, & Brink, 2004; Mouzak, Agathos, Kerezoudi, Mantas, & Vourdeli-Yiannakoura, 2000; Renard, Taieb, Gras-Combe, & Labauge, 2012; Singh, Pan, Muengtaweepansa, Geller, & Cruz-Flores, 2012; Wolff & Jouanjus, 2017; Wolff et al., 2011). These reports have shown that strokes tend to occur during or shortly after cannabis inhalation in people who heavily use cannabis (Geller et al., 2004; Mouzak et al., 2000). While more studies are needed to confirm the effects of cannabis use on cerebrovascular events, there is limited evidence in the available literature of a significant association between cannabis use and ischemic stroke or subarachnoid hemorrhage (National Academies of Sciences, Engineering, and Medicine, 2017).

Regular and Heavy Cannabis Use

Although there is no single definition in the scientific literature as to what constitutes regular cannabis use, the phrase generally refers to a pattern that entails weekly or more frequent use over periods of months or years and that poses a risk for adverse health effects. Terms that are often used interchangeably with regular use include frequent use, chronic use and long-term use. Heavy use, by contrast, typically refers to daily or more frequent use, and can be a sign of dependence and cannabis use disorder.

Artery Inflammation or Arteritis

Cannabis arteritis is a little-known and often underdiagnosed peripheral atherosclerotic disease mostly observed in young patients,⁶ which resembles thromboangiitis obliterans⁷ (Grotenhermen, 2010, Subramaniam, Menezes, DeSchutter, & Lavie, 2019, Santos, Resende, Vieira, & Brito, 2017). In contrast with thromboangiitis obliterans, which is strongly linked with heavy tobacco use, cannabis arteritis seems to affect young adults who regularly use cannabis, independent of tobacco consumption (Martin-Blondel, Koskas, Cacoub, & Sene, 2011). Several reports describe severe cases of arteritis that might be associated with the use of cannabis. For example, a young adult male (36 years old) without any significant medical history and vascular risk factor who regularly used cannabis developed digital necrosis⁸ on the right second toe (Peyrot et al., 2007). Arteriography revealed distal segmental lesions and popliteal artery occlusion.⁹ After eliminating other causes, the arteritis was attributed to cannabis use. Because the patient did not reduce or stop his cannabis consumption, and despite the vascular treatments, the symptoms worsened and the toe had to be amputated (Peyrot et al., 2007). More recent similar cases were reported in a 30-year-old male (Santos, Resende, Vieira, & Brito, 2017) and 27-year-old female (El Omri et al., 2017). Both subjects had no significant medical history and regularly used cannabis. The male was hospitalized for distal necrosis of the left big toe and the female for digital necrosis in the left hand. Despite medical treatment, oxygen therapy and cessation or reduction of both cannabis and tobacco consumption, necrotic parts had to be amputated in both cases. The most effective treatment for cannabis arteritis seems

⁵ Aneurysmal subarachnoid haemorrhage is the rupture of a blood vessel causing bleeding in the space between the brain and the tissue covering the brain, the subarachnoid space.

⁶ Peripheral atherosclerotic disease is characterized by narrowed arteries and reduced blood flow to the limbs, brain and heart.

⁷ Thromboangiitis obliterans or Buerger disease is an inflammatory condition related to tobacco smoking that causes blood clot formation in the small and medium-sized arteries of the hands and feet.

⁸ Digital necrosis is the death of most or all of the finger or toe cells.

⁹ The popliteal artery is the direct continuation of the femoral artery. It is localised behind the knee and supplies blood to the knee and lower extremity.

to be the complete cessation of cannabis smoking. Clinical features of cannabis arteritis include claudication,¹⁰ rest pain and gangrene (Thomas, Kloner, & Rezkalla, 2014). Atherosclerotic alterations ranging from mild atherosclerotic plaques to total artery occlusion are often observed by angiography (Thomas et al., 2014). Symptoms can affect both the upper and lower extremities, but most commonly seem to affect the digits of the feet (Ducasse et al., 2004; Peyrot et al., 2007; Subramaniam et al., 2019). However, the hypothesis that cannabis use is a causative factor or a co-factor of arteritis similar to tobacco use for thromboangiitis obliterans is still controversial and not always supported by the available evidence (Grotenhermen, 2010). More scientific studies are needed to support the hypothesis.

Although there is a growing body of evidence relating adverse cardiovascular, cerebrovascular and peripheral vascular disorders to cannabis use, relatively little is known about the underlying mechanisms of these effects. Several hypotheses have been proposed to explain the association between cannabis use and adverse cardiovascular effects.

Cannabis might decrease myocardial oxygen delivery (Gottschalk, Aronow, & Prakash, 1977) and increase vascular resistance and velocity (Herning, Better, Tate, & Cadet, 2005). Cannabis is also able to slow coronary microcirculation (Karabulut & Cakmak, 2010; Rezkalla, Sharma, & Kloner, 2003) and increase platelet coagulability (Dahdouh, Roule, Lognoné, Sabatier, & Grollier, 2012). It has also been demonstrated that cannabis can increase catecholamine levels (Jones, 2002) and induce cerebral vasoconstriction (Ducros et al., 2007; Herning et al., 2005). Cannabis smoking is also associated with an increase in carboxyhemoglobin, which results in increased myocardial oxygen demand and decreased oxygen supply (Aronow & Cassidy, 1975). All of these potential effects induced by cannabis use might lead to adverse cardiovascular, cerebrovascular and peripheral vascular disorders, especially in patients suffering from heart diseases. Further studies are needed to better understand the relationship between cannabis smoking and the onset of these conditions.

How Smoking Cannabis Affects Your Health

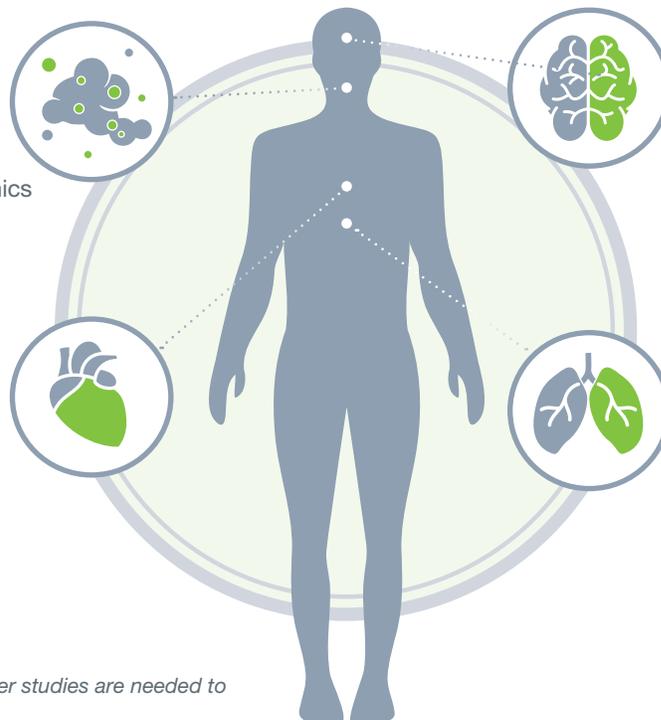
Chemicals In Cannabis Smoke

- Heavy metals
- Aromatic amines
- Carbonyls
- Miscellaneous organics
- Nitride oxids
- Hydrogen cyanide
- Ammonia
- Polycyclic aromatic hydrocarbons

Cerebrovascular Effects

- Impact on heart rate
- Impact on blood pressure

↑ Potential risk of heart attack*



Cardiovascular Effects

↑ Potential risk of stroke*

Effects on the Throat and Lungs

- Sore throat
- Hoarse voice
- Coughing
- Wheezing
- Tightness in chest
- Chronic bronchitis

*Evidence is limited and further studies are needed to confirm this relationship.

¹⁰ Claudication refers to muscle pain or cramping in arms or legs, often triggered by physical activity. The claudication pain results from decreased blood flow into the limbs.

Respiratory Effects of Cannabis Smoking

Regular cannabis smoking can lead to respiratory bronchitis in a high proportion of people who use cannabis. It is puzzling that acutely, cannabis acts a bronchodilator, widening the air passages of the lung (Tashkin, Shapiro, & Frank, 1973; Vachon, Fitzgerald, Solliday, Gould, & Gaensler 1973). However, those who smoke regularly are more likely to report a wide range of respiratory symptoms, including chronic bronchitis. Chronic bronchitis is an inflammation of the lining of the bronchial tubes, the airways which carry air to the lungs, and is defined as “chronic phlegm production or productive cough for three consecutive months per year for at least two consecutive years” (National Academies of Sciences, Engineering, and Medicine, 2018). Although not all individuals who use cannabis will suffer from the most serious conditions, it appears that cannabis smoking is associated with a range of respiratory problems, similar to those observed in people who use tobacco (Moore, Augustson, Moser, & Budney, 2005). In addition, people who regularly smoke cannabis present an elevated risk of outpatient medical services use for respiratory and other illnesses (Moore et al., 2005; Polen, Sidney, Tekawa, Sadler, & Friedman, 1993).

Several studies have indicated that, compared to people who do not smoke, those who smoked cannabis with or without tobacco were more likely to experience chronic coughing, wheezing, aggravation of asthma, sputum production, sore throat, chest tightness, shortness of breath and hoarse voice (Hancox, Shin, Gray, Poulton, & Sears, 2015; Moore et al., 2005; Taylor, Poulton, Moffit, Ramankutty, & Sears, 2000; Tetrault, et al., 2007). Moreover, a national survey in the United States indicated that people who use cannabis reported rates of respiratory symptoms similar to people who had smoked tobacco and were 10 years older, even when accounting for tobacco use, age, gender and current asthma (Moore et al., 2005). These respiratory symptoms likely stem from airway inflammation that can lead to chronic bronchitis (Tashkin, Baldwin, Sarafian, Dubinett, & Roth, 2002). A longitudinal study conducted among 299 participants over a period of approximately 10 years examined the relationship between cannabis use and the onset of symptoms for chronic bronchitis. The study found that people who currently smoke cannabis were more likely to develop coughing, sputum and wheezing when compared to people who never smoke cannabis. More frequent episodes of bronchitis were also observed in people who smoke cannabis currently as compared to individual who never smoke cannabis (Tashkin, Simmons, & Tseng, 2012).

Despite the evidence for a link between cannabis smoking and a wide range of respiratory symptoms, research on the relationship between cannabis and COPD is unclear and conflicting results have been demonstrated. COPD is a progressive lung disease involving damage to the air sacs in the lungs and the narrowing and blocking of the airways. Symptoms include shortness of breath, coughing, excess mucus production and wheezing. While a few older studies have observed a relation between regular cannabis smoking and higher airway obstruction compared to people who do not smoke (Sherrill, Krzyzanowski, Bloom, & Lebowitz, 1991; Taylor et al., 2000; Taylor et al., 2002), many newer reports have observed no relationship (Hancox et al., 2010; Moore et al., 2005; Tashkin, Simmons, Sherrill, & Coulson, 1997).

A review of the literature suggested that the risk of developing COPD is negligible among individuals who occasionally smoke cannabis, but the authors cautioned that further research is needed to eliminate the possibility that chronic regular use can lead to its development (Joshi, Joshi, & Bartter, 2014). A systematic review of 14 studies indicated no dependable relationship between long-term cannabis smoking and airway obstruction (Tetrault et al., 2007). A cohort study that followed 5,115 participants for 20 years observed a non-linear relationship between cannabis smoking and airway obstruction. Essentially, among those with low levels of exposure there was no evidence of adverse effects, whereas among people who use cannabis heavily decreases in air function were found, although the sample size of individuals was small (Pletcher et al., 2012). The largest cross-sectional population study to date in the United States reported that cumulative lifetime cannabis use, up to 20 joint years,¹¹ is not associated with COPD (Kempker, Honig, & Martin, 2015).

Within Canada, a cohort study of 878 individuals over the age of 40 observed that compared to smoking tobacco alone, the combined use of cannabis and tobacco was related to three times the risk of developing COPD. However, this effect was only observed among individuals who reported smoking more than 50 joints in their lifetime, and no association was found between cannabis use alone and COPD (Tan et al., 2009). These effects persisted even after adjustment for potential confounding factors such as age, sex, asthma and other comorbidities, and comparable tobacco exposure in pack years. A population-based cohort study conducted with 1,037 individuals compared the associations between substance use and lung function and found a relationship between cannabis inhalation and hyperinflation. However, no association between cannabis

¹¹ The article defined joint years as the number of joints smoked per day multiplied by the number of years of smoking. For example, if an individual smoked two joints per day for 10 years, they would have a smoking history of 20 joint-years.



use and air flow obstruction was observed (Hancox et al., 2010). Conversely, a population-based study conducted with 5,291 individuals showed that the risk of COPD was significantly increased among individuals aged 40 years and older who use cannabis regularly (Tan et al., 2019). However, these findings should be interpreted with caution as this study had several limitations, including the small number of people who used cannabis only. A cross-sectional study conducted on 339 New Zealanders found that smoking cannabis was associated, depending on dose, with impairment of large airways function resulting in airway obstruction and hyperinflation. However, unlike tobacco smoking, cannabis smoking did not seem to be associated with macroscopic emphysema¹² (Aldington et al., 2007). Due to such conflicting findings, definitive conclusions about the relation between smoking cannabis and COPD cannot be determined based on the existing data.

The relations of other respiratory conditions to cannabis smoking have been examined to a lesser extent. For instance, Ribeiro and Ind reviewed 57 individual cases of bullous lung disease (2018). This disease, also referred to as bullous emphysema, usually presents together with pneumothorax¹³ and is characterized by blisters on the lung that are filled with air from the deterioration of healthy airspace tissue. The majority of the cases described were people who use cannabis heavily. Among the 57 cases, most had predominantly upper lobe involvement often associated with peripheral emphysema. Despite the abnormalities observed, the overall lung function of these individuals was unaffected (Ribeiro & Ind, 2016; Ribeiro & Ind, 2018). Conversely, a case series of 10 patients who were regularly smoking cannabis found that they presented respiratory symptoms (including dyspnoea, pneumothorax and chest infection) associated with asymmetrical emphysematous bullous changes. However, the spirometry, chest radiographs and lung function were normal in most patients (Hii, Tam, Thompson, & Naughton, 2008). Given that these cases are anecdotal in nature, more studies and larger-scale research are required to clarify whether a clear link exists before establishing a definitive conclusion. Similarly, several cases of pneumothorax have been documented in relation to cannabis smoking (Goodyear, Laws, & Turner, 2004; Beshay, Kaiser, Niedhart, Reymond, & Schmid, 2007). These incidences of bullous lung disease and pneumothorax have been thought to arise from the deep inhalation and breath-holding techniques commonly used by people who smoke cannabis.

The research on cannabis smoking and respiratory conditions is too limited to provide estimates of the prevalence of these and other serious health threats. However, given the harms known to be associated with tobacco smoking and the existing evidence suggesting that people who smoke cannabis might demonstrate comparable respiratory symptoms with shorter smoking histories, there is valid concern that prolonged cannabis use could put people who smoke cannabis at potential risk of acquiring serious lung and airway diseases.

Cannabis and the Lung's Immune System Defence

Smoking cannabis regularly can alter the lung's immune system defence. Indeed, the inhalation of THC from cannabis smoke can penetrate into the lungs and airways and cause airway inflammation, consequently increasing the risk of adverse pulmonary conditions (Sarafian et al., 2006). For instance, inflammation, injury and increase in mucoid secretions were observed in the central airways of people who smoke cannabis or tobacco or a combination of both as compared to people who do not smoke (Roth et al., 1998). Biopsies of the central airway mucosa obtained from these subjects showed histological abnormalities such as vascular hyperplasia, abnormal dilatation of blood vessels, accumulation of fluid in submucosa and mononuclear cell infiltrates. The authors speculated that the central airway inflammation observed in people who smoke cannabis was linked with cough and sputum, as well as with abnormal measures of both airway resistance and conductance identified in those subjects (Roth et al., 1998).

THC in human airways can induce cellular changes, especially to mitochondrial cells, which are responsible, in part, for the health of cells and their energy production (Sarafian et al., 2006). Airway inflammation and impairment in mitochondrial energetic functions induced by THC may promote inflammation and infection in the lungs that can in turn lead to severe respiratory illnesses. Data from outpatient medical clinics revealed that, over a two-year assessment period, people who only smoke cannabis used healthcare services for respiratory illnesses more often than people who do not smoke (Polen et al., 1993).

Other cells affected by THC are the alveolar macrophages, which are key defence cells against infections and other toxic damage in the lungs. An accumulation of alveolar macrophages was observed in the lungs of people who smoke cannabis at about twice the level as in people who

¹² Emphysema is a lung condition caused by the damage of alveoli resulting in abnormal presence of air or other gas within lung tissues. Emphysema and chronic bronchitis are two conditions that can lead to chronic obstructive pulmonary disease (COPD).

¹³ Pneumothorax refers to air leaks that put pressure on the space between the lung and chest resulting in a collapsed lung.

do not smoke cannabis. This increased number of alveolar macrophages is believed to be an immune response to chronic lung inflammation induced by chronic exposure to lung irritants found in cannabis smoke (Barbers, Evans, Gong Jr, & Tashkin, 1991; Barbers, Gong Jr, Tashkin, Oishi, & Wallace, 1987). The alveolar macrophages found in the lungs of people who smoke cannabis also showed abnormal cytoplasmic inclusions, a feature that might interfere with the normal immune function of these cells (Fligel, Venkat, Gong Jr, & Tashkin, 1988). Indeed, *ex vivo* studies of alveolar macrophages from people who smoke cannabis showed impairments in their fungicidal, bactericidal and tumoricidal activities, functions that are not altered in alveolar macrophages from people who do not smoke cannabis (Baldwin et al., 1997; Sherman, Campbell, Gong Jr, Roth, & Tashkin, 1991). The THC present in the tar generated from cannabis smoke might be responsible for these alveolar macrophage dysfunctions (Baldwin et al., 1997). THC can also act as an immunosuppressive agent by inhibiting the ability of T-cells to protect the body from foreign pathogens (Shay et al., 2003; Tashkin & Roth, 2007). By its ability to inhibit both T-cells and alveolar macrophage activities, cannabis smoking might cause deficiencies in the immune system and increase susceptibility to opportunistic infections.

A weakened immune response in the lungs could predispose people who smoke cannabis to affliction by viral, bacterial or fungal pathogens that would pose little threat to a healthy immune system (Shay et al., 2003). In fact, fungal contamination has been highlighted as a potential risk of cannabis smoking. In this regard, several case reports of lung infections stemming from a species of fungus that is present on cannabis plants (*Aspergillus fumigatus*) have been observed (Gargani, Bishop, & Denning, 2011; Tashkin, 2005).

It is also believed that cannabis consumption may also worsen illnesses of vulnerable patients. For example, HIV can progress faster to AIDS in HIV-positive patients who smoke cannabis (Tindall et al., 1988). In another study conducted on HIV-positive people matched to HIV-negative controls, researchers evaluated the association between the use of injected drugs and the risk of bacterial pneumonia. They found that cannabis smoking was significantly associated with an increased risk of developing bacterial pneumonia (Caiaffa et al., 1994). However, a detailed analysis of the same cohort over a longer time period failed to find a significant association between HIV-positive or HIV-negative subjects, cannabis smoking and increased risk of pneumonia (Tashkin, Quint, & Detels, 2018). A significant

association between cannabis smoking and pneumonia has recently been reported in HIV positive patients who smoke cannabis, independent of tobacco smoking and other risk factors for lung disease (Lorenz, Uno, Wolinsky, & Gabuzda, 2019). The significant association between cannabis smoking and pneumonia was not found in the HIV-negative patients of the cohort (Lorenz et al., 2019). Overall, the link between cannabis use and negative effects on the immune system in individuals with HIV is still unclear, and more studies are needed to confirm whether cannabis use can worsen illnesses in patients infected with HIV.

There have not been many studies examining the effects of THC and other cannabinoids on the human immune system and more studies are needed to confirm the effects of THC on immune competencies in both healthy and compromised individuals (National Academies of Sciences, Engineering, and Medicine, 2017). However, there is a growing body of preclinical evidence that supports the hypothesis that THC can have the potential to harm immune functioning.

Lung Cancer

The Canadian Cancer Society estimated that 21,200 Canadians would die of lung cancer in 2020, which underscores the importance of examining the carcinogenic effects of smoking cannabis. As noted earlier, cannabis smoke contains many of the same carcinogens that exist in tobacco smoke, making the link between cannabis smoking and lung cancer worth exploring (Tashkin, 2005). There is consistent evidence to suggest that smoking cannabis is associated with premalignant cancerous changes in the lung (Hall & Degenhardt, 2014; Mehra et al., 2006). Despite this evidence, efforts to establish a relationship between cannabis smoking and lung cancer, while also accounting for tobacco smoking, have yielded weak if not non-existent relationships, especially among people who occasionally or moderately smoke cannabis (Tashkin, 2013; Mehra et al., 2006)

A population-based cohort study of 49,321 Swedish male conscripts followed for 40 years observed that lifetime cannabis smoking of at least 50 times at the initial assessment point (i.e., at age 18 to 20 years old) was related to twice the risk of developing lung cancer even when controlling for baseline tobacco use and other confounding factors. This study had several strengths, including a large sample size and long follow-up period. However, the study relied only on the initial assessment of cannabis and tobacco smoking and so it cannot account for these behaviours across the 40-year follow-up. This gap is particularly problematic as 91% of people who smoke cannabis in this

study concurrently smoked tobacco (Callaghan, Allebeck, & Sidorchuk, 2014). Another study that pooled together three samples of male individuals who smoke cannabis in North Africa reported that the odds of developing lung cancer were over twofold greater among individuals who had ever smoked cannabis, although cannabis is usually smoked mixed with tobacco or kief¹⁴ in this region and the effect of tobacco could not be disentangled from any effect of cannabis (Berthiller et al., 2008). A study of lung cancer patients in New Zealand observed an 8% higher risk of lung cancer for every year an individual smoked one joint per day, although once tobacco smoking was accounted for this relationship was only present for those who had more than 10 joint years (Aldington et al., 2008). Conversely, a systematic review of 19 studies spanning from 1996 to 2006 reported no significant relationship between cannabis smoking and lung cancer when controlling for tobacco use (Mehra et al., 2006). A retrospective study of health records across eight years from over 64,855 patients in California found no significant relationship between cannabis smoking and lung cancer when accounting for tobacco. However, the subjects were quite young at the time of the study (between 15 and 49 years old), as well as after the nine-year-follow-up study (Sidney, Quesenberry, Friedman, & Tekawa, 1997). Further, a case control study of 1,212 lung and upper aerodigestive tract cancers compared to 1,040 cancer-free cases did not find a significant relationship between cannabis smoking and cancer once age, gender, ethnicity, education, alcohol and tobacco use were accounted for (Hashibe et al., 2006). The International Lung Cancer Consortium conducted a pooled analysis of 2,159 lung cancer cases and compared them to 2,985 controls. This research group observed little to no significant relation between smoking cannabis and lung cancer, although there was a weak increasing trend among people who regularly and heavily smoke cannabis and lung cancer; however, this group was quite small (Zhang et al., 2015). Finally, a recent systematic review and meta-analysis assessing regular use of cannabis and the risk for developing different types of cancers, including lung, head, neck and urogenital cancer, concluded that despite a potential low risk for development of testicular germ cell tumors, the evidence regarding other types of cancers associated with regular use of cannabis was insufficient (Ghasemiesfe, Barrow, Leonard, Keyhani, & Korenstein, 2019).

Some evidence against an association between cannabis and lung cancer also exists. Cell culture systems and animal model studies show that THC and other cannabinoids directly infused into the tumours might inhibit their growth by regulating certain cell processes, leading to growth arrest and cell death, as well as by inhibiting tumour growth

(for reviews, see Bifulco, Laezza, Pisanti, & Gazzero, 2006; Hall, Christie, & Currow, 2005; Velasco, Sánchez, & Guzmán, 2012). It is important to keep in mind, however, that these inhibitory effects have been demonstrated using THC and other cannabinoids, not cannabis smoke, in preclinical and preliminary clinical testing. The findings do not necessarily imply that exposure to cannabis smoke can prevent cancer occurrence in humans (Velasco et al., 2012). Moreover, the concentrations required to reach such effects are much greater (e.g., 10 times) than the peak blood concentration that would arise from an individual smoking a high dose of cannabis (Sarfraz, Afaq, Adhami, & Mukhtar, 2005).

Overall, the evidence regarding an association between cannabis smoking and lung cancer is unclear and suggests that smoking cannabis does not seem to increase the risk for developing lung cancer. However, more epidemiologic long-term studies are needed to draw a definitive conclusion.

Cannabis Vaping

Vaping is the use of an electronic device (e-cigarette, vape, vape-pen, etc.) with a heating element that, when activated, vaporizes a liquid so that the person who vapes can inhale the vapour. The liquid, made for this purpose and commonly called an “e-liquid,” contains solvents, additives, water, flavourings and diverse active ingredients, usually liquid nicotine or cannabinoids, such as THC and cannabidiol, suspended in oils. The vapours of an e-liquid with THC when inhaled produce psychoactive effects. While nicotine and cannabinoids are the most common psychoactive drugs consumed through vaping (Jones, Hill, Pardini, & Meier, 2016; Tucker et al., 2019), recent evidence shows that e-cigarettes can also be used as a way to deliver other non-medical psychotropic substances, such as methamphetamine and heroin (Breitbart, Morgan, & Jones, 2018; Krakowiak, Poklis, & Peace, 2019).

Earlier studies have suggested that vaping is less harmful to the lungs and respiratory system than cigarette smoking (National Academies of Sciences, Engineering, and Medicine, 2018). Consequently, vaping has emerged as a popular trend for consuming cannabinoids and nicotine, with 29% of cannabis-using individuals (aged 15 years and older) in Canada indicating that vaping is their preferred method for consuming cannabis (Statistics Canada, 2017). While it is believed by consumers that vaping is a healthier alternative to conventional joints, it has recently been demonstrated that this method of cannabis use was linked with severe lung and pulmonary illnesses (Centers for Disease Control and Prevention [CDC], 2019;

¹⁴ Kief is the collected trichomes sifted from dried cannabis.

Health Canada, 2019). The reported symptoms included respiratory dysfunctions (shortness of breath, cough and pleuritic chest pain) and gastrointestinal disorders (diarrhea, nausea and vomiting). A high percentage of patients also showed leukocytosis (high white blood cell count), indicating a strong inflammatory response by the immune system (Layden et al., 2019).

Although no substance or product has yet been clearly identified as the cause for the lung illnesses, it is believed that chemical exposure might play a key role. For example, vitamin E acetate is a compound often used to thicken cannabinoid-infused oils sold in the illicit market and represents a key chemical of concern. Indeed, CDC laboratory analyses found vitamin E acetate in 48 of the 51 fluid samples obtained from the lungs of patients suffering from lung illnesses associated with vaping. Vitamin E acetate is a form of vitamin E usually found in skin care products or dietary supplements. When applied topically or taken orally over a short-term period, vitamin E acetate is harmless. However, the effects of inhaling high doses of vitamin E are currently unknown and while more studies are needed, the CDC and the U.S. Food and Drug Administration have warned that when inhaled vitamin E may alter lung health and provoke severe lung injuries. Indeed, the pyrolysis of vitamin E acetate can produce toxic ketene gas, as well as carcinogen alkenes and benzene, chemicals known for their negative long-term medical effects (Wu & O'Shea, 2020). Other potential toxicants in e-liquids such as flavouring substances, toxic solvents and even pesticides are being investigated.

Vaping cannabis products purchased from legal and regulated retailers and producers in Canada are strictly regulated and assessed for quality and the presence of contaminants. However, although cannabinoid e-liquids in newly legalized products are strictly tested and regulated, concerns about the health effects of vaping cannabis remain. Due to the lack of epidemiological studies and large clinical trials, the short- and long-term health effects of vaping are not known and more studies are required to determine their health impacts.

Quitting Cannabis Smoking

The respiratory health benefits of quitting tobacco cigarette smoking are well known (Anthonisen, Connett, & Murray, 2002; Anthonisen et al., 2005; Doll, Peto, Boreham, & Sutherland, 2004). There are, however, only two studies showing the respiratory effects of quitting cannabis, although they have demonstrated promising findings. In the 10-year longitudinal study conducted by Tashkin et al. (2012), quitting smoking cannabis reduced the likelihood of having chronic bronchitis compared to that of people

who had never smoked. A larger longitudinal study that comprised 1,037 participants followed up at ages 26, 32 and 38 revealed that symptoms of coughing and sputum production were improved among individuals who stopped cannabis smoking regularly (52 or more times in the past year). Among participants who continued smoking, symptoms were maintained or got worse (Hancox et al., 2015). This study also observed that by the age of 38 years, morning cough and wheezing among people who regularly smoke cannabis was persistent even after reducing or quitting cannabis, suggesting that earlier cessation might be most beneficial for improving respiratory symptoms.

Conclusions and Implications

Research indicates that smoking cannabis can harm the lungs, airways, arteries and heart. These harms are evident in the commonly reported symptoms of people who smoke cannabis. Although the evidence is unclear as to whether cannabis smoking is linked with lung cancer, the fact that cannabis smoke contains many of the carcinogens found in tobacco smoke necessitates further research on this topic. Exposure to the lungs to THC is of concern, as it might compromise the immune system defences of the lungs — specifically the ability to defend against foreign pathogens. The cardiovascular effects of cannabis smoking are also a matter for concern. Cannabis can potentially be a trigger for stroke, acute myocardial infarction or arteritis, especially in people suffering from cardiovascular diseases who smoke cannabis heavily.

The dissemination of information on respiratory harms — and indeed all potential harms — linked with cannabis use is intended to convey a clear message that it is not harmless and is associated with a risk of personal harm. The potential for harm to the lungs, airways and immune systems of people who smoke or vape cannabis should be of concern to anyone who inhales cannabis, and to healthcare professionals and policy makers. Effective, evidence-informed initiatives should be implemented to promote knowledge of the respiratory and cardiovascular risks and harms of cannabis smoking, as well as the health benefits of cessation. The public health experience with tobacco smoking prevention, reduction and cessation provides a valuable source of evidence to inform these initiatives. The fact that some of the cardiovascular and respiratory effects of cannabis smoking are similar to tobacco smoking (Ribeiro and Inds, 2016) illustrates the need to achieve similar levels of success with public health campaigns around cannabis use.

The findings from this review have important implications for those who use fresh, dried and oil forms of cannabis for medical purposes. For example, there is concern about the

risk of contaminants, as there can be severe lung harms from smoking contaminated dried cannabis by individuals with compromised immune systems (Thompson et al., 2017; Raber, Elzinga, & Kaplan, 2015). Fortunately, cannabis is regulated for quality in Canada, but there have still been some instances of recalls due to contaminants. This report suggests that cannabis smoking can induce cardiovascular and respiratory symptoms and it is advisable for individuals who have pre-existing cardiovascular or respiratory issues to use alternative medicines, formats or methods of delivery. Indeed, in their preliminary guidance document, the College of Family Physicians of Canada recommends that dried cannabis is not appropriate for individuals who have respiratory disease (2014).

While the effects described in this report pertain to inhaling cannabis smoke, there is emerging evidence that ingesting edible cannabis products can induce similar negative effects on the cardiovascular system. For instance, an observational study comparing adult emergency department visits in Colorado related to edible and inhaled cannabis exposure showed that there were more hospital visits due to cardiovascular symptoms in patients who used edible cannabis products rather than inhaled cannabis products. The severe adverse cardiovascular events reported included myocardial infarction and ventricular dysrhythmia (Monte et al., 2019). While in this study the cannabis doses ingested could not be verified, authors suggested that ingested doses may have been larger than inhaled doses. In addition, some rare cases of cannabis-associated hemorrhagic stroke have also been reported after the ingestion of a large amount of edible cannabis and without any other identified risk factors (Atchaneeyasakul, Torres, & Malik, 2017). These findings should be considered carefully because of the recent legalization of new edible cannabis products and cannabis extracts in Canada. For a more comprehensive account of edible cannabis products, cannabis extracts and cannabis topicals, see Gabrys, 2020.

Further research is also required to examine the long-term safety of cannabis vaping techniques. This research is important as individuals might perceive vaping as a safer alternative despite a lack of research evidence to support this view. Although mostly associated with vaping unregulated cannabis, the recent outbreak of severe lung illnesses remains a concern for public health and reaffirms that more studies are needed to determine the safety of vaping as a method of cannabis use.

Most of the studies in the current review examined self-reported cannabis use, so there remains a gap in our understanding of the different effects on respiratory function according to the type, form and method of use

of cannabis. Cannabis is not a single uniform product and the safety of one cannabis product does not guarantee the safety of another. Indeed, the respiratory effects of other cannabis formulations that are used non-medically, such as “dabs” and “shatter,” are unknown. These products are highly concentrated and produced by extracting THC and other cannabinoids using a solvent (e.g., butane or carbon dioxide). Dabbing is becoming a more common method of inhaling cannabis concentrates, particularly among youth (Stogner & Miller, 2015). A case series conducted in the United States demonstrated that dabbing is associated with significant adverse health effects, including psychosis, neurotoxicity and cardiotoxicity (Alzghari, Fung, Rickner, Chacko, & Fleming, 2017). Although further research is needed, because of their high THC levels, the use of concentrates is associated with a higher risk of over-intoxication than that associated with dried cannabis use (Allen et al., 2017). For a more comprehensive account of the different cannabis product types and methods of delivery, see Gabrys, 2020.

There have also been reports that THC concentrations have been increasing. For example, a recent study of the Washington state legal cannabis market found that cannabis concentrates are now averaging 70% to 80% THC (Davenport, 2019). Determining whether higher levels of THC result in different effects on the respiratory system remains a key area for exploration.

As most individuals initiate cannabis use during adolescence, determining the effects of cannabis smoke on the developing lung is essential. The lung is still undergoing substantial development during adolescence and long-term functional impairments from air pollutant exposure during this time have been demonstrated (Gauderman et al., 2004). Findings such as these raise the question as to what impact cannabis smoke might have during this critical period. Research is also needed to determine whether there are any cardiovascular or respiratory effects due to second-hand cannabis smoke exposure.

Older adults who smoke or ingest cannabis are another population with cardiovascular and respiratory health concerns. Indeed, according to the recent data from the national cannabis survey, cannabis consumption among older adults (ages 65 years and older) has been rising (Statistic Canada 2019). Indeed, more than 400,000 older adults in Canada have used cannabis in the past three months, a dramatic increase from the 40,000 older adults who reported using cannabis in 2012. Since the older population is at greater risk for stroke, and respiratory and cardiovascular complications, cannabis use could be a trigger for accelerating these conditions.

Regular cannabis smoking among youth, and young and older adults has the potential to increase the burden on healthcare systems. The negative effects of cannabis smoking are compounded when a person who smokes cannabis also regularly smokes tobacco (Ribeiro & Ind, 2016). More research is needed to better understand the impact of long-term regular use of cannabis on respiratory

and cardiovascular systems. Healthcare professionals must inform people who smoke cannabis, whether potential, confirmed or suspected, and whether for non-medical or medical purposes, of the potential harms associated with smoking cannabis, and develop strategies to promote further awareness and general cardiovascular and respiratory health.

References

- Aldington, S., Williams, M., Nowitz, M., Weatherall, M., Pritchard, A., McNaughton, A., & Beasley, R. (2007). Effects of cannabis on pulmonary structure, function and symptoms. *Thorax*, 62(12), 1058–1063.
- Aldington, S., Harwood, M., Cox, B., Weatherall, M., Beckert, L., Hansell, A., ... Beasley, R. (2008). Cannabis use and risk of lung cancer: A case-control study. *European Respiratory Journal*, 31(2), 280–286.
- Allen, J.A., Davis, K.C., Duke, J.C., Nonnemaker, J.M., Bradfield, B.R., & Farrelly, M.C. (2017). New product trial, use of edibles, and unexpected highs among marijuana and hashish users in Colorado. *Drug and Alcohol Dependence*, 176, 44–47.
- Alzghari, S.K., Fung, V., Rickner, S.S., Chacko, L., & Fleming, S.W. (2017). To dab or not to dab: Rising concerns regarding the toxicity of cannabis concentrates. *Cureus*, 9(9), e1676.
- Anthonisen, N.R., Connett, J.E., & Murray, R.P. (2002). Smoking and lung function of Lung Health Study participants after 11 years. *American Journal of Respiratory and Critical Care Medicine*, 166(5), 675–679.
- Anthonisen, N.R., Skeans, M.A., Wise, R.A., Manfreda, J., Kanner, R.E., & Connett, J.E. (2005). The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. *Annals of Internal Medicine*, 142(4), 233–239.
- Aronow, W.S., & Cassidy, J. (1974). Effect of marijuana and placebo-marijuana smoking on angina pectoris. *New England Journal of Medicine*, 291(2), 65–67.
- Aronow, W.S., & Cassidy, J. (1975). Effect of smoking marijuana and of a high-nicotine cigarette on angina pectoris. *Clinical Pharmacology and Therapeutics*, 17(5), 549–554.
- Arora, S., Goyal, H., Aggarwal, P., & Kukar, A. (2012). ST-segment elevation myocardial infarction in a 37-year-old man with normal coronaries — It is not always cocaine! *American Journal of Emergency Medicine*, 30(9), 2091.e3–2091.e5.
- Atchaneeyasakul, K., Torres, L.F., & Malik, A.M. (2017). Large amount of cannabis ingestion resulting in spontaneous intracerebral hemorrhage: A case report. *Journal of Stroke and Cerebrovascular Diseases*, 26(7), e138–e139.
- Bachs, L., & Mørland, H. (2001). Acute cardiovascular fatalities following cannabis use. *Forensic Science International*, 124(2-3), 200–203.
- Baldwin, G.C., Tashkin, D.P., Buckley, D.M., Park, A.N., Dubinett, S.M., & Roth, M.D. (1997). Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American Journal of Respiratory and Critical Care Medicine*, 156(5), 1606–1613.
- Barbers, R.G., Evans, M.J., Gong Jr, H., & Tashkin, D.P. (1991). Enhanced alveolar monocyte phagocyte(macrophage) proliferation in tobacco and marijuana smokers. *American Journal of Respiratory and Critical Care Medicine*, 143(5), 1092–1095.
- Barbers, R.G., Gong Jr, H., Tashkin, D.P., Oishi, J., & Wallace, J.M. (1987). Differential examination of bronchoalveolar lavage cells in tobacco cigarette and marijuana smokers. *American Review of Respiratory Disease*, 135(6), 1271–1275.
- Benowitz, N.L., & Jones, R.T. (1975). Cardiovascular effects of prolonged delta-9-tetrahydrocannabinol ingestion. *Clinical Pharmacology and Therapeutics*, 18(3), 287–297.
- Benowitz, N.L., & Jones, R.T. (1981). Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *Journal of Clinical Pharmacology*, 21(S1), 214S–223S.
- Benson, M.K., & Bentley, A.M. (1995). Lung disease induced by drug addiction. *Thorax*, 50(11), 1125–1127.
- Berthiller, J., Straif, K., Boniol, M., Voirin, N., Benhaim-Luzon, V., Ayoub, W.B., ... Sasco, A.J. (2008). Cannabis smoking and risk of lung cancer in men: A pooled analysis of three studies in Maghreb. *Journal of Thoracic Oncology*, 3(12), 1398–1403.
- Beshay, M., Kaiser, H., Niedhart, D., Reymond, M.A., & Schmid, R.A. (2007). Emphysema and secondary pneumothorax in young adults smoking cannabis. *European Journal of Cardio-Thoracic Surgery*, 32(6), 834–838.
- Bifulco, M., Laezza, C., Pisanti, S., & Gazzero, P. (2006). Cannabinoids and cancer: Pros and cons of an antitumour strategy. *British Journal of Pharmacology*, 148(2), 123–135.
- Breitbarth, A.K., Morgan, J., & Jones, A.L. (2018). E-cigarettes — An unintended illicit drug delivery system. *Drug and Alcohol Dependence*, 192, 98–111.
- Brook, R.D., Rajagopalan, S., Pope III, C.A., Brook, J.R., Bhatnagar, A., Diez-Roux, A.V., ... Mittleman, M.A. (2010). Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation*, 121(21), 2331–2378.

- Burnett, R., Krewski, D., Jgrrett, M., Shi, Y., & Calle, E. (2009). Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: Shape of the exposure-response relationship. *Circulation*, 120(11), 941–948.
- Caiaffa, W.T., Vlahov, D., Graham, N., Astemborski, J., Solomon, L., Nelson, K.E., & Munoz, A. (1994). Drug smoking, pneumocystis carinii pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *American Journal of Respiratory and Critical Care Medicine*, 150(6), 1493–1498.
- Callaghan, R., Allebeck, P., & Sidorchuk, A. (2013). Marijuana use and risk of lung cancer: A 40-year cohort study. *Cancer Causes and Control*, 24(10), 1811–1820.
- Cascini, F., Aiello, C., & Di Tanna, G. (2012). Increasing delta-9-tetrahydrocannabinol (Δ -9-THC) content in herbal cannabis over time: Systematic review and meta-analysis. *Current Drug Abuse Reviews*, 5(1), 32–40.
- Casier, I., Vanduyhoven, P., Haine, S., Vrints, C., & Jorens, P.G. (2014). Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. *Acta Cardiologica*, 69(2), 131–136.
- Celermajer, D.S., Sorensen, K.E., Gooch, V., Spiegelhalter, D., Miller, O., Sullivan, I., & Deanfield, J. (1992). Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *The Lancet*, 340(8828), 1111–1115.
- Centers for Disease Control and Prevention. (2020). Outbreak of lung injury associated with e-cigarette use, or vaping. Retrieved from https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.
- College of Family Physicians of Canada. (2014). *Authorizing dried cannabis for chronic pain or anxiety: Preliminary guidance*. Mississauga, Ont.: Author.
- Dahdouh, Z., Roule, V., Lognoné, T., Sabatier, R., & Grollier, G. (2012). Cannabis and coronary thrombosis: What is the role of platelets? *Platelets*, 23(3), 243–245.
- Davenport, S. (2019). Price and product variation in Washington's recreational cannabis market. *International Journal of Drug Policy*, 102547.
- Desai, R., Patel, U., Sharma, S., Amin, P., Bhuva, R., Patel, M.S., & Savani, S. (2017). Recreational marijuana use and acute myocardial infarction: Insights from nationwide inpatient sample in the United States. *Cureus*, 9(11), e1816.
- Dines, A.M., Wood, D.M., Galicia, M., Yates, C.M., Heyerdahl, F., Hovda, K.E., ... Dargan, P.I. (2015). Presentations to the emergency department following cannabis use — A multi-centre case series from ten European countries. *Journal of Medical Toxicology*, 11(4), 415–421.
- Doll, R., Peto, R., Boreham, J., & Sutherland, I. (2004). Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*, 328, 1519.
- Drummer, O.H., Gerostamoulos, D., & Woodford, N.W. (2019). Cannabis as a cause of death: A review. *Forensic Science International*. 298, 298–306.
- Ducasse, E., Chevalier, J., Dasnoy, D., Speziale, F., Fiorani, P., & Puppink, P. (2004). Popliteal artery entrapment associated with cannabis arteritis. *European Journal of Vascular and Endovascular Surgery*, 27(3), 327–332.
- Duchene, C., Olindo, S., Chausson, N., Jeannin, S., Cohen-Tenoudji, P., & Smadja, D. (2010). Cannabis-induced cerebral and myocardial infarction in a young woman. *Revue Neurologique*, 166(4), 438–442.
- Ducros, A., Boukobza, M., Porcher, R., Sarov, M., Valade, D., & Bousser, M.-G. (2007). The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain*, 130(12), 3091–3101.
- El Omri, N., Eljaoudi, R., Mekouar, F., Jira, M., Sekkach, Y., Amezyane, T., & Ghafir, D. (2017). Cannabis arteritis. *Pan African Medical Journal*, 26(53), 11694.
- Exley, C., Begum, A., Woolley, M.P., & Bloor, R.N. (2006). Aluminum in tobacco and cannabis and smoking-related disease. *American Journal of Medicine*, 119(3), 276.e9–276.e11.
- Fant, R.V., Heishman, S.J., Bunker, E.B., & Pickworth, W.B. (1998). Acute and residual effects of marijuana in humans. *Pharmacology Biochemistry and Behavior*, 60(4), 777–784.
- Flammer, A.J., Anderson, T., Celermajer, D.S., Creager, M.A., Deanfield, J., Ganz, P., & Taddei, S. (2012). The assessment of endothelial function: from research into clinical practice. *Circulation*, 126(6), 753–767.
- Fligiel, S.E., Venkat, H., Gong Jr, H., & Tashkin, D.P. (1988). Bronchial pathology in chronic marijuana smokers: A light and electron microscopic study. *Journal of Psychoactive Drugs*, 20(1), 33–42.
- Frost, L., Mostofsky, E., Rosenbloom, J.I., Mukamal, K.J., & Mittleman, M.A. (2013). Marijuana use and long-term mortality among survivors of acute myocardial infarction. *American Heart Journal*, 165(2):170–175.
- Gabrys, R. (2020). *Clearing the smoke on cannabis: Edible cannabis products, cannabis extracts and cannabis topicals*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction.
- Gabrys, R., & Porath, A.J. (2019). *Clearing the smoke on cannabis: Regular use and cognitive functioning*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction.
- Galiègue, S., Mary, S., Marchand, J., Dussossoy, D., Carrière, D., Carayon, P., & Casellas, P. (1995). Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *European Journal of Biochemistry*, 232(1), 54–61.
- Gargani, Y., Bishop, P., & Denning, D.W. (2011). Too many mouldy joints — Marijuana and chronic pulmonary aspergillosis. *Mediterranean Journal of Hematology and Infectious Diseases*, 3(1), e2011005.
- Gauderman, W.J., Avol, E., Gilliland, F., Vora, H., Thomas, D., Berhane, K., ... Peters, J. (2004). The effect of air pollution on lung development from 10 to 18 years of age. *New England Journal of Medicine*, 351(11), 1057–1067.

- Gaziano, J.M. (2008). Marijuana use among those at risk for cardiovascular events. *American Heart Journal*, 155(3), 395–396.
- Ghasemiesfe, M., Barrow, B., Leonard, S., Keyhani, S., & Korenstein, D. (2019). Association between marijuana use and risk of cancer: A systematic review and meta-analysis. *JAMA Network Open*, 2(11), e1916318.
- Geller, T., Loftis, L., & Brink, D.S. (2004). Cerebellar infarction in adolescent males associated with acute marijuana use. *Pediatrics*, 113(4), e365–e370.
- Goodyear, K., Laws, D., & Turner, J. (2004). Bilateral spontaneous pneumothorax in a cannabis smoker. *Journal of the Royal Society of Medicine*, 97(9), 435–436.
- Gottschalk, L.A., Aronow, W.S., & Prakash, R. (1977). Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological cardiovascular functioning in anginal patients. *Biological Psychiatry*, 12(2), 255–266.
- Grotenhermen, F. (2010). Cannabis-associated arteritis. *VASA. Zeitschrift für Gefässkrankheiten*, 39(1), 43–53.
- Hall, W., Christie, M., & Currow, D. (2005). Cannabinoids and cancer: Causation, remediation, and palliation. *The Lancet Oncology*, 6(1), 35–42.
- Hall, W., & Degenhardt, L. (2014). The adverse health effects of chronic cannabis use. *Drug Testing and Analysis*, 6(1–2), 39–45.
- Hancox, R.J., Poulton, R., Ely, M., Welch, D., Taylor, D.R., McLachlan, C.R., ... Sears, M.R. (2010). Effects of cannabis on lung function: A population-based cohort study. *European Respiratory Journal*, 35(1), 42–47.
- Hancox, R.J., Shin, H.H., Gray, A.R., Poulton, R., & Sears, M.R. (2015). Effects of quitting cannabis on respiratory symptoms. *European Respiratory Journal*, 46(1), 80–87.
- Hartung, B., Kaufenstein, S., Ritz-Timme, S., & Daldrup, T. (2014). Sudden unexpected death under acute influence of cannabis. *Forensic Science International*, 237, e11–e13.
- Hashibe, M., Morgenstern, H., Cui, Y., Tashkin, D.P., Zhang, Z.F., Cozen, W., ... Greenland, S. (2006). Marijuana use and the risk of lung and upper aerodigestive tract cancers: Results of a population-based case-control study. *Cancer Epidemiology Biomarkers and Prevention*, 15(10), 1829–1834.
- Hashibe, M., Straif, K., Tashkin, D.P., Morgenstern, H., Greenland, S., & Zhang, Z. (2005). Epidemiologic review of marijuana use and cancer risk. *Alcohol*, 35(3), 265–275.
- Health Canada. (2019). Information Update - Health Canada warns of potential risk of pulmonary illness associated with vaping products. Retrieved from <https://healthykanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/70919a-eng.php>
- Heart and Stroke Foundation of Canada. (2018). 2018 Stroke Report. Ottawa, Ont.: Author. Retrieved from <https://www.heartandstroke.ca/-/media/pdf-files/canada/stroke-report/strokereport2018.ashx?rev=8491d9c349f7404491f36be67f649c0b&hash=1BC-C40A8A71C6EE5CBB3BEE2AD1941B7>
- Hemachandra, D., McKetin, R., Cherbuin, N., & Anstey, K.J. (2016). Heavy cannabis users at elevated risk of stroke: Evidence from a general population survey. *Australian and New Zealand Journal of Public Health*, 40(3), 226–230.
- Herning, R.I., Better, W.E., Tate, K., & Cadet, J.L. (2005). Cerebrovascular perfusion in marijuana users during a month of monitored abstinence. *Neurology*, 64(3), 488–493.
- Hii, S.W., Tam, J.D., Thompson, B.R., & Naughton, M.T. (2008). Bullous lung disease due to marijuana. *Respirology*, 13(1), 122–127.
- Johnson, S., & Domino, E.F. (1971). Some cardiovascular effects of marijuana smoking in normal volunteers. *Clinical Pharmacology and Therapeutics*, 12(5), 762–768.
- Jones, C.B., Hill, M.L., Pardini, D.A., & Meier, M.H. (2016). Prevalence and correlates of vaping cannabis in a sample of young adults. *Psychology of Addictive Behaviors*, 30(8), 915–921.
- Jones, R.T. (2002). Cardiovascular system effects of marijuana. *Journal of Clinical Pharmacology*, 42(S1), 58S–63S.
- Joshi, M., Joshi, A., & Bartter, T. (2014). Marijuana and lung diseases. *Current Opinion in Pulmonary Medicine*, 20(2), 173–179.
- Jouanjus, E., Leymarie, F., Tubery, M., & Lapeyre-Mestre, M. (2011). Cannabis-related hospitalizations: Unexpected serious events identified through hospital databases. *British Journal of Clinical Pharmacology*, 71(5), 758–765.
- Karabulut, A., & Cakmak, M. (2010). ST segment elevation myocardial infarction due to slow coronary flow occurring after cannabis consumption. *Kardiologia Polska*, 68(11), 1266–1268.
- Kempker, J.A., Honig, E.G., & Martin, G.S. (2015). The effects of marijuana exposure on expiratory airflow. A study of adults who participated in the U.S. National Health and Nutrition Examination Study. *Annals of the American Thoracic Society*, 12(2), 135–141.
- Konefal, S., Gabrys, R., & Porath, A.J. (2019). *Clearing the smoke on cannabis: Regular use and mental health*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction.
- Kotsalou, I., Georgoulas, P., Karydas, I., Fourlis, S., Sioka, C., Zoumboulidis, A., & Demakopoulos, N. (2007). A rare case of myocardial infarction and ischemia in a cannabis-addicted patient. *Clinical Nuclear Medicine*, 32(2), 130–131.

- Krakowiak, R.I., Poklis, J.L., & Peace, M.R. (2019). The analysis of aerosolized methamphetamine from e-cigarettes using high resolution mass spectrometry and gas chromatography mass spectrometry. *Journal of Analytical Toxicology*, 43(8), 592–599.
- Layden, J.E., Ghinai, I., Pray, I., Kimball, A., Layer, M., Tenforde, M., ... Meiman, J. (2019). Pulmonary illness related to e-cigarette use in Illinois and Wisconsin — Preliminary report. *New England Journal of Medicine*.
- Lindsay, A.C., Foale, R.A., Warren, O., & Henry, J.A. (2005). Cannabis as a precipitant of cardiovascular emergencies. *International Journal of Cardiology*, 104(2), 230–232.
- Lorenz, D.R., Uno, H., Wolinsky, S.M., & Gabuzda, D. (2019). Effect of marijuana smoking on pulmonary disease in HIV-infected and uninfected men: a longitudinal cohort study. *EClinicalMedicine*, 7, 55–64.
- Martin-Blondel, G., Koskas, F., Cacoub, P., & Sene, D. (2011). Is thromboangiitis obliterans presentation influenced by cannabis addiction? *Annals of Vascular Surgery*, 25(4), 469–473.
- Mathew, R., Wilson, W., Humphreys, D., Lowe, J., & Wieth, K. (1992). Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta Psychiatrica Scandinavica*, 86(2), 173–178.
- Mehra, R., Moore, B.A., Crothers, K., Tetrault, J., & Fiellin, D.A. (2006). The association between marijuana smoking and lung cancer: A systematic review. *Archives of Internal Medicine*, 166(13), 1359–1367.
- Merritt, J.C., Cook, C.E., & Davis, K.H. (1982). Orthostatic hypotension after Δ 9-tetrahydrocannabinol marijuana inhalation. *Ophthalmic Research*, 14(2), 124–128.
- Mittleman, M.A., Lewis, R.A., Maclure, M., Sherwood, J.B., & Muller, J.E. (2001). Triggering myocardial infarction by marijuana. *Circulation*, 103(23), 2805–2809.
- Moir, D., Rickert, W.S., Levasseur, G., Larose, Y., Maertens, R., White, P., & Desjardins, S. (2008). A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chemical Research in Toxicology*, 21(2), 494–502.
- Monte, A.A., Shelton, S.K., Mills, E., Saben, J., Hopkinson, A., Sonn, B., ... Abbott, D. (2019). Acute illness associated with cannabis use, by route of exposure: An observational study. *Annals of Internal Medicine*, 170(8), 531–537.
- Moore, B.A., Augustson, E.M., Moser, R.P., & Budney, A.J. (2005). Respiratory effects of marijuana and tobacco use in a U.S. sample. *Journal of General Internal Medicine*, 20(1), 33–37.
- Mouzak, A., Agathos, P., Kerezoudi, E., Mantas, A., & Vourdeli-Yiannakoura, E. (2000). Transient ischemic attack in heavy cannabis smokers — How ‘safe’ is it? *European Neurology*, 44(1), 42–44.
- Mukamal, K.J., Maclure, M., Muller, J.E., & Mittleman, M.A. (2008). An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *American Heart Journal*, 155(3), 465–470.
- National Academies of Sciences, Engineering, and Medicine. (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, D.C.: National Academies Press.
- National Academies of Sciences, Engineering, and Medicine (2018). *Public health consequences of e-cigarettes*. Washington, D.C.: National Academies Press.
- Orsini, J., Blaak, C., Rajayer, S., Gurung, V., Tam, E., Morante, J., ... Malik, R. (2016). Prolonged cardiac arrest complicating a massive ST-segment elevation myocardial infarction associated with marijuana consumption. *Journal of Community Hospital Internal Medicine Perspectives*, 6(4), 31695.
- Pearl, W., & Choi, Y.S. (1992). Marijuana as a cause of myocardial infarction. *International Journal of Cardiology*, 34(3), 353.
- Peyrot, I., Garsaud, A.M., Saint-Cyr, I., Quitman, O., Sanchez, B., & Quist, D. (2007). Cannabis arteritis: A new case report and a review of literature. *Journal of the European Academy of Dermatology and Venereology*, 21(3), 388–391.
- Pletcher, M.J., Vittinghoff, E., Kalhan, R., Richman, J., Safford, M., Sidney, S., ... Kertesz, S. (2012). Association between marijuana exposure and pulmonary function over 20 years. *JAMA*, 307(2), 173–181.
- Polen, M.R., Sidney, S., Tekawa, I.S., Sadler, M., & Friedman, G.D. (1993). Health care use by frequent marijuana smokers who do not smoke tobacco. *Western Journal of Medicine*, 158(6), 596–601.
- Porath, A.J., Konefal, S., & Kent, P. (2018). *Clearing the smoke on cannabis: Maternal cannabis use during pregnancy — An update*. Ottawa, Ont.: Canadian Centre on Substance Use and Addiction.
- Raber, J.C., Elzinga, S., & Kaplan, C. (2015). Understanding dabs: Contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing. *Journal of Toxicological Sciences*, 40(6), 797–803.
- Renard, D., Taieb, G., Gras-Combe, G., & Labauge, P. (2012). Cannabis-related myocardial infarction and cardioembolic stroke. *Journal Stroke Cerebrovascular Diseases*, 21(1), 82–83.
- Rezkalla, S.H., Sharma, P., & Kloner, R.A. (2003). Coronary no-flow and ventricular tachycardia associated with habitual marijuana use. *Annals of Emergency Medicine*, 42(3), 365–369.
- Ribeiro, L., & Ind, P.W. (2016). Effect of cannabis smoking on lung function and respiratory symptoms: A structured literature review. *Nature Partner Journals Primary Care Respiratory Medicine*, 26, 16071.
- Ribeiro, L., & Ind, P.W. (2018). Marijuana and the lung: Hysteria or cause for concern? *Breathe*, 14(3), 196–205.
- Rooke, S.E., Norberg, M.M., Copeland, J., & Swift, W. (2013). Health outcomes associated with long-term regular cannabis and tobacco smoking. *Addictive Behaviors*, 38(6), 2207–2213.

- Roth, M.D., Arora, A., Barsky, S.H., Kleerup, E.C., Simmons, M., & Tashkin, D.P. (1998). Airway inflammation in young marijuana and tobacco smokers. *American Journal of Respiratory and Critical Care Medicine*, 157(3), 928–937.
- Roth, W.T., Tinklenberg, J.R., Kopell, B.S., & Hollister, L.E. (1973). Continuous electrocardiographic monitoring during marijuana intoxication. *Clinical Pharmacology and Therapeutics*, 14(4part1), 533–540.
- Rumalla, K., Reddy, A.Y., & Mittal, M.K. (2016a). Association of recreational marijuana use with aneurysmal subarachnoid hemorrhage. *Journal of Stroke and Cerebrovascular Diseases*, 25(2), 452–460.
- Rumalla, K., Reddy, A.Y., & Mittal, M.K. (2016b). Recreational marijuana use and acute ischemic stroke: A population-based analysis of hospitalized patients in the United States. *Journal of the Neurological Sciences*, 364, 191–196.
- Safaa, A.M., Markham, R., & Jayasinghe, R. (2012). Marijuana-induced recurrent acute coronary syndrome with normal coronary angiograms. *Drug and Alcohol Review*, 31(1), 91–94.
- Santos, R.P., Resende, C.I., Vieira, A.P., & Brito, C. (2017). Cannabis arteritis: Ever more important to consider. *BMJ Case Reports*, 2017, bcr2016219111.
- Sarafian, T.A., Habib, N., Oldham, M., Seeram, N., Lee, R.P., Lin, L., ... Roth, M.D. (2006). Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, 290(6), L1202–L1209.
- Sarfraz, S., Afaq, F., Adhami, V.M., & Mukhtar, H. (2005). Cannabinoid receptor as a novel target for the treatment of prostate cancer. *Cancer Research*, 65(5), 1625–1641.
- Shay, A.H., Choi, R., Whittaker, K., Salehi, K., Kitchen, C.M., Tashkin, D.P., ... Baldwin, G. C. (2003). Impairment of antimicrobial activity and nitric oxide production in alveolar macrophages from smokers of marijuana and cocaine. *Journal of Infectious Diseases*, 187(4), 700–704.
- Sherman, M.P., Campbell, L.A., Gong Jr, H., Roth, M.D., & Tashkin, D.P. (1991). Antimicrobial and respiratory burst characteristics of pulmonary alveolar macrophages recovered from smokers of marijuana alone, smokers of tobacco alone, smokers of marijuana and tobacco, and nonsmokers. *American Review of Respiratory Disease*, 144(6), 1351–1356.
- Sherrill, D.L., Krzyzanowski M, Bloom J.W., & Lebowitz, M.D. (1991). Respiratory effects of non-tobacco cigarettes: A longitudinal study in general population. *International Journal of Epidemiology*, 20 (1),132–137.
- Sidney, S., Quesenberry Jr, C. P., Friedman, G. D., & Tekawa, I. S. (1997). Marijuana use and cancer incidence (California, United States). *Cancer Causes and Control*, 8(5), 722–728.
- Sidney, S. (2002). Cardiovascular consequences of marijuana use. *Journal of Clinical Pharmacology*, 42(S1), 64S–70S.
- Singh, N.N., Pan, Y., Muengtaweepansa, S., Geller, T.J., & Cruz-Flores, S. (2012). Cannabis-related stroke: Case series and review of literature. *Journal of Stroke and Cerebrovascular Diseases*, 21(7), 555–560.
- Staiano, R.I., Loffredo, S., Borriello, F., Iannotti, F.A., Piscitelli, F., Orlando, P., ... Fiorelli, A. (2016). Human lung-resident macrophages express CB1 and CB2 receptors whose activation inhibits the release of angiogenic and lymphangiogenic factors. *Journal of Leukocyte Biology*, 99(4), 531–540.
- Statistics Canada. (2017). *Canadian Tobacco, Alcohol and Drugs Survey (CTADS): Summary of results for 2017*. Ottawa, Ont.: Author.
- Stogner, J.M., & Miller, B.L. (2015). Assessing the dangers of “dabbing”: Mere marijuana or harmful new trend? *Pediatrics*, 136(1), 1–3.
- Subramaniam, V.N., Menezes, A.R., DeSchutter, A., & Lavie, C.J. (2019). The cardiovascular effects of marijuana: Are the potential adverse effects worth the high? *Missouri Medicine*, 116(2), 146–153.
- Tan, W.C., Lo, C., Jong, A., Xing, L., FitzGerald, M.J., Vollmer, W.M., ... Sin, D.D. (2009). Marijuana and chronic obstructive lung disease: A population-based study. *Canadian Medical Association Journal*, 180(8), 814–820.
- Tan, W.C., Bourbeau, J., Aaron, S.D., Hogg, J.C., Maltais, F., Hernandez, P., ... FitzGerald, J. M. (2019). The effects of marijuana smoking on lung function in older people. *European Respiratory Journal*, 54(6), 1900826.
- Tashkin, D.P. (2005). Smoked marijuana as a cause of lung injury. *Monaldi Archives for Chest Disease*, 63(2), 93–100.
- Tashkin, D.P. (2013) Effects of marijuana smoking on the lung. *Annals of the American Thoracic Society*, 10, 239–247.
- Tashkin, D.P., Baldwin, G.C., Sarafian, T., Dubinett, S., & Roth, M.D. (2002). Respiratory and immunologic consequences of marijuana smoking. *Journal of Clinical Pharmacology*, 42(S1), 71S–81S.
- Tashkin, D.P., Gliederer, F., Rose, J., Chang, P., Hui, K.K., Yu, J.L., & Wu, T.C. (1991a). Effects of varying marijuana smoking profile on deposition of tar and absorption of CO and delta-9-THC. *Pharmacology Biochemistry and Behavior*, 40(3), 651–656.
- Tashkin, D.P., Gliederer, F., Rose, J., Chang, P., Hui, K.K., Yu, J.L., & Wu, T.C. (1991b). Tar, CO and delta 9 THC delivery from the 1st and 2nd halves of a marijuana cigarette. *Pharmacology Biochemistry and Behavior*, 40(3), 657–661.
- Tashkin, D., Quint, J., & Detels, R. (2018). Marijuana smoking and pneumonia risk: Findings from the Multi-Center AIDS Cohort Study. American Thoracic Society International Conference Abstracts. Retrieved from https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6097

- Tashkin, D.P., & Roth, M.D. (2007). Effects of marijuana on the lung and immune defenses. In ElSohly, M.A. (Ed.) *Marijuana and the cannabinoids*, pp. 253–275. Totowa, New Jersey: Humana Press.
- Tashkin, D.P., Shapiro, B.J., & Frank, I.M. (1973). Acute pulmonary physiologic effects of smoked marijuana and oral Δ^9 -tetrahydrocannabinol in healthy young men. *New England Journal of Medicine*, 289(7), 336–341.
- Tashkin, D.P., Simmons, M.S., Sherrill, D.L., & Coulson, A.H. (1997). Heavy habitual marijuana smoking does not cause an accelerated decline in FEV1 with age. *American Journal of Respiratory and Critical Care Medicine*, 155(1), 141–148.
- Tashkin, D.P., Simmons, M.S., & Tseng, C.H. (2012). Impact of changes in regular use of marijuana and/or tobacco on chronic bronchitis. *Journal of Chronic Obstructive Pulmonary Disease*, 9(4), 367–374.
- Taylor, D.R., Fergusson, D.M., Milne, B.J., Horwood, L.J., Moffitt, T.E., Sears, M.R., & Poulton, R. (2002). A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction*, 97(8), 1055–1061.
- Taylor, D.R., Poulton, R., Moffitt, T.E., Ramankutty, P., & Sears, M.R. (2000). The respiratory effects of cannabis dependence in young adults. *Addiction*, 95(11), 1669–1677.
- Tetrault, J.M., Crothers, K., Moore, B.A., Mehra, R., Concato, J., & Fiellin, D.A. (2007). Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. *Archives of Internal Medicine*, 167(3), 221–228.
- Thomas, G., Kloner, R.A., & Rezkalla, S. (2014). Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: What cardiologists need to know. *American Journal of Cardiology*, 113(1), 187–190.
- Thompson, G.R., Tuscano, J.M., Dennis, M., Singapuri, A., Libertini, S., Gaudino, R., ... Engelthaler, D.M. (2017). A microbiome assessment of medical marijuana. *Clinical Microbiology and Infection*, 23(4), 269–270.
- Tindall, B., Cooper, D., Donovan, B., Barnes, T., Philpot, C., Gold, J., & Penny, R. (1988). The Sydney AIDS Project: Development of acquired immunodeficiency syndrome in a group of HIV seropositive homosexual men. *Australian and New Zealand Journal of Medicine*, 18(1), 8–15.
- Torney, W.P. (2012). Cannabis misinterpretation and misadventure in a coroner's court. *Medicine, Science and the Law*, 52(4), 229–230.
- Tucker, J.S., Pedersen, E.R., Seelam, R., Dunbar, M.S., Shih, R.A., & D'Amico, E. (2019). Types of cannabis and tobacco/nicotine co-use and associated outcomes in young adulthood. *Psychology of Addictive Behaviors*, 33(4), 401–411.
- Vachon, L., FitzGerald, M. X., Solliday, N. H., Gould, I. A., & Gaensler, E. A. (1973). Single-dose effect of marijuana smoke: bronchial dynamics and respiratory-center sensitivity in normal subjects. *New England Journal of Medicine*, 288(19), 985–989.
- Velasco, G., Sánchez, C., & Guzmán, M. (2012). Towards the use of cannabinoids as antitumour agents. *Nature Reviews Cancer*, 12(6), 436–444.
- Wang, X., Derakhshandeh, R., Liu, J., Narayan, S., Nabavizadeh, P., Le, S., ... Springer, M.L. (2016). One minute of marijuana secondhand smoke exposure substantially impairs vascular endothelial function. *Journal of the American Heart Association*, 5(8), e003858.
- Westover, A.N., McBride, S., & Haley, R.W. (2007). Stroke in young adults who abuse amphetamines or cocaine: A population-based study of hospitalized patients. *Archives of General Psychiatry*, 64(4), 495–502.
- Widlansky, M.E., Gokce, N., Keaney, J.F., & Vita, J.A. (2003). The clinical implications of endothelial dysfunction. *Journal of the American College of Cardiology*, 42(7), 1149–1160.
- Wolff, V., & Jouanous, E. (2017). Strokes are possible complications of cannabinoids use. *Epilepsy and Behavior*, 70(Part B), 355–363.
- Wolff, V., Lauer, V., Rouyer, O., Sellal, F., Meyer, N., Raul, J.S., ... Marescaux, C. (2011). Cannabis use, ischemic stroke, and multifocal intracranial vasoconstriction: A prospective study in 48 consecutive young patients. *Stroke*, 42(6), 1778–1780.
- Wu, D., & O'Shea, D.F. (2020). Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. *Proceedings of the National Academy of Sciences*, 117(12), 6349–6355.
- Yurtdaş, M., & Aydın, M.K. (2012). Acute myocardial infarction in a young man; fatal blow of the marijuana: A case report. *Korean Circulation Journal*, 42(9), 641–645.
- Zhang, L.R., Morgenstern, H., Greenland, S., Chang, S.C., Lazarus, P., Teare, M.D., ... Hung, R.J. (2015). Cannabis smoking and lung cancer risk: Pooled analysis in the international lung cancer consortium. *International Journal of Cancer*, 136(4), 894–903.

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