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Implementation of a Dose Response to Wood Smoke PM: A Potential Method to Further Explain CVD in Wildland Firefighters.

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IMPLEMENTATION OF A DOSE REPONSE TO WOOD SMOKE PM: A POTENTIAL METHOD TO FUTHER EXPLAIN CVD IN WILDLAND FIREFIGHERS

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Implementation of a Dose Response to Wood Smoke PM: A Potential Method to Further Explain CVD in Wildland Firefighters.

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The presentation of cardiovascular disease (CVD) and comorbidities in aging and retired wildland firefighters (WLFF) continues to be one of the top health priorities to address by The United States Forest Service. In the past 20 years, experts at multiple meetings and conferences have confronted this growing concern as a formal call to action to investigation the individual components related to working in the wildland fire setting. The inhalation of wood smoke particulate matter (PM) shows evidence of altering homeostasis in WLLF's in the areas of oxidative stress, inflammation, and arterial stiffness, all of which contribute to the development of (CVD).

To date, comprehensive investigation into the dose response of wood smoke PM and subsequent cardiovascular outcomes remains under studied. Emphasis on a wood smoke PM dose response is based on the inclusion of key variables measuring the size, concentration, sources, and inhalation rate of PM. The literature investigating wood smoke PM induced phycological changes is significantly lack in comparison to the reach studying anthropogenic PM and pollution. Recently, published studies in both field experiments and laboratory simulations provide new insight on how the PM dose of acute exposures alters normative cardiovascular function. There is a growing consensus within the scientific community of wood smoke PM inducing oxidative stress, upregulating inflammatory markers, and elevating pulmonary and systemic inflammation. At this time, fluctuations in autonomic nervous system control of heart rate and vascular tone do not warrant the same strength of confidence as the direct influence of wood smoke PM inhalation. Furthermore, the concentrations, volumes, PM size, and ventilation rates are contextual to each individual dose. What is true in one scenario cannot be extrapolated all wood smoke PM exposures and settings.

Based on the findings of this academic exercise, we recommend that future scientific investigations in this area implement directed dose-response methodology, in combination with clinically relevant outcome measures, in order to determine the effects from multiple PM smoke exposures on the development of CVD aging and pathology.

Chapter 1:

Introduction:

In order to address the increasing occurrence of cardiovascular disease (CVD) in wildland firefighters, additional steps need to be taken to advance the study through the implementation of an acute dose response to wood smoke particulate matter (PM). A dose response to biomass combustion has been suggested as a contributing factor (Morandi & Ward, 2010) to chronic disease pathologies which occur later on in the careers of wildland firefighters. The working environment of a wildland firefighter is everchanging, but one consistent outcome within the job description is the detrimental health consequences from the inhalation of wood smoke PM (Cascio, 2018; Navarro et al., 2019).

The United States Forest Service employs nearly 10,000 firefighters in various positions including hand crews, hot shot crews, helitack crews, and smoke jumpers (USDA, 2019). Within a single season of fighting wildland fires, firefighters are subjected to consecutive days, even weeks of wood smoke PM (Coker, Murphy, Johannsen, Galvin, & Ruby, 2019; Navarro et al., 2019). Furthermore, the duration of the wildland fire seasons are increasing in length compared to the previous decades, and is linked to human-caused climate change (Abatzoglou & Williams, 2016). Consequently, the wildlands consumed by fires tracked by the National Interagency Fire Center since 1960, show the five largest fires measured by acreage burned, were consumed between 2006-2017(Hoover, 2018) exposing firefighters to a greater volume of wood smoke PM.

While the negative health consequences of inhaling particulate matter, including size, volume, and source type parameters, have been thoroughly reviewed (Booze, Reinhardt, Quiring, & Ottmar, 2004; Danielsen et al., 2011; Navarro et al., 2019; Newby et al., 2015; Pope & Dockery, 2006; Rappold, Reyes, Pouliot, Cascio, & Diaz-Sanchez, 2017; Rappold G. et al., 2011),

measuring the effects on autonomic function, oxidative stress, and inflammation require further analysis to explain why wildland firefighters are predisposed to cardiovascular disease (Navarro et al., 2019)? To our knowledge, research to this point has yet to compile a review measuring the combination of wood smoke PM exposure and differentiating the acute post exercise response with changes in autonomic regulation of heart rate, vascular tone, oxidative stress, and inflammation. Collectively, these areas of interest may provide the necessary details to further explain the acute changes post exposure which accumulate over time, and eventually develop into CVD.

A wealth of research indicates career wildland firefighters are more likely to suffer from cardiovascular disease, morbidity, and mortality than those who aren't exposed to wildland firefighting environments (O. Adetona et al., 2016; Bortolotto et al., 1999; Navarro et al., 2019). Furthermore, within the community of wildland firefighters, the greater number of days spent on a fire line, and years working as a firefighter facilitates additional susceptibility for CVD (Navarro et al., 2019). Paradoxically, wildland firefighters require an aerobic capacity and fitness necessary to generate vocational work output high enough to fulfill the criteria for aerobic exercise to significantly reduce symptoms of cardiovascular disease. (Garber et al., 2011).

The pyrolysis of organic biofuels generate various PM sizes and volumes, and has been studied in multiple countries around the world (Abreu et al., 2017; Dorman & Ritz, 2014; Gaughan et al., 2014; Gianniou et al., 2018). However, the physiologic consequences in humans of wood smoke PM inhalation are still in the early stages of research to identify the different systematic organ responses from acute wood smoke exposures (Abreu et al., 2017; O. Adetona, Hall, & Naeher, 2011; Dorman & Ritz, 2014; Ferguson, Semmens, Dumke, Quindry, & Ward, 2016; Gaughan et al., 2014; Gianniou et al., 2018; Hunter et al., 2014; Peters et al., 2018; Swiston et al., 2008; Unosson et al., 2013). An essential step to understand the frequent occurrences of CVD in

wildland firefighters, is achievable through the implementation of a dose response to an acute wood smoke exposure. A dose response in the simplest term identifies what PM is inhaled and how much. The dose response to wood smoke PM compiles four key variables necessary to track the specificity of the contaminates and rate of consumption. The variables of interest range from the combustion of organic source PM, the size of the PM, the volume of the PM, and the ventilation rate determining the quantity of consumption. The increased ventilatory demand necessary to perform vocational wildland firefighting related tasks, are responsible for the non-environmental contributions of a dose response. The tasks generating this increase in ventilation are the physical demands of digging line, hiking, and fire suppression during a shift (Sol, Ruby, Gaskill, Dumke, & Domitrovich, 2018). Furthermore, wildland firefighters shifts can last between 12-16 hours per day, and firefighters can spend multiple days, even weeks exposed to wood smoke PM. (Butler, Marsh, Domitrovich, & Helmkamp, 2017; Sol et al., 2018).

Exposures to wood smoke PM vary depending on wildland firefighters' responsibilities. Wildland firefighter classifications are broken down into two categories predisposing firefighters to different levels and conditions of PM (Booze et al., 2004). Type I crews are highly trained hotshot crews and smoke jumpers who specialize in operating in a more hazardous work environments, while Type II crews, are local district crews working on sanctioned prescribed burns. While both types of crews face different work settings, it appears that both situations can result in physiologic deterioration to the cardiovascular system. Recent evidence shows a single season of wildland fighting can present a decline in cardiovascular functioning in wildland firefighters (Coker et al., 2019). In addition, a discovery by (O. Adetona, Hall, et al., 2011) found that an acute exposure to wood smoke PM during prescribed wildland burns impairs lung function as well.

The arising physiological complications in response to wood smoke PM are dependent on the volume of PM, the size of the particle. Various degrees of wood smoke PM volume elicit different complications with in humans depending on individual health status. For example, the National Ambient Air Quality Survey (NAAQS) determines classifications of PM volumes and sub-populations which may be effected by poor air quality like those with cardiorespiratory complications and the elderly (Rappold et al., 2017). The size of PM range from 0.1-10 microns, and generate different complications with in the human body such as; increased respiratory dysfunction, morality, and inflammation (O. Adetona et al., 2016; Liu, Pereira, Uhl, Bravo, & Bell, 2015). Beyond the acute respiratory dysfunction associated with wood smoke PM inhalation (Liu et al., 2015; Pope & Dockery, 2006), wood smoke also causes impairments in multiple organ systems (Hunter et al., 2014; McCracken et al., 2011; Swiston et al., 2008). $PM_{2.5}$ is particularly problematic for cardiovascular function and is associated with the upregulation of sympathetic management of cardiac control, and increases vascular tone (Giorgini et al., 2016; Magari et al., 2001; Pope & Dockery, 2006; Unosson et al., 2013). Pollutants comprised of $PM_{2.5}$ have the ability to be suspended in the air for a longer periods of time (days and weeks), travel further in distance from the source, and when inhaled invade into deeper portions of the lungs, and pass into systemic circulation (Anderson, Thundiyil, & Stolbach, 2012). PM_{10} can also travel in distance, but has a much smaller radius and life span (minutes – hours) (Kim, Kabir, & Kabir, 2015). PM_{10} impairs homeostatic functioning by primarily causing upper respiratory irritation in the nasal passages and throat (Kim et al., 2015), although there is some evidence of influence on the ANS (Pope & Dockery, 2006) and increasing the likelihood of cardiovascular morbidity and mortality (Anderson et al., 2012). While some studies report the PM-induced physiological impairments to different organ systems individually (McCracken et al., 2011), these interconnected systems can

be studied simultaneously (O. Adetona, Hall, et al., 2011; Ferguson et al., 2016; Hunter et al., 2014; Peters et al., 2018; Unosson et al., 2013). When humans participate in exercise, the balance between autonomic control of HR shifts, at the same time changes in vascular tone are present, while observing increases in ventilation (Bassett et al., 2001; Garber et al., 2011; Michael, Graham, & Oam, 2017).

In contrast to the deleterious impacts of inhaling wood smoke, the known benefits of exercise of cardiovascular health and longevity are justified throughout the literature (Fiuza-Luces et al., 2018; Garber et al., 2011; S. K. Powers, Sollanek, Wiggs, Demirel, & Smuder, 2014; Scott K. Powers, Smuder, Kavazis, & Quindry, 2014), and also provides a context to understand multiple facets of human physiology including changes in the autonomic nervous system (ANS) managing HR concordant with vascular tone, exercise induced oxidative stress, and inflammation. Before we discuss the exercise response in ANS, vascular tone, oxidative stress, and inflammation occurring in wildland firefighters, we will explain each area of interest independently at rest in order to provide context to management during exercise and regulation post exercise. Furthermore, we can identify normative changes physiology post exercise, and those that may suggest and an underlying pathology, and negative markers which may manifest into a future pathology.

Autonomic Control:

The balance of autonomic control is carried out by the sympathetic and parasympathetic portions of the ANS working in a counterregulatory fashion. The SNS responsible for the increasing HR, the preservation of vascular tone, vasoconstriction of arterioles, and short-term management of blood pressure during times of stress or physical activity (Shaffer, McCraty, & Zerr, 2014; Thayer, Yamamoto, & Brosschot, 2010). The PNS depresses SNS and HR through the innervation of the vagal nerve and is more active during extended periods of rest (Thayer et al.,

2010). The variation between sympathetic and parasympathetic regulation of cardiac control fluctuates, depending on the health of an individual (Thayer et al., 2010). An increased presence in PNS tone at rest signifies a larger variation in heart beat frequency which is an overall measure of good health, while a reduction in PNS tone has been accordant with cardiac pathologies (Shaffer et al., 2014; Weber et al., 2010; Young & Benton, 2018).

The management of ANS during exercise, however, requires an adjustment between the SNS and PNS. When humans exercise the ANS responds accordingly to the intensity and the duration of the mode of physical activity (Arai et al., 1989; Robinson, Epstein, Beiser, & Braunwald, 1966). Both parasympathetic drive and sympathetic drive are active, contributing to different portions of cardiac control. Cardiac sympathetic nerve activity moderates contractility in a tone setting manner, whereas cardiac parasympathetic nerve activity functions as a moderator (Michael et al., 2017).

At the cessation of an acute bout of exercise, a gradual adjustment between sympathetic tone and vagal tone occurs. As sympathetic regulation wanes, there is a slow rise in vagal tone (Arai et al., 1989; Scher & Young, 1970). Parasympathetic simulation is reduced in all healthy individuals post exercise, and is a physiological normative response (Stanley, Peake, & Buchheit, 2013). The overall fitness plays a role in this response, as unhealthy or sedentary individuals have a significantly larger decrement in PNS and can remain so even 90 minutes post exercise compared to healthier individuals who's PNS drive is restored much quicker (Stanley et al., 2013). One method used to measure the balance between PSN and SNS is the quantification of heart rate variability (HRV) Michael et al., 2017; Shaffer & Ginsberg, 2017; Shaffer, McCraty, & Zerr, 2014; Thayer, Yamamoto, & Brosschot, 2010), a technique that will be further explained during in the literature review portion of this proposal.

Vascular Tone (Arterial stiffness):

Autonomic tone controls the major vessels through vasodilation and vasoconstriction via sympathetic nerve innervation of the surrounding smooth muscle around the major arteries (Bruno et al., 2012). The mechanisms controlling vascular tone are Nitric Oxide (NO), Reactive Oxygen Species (ROS), endothelin, and the rennin angiotensin system (Bruno et al., 2012) also influence conductance at the microvascular level. Furthermore, vascular pliability of arteries is important facet of physiologic regulation for health, longevity, and vascular function (Green & Smith, 2018). In humans presenting arterial stiffness at rest, however, this untoward physiologic alteration is associated with an elevated risk for mortality (Laurent et al., 2001).

In contrast, exercise is associated with an improvement in vascular tone, the direct result of a hermetic shear stress acting on the endothelial cells. The force generating this increase shear includes the elevation of mean arterial pressure and elevated cardiac output necessary to nourish active muscle groups during repetitive muscular contractions. This mechanical stimulus further upregulates endothelial nitric oxide synthase (eNOS) throughout the bout of exercise (Bruno et al., 2012; Green & Smith, 2018). When eNOS is stimulated through repetitive bouts of exercise, it results in the increased production of endogenous NO (Harrison et al., 2006), to help maintain vascular tone as an individual ages.

Interestingly, the hermetic stress of an acute exercise bout is a known to temporary decrease vascular function in the immediate post exercise period (Dawson, Green, Timothy Cable, & Thijssen, 2013). This outcome is in specific response in the increased pressure, conductance, and shear stress during exercise(Green, Hopman, Padilla, Laughlin, & Thijssen, 2017). In longer more strenuous bouts of aerobic exercise, the vessels associated with exercising muscle present a decrease in endothelial function, compared to non-used vessels (Dawson et al., 2008). The

exhibiting vascular dysfunction is temporary, and rebounds post exercise (Pierce, Doma, & Leicht, 2018).

Oxidative Stress:

Beyond the measurable changes in autonomic function and vascular tone, is the proliferation of oxidative stress. The occurrence of oxidative stress or reactive oxygenated species (ROS), however, is also an obligatory response to an acute bout of vigorous exercise. In contrast to the acute spikes in oxidative stress experienced during exercise, chronic levels of oxidative stress or the production of ROS are markers associated with various pathologies (Münzel et al., 2017; S. K. Powers et al., 2014; Scott K. Powers et al., 2014) and will be expanded upon further the literature review portion of the proposal.

Accordingly, exercise induced oxidative stress is now understood to be an adaptive response to physical activity. Exercised induced ROS occur in skeletal muscle fibers and the mitochondria. In addition, enzymes managing substrate utilization, and cell signaling pathways also up regulate as a result from exercise (Scott K. Powers, Duarte, Kavazis, & Talbert, 2010). The acute exercise induced oxidative stress is not limited to skeletal muscle, but also presents in the heart from aerobic exercise. Cardiomyocytes undergo a transformation allowing the tissue to generate cardioprotective mechanisms in the event of a MI (Lennon et al., 2004; Scott K. Powers et al., 2014).

Inflammation:

In addition to the presentation of oxidative stress, inflammation also occurs, but likewise, is contextual to the ongoing narrative that exercise is a hermetic stress. At rest systemic inflammation within blood vessels impairs endothelial dependent dilation (Hingorani et al., 2000; Vlachopoulos et al., 2005), and subsequently, vascular function. Systemic inflammation occurs

when there is undue endothelial shear stress within the vessel, without the production of NO (Harrison et al., 2006). The literature has observed a link between increased and chronic levels of inflammation with the presence of CVD (Lopez-Candales, Hernández Burgos, Hernandez-Suarez, & Harris, 2017). Exercise induced inflammation occurs concordantly with oxidative stress. Exercise generates inflammation in lung function through increased respirations, fluid evaporation, inhalation of environmental PM (Araneda, Carbonell, & Tuesta, 2016). Acute exercise induces inflammation into the lungs through the presence of additional macrophages and granulocytes (Araneda et al., 2016). The inflammatory response during and post exercise is sensitive to both air quality (pollutants) and particulate matter(size, source, volume) inhaled by an individual (Giorgini et al., 2016).

Ventilation Rate:

The ventilatory rate, first addressed earlier in the introduction is key to the dose consumption of wood smoke PM. Published studies use a broad range of ventilation rates when exposing subjects to wood smoke PM including at rest (McCracken et al., 2011) and during exercise (Ferguson et al., 2016; Ghio et al., 2012; Hunter et al., 2014; Peters et al., 2018; Unosson et al., 2013). The periods of increasing ventilation are proportional and positively correlated to the vocational work demands in wildland firefighting (Sol et al., 2018). Instead of quantifying the wildland firefighter's inhalation of wood smoke PM as constant or an average, a more appropriate estimation should consider a nuanced approach which matches the variable work demands experienced during a work shift. Hiking with a weighted pack, digging containment lines, clearing brush / trees are achieved with various exercise intensities (Sol et al., 2018). Each portion of a total work shift corresponds in theory, to a different dose of PM than the average during a total work shift. A recently published study measuring the metabolic demands in wildland fire fighting

through the use of VO_2 estimates for different work-related hikes[1]. For instance, ingress hikes elicited a higher VO_2 estimates than those observed during a work shift hikes and egress hikes at the end the day (Sol et al., 2018).

Particulate Matter (PM):

PM acts as the trigger of which all these negative health outcomes discussed above, are derived (Magari et al., 2001), but not all forms of PM are created equal i.e. (urban air pollution PM vs. wood smoke PM). PM size classifications are divided into three different sub categories, coarse PM, fine PM, and ultra-fine PM and will be addressed in detail in the next section of this review paper.

PM is generated from multiple forms and molecular sizes contributing to inflammation, respiratory complications, changes in autonomic regulation of cardiac control, and cardiovascular morbidity (Anderson et al., 2012; Cascio, 2018; Dorman & Ritz, 2014; Liu et al., 2015; McCracken et al., 2011; Newby et al., 2015; Rappold et al., 2017; Silva, Adelman, Fry, & West, 2016; Swiston et al., 2008). Based on a growing body of literature, it now appears that inhalation of PM is a significant contributor to negative health outcomes in wildland firefighters (Cascio, 2018; Navarro et al., 2019; Pope & Dockery, 2006; Swiston et al., 2008). While there is a broad range of $PM_{(1-10)}$, $PM_{2.5}$ has been linked to disturbances in pulmonary functioning such as chronic obstructive pulmonary disease (COPD), asthma, bronchitis, and pneumonia (Cascio, 2018). Wood smoke PM can impact health in several key ways, causing disturbances in the nervous system and the lungs (O. Adetona, Hall, et al., 2011; Swiston et al., 2008; Unosson et al., 2013). These outcomes then

[1](Sol et al., 2018)
Ingress hike: morning hike starting at crew vehicle / starting point to the work site. ~ 22ml/kg/min
Shift hike: classified as hiking during a work shift
Egress hike: leaving fire line / worksite and returning to vehicles.
Training hike: self-selected intensity and location while wearing work attire and gear.

elevate blood pressure and alter cardiac functioning (Newby et al., 2015). In addition, wood smoke PM interferes with alveolar-capillary gas exchange producing ROS and an inflammatory response (Newby et al., 2015).

Although additional research is needed, the medical field believes the positive effects of exercise outweigh the acute rise in PM exposure and consumption, and short term complications for the general public (Giorgini et al., 2016). Special considerations and contraindications to exercise in the presence of PM exists, however, for specific populations like those with respiratory disorders or those with symptoms of CVD (Giorgini et al., 2016).

Variations in PM size and associated complications:

As previously mentioned the three classifications of PM are coarse, >2.5µm, fine <2.5 µm, and ultra-fine <.1 µm and when a portion of ambient air is measured, all three size classifications of PM are inside the sample. The size specific criteria for a ambient PM sample refer to the boundaries of particles collected (Pope & Dockery, 2006). A hypothetical distribution of an environment ambient sample of PM_{10} in Fig. 1 (Anderson et al., 2012) provides additional details.

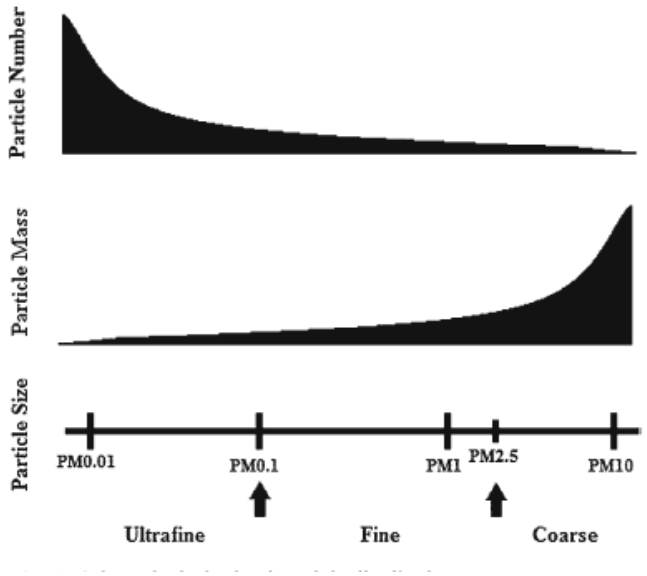

Fig 1.) (Anderson et al., 2012)

The physiologic difficulties resulting from anthropogenic PM exposure remains a topic of interest within the scientific community (Anderson et al., 2012; Giorgini et al., 2016; Newby et al., 2015; Silva et al., 2016). Relative to declines in long term health, prior work demonstrates that urban-based PM exposure, and subsequent pathologies, occur in response to short and long-term exposure time frames, different durations of exposure, fluctuations in autonomic function, and systemic inflammation. Of the 18 studies focusing on short term daily increases of exposure (+10 $\mu g/m^3$ $PM_{2.5}$, + 20 $\mu g/m^3$ PM_{10}), 16 of the investigations indicate an overall increase in the likely-hood of all-cause mortality, while 8 studies suggest an increased likely hood of cardiovascular mortality, and 5 studies reveal an elevated prevalence of respiratory mortality (Pope & Dockery, 2006). When (Pope & Dockery, 2006) investigated long-term particulate exposure (+10 $\mu g/m^3$ $PM_{2.5}$, + 20 $\mu g/m^3$ PM_{10}), comprised of 20 studies, 19/20 found an increase of all-cause mortality, and 16 studies develop a propensity of cardiopulmonary mortality. The studies of time scales estimating risk ranging from 1-3 days to upwards of more than 10 years present a linear tend in all-cause mortality and cardiovascular / cardiopulmonary mortality, and respiratory mortality (Pope & Dockery, 2006). 15 Studies measuring autonomic control of heart rate in response to coarse, fine, and ultra-fine PM exposure typically suggest declines in autonomic management of cardiac control (Pope & Dockery, 2006). Findings from 18 of the aforementioned studies indicate reduction in red blood cells, and increases in blood plasma viscosity, elevated polymorphonuclear leukocytes / neutrophils, lymphocytes, endothelial adhesion molecules, Interleukin- 8 (IL-8), and C-reactive protein (CRP) (Pope & Dockery, 2006).

The epidemiologic study of wildland fire PM lacks the density of research in comparison to urban pollution PM since the creation of Clean Air Act. Additionally, wood smoke PM comprises a small portion of the total research of health implications from PM exposure. In the

1970's wildland fires were less predictable and often occurred in areas outside of established PM monitoring sites (Cascio, 2018). Furthermore, the total area consumed by forest fires doubled during the span from 1984-2015 (Abatzoglou & Williams, 2016), and subsequently a need to study wood smoke PM's impact on human health. The recent literature can identify some health outcomes from the exposure to wood smoke PM. The most consistent reports determine all-cause mortality (Reid et al., 2016) and respiratory complications from PM_{10} (O. Adetona et al., 2016) and $PM_{2.5}$ (Cascio, 2018). Reports range from an increase in hospitalizations for asthma related complications and respiratory dysfunction, and in those with COPD (O. Adetona et al., 2016). The same strength of a relationship cannot be said at this time for cardiovascular morbidity. Currently, there is only a weak association when determining a connection between cardiovascular morbidity and wood smoke $PM_{2.5}$ and PM_{10} (O. Adetona et al., 2016; Cascio, 2018; Reid et al., 2016).

PM Sources are not Equal

In 1970, The Clean Air Act passed leading to the establishment of the National Ambient Air Quality Standards (NAAQS) (EPA, 2016; N.A, 2017). The six pollutants the Environmental Protection Agency (EPA) imposed regulations on were carbon dioxide, carbon monoxide, lead, nitrogen dioxide, sulfur dioxide, and particulate matter (NAAQS). Since the inception of the NAAQS, there have been multiple revisions determining acceptable daily and annual limits of $PM_{2.5}$ and PM_{10} exposure (EPA, 2016). One limitation to the NAAQS, however, is that the PM guidelines are based on manmade urban air pollution PM rather than the burning of biomass. Examples of manmade PM are; automotive or transportation emissions, tobacco smoke, and PM generated from machines or industrial productions, while naturals sources come from natural disasters such as volcanic eruptions, fires, dust storms (Anderson et al., 2012). Currently, the EPA

does not classify limitations of PM exposure differentiating between manmade and natural PM sources in the NAAQS table (EPA, 2016).

Different sources of urban PM and air pollution and subsequent health outcomes from exposure still leave many remaining unanswered questions. Perhaps the most important questions posed in a 2018 review asking, "whether exposure to PM to specific source is associated with adverse health effects, but whether exposure to PM from some emission sources is associated with worse health outcomes than equivalent exposure to PM from another source" (Hime, Marks, & Cowie, 2018)? (Hime et al., 2018) compiled findings and broke down emission sources of total traffic related air pollution (TRAP)[2], coal fired power plants, and diesel exhaust. The following are health risks from the exposure of manmade PM; impaired lung function, all-cause mortality, cardiovascular morbidity, MI, reduced lung function in children, increased blood pressure, cytotoxicity, pulmonary inflammation, ischemic heart disease, allergic inflammation, and respiratory mortality (Hime et al., 2018). To our knowledge, a publication has yet to delineate a specific source of air pollution PM being worse or more severe than another.

While the Clean Air Act has helped in the reduction of human generated pollution in the United States, the PM from natural disasters in particular wildland fire prone areas contributes a significant amount of the overall generated PM. From 1988-2016, rural testing sites across the country measured $PM_{2.5}$ and observed a trend demonstrating an overall decrease in $PM_{2.5}$, except in the Northwest region of the lower 48 states (McClure & Jaffe, 2018). The authors concluded that wildfires were responsible for the increase of $PM_{2.5}$, and could potentially counter the national ambient reduction in overall $PM_{2.5}$ (McClure & Jaffe, 2018). Due to anthropogenic climate change, wildland fires and PM looks to continue to be a problem in the future (Abatzoglou & Williams,

[2] TRAP particles from exhaust emissions (carbon dioxide, carbon monoxide, hydrocarbons, and nitrogen oxides) and the redistribution of non-exhaust PM from roads, tires, and break wear (Hime et al., 2018).

2016). A 2016 review paper, studies from around the world by found an increased presentation of asthma, COPD, and hospital visits from combustion of multiple fuel sources such as forests, brush, and sugar cane (O. Adetona et al., 2016). Currently, evidence summarizing cardiovascular complications from wildland fire smoke PM lacks the same strength of association as it does with ambient PM concentrations (O. Adetona et al., 2016).

Acknowledgement:

The literature has cited additional factors such as lifestyle behaviors, contributes to the prognosis of CVD (poor diet and tobacco use) (A. M. Adetona et al., 2017; Gaughan et al., 2014) in wildland firefighters and while they are important, they are out of the scope of this review.

Statement of Problem:

- The physiologic response in autonomic control, oxidative stress, and inflammation from a dose of wood smoke PM remains unclear in the wildland firefighting community.

Purpose of Professional Paper

- Conduct a literature review to identify stress markers (autonomic control, inflammation, oxidative stress, and vascular tone) sensitive to the consumption of a known quantity and source of wood smoke PM, and the role these same stress markers may play in development of CVD in wildland firefighters.

Significance of Review

- The physiologic response combining exercise and dose response of wood smoke PM remains relatively unanswered. We aim to provide a methodology to advance research within the wildland firefighting community by including autonomic fluctuations, oxidative stress, inflammatory markers, in response to wood smoke$PM_{2.5}$.

Limitations:

- The published studies cited within this document use primarily original studies focusing on the wildland firefighter population. Due to the limited availability in primary research using wildland fire fighters, we will supplement the gaps in the literature with structural firefighters when necessary. Structure firefighters work shorter shift durations, have respiratory protection, and are exposed to different air pollutants and combustible fuel sources.
- Studies focusing on course PM (greater than 2.5 microns). Research provides a wealth of evidence that CVD , oxidative stress, and arterial stiffness, is commonly associated with

chronic inhalation of fine PM sourced from biomass combustion. (Cascio, 2018; Ferguson et al., 2016; Navarro et al., 2019; Peters et al., 2018).

- Lifestyle and behavioral contributions of wildland firefighters can increase the risk of developing CVD (A. M. Adetona et al., 2017; Gaughan et al., 2014) are not associated with the damage from the inhalation wood smoke PM.

Delimitations:

- Wildland firefighting research is limited when addressing combination of oxidative stress, ANS, vascular tone, and inflammation requiring us to use both laboratory and field experiment studies to complete thorough literature review.
- Use studies primarily associated with wood smoke PM rather than other pollutants.
- Establish a dose response of wood smoke PM when the volumes of wood smoke PM are provided.
- Clarify exercise intensity, mode, and duration when simulating firefighting activities.

Basic Assumptions:

- There is sufficient evidence in the field of wildland firefighting providing justification to compile a literature review combining wood smoke PM, autonomic control of heart rate, vascular tone, oxidative stress, and inflammation.
- No paper to date has addressed all five of these areas of interest in the context of differentiating the post exercise response within a single review paper.

Definition of Terms:

AM – Alveolar Macrophage

ANS- Autonomic nervous system

CRP - C Reactive protein

EBC – Exhaled Breathing Condensate

HF- High Frequency

HR – Heart Rate

HRV- Heart rate variability

IL-8 Interleukin 8

LF- Low Frequency

MI- Myocardial Infarction

PM- Particulate matter

PNS- Parasympathetic nervous system

PNN50 – Percentage Normal successive sinus rhythm beasts exceeds 50 m^{s-}

PTX-3 – Pentraxin 3

PWV- Pulse wave velocity

ROS- reactive oxygenated species

RMSSD – Root mean squares sum deviation

SDNN – Standard deviation of normal intervals

SNS-sympathetic nervous system

TNF – Tumor Necrosis Factor

VEGF – Vascular Endothelial Growth Factor

Chapter Two:

Literature Review

Wildland firefighting research over the past 20 years indicates CVD is a cause of premature death in wildland firefighters. The presenting symptoms elevating CVD risk in wildland firefighters includes a history of inactivity, atherosclerosis, being overweight, smoking tobacco use, diabetes, and hypertension (Sharkey, 2001). The annual meeting of the International Association of Wildland Fire in 2001, resulted in the issuing of a statement that heart attacks were a significant contributor to the fatalities in wildland firefighting (Sharkey, 2001). Since the annual International Association of Wildland Fire meeting, researchers have observed the interference between wood smoke PM negatively effecting multiple organ systems (cardiovascular, pulmonary, ANS) is an essential step (O. Adetona, Hall, et al., 2011; Dorman & Ritz, 2014; Ferguson et al., 2016; Gaughan et al., 2014; Gianniou et al., 2018; Hunter et al., 2014; Leonard et al., 2000; McCracken et al., 2011; Peters et al., 2018; Swiston et al., 2008; Unosson et al., 2013; van Eeden et al., 2001). Despite the implementation of the pack test to evaluate physical fitness and readiness for active duty, administering heath history questionnaires, and medical exams to identify specific symptoms in an attempt to reduce wildland firefighter deaths, CVD persists as a prominent medical issue within the wildland firefighting community (National Wildfire Coordinating Group, 2017). Myocardial infarctions (MI), or heart attacks, are now the leading cause of death amongst wildland firefighters (National Wildfire Coordinating Group, 2017). During an eleven-year period (2006-2017) MIs represented 24% of wildland fire operations deaths, which is a 1% increase from 1999-2006, and a 3% increase from 1990-1998 (Butler et al., 2017; National Wildfire Coordinating Group, 2017). Furthermore, we know a single season of wildland freighting increases the lipid profile of wildland firefighters and visceral fat, potentially increasing the likelihood of CVD

(Coker et al., 2019) which can manifest into a MI. The development of CVD disease is somewhat nuanced within wildland firefighters. There are unavoidable portions of the job description such as the inhalation of various types, volumes, and size of wood smoke PM, and the physical stress required to perform wildland fire suppression. There has been a growing body of work appearing in the literature studying the effects of sleep deprivation and wildland firefighter health (Aisbett, Wolkow, Sprajcer, & Ferguson, 2012; Cvirn et al., 2017). In addition, we support and encourage the further holistic perspective of including risk factors such as sleep deprivation and occupational stress management to gain a deeper insight of the collective contributing factors impairing wildland firefighters (Vincent et al., 2018; Wolkow, Aisbett, Reynolds, Ferguson, & Main, 2016). For the interest of our review, however, we take a wood smoke PM and cardiovascular centric focus to address a single gap in the literature. As a result, the PM / cardiovascular emphasis for this review provides a unique opportunity for study wildland firefighting. There is a clear distinction that needs to be drawn between wildland firefighters and structure firefighters in the United States. Wildland firefighters are not afforded the same respiratory protective gear as structure firefighters, leaving them vulnerable to poor air quality and PM inhalation (Gaughan et al., 2014).

The wildland firefighter work environment has been established as a significant contributor to the prognosis of CVD within wildland fire fighters(O. Adetona et al., 2016; Butler et al., 2017; Cascio, 2018; Navarro et al., 2019). In addition, there are non-environmental factors responsible for the etiology of CVD in wildland fire fighting related to the health status of the firefighter, the ventilation rate (L/min) during a shift, the number days of wood smoke PM exposure during a season, and the duration of a wildland firefighting career (Navarro et al., 2019). A conclusion to be drawn from the aforementioned literature is that fitness and health should be the top priority in

the prevention of MI and CVD in the wildland firefighting environment, and to prevent CVD-related fatalities (National Wildfire Coordinating Group, 2017).

In order to address the susceptibility of CVD within wildland firefighters, we need to investigate individual areas of human physiology which report complications thus far. Wood smoke PM exposure has a prominent pernicious effect on homeostasis. Research indicates evidence of wood smoke PM impairing autonomic function (Unosson et al., 2013), arterial stiffness (Gaughan et al., 2014; Unosson et al., 2013), elevating oxidative stress(Abreu et al., 2017; Ferguson et al., 2016; Gaughan et al., 2014; Ghio et al., 2016; Peters et al., 2018; Swiston et al., 2008), DNA damage (Abreu et al., 2017; Danielsen et al., 2011; Leonard et al., 2000), and increasing inflammation (O. Adetona, Hall, et al., 2011; Dorman & Ritz, 2014; Ghio et al., 2012; Kocbach, Namork, & Schwarze, 2008; Swiston et al., 2008); moreover, impairments to aren't only observed in during the suppressions of wildland fires. In addition, there is evidence that the inhalation of wood smoke PM during prescribed wildland burns still result in physiologic detriments (A. M. Adetona et al., 2017; O. Adetona, Dunn, et al., 2011; O. Adetona, Hall, et al., 2011).

In order to continue the discussion of measuring physiologic changes to a dose response to wood smoke exposure, studies conducted in a field setting should be separated from controlled simulations. While both provide pertinent findings continuing the understanding of complications which may develop into CVD, they should be discussed separately due to the individual study designs intended limitations. Furthermore, many of the studies examined currently measure multiple areas of physiologic responses to wood smoke PM and will be expanded upon in detail of the respective areas of study including; autonomic control, vascular function, oxidative stress, and inflammation.

Known Physiologic Responses to Wood smoke PM:

ANS and Wood Smoke Exposure:

The literature is limited with respect to understanding how wood smoke PM impacts autonomic function of cardiac control. Additionally, the research methods chosen to investigate autonomic management of HR and wood smoke PM exposures to this point have only been conducted in controlled simulations and one field setting. As a result, the volume size of the PM can be managed throughout the exposure in the laboratory setting, whereas other contaminants potentially interfere with a field test. Furthermore, of the three studies, only two utilize an exercise setting which is important to consider for the dose response of PM consumption due to the elevated respiration rates. To date, a dose response to wood smoke PM combined with experiments using exercise testing and a resting condition, shows a minimal or weak impairment in HRV (Ghio et al., 2012; McCracken et al., 2011; Unosson et al., 2013).

During a resting, or sedentary, model of a wood smoke exposure, $PM_{2.5.}$was measured in 534 households with 119 participants fulfilling the criteria for inclusion in numerous mountain villages in Guatemala. Wood combustion is a prominent ubiquitous fuel source used for heating and cooking in the region. Subjects wore an air-samplers to determine the ambient concentration of $PM_{2.5}$ prior to data collection. HRV variability was measured for 30 minutes measuring LF, HF, LF:HF ratio, and SDNN. The results concluded humans subjects exposed to wood smoke PM in a resting situation presented no change in HRV $PM_{2.5}$ 102-266ug/m^3 (McCracken et al., 2011).

When both physical activity and wood smoke PM are measured simultaneously, the findings thus far are mixed. The referenced-controlled exposure studies (Ghio et al., 2012; Unosson et al., 2013) utilize similar exercise modalities - recumbent bikes, and cycle ergometers - but the exercise rates, smoke exposures, and exercise durations differ. Different durations and

intensities of aerobic exercise generates a respective alteration in HRV post exercise (Arai et al., 1989; Robinson et al., 1966).

The first studies utilizing a dose response model were conducted by (Ghio et al., 2012) and (Unosson et al., 2013) and provide a crucial foundation to understand the ANS response to wood smoke PM exposure. To date, no study has confirmed or disputed the findings. Nonetheless, in a randomized double-blind cross over design study (Unosson et al., 2013), 14 subjects rode a cycle ergometer for three hours. After 15 minutes of exercise subjects received a rest interval to generate an average ventilatory rate of 20L/min/m^2. The average concentration of wood smoke during the exposure was 314 ug/m^3 of PM_1. When HRV was measured one-hour post exercise, the PM_1 exposure setting presented a reduction in SDNN, RMSSD, and PMN50. The findings of a reduction in HRV is indicative of a risk factor for mortality (Thayer et al., 2010). Unosson et al., 2013 present the only known findings in the literature of wood smoke PM exposure reducing HRV.

The only other study to include the necessary metrics for an acute dose response with a simulated exposure to a known PM size, volume, and ventilation rate is (Ghio et al., 2012). Ten volunteer subjects pedaled a on a recumbent cycle ergometer for fifteen minutes of exercise, followed by fifteen minutes of rest for a total trial of two hours. The two exercise trials were completed, one with wood smoke PM and the other with ambient air. Central to this study design, there was a three-week washout period between trials. The subjects exercised at a rate of ventilation rate of 25L/m^2 of body surface area, per minute. The wood smoke volume during the exposure trial was 500ug/m^3 and particle size was PM_1. HRV was recorded immediately post exercise and 20 hours post exercise and found minimal changes (Ghio et al., 2012).

One might then wonder from a mechanistic level how PM impacts HRV. Unfortunately, we have conflicting results explaining wood smoke PM influencing HRV in a laboratory-

controlled exposure setting. While both exercise studies utilized the same PM size of 1 micron, the volumes of PM_1 as well as the durations and intensities of exercise are different (Ghio et al., 2012; Unosson et al., 2013). In addition, the study conducted by (McCracken et al., 2011) measured HRV in response to wood smoke $PM_{2.5}$. At this time, we can't determine from the literature whether or not wood smoke PM post exposure impairs HRV at rest or post exercise suggesting wood smoke PM may not itself interfere with cardiac control, but additional studies are needed to confirm previous observations.

Measurements of Autonomic Regulation:

As referenced previously during the introduction, researchers use a noninvasive method to measure autonomic activity with the assistance of Heart Rate Variability (HRV). Before discussing the autonomic management of cardiac control, we must explain some of the measurements that can be utilized with HRV to clarify how central command is mitigating sympathetic and parasympathetic management of heart rate. HRV provides an application to consistently monitor frequencies of RR intervals throughout a recording to determine the contributions of SNS & PNS management of heart rate through the use of LF/HF ratio. The HF band represents the parasympathetic activity moderating cardiac control through the innervation of the Vagus nerve and is sensitive to respiratory cycle (McCraty & Shaffer, 2015). While the LF band is sensitive to changes in pressure and baroreceptive activity, it is not isolated with pressure sensitivity. When HRV is measured during a 24 hour recording, the LF band is representative of sympathetic nerve activity (McCraty & Shaffer, 2015). A reduction in the LF:HF ratio suggests increased parasympathetic control relative to sympathetic control. In contrast, an elevated LF:HF provides the inverse situation suggesting sympathetic control is elevated relative to parasympathetic control (McCraty & Shaffer, 2015).

Vascular Function in Response to Wood Smoke:

The presenting dysfunction in vascular health such as arterial stiffness or atherosclerosis are considered to be synergistic properties of cardiovascular disease (Palombo & Kozakova, 2016). While the impairments of each pathology provide different physiologic mechanisms, vascular impairment plays a crucial role in the prognosis of CVD (Laurent et al., 2001; Palombo & Kozakova, 2016). Research investigating the vascular response to wood smoke PM exposure in both field experiments and laboratory-controlled wood smoke exposures (Fahs et al., 2011; Gaughan et al., 2014; Hunter et al., 2014; Unosson et al., 2013) suggesting vascular function is sensitive to wood smoke exposures.

Field Experiment:

Currently, the literature is limited to one field experiment measuring arterial stiffness within field experiments of wildland firefighting scenarios. (Gaughan et al., 2014) studied two Colorado based hot shot fire crews (type I crews) during the 2011 wildland fire season. As stated in the introduction, type I crews are exposed to more vigorous work environments, larger volumes of smoke exposure, and days of wildland fire suppression compared to members of a type II crew (Booze et al., 2004). Twenty members of a single hot shot crew participated in fire suppression for two days on a 495-acre wildland fire, with an average shift duration of 16 hours, 12.5 hours of the work shift are attributed to firefighting work-related duties. The hot shot crew described the wildfire conditions were high or extreme during the first day, while the second day was considered low or smoldering. Four days after the two consecutive days of wood smoke PM exposure, the research team administered a Pulse Wave Velocity (PWV) augmentation index and found a higher presentation of wave reflection (Gaughan et al., 2014).

While an increased presentation of arterial stiffness is a hallmark sign for a developing a vascular pathology and CVD (Pereira, Correia, & Cardoso, 2015), Gaughan and colleagues have many limitations with their finding. First, in the context of measuring a dose response, we are unware of the volume of wood smoke PM during the wildland fire in addition to the PM size. Different sizes of wood smoke PM can translocate across membranes which have shown to effect distinct organ systems (Liu et al., 2015). Second, the research fit a qualitative research design and lacked a controlled crossover experiment in which physical activity was performed without wood smoke PM inhalation (Gaughan et al., 2014). Third, the time measurements of the PWV was four days post wood smoke exposure, which allows for multiple potential physical activity and dietary influences or ambient contaminants to be inhaled and interfere with the isolated wood smoke PM exposure. Fourth, the study lacked a sample size to generate statistical significance with their findings. Due to the lacking research in wildland firefighting and vascular tone, (Gaughan et al., 2014) findings are still crucial to include in this review. However, the authors suggest future research should include a study design with a cross-over control when wildland firefighters are not being exposed to wood smoke PM (Gaughan et al., 2014). As of today, a field experiment controlling for exercise or vocational work in a non-wood smoke contaminated environment has yet to be conducted. However, laboratory-controlled wildfire simulations include a non-wood smoke exposure trial within the study designs (Hunter et al., 2014; Unosson et al., 2013).

Simulated Tests:

In contrast to isolated findings from field studies, simulated wood smoke PM exposures determine contrasting evidence arterial stiffness is sensitive to wood smoke PM (Hunter et al., 2014; Unosson et al., 2013) as well as in structure fire simulations (Fahs et al., 2011). In the growing field of wildland fire research, additional studies are needed to confirm findings

measuring arterial function post wood smoke exposure. We include a structure fire simulation study to supplement the limited research in the field of wildland firefighting. Furthermore, all the studies cited in the simulated tests section, are homogenous in the study design of testing post exercise or post vocational work.

As referenced during the autonomic control of heart rate, (Unosson et al., 2013) also evaluated arterial stiffness post wood smoke exposure. Subjects rode for three hours of cycling with a rest interval every fifteen minutes with a ventilation rate averaging ($20L/m^2$) while inhaling 314 ug/m^3 of wood smoke $PM_{1,}$ and a second trial when inhaling filtered air. Carotid-femoral PWV measurements administered prior to exercise, and then in ten-minute intervals beginning at the termination of exercise until one-hour post exercise. Through the implementation of a central arterial PVW augmentation index, when comparing the wood smoke exposure with the controlled filtered air, a statistical increase was seen in arterial stiffness immediately post exercise (Unosson et al., 2013). The significance of (Unosson et al., 2013) findings provide a known deviated autonomic response in vascular tone resulting from the consumption of wood smoke PM_1. An acute instance of wood smoke PM increasing vascular tone post exposure is of concern for the wildland fire fighting community. Wildland firefighters are chronically exposed wood smoke PM and may be at a further risk developing alterations in vascular tone. Instances where arterial stiffness measured through PVW increases $5m^{s-}$, is the equivalent of aging 10 years (Laurent et al., 2001).

A follow up study one year later aimed to build on the initial findings by (Unosson et al., 2013), but with an increased level of wood smoke PM_1 and a shorter duration of exercise. (Hunter et al., 2014) tested 16 healthy males on a cycle ergometer for one hour with rest intervals every 15 minutes. Subjects were randomly assigned into two situations, either inhaling 1000 ug/m^3 of wood

smoke PM_1, or inhaling filtered air, and repeated the second condition one week later. The cycling output during both trials averaged to $20L/m^2$. When comparing the augmentation index, PWV pressure augmentation, both trails indicate a significant increase in PWV pressure from base line values (Hunter et al., 2014). The similar presentation suggests the exercise in both situations caused the increase in PVW rather than the wood smoke PM_1 as seen in (Unosson et al., 2013).

While we cannot definitively conclude why Hunter et al., did not replicate the (Unosson et al., 2013) findings, one can postulate why these prior studies are dissimilar. The time frames between the two studies are significantly different comparing three hours of exercise (Unosson et al., 2013) to one hour of exercise (Hunter et al., 2014) while exercising at the same ventilation rate ($20L/m^2$). In context to a dose response, subjects inhaled PM_1 for a longer time frame which could have been enough to alter the response in vascular tone. We also can't definitively clarify why a wood smoke PM_1 exposure with more than three times the concentration did not alter vascular tone ($1000ug/m^3$ compared to $330ug/m^3$) and this still remains an unanswered question. One possible reason could be the subject selection for the two studies. The health of the subjects in (Unosson et al., 2013) are only described as non-smokers, whereas the subject pool in (Hunter et al., 2014) included firefighters who all obtained from wildland fire or structure fire duty in the week prior to the study (Hunter et al., 2014).

Supplement Structure Fire Study:

During a structure fire simulation, 69 male firefighters wearing firefighter gear including breathing apparatuses conducted drills various structure fire situations for 15-25 minutes work intervals, with a rest interval of 10-15 minutes in between simulations. Subjects were separated between engine crews and truck crews. Engine crews were responsible for obtaining water, fire hose advancement, and extinguishing fires while truck crews executed forcible entries, search and

rescue, and ventilation tasks (Fahs et al., 2011). The simulated work scenarios were carried out in a basement, restaurant, single family dwelling, two story taxpayer building, and a standpipe operation (Fahs et al., 2011). Pre and post carotid-femoral PVW measurements resulted in statistically significant increase central arterial stiffness and augmentation index after the three hours of simulations (Fahs et al., 2011). The presenting changes in vascular function are supported in the literature in response from an acute bout of exercise or physical activity (Mutter, Cooke, Saleh, Gomez, & Daskalopoulou, 2017; Pierce et al., 2018).

Excluding the different setting (structure fire) and exposure of PM, and the use of personal self-contained oxygen apparatuses in (Fahs et al., 2011), the finding supports the notion of a time frame contributing to the increase in arterial stiffness seen in (Fahs et al., 2011; Unosson et al., 2013). To our knowledge, no other study of wildland fire has reported wood smoke PM increasing arterial stiffness post exposure. We can confirm, however, the freighting tasks in both structure and wildland settings including simulations, generate enough physical stress to increase arterial stiffness.

In the next section of the review, the oxidative stress response in from wildland fires is addressed. While (Gaughan et al., 2014) lacked a statistical difference in arterial stiffness, the authors found a correlation exists between elevated arterial stiffness and presentation of oxidative stress post exercise in wildland firefighting (Gaughan et al., 2014).

Oxidative Stress, inflammatory mediators / cytokines:

The presence of oxidative stress, inflammatory, mediators, and cytokines are under certain terms are related. The occurrence of oxidative stress in response to wood smoke PM presents a systematic response and is associated production cytokines and inflammatory mediators in the presence of oxidative stress (See Table 1. Pg 33). As mentioned in the introduction, the

upregulation of oxidative stress and ROS post wood smoke PM exposure is not the same as the acute ROS production from a bout of exercise. Oxidative stress markers such as ROS (super oxide, hydroxyl radical, hydroxyl ions, and hydrogen peroxide) are known to effect homeostasis (Rao, Zhong, Brook, & Rajagopalan, 2018) and markers of lipid oxidation (8-iso prostane, lipid hyperoxides) and protein oxidation (protein carbonyls, 3-nitrotyrosine) are measured in response to wood smoke PM (Ferguson et al., 2016; Peters et al., 2018) . Chronic levels of oxidative stress generated from environmental contaminants act as potential signals for increasing the risk for developing CVD (Giorgini et al., 2016). The primarily mechanism of non-exercise induced oxidative stress in wildland firefighters post wood smoke PM exposure presents in lungs, vasculature, serum, and urine (Ferguson et al., 2016; Ghio et al., 2012, 2016; Gianniou et al., 2018; Peters et al., 2018). Research conducted over the past 15 years, identify specific markers known to be sensitive to wood smoke PM exposure in both laboratory and field experiments. The known inflammatory markers of interest upregulated when exposed to wood smoke PM in laboratory and field experiments are: IL-8 (Gaughan et al., 2014; Ghio et al., 2012; Gianniou et al., 2018; Kocbach et al., 2008; Swiston et al., 2008), TNF-α (Gianniou et al., 2018; Leonard et al., 2000; van Eeden et al., 2001), Pentraxin3 (Ferguson et al., 2016), 8-Isoprostane (oxidative stress marker) (Ferguson et al., 2016; Gaughan et al., 2014; Peters et al., 2018), and VEGF Vascular Endothelial Growth Factor (Gianniou et al., 2018). Due to large volume of research presenting cytokines response to wood smoke PM, this following section will be expanded by individual cytokine, rather than by individual study as in the autonomic regulation of cardiac control and vascular tone.

Table 1.)

Inflammatory markers / oxidative stress / cytokine responses		
Inflammatory markers	**Cytokine responses to WSPM**	**Examples of known oxidative stress markers**
Interleukin 8 (IL-8)	Pro inflammatory mediator, attracts neutrophils, also released from Polymorphonuclear leukocytes.	ROS. (Hydrogen peroxide, Hydroxyl radical, Hydroxyl ions, Superoxide)
Tumor Necrosis Factor Alpha (TNF-a)	Pro inflammatory cytokine link with CVD and induces systemic inflammation.	8-Isoprostane (8-Iso), Lipid hyperoxides (LOOH), Protein Carbonyls, 3-Nitrotyrosine
Pentraxin 3 (PTX-3)	Representative to vascular damage and inflammation, and CVD.	
Vascular Endothelial Grow Factor (VEGF)	Prominent in development of atherosclerosis.	
* The examples of inflammatory makers sensitive to the exposure of wood smoke PM. Cytokine responses are the physiologic responses from wood smoke PM. Oxidative stress are known markers to interfere with homeostasis. ROS (family), 8-Iso and LOOH are markers of lipid oxidative stress. Protein carbonyls and 3-Nirtro are markers of protein oxidative stress.		

Interleukin-8 (IL-8):

IL-8 is a proinflammatory mediator, and attracts neutrophils. When IL-8 levels remain elevated, it can result in damaged tissue (Dinarello, 2000). Across multiple studies investigating wildland freighting, collectively, they indicate IL-8 is sensitive to the consumption of wood smoke PM. (Gaughan et al., 2014; Ghio et al., 2012; Gianniou et al., 2018; Kocbach et al., 2008; Swiston et al., 2008). In addition, studies measuring IL-8 have been conducted in both *in vitro* (Ghio et al., 2012; Kocbach et al., 2008) and *in vivo* (Gianniou et al., 2018; Swiston et al., 2008).

In vitro studies indicate IL-8 increases in response to wood smoke PM exposure. BEAS-2B cells were grown in keratinocyte growth medium and subsequently exposed to phosphate buffered saline solution and two categories of wood smoke PM_1 , 50ug/ml and 100ug/ml for 24 hours (Ghio et al., 2012). The presentation of IL-8 act as an inflammatory mediator from the phosphorylation of cell signaling in response to the oxidative stress induced by wood smoke PM_1 (Ghio et al., 2012). An additional *in vitro* study also demonstrates wood smoke PM_1 generates the release of IL-8 from human monocytic cell lines THP-1 cells (Kocbach et al., 2008). THP-1 cells

were tested under 5 different concentrations of wood smoke PM (30ug/ml, 70ug/ml, 140 ug/ml, 210ug/ml, and 280ug/ml) and a control of 0ug/ml. All 5 concentrations generate a significant increase in the THP-1 release of IL-8 in a linear presenting fashion (Kocback et al., 2008). When *in vivo* studies have measured cytokine presentation post wood smoke exposure, they have also presented the upregulation of IL-8. Swiston et al., conducted a field study analyzing 52 wildland firefighters comprised of both sexes who either participated in wildland fire suppression or participated in physical activity mimicking similar outputs to wildland fighting without wood smoke exposure. Baseline measurements for each group were taken simultaneously while post exposure measurements occurred four hours after firefighting. Findings show significant increase in the presentation of IL-8 post firefighting in comparison to physical activity without wood smoke $PM_{3.5}$. Estimated levels of $PM_{3.5}$ peaked at 2800 ug/m^3 with more than six hours of exposure of 1000 ug/m^3 which is significantly higher than levels of laboratory simulated exposures. In addition, levels of IL-8 did not statistically increase when compared to baseline levels in the subjects with physical activity and no wood smoke exposure. $PM_{3.5}$ is a unique size to study in comparison to $PM_{2.5}$ as it fulfills the criteria to be considered coarse PM rather than criteria to be fine PM and to our knowledge, few studies measure $PM_{3.5}$ in the wildland firefighting literature (Reinhardt & Ottmar, 2000). Therefore, we should interpret the findings by Swiston et al., as potentially novel until future research can confirm the reaction of serum IL-8 post wood smoke $PM_{3.5}$ exposure.

A recent field study also demonstrates upregulation in IL-8 post wood smoke PM exposure. During the summer of 2008, 60 wildland firefighters participated in an experiment while fighting a wildland fire in Greece. (Gianniou et al., 2018) findings indicate both serum and sputum levels of IL-8 elevate significantly through the analysis of blood and bronchoscopy lavage compared to baseline measurements after several days of fighting wildland fires (Gianniou et al., 2018). A key

difference in the study design of (Gianniou et al., 2018) is the time frame measurements. Data collection occurred between 24-48 hours post wood smoke exposure for blood analysis and 48 hours after the first post exposure visit. Polymorphonuclear leukocytes (PMN) respond uniquely to wood smoke PM and not the stress induced by exercise (Swiston et al., 2008)

TNF-α.

Multiple studies determine Tumor Necrosis Factor alpha (TNF-α) is sensitive to the consumption of wood smoke PM (Gianniou et al., 2018; Kocbach et al., 2008; Leonard et al., 2000; van Eeden et al., 2001). TNF-α like IL-8 is also a proinflammatory cytokine and is linked with the presence of cardiovascular dysfunction (Ferrari, 1999). Specifically, TNF-α effects the contractility of the myocardium and in the case of congestive heart failure (CHF) circulating levels of TNF-α remain upregulated (Ferrari, 1999). The release of TNF-α induces both a local and systemic inflammatory response from the inhalation of PM deposits inside the lungs (van Eeden et al., 2001).

Two studies nearly 20 years ago provide some of the first evidence of TNF-α upregulating in response to wood smoke PM(Leonard et al., 2000; van Eeden et al., 2001). In an animal model study, peritoneal macrophages were obtained from mice (RAW 264.7 cells) and were exposed to 100 ul/ml wood smoke solution and then exposed for additional 12 and 24 hours. Results show TNF-α release elevate at both 12 and 24 hours of exposure, with a two-fold increase in 24 hours when compared to the control (Leonard et al., 2000). We note that the RAW 264.7 cells from the peritoneal macrophages are not the same as a primary peritoneal macrophage, however, it's noted the RAW264.7 cells do respond to the production of TNF-α release similar to primary alveolar macrophages (Leonard et al, 2000). A year after (Leonard et al., 2000) publication, (van Eeden et

al., 2001) found that primary alveolar macrophages (AM)[3] produce TNF-α in a dose dependent fashion when phagocytosing atmospheric particles (van Eeden et al., 2001). An additional study, (previously mentioned during the description of IL-8) found a similar outcome to Leonard et al., when exposing laboratory grown human grown monocytic THP-1 cells to 30 ug/ml of a wood smoke solution for 12 hours (Kocbach et al., 2008). The single field study investigating TNF-α in wildland firefighting suppression demonstrate both serum and sputum levels TNF-α are significantly higher than baseline tests, after several days of firefighting (Gianniou et al., 2018). Furthermore, the average work day duration plays an additional role within the upregulation of TNF-α. Wildland firefighting shifts with more than 10 hours of wood smoke PM exposure generated significantly higher levels of TNF-α in comparison to shift durations with less than 6 hours of wood smoke PM exposure (Gianniou et al., 2018).

Pentraxin3:

Pentraxin 3 (PTX-3) is a widely known cytokine of interest within the development of CVD. PTX-3 is responsible for various components of CVD including atherosclerosis, endothelial function, hypertension, myocardial infarction and angiogenesis (Fornai et al., 2016). In addition PTX-3 is an acute phase protein and accompanies vascular damage (Presta, Camozzi, Salvatori, & Rusnati, 2007), and vascular inflammation (Bevelacqua et al., 2006). Recently, a new stimulus was found to upregulate the presentation of PTX-3, wood smoke PM. In a laboratory-controlled wood smoke exposure 10 subjects walked on a treadmill 3.5 mph at incline 5.7% for 90 minutes under three different exposure settings, filtered air, and two different volumes of wood smoke $PM_{2.5.}$ 250 ug/m^3 and 500 ug/m^3. Plasma levels of PTX-3 increased significantly after both

[3] Human Alveolar Macrophages were harvest from bronchial lavage fluid (van Eeden et al., 2001).

volumes of exposures in comparison to filtered air post exercise, and one hours post exercise (Ferguson et al., 2016).

8-Isoprostane:

8-Isoprostane (8-ISO) is a lipid oxidative stress marker and acts as an independent risk factor for multiple causes of mortality including total mortality, CVD, and non-CVD in middle aged humans with normal BMI <24.9 (Godreau et al., 2012). When 8-Iso has been measured in EBC and urine, both samples demonstrate sensitivity to wood smoke PM consumption (Gaughan et al., 2014; Peters et al., 2018). Additionally, there is evidence linking the oxidative stress production with arterial stiffness in response to wood smoke PM (Gaughan et al., 2014).

Simulations:

Two research studies simulating wildland firefighting environments indicate 8-ISO upregulation in response to $PM_{2.5}$ (Ferguson et al., 2016; Peters et al., 2018). Ten subjects walking on a treadmill at 3.5 mph at a 5.7% incline on a treadmill for 90 minutes in a laboratory-controlled wood smoke environment while inhaling volumes filtered ambient air, two wood smoke settings of $PM_{2.5.}$ (250 ug/m^3 and 500 ug/m^3), generated a statistically significant increase levels of 8-isoprostane immediately post-exercise, and one hour post-exercise as measured through EBC (Peters et al., 2018). EBC 8-ISO response from the volumes of both wood smoke $PM_{2.5}$ conditions were similar and therefore only compared to the filtered ambient air. In a similar study design as (Peters et al., 2018) , Ferguson et al., 2016 measured the change in plasma 8-ISO in response to three conditions of wood smoke $PM_{2.5}$ (0 ug/m^3, 250 ug/m^3, 500 ug/m^3) and found an increase in both levels of wood smoke immediately post exercise, but values returned close baseline measurements one hour post exercise (Ferguson et al., 2016).

Field Test:

Field research measuring two hot shot crews over the course of two days of indicates a release of 8-Isoprostane, through the in the presence of urinary levoglucosan concentration (Gaughan et al., 2014). The key finding in (Gaughan et al., 2014) field study, was observing a connection with presentation of 8-ISO, levoglucosan, and seeing a pattern of higher outputs in PWV augmentation index (Gaughan et al., 2014), as cited in the vascular response section. While experiment lacked the power to generate statistical significance, the findings within simulation studies is encouraging in that 8-ISO is responsive enough to multiple volumes of PM (Ferguson et al., 2016; Peters et al., 2018) that future study may be able to determine a statistically significant link to the presentation of 8-ISO and changes in vascular tone in wildland firefighters.

Vascular Endothelial Growth Factor

Vascular Endothelial Growth Factor (VEGF) is a recent cytokine like Pentraxin-3 to be measured in response to wood smoke PM. We choose to include this relatively new cytokine in our literature review due to evidence it too is sensitive to wood smoke PM consumption (Gianniou et al., 2018) and the role it may play in development of cardiovascular disease. Serum levels of VEGF significantly increase in wildland firefighters after multiple days of firefighting (Gianniou et al., 2018). Upregulation of serum VEGF is associated with increasing the risk of developing atherosclerosis, even within healthy populations (Kimura et al., 2007).

Conclusions in Oxidative Stress:

Unlike the areas of autonomic control, and maintenance of vascular tone, the literature studying the oxidative stress from wood smoke PM is much more consistent (Ferguson et al., 2016; Gaughan et al., 2014; Leonard et al., 2000; Peters et al., 2018; Swiston et al., 2008; van Eeden et al., 2001). Lipid and protein oxidation in addition to the presentation of ROS occurs in response to the consumption of wood smoke PM in healthy individuals (Ferguson et al., 2016; Leonard et

al., 2000; Peters et al., 2018). More so, the evidence demonstrates wood smoke particulate matter induced oxidative stress occurs in both pulmonary and systemic circulations (Ferguson et al., 2016; Gaughan et al., 2014; Ghio et al., 2012; Gianniou et al., 2018; Peters et al., 2018; Swiston et al., 2008). 8-Iso prostane, previously discussed as an lipid oxidative stress marker, has been linked to the CVD mortality in middle aged adults (Godreau et al., 2012) which is of particular concern for aging wildland firefighters. We have also included four inflammatory markers relevant to CVD and are also sensitive to a range of sizes of wood smoke PM. Additional research must expand on the previous published work of IL-8 and TNF-α, and should be conducted to determine if PM size differentiates systemic outcomes. PTX-3 and VEGF are more recently discovered signaling molecules and require further investigation to confirm the presence of vascular damage and dysfunction post wood smoke PM exposure.

Inflammation:

Pulmonary and systemic responses in wildland firefighting and simulations demonstrate an inflammatory response to wood smoke PM. In addition, pulmonary dysfunction is being effected from the consumption of wood smoke PM (Liu et al., 2015). Inflammation is present in lungs which has been observed through reductions in lung function in Forced Vital Capacity (FVC) and Forced Expiratory Volume (FEV_1) (Dorman & Ritz, 2014) and resulted in a decrease in Forced Expiratory Flow (FEF) post wood smoke exposure (Gianniou et al., 2018). Wood smoke PM jeopardizes lung function through alveoli instability via surfactant deactivation, in addition to patchy interstitial edema, and amorphous alveolar edema. (Steinberg et al., 2005). Furthermore alveoli impairment increases with the time and accumulative wood smoke exposures, (Steinberg et al., 2005).

There is a well-characterized systemic response from acute exposures to wood smoke PM (Kocbach et al., 2008) Small changes in vascular tone can generate even mild cases of inflammation (Hingorani et al., 2000) occur in wildland fire fighting (Gaughan et al., 2014; Unosson et al., 2013). Systemic inflammatory markers in wildland freighting can be detected in exhaled breathing condensate (EBC), urine, and blood, but present at different times frames post PM exposure. (Ferguson et al., 2016; Kocbach et al., 2008; Peters et al., 2018) and collectively are linked with cardiovascular disease (Dorman & Ritz, 2014; Swiston et al., 2008). Duration of fighting wildland fires is related to the inflammatory response. Situations in which firefighters spend greater than 10 hours in firefighting operations experienced elevated levels of inflammation compared to those who spent less than 10 hours in operations. (Gianniou et al., 2018).

Conclusion:

The inclusion of a dose response to provide context to identifiable markers of oxidative stress, conflicting evidence of a reduction in HRV, the increases in arterial stiffness, pulmonary inflammation, and systemic inflammation, post wood smoke exposure can act at a starting point to begin a deeper understanding on the overall impact wildland firefighting has on CVD. Currently, there are still too many unanswered questions within the cohort of markers in wildland firefighter research to address the overarching question, "What is the mechanism responsible for the increased risk of developing cardiovascular disease in wildland firefighters?" We confirm from the this review the strong association between the inhalation of wood smoke PM and an additional likelihood of the development of CVD (O. Adetona et al., 2016; Cascio, 2018; Navarro et al., 2019), is likely to be on the rise with the continuing occurrence of anthropogenic climate change increasing quantity and severity of wildland fires (Abatzoglou & Williams, 2016). At this time, PM generated from wood smoke PM does not hold the same strength of a relationship from man-

made sources when measuring through HRV. In addition, vascular dysfunction presents a trend of impairment post wood smoke PM exposure, but will require additional research to differentiate the normative vascular decrease after vocational work or physical activity. Future studies may be able to determine a list of considerations through the implementation of a dose response into research designs in order fill current voids within wildland firefighter research, and susceptibility to CVD.

Chapter Three: Methodology

Research Design

This review paper was completed with a theory-building approach working off previous research to understand how underlying markers of ROS, arterial stiffness, mismanagement of the ANS, and inflammation in response to wood smoke PM exposure contribute to the development of CVD. The negative health effects associated from wood smoke PM inhalation are clearly stated ranging from increased hospital admissions for respiratory complications (COPD and asthma), increase of cardiac events, the presentation of acute phase proteins sensitive wood smoke PM (TNF-α, PTX-3, IL-8, ISO-8), and the increased presentation of arterial stiffness and systemic inflammation. We also included the normative response from exercise in these organ systems to differentiate the known expected exercise response and that from the consumption of wood smoke PM.

The original research cited in this review are comprised from experiments using field and laboratory-controlled experiment methods to encompass the collective body of wildland fire fighter research. While field experiments provide the validity to the realistic work scenario wildland firefighters are exposed to each season, laboratory simulations are necessary to supplement areas where field experiment are not achievable. Future studies looking to include a dose response into the methodology of their data collection should consider conducting a laboratory-controlled simulation scenario first. The difficulty of tracking all the stress markers in a wildfire setting are possible, but present many challenges to effectively collect all they require data for each subject. In addition, there is an increased likelihood of injuries in wildland firefighters which may result in the loss of subjects for a study.

Research Procedures:

We compiled a thorough literature review of previous studies measuring physiologic responses in; wood smoke PM, the acute exercise response, inflammation, and autonomic control. Supplement gaps in the wild land firefighter literature with structure firefighting and fill gaps PM exposure from other organic sources besides wood smoke (Rappold G. et al., 2011). In addition, multiple review articles referenced establish the consensus of the most recent findings in the collective research investigating known physiologic outcomes from PM exposure (O. Adetona et al., 2016; Cascio, 2018; Navarro et al., 2019; Pope & Dockery, 2006).

The articles obtained for this project come from multiple web-based sources. Primarily, we relied on the PubMED data base through National Institute of Health. We sought original research and used the following key phrases "wildland fire, wood smoke particulate matter & oxidative stress (or ROS), arterial stiffness, wood smoke PM and autonomic control". Due to the limited availability of original studies we gained deeper access to multiple journals through subscriptions through The Mansfield Library, at the University of Montana. In addition, multiple review papers referenced establish a consensus of previous findings with in the literature. At this current time, no review paper has been published including the effectiveness of the implementation of dose response to help explain the prevalence of CVD within the wildland firefighting population.

Treatment of Research:

We constructed an empirically supported suggestion to include a dose response (PM size, source, volume, and ventilation rate) when studying the health effects from the inhalation from wood smoke PM to help explain the health consequences presenting in wildland firefighters. We explained the differentiation of how oxidative stress, vascular function, fluctuations in HRV, and

inflammation occur in response from exercise and how the same markers present differently post wood smoke PM inhalation. Furthermore, we introduced the notion of separating sources of PM (natural vs. man-made) with evidence showing PM of the same size does not result in the same physiologic responses.

Preliminary Suggestions:

Our suggestions to build upon the findings within this literature review are broken down into the individual areas reported on in Chapter 2. We made an inquiry into the organ systems previous research determines most relevant to the development of CVD (ANS, ROS, inflammation, and arterial stiffness). At this time, the results in the area of the autonomic response to wood smoke PM demonstrates an inconsistent relationship from wood smoke PM exposure collectively exacerbate wildland firefighter's susceptibility in the advancement of CVD. The limited research afforded the opportunity, however, to expand upon the findings in areas of oxidative stress, and vascular impairment (arterial stiffness), and inflammation.

We can denote interference of wood smoke PM consumption and the autonomic management of cardiac control is weak at this time in comparison to PM from man-made sources and supports a previous review article (O. Adetona et al., 2016). Of the three studies referenced in our review, (Hunter et al., 2014; McCracken et al., 2011; Unosson et al., 2013), only one study demonstrated a statistically significant response from the inhalation of wood smoke PM (Unosson et al., 2013). Research may include HRV to measure ANS activity in future studies, but should consider an acute response from a single wood smoke PM exposure does not seem to alter the ANS's control of HR at this time.

The oxidative stress markers in this review indicated a strong relationship from the inhalation of wood smoke PM. In addition, each one of the inflammatory markers referenced plays

a role in elevating the risk of CVD and in vascular damage (8-Iso, PTX-3, VEGF) (Bevelacqua et al., 2006; Fornai et al., 2016; Godreau et al., 2012; Presta et al., 2007), and cardiovascular dysfunction (IL-8 and TNF-α) (Dinarello, 2000; Ferrari, 1999). Research is unable to establish a single acute phase protein solely being responsible for the progress of CVD in response to wood smoke PM, suggesting, the inclusion of a panel of markers provides a better chance of elucidating the key culprits. We don't expect future research to prefer the panel listed in this review, although these cytokines have are referenced in multiple studies (Ferguson et al., 2016; Gaughan et al., 2014; Gianniou et al., 2018; Kocbach et al., 2008; Peters et al., 2018; Swiston et al., 2008), suggesting a portion of the discussed cytokines should be considered. One question worth attempting to answer with the assistance of additional research in the future would be to investigate if any of the mentioned cytokines above remain elevated during a wildland fire season? The scientific community may be able to shine light how the acute spikes from multiple exposures of wood smoke PM induced oxidative stress may play a role during a single season, and through additional exposures during subsequent seasons translates into wildland firefighters developing CVD later on in life.

The examination in vascular dysfunction should continue in the future studies involving the exposure to wood smoke PM. Upon the completion of this review, vascular function post wood smoke PM exposure presents mixed results. Three of the four studies we cited utilize wildland firefighters or simulations (Gaughan et al., 2014; Hunter et al., 2014; Unosson et al., 2013)[4] and only two of the studies observe an increase in arterial stiffness through PWV (Gaughan et al., 2014; Unosson et al., 2013) (2 x 16 hour work shifts; 3 hour simulation) had much longer time frames

[4] The fourth study (Fahs et al., 2011) features a structure fire simulation where there was no exposure to wood smoke PM. A statistical significance was found in arterial stiffness after a 180-minute simulation of structure fire work setting.

of an exposure period than the wildfire simulation of (Hunter et al., 2014) (1 hour). We are unware of the volume of PM consumption in (Gaughan et al., 2014) as it was a field experiment, however, (Unosson et al., 2013) found a significant increase in arterial stiffness in their simulation with two-thirds of the volume of PM and a longer testing duration. Furthermore, looking through the inclusion of a dose response, both studies (Hunter et al., 2014; Unosson et al., 2013) used the same PM size (PM_1), source (Birch), and exercise intensity (20L/min), see table 3. The conclusion we most notably drew is perhaps the duration of exposure may play a bigger role in the vascular response to wood smoke PM rather than the volume of PM consumption. Additional research can build upon this finding by repeating a simulation which includes two different time durations, and two different volumes of PM in a randomized repeated measures study design to clarify whether or not the duration of exposure is relevant to include in the dose response model.

PM induced pulmonary and systemic inflammation and consistent across multiple studies as discussed previously(Dorman & Ritz, 2014; Ferguson et al., 2016; Gianniou et al., 2018; Liu et al., 2015; Peters et al., 2018; Unosson et al., 2013). The wood smoke PM generates pulmonary inflammation interference with gas exchange by hampering the function alveoli, which is supported by a decrement in lung function when measured with spirometry (Dorman & Ritz, 2014; Gianniou et al., 2018). When ultrafine PM diffuses through the lungs and into systemic circulation it presents as vascular inflammation and damage to the endothelial tissue presenting in stress markers discussed earlier (PTX-3, 8-Iso, VEGF). Systemic inflammation in response to wood smoke PM consumption follows a similar trend as arterial stiffness, in which duration may play a more important role. Wildland firefighters are at a greater vulnerability for systemic inflammation to magnify when times frames exceed 10 hours compared to settings of shorter duration (Gianniou et al., 2018). The forthcoming studies in wildland firefighting research may corroborate this

finding within a field test using wildland crews during an upcoming forest fire season, or may include differentiating the exposure time frames within a simulation with inflammatory markers when studying the different durations while measuring vascular function.

Wildland firefighting research teams should implement a dose response into their data collection methods in both laboratory-controlled simulations, and field experiments. There sufficient evidence in the simulations (Ferguson et al., 2016; Ghio et al., 2012; Hunter et al., 2014; Peters et al., 2018; Unosson et al., 2013) to continue the investigation of different PM sizes, volumes, and sources. In addition, the ability to use portable PM samplers can improve upon the results seen field studies (Gaughan et al., 2014; Gianniou et al., 2018; Swiston et al., 2008) to tell a more complete story of the working environment wildland firefighters face each year. Together the scientific community may start to identify ways to adjust the numbers of exposures, or an acceptable upper-limit of wood smoke PM volume in an attempt to reduce in occurrence of CVD in wildland firefighters.

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Tables:

Appendix Table 1.) Oxidative Stress

Tabe 1.) Oxidative Stress

Study Name	Lab / Field Study	PM Size	Volume	Source	Exposure Duration	Ex. Rate	Outcomes
Ferguson et al., 2016	Laboratory Controlled	PM 2.5 +	0 ug/m^3 250 ug/m^3 500 ug/m^3	Western Larch	90 minutes	22.m ml/kg/min	↑Serum 8-Iso Prostane ↑ PTX-3 ↓
Ghio et al., 2012	Laboratory Controlled	WSP	500 ug/m^3	Red Oak	120 minutes	25L/BSAm^ 2/min	↑ IL-8
Gianniou et al., 2018	Field Study	WSP	Unknown	unknown	1 season / 3 months post exposure	Unknown	↑ serum VEGF ↑serum & suptum IL-8 ↑ serum & sputum TNF-a
Peters et al., 2018	Laboratory Controlled	PM 2.5 +	0 ug/m^3 250 ug/m^3 500 ug/m^3	Western Larch	90 minutes	< 57% of VO2 max	↑Serum 8-Iso
Gaughan et al., 2014	Field Study	WSP	unknown	Sand Gulch Fire, Westmore , CO.	2 - 16 hour shifts	Wildland Firefighting related activities	↑Serum 8-Iso
Swiston et al., 2008	Field Study	WSP	<2000ug/m ^3	Wildfire PM	1 fire shift / day of exericse ~ 8 hours each	Wildland Firefighting related activities	↑ Serum IL-8 & Serum IL-6
Kocback et al., 2008	⌽ Laboratory Controlled. Human grown THP-1 Cells	WSP	0 ug, 30 ug, 70 ug / well plate	unknown	12 hours	NA	↑ IL-8 , ↑ TNF- a

* Ultrafine PM, + fine PM, WSP (wood smoke particle), ⌽In vitro,

Appendix Table 2.) HRV

Tabe 2.) HRV

Study Name	Lab / Field Study	PM Size	Volume	Source	Exposure Duration	Ex. Rate	Outcomes
McCracken et al., 2011	Field Study	PM 2.5 +	102-266ug/m^3	wood and crop residue	30 minutes	unknown	No change in HRV
Ghio et al., 2012	Laboratory Controlled	WSP	500 ug/m^3	Red Oak	120 minutes	25L/BSAm^2/min	Minimal Change
Unosson et al., 2013	Laboratory Controlled	PM 1 *	314ug/m^3	Birch	180 minutes	20L/min/m^2	Significant change in HRV. SDNN, RMSSD, PNN50

* Ultrafine PM, + fine PM, WSP (wood smoke particle)

Appendix Table 3.) Arterial Stiffness

Tabe 3.) Arterial Stiffness

Study Name	Lab / Field Study	PM Size	Volume	Source	Exposure Duration	Ex. Rate	Outcomes
Gaughan et al., 2014	Field	WSP	Unkown	Sand Gulch Fire, Westmore, CO.	32 hours , 2 x 16 hours shifts	NA	increase in PWV augmentation index
Hunter et al., 2014	Laboratory Controlled	PM 1 *	0 ug/m^3 1000 ug/m^3	Birch	1 hour	20L/min	no difference in PVW augmentation index immediate post exercise
Unosson et al., 2013	Laboratory Controlled	PM 1 *	314 ug/m^3	Birch	180 minutes	20L /min	Sig increasae in PVW augmentation index immediate post exercise
Fahs et al., 2011 ⍁	Laboratory Simmulated	NA	NA	NA	180 minutes	NA	Firefighting vocational work resulsts in increased PWV post simulation

* Ultrafine PM, + fine PM, WSP (wood smoke particle) ⍁ Indicates structure fire simulation with personal resperators