

The Cardiovascular Pathology of Stimulant Overdose Decedents in King County, Washington

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**Abstract**

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**Background** In King County, Washington, the number of methamphetamine related overdose deaths has more than quadrupled since 2010. Compared to the body of evidence on cocaine poisoning, little is known about the risk factors for or pathophysiology of methamphetamine overdose. **Aim** To determine the prevalence of acute and chronic cardiovascular pathology among decedents who died from methamphetamine, mixed methamphetamine-heroin, cocaine, and mixed cocaine-heroin overdose compared with a group of heroin overdose decedents.

**Design** Retrospective case-comparison. **Findings** Acute cardiovascular events occurred exclusively among stimulant related deaths. After controlling for sex, weight, age, gender, and race, the methamphetamine group had significantly greater mean heart weight. The cocaine group had significantly greater prevalence of coronary artery disease, cardiomegaly, hypertensive cardiovascular disease, and greater heart weight. The mixed methamphetamine-heroin group was similar to the heroin comparison group across all demographic and cardiovascular variables. **Conclusions** Methamphetamine related overdose deaths are strongly associated with greater heart weight in comparison to heroin overdose deaths, but unlike cocaine overdose deaths, they are not associated with chronic cardiovascular pathology.

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## **CHAPTER 1:**

### **Introduction**

#### **Background**

Drug overdose is the leading cause of unintentional death in the United States, now surpassing deaths by firearm and motor vehicle accidents.<sup>1</sup> In King County, Washington the number of lives lost to accidental drug poisoning has risen steadily since 2010 with methamphetamine causing a growing proportion of these deaths. The King County Medical Examiner reported 85 methamphetamine-related deaths in 2015, more than quadruple the amount in 2010. Of note is the recent trend in mixed methamphetamine-heroin overdose, with 40 of all methamphetamine deaths including concurrent heroin in 2015, compared with 14 methamphetamine-heroin combination deaths in 2013.<sup>2</sup> In the United States, 12 million people (4.7% of the population) have tried methamphetamine at least once and 1.2 million have used methamphetamine in the past year.<sup>3</sup> Given the popularity of the drug, it is important to understand the circumstances of methamphetamine overdose. A King County autopsy records may elucidate which populations are most vulnerable to methamphetamine-related overdose death.

Previous research demonstrates that methamphetamine use is associated with acute cardiovascular complications including arrhythmias, hypertension, myocardial infarction, aortic dissection and coronary vasospasm.<sup>4-7</sup> It may also lead to chronic cardiovascular pathology such as premature accelerated coronary artery disease, greater heart weight, left ventricular hypertrophy and cardiomyopathy.<sup>8,9</sup> The pathophysiologic mechanisms underlying the cardiotoxic effects of methamphetamine relate to increased levels of circulating catecholamines (epinephrine, norepinephrine and dopamine) that cause vasoconstriction, coronary artery

vasospasm, and tachycardia. The combined effect of these cardiovascular changes can result in an increased myocardial oxygen demand, with a concurrent decreased oxygen supply.<sup>8</sup>

Although the existing research provides a framework for understanding methamphetamine cardiotoxicity, little is known about the combined cardiovascular effects of methamphetamine and heroin. Additionally, it is unknown if the presence of chronic cardiovascular pathology itself, such as coronary artery disease and left ventricular hypertrophy, is associated with death in the setting of increased myocardial oxygen demand secondary to methamphetamine use.

## **Objectives**

The broad objective of this study is to identify the demographic trends and prevalence of cardiovascular pathologies among methamphetamine and methamphetamine-heroin combination overdose decedents in light of the rising incidence of these deaths in King County, Washington.

The specific objectives of the study include the following:

- Determine the race, sex, and age distributions among people who died secondary to methamphetamine, combination methamphetamine-heroin, cocaine, combination cocaine-heroin or heroin overdose.
- Describe the types of locations where overdose deaths occurred.
- Establish the distributions of BMI and heart weight across drug overdose groups.
- Determine the prevalence of the following cardiovascular pathologies among drug overdose groups: intracerebral hemorrhage, acute myocardial infarction, myocardial fibrosis, coronary artery disease, left ventricular hypertrophy, cardiomegaly, dilated cardiomyopathy, other cardiomyopathies and hypertensive cardiovascular disease.

## Literature Review

After marijuana, amphetamine-type stimulants are the most commonly consumed drug in the world.<sup>10</sup> Methamphetamine is a potent synthetic stimulant with two isomeric forms, dextro- and levomethamphetamine. The l-isomer is a vasoconstrictor used in several over-the-counter nasal decongestants.<sup>11</sup> The d-isomer causes euphoric and stimulant effects and is preferentially manufactured by clandestine “meth labs”; it is also the active ingredient in the prescription drug, Desoxyn®, used for the treatment of attention deficit disorder with hyperactivity and exogenous obesity.<sup>12</sup> Routes of illicit methamphetamine administration include intranasal, smoking, oral ingestion, intramuscular injection, intravenous injection, and transmucosal per-rectum. The lipophilic drug readily crosses the blood brain barrier and has a long plasma half-life of 12–34 hours.<sup>12</sup> Amphetamine is a metabolite of methamphetamine and perpetuates the psychostimulant effects.

Methamphetamine is a sympathomimetic that releases catecholamines in the central and peripheral nervous systems. Acutely, it floods the brain with dopamine, particularly in the caudate, putamen, and ventral striatal regions.<sup>13</sup> In contrast to cocaine, methamphetamine induces even higher synaptic dopamine concentrations through multiple mechanisms leading to its euphoric and addictive effects.<sup>14, 15</sup> Not only does it competitively inhibit presynaptic reuptake of catecholamines, as does cocaine, but it also induces catecholamine release into the synapse and inhibits norepinephrine and dopamine metabolism.<sup>16-19</sup> One study found that a dose of 1 mg/kg of methamphetamine in adult male rhesus monkeys increased dopamine levels in the striatum by 1350% compared to baseline.<sup>20</sup> These dopaminergic properties are associated with the reinforcing and behavioral-stimulant effects in animals and humans.<sup>21</sup> However, chronic, high dose methamphetamine administration is shown to ultimately result in dopaminergic

deficits.<sup>16</sup> The low dopamine levels seen after repeat dosing are thought to mediate the dysphoric effects and drug tolerance seen among those who use the drug chronically.<sup>22</sup>

The noradrenergic, serotonergic, and glutamatergic systems are affected as well.<sup>23</sup> Importantly, methamphetamine induces cardiovascular stress by releasing epinephrine and norepinephrine from sympathetic nerve endings. A cascade of biologic responses ensues including tachycardia (through stimulation of  $\beta_1$ -adrenergic receptors), peripheral vasoconstriction (through stimulation of  $\alpha_1$ -adrenergic receptors), increased cardiac contractility, hypertension, tachypnea, and bronchodilation. Many of the acute cardiovascular complications of methamphetamine poisoning are linked to this hyperadrenergic state.

In the United States, methamphetamine related complications were responsible for over 100,000 emergency department admissions in 2011.<sup>24</sup> However, the pathophysiology by which methamphetamine causes overdose is not fully understood. Multiple findings are reported in the literature, with catastrophic cardiovascular and neurologic events being the most ubiquitous diagnoses in fatal methamphetamine poisoning. Chronic cardiovascular conditions, such as coronary artery disease and cardiomyopathy, are thought to be both exacerbated by methamphetamine use and contributing causes of death in some cases of methamphetamine poisoning.<sup>25</sup> Elevated temperature is one of the acute toxic effects of methamphetamine. Lethal hyperthermia is well documented among people using high doses of methamphetamine and results in rhabdomyolysis, increased production of reactive oxygen species, multi-organ failure and release of excitotoxic neurotransmitters.<sup>26-28</sup> In an Australian case series of 371 methamphetamine-related overdose deaths by Kaye et al., the authors conclude that “cardiovascular complications or disease arising from or complicated by methamphetamine use was the direct cause of death” in 14% of the cases. The implicated cardiovascular pathology included coronary artery atherosclerosis, cardiac arrhythmia, cardiomegaly, ischemic heart

disease, myocardial infarction or ischemia, cardiomyopathy, left ventricular hypertrophy, aortic rupture and endocarditis.<sup>29</sup> Although the exact pathophysiology of methamphetamine overdose is largely unknown, these data show that hyperthermia and cardiovascular failure may be implicated in a portion of these deaths.

The dose at which methamphetamine causes overdose varies by orders of magnitude.<sup>30</sup> Logan et al. found that among solely methamphetamine-caused deaths, the methamphetamine serum concentration ranged from 0.09-18.0 mg/L with a median level of 0.96 mg/L. Fatal polysubstance overdoses involving methamphetamine had lower median serum methamphetamine concentration at 0.37 mg/L (range 0.05-68.90 mg/L), indicating a lower threshold for methamphetamine overdose with concurrent use of other drugs. Additionally, lower concentrations of methamphetamine were found among decedents with cardiovascular and natural disease processes.<sup>25</sup> These data are not conclusive, but suggest a link between preexisting cardiovascular disease and susceptibility to methamphetamine-related death even at relatively low methamphetamine serum concentrations.

The acute cardiovascular complications of methamphetamine are not as well described as those of cocaine. However, a number of retrospective case reports and case series show a pattern of acute cardiovascular complications related to methamphetamine intoxication. Angina pectoris is a common presenting symptom. An Australian study of 156 patients admitted for methamphetamine intoxication found 4.5% had chest pain.<sup>31</sup> Another study of 36 methamphetamine-related emergency department admissions showed that acute coronary syndrome was diagnosed in 25% and other potentially life-threatening cardiac complications, including ventricular fibrillation, ventricular tachycardia and supraventricular tachycardia occurred in 8% of admissions. The mean age of these patients was relatively young (41 years

old) for the severity of their cardiovascular complications.<sup>4</sup> A population-based epidemiologic study (study size = 3,148,165) of hospital patients in Texas found a significant association between methamphetamine use and acute myocardial infarction even after controlling for cocaine use, alcohol consumption, hypertension, diabetes mellitus, lipid disorders, obesity, congenital defects and coagulation disorders (adjusted odds ratio = 1.61, 95% CI = 1.24-2.04).<sup>32</sup> Among 2356 adults admitted to level 1 trauma centers who had methamphetamine exposure, 6.5% showed evidence of myocardial ischemia by electrocardiogram and troponin level.<sup>33</sup>

In addition to the acute coronary syndromes, methamphetamine is implicated in aortic dissection. Methamphetamine is the second most common risk factor for fatal acute aortic dissection after hypertension.<sup>34</sup> Wako et al. conducted a retrospective review of 6 cases of methamphetamine induced acute aortic dissection presenting to the Cardiothoracic Surgery Division of the University of Washington. The patients represented 5.5% of all aortic dissection cases treated in the study time period and the methamphetamine-positive patients were notably younger, representing 20% of all aortic dissection cases under 50 years old. The authors recommend routine screening for methamphetamine in all patients less than 50 years old with acute aortic dissection, particularly in the absence of the stigmata of connective tissue disorder.<sup>35</sup> This is important because medical management is different for methamphetamine-related aortic dissection. Additionally, one case report describes methamphetamine related spontaneous dissection of multiple coronary arteries<sup>36</sup> and separate case series describes 4 patients with methamphetamine-associated ruptured berry aneurysm.<sup>37</sup>

Evidence suggests that there is also increased risk of intracerebral hemorrhage after use of methamphetamine or cocaine. One case control study of 1368 Kaiser Permanente patients in Northern and Southern California looked at the risk of stroke among female cocaine and/or

methamphetamine users found an 8.5 increased odds (95% CI = 3.6-20.0) of stroke after matching for age.<sup>38</sup> In fact, methamphetamine use may pose an even greater risk of intracerebral hemorrhage compared with cocaine use. A cross sectional study of ischemic and hemorrhagic strokes in Texas hospitals over a three year period found that, after controlling for other risk factors, amphetamine abuse was associated with a two fold increased risk of hemorrhagic stroke compared with cocaine abuse, and amphetamine use was not associated with increased risk of ischemic stroke.<sup>39</sup>

In contrast to methamphetamine research, the chronic cardiovascular conditions associated with cocaine use are well studied. For example, Darke et al. found that left ventricular hypertrophy, moderate to severe atherosclerosis of the left anterior descending coronary artery, and cerebrovascular atherosclerosis were all significantly more common among cocaine overdose decedents than comparison groups of people who had died secondary to opioid overdose or non-drug-related hanging.<sup>40</sup> Few studies have examined the chronic cardiovascular effects of methamphetamine use. Most of the extant studies are retrospective case series based on autopsy reports and therefore fail to demonstrate a temporal relationship between chronic methamphetamine use and the subsequent development of cardiovascular pathologies. However, when taken as a whole, a pattern of chronic cardiovascular conditions begins to emerge. For example, Kaye et al. found that among 220 methamphetamine-related overdose decedents, cardiac hypertrophy was present in 12%, coronary artery disease (CAD) was prevalent in 35% and 18% had severe CAD. The authors concluded that the methamphetamine might cause premature and accelerated development of such disease and exacerbate pre-existing pathology, particularly CAD.<sup>29</sup> A case control study by Karch et al. compared 413 deaths with positive methamphetamine toxicology with a control group of 114 drug-free trauma victims. CAD was found in 19% of the methamphetamine group compared with only 5% of the drug-free controls.

Cases and controls had no significant differences in BMI, sex or race. The authors suggest that an “incubation period” of years may be required before the occurrence of chronic methamphetamine cardiovascular complications with fatal outcomes.<sup>9</sup>

Cardiomyopathy is strongly associated with methamphetamine use, but is not as well studied as cocaine-associated cardiomyopathy. It is typically dilated, non-ischemic cardiomyopathy, although hypertrophic and stress cardiomyopathy have also been described.<sup>41-45</sup> Methamphetamine-associated cardiomyopathy (MAC) has insidious onset thought to follow chronic methamphetamine consumption. A case control study of 286 patients from a tertiary care medical center in Hawaii demonstrated that people who used methamphetamine had a 3.7-fold increased odds ratio of cardiomyopathy (95% CI = 1.8-7.8). In fact, they found 4 out of 10 study participants  $\leq$  45 years old with cardiomyopathy had used methamphetamine.<sup>46</sup> In another study of 59 patients younger than 45 years old with diagnoses of heart failure and/or cardiomyopathy, 28 (48%) abused methamphetamine.<sup>47</sup> Patients with MAC have a significantly lower left ventricular ejection fraction and worse ventricular dilation compared to people with other types of cardiomyopathy.<sup>46-48</sup> Indeed, repeated binge administration of methamphetamine causes left ventricular dilation as well as systolic and diastolic dysfunction in rats.<sup>49</sup>

Cardiac enlargement, both hypertrophic and dilated, is an independent risk factor for sudden cardiac death.<sup>50</sup> Methamphetamine overdose decedents may have greater heart weights, even after normalizing for body weight, with one autopsy-based study showing that the hearts of the methamphetamine users were significantly heavier (378 g vs. 341 g) than drug-free controls.<sup>9</sup> Another study showed 16% of methamphetamine-related decedents had cardiomegaly.<sup>29</sup>

Whether chronic methamphetamine use actually causes these chronic cardiovascular pathologies remains to be proven. It is also unknown if pre-existing chronic cardiovascular

pathologies put people at increased risk of methamphetamine-related death, although the extant evidence suggest that they do.

Despite the literature on the acute and chronic cardiovascular effects of methamphetamine use, little is known about the cardiovascular effects of concurrent or overlapping use of methamphetamine and heroin (“goofballs”). No studies to date have looked specifically at the acute or chronic cardiovascular pathologies among heroin-methamphetamine combination overdose decedents. However, polypharmacy is increasingly common among those who use methamphetamine, with heroin found on toxicology in 48% of methamphetamine-related overdoses in 2015 in King County and 57% involving some form of opioid (prescription and/or heroin). Local syringe exchange survey data show significant increases in the proportion who reported using methamphetamine and heroin together from 14% to 37% between 2011 to 2015.<sup>2</sup> This polypharmacy causes euphoric and/or modulating effects compared with methamphetamine use alone, which may explain the high prevalence of polypharmacy. Ranaldi, et al. found that rats who self-administered a methamphetamine-heroin combination experience greater rewarding effectiveness and higher extracellular dopamine compared with rats who self-administered methamphetamine alone.<sup>51</sup> In light of the high prevalence of combination drug use, it is important to understand more about the cardiovascular pathologies in this population and to determine if combination methamphetamine-heroin use poses unique risks.

## **CHAPTER 2:**

### **Methods**

#### **Study Setting**

This retrospective case-comparison study is based on autopsy data obtained from the King County Medical Examiner's (KCME) Office. Records included all accidental drug overdose deaths involving methamphetamine, heroin, and/or cocaine that occurred between January 1, 2013 and December 31, 2015 in King County, Washington. Acute drug poisoning was determined by forensic pathologists to be the direct cause of death, or a significant contributing factor to death, for all cases examined. After obtaining approval from the University of Washington Institutional Review Board and the King County Department of Public Health, secondary data was compiled from the KCME internal database of autopsy records. Between January and June of 2016, in collaboration with KCME forensic pathologists, the author of this study reviewed autopsy reports and abstracted the variables of interest into a database for statistical analyses. For all autopsy reports used in this study, the standard KCME forensic and toxicology procedures were used to determine acute and chronic cardiovascular pathologies and the presence of methamphetamine, heroin or cocaine in overdose deaths. Toxicology was obtained for all suspected drug-related deaths and is based on peripheral blood or urine samples tested by the Washington State Patrol Forensic Laboratory Service Bureau. The cause of death is determined by the medical examiner based on toxicology results, autopsy, histology and descriptive reports of the circumstances of death.

Since polypharmacy is common in overdose deaths, with 75% of methamphetamine, cocaine or heroin-related deaths in the 2013-2015 KCME records containing more than one drug on toxicology, it would not be representative to exclude decedents with more than one drug

present on toxicology. Therefore, in addition to the drugs of interest (methamphetamine, cocaine and heroin), decedents who were positive for other drugs on toxicology were not necessarily excluded from the study. The presence of ethyl alcohol, benzodiazepines, prescription opioids, tricyclic antidepressants (TCA) and selective serotonin reuptake inhibitors or serotonin norepinephrine reuptake inhibitors (SSRI/SNRI) were categorically recorded for all cases in which the respective drugs were found. Additionally, a category of “other drugs” was created to record toxicology that was positive for miscellaneous drugs not categorically identified in the study design. These “other drugs” included trazodone, zolpidem, diphenhydramine, lidocaine, gabapentin, dextromethorphan, phenobarbital, cyclobenzoprine, bupropion, gamma hydroxybutyrate (GHB), and phencyclidine.

Cases involving drugs where the manner of death was suicide, undetermined, or natural (for example necrotizing fasciitis related to chronic injection of black tar heroin or diabetic ketoacidosis with methamphetamine positive toxicology) were excluded from the study. All decedents were 18 years of age or older, after excluding fetal deaths. Cases that did not include internal autopsy exam or where internal organs were harvested prior to autopsy were excluded from the study. One case with cardiac transplant was excluded.

### **Case Selection**

Deaths involving cocaine or methamphetamine were considered to be the cases of interest. Cocaine-related overdose deaths were included in the study because, compared to methamphetamine, there exists a stronger body of evidence showing that cocaine is strongly associated with a number of cardiovascular pathologies. Since it is expected that there will be a high prevalence of acute and chronic cardiovascular pathologies among cocaine overdose decedents, this group is used as a comparison group for cardiovascular pathologies among

methamphetamine positive decedents. Including cocaine-involved deaths also allows for a degree of validation of study procedures by providing a positive control in the study. If the study yielded similar findings for cocaine as other studies, it suggests that study procedures are adequate to identify cardiovascular findings for methamphetamine-involved deaths as well. Additionally, because so little is known about the cardiovascular effects of combined stimulant-heroin combination drug use, the study was designed to determine if there is difference in demographic characteristics and cardiovascular pathologies among mixed methamphetamine-heroin compared to mixed cocaine-heroin overdose decedents. With these comparisons in mind, accidental overdose deaths were categorized into the following four groups based on toxicology findings:

1. Methamphetamine overdose deaths (M).
2. Methamphetamine and heroin combination overdose deaths (MH).
3. Cocaine overdose deaths (C).
4. Cocaine and heroin combination overdose deaths (CH).

The methamphetamine (M) group consists of decedents who were positive for d-methamphetamine on toxicology. Cases that were positive for amphetamine, but not d-methamphetamine, or were positive for any opioids or other stimulants were excluded from the M group. The MH group includes cases that died secondary to combination methamphetamine-heroin overdose, but had no other stimulants present on toxicology. Prescription opioids were permitted in the MH group. The C group included those who died secondary to cocaine overdose, but were negative for other stimulants (including methamphetamine), heroin and other opioids on toxicology. The CH group consists of decedents that died secondary to combination cocaine-heroin overdose, but that did not have other stimulants on toxicology. As with the MH group, prescription opioids were allowed in the CH group. All groups were allowed to have other

drugs, benzodiazepines and/or ethanol. The KCME has well specified procedures to identify overdoses that likely involved heroin.<sup>52</sup>

### **Comparison Selection**

Comparisons were decedents who had heroin-involved drug caused deaths (H). This heroin poisoning comparison group was chosen as a means to minimize potential confounding lifestyle factors such as use of tobacco products. Previous research shows high smoking prevalence across people with methamphetamine, cocaine and opiate use disorders. For example, a systematic review of 54 studies found that among substance use disorder treatment clients, smoking rates were 85.1% for opiate users, 80.9% for people using alcohol and other drugs, and 75.2% for those using alcohol alone.<sup>53</sup> In this study, cases in the H group were determined to have had heroin present based on the KCME's heroin determination protocol, but were negative for stimulants including methamphetamine and cocaine. Positive toxicology for other opioids was permitted. The same inclusion criteria were applied to comparisons as cases; that is, all comparisons were at least 18 years old, heroin overdose was the direct cause or a significant contributing factor to death and the manner of death was determined to be accidental. Cases were excluded from the H group if they were positive for some form of opioid on toxicology, but were reported as "unknown if heroin or prescription morphine" on the autopsy record.

### **Data Collection**

The demographic data provided on all cases and comparisons includes the following information: age, sex, race (black, white, Native American, Asian, and other race) and a description of the type of location at the time of death. Sex was recorded based on external and/or internal sex organs, but information on gender identity was excluded due to a lack of

information. Death location was categorized into five groups based on the following descriptions provided on autopsy report:

1. Residence

- Descriptions included “residence,” “storage shed,” “yard,” “boat/ship,” “shelter,” “trailer home,” “other residence” or “boat.”

2. Hotel/Motel

- Descriptions included “hotel/motel” or “motel.”

3. Public Inside

- Descriptions included “business,” “restaurant” or “school.”

4. Public Outside

- Descriptions included “alley,” “outdoors,” “park,” “parking lot,” “sidewalk,” “roadway,” “trail,” “woods,” “vehicle,” “camper” or “camp site.”

5. Medical Facility

- Descriptions included “hospital,” “hospital inpatient,” “hospital ER” or “hospice facility.”

6. Other

- Descriptions included “jail,” “other” or “unknown.”

Relevant secondary data was pulled by myself and one KCME forensic pathologist from autopsy reports on the KCME database and abstracted into file that included the following variables of interest: body weight (pounds), height (inches), body mass index (BMI), heart weight (grams) and acute and/or chronic cardiovascular pathologies. BMI was categorized according to the Center for Disease Control convention as underweight (< 18.5), normal weight (18.5- 24.9), overweight (25 – 29.9), and obese ( $\geq$  30). There were two primary acute

pathologies of interest: acute myocardial infarction (MI) and intracerebral hemorrhage (ICH).

Although autopsy data includes the specific anatomic location and severity of these pathologies, for the purposes of this study, MI and ICH were coded simply as binary data.

The chronic cardiovascular pathologies of interest included coronary artery disease (CAD), myocardial fibrosis (MF), left ventricular hypertrophy (LVH), dilated cardiomyopathy, other cardiomyopathies (e.g. obesity-related or arrhythmogenic right ventricular cardiomyopathy) and hypertensive cardiovascular disease (HCD). The forensic pathologist examined the major extramural coronary arteries (left anterior descending, left circumflex, and right coronary arteries) in transverse sections. CAD is then graded on a scale of 0 - 3 according to percent occlusion of the coronary artery lumen. Minimal occlusion ( $\leq 24\%$ ) is grade 0, mild occlusion (25 – 49%) is grade 1, moderate occlusion (50 – 74%) is grade 2, and severe occlusion ( $\geq 75\%$ ) is grade 3. Myocardial fibrosis represents a morphological change in the heart as the result of chronic ischemic heart disease. It is characterized by diffuse replacement of the myocardium with fibrotic connective tissue causing impaired action of the heart, and is most commonly a result of coronary artery disease. For the purposes of this study MF was categorized as bivariate (with or without MF) based on gross examination and characteristic histopathology (fibrous scar tissue surrounded by viable myocytes often with a characteristic “tiger spotted” aspect). Left ventricular hypertrophy was categorized as binary. Decedents are considered to have LVH if the left ventricular wall thickness measures greater than 1.5 cm, the weight of heart is greater than 400 grams (or more than 0.4% of the body weight in kilograms) and is verified by microscopic examination confirming cardiomyocyte hypertrophy with increased nuclear diameter. Hypertrophic cardiomyopathy is diagnosed based on the presence of hypertrophied, non-dilated left ventricle, thickening of the ventricular septum, and characteristic histologic findings including myocyte hypertrophy and disarray. Other cardiomyopathies include

arrhythmogenic right ventricular cardiomyopathy (ARVC) and obesity related cardiomyopathy. The etiology of ARVC is largely unknown, although there are genetic links. It is characterized by thinning of the right ventricle with fibro-fatty changes and a “moth-eaten” appearance on microscopy. Obesity related cardiomyopathy is diagnosed in decedents with morbid obesity, a fatty heart, and left ventricular heart failure resulting from excess adiposity. Lastly, hypertensive cardiovascular disease is determined by the forensic pathologist through a number of information sources including past medical history when available, hospital admission diagnoses, use of antihypertensives, reports from friends and next of kin and pathology on autopsy (e.g. presence of CAD, cerebrovascular disease, LVH or granular contracted kidneys).

As a quality control measure, a secondary reviewer (E.R.) analyzed 6% (n=442) of the autopsy reports for agreement with the study. Data elements reviewed included toxicology, death location type, body weight, height, body mass index, heart weight, and acute and/or chronic cardiovascular pathologies. There was found to be 97% inter-rated reliability on cases that were re-reviewed.

### **Testable Hypotheses**

1. Is there a difference in mean heart weight among people who died from methamphetamine, methamphetamine-heroin combination, cocaine or cocaine-heroin combination overdose compared with those who died from heroin overdose?

2. Is there a difference in the proportion of individual cardiovascular pathologies (MI, ICH, CAD, MF, LVH, cardiomegaly, dilated cardiomyopathy, other cardiomyopathy and HCD) among those who died from methamphetamine, methamphetamine-heroin combination, cocaine or cocaine-heroin combination, compared with those who died from heroin overdose?

## Statistical Analyses

Descriptive statistics for all variables were calculated. Bi-variate analyses included the use of two-sample, 2-sided t-tests at a significance level of  $\alpha = 0.05$  for calculation of mean heart weight comparing each drug group separately with the H comparison group. Calculation of unadjusted odds ratios and chi-square tests at a significance level of  $\alpha = 0.05$  and 95% confidence interval was employed for binary responses including each cardiac pathology of interest (MI, ICH, MF, CAD, LVH, cardiomegaly, dilated cardiomyopathy, other cardiomyopathy, and HCD) among the M group, MH group, C group, and CH group compared with the H group. Additionally, 2-sided Fisher's exact tests were used for variables that were less than 5.

## **CHAPTER 3:**

### **Results**

#### **Demographic Characteristics**

Of the original 595 cases that were positive for methamphetamine, cocaine or heroin on toxicology, 442 met inclusion criteria for the study. 65 cases each met criteria for the M group, MH group, and CH group respectively, while 54 were included in the C group and 193 in the reference H group. Decedents were significantly less likely to be female in the M group (13.8% female) compared with the reference H group (27.5% female). Additionally, the mean age was significantly greater than the reference H group (39.7 years) among the M group (44.9 years), the C group (50.4 years), and the CH group (46.0 years).

There were statistically significant differences in race, particularly among cocaine-involved overdose deaths. 37.0% of C group decedents and 18.5% of CH group decedents were black compared with only 6.2% of the reference H group. Overall, the M group was significantly less likely to be white (75.4%) compared with the reference H group (86.0%). The C group had significantly more Asian decedents at 7.4% than the H comparison group (OR 5.1, 95% CI 0.82-35.4, 2-sided Fisher's exact  $p=0.0428$ ).

#### **Death Location**

Of the five death location categories, only two showed significant differences across case groups compared with the reference H group. CH group decedents were more likely to have died in a hotel/motel compared to the H group (12.3% versus 3.6%). The M and C groups had a higher prevalence of death in public outdoor locations compared with the reference H group (20.0% and 20.4% compared with 9.3%). However, regardless of study group the majority of all overdose deaths occurred in a residence.

## **Other Drugs**

Prescription opioids, ethyl alcohol and benzodiazepines were the drugs most frequently combined with the drugs of interest (methamphetamine, cocaine, and/or heroin). Only the MH, CH and H groups had inclusion criteria that allowed for prescription opioids. One-third of heroin-involved groups taken as a whole had toxicology that was also positive for prescription opioids. Of the total study population, 29.4% were positive for ethyl alcohol on toxicology. The M group and MH group decedents were significantly more likely to have ethyl alcohol detected compared with the H group. 12.2% of all decedents were positive for benzodiazepines, but M and C groups were significantly less likely to be benzodiazepine positive compared with the H reference group. Only 8 decedents were positive for tricyclic antidepressants overall, and there were no significant differences in TCA presence across study groups. SSRI/SNRI drugs were present in 8.8% of all decedents, but the M and MH groups were significantly less likely to have SSRI/SNRI positive toxicology. Less than 10% of the total study population was positive for drugs other than those previously listed. The most common “other drugs” included diphenhydramine (2.7% positive), trazodone (2.0% positive), and bupropion (0.9% positive).

	<b>Meth</b>	<b>Meth- Heroin</b>	<b>Cocaine</b>	<b>Cocaine- Heroin</b>	<b>Heroin (Reference)</b>
<b>Total # (%)</b>	65 (14.7)	65 (14.7)	54 (12.2)	65 (14.7)	193 (43.7)
<b>Female # (%)</b>	9 (13.8)**	13 (20.0)	13 (24.1)	15 (23.1)	53 (27.5)
<b>Age Mean (s.d.)</b>	44.9 (11.3)*	38.1 (12.3)	50.4 (8.4)*	46.0 (12.7)*	39.7 (13.0)
<b>Age Median</b>	47	36	51	48	37
<b>Race:</b>					
<b>White # (%)</b>	49 (75.4)**	56 (86.2)	30 (55.6)*	46 (70.8)*	166 (86.0)
<b>Black # (%)</b>	8 (12.3)	6 (9.2)	20 (37.0)*	12 (18.5)*	12 (6.2)
<b>Native American # (%)</b>	4 (6.2)	2 (3.1)	0	4 (6.1)	10 (5.2)
<b>Asian # (%)</b>	3 (4.6)	1 (1.5)	4 (7.4)**	3 (4.6)	3 (1.6)
<b>Other # (%)</b>	1 (1.5)	0	0	0	2 (1.0)
<b>Death Location:</b>					
<b>Residence # (%)</b>	41 (63.1)	45 (69.2)	39 (72.2)	46 (70.8)	144 (74.6)
<b>Hotel/Motel # (%)</b>	3 (4.6)	5 (7.7)	0	8 (12.3)*	7 (3.6)
<b>Public Inside # (%)</b>	1 (1.5)	1 (1.5)	0	2 (3.1)	12 (6.2)
<b>Public Outside # (%)</b>	13 (20)**	10 (15.4)	11 (20.4)**	7 (10.8)	18 (9.3)
<b>Medical Facility # (%)</b>	5 (7.7)	2 (3.1)	3 (5.5)	2 (3.1)	6 (3.1)
<b>Other # (%)</b>	2 (3.1)	2 (3.1)	1 (1.9)	0	6 (3.1)
<b>Other Drugs:</b>					
<b>Alcohol # (%)</b>	10 (15.4)*	14 (21.5)**	19 (35.2)	19 (29.2)	68 (35.2)
<b>Benzodiazepine # (%)</b>	3 (4.6)**	10 (15.4)	0*	8 (12.3)	33 (17.1)
<b>TCA # (%)</b>	0	1 (1.5)	0	3 (4.6)	4 (2.1)
<b>SSRI/SNRI # (%)</b>	1 (1.5)*	2 (3.1)**	3 (5.6)	9 (13.8)	24 (12.4)

\*P<0.01 \*\*0.01<P<0.05

Table 1. Demographic characteristics by study group.

## Autopsy Findings

Mean body mass index was similar across study groups, with the exception of the MH group which had a lower BMI (27.5) compared to the reference H group (29.8). The BMI categories were similar across groups, with only the C group having a greater proportion of underweight decedents (6.1% compared with 0.5% in the reference group). The mean heart weight was significantly greater among the M (496 grams) compared with the reference H group (425 grams). However, median heart weight was not statistically different across drug groups.

Acute cardiovascular events occurred only in the stimulant positive groups. There were 4 instances of intracerebral hemorrhage in the M group and 6 in the C group. Acute myocardial infarction was found among 3 in the C group (OR 2.9) and 3 in the CH group (OR 2.4). All acute cardiovascular events that occurred among stimulant positive groups were statistically significant (with 2-sided Fisher exact  $p < 0.05$ ), but 95% confidence intervals could not be calculated since no acute cardiovascular events occurred in the H comparison group.

Coronary artery disease was much more common among stimulant positive groups as well, particularly among the C group. The unadjusted odds ratio (OR) of grade 3 CAD was 6.4 (95% CI 2.6-15.4) among the C group compared with the control group and 2.8 for both the M and CH groups (95% CI 1.1-7.2). A pattern of significantly greater odds of chronic cardiovascular pathologies was apparent among the C group compared with the H group: the unadjusted OR for myocardial fibrosis was 4.6 (95% CI 1.3-17.4), cardiomegaly was 4.2 (95% CI 1.9-9.1) and hypertensive cardiovascular disease was 4.6 (95% CI 2.3-9.1). The M group was more likely to have acute myocardial fibrosis (OR 3.8, 95% CI 1.0-14.0), the CH group was more likely to have cardiomegaly (OR 2.3, 95% CI 1.0-5.1) and HCD (OR 2.5, 95% CI 1.3-4.8). Notably, the MH group had no significant differences in odds of chronic CV pathologies compared with the H group. There were 9 cases of dilated cardiomyopathy in the entire study

population. Other cardiomyopathies included 8 total cases of obesity related cardiomyopathy and 3 total cases of ARVC. There were no significant differences in any type of cardiomyopathy across study groups.

	<b>Meth</b>	<b>Meth-Heroin</b>	<b>Cocaine</b>	<b>Cocaine-Heroin</b>	<b>Heroin (Reference)</b>
<b>BMI Mean (s.d.)</b>	31.0 (10.8)	27.5 (5.7)*	28.2 (6.2)	28.8 (8.1)	29.8 (8.4)
<b>BMI Median</b>	27.7	26.1	27.4	27.9	27.8
<b>BMI Categories:</b>					
<b>Underweight # (%)</b>	1 (1.5)	1 (1.5)	1 (1.8)	4 (6.1)**	1 (0.5)
<b>Normal # (%)</b>	18 (27.7)	22 (33.8)	15 (27.8)	17 (26.2)	53 (27.5)
<b>Overweight # (%)</b>	21 (32.3)	24 (36.9)	19 (35.2)	17 (26.2)	66 (34.2)
<b>Obese # (%)</b>	25 (38.5)	18 (27.7)	19 (35.2)	27 (41.5)	73 (37.8)
<b>Mean Heart Weight (s.d.)</b>	496 (187)*	414 (85)	481 (147)	457 (129)	425 (112)
<b>Median Heart Weight</b>	447	400	485	434	403
<b>CV Pathology:</b>					
<b>CAD Grade 0 # (%)</b>	41 (63.1)	48 (73.8)	22 (40.7)*	44 (67.7)	143 (74.1)
<b>CAD Grade 1 # (%)</b>	8 (12.3)	10 (15.4)	4 (7.4)	5 (7.7)	19 (9.8)
<b>CAD Grade 2 # (%)</b>	5 (7.7)	5 (7.7)	11 (20.4)**	5 (7.7)	18 (9.3)
<b>CAD Grade 3 # (%)</b>	11 (16.9)**	2 (3.1)	17 (31.5)*	11 (16.9)**	13 (6.7)
<b>CAD Grade ≥ 1 # (%)</b>	24 (36.9)	17 (26.2)	32 (59.3)*	21 (32.3)	50 (25.9)
<b>CAD Grade ≥ 2 # (%)</b>	16 (24.6)	7 (10.8)	28 (51.9)*	16 (24.6)	31 (16.1)
<b>Intracerebral Hemorrhage # (%)</b>	4 (6.2)	0	6 (11.1)	0	0
<b>Acute MI # (%)</b>	0	0	3 (5.6)	3 (4.6)	0
<b>Myocardial Fibrosis # (%)</b>	7 (10.8)**	4 (6.2)	7 (13.0)*	4 (6.2)	6 (3.1)
<b>LVH # (%)</b>	7 (10.8)	9 (13.8)	10 (18.5)	9 (13.8)	24 (12.4)
<b>Cardiomegaly # (%)</b>	12 (18.5)	5 (7.7)	19 (35.2)*	15 (23.1)**	22 (11.4)
<b>Dilated Cardiomyopathy # (%)</b>	3 (4.6)	2 (3.1)	0	1 (1.5)	3 (1.6)
<b>Other Cardiomyopathy # (%)</b>	5 (7.7)	0	1 (1.8)	0	5 (2.6)
<b>Hypertensive CV Disease # (%)</b>	20 (30.8)	8 (12.3)	28 (51.9)*	24 (36.9)*	37 (19.2)

\*P < 0.01 \*\*0.01<P<0.05

Table 2. Body mass index, heart weight (grams) and prevalence of cardiovascular pathologies on autopsy by study group compared with reference group.

	<b>Meth</b>	<b>Meth-Heroin</b>	<b>Cocaine</b>	<b>Cocaine-Heroin</b>
<b>CAD Grade 0 OR (95% CI)</b>	0.6 (0.3 – 1.1)	1.0 (0.5 – 2.0)	0.2 (0.1 – 0.5)*	0.7 (0.4 – 1.4)
<b>CAD Grade 1 OR (95% CI)</b>	1.3 (0.5 – 3.3)	1.7 (0.6 – 4.0)	0.7 (0.2 – 2.3)	0.8 (0.2 – 2.2)
<b>CAD Grade 2 OR (95% CI)</b>	0.8 (0.2 – 2.4)	0.8 (0.2 – 2.4)	2.5 (1.0 -6.0)**	0.8 (0.2 – 2.4)
<b>CAD Grade 3 OR (95% CI)</b>	2.8 (1.1- 7.2)**	0.4 (0.0 – 2.0)	6.4 (2.6 – 15.4)*	2.8 (1.1- 7.2)**
<b>CAD Grade ≥ 1 OR (95% CI)</b>	1.7 (0.9 – 3.2)	1.0 (0.5 – 2.0)	4.2 (2.1 – 8.2)*	1.4 (0.7 – 2.6)
<b>CAD Grade ≥ 2 OR (95% CI)</b>	1.7 (0.8 – 3.5)	0.6 (0.2 – 1.6)	5.6 (2.8 – 11.4)*	1.7 (0.8 – 3.5)
<b>Intracerebral Hemorrhage OR<sup>x</sup></b>	3.2*	-	6.1*	-
<b>Acute Myocardial Infarction OR<sup>x</sup></b>	-	-	2.9**	2.4**
<b>Myocardial Fibrosis OR (95% CI)</b>	3.8 (1.0 - 14.0)**	2.0 (0.4 – 8.9)	4.6 (1.3 – 17.4)*	2.0 (0.4 - 8.9)
<b>LVH OR (95% CI)</b>	0.8 (0.3 - 2.2)	1.1 (0.4 - 2.7)	1.6 (0.6 - 3.8)	1.1 (0.4 - 2.7)
<b>Cardiomegaly OR (95% CI)</b>	1.8 (0.7 - 4.0)	0.6 (0.2 - 1.9)	4.2 (1.9 - 9.1)*	2.3 (1.0 - 5.1)**
<b>Dilated Cardiomyopathy OR (95% CI)</b>	3.1 (0.4 – 23.4)	2.0 (0.2 - 17.9)	0	1.0 (0.0 -12.6)
<b>Other Cardiomyopathy OR (95% CI)</b>	3.1 (0.7 -14.0)	0	0.7 (0.0 - 6.5)	0
<b>Hypertensive CV Disease OR (95% CI)</b>	1.9 (0.9 – 3.7)	0.6 (0.2 – 1.4)	4.6 (2.3 - 9.1)*	2.5 (1.3 -4.8)*

\*P < 0.01 \*\*0.01<P<0.05 <sup>x</sup>95% CI could not be calculated since comparison group values were zero

Table 3. Unadjusted odds ratios (95% CI) for cardiovascular pathologies by study group compared with reference group.

## CHAPTER 4:

### Discussion

Many cardiovascular pathologies were more prevalent among the stimulant positive cases compared with the heroin comparison group, but the MH group was an exception. Those who died from methamphetamine-heroin combination poisoning were not significantly different from the H group in terms of both demographics and cardiovascular pathologies. Little was previously known about methamphetamine-heroin combination death, although the incidence of these fatalities has been on the rise in King County. These data suggest that this group is more likely to be male, younger (median age of 36), white and to die in a residence compared with those who die from heroin overdose. However, the mean heart weight was significantly greater among the M group compared with the H group. Like the heroin overdose group, methamphetamine-heroin combination overdose decedents had no acute cardiovascular events (ICH or MI) and were less likely to have chronic cardiovascular pathologies. One possible explanation for these findings is that the mechanism of death in the MH group is more likely to be a result of the respiratory depression also seen in heroin overdoses and less likely a complication of the cardiotoxic effects of the methamphetamine.

The C group stands out for its significantly higher unadjusted odds ratios of grade 2 or 3 coronary artery disease, myocardial fibrosis, cardiomegaly and hypertensive cardiovascular disease. These results are in close agreement with the high prevalence of chronic cardiovascular pathologies found on prior autopsy-based studies of cocaine overdose decedents.<sup>40, 54, 55</sup> The C group had a greater number of cardiovascular risk factors including older median age (51 years compared with 37 years in the H group) and greater proportion of black decedents (37.0%

compared with 6.2% in the H group). The CH group, like the C group, was older (median age 46) and 18.5% were black. They also had significantly greater odds of grade 3 CAD, cardiomegaly and hypertensive cardiovascular disease. The next step in this study will be to perform multivariate regression analysis to control for demographics in order to understand factors independently associated with cardiovascular findings and drugs identified. These data show that people who are dying from cocaine and cocaine-heroin combination overdose in King County tend to be older, black and often have chronic cardiovascular pathologies, thus underlining the clinical importance of managing these conditions in this population of people who use cocaine and may be more vulnerable to overdose.

Decedents in the M group had fewer chronic cardiovascular pathologies compared with the C and CH groups. However, the M group had 2.8 greater odds of grade 3 CAD and 3.8 greater odds of MF compared with the H group, although this could be partially explained by the fact that the M group had a median age of 47 (versus 37 in the control group) and were significantly more likely to be male (86.2% versus 72.5%). In the next step of this study, it will be important to control for factors such as age, sex, race, and BMI in order to determine whether stimulant use itself is associated with these cardiovascular pathologies. If the associations still exist after controlling for these other variables, it could point to two possible explanations. One, that stimulant (methamphetamine or cocaine) use contributes to the development of these cardiovascular conditions over time and/or two, that stimulant use in the presence of pre-existing chronic cardiovascular pathology may play a role in the acute cardiotoxic effects that lead to overdose death.

Notably, acute cardiovascular events occurred exclusively in the stimulant positive cases. The total numbers and proportions were quite small and they therefore do not appear to be

primary drivers of the relationship between drugs used and mortality. There were 3 cases of intracerebral hemorrhage in the M group and 6 cases in the C group, along with 3 cases of acute MI in the C group and 3 in the CH group. Although the numbers were too small to draw strong conclusions about the prevalence ICH and acute MI, these data confirm a trend in acute, catastrophic cardiovascular events among cocaine and methamphetamine users that has been previously demonstrated in the literature, and is not seen among the heroin overdose group.<sup>4, 32, 33, 38, 39</sup>

Taken as a whole, the study decedents are more likely to be overweight or obese compared with the latest available data on adult BMI trends in King County, Washington. As of 2013, 22% of all adults in the county were obese.<sup>56</sup> Compare this with the study groups, which ranged from 27.7 - 41.5% obese. The only significant difference across BMI categories was that the CH group was more likely to be underweight. It is probable that the high prevalence of obesity is a contributing factor in the cardiovascular pathologies in these groups, and in subsequent phases of this study should be controlled in statistical analyses. These data also highlight that poor nutrition, exercise or genetics may be more likely to be an issue for people who use stimulants and/or heroin in King County compared with the general population.

Human heart weight is determined by body weight, gender, age, various diseases, and is associated with the most prevalent types of cardiovascular disease.<sup>57</sup> Recent research suggests that heart weight should comprise approximately 0.51 – 0.53% of normal adult body weight.<sup>58,59</sup> For the purposes of this study, heart weight was used as a rough estimate of overall cardiovascular health. Significantly greater mean heart weights were seen in the M group (496 grams) compared with the heroin reference group (425 grams). If this difference remains after controlling for weight, age, and sex in the next phase of this study, heart weight could serve as a

crude gage of overall cardiac health among those who died secondary to methamphetamine toxicity.

This study shows that across all overdose deaths, people in King County are most likely to die in a residence, with 13% dying in public, outdoor spaces. However, 20% of overdose deaths due to cocaine or methamphetamine occurred in a public location outdoors. Similarly, a study of opioid overdose in San Francisco by Visconti et al. found that the majority of overdose deaths occurred in private residences, however only 6.9% occurred in public spaces.<sup>60</sup> This may indicate that people using stimulants without opiates in the Seattle area are more likely to use in public settings and perhaps have housing instability.

Alcohol was significantly less likely to be present in the M and MH groups compared with the H group (15.4%, 21.5% and 35.2%, respectively). Previous research suggests that methamphetamine combined with alcohol increases heart rate significantly more than either substance used alone.<sup>61, 62</sup> Additionally, a systematic review and meta analysis shows that consumption of 2.5–14.9 g of alcohol ( $\leq 1$  drink) per day is protective against coronary heart disease and stroke incidence and mortality compared with no alcohol, but for people who consume  $>60$  g/day there is significantly increased risk stroke compared with abstainers (relative risk 1.62).<sup>62</sup> These data suggest that the relationship of alcohol and cardiovascular conditions, particularly when combined with other substances, is complex. Although the chronicity of alcohol consumption among this study population cannot be determined, the acute effects of alcohol will be controlled for through multivariate logistic regression in the next phase of the study.

The prescription drug classes of SSRI, SNRI and TCA were present in 10.6% of the total study population. This is unlikely to be relevant to the cardiovascular pathologies of interest. However, it suggests that at least 1 in 10 of these individuals were under medical care for a mental health issue, and this points toward opportunities intervene in clinical care settings. Benzodiazepines were found in highest proportion in cases with any heroin on toxicology (15.4% of the MH group, 12.3% of the CH group and 17.1% of the H group, compared with 4.6% of the M group and 0% of the C group). It is thought that people combine benzodiazepines with opioids in order to maximize euphoric effects. This combination also increases the risk of overdose.<sup>64</sup> Therefore it is not surprising that higher rates of benzodiazepines were found among heroin positive decedents.

Selection bias could be an issue in this study design since overdose death cases may not be representative of a broader population that uses methamphetamine and/or heroin without overdosing. Information on important confounders such as tobacco use, a well-known risk factor for cardiovascular disease, was not available. Instead, a heroin comparison group was carefully selected in order to minimize likely differences in smoking history across groups. Nonetheless, the exact pattern of nicotine use among the cases was not known and could impact the results of the study. Another issue with the study was there were too few cases of ICH and acute MI to calculate the odds of these acute cardiovascular events. A study with larger numbers may have provided adequate statistical power calculate odds ratios, however, the small proportion is what matters most in understanding the relative importance of various acute cardiovascular conditions. Finally, in order to better understand the independent relationship between drug overdose and the pathologies of interest, multivariate logistic regression will need to be conducted in order to control for the effect of variables such as age, sex, race, and BMI.

The results found in this study highlight that people who die from methamphetamine or cocaine overdose are likely to have multiple, intersecting risk factors for cardiovascular pathology. The higher prevalence of both acute and chronic cardiovascular conditions found among methamphetamine and cocaine overdose decedents suggests that there are cardiotoxic effects unique to stimulants which are not seen with heroin. Future studies should aim to demonstrate a temporal relationship between the development of chronic cardiovascular pathology and the repeated, long-term use of methamphetamine and cocaine.

## **CHAPTER 5:**

### **Reflection**

There were a number of unexpected challenges in bringing this thesis to life. However, it was a valuable learning experience from beginning to end. I was lucky to have such dedicated thesis advisors. They gave me autonomy in the process, but offered the guidance needed to see the forest when I was lost in the trees. I did not expect to collaborate with so many knowledgeable and generous researchers along the way. Working with Dr. Ariyaratne and Dr. Harruff at the KCME office and Dr. Coffin from UCSF fueled my excitement about the project. Their expertise and encouragement lent me more confidence in my research and helped me hone in on the most important findings. Because of all of the help I received during this project - it really was a team effort, I feel that I am now a stronger researcher. I learned from my mistakes and borrowed insights from my many mentors.

I underestimated the time it required to complete nearly every step of the process: from brainstorming the most valuable and feasible ways to study drug overdose, to formulating testable hypotheses, obtaining the dataset, crunching the numbers and writing up the results. I did not understand the IRB process prior to this study, so obtaining permission from all of the various entities involved was arduous and unnecessarily time consuming. In total, it took about 6 months to obtain my complete dataset. It would have been a bonus to be able to gather all of the data from the autopsy reports myself, but since I was working under an outside organization, I was obliged to follow their procedures and allow the forensic pathologist to compile the data on my behalf. I was able to cross check a number of records for inter-rater reliability, which was a surprisingly fascinating process in itself. Frankly, I am surprised I was able to complete this

study in less than a year. In the future, I will understand that research does not always fit neatly in a predetermined time frame.

Another unanticipated challenge was that my knowledge in statistical analyses was not adequate for the study I had originally planned. If I were able to do my MPH over again, I would have taken more advanced statistics classes. There were too few cases to reasonably allow for matching on race, age and sex, so the other alternative was to conduct a multivariate regression analysis to control for these possible confounders. Unfortunately, limited time and my inexperience with the statistical software (Stata) was a barrier to including these adjusted odds ratios in my thesis. Luckily, after some pointers from Dr. Banta-Green, I was ultimately able to run the multivariate logistic regression analyses to control for those variables. Those results will be included in the manuscript I am submitting for publication. I do feel that the unadjusted odds ratios that I originally calculated are worthy of a thesis paper and serve as a good start for the manuscript, but they do not provide a full picture.

My overarching concern throughout this research is whether or not it is translational. What difference will these data make? Is it likely or even possible that it will have a positive impact on those at most risk for dying from drug overdose? I have lost many friends to drug use and its complications. It is my hope that all of the work and fretting that went into this study will make a difference for people like my friends, that it will ultimately make overdose more avoidable for some. I know that it probably won't have a direct impact, but perhaps this study can be one tiny part of a bigger effort that helps us better understand substance use disorder and its consequences.

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