A Profile of Methamphetamine Use in Coronial Cases in South Australia Over the Last 20 Years

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Abstract

Methamphetamine is a globally popular drug of abuse which induces euphoria and affects cognitive/psychomotor performance and sleep, provoking risk-taking and violent behaviour. There have been significant increases in cases of methamphetamine abuse in Australia due to its ready availability and low cost. Currently, there are no studies that analyse the effects of methamphetamine on a post-mortem cohort at a state-specific level. With Adelaide, South Australia having amongst the highest methamphetamine uses globally, this study aimed to analyse trends in the use of this drug in South Australia over a 20-year period (2000 – 2019) using information provided in pathology and toxicology reports. Information collected included the decedent's age, sex, manner of death, concentration of methamphetamine, and presence of ischaemic heart disease or chronic obstructive pulmonary disease (COPD). The results demonstrated which demographics are more at risk of death when using methamphetamine and whether enough is being done to minimise use. The results showed a significant increase in methamphetamine use in individuals presenting for medicolegal autopsy in South Australia over the time period of the study ($p < 0.0001$). Furthermore, there were significantly more males than females with methamphetamine detected, however there is no difference in drug concentrations between the sexes ($p > 0.05$). The age of users has significantly increased over time ($p < 0.0001$), however there was no significant change in methamphetamine concentrations between different manners of death. There was also a significant increase in ischaemic heart disease over time ($p < 0.01$), but not COPD ($p > 0.05$).

Word Count: 249

Introduction

Methamphetamine abuse has become a public health concern worldwide.[1] This highly addictive drug works in a similar fashion to cocaine and other stimulants by inducing a state of euphoria.[2] It can be ingested orally, nasally ("snorting"), smoked, or injected and creates short-and long-term health effects for users who are dependent.[3] Within the brain, three major substances contribute to normal cerebral function: dopamine, serotonin and norepinephrine.[4] When methamphetamine reaches the brain, these neurotransmitters are overproduced with high levels of dopamine released into synaptic clefts. In addition, methamphetamine also blocks the re-uptake of dopamine by storage vesicles.[4] Persistent methamphetamine abuse causes paranoia and delusions, as well as both visual and auditory hallucinations.[5] In 2010, it was reported in the United States (US) that 50-73% of law enforcement agencies identified methamphetamine as the primary drug contributing to violent and aggressive behaviour. The violence stemmed from both the direct pharmacological effects of the drug, as well as from the drug trafficking/distribution environment and culture.[6]

Methamphetamine abuse has significantly increased since the 1990's with increasing utilization of precursor chemicals such as methylamine, ephedrine and pseudoephedrine, as well as the equipment required for the manufacturing process.[7] In 1997, it was reported in the US that 10% of people aged 40 or older had admitted to having been treated for methamphetamine abuse, compared to 23% in 2007.[8] Globally there have been increases in the quantities of methamphetamine seized by drug agency officials and law enforcement officers, as well as an increase in the number of home-based clandestine laboratories.[8] Australia has also had an increase in methamphetamine abuse in recent years, with most methamphetamine being produced domestically.[9] The Australian Criminal Intelligence Commission's 2015-2016 Illicit Drug Report stated that 67% of the illicit drug seizures in South Australia were related to amphetamine-type substances.[10] The number of national illicit

drug seizures has increased by 84.7% over the previous decade, with a 61.5% increase in clandestine laboratories detected over the same time period.[10] A study by González-Mariño *et al.*[11] analysed wastewater samples for levels of amphetamine, 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine between 2011 to 2017. This included 120 cities in 37 countries. The study showed that Adelaide, South Australia had the highest levels globally (507-659 mg/1000 people per day) with levels far above the next closest city, Seattle, US (418 mg/1000 people per day).[11] Cities were considered to have a high level of methamphetamine use if their averaged levels exceeded 150 mg/1000 people per day.

As noted, one of the main problems with methamphetamine abuse is that it may provoke violent and psychotic behaviour.[12-16] Studies report that methamphetamine increases the likelihood of unnatural deaths, such as accidents, particularly motor vehicle accidents (MVA), suicides and homicides.[17-19] The incidence of amphetamines associated with homicides has increased by 27%, whereas the incidence of suicides has increased by 15%.[20] Stretesky[21] suggested that an individual who uses methamphetamine is nine times more likely to commit a homicide. In fact, methamphetamine was the only drug that was strongly linked to homicide, even compared to alcohol, heroin, cocaine, PCP and LSD.[21] In addition, Darke *et al*.[22] found that 18.2% of all methamphetamine-related deaths in Australia between 2009-2015 resulted from suicide. Males had a significantly higher suicide rate than females, with the mean age being 33.1 years. Hanging was reported in 70.3% of cases.[22] Methamphetamine use also increases the risk of MVAs, particularly off-road accidents, due to high-risk driving, disorientation, or altered consciousness.[23-25] Predicting behaviour from blood levels is however, difficult. For example, Lemos[26] reported two cases where one driver was driving at low speed and was cooperative with police, however, another driver travelled at dangerously high speeds and was aggressive/violent with officers. Interestingly, both drivers had very

similar methamphetamine blood concentrations. In Australia, one in seven methamphetamine-related deaths involved an accident, with MVAs being most common.[27]

Cost of Illness (COI) studies have determined that the economic and social costs associated with methamphetamine abuse in Australia have risen from $3.7 billion in 2007 to approximately $9.4 billion for the 2013/14 financial year.[28] The cost categories examined included those associated with the criminal justice system, workplace, clandestine laboratories, health care/rehabilitation facilities, child protection, road crashes, and drug prevention programs. A statistical life year, estimated at $281,768, was also added for each decedent, accounting for the economic loss due to premature mortality.[28]

Determining the significance of methamphetamine in post-mortem blood samples is problematic. Blood concentrations greater than 0.5 mg/L are typically seen in methamphetamine-related deaths, however concomitant drugs or pre-existing disorders can also contribute to death with levels as low as 0.05 mg/L.[18] Pilgrim *et al.*[29] analysed 169 post-mortem cases where amphetamine-class drugs were detected, finding that methamphetamine concentrations ranged from 0.2 – 5.6 mg/L. All cases had a natural disease present and deaths were considered to be related to methamphetamine. Frequent use of methamphetamine can also build tolerance, meaning that more of the drug is required to produce an effect.[30, 31] Pre-existing conditions, such as cardiovascular abnormalities, often lead to fatalities at smaller concentrations.[32] Therefore, blood concentrations alone within the living or the dead do not determine what effect the stimulant drugs will have on an individual.[8]

Hypertension induced by methamphetamine has been associated with haemorrhagic cerebrovascular accidents (‘strokes’) and the high concentrations of dopamine induced by methamphetamine may also contribute to neurobiological damage.[4, 33-36] A variety of cardiovascular problems are also linked to methamphetamine abuse which may result in

myocardial infarctions at relatively young ages.[37-39] This includes the development of coronary artery atherosclerosis, cardiomyopathy, hypertension, dysrhythmias, and sudden cardiac death.[40] The mechanisms behind methamphetamine abuse and lung injury is unknown, however the drug has been reported to cause pulmonary oedema, pneumonia, and pulmonary hypertension.[41] The relationship between methamphetamine use and acute chronic obstructive pulmonary disorder (COPD) is unclear, although a 2019 study suggested that COPD exacerbation was higher in women who abuse methamphetamine.[42]

Currently, the role of methamphetamine in South Australia in contributing to or causing death in forensic cases is unknown. Studies which use national data to evaluate trends do not reflect the methamphetamine problem at a state level. Thus, the high rates of methamphetamine abuse in the South Australian population provide an excellent and novel opportunity to analyse the effects of this drug over time. This study hypothesises that the incidence and nature of deaths with methamphetamine in post-mortem blood samples has increased and changed over time in the South Australian population. The study aims to analyse trends/changes of methamphetamine in post-mortem blood samples, identify trends in age and sex of cases, provide an analysis of the types of medicolegal deaths where methamphetamine was detected, and identify specific medical conditions which may be increased in individuals taking methamphetamine. This study will create awareness of the effects of methamphetamine use and provide a novel insight into how methamphetamine has changed over the last 20 years in individuals presenting for medicolegal autopsy in South Australia. Within forensic and medical research, this analysis will show which age groups are more at risk and whether the occurrence of ischaemic heart disease and COPD has changed over time in methamphetamine abusers. Ultimately, this could be used to inform medical professionals and to reduce the likelihood of methamphetamine-related deaths in the future.

Materials & Methods

This study was approved by the University of Adelaide's Human Research Ethics Committee (H-2020-033). Analysis of autopsy and toxicology casefiles at Forensic Science South Australia (FSSA), Adelaide, South Australia was undertaken from January 1 to December 31 in 2000, 2004, 2009, 2014, and 2019. This type of stepwise analysis was chosen to give an indication of temporal trends, as the total number of cases over 20 years was too large to be effectively processed within the time frame of the study. All adult cases (≥ 18 years) where methamphetamine was detected in post-mortem blood samples were selected. Overall, 239 cases were identified. All cases had full police and coronial investigations with complete autopsies including toxicology. Information that was assessed included the age and sex of the decedent, the cause and manner of death, and the concentration of methamphetamine and other concomitant drugs.[32] Manner of death was separated into seven categories, these being natural, suicide (overdose), suicide (other), accident (overdose), accident (other), methamphetamine-related homicide, and undetermined.[17] The presence of ischaemic heart disease and COPD were also documented. Ischaemic heart disease was positively identified if the pathology report recorded moderate to severe coronary artery atherosclerosis, coronary artery thrombosis, acute myocardial infarction, myocardial fibrosis, cardiomegaly, hypertension, or hypertrophy.[27] Unique myocardial abnormalities were listed under a miscellaneous category. These variables were collated on an Microsoft Excel Spreadsheet.

Although methamphetamine screening has changed significantly over this 20-year period, the detection limit has remained at 0.01 mg/L throughout. In 2000 and 2004, methamphetamine was screened and analysed using a HP 5890 series II Plus gas chromatograph (GC) with dual nitrogen-phosphorus detectors and a 7673A autosampler.[43] Samples that appeared positive for the drug were derivatised and reanalysed using gas

chromatography-mass spectrometry (GCMS) to confirm methamphetamine presence.[43] Screening in 2009 used an Applied Biosystems 4000Q-Trap with an Agilent 1200 LC system, involving liquid chromatography with tandem mass spectrometry detection. Methamphetamine was extracted using mixed mode solid phase extraction before being analysed. For 2014 and 2019, screening was performed using an alkaline liquid-liquid extraction with analysis by liquid chromatography quadrupole time-of-flight mass spectrometry (LC/QTOF).[44] Chromatographic separation was conducted using an Agilent 1290 Infinity II liquid chromatography system and methamphetamine was detected through an Agilent 6545 QTOF system in conjunction with a Jetstream electrospray ionisation source according to standard methodology.[44]

Statistical analyses were performed using the computer program R (version 4.0.2), in conjunction with RStudio IDE (version 1.3.959).[45] The number of cases containing methamphetamine in a post-mortem blood sample were analysed as a proportion of the total number of toxicology cases for those years. Firstly, a chi-squared test was used to determine if there had been any significant change in the proportion of positive tests for methamphetamine. Then, pairwise tests for proportion, with Bonferroni corrections, were used to analyse differences between each of the years. A one-way analysis of variance (ANOVA) analysed whether methamphetamine concentrations were the same across all of the years, with a pairwise independent sample (Welch's) t-test, adjusted using Tukey's method, showing exactly which years are significantly different. The average age for males and females in each year was calculated and plotted on a graph using Microsoft Excel, as well as the number of male and female cases in each year. A one-way ANOVA was performed to determine whether methamphetamine concentration was the same for all manners of death. Finally, a Fisher's exact test analysed whether year had a significant effect on the proportion of cases with ischaemic heart disease and COPD. Pairwise Fisher's exact

tests, with Bonferroni corrections, determined which of these years are significantly different. Error bars represent 95% confidence intervals and provides an estimate for the variability of the data.

Results

Aim 1: To analyse trends/changes of methamphetamine in post-mortem blood samples over time.

There were 239 cases where methamphetamine was detected in a post-mortem blood sample in South Australia for the years 2000, 2004, 2009, 2014, and 2019. An initial chi-squared test showed that the year had a significant effect on the proportion of positive tests for methamphetamine ($p < 0.0001$). Pairwise testing confirmed that the proportion of cases in 2004 was significantly different to the proportion in 2019 ($p < 0.01$*). Likewise, the proportion in 2009 was significantly different to the proportion in 2019 ($p < 0.001$**). The bar heights in Figure 1 show the observed proportion of positive tests in each year, with the error bar in 2019 being considerably higher than the error bars for 2004 and 2009.

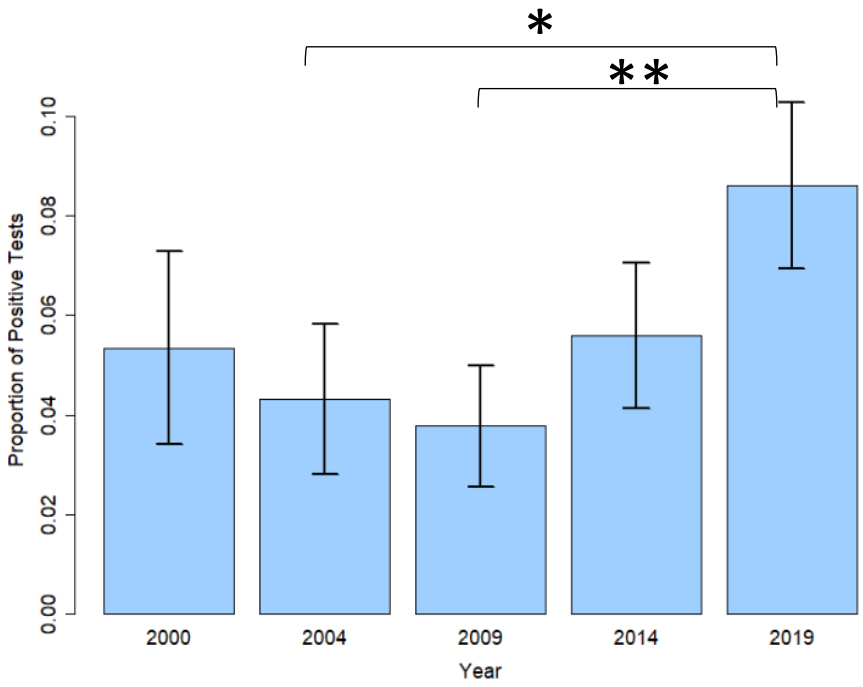

Figure 1: Proportion of toxicology cases with methamphetamine detected in a post-mortem blood sample.

The side-by-side boxplot in Figure 2 does not show significant differences between methamphetamine concentration and year. Therefore, the levels of methamphetamine being detected in a post-mortem blood sample have not significantly increased or decreased from 2000 to 2019. A Welch's t-test found that the mean log(methamphetamine concentration) in 2009 was significantly different to the mean log(methamphetamine concentration) in 2019 ($p < 0.0001$***). Figure 2 shows that 2019 had the highest median methamphetamine concentration, and 2009 had the lowest compared to all years analysed. Also, the top 50% of methamphetamine concentrations in 2019 lie above the bottom 75% in 2009, and the bottom 50% of methamphetamine concentrations in 2009 lie below the top 75% in 2019. There were no other significant trends identified between years. The average methamphetamine

concentrations were 0.67 (2000), 0.28 (2004), 0.14 (2009), 0.42 (2014), and 0.82 (2019) mg/L.

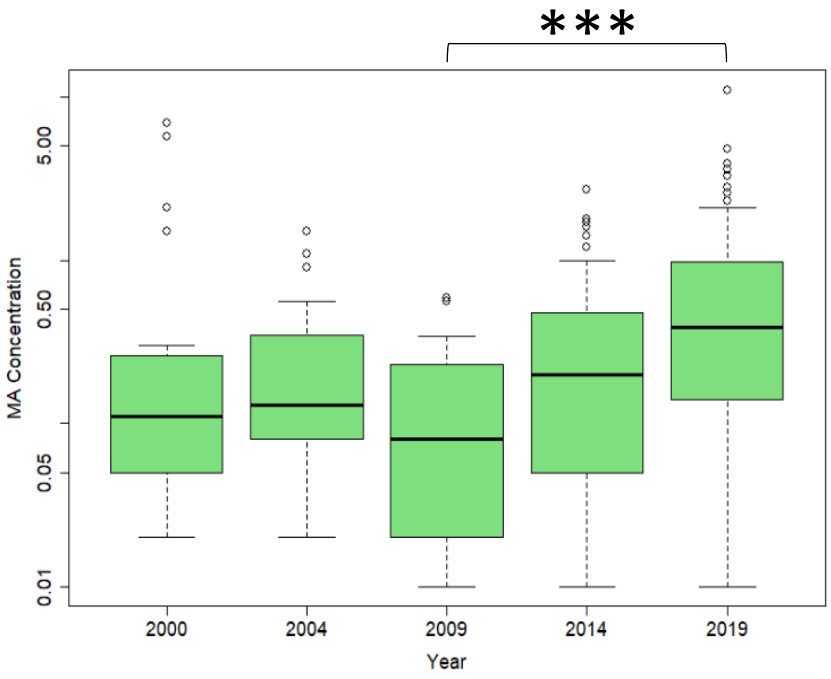

Figure 2: Methamphetamine (MA) concentrations detected in post-mortem blood samples over time.

Aim 2: To identify trends in age and sex of cases where methamphetamine was detected in a post-mortem blood sample in South Australia over 20 years (2000 – 2019).

A pairwise t-test determined that the mean age for methamphetamine users significantly increased with year ($p < 0.0001$). The results showed four significant differences between the years, these being 2000 and 2019 ($p < 0.0001$), 2004 and 2019 ($p < 0.0001$), 2009 and 2019 ($p < 0.05$), and 2014 and 2019 ($p < 0.05$). Figure 3 shows that the average age for males has been steadily increasing since 2004, whereas the average age for females has seen a dramatic increase between 2000 and 2004, and 2014 and 2019. The average age of all

cases increased from 32.6 in 2000 (range = 18 – 56) to 42.2 years in 2019 (range = 23 – 60). Only 14.6% of cases were over the age of 50.

Figure 3: The average age of decedents in both male and female categories.

Of the 239 cases analysed, 192 decedents were male (80.3%) and 47 were female (19.7%). A Welch's two-sample t-test concluded that there is no evidence of a difference in methamphetamine concentration between males and females ($p > 0.05$). Figure 4 shows a higher number of male than female cases where methamphetamine was detected in a post-mortem blood sample in each of the years. The male to female ratio in 2000 was 25:2, whereas the ratio in 2019 was 73:21.

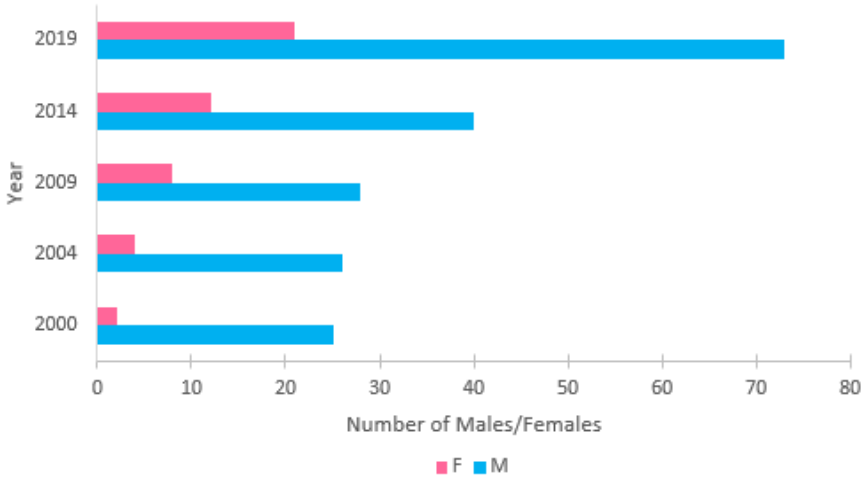

Figure 4: Number of male and female cases in each year.

Aim 3: To provide an analysis of the types of medicolegal deaths where methamphetamine was detected in a post-mortem blood sample in South Australia over 20 years (2000 – 2019).

A one-way ANOVA was performed to determine if the mean log(methamphetamine concentration) was the same for all manners of death. This recorded a p-value greater than 0.05, indicating that there was insufficient evidence of any statistically significant difference between methamphetamine concentration and manner of death. The data comprises of 51 natural deaths, 9 suicides (overdose), 65 suicides (other), 45 accidents (other), 42 accidents (overdose), 14 methamphetamine-related homicides, and 13 undetermined deaths. Of the 65 suicides (other) recorded, there were 10 gas poisonings, 45 hangings, 5 gunshot wounds, 2 as a result of sharp trauma, 1 fall from a large distance and 2 miscellaneous cases. The accidents (other) recorded 32 motor vehicle accidents, 6 drownings, 2 deaths due to the effects of fire, 2 due to asphyxiation, 2 as a result of sharp trauma, and 1 decedent who was crushed. The most common type of methamphetamine-related homicide involved 6 cases of sharp trauma, whereas there were 5 cases of blunt trauma, 2 as a result of a gunshot wound, and 1 asphyxiation.

Figure 5 demonstrates that the boxplot for suicide (overdose) is lower than the other categories, whereas accident (other) is very broad. Accident (other) also had the highest average methamphetamine concentration (0.91 mg/L) and suicide (overdose) had the lowest (0.15 mg/L). Natural, suicide (other), accident (overdose), and methamphetamine-related homicide all had boxplots with similar characteristics.

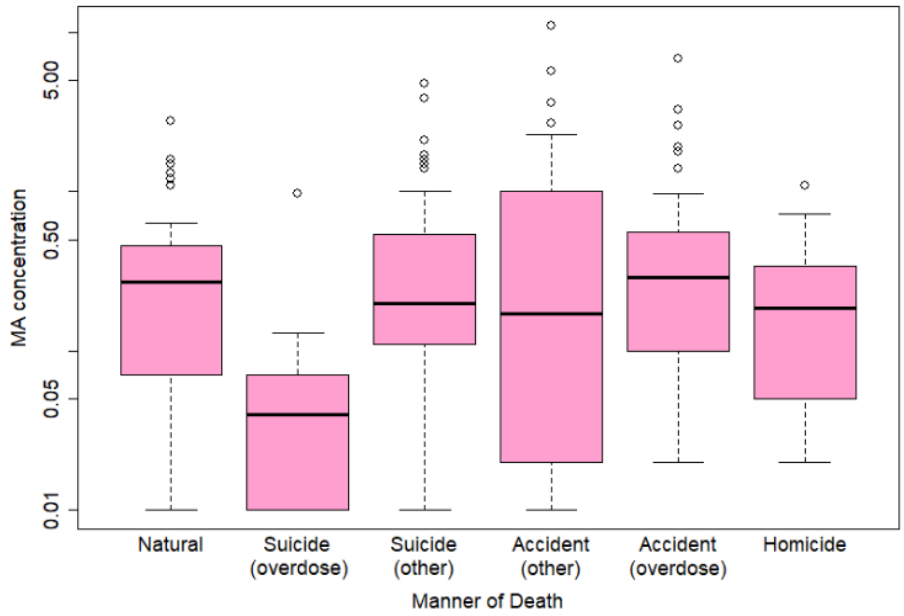

Figure 5: Methamphetamine (MA) concentrations recorded for different manners of death.

Aim 4: To identify specific medical conditions which may be increased in individuals taking methamphetamine.

Out of the 239 cases analysed, 73 (30.5%) people had ischaemic heart disease and 25 (10.5%) had COPD. There were 15 (6.3%) individuals who had both pre-existing conditions. A Fisher's exact test showed very strong evidence that year had some effect on the proportion of ischaemic heart disease cases ($p < 0.01$), however no evidence that year had any effect on the proportion of COPD cases ($p > 0.05$). Further analysis concluded that the likelihood of

ischaemic heart disease in 2000 was different to the likelihood of ischaemic heart disease in 2009, 2014, and 2019. The mean age for ischaemic heart disease was 45 years (range 25 – 60), with 83.6% male.

Figure 6 shows that cases with ischaemic heart disease are increasing over time. COPD numbers were lower than ischaemic heart disease, however COPD increased between 2004 to 2009 and then declined between 2009 and 2014. The error bars for ischaemic heart disease are also appreciably higher in 2009, 2014, and 2019 than the error bar for 2000.

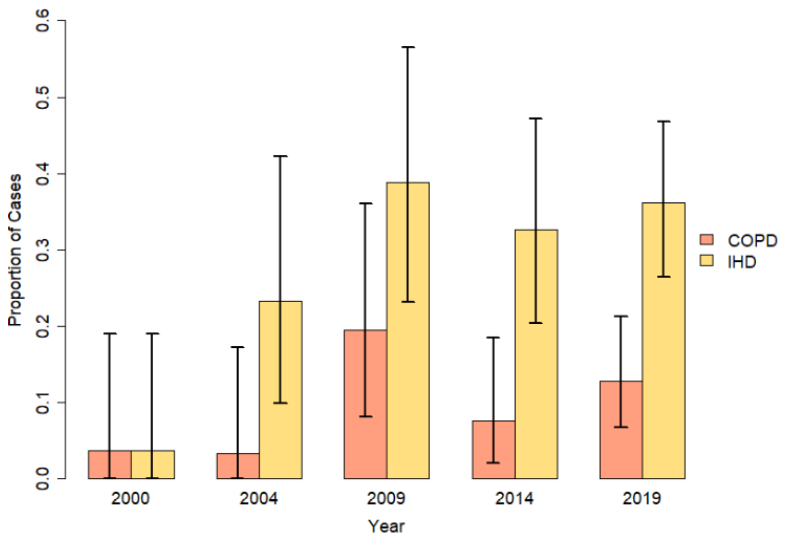

Figure 6: The proportion of ischaemic heart disease and COPD cases over time.

Discussion

Australia's increase in methamphetamine abuse is reflected in the autopsy population from South Australia between 2000 – 2019. This study has shown that there was a higher rate of methamphetamine detected in post-mortem blood samples in 2019 compared to earlier years. With an 84.7% increase of methamphetamine seizures between 2005-06 and 2015-16, the data indicates that South Australia's illicit drug problem is far from under control.[10]

Whether directly or indirectly, the effects of methamphetamine have led to more cases presenting for medicolegal autopsy in recent years. There were 239 cases where methamphetamine was detected in a post-mortem blood sample for the five years analysed over the 20-year period. A Victorian study recorded 169 cases over a five-year period (2001 – 2005) which included all amphetamine-class drugs.[29] This shows that South Australia's methamphetamine use can not only be assessed in wastewater samples, as stated in González-Mariño *et al.*[11], but also in post-mortem cohorts. Interestingly, the data showed no statistically significant difference between methamphetamine concentration and year. Therefore, people have not been taking more or less of the drug over time. There was a difference in concentration between 2009 and 2019, however further investigation is required to determine the reasons for this result. The lowest average methamphetamine concentration detected was 0.14 mg/L in 2009, compared to 0.82 mg/L in 2019. The literature states that most methamphetamine-related deaths occur above 0.5 mg/L, with another study reporting concentrations of 0.2 mg/L.[18, 29] This highlights the difficulty in determining the significance of methamphetamine concentrations as the effects of this drug varies among users.

The age of methamphetamine users presenting for medicolegal autopsy is also increasing. The average age increased from 32.6 in 2000, to 42.2 years in 2019. Therefore, the average age of decedents in this population has risen by almost 10 years. An older age would certainly be expected to be associated with an increase in degenerative and pre-existing diseases. Whether the older age is a reflection of the natural aging of a cohort of younger drug users or has been influenced by greater toxicological screening (from 51 to 72% of cases) of autopsy cases in the local South Australian medicolegal environment is uncertain. A study of 413 methamphetamine-related deaths in San Francisco reported a mean age of 36.8 years, with 11% of cases over the age of 50.[46] This is consistent with the results found in this study, with 14.6% of South Australian cases being over 50 years.

There was a marked male predominance in this post-mortem cohort, comprising 80.3% of cases. However, when analysed over time, there was no significant difference over the years. This is consistent with other studies where 85.2% of the population was male.[46]

The manners of death where methamphetamine was detected showed that suicide (other) was most common. Of these suicides, 69.2% were due to hanging. These findings are consistent with previous literature.[22] The major effect of methamphetamine is to bind to monoamine receptors, mainly those of dopamine and norepinephrine, and disrupt the proton gradient to initiate their release from cells.[36] The drug also inhibits the reuptake of these monoamines, creating a longer duration of euphoria for users compared to other stimulants.[36] When the drug levels wane, the user is left feeling depressed and anxious, feelings predisposing to suicide. It was reported that 18.2% of all methamphetamine related deaths are due to suicide and methamphetamine is detected in 1.6% of all completed suicides in Australia.[22]

Natural death due to pre-existing conditions were also very common. Methamphetamine is known to create many physical health problems for users.[32]

Studies have shown that areas of the brain, specifically the ventromedial prefrontal cortex, orbital frontal cortex, and the insula, shrink by approximately 10% in cases of chronic methamphetamine abuse, while glucose metabolism and cerebral perfusion are also affected.[8, 35] Decreased glucose metabolism and cerebral perfusion have been found in patients with schizophrenia and Alzheimer's disease, resulting in psychosis.[35] Methamphetamine-induced psychosis is clinically similar to these diseases, however psychosis associated with methamphetamine use can resolve within one month or persist for six months or longer. Symptoms can also reoccur after years of methamphetamine abstinence.[35] The current study has shown a very high number of accidents occurring when using methamphetamine,

particularly MVAs. Most of these were single vehicle accidents, whereas if more than one car was involved, the cause was usually due to driving erratically on the wrong side of the road.[27] Therefore, the cognitive and behavioural effects of methamphetamine have significantly contributed to a high number of deaths while driving in South Australia.

Statistical analysis showed that, although some manners of death dominated the dataset, the methamphetamine concentration across all categories did not vary. This, again, shows that the effects of any level of methamphetamine are unpredictable, with effects varying among individuals.

The current study has also shown a significant increase in the incidence of ischaemic heart disease over time. The percentage of cases with ischaemic heart disease out of the total number of autopsy cases where methamphetamine was detected increased by a factor of nearly 10 from 2000 to 2019. Cardiovascular disease is a common occurrence in methamphetamine users, with the drug interacting with the L-type calcium channels of cardiomyocytes.[8] When small concentrations of calcium are passed through L-type calcium channels, calcium ions (Ca^{2+}) are released from the sarcoplasmic reticulum of muscle cells, initiating systole (e.g. contraction) and moving blood into the aorta and pulmonary trunk.[8] Atherogenic factors, such as reactive oxygen species (ROS), Interleukin-6 and Interleukin-1β, are promoted through methamphetamine use as a proinflammatory response, encouraging cardiotoxicity.[47] Coronary artery atherosclerosis was the most common problem found in this cohort (64.4%). This is a high percentage of people with atherosclerosis when compared to the literature at 19%.[39] Males were more likely to have ischaemic heart disease than females, with 83.6% in the current study.[39] Whatever the reasons for the increase in the number of cases of ischaemic heart disease within individuals in the South Australian post-mortem population who had been taking methamphetamine, it is clear that the physiological effects of such comorbidities will have to be considered in the evaluation of these deaths. If this is a

continuing trend, it may be that underlying organic illnesses may be contributing more to terminal mechanisms in such cases with death occurring at lower blood levels of the drug.

The proportion of COPD cases did not vary over time when compared to the number of toxicology cases undertaken per year. Studies analysing the relationship between methamphetamine and developing COPD are, however, rare. Mice models have shown that methamphetamine inhalation increases free radical formation, causing significant lung injury as ROS can promote pathological reactions when homeostasis is disturbed.[48, 49] The current results suggest that methamphetamine abuse may not be associated with developing COPD, however further studies with a larger post-mortem cohort should be undertaken.[41]

A limitation to this study is that this is only a single population and the findings may not apply elsewhere. Furthermore, some cases would not have been identified if toxicology testing was not requested or if the deceased did not have a coronial referral. It is standard practice for analyses to be performed on peripheral blood from the femoral vein when possible due to post-mortem redistribution.[50] Therefore, certain cases where peripheral blood could not be obtained, such as those in an advanced stage of decomposition, were excluded from the analysis. Another limitation is that there were 13 undetermined deaths, where either there was significant decomposition or where there was not enough information in the casefile to distinguish between an accident or suicide. Therefore, the numbers in the manner of death categories may be slightly different. Finally, as mentioned previously, determining the significance of methamphetamine levels in blood is notoriously difficult.

In conclusion, this is the first study to analyse the effects of methamphetamine in relation to coronial deaths in South Australia. Providing this information at a state-level, as opposed to using national data, allows state governments and law enforcement to see there needs to be more effective preventative strategies. The increasing number of cases where

methamphetamine is detected shows that drug education and prevention programs need re-evaluation. This study has found that middle-aged and older males with a chronic heart disease are at a higher risk of death when using methamphetamine and thus require monitoring. There were no significant differences found between methamphetamine concentration and manner of death, showing how problematic and difficult it is to determine the significance of methamphetamine in the blood. Perhaps pathologists should consider toxicological testing of all coronial deaths for methamphetamine. It was important that the high rates of methamphetamine abuse in the South Australian population be investigated to determine the incidence of methamphetamine deaths in a high-risk autopsy population and to analyse changes over time. Future studies will be required to monitor these trends and to evaluate the reasons for these changes. Other states/countries could also determine the effect methamphetamine is having on their population and develop appropriate strategies to combat this growing problem.

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Statistician: Max Glonek

References

1. Stoneberg DM, Shukla RK, Magness MB (2018). Global methamphetamine trends: an evolving problem. *Int Crim Justice Rev* **28**, 136-161.
2. Richards JR, Laurin EG (2020). *Methamphetamine toxicity*. StatPearls Publising, Florida.
3. Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S (2000). History of the methamphetamine problem. *J Psycho Drugs* **32**, 137-141.
4. Radfar SR, Rawson RA (2014). Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. *Addiction & Health* **6**, 146.
5. Wearne TA, Cornish JL (2018). A comparison of methamphetamine-induced psychosis and schizophrenia: a review of positive, negative, and cognitive symptomatology. *Front Psychiatry* **9**, 491.
6. Brecht ML, Herbeck DM (2013). Methamphetamine use and violent behavior: user perceptions and predictors. *J Drug Issues* **43**, 468-82.
7. Galbraith N (2015). The methamphetamine problem: commentary on… psychiatric morbidity and socio-occupational dysfunction in residents of a drug rehabilitation centre. *BJPsych bulletin* **39**, 218-220.
8. Karch SB, Drummer OH (2016). *Karch's pathology of drug abuse*. Taylor & Francis Inc, United States.
9. Degenhardt L, Roxburgh A, Black E, Bruno RB, Campbell G, Kinner S, Fetherston J (2008). The epidemiology of methamphetamine risk and harm in Australia. *Drug Alcohol Rev* **27**,243-52.
10. Australian Criminal Intelligence Commission (2017). *Illicit Drug Data Report 2015-16*. Canberra, Australia.

11. Gonzalez-Marino I, Baz-Lomba JA, Alygizakis NA, Andres-Costa MJ, Bade R, Bannwarth A, Barron LP, Been F, Benaglia L, Berset JD, Bijlsma L *et al* (2020). Spatio-temporal assessment of illicit drug use at large scale: evidence from 7 years of international wastewater monitoring. *Addiction* **115**, 109-120.
12. Glasner-Edwards S, Mooney LJ (2014). Methamphetamine psychosis: epidemiology and management. *CNS Drugs* **28**, 1115-26.
13. McKetin R, Lubman DI, Najman JM, Dawe S, Butterworth P, Baker AL (2014). Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. *Addiction* **109**, 798-806.
14. Liu Y, Hao B, Shi Y, Xue L, Wang X, Chen Y, Zhao H (2017). Violent offences of methamphetamine users and dilemmas of forensic psychiatric assessment. *Forensic Sci Res* **2**, 11-7.
15. Hamilton AB, Goeders NE (2010). Violence perpetrated by women who use methamphetamine. *J Subst Use* **15**, 313-29.
16. Plüddemann A, Flisher AJ, McKetin R, Parry C, Lombard C (2010). Methamphetamine use, aggressive behavior and other mental health issues among high-school students in Cape Town, South Africa. *Drug Alcohol Depend* **109**, 14-9.
17. Kuo CJ, Liao YT, Chen WJ, Tsai SY, Lin SK, Chen CC (2011). Causes of death of patients with methamphetamine dependence: a record-linkage study. *Drug Alcohol Rev* **30**, 621-628.
18. Logan BK, Fligner CL, Haddix T (1998). Cause and manner of death in fatalities involving methamphetamine. *J Forensic Sci* **43**, 28-34.
19. Richards JR, Bretz SW, Johnson EB, Turnipseed SD, Brofeldt BT, Derlet RW (1999). Methamphetamine abuse and emergency department utilization. *West J Emerg Med* **170**, 198.

20. Byard RW, Donkin J, Vink R (2018). The forensic implications of amphetamine intoxication in cases of inflicted blunt craniocerebral trauma. *J Forensic Sci* **63**, 151-3.
21. Stretesky PB (2009). National case-control study of homicide offending and methamphetamine use. *J Interpers Violence* **24**, 911-924.
22. Darke S, Kaye S, Duflou J, Lappin J (2019). Completed suicide among methamphetamine users: a national study. *Suicide Life Threat Behav* **49**, 328-337.
23. Logan BK (1996). Methamphetamine and driving impairment. *J Forensic Sci* **41**, 457-464.
24. Bosanquet D, MacDougall HG, Rogers SJ, Starmer GA, McKetin R, Blaszczynski A, McGregor IS (2013). Driving on ice: impaired driving skills in current methamphetamine users. *Psychopharmacol* **225**, 161-72.
25. Gustavsen I, Morland J, Bramness JG (2006). Impairment related to blood amphetamine and/or methamphetamine concentrations in suspected drugged drivers. *Accid Anal Prev* **38**, 490-5.
26. Lemos NP (2009). Methamphetamine and driving. Sci Justice **49**, 247-249.
27. Darke S, Kaye S, Duflou J (2017). Rates, characteristics and circumstances of methamphetamine-related death in Australia: a national 7-year study. *Addiction* **112**, 2191-201.
28. Tait RJ, Whetton S, Shanahan M, Cartwright K, Ferrante A, Gray D, Kaye S, McKetin R, Pidd K, Ritter A, Roche A (2018). Quantifying the societal cost of methamphetamine use to Australia. *Int J Drug Policy* **62**, 30-6.
29. Pilgrim JL, Gerostamoulos D, Drummer OH, Bollmann M (2009). Involvement of amphetamines in sudden and unexpected death. *J Forensic Sci* **54**, 478-485.

30. Berro LF, Andersen ML, Howell LL (2017). Assessment of tolerance to the effects of methamphetamine on daytime and nighttime activity evaluated with actigraphy in rhesus monkeys. *Psychopharmacol* **234**, 2277-87.
31. Vasan S, Olango GJ (2019). *Amphetamine toxicity*. StatPearls Publishing, Florida.
32. Kaye S, Darke S, Duflou J, McKetin R (2008). Methamphetamine-related fatalities in Australia: demographics, circumstances, toxicology, and major organ pathology. *Addiction* **103**, 1353-1360.
33. Yen DJ, Wang SJ, Chen CC, Liao KK, Fuh JL, Hu HH (1994). Stroke associated with methamphetamine inhalation. *Eur Neurol* **34**, 16-22.
34. Lappin JM, Darke S, Farrell M (2017). Stroke and methamphetamine use in young adults: a review. *J Neurol Neurosurg Psychiatry* **88**, 1079-91.
35. Vuletic D, Dupont P, Robertson F, Warwick J, Zeevaart JR, Stein DJ (2018). Methamphetamine dependence with and without psychotic symptoms: a multi-modal brain imaging study. *NeuroImage Clin* **20**, 1157-62.
36. Rusyniak DE (2013). Neurologic manifestations of chronic methamphetamine abuse. *Psychiatr Clin North Am* **36**, 261-275.
37. Chiu VM, Schenk JO (2012). Mechanism of action of methamphetamine within the catecholamine and serotonin areas of the central nervous system. *Curr Drug Abuse Rev* **5**, 227-42.
38. Schwarzbach V, Lenk K, Laufs U (2020). Methamphetamine-related cardiovascular diseases. *ESC Heart Failure* **7**, 407-14.
39. Darke S, Duflou J, Kaye S (2017). Prevalence and nature of cardiovascular disease in methamphetamine-related death: a national study. *Drug Alcohol Depend* **179**, 174-9.
40. Baloch ZQ, Hussain M, Abbas SA, Perez JL, Ayyaz M (2018). Methamphetamine-induced cardiomyopathy (MACM) in a middle-aged man; a case report. *Emerg* **6**, e9.

41. McCarthy E, McClain E (2019). Methamphetamine-induced lung injury. *Eur J Case Rep Intern Med* DOI: 10.12890/2019_001067.

42. Tsai H, Lee J, Hedlin H, Zamanian RT, de Jesus Perez VA (2019). Methamphetamine use and association with pulmonary diseases: a retrospective investigation of hospital discharges in California from 2005 to 2011. *ERJ open research* DOI: 10.1183/23120541.00017-2019.

43. Felgate HE, Felgate PD, James RA, Sims DN, Vozzo DC (1998). Recent paramethoxyamphetamine deaths. *J Anal Toxicol* **22**, 169-72.

44. Partridge E, Trobbiani S, Stockham P, Scott T, Kostakis C (2018). A validated method for the screening of 320 forensically significant compounds in blood by LC/QTOF, with simultaneous quantification of selected compounds. *J Anal Toxicol* **42**, 220-231.

45. Gentleman R, Ihaka R (2000). Lexical scope and statistical computing. *J Comput Graph Stat* **9**, 491-508.

46. Karch SB, Stephens BG, Ho CH (1999). Methamphetamine-related deaths in San Francisco: demographic, pathologic, and toxicologic profiles. *J Forensic Sci* **44**, 359-68.

47. Shah A, Kumar S, Simon SD, Singh DP, Kumar A (2013). HIV gp120- and methamphetamine-mediated oxidative stress induces astrocyte apoptosis via cytochrome P450 2E1. *Cell Death Dis* **4**, e850.

48. Wells SM, Buford MC, Braseth SN, Hutchinson JD, Holian A (2008). Acute inhalation exposure to vaporized methamphetamine causes lung injury in mice. *Inhal Toxicol* **20**, 829-38.

49. Domej W, Oettl K, Renner W (2014). Oxidative stress and free radicals in COPD – implications and relevance for treatment. *Int J Obstruct Pulmon Dis* **9**, 1207-24.

50. Hilberg T, Rogde S, Morland J (1999). Post-mortem drug redistribution – Human cases related to results in experimental animals. *J Forensic Sci* **44**, 3-9.