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ORIGINAL PAPER

Pathology/Biology

Increased lung weight in fatal intoxications is not unique to opioid drugs

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Email: torfinn.beer@umu.se**Abstract**

Fatal intoxications with opioids are known to be associated with an increased lung weight, as well as with brain and pulmonary edema and urinary retention. However, there is evidence to suggest that fatal intoxications with non-opioid substances are also associated with increased lung weight; however, the latter aspect has not been comprehensively analyzed. To determine to what extent opioid and non-opioid substances are associated with increased lung and brain weight, we studied these organs in cases where the cause of death was attributed to intoxication with a single agent. Using data from cases autopsied at the National Board of Forensic Medicine (NBFM) in Sweden from 2009 through 2019 where the cause of death was attributed to a single substance, we created models of combined lung weight and brain weight. The models used age and sex as predictors as well as nested varying effects for the specific intoxicant and category of intoxicant. Suicidal hanging with negative toxicology cases served as controls. The population majority was male among both intoxications (68%) and controls (83%). The most common single substance group was opioids. All tested substances were associated with heavier lungs than controls, with the largest effect in the opioid group. Our findings show that several substances are associated with increased lung weight and that among intoxication deaths there is no difference in expected brain weight between substances. Hence, heavy lungs, without a reasonable explanation, should prompt a broad toxicological screening.

KEYWORDS

autopsy, cause of death, fatal intoxication, forensic pathology, lung weight, opioid, organ weight

Highlights

- Increased lung weight is not unique to single substance opioid deaths.
- Increased combined lung weight was observed in intoxication deaths from several other single substances.
- Unexplained increased lung weight should prompt toxicological screening, not limited to opioids.
- Single intoxication deaths and hanging deaths have similar brain weights.

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1 | INTRODUCTION

Diagnosing fatal intoxication may be difficult as interpretation of the toxicological findings is often not straightforward and requires correlation with both case history and autopsy findings [1]. Common findings in opioid intoxications are, among others, urinary retention, and brain and pulmonary edema, or the surrogate measure “increased weight” of these organs [2–8]. The utility of these findings in practice has been somewhat disappointing [4, 5], but, in some cases, they may be the only indication of intoxication. These findings have not been widely studied outside of opioid deaths, but some earlier studies have indicated that some non-opioid substances may be associated with increased lung weight [3, 5, 9]. However, no previous study has comprehensively analyzed to what extent substances affect organ weight in cases of non-opioid fatal intoxication.

To analyze if substances other than opioids are associated with an increased lung and brain weight, and if so, what substances and to what extent, we studied fatal intoxication cases in which the death was attributed to intoxication with a single intoxicant only.

2 | MATERIALS AND METHODS

2.1 | Study population

In Sweden, all medicolegal autopsies are performed at one of six units of forensic medicine at the National Board of Forensic Medicine (NBFM). To find intoxication cases, we searched the NBFM autopsy database from 2009 through 2019 for cases in which the underlying cause of death was fatal intoxication ($N = 4783$). Furthermore, we selected cases in which one of any substances on a predetermined list was mentioned on the death certificate ($N = 4339$, see Table S1). For each of the included intoxicants, we reviewed all cases where that substance was mentioned on the cause of death certificate and selected cases that had a cause of death attributed only to that single intoxicant ($N = 1201$). All decedents younger than 18 years, with a post-mortem interval (PMI) larger than 7 days, not registered as having been found dead (as to remove cases which could potentially have undergone cardiopulmonary resuscitation), or a state of decomposition registered as anything but “none” or “not registered”, were excluded ($N = 483$). Finally, cases with missing information on lung and/or brain weight ($N = 11$), sex ($N = 1$) or age ($N = 1$) were omitted, leaving 470 cases for analysis.

As control cases, we chose suicidal hangings. In the NBFM database from 2012 through 2019, all cases with suicidal hanging as the underlying cause of death were identified. After using the same inclusion and exclusion criteria as in the intoxication population with the added criteria that all cases had undergone a negative drug and alcohol screening, save for at most 0.5 mg of ethanol per gram of femoral vein blood ($N = 104$) and omitting cases with missing data ($N = 3$), a total of 101 controls remained for analysis.

Individual cases were not re-examined to validate the diagnoses set by the forensic pathologist. However, in all the included cases,

a full autopsy was conducted. In all cases, femoral vein blood, urine and aqueous humor samples were taken (if possible), and toxicological analyses were performed. In Sweden, all medicolegal autopsy cases are also independently reviewed by at least two forensic pathologists (one of whom performed the autopsy and at least one of whom is board certified) indicating that there should be few erroneous causes of death determinations.

Lung weight was defined as the combined weight of both lungs. All continuous variables were standardized to a mean of 0 and a standard deviation (SD) of 1.

2.2 | Methods

We assumed that organ weights are influenced by case factors as shown in the simplified causal model in Figure 1. To remove confounders for the effect of intoxicants on organ weight, under the proposed model, we adjusted for decomposition and PMI through case selection, while age and sex was adjusted for through regression parameters.

Using this data, Bayesian regression models of brain and lung weight were fit with varying intercepts for the specific intoxicant nested in groups and using age and sex as linear predictors (Figure 2).

The modeled difference in mean brain or lung weight was calculated by subtracting the posterior distribution of the suicidal hanging intercept from the posterior distributions of the group and intoxicant intercepts.

As this model is not frequentist and as such does not test any null hypothesis (i.e., $\Pr(X \geq x | H_0)$), there is no defined binary cut-off where the effect is said to exist, in other words, there is no significance level. However, to directly test the hypothesis that there was no difference between controls and intoxication cases, we defined a region of practical equivalence (ROPE) as 0 ± 0.1 SD meaning that any difference in the ROPE was treated as no differences as it would, in our opinion, be too small to matter. The probability that the differences in mean brain and lung weight between intoxication cases and controls were inside the ROPE was then calculated.

Model results are presented using mean values from the posterior distribution with related 95% highest posterior density intervals (HPDI). All analyses were done in R version 4.0.2 and Bayesian modeling was done in Stan 2.21.0. Only results from groups with more than ten cases are presented in the main text. Results from all groups (Figures S1 and S2) as well as explanations of prior distributions used are found in the Appendix S1.

3 | RESULTS

3.1 | Population

The study population was predominantly male (71%) with a smaller proportion of men among intoxications (68%) and controls (83%), and with similar brain weights (intoxications mean 1458 g, SD 143;

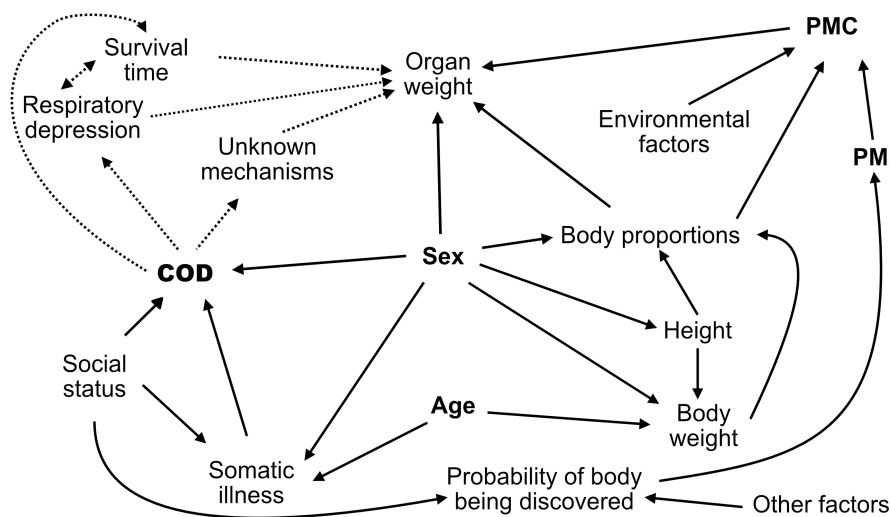


FIGURE 1 A directed acyclic graph (DAG) showing the proposed causal model with arrows representing causal paths between variables. Bolded text represents variables adjusted for, and dashed arrows causal paths from the exposure (cause of death [COD]) to the outcome, organ weight. PMC, post-mortem changes; PMI, post-mortem interval.

controls mean 1497g, SD 139). The intoxication group was overall younger (median 37years, SD 17) than controls (median 43years, SD 19) and had overall heavier lungs (mean combined lung weight 1394g, SD 326 versus mean 1270g, SD 269). Opioids constituted the most common intoxicant group ($N = 336$), distantly trailed by "other sedatives" ($N = 33$), Z-drugs and benzodiazepines ($N = 31$) (Figure 1).

3.2 | Model

Overall, intoxication cases had heavier lungs than controls when accounting for age and sex (Figure 2). The largest difference observed was in the opioid intoxication group where the mean effect was around +0.47 SD, varying between oxycodone at the smallest (+0.33 SD) and heroin at the largest (+0.61 SD). The posterior distributions of most intoxicant groups overlapped with the opioid group to a varying extent.

Overall, all intoxication cases had lower brain weight than controls, but notably, there was a clear overlap between opioid and non-opioid substances (Figure 3). It was highly probable that differences in mean brain weights between opioids and any other intoxicants were inside the ROPE (Table 1).

4 | DISCUSSION

Our findings show that many non-opioid substances are associated with increased lung weight, in line with some previous research [3, 5, 9]. We also found that it was highly probable that there were no differences in mean brain weight among intoxicant groups, though all were lower than that of controls. This suggests that if higher brain weight is expected in an intoxication death, it is not unique to opioid

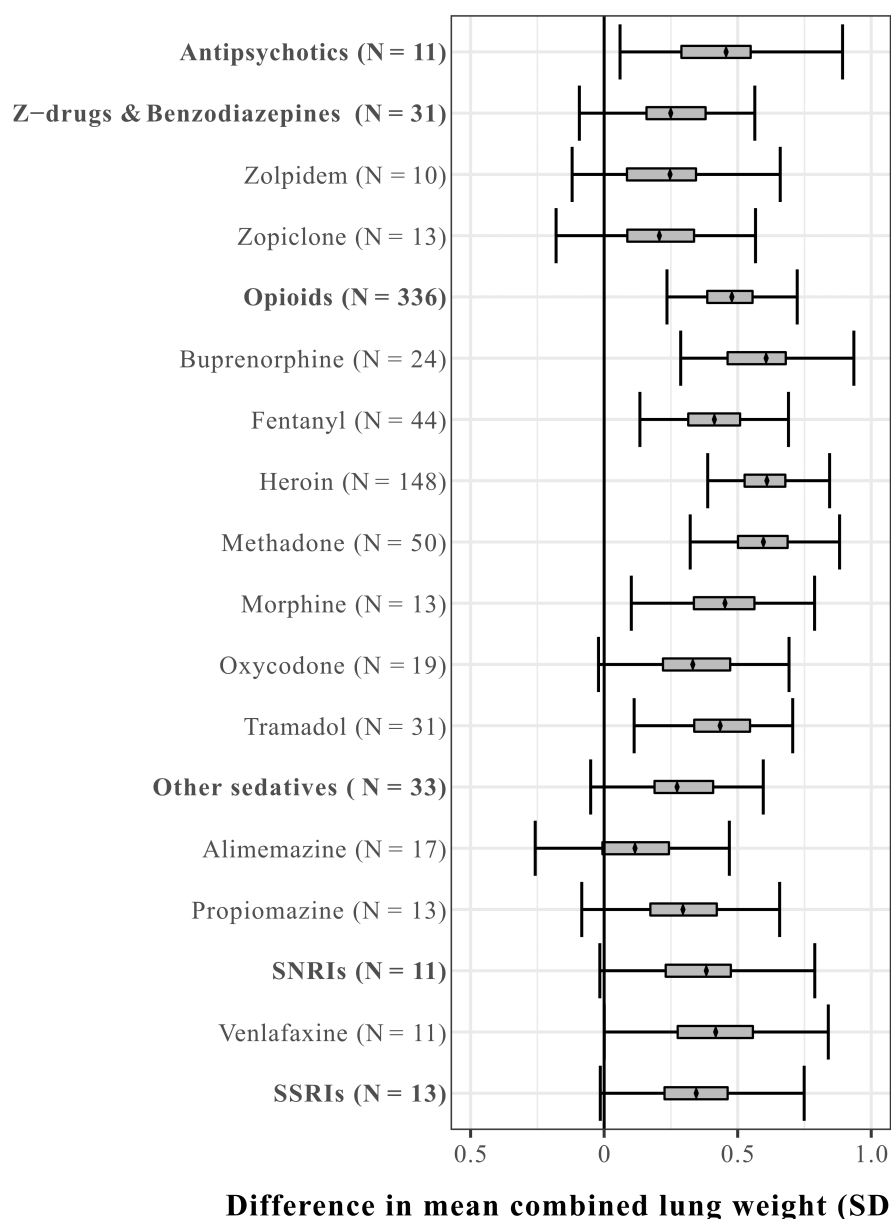
deaths. Furthermore, any increase in brain weight is probably less pronounced than what has been reported in suicidal hanging deaths [10–12].

Opioids had the largest credible difference in lung weight compared to controls (i.e., the largest difference between the lower bound of the HPDI and 0), but the posterior mean values were only slightly larger (Figure 2). In our opinion, this is likely an effect of the opioid group being much larger than any other substance group, meaning that the model was more informed by the data and thus uncertainty was reduced.

Any suitable control group in a study such as this must be both frequent enough to provide a large enough sample and be close to a "true" value of normal. We chose hanging deaths as controls because in our mind these should constitute somewhat close to "normal" medicolegal autopsies. This choice is not without issue as previous studies have indicated that hanging itself might be associated with a higher brain weight [10–12]. There are, however, conflicting results regarding whether this effect actually exists [13]. Even with this issue, we have not been able to come up with a better alternative. It would perhaps be possible to identify suitable cases through careful evaluation and exclusion of cases with confounding factors (e.g., hypovolemia causing lower organ weights in trauma deaths). However, any such approach would be susceptible to selection bias, and determining what is and is not confounding in each case is not a trivial task.

Many of the included intoxicant groups had small sample sizes as most intoxications were mixed, particularly among intoxications including non-opioid substances (Table S1). We addressed this problem by modeling data with nested random effects, partially pooling data across groups where the model deemed it useful. Nonetheless, readers should interpret groups with low numbers of cases with caution as the distributions are largely the result of higher order group effects (e.g., levomepromazine with $N = 1$ is highly informed by the

FIGURE 2 Posterior distributions of the difference in mean combined lung weight between fatal intoxications with a single intoxicant and suicidal hangings, distributions based on less than ten cases are omitted. Bolded text represents substance groups. The bars represent a 95% highest posterior density interval (HPDI), while the grayed area represents a 50% HPDI. The diamond represents the posterior mean.



“other sedatives” group intercept; see Figure S1). We chose to include them even so, as the data do not refute the idea that intoxications with those substances are associated with changes in organ weight.

Our study only had access to the information in the NBFM autopsy database and the study is hence limited to the cause of death as determined by the pathologist. Although this means that there might be some cases where the stated cause of death is only weakly supported by the evidence, the fact that most cases were intoxications with multiple substances (and as such not included) speaks against this. If anything, the study is perhaps too strict and underincludes cases.

As resuscitation attempts might influence postmortem organ weight [3], we only included cases registered as being found dead. This is not without issue as this is a quite blunt method which excludes many cases even though presumably only a minority of them had undergone

cardiopulmonary resuscitation. Nonetheless, a sufficient number of cases were included as to not impact the main thrust of this paper.

The modeled difference in mean lung weight between intoxication deaths and controls was smaller than in previous studies [3, 4]. This might be explained by the fact that those other studies included cases of hypovolemic deaths as controls, thus introducing bias through blood loss. This hypothesis is also supported by the results of Molina et al. [4], who compared opioid deaths to cardiac deaths, and the latter group had lung and brain weights more in line with those observed in the present study.

We accounted for potential confounders (age and sex) when estimating the difference in organ weights, an approach not previously observed in the literature. Lung weight was used as a surrogate for edema - a practice which might cause confounding as it can confound the effects of intoxication with findings such as pneumonia [3], something we could not account for.

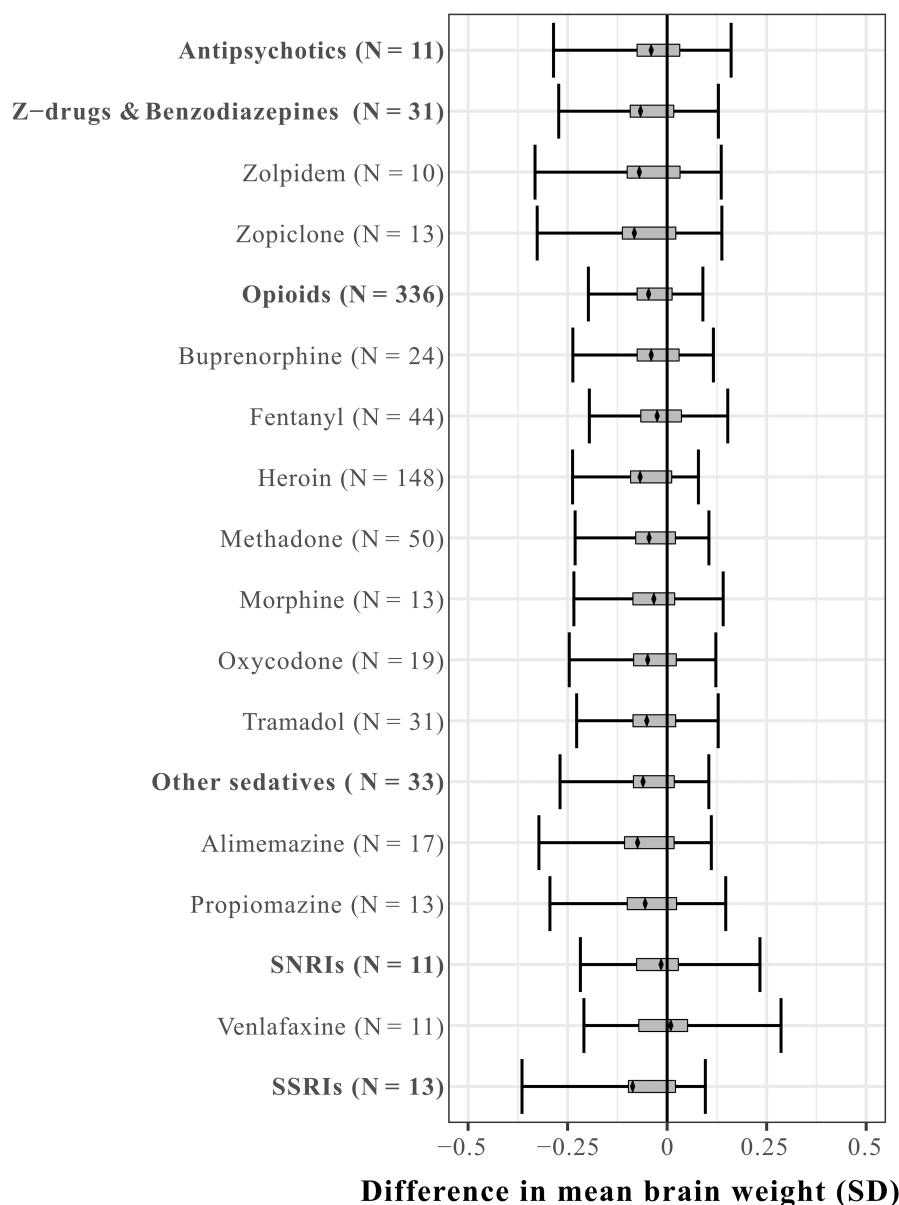


FIGURE 3 Posterior distributions of the difference in mean brain weight between fatal intoxications with a single intoxicant and suicidal hangings, distributions based on less than ten cases are omitted. Bolded text represents substance group. The bars represent a 95% highest posterior density interval (HPDI), while the grayed area represents a 50% HPDI. The diamond represents the posterior mean.

TABLE 1 The probability that difference in mean brain weight between tested substance groups (with at least 10 cases) and opioids is within the region of practical equivalence (ROPE, 0 ± 0.1 standard deviations), i.e., that there is no difference

| Substance group | Probability that value is in ROPE |
|-----------------------------|-----------------------------------|
| Antipsychotics | 79% |
| Z-drugs and benzodiazepines | 82% |
| Other sedatives | 82% |
| SNRIs | 77% |
| SSRIs | 76% |

Abbreviations: SNRI, serotonin norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

We did not set out to calculate the predictive value of these findings in diagnosing fatal intoxications, but the findings do suggest that increased lung weight is a common finding in many types of fatal

intoxications. Readers should note that previous studies on the predictive power of increased lung weight to diagnose fatal intoxication have shown overall poor results [3–5]. This is possibly due to base-rate neglect, i.e., calculating the predictive power in differentiating intoxications from a set number of controls instead from a population in which the test would be used. One previous study attempted to analyze the predictive power in an unselected population [5], but its poor results might have been caused by overinclusion, i.e., including cases where a competing cause of death was present at autopsy, decreasing a prior probability of intoxication.

It seems puzzling that no study has succeeded to calculate useful predictive values of increased lung and brain weight in diagnosing fatal intoxication when these findings anecdotally are reported to work. It is easy to blame the belief in such anecdotes on recall bias, but perhaps the poor results in previous studies were due to the issues with case selection. A study analyzing lung weight and brain weight when accounting for case history and whether there

is a macroscopically present competing cause of death could conceivably be the best approach, as perhaps increased lung and brain weight are most useful diagnostically in cases where there are no competing findings, and the case history is sparse.

5 | CONCLUSIONS

Single substance intoxications were associated with an increased lung weight overall. Strong evidence is presented against the hypothesis that increased lung or brain weight is specific for opioid intoxications. Although the predictive value of these findings remains unclear, our results support the recommendation that unexplained pulmonary edema should prompt a toxicological analysis [1].

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