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Interpreting interaction effects in estimates of the risk of traffic injury associated with the use of illicit drugs

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ABSTRACT

Interactions characterise the relationship between use of amphetamines, cannabis and opiates as a driver and the risk of traffic injury associated with the use of these drugs. Inverse risk curves have been found for these drugs, meaning that the higher the proportion of drivers in normal traffic testing positive for the drugs, the lower is the increase in risk associated with them. The inverse risk curves can arise in many ways. The paper discusses ten different interpretations of the curves; seven of these are methodological and claim that the risk curves are statistical artefacts. Some support for these interpretations is found; however, this does not rule out that substantive interpretations, proposing causal mechanisms underlying the curves may also be correct. Unfortunately, there is insufficient evidence to assess the support for

the substantive interpretations. There is, accordingly, a large element of uncertainty about how the inverse risk curves arise and whether they can be modified.

Key words: illicit drugs; risk of traffic injury; meta-analysis; methodological interpretations; substantive interpretations

1 INTRODUCTION

Many studies have been made to assess the risk of traffic injury associated with the use of illicit drugs. For a few drugs, there are enough studies to synthesise their findings by means of meta-analysis (Elvik 2013, 2015). Evidence from primary studies is then summarised in terms of a single, or a few, summary estimates of the risk of injury associated with using a drug.

One of the problems in trying to synthesise the findings of studies of the risk associated with illicit drugs is that estimates vary enormously. When there is great variation in estimates of risk, it may not be very informative to summarise them in terms of a single weighted mean estimate. In any meta-analysis, it is recommended to perform an exploratory analysis in order to test whether the distribution of estimates in primary studies is "well-behaved", i.e. unimodal, showing a bell-shaped distribution. A graphical tool, the funnel plot, can be employed to test whether the distribution of estimates of risk has this shape. In a funnel plot, estimates of risk are plotted on the abscissa and an indicator of their statistical precision on the ordinate.

Figure 1 presents an example of a funnel plot. It shows estimates of the risk of fatal injury associated with the use of amphetamines. The abscissa shows the natural

logarithm of the estimate of risk (values greater than 0 indicate an increase in risk), the ordinate shows the standard error of each estimate of risk, with the scale inverted so that estimates with small standard errors are plotted on top of the diagram.

Figure 1 about here

The distribution of estimates of risk in a funnel plot should, ideally speaking, resemble a funnel turned upside down (i.e. with the narrow opening on top). The data points shown in Figure 1 are spread all over the place and do not show a distribution resembling a funnel. Five data points to the right in the diagram are trimmed away when the trim-and-fill method is applied to test for the possible presence of publication bias (Duval and Tweedie 2000A, 2000B; Duval 2005). Yet, even when these data points are trimmed away, no clear funnel shape emerges. Many analysts would conclude that the data points in Figure 1 are too widely and unsystematically dispersed for a summary estimate of risk to make sense.

A completely different picture emerges in Figure 2. Figure 2 shows estimates of the risk of fatal injury as a function of the percentage of drivers testing positive for amphetamine in normal traffic. Figure 2 includes 10 of the 13 estimates shown in Figure 1.

Figure 2 about here

A clear negative relationship is found: The higher the percentage of drivers testing positive for amphetamines in roadside surveys intended to represent normal traffic, the lower is the increase in risk associated with the use of amphetamines. Thus, the wide and unsystematic dispersion of estimates of risk in Figure 1 hides a very clear

relationship: the lower the share of drivers testing positive for amphetamine, the higher is their risk.

Similar patterns in the variation of risk have been observed for other illicit drugs, including cannabis and opiates (Elvik 2015). This suggests that the association between the use of an illicit drug and the risk of traffic injury is best summarised by means of a function describing the relationship between the share of drivers testing positive for a drug in normal traffic and the increase in risk associated with use of the drug. Unfortunately, curves like the one shown in Figure 2 can arise in many ways and may fully or partly be the result of statistical artefacts. One cannot propose substantive explanations of a relationship like the one shown in Figure 2 unless methodological interpretations can be ruled out, or at least shown not to contribute much to the observed relationship.

A relationship like the one shown in Figure 2 is referred to as an interaction in epidemiology (Szklo and Nieto 2014). An interaction is found whenever the relationship between a risk factor (here: an illicit drug) and risk (here: risk of traffic injury) depends on a third factor or moderator (here: the share of drivers in normal traffic testing positive for a drug). The objectives of this paper are: (1) to give an overview of possible interpretations of interaction in estimates of the risk of traffic injury associated with the use of illicit drugs and (2) to assess the support for the various interpretations.

2 AN OVERVIEW OF INTERPRETATIONS OF INTERACTION

A total of ten possible interpretations of interaction effects in estimates of the risk of traffic injury associated with the use of illicit drugs have been identified. These are:

1. Differing statistical weights: A curve based on giving all data points equal statistical weights disappears when data points are weighted according to their statistical precision.
2. Unequal variance in exposure estimates: Estimates showing a low percentage of control group drivers testing positive may be more uncertain than estimates showing a high percentage of control group drivers testing positive.
3. Selective reporting: Studies reporting the share of control group drivers testing positive for a drug differ in estimates of risk from those that do not report the share of control group drivers testing positive for a drug.
4. Unequal adjustment for confounding factors: There may be differences in how well estimates of risk adjust for confounding factors; poor control for confounding factors tends to be associated with higher estimates of risk.
5. Different estimators of risk: Odds ratios may overstate relative risks; risk estimates based on culpability studies are (almost) consistently erroneous (see further explanation below).
6. Small sample bias in estimates of odds ratios: This could arise if high estimates of risk are based on smaller samples than low estimates of risk.
7. Publication bias: A curve like the one shown in Figure 2 is only one tail of the distribution of data points and will vanish when adjusted for publication bias.
8. Dose-response curve: Some data points could be points on a dose response curve: higher doses of a drug may be taken more rarely (lower percentage testing positive), but associated with higher risk.

9. Learning curve: When a high share of control group drivers test positive for a drug, there could be more drivers who have used a drug for a long time and developed increased tolerance for it.
10. Selective recruitment of drivers: In societies where few drive under the influence of drugs, those who do so are a more extreme group.

Table 1 explains how each of these points will be evaluated and what findings will be regarded as supporting or contradicting the interpretation.

Table 1 about here

The first seven points represent methodological interpretations, i.e. they all claim that an apparent interaction is an artefact and will disappear once one or more of the seven points have been addressed. The final three points represent substantive interpretations, i.e. they identify causal mechanisms that produce an interaction and show that it is real.

The ten possible interpretations of interaction in estimates of risk will be discussed for three illicit drugs for which there are enough studies to show interaction. These drugs are amphetamines, cannabis and opiates. Patterns of interaction will be discussed separately for fatal injury, non-fatal injury and property-damage-only. Five estimates of risk are regarded as the minimum number needed to detect interaction. Thus, in Figure 2, ten estimates of the risk of fatal injury are plotted for amphetamines. There are four estimates of the risk of non-fatal injury associated with the use of amphetamines, but these will not be discussed further, because they are too few to meaningfully assess the ten possible interpretations of interaction.

3 METHODOLOGICAL INTERPRETATIONS

3.1 Statistical weighting

The curve shown in Figure 2 was fitted by treating all estimates of risk as equally precise. However, the precision of the estimates varies. Will the inverse relationship be reproduced if estimates of risk are assigned statistical weights that are inversely proportional to their sampling variance?

To test the robustness of curves with respect to statistical weighting, six different forms of curves have been fitted: linear, logarithmic, inverse, quadratic, power or exponential. If the curve fitted to weighted estimates is of a different form than the curve fitted to unweighted estimates, it will be concluded that the statistical weights make a difference. Likewise, if the coefficient describing the slope or curvature of a function is statistically significantly different for the simple and weighted estimates, statistical weighting makes a difference.

Curves were fitted using SPSS and for each coefficient a standard error was produced. To test whether two coefficients were different, the difference between them and the standard error of the difference were computed:

Difference = $Coefficient_{simple} - Coefficient_{weighted}$

Standard error (SE) of difference = $\sqrt{SE_{simple}^2 + SE_{weighted}^2}$

As an example, an inverse function best fitted crude estimates of the risk of non-fatal injury associated with the use of cannabis. When data points were weighted statistically, the value of the coefficient changed a little. The difference is 0.029. The standard error of the difference is 0.186. Since the standard error of the difference is

considerably greater than the difference itself, it is concluded that there is no evidence of a real difference. The results of the analyses are presented in Table 2.

Table 2 about here

It is seen that the number of estimates of risk is by far greatest for cannabis. Statistical weighting was found to influence the risk curves in three of the six cases that were tested. For amphetamines, the crude risk curve was best described as a power function; the statistically weighted risk curve was best described as an inverse function. A plot of the functions found that they were located close to each other and had the same shape. With respect to the risk of fatal injury associated with the use of cannabis, a logarithmic function fitted best to the crude estimates of risk. A quadratic function fitted best to the weighted estimates. Since these functions are of different forms, comparing their coefficients does not make sense. The two curves are shown in Figure 3. The quadratic curve is quite flat in the range below 10 percent of control group drivers testing positive for cannabis. The quadratic curve implies a negative estimate of risk when the percentage of control group drivers testing positive for cannabis exceeds 40 percent, but is positive in the range of values represented in the data.

Figure 3 about here

The third case where the crude and weighted curves were found to differ was with respect to the risk of non-fatal injury associated with the use opiates. The curve fitting best to the weighted data points was quadratic; however, it was rejected as it implied negative estimates of risk when the percentage of control group drivers testing positive for opiates was between 5.6 and 7.4. A linear function fitted second

best and was preferred. Figure 4 shows the two curves that were found to best fit estimates of risk.

Figure 4 about here

The two curves are quite different. Although both are consistent with an inverse relationship between the prevalence of opiates in normal traffic and the risk associated with it, the weighted curve is a straight line, whereas the crude curve has a marked curvature.

3.2 Unequal uncertainties in estimates of exposure

Exposure to illicit drugs in normal traffic is generally stated as the proportion of control group drivers testing positive for a drug. Thus, for amphetamines (Figure 2), the proportion of control group drivers testing positive varies between 0.05 percent (0.0005 as a proportion) and 3.3 percent (0.033 as a proportion). Estimates of the proportion of control group drivers testing positive are uncertain. The question is whether some of the estimates are more uncertain than others. If, for example, an estimated proportion of 0.0005 is more uncertain than an estimated proportion of 0.033, the distribution of data points could in principle be different from the one shown in Figure 2, and the curve fitted to the data points might have a different shape.

The uncertainty of estimates is indicated by their standard error. The standard error of a proportion p is:

$$\text{Standard error of a proportion} = \sqrt{\frac{p \cdot (1-p)}{n}}$$

Thus, the standard error of the smallest of the proportions of control group drivers testing positive for amphetamines is:

$$\text{Standard error} = \sqrt{\frac{0.0005 \cdot (1-0.0005)}{21917}} = 0.00015$$

In general, the standard error of a proportion, at a given sample size (n) is smallest when the proportion is close to zero, and greatest when it is 0.5. The standard errors of the proportions of control group drivers testing positive for amphetamines are small. Figure 5 shows the relationship between the proportions and their standard errors.

Figure 5 about here

With one exception, the standard errors all have a smaller value than the estimated proportion. For one estimate, the standard error is 1.42 times the estimate. There is a probability of 5 percent that this estimate, 0.0012, could be as high as 0.0046. However, even if the true location of the data point would be at a proportion of 0.0046, this would by itself not alter the shape of the curve shown in Figure 2.

As far as cannabis is concerned, a similar pattern was found. On the average, standard errors were much smaller than estimated proportions. Only two standard errors (out of 63) were larger than 50 percent of the estimate, suggesting that these estimates were not significantly different from zero. These two estimates are, however, too few to alter the shape of the risk curves relating risk to the proportion of control group drivers testing positive for cannabis.

Findings for opiates were more complex. There were seven estimates of the risk of fatal injury for which the proportion of control group drivers testing positive for

opiates was known. One estimate of the proportion of control group drivers testing positive had a considerably greater standard error than the other six. This estimate indicated that only 0.25 percent of control group drivers tested positive and that the odds of fatal injury was 9.6. Given the standard error, and assuming that the proportion cannot be negative, the lower 95 percent confidence limit for this estimate is 0.01 percent and the upper 95 percent confidence limit is 0.73 percent. When the lower limit was assumed, the best fitting risk curve was an inverse function, which fitted the data much better than when the original value of 0.25 percent was used. When the upper limit value was assumed, the risk curve changed completely and a power function with a positive exponent best fitted the data points. Thus, the large uncertainty in the estimate of the proportion of control group drivers testing positive for opiates had a decisive influence on the shape of the risk curve relating the risk of fatal injury to the proportion of control group drivers testing positive for opiates. One should therefore regard the risk curve as highly uncertain and perhaps artefactual.

There were eight estimates of the risk of non-fatal injury for which the percentage of control group drivers testing positive for opiates was known. Three of these estimates had large standard errors. By inserting the lower or upper 95 percent confidence limits of these estimates, the risk curve was re-estimated. The shape of the curve was found to be robust with respect to the three uncertain data points. A quadratic function fitted best in all cases, but it was mostly illogical by implying negative estimates of risk. A linear function was second best.

3.3 Selective reporting

In Figure 1, thirteen estimates of the risk of fatal injury associated with the use of amphetamines were shown. In Figure 2, the risk curve was fitted to only ten estimates of risk. Three estimates did not report the percentage of control group drivers testing positive for amphetamines and could therefore not be included. Even among cases, reporting of drug use is incomplete and variable, see for example the survey of drug involvement in fatally injured drivers reported by the National Highway Traffic Administration (US Department of Transportation 2010). Is it possible that these three data points could alter the risk curve shown in Figure 2 (whose shape was confirmed when data points were weighted)?

To try to answer this question, a procedure that may be called "worst case imputation" has been used. Worst case imputation means that the estimates of risk not stating the percentage of control group drivers testing positive for amphetamines were added to those stating this percentage in the way that would be most inconsistent with the distribution of the estimates stating the percentage of control group drivers who tested positive for amphetamines.

The three estimates not stating the percentage of control group drivers testing positive for amphetamines estimated the odds ratio for fatal injury as 20.9, 2.7 and 2.3. Based on the data points stating the percentage of control group drivers testing positive for amphetamines, one would expect the first of these estimates to be located in the left part of the diagram, in which the percentage of control group drivers testing positive is low. The other two estimates would be expected to be located further to the right in the diagram. The assumption was therefore made that,

unlike most other data points, for the three data points that did not report the percentage of control group drivers testing positive for amphetamines, there was a positive relationship between risk and the percentage of control group drivers testing positive.

The three highest values found in the data set for the percentage of control group drivers testing positive for amphetamines were 3.30, 3.11 and 0.78. The three estimates of risk were therefore imputed as (20.9; 3.30), (2.7; 3.11), and (2.3; 0.78). These data points are marked by red squares in Figure 6.

Figure 6 about here

One may obviously not rule out that the estimates not reporting the percentage of control group drivers testing positive for amphetamines could have reported higher percentages than any found in the studies reporting the percentage of control group drivers testing positive for amphetamines. The data points should then have been imputed even further to the right in the diagram, but it was judged as too arbitrary to do so. The three percentages at which the estimates were imputed were at least found in the data set.

With the three imputed estimates added to the data set, the curve fitting routine was run again. An inverse function was found to best fit the data points, reproducing the result based on the ten original data points. Based on this, selective reporting was judged to be unlikely to have an influence on the risk curve for fatal injury associated with the use of amphetamines.

Four data points were imputed for studies of the risk of fatal injury associated with the use of cannabis. When these data points were added, the relationship between the

percentage of control group drivers testing positive for cannabis and the risk of fatal injury vanished completely. With respect to the risk of fatal injury associated with the use of cannabis, one therefore cannot rule out bias due to the fact that not all studies reported the percentage of control group drivers testing positive for cannabis. No missing data points were imputed for studies of the risk of non-fatal injury associated with the use of cannabis. Five data points were imputed for studies of the risk of property-damage-only accidents. A quadratic curve was found to best fit the imputed data set, indicating a high risk when a low percentage of control group drivers test positive for cannabis as well as when a high percentage of control group drivers test positive for cannabis. It is difficult to make sense of this relationship, but it had the same form as the relationship fitted to the original data set.

There were seven estimates of the risk of fatal injury associated with the use of opiates that reported the percentage of control group drivers testing positive for opiates; three estimates did not report the percentage of control group drivers testing positive. When these estimates were imputed, a power function best fitted as a risk curve. This function was rising as the percentage of control group drivers testing positive for opiates increased. This risk curve had the opposite sign of the risk curve fitted to the original data points, which indicated a declining risk as the percentage of control group drivers testing positive for opiates increased. It therefore cannot be ruled out that the negative relationship was attributable to the fact that not all studies reported the percentage of control group drivers testing positive for opiates.

Eight estimates of the risk of non-fatal injury associated with the use of opiates stated the percentage of control group drivers testing positive for opiates; twelve

estimates of risk did not state this percentage. Eight data points were imputed using the worst-case rule. The original relationship then vanished completely, showing that it cannot be ruled out that the negative relationship found between the percentage of control group drivers testing positive for opiates and the risk of non-fatal injury associated with the use of opiates, was attributable to the fact that many studies do not report the percentage of control group drivers testing positive for opiates.

3.4 Unequal adjustment for potential confounding factors

It is well known that the results of studies evaluating a certain risk factor are often greatly influenced by how well the study controls for other risk factors (Elvik 2011). Risk factors tend to be correlated. A study that examines only the simple bivariate relationship between a risk factor and the level of risk is therefore likely to overestimate the contribution of the risk factor. Numerous studies have found that when potentially confounding factors are controlled for, estimates of risk are usually adjusted downwards. Table 3 gives some examples of this.

Table 3 about here

The examples given in Table 3 all show that adjusted estimates of risk are lower than crude estimates, often by 40-50 percent. One can find examples of the opposite tendency, but they are far fewer than the examples of studies finding that adjusting for potentially confounding factors reduces estimates of risk. In principle, therefore, the risk curves found for illicit drugs could be the result of unequal adjustment for confounding factors. In particular, the highest estimates of risk might be the least well-controlled.

To test whether this is the case, estimates of risk were sorted according to the number of confounding factors controlled for in estimation. For amphetamines, for example, estimates of the risk of fatal injury were available that had controlled for 0, 1, 2, 4 or 6 confounding factors. The weighted (fixed-effects model) mean estimate of risk for each number of confounding factors controlled for was estimated. Curves were then fitted to the data points in order to assess whether there was a relationship between how well studies controlled for confounding factors and estimates of risk.

Estimates of the risk of fatal injury associated with the use of amphetamines were weakly positively related to the number of confounding factors controlled for, i.e. estimates of risk tended to be higher the more confounding factors studies controlled for. However, the best fitting curve, an exponential function, explained only 23.4 percent of the variance and there were only five data points.

For cannabis, estimates of the risk of fatal injury were found to depend weakly on the number of confounding factors controlled for. The summary estimate of risk was reduced from 1.82 when 0 confounding factors were controlled for to 1.21 when 6 confounding factors were controlled for, and increased to 1.29 when 8 confounding factors were controlled for. The summary estimate of the risk of non-fatal injury declined monotonically from 1.86 when 0 confounding factors were controlled for to 1.24 when 11 confounding factors were controlled for. For property-damage-only accidents a quadratic relationship was again found, with the summary estimate of risk first declining as more confounding factors were controlled for, then increasing again, but not to the same level as when no confounding factors were controlled for. These results suggest that there is a tendency for summary estimates of risk to

become lower as more confounding factors are controlled for. The data underlying the estimated relationships are, however, very noisy and the results are not sufficiently clear to undermine the negative relationship between the share of control group drivers testing positive for cannabis and the risk associated with the use of cannabis.

There were few estimates of risk for opiates, but an attempt was nevertheless made to determine if there was a relationship between how well studies controlled for confounding factors and estimates of risk. A quadratic relationship was found between the number of confounding factors controlled for and estimates of the risk of fatal injury. The relationship was nonsensical, as it predicted negative estimates of risk when seven or more confounding factors were controlled for. Other functions fitted to the data (linear and exponential) indicated no relationship between the number of confounding factors controlled for and the estimate of risk. For non-fatal injury, a very clear negative relationship was found between the number of confounding factors controlled for and estimates of risk. Thus, the crude risk curve, showing a negative relationship between the percentage of control group drivers testing positive for opiates and the increase in risk associated with the use of opiates, would vanish completely if all studies had controlled as well for confounding factors as the best studies did.

3.5 Choice of estimator of risk

By far the two most common estimators of risk used in studies of the risk associated with the use of drugs is the odds ratio based on case-control studies, and the odds

ratio based on culpability studies. A few registry-based studies use standardised incidence ratio, which is the incidence of accidents in a population of users of a drug (often prescribed) divided by the incidence of accidents in a control population, adjusted for age and gender and possibly other confounding factors.

Røgeberg and Elvik (2016) point out that the odds ratio based on culpability studies, as estimated in virtually all studies relying on this approach, does not show the odds ratio of accident involvement, but rather the odds ratio of being culpable in an accident. The difference between the two can be shown as follows:

$$\text{Odds ratio of being culpable} = \frac{\left(\frac{culp_+}{culp_-}\right)}{\left(\frac{nonculp_+}{nonculp_-}\right)}$$

Culpable drivers are those who are held guilty or responsible for an accident, nonculpable drivers are those who are innocently involved in accidents and who are generally assumed to be representative of normal traffic. Subscript + denotes testing positive for a drug, subscript – denotes testing negative for a drug. Culpability studies in general estimate the odds ratio of being culpable. However, the odds ratio of becoming involved in an accident is:

$$\text{Odds ratio of accident involvement} = \frac{\left(\frac{culp_+ + nonculp_+}{culp_- + nonculp_-}\right)}{\left(\frac{nonculp_+}{nonculp_-}\right)}$$

As can be seen, the odds ratio of accident involvement will be lower than the odds ratio of being culpable, since accident involvement includes involvement both as the culpable driver and as the nonculpable driver. How large the difference between the two estimators is depends on the share of accidents involving nonculpable drivers.

As an example, consider data presented by Terhune (1992) concerning culpability and use of drugs. Thus, for amphetamines: Culpable and positive: 10; Nonculpable and positive: 2; Culpable and negative: 541; Nonculpable and negative: 258. The odds of being culpable (the usual estimator in culpability studies) is: (10/541)/(2/258) = 2.38. The odds of accident involvement is: (12/799)/(2/258) = 1.94.

To the extent that the highest estimates of risk are based on culpability studies, they may be inflated and therefore to some extent explain the negative relationship between the percentage of control group drivers testing positive for a drug and the risk associated with the drug. For amphetamines, all the highest estimates of risk were based on case-control studies, not culpability studies. One can therefore rule out that the inverse risk curve was generated by inflated estimates of risk based on culpability studies.

A majority (20 out of 27) of the estimates of the risk of fatal injury associated with the use of cannabis were based on culpability studies. Risk curves fitted to estimates based on culpability studies and estimates based on case-control studies were similar, suggesting that the risk curve is unlikely to be an artefact of inflated estimates of risk in culpability studies. For non-fatal injury and property-damage-only, too few estimates of the risk associated with the use of cannabis were based on culpability studies to make a comparison with case-control studies meaningful.

Four of seven estimates of the risk of fatal injury associated with the use of opiates were based on culpability studies. However, these four estimates were the lowest and could therefore not have generated the negative relationship between the percentage

of control group drivers testing positive for opiates and the risk of fatal injury associated with the use of opiates. No estimate of the risk of non-fatal injury associated with the use of opiates was based on a culpability study.

3.6 Small sample bias in estimates of odds ratios

When the odds ratio of injury associated with the use of a drug is estimated by means of a maximum-likelihood logistic regression model, it will have an upward bias in small samples (Greenland 2000, Nemes et al. 2009). The size of the bias can be substantial. This is a potential source of error if the highest estimates of risk underlying the risk curves were based on logistic regression models fitted to small samples. The analysis in this paper does not aim to correct any bias, merely assess whether it is a potential source of error in the risk curves.

To probe whether small sample bias in logistic regression models could be a source of error in the estimated risk curves, the statistical weights assigned to studies using logistic regression were compared to the statistical weights of studies not using logistic regression. Fixed-effects statistical weights indicate sample size. If the highest estimates of risk, associated with a low percentage of control group drivers testing positive for a drug, are based on logistic regression models developed in small samples (small statistical weights), the resulting risk curves could be partly artefactual.

For each study, it was noted whether statistical analysis was based on logistic regression. It was found that logistic regression models are very widely used to estimate odds ratios that control for various confounding factors. For amphetamines, three of the high estimates of the risk of fatal injury were based on logistic

regression. However, when these were removed, the remaining estimates still indicated an inverse risk curve, i.e. a curve showing the lowest risk for the highest percentage of control group drivers testing positive for amphetamines. Such a risk curve would emerge even if the estimates based on logistic regression were retained, but arbitrarily divided by 2 to adjust for a potential bias.

A similar assessment was made for studies of the risk associated with cannabis. For fatal injury, a negative risk curve remained both when four high estimates of risk based on logistic regression were deleted and when the estimates of risk were divided by two. Biased estimates of risk do therefore not seem to explain the negative risk curve with respect to fatal injury. With respect to non-fatal injury, the inverse risk curve disappeared when five high estimates of risk based on logistic regression were removed, but re-appeared when these estimates were included but divided by two. This result is somewhat ambiguous, but suggests that it cannot be ruled out that the risk curve for non-fatal injury is to some extent influenced by biased estimates of risk based on logistic regression. As far as property damage is concerned, removing potentially biased estimates of risk did not change the relationship to the percentage of control group drivers testing positive for cannabis, which remained quadratic.

For opiates, there were no high estimates if the risk of fatal injury based on logistic regression. There were two high estimates of the risk of non-fatal injury based on logistic regression; however, removing these or dividing them by two did not change the inverse risk curve.

3.7 Publication bias

To assess the possible presence of publication bias, the trim-and-fill technique was applied (Duval and Tweedie 2000A, 2000B, Duval 2005). As already noted, five data points were trimmed away in studies of the risk of fatal injury associated with amphetamines. For four of these data points, the percentage of control group drivers testing positive for amphetamines was reported. When these four data points were filled in, to represent non-published results, an inverse risk curve was still found. Thus, publication bias does not explain the inverse risk curve for the risk of fatal injury associated with amphetamines.

For cannabis, an analysis adding two missing data points for fatal injury reproduced a quadratic function, suggesting that publication bias did not influence the form of the relationship between the percentage of control group drivers testing positive for cannabis and the risk of fatal injury associated with the use of cannabis. The risk curve for non-fatal injury associated with the use of cannabis, adjusted for publication bias, was an inverse function. This is the same functional form as found without adjusting for publication bias. The risk of property-damage-only, adjusted for publication bias, was a quadratic function of the percentage of control group drivers testing positive for cannabis. This functional form was the same as found without adjusting for publication bias. On the whole, publication bias does not appear to influence the risk curves for cannabis very much.

The risk of fatal injury associated with opiates, adjusted for publication bias, was best described as an exponential function of the share of control group drivers testing positive for opiates. Estimated risk was increasing as a function of the percentage of control group drivers testing positive for opiates. This risk curve was very unlike the

inverse function found when publication bias was not considered. It may therefore not be ruled out that the inverse function originally found can be influenced by publication bias. The risk of non-fatal injury associated with the use of opiates, adjusted for publication bias, was best described as a quadratic function of the percentage of control group drivers testing positive for opiates. This function was not the same as found without considering publication bias, again suggesting that it may have influenced the risk curve found initially.

4 SUBSTANTIVE INTERPRETATIONS

4.1 Dose-response curve

An inverse function relating the risk of injury associated with a drug to the frequency of use of drug in normal traffic can, at least in part be a dose-response curve. It could, for example, be the case that low doses, associated with small increases in risk, are taken frequently and higher doses, associated with larger increases in risk, are taken more rarely. If the percentage of control group drivers testing positive for a drug indicates the frequency of use, an inverse risk curve could be a dose-response curve.

Unfortunately, few studies of the risk associated with illicit drugs have tried to estimate a dose-response relationship. For amphetamines and opiates, no study has been found reporting a dose-response relationship between the dose taken of the drug and the increase in accident risk. For cannabis, a few studies have compared risks associated with different doses of the drug. Based on these studies, an attempt has been made to test whether an inverse risk curve for cannabis can arise as a result

of a dose-response relationship. Since the dose taken was not coded the same way in all studies, it was categorised as low, medium and high.

In the study by Mann et al. (2007), use of cannabis at least once during lifetime was coded as "low", and use within the last hour as "high". In the study by Fergusson et al. (2008), self-reported cases of driving under the influence of cannabis 1-10 times per year was coded as "low", 11-20 times per year as "medium" and 21 times or more per year coded as "high". In the study by Pulido et al. (2010) weekly use of cannabis was rated as "low", use 1-4 times per week as "medium" and use more than 4 times per week as "high". Gadegbeku et al. (2011) specified the concentration of tetra-hydro-cannabinol (THC) in blood as 1-3 ng/ml ("low"), 3-5 ng/ml ("medium") or ≥ 5 ng/ml ("high"). A similar scale was used by Poulsen et al. (2014), with intervals given as < 2 ng/ml ("low"), 2-5 ng/ml ("medium") or > 5 ng/ml ("high"). Using these codes, the curves shown in Figure 7 emerge.

Figure 7 about here

There were five estimates of risk at a high dose, four at a medium dose and five at a low dose. At high or medium doses, risk is found to decrease as the percentage of control group drivers testing positive for cannabis increases. At low doses, no such tendency can be found. When all data points are considered as a whole, there is a clear negative relationship between the percentage of control group drivers testing positive for cannabis and the risk associated with the use of cannabis. Hence, an inverse risk curve may, at least to some extent, be the result of a dose-response relationship.

4.2 Learning curve

An inverse risk curve could be a learning curve, if those who are located to the left are inexperienced and do not tolerate a drug very well, whereas those to the right have a long history of using a drug, tolerate it well and therefore are less at risk when taking the drug than less experienced users. To evaluate this hypothesis, one needs to know whether high-risk users of a drug are novice users of it and low-risk users of a drug are seasoned users of it.

Unfortunately, data of this kind are completely absent from studies of the risk associated with drug use. These studies are almost exclusively case-control studies or culpability studies. Both these study designs are cross-sectional, i.e. they compare different individuals at a given point in time and do not follow the same individuals over time. Thus, if a group is identified in a case-control study as having a particularly high risk, it will consist of different individuals than a group identified in the same case-control study as having low risk. Even if drug use history was known for both groups, one cannot know whether the difference in risk was caused by differences in drug use history or another factor, since it is impossible to control for all factors that may explain differences in risk. Indeed, most case-control studies control for just a few confounding factors and are quite likely to be influenced by omitted variable bias.

A few studies provide data and/or analyses that may shed a little light on the learning curve hypothesis. Fergusson et al. (2001) estimated a negative coefficient for cannabis use in logistic regression, suggesting that an increase in use was associated with a lower accident risk. The coefficient was not statistically significant. Gerberich

et al. (2003) found that males who reported using cannabis more than five years had lower accident risk than those who reported using cannabis less than five years. Among females, the opposite was found: the longer the use of cannabis, the higher the accident risk. Use of cannabis more than once per week among males was associated with lower risk than use of cannabis less than once per week. Again, however, the pattern was the opposite among females.

Engeland et al. (2007) found a weak tendency for risk to be reduced after 14 days of using opioids prescribed as a painkiller, compared to the risk associated with 7 days of usage. Gibson et al. (2009) also found that prolonged use of opioids was associated with lower risk. Majdzadeh et al. (2009) found an increase in risk during the first few hours after consumption of opioids, then a decline. The study covered six hours after consumption. Romano et al. (2014) found a negative coefficient for use of cannabis in logistic regression, reproducing the finding of Fergusson et al. (2001).

The results of these studies give, at best, a weak indication that long-term use of a drug may be associated with lower risk. The findings are, however, too few to support a claim that the negative risk curves can be explained in terms of habituation and increased tolerance of drugs.

4.3 Selective driver recruitment

The final hypotheses about how a negative risk curve can arise is that the high-risk end of the curve is associated with a selective recruitment of drivers; that the high risk found is the result not only, or perhaps primarily, of drug use, but of behaviour

which is socially deviant in many respects. Few, if any, studies present data or analyses that shed light on this hypothesis. Some studies, for example Gjerde et al. (2011, 2013), contain tables showing characteristics of cases and controls, like age, gender, place of residence etc. These are easily observable characteristics, and there are usually no dramatic differences between cases and controls with respect to these characteristics.

Gjerde et al. (2011) note that "the use of illegal drugs, the abuse of psychoactive medicinal drugs, binge drinking of alcohol can all be related to risk taking behaviour, and subsequently careless or aggressive driving. This may have been a significant confounding factor that cannot be adjusted for in the calculations." Indeed, a report prepared by the Traffic Police in Norway (Pasnin et al. 2009) found that a large share of drivers who were involved in fatal accidents had a criminal record. The criminal record included all types of offences – violence, burglary, rape, etc. – and not just traffic offences. Thus, in a society like Norway, where using drugs is still an offence and widely disapproved of by most people, those who take drugs and drive are a very atypical group.

It requires extensive data collection to be able to statistically control for various forms of social deviancy. It is fair to say that none of the studies included in this paper have controlled very well for driver characteristics. It is, to be sure, not easy. In particular, when the groups of interest are so small as they probably are in Norway, one simply does not have statistical power to estimate the effects of more than a few driver characteristics, which, to make things even more difficult, are highly correlated.

It is therefore to a large extent unknown whether unmeasured driver characteristics may explain the high risk found when few drivers in normal traffic test positive for a drug.

5 DISCUSSION

An analyst preparing for meta-analysis will often develop funnel plots and examine them critically. Were one to do so for studies of the risk associated with the use of amphetamines, cannabis and opiates, the most logical conclusion would be not to perform a meta-analysis, because the estimates of risk are too widely and unsystematically dispersed for a weighted mean estimate of risk to make sense. Funnel plots, however, are not a perfectly reliable screening device to help decide whether to proceed with a meta-analysis or abstain from it. An untidy funnel plot may hide a very systematic pattern in results. For the drugs included in this paper, inverse risk curves were found to describe reasonably well the relationship between use of a drug and the risk associated with it. All these risk curves indicated that the less widespread the use of a drug is in normal traffic, the higher is the risk of traffic injury associated with it. Thus, rather than summarising the results of studies in terms of a single point estimate of risk, it would seem more informative to summarise the studies in terms of risk curves.

However, summarising knowledge by means of curves makes sense only if the curves can be given a meaningful interpretation. While a risk curve may be a statistically more precise way of summarising knowledge than a single mean estimate of risk, the question that immediately comes to mind is how the risk curve arises. Unfortunately,

the inverse risk curves found for the illicit drugs discussed in this paper can arise in many ways. Ten interpretations were proposed; seven of them suggest that the curves are statistical artefacts. Should these interpretations be supported, it would in a sense create a knowledge vacuum: We found these curves, but we have no idea about how they arise and we are not even sure they are real.

There are, to be sure, substantive interpretations of the curves, pointing out causal mechanisms that may produce them. In general, the review of studies in this paper found that most papers do not report the information needed to assess support for the substantive interpretations. These interpretations therefore remain speculative, although they all seem plausible. But plausibility cannot replace hard evidence. Table 4 summarises the assessment of the various interpretations of the risk curves.

Table 4 about here

It is seen, that in the majority of cases, more than one interpretation is supported. Although there is some support for the methodological interpretations, this of course does not rule out that the substantive interpretations can be correct. The risk curves therefore show that there is deep uncertainty about the relationship between the use of illicit drugs and the risk of traffic injury. One cannot rely on the risk curves to predict the impact of policies designed to discourage the use of drugs when driving. Suppose, for example, that by means of targeted enforcement, one could reduce the share of drivers using a drug from 6 % to 3 %. Would the number of accidents be reduced correspondingly? Perhaps not. Perhaps the remaining 3 % of drivers would represent a higher risk than the original 6 %. But, then again, the remaining 3 % were included in the original 6 %, so perhaps there would be a net reduction of accidents

after all. It would, however, most likely not be a linear function of the percentage of drivers taking the drugs. It is pure fantasy to try to use the risk curves to predict the impacts of any policy intervention.

6 CONCLUSIONS

The following main conclusions can be drawn from the study presented in this paper:

1. A negative risk curve has been found for amphetamines, cannabis and opiates, meaning that the higher the proportion of drivers in roadside surveys testing positive for these drugs, the lower is the estimated risk of traffic injury associated with them.
2. Negative risk curves can arise in many ways. Ten sources of such curves are identified.
3. In general, it cannot be ruled out that the negative risk curves found for illicit drugs are statistical artefacts.
4. There is insufficient evidence to assess the support for a substantive interpretation of the risk curves.

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Summary of support for interpretations of interaction in estimates of the risk of traffic injury associated with the use of drugs

Figure 1:

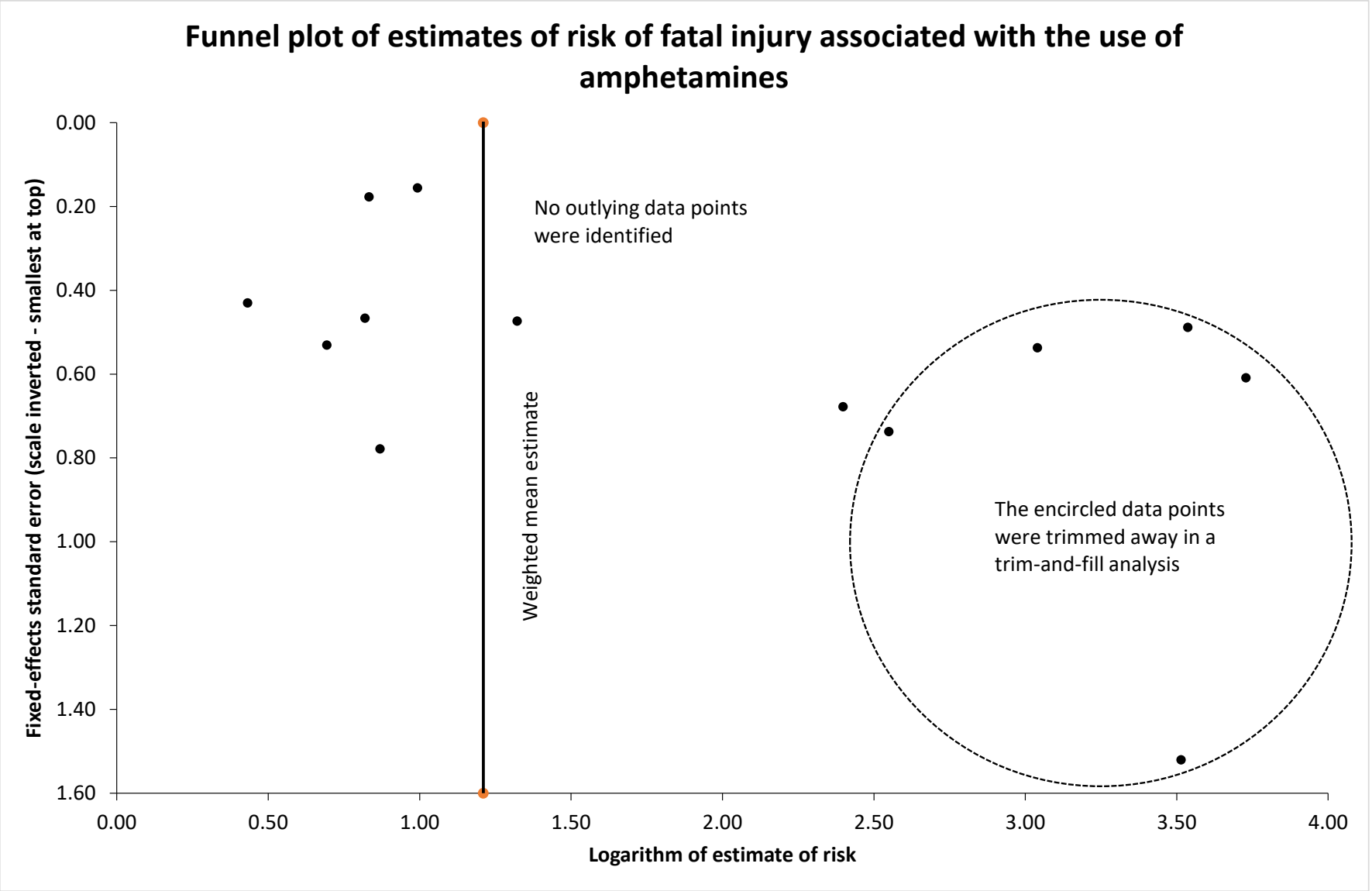
Funnel plot of estimates of risk of fatal injury associated with the use of amphetamines
Fixed-effects standard error (scale inverted - smallest at top)
0.00
0.20
0.40
0.60
0.80
1.00
1.20
1.40
1.60
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
Logarithm of estimate of risk
No outlying data points were identified
Weighted mean estimate
The encircled data points were trimmed away in a trim-and-fill analysis

Figure 2:

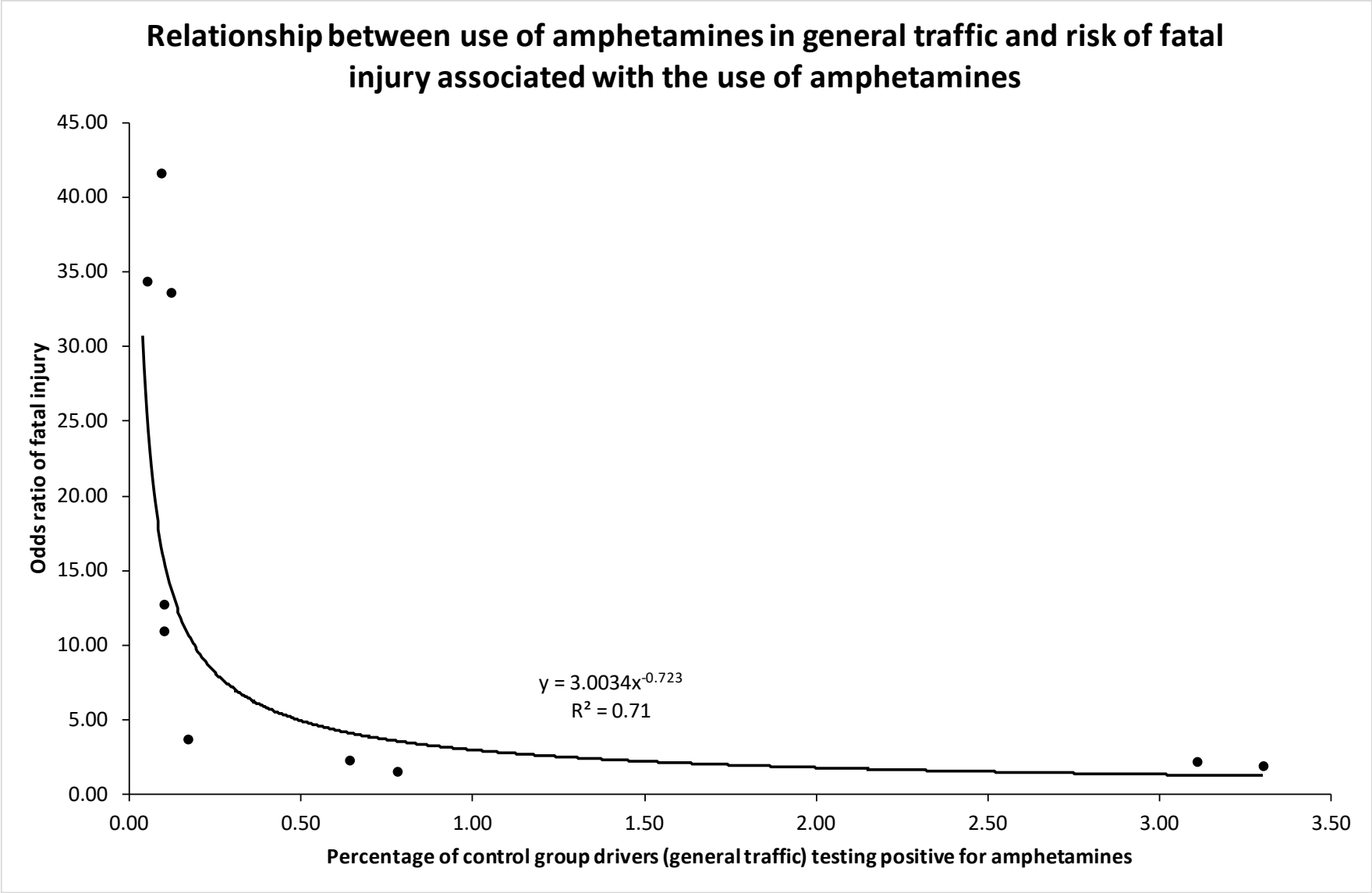
Relationship between use of amphetamines in general traffic and risk of fatal injury associated with the use of amphetamines
Odds ratio of fatal injury
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
y = 3.0034x-0.723
R² = 0.71
Percentage of control group drivers (general traffic) testing positive for amphetamines

Figure 3:

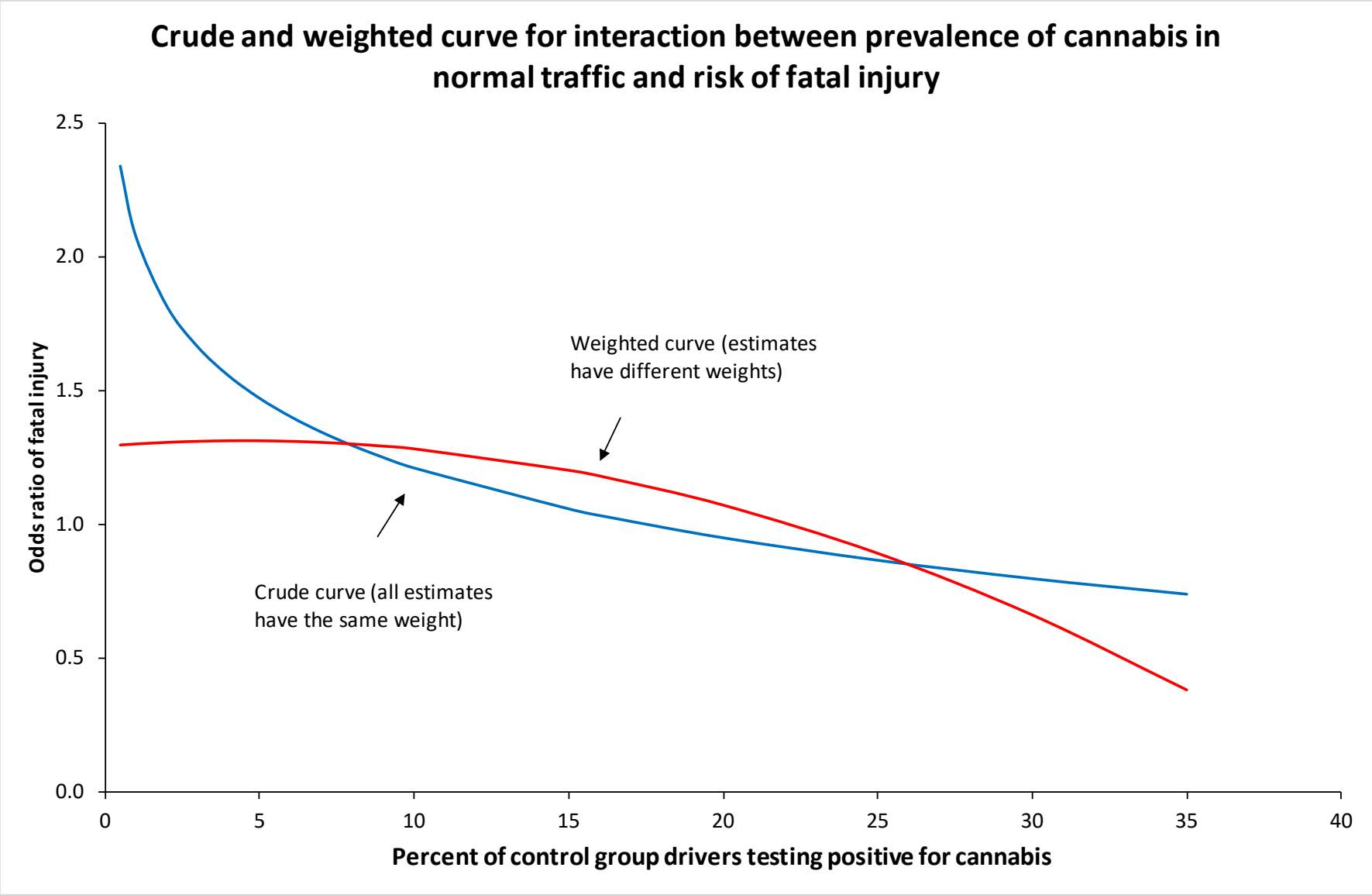
Crude and weighted curve for interaction between prevalence of cannabis in normal traffic and risk of fatal injury
Odds ratio of fatal injury
2.5
2.0
1.5
1.0
0.5
0.0
0
5
10
15
20
25
30
35
40
Weighted curve (estimates have different weights)
Crude curve (all estimates have the same weight)
Percent of control group drivers testing positive for cannabis

Figure 4:

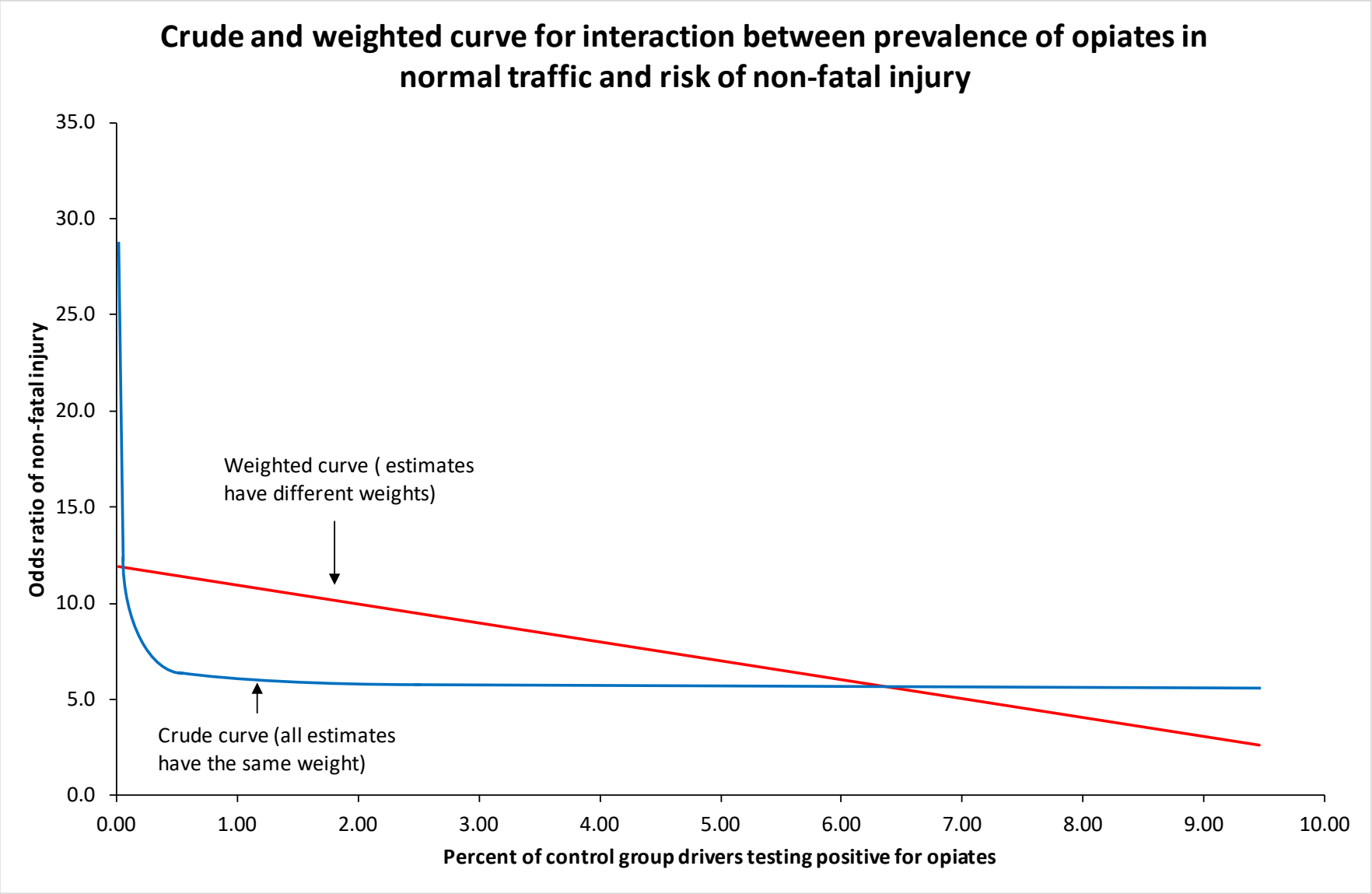
Crude and weighted curve for interaction between prevalence of opiates in normal traffic and risk of non-fatal injury
Odds ratio of non-fatal injury
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Weighted curve (estimates have different weights)
Crude curve (all estimates have the same weight)
0.00
1.00
2.00
3.00
4.00
5.00
6.00
7.00
8.00
9.00
10.00
Percent of control group drivers testing positive for opiates

Figure 5:

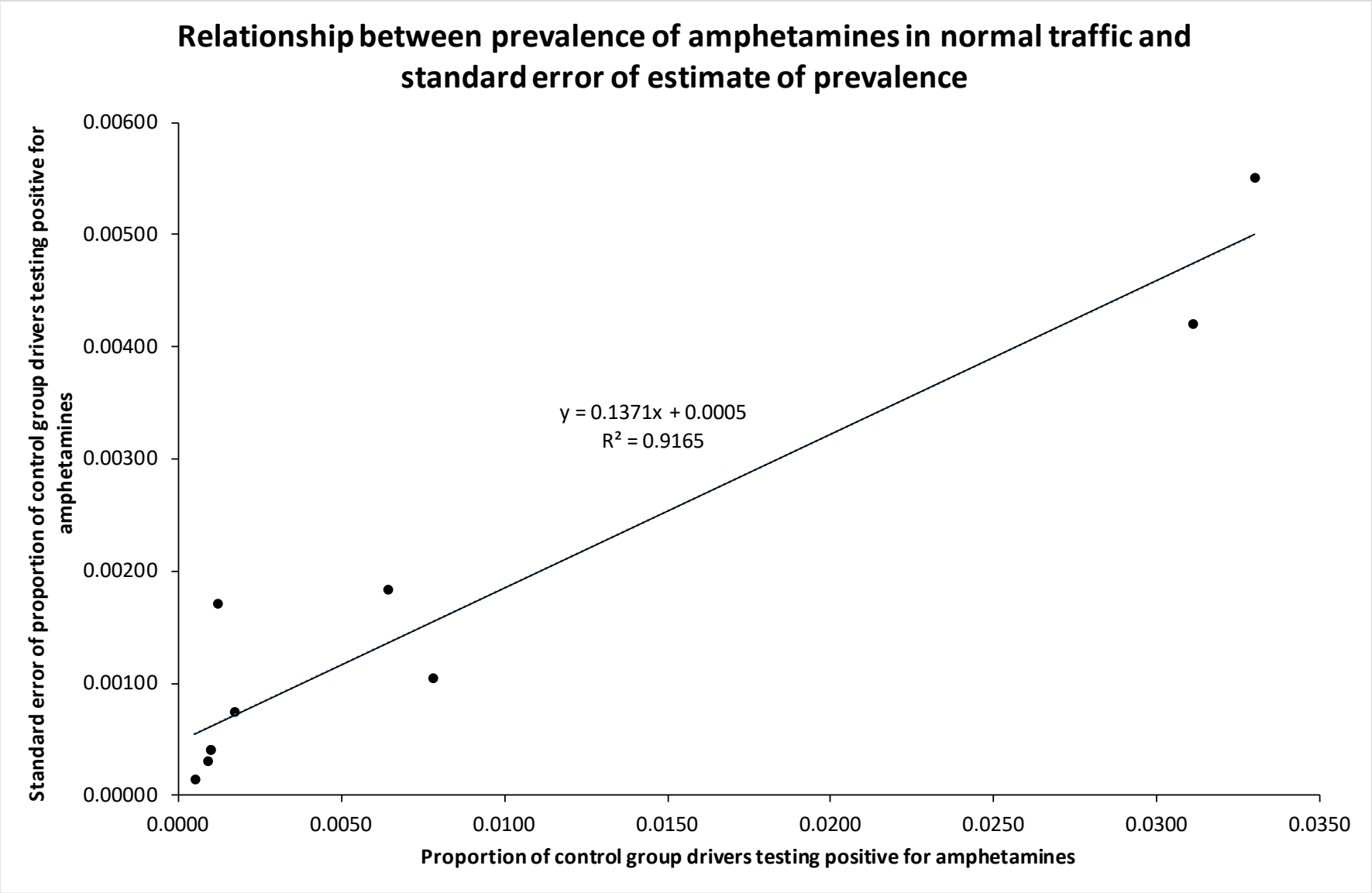
Relationship between prevalence of amphetamines in normal traffic and standard error of estimate of prevalence
Standard error of proportion of control group drivers testing positive for amphetamines
0.00600
0.00500
0.00400
0.00300
0.00200
0.00100
0.00000
y = 0.1371x + 0.0005
R² = 0.9165
0.0000
0.0050
0.0100
0.0150
0.0200
0.0250
0.0300
0.0350
Proportion of control group drivers testing positive for amphetamines

Figure 6:

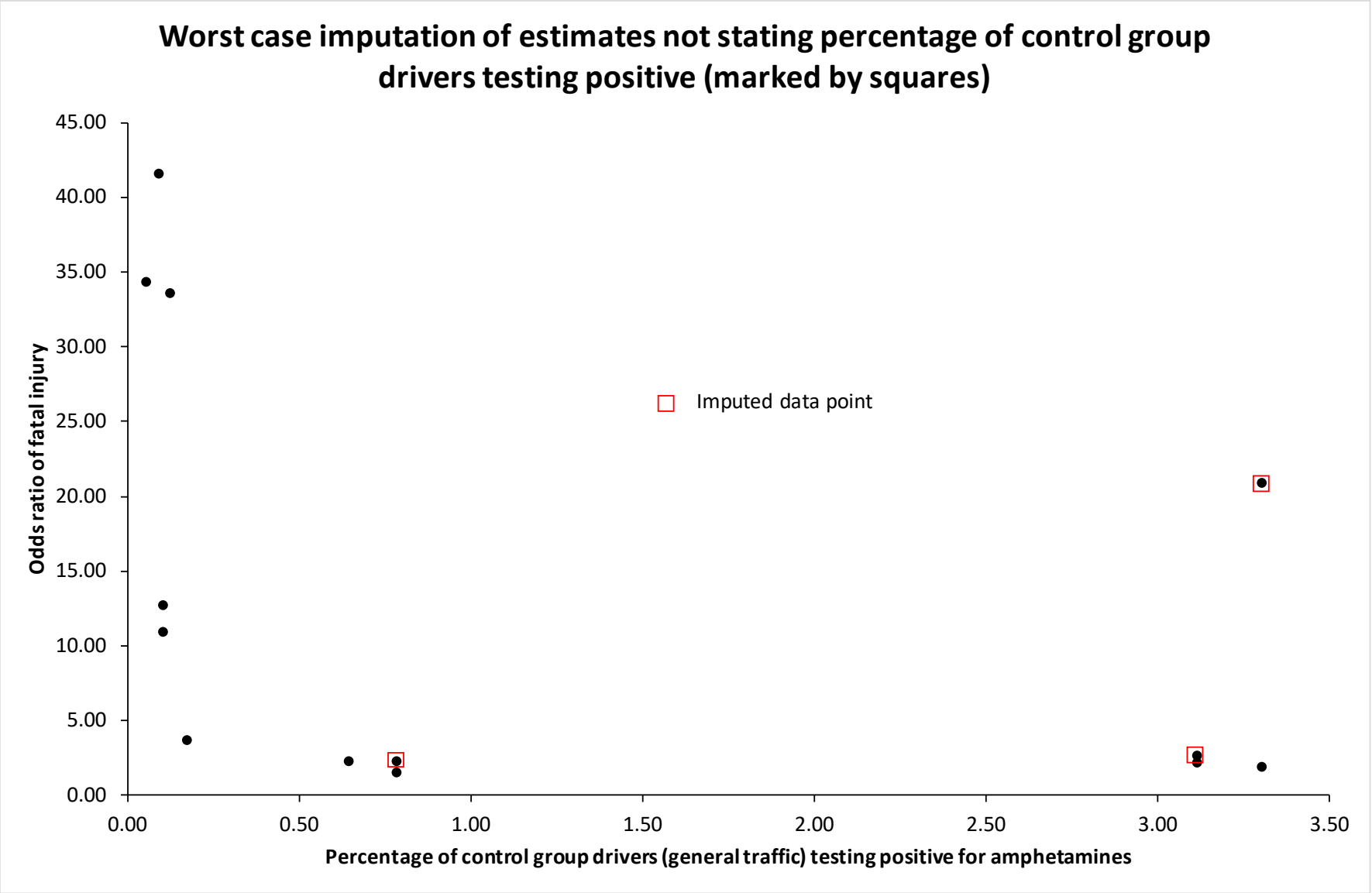
Worst case imputation of estimates not stating percentage of control group drivers testing positive (marked by squares)
Odds ratio of fatal injury
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
Imputed data point
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
Percentage of control group drivers (general traffic) testing positive for amphetamines

Figure 7:

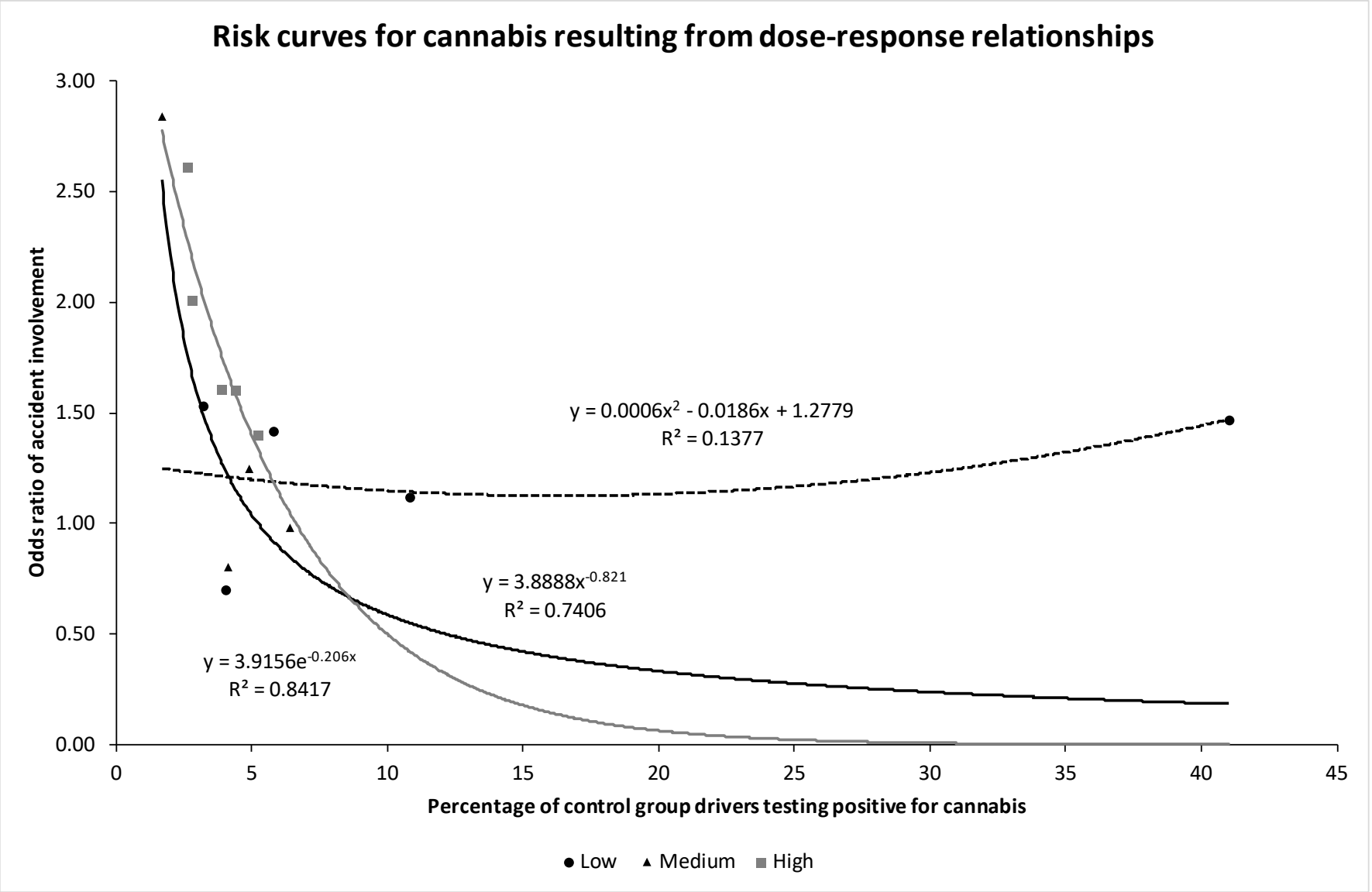
Risk curves for cannabis resulting from dose-response relationships
Odds ratio of accident involvement
3.00
2.50
2.00
1.50
1.00
0.50
0.00
0
5
10
15
20
25
30
35
40
45
Percentage of control group drivers testing positive for cannabis
y = 0.0006x² - 0.0186x + 1.2779
R² = 0.1377
y = 3.8888x-0.821
R² = 0.7406
y = 3.9156e-0.206x
R² = 0.8417
Low
Medium
High

Table 1:

Interpretation of interaction	Evaluation of interpretation	Evidence for or against interpretation
1 Statistical weighting of data points	Compare curve fitted by giving all data points the same weight to curve fitted to data points with inverse-variance weights	If the weighted curve is flatter than the crude curve or of a different form, the statistical weighting interpretation is supported
2 Unequal variance of estimates of use in control group	Compare variance of estimates of share of control group drivers testing positive across range of estimates	If variance is larger when the share of control group drivers testing positive is low than when it is high, the unequal variance interpretation is supported
3 Selective reporting of drug use in normal traffic	Impute data points not reporting use of drug in normal traffic in a way that is maximally inconsistent with the pattern for data points reporting the use of a drug in normal traffic	If the risk curve including both original and imputed data points differs from the original risk curve, failure to report the use of a drug in normal traffic may have influenced the risk curves
4 Unequal adjusting for confounding factors	Compare mean number of confounding variables controlled for between studies reporting a high share of control group drivers testing positive and studies reporting a low share of control group drivers testing positive	If there is poorer control for confounding variables in studies reporting a low share of control group drivers testing positive, the unequal adjusting interpretation is supported
5 Confounding by different estimators of risk	Compare estimates of risk based on culpability ratio, odds ratio and relative risk across range of share of control group drivers testing positive	If the culpability and odds ratio estimators are more common in studies showing a low share of control group drivers testing positive than in studies showing a high share of control group drivers testing positive, the bias by choice of estimator interpretation is supported
6 Small sample bias in odds ratio	Compare sample size serving as basis for estimating odds ratio across the range of share of control group drivers testing positive	If studies finding high risk are based on smaller sample sizes than those finding low risk, the small sample bias interpretation is supported
7 Publication bias	Conduct a trim-and-fill analysis to test for publication bias; fit curve to trimmed data set	If the curve fitted to the trimmed data set is flatter than the curve fitted to the complete data set, the publication bias interpretation is supported
8 Dose-response curve	Identify data points belonging to a dose-response curve and compare them to data points not belonging to a dose-response curve	If a curve fitted to data points not belonging to a dose-response curve is flatter than a curve fitted to data points belonging to a dose-response curve, the dose-response interpretation is supported
9 Learning curve	Check if studies showing a high share of control group drivers testing positive provide evidence of tolerance or long-term drug use among these drivers more often than studies showing a low share of control group drivers testing positive	If there is evidence of more tolerance or long-term drug use in studies showing a high share of control group drivers testing positive, the learning curve interpretation is supported
10 Social deviance; selective recruitment	Check if evidence of social deviance is found more often in studies indicating high risk than in studies indicating low risk	If there is stronger evidence of social deviance in studies showing high risk than in studies showing low risk, the social deviance interpretation is supported

Table 2:

Drug	Injury severity	Estimates	Statistical weighting	Best fitting curve	Coefficient	Standard error	Difference	Standard error of difference	Conclusion
Amphetamines	Fatal	10	No	Power	-0.740	0.194			
			Yes	Inverse	1.850	0.213	Not defined	Not defined	Difference
Cannabis	Fatal	27	No	Logarithmic	-0.377	0.093			
			Yes	Quadratic	0.009; -0.001	0.004; 0.000	Not defined	Not defined	Difference
Cannabis	Non-fatal	22	No	Inverse	1.427	0.159			
			Yes	Inverse	1.398	0.097	0.029	0.186	No difference
Cannabis	Property damage	14	No	Quadratic	-0.119; 0.003	0.078; 0.002			
			Yes	Quadratic	-0.109; 0.003	0.004; 0.000	-0.010; 0.000	0.078; 0.002	No difference
Opiates	Fatal	7	No	Inverse	2.290	0.422			
			Yes	Inverse	1.311	0.361	0.979	0.555	No difference
Opiates	Non-fatal	8	No	Inverse	0.466	0.238			
			Yes	Linear	-0.982	0.252	Not defined	Not defined	Difference

Table 3:

Drug	Injury or accident severity	Study	Crude estimate of risk	Adjusted estimate of risk	Number of confounding variables controlled for	Percentage change in estimate of risk
Amphetamines	Fatal	Gjerde et al. 2011	26.70	20.90	4	-22 %
Cannabis	Fatal	Bedard et al. 2007	1.39	1.29	7	-7 %
Cannabis	Fatal	Gadegbeku et al. 2011	2.26	1.53	4	-32 %
Cannabis	Fatal	Gadegbeku et al. 2011	4.54	2.84	4	-37 %
Cannabis	Fatal	Gadegbeku et al. 2011	3.51	2.01	4	-43 %
Cannabis	Fatal	Gjerde et al. 2013	2.40	1.90	7	-21 %
Cannabis	Fatal	Poulsen et al. 2014	2.40	1.42	8	-41 %
Cannabis	Fatal	Poulsen et al. 2014	1.97	0.98	8	-50 %
Cannabis	Fatal	Poulsen et al. 2014	2.95	1.61	8	-45 %
Cannabis	Non-fatal	Blows et al. 2005	11.40	0.80	11	-93 %
Cannabis	Non-fatal	Blows et al. 2005	12.70	9.50	11	-25 %
Cannabis	Property damage	Mann et al. 2010	3.28	1.84	8	-44 %
Cannabis	Property damage	Compton and Berning 2015	1.25	1.00	4	-20 %
Opiates	Injury	Gibson et al. 2009	1.44	0.90	8	-37 %
Opiates	Injury	Hels et al. 2013	2.40	1.18	4	-51 %

Table 4:

Interpretation	Amphetamines fatal injury	Cannabis fatal injury	Cannabis non-fatal injury	Cannabis property-damage-only	Opiates fatal injury	Opiates non-fatal injury
Statistical weighting	Not an issue	Does matter	Not an issue	Not an issue	Not an issue	Does matter
Unequal variance of exposure	Not an issue	Not an issue	Not an issue	Not an issue	Does matter	Not an issue
Selective reporting of exposure	Not an issue	Does matter	Not an issue	Not an issue	Does matter	Does matter
Unequal control for confounding	Not an issue	Weak effect found	Weak effect found	Weak effect found	Not an issue	Strong effect found
Choice of estimator of risk	Not an issue	Not an issue	Cannot be tested	Cannot be tested	Not an issue	Not an issue
Biased estimates of risk	Not an issue	Not an issue	Maybe a problem	Not an issue	Cannot be tested	Not an issue
Publication bias	Not an issue	Not an issue	Not an issue	Not an issue	Does matter	Does matter
Dose-response relationship	Cannot be tested	Cannot be tested	Is supported	Is supported	Cannot be tested	Cannot be tested
Learning curve	Cannot be tested	Cannot be tested	Weak tendency	Weak tendency	Cannot be tested	Weak tendency
Selective driver recruitment	No relevant data	No relevant data	No relevant data	No relevant data	No relevant data	No relevant data