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Risk of road accident associated with the use of drugs: A systematic review and meta-analysis of evidence from epidemiological studies

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ABSTRACT

This paper is a corrigendum to a previously published paper where errors were detected. The errors have been corrected in this paper. The paper is otherwise identical to the previously published paper. A systematic review and meta-analysis of studies that have assessed the risk of accident associated with the use of drugs when driving is presented. The meta-analysis included 66 studies containing a total of 264 estimates of the effects on accident risk of using illicit or prescribed drugs when driving. Summary estimates of the odds ratio of accident involvement are presented for amphetamines, analgesics, anti-asthmatics, anti-depressives, anti-histamines, benzodiazepines, cannabis, cocaine, opiates, penicillin and zopiclone (a sleeping pill). For most of the drugs, small or moderate increases in accident risk associated with the use of the drugs were found. Information about whether the drugs were actually used while driving and about the doses used was often imprecise. Most studies that have evaluated the presence of a dose-response relationship between the dose of drugs taken and the effects on accident risk confirm the existence of a dose-response relationship. Use of drugs while driving tends to have a larger effect on the risk of fatal and serious injury accidents than on the risk of less serious accidents (usually property-damage-only accidents). The quality of the studies that have assessed risk varied greatly. There was a tendency for the estimated effects of drug use on accident risk to be smaller in well-controlled studies than in poorly controlled studies. Evidence of publication bias was found for some drugs. The associations found cannot be interpreted as causal relationships, principally because most studies do not control very well for potentially confounding factors.

1. Introduction

It is well-established that driving under the influence of alcohol increases the risk of accident involvement. This has been known at least since the famous Grand Rapids study was made in the early nineteen sixties (Borkenstein et al., 1964). Less is known about the effects of drugs (medicinal or illicit) on the risk of accident involvement. A few systematic literature reviews and meta-analyses of the effects of drugs on accident risk have been reported (Thomas, 1998; Bates and Blakely, 1999; Ramaekers et al., 2004; Baldock, 2007; Orriols et al., 2009; Rapoport et al., 2009; Smink et al., 2010; Dassanayake et al., 2011; Asbridge et al., 2012). These studies deal only with a single drug or a few drugs and not all of them include a meta-analysis providing a summary estimate of the effect of drug use on accident risk.

Thomas (1998) reviewed studies of the association between benzodiazepine use and motor vehicle accidents. He listed 23 estimates of risk (Table 3 of the paper). Twelve of these indicated an odds ratio of accident involvement for users of benzodiazepines of between 1.01 and 1.50. Three estimates indicated an odds ratio between 2.01 and 2.50. Thomas concluded that use of benzodiazepines approximately doubles the risk of motor vehicle accidents. The study did not include a meta-analysis of the estimates of risk.

Bates and Blakely (1999) reviewed studies of the role of cannabis in motor vehicle accidents. The study did not include a meta-analysis. It listed the findings of a few studies and concluded that there was no evidence that the use of cannabis alone increased the risk of being held culpable for an accident. The authors added that it cannot be ruled out that use of cannabis leads to an increased risk of accidents causing less serious injuries or property damage. Ramaekers et al. (2004) argued that the effect of cannabis on the risk of accident involvement depends on the dose taken and on how long after taking cannabis driving takes place. They pointed out that the absence of a relationship between cannabis use and risk of accident involvement in some studies is probably attributable to the fact that these studies only found inactive metabolites of cannabis

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in body fluids. Metabolites of cannabis can persist for a long time after it was taken, particularly in urine. The study did not include a meta-analysis.

Baldock (2007) reviewed the literature on cannabis and the risk of accident involvement. The review was a traditional narrative review and did not include a meta-analysis. Baldock argued that many studies have methodological flaws, in particular with respect to the control for potentially confounding factors.

Orriols et al. (2009) presented a systematic review of studies of the risk associated with the use of medicinal drugs. The review included 22 studies of variable methodological quality. An assessment of study quality was made and studies rated as good, average or poor. A meta-analysis was not performed. It was concluded that the use of benzodiazepines is associated with an increased risk of accident, but that there is too little evidence to conclude anything for other medicinal drugs. Poor control for confounding factors was cited as a weakness of many studies.

Rapoport et al. (2009) reported a meta-analysis of benzodiazepine use and accident risk. The meta-analysis was based on six case–control studies and three cohort studies (a short definition of study designs is given later in this paper). The summary estimate of the odds ratio of accident involvement for benzodiazepine users was 1.61 according to the case–control studies and 1.60 according to the cohort studies. The meta-analysis did not score studies formally with respect to study quality and did not test for publication bias. Smink et al. (2010) conducted a systematic literature review of studies assessing the relationship between use of benzodiazepines and accident involvement, but did not perform a meta-analysis.

Dassanayake et al. (2011) performed a systematic literature review and meta-analysis of studies of the effects on accident risk of benzodiazepines, antidepressants and opioids. A meta-analysis was only feasible for studies of benzodiazepines. The summary estimates of the odds ratio of accident involvement for benzodiazepine users were 1.59 for case–control studies, 1.81 for cohort studies and 1.41 for culpability studies. These estimates are close to those reported by Rapoport et al. (2009). The study did not score studies formally for quality and did not test for publication bias.

Asbridge et al. (2012) conducted a meta-analysis of observational studies of the effects of acute cannabis use on the risk of accident involvement. Nine studies were included. The summary estimate of the odds ratio of accident involvement associated with use of cannabis was 2.10 for fatal accidents and 1.74 for non-fatal accidents. Study quality was scored formally by means of the Newcastle-Ottawa quality assessment scale. A test for the possible presence of publication bias was not included.

The systematic reviews and meta-analyses quoted above included only a few drugs, in particular benzodiazepines and cannabis. Not all reviews included a meta-analysis. Not all meta-analyses considered study quality. No meta-analysis addressed the possibility of publication bias.

The aim of this paper is to summarize current knowledge regarding the risks associated with the use of drugs while driving. The paper seeks to improve previous reviews by: (1) including as many drugs as possible in the systematic literature review and meta-analysis; (2) assessing study quality and testing how it influences study findings; (3) testing and adjusting for the possible presence of publication bias. Alcohol is not included in this study. The focus is on drugs used in regular medical treatment or illicit drugs used recreationally.

2. Systematic review of literature

2.1. Literature search and study retrieval

A literature search was made of several databases, including the TRANSPORT literature database, PubMed, Sciencedirect (searching the journals Accident Analysis and Prevention, Drugs and Alcohol Dependence and Journal of Safety Research) and the SafetyLit database. In general, "drugs AND accident risk" was used as search term. Studies that were judged as relevant based on the title and the abstract were obtained and assessed with respect to inclusion in the systematic literature review and meta-analysis. A total of 102 studies were reviewed in detail. 66 of these studies were included in the meta-analysis. 36 studies could, for various reasons, not be included in the meta-analysis. Tables 2 and 3 list studies included and not included.

Table 1
Coding of studies in systematic review.

Variable coded	Codes applied
Study identification	By authors; studies numbered chronologically (oldest = 1; newest = 66)
Year of publication	1976 through 2011
Country of publication	By name: Australia, Canada, Finland, France, Great Britain, Iran, Netherlands, New Zealand, Norway, Spain, Taiwan, Thailand, United States
Study design	Coded as: (1) Case–control study; (2) Case-crossover study; (3) Cohort study (prospective or retrospective); (4) Culpability study; (5) Registry-based cohort study; (6) Sample survey
Drugs assessed	Main types: (1) Amphetamines; (2) Analgesics; (3) Anti-asthmatics; (4) Anti-depressives; (5) Anti-histamines; (6) Benzodiazepines (including barbiturates and diazepam); (7) Cannabis (including marijuana); (8) Cocaine; (9) Opiates (including morphine); (10) Zopiclone; (11) Penicillin; (12) Miscellaneous other drugs (very many)
Accident severity	Coded as: Fatal, serious injury, injury, property-damage-only
Estimator of risk	Coded as: Odds ratio (OR); relative risk (RR); standardized incidence ratio (SIR) (SIR is a measure of relative risk based on a population registry)
Measure of drug use	Coded as: Determined by clinical analysis; by prescriptions; by self-reports
Confounders controlled	Coded as: A = age; B = driver behavior; C = smoking; D = other drug use; E = education; F = body mass index; G = gender; H = drug use history; I = other disease (than drug addiction); J = use of alcohol; K = type of accident; L = time after prescription; M = miles driven; N = location or region; O = marital status; P = ethnicity; Q = mental distress, depression; R = place of residence; S = driving speed; T = time of day; V = attitude to violations; X = driver experience; Y = season; W = any other confounding variable
Dose-response assessed	Coded as yes or no
Dose-response found	Coded as yes or no

2.2. Coding of studies for systematic review

As part of the systematic review, studies were coded according to the following characteristics:

1. Year of publication. Studies were published between 1976 and 2011.
2. Country where study was made. Thirteen countries, listed in Table 1, were represented.
3. Study design. Six different study designs were identified. These are listed in Table 1.
4. Types of drug. Twelve categories, listed in Table 1, were formed to identify the drugs studied.
5. Accident severity. This was coded as fatal accident, injury accident, and property-damage-only (PDO) accident.
6. Estimator of risk. Three estimators of risk have been applied in the studies: odds ratio, relative risk, and standardized incidence ratio.

Table 2
Studies included in meta-analysis.

Study number	Authors	Year	Country	Design	Drugs assessed (see Table 1)	Accident severity	Estimator of risk	Measure of drug use	Confounders controlled (see Table 1)	Dose-response assessed	Dose-response found
1	Smart, Fejer	1976	Canada	Sample survey	1-6-7-9-12	Mostly PDO	Odds ratio	Self report	A	No	No
2	Skegg et al.	1979	Great Britain	Case–control	2-3-5-11-12	Serious injury	Odds ratio	Prescriptions	AGR	No	No
3	Honkanen et al.	1980	Finland	Case–control	2-6-12	Injury	Odds ratio	Self report	None	No	No
4	Jick et al.	1981	United States	Culpability	5-6	Injury	Odds ratio	Prescriptions	None	No	No
5	Hingson et al.	1982	United States	Sample survey	7	Mostly PDO	Odds ratio	Self report	AEGJM	Yes	Yes
6	Terhune	1983	United States	Culpability	7	Mostly PDO	Odds ratio	Lab analysis	None	No	No
7	Williams et al.	1985	United States	Culpability	7	Fatal	Odds ratio	Lab analysis	None	No	No
8	Oster et al.	1987	United States	Cohort	6	Injury	Odds ratio	Prescriptions	ADGQ	No	No
9	Oster et al.	1990	United States	Cohort	6	Injury	Relative risk	Prescriptions	ADG	Yes	Yes
10	Ray et al.	1992	United States	Cohort (retro)	4-6	Injury	Relative risk	Prescriptions	AGPRY	Yes	Yes
11	Terhune et al.	1992	United States	Culpability	1-6-7-8	Fatal	Odds ratio	Lab analysis	None	No	No
12	Benzo group	1993	France	Culpability	6	Injury	Odds ratio	Lab analysis	J	No	No
13	Leveille et al.	1994	United States	Case–control	2-4-5-6	Injury	Odds ratio	Prescriptions	AEGIMOP	Yes	Yes
14	Currie et al.	1995	Great Britain	Culpability	4-6	Injury	Odds ratio	Lab analysis	None	No	No
15	Drummer	1995	Australia	Culpability	1-6-7-9-12	Fatal	Odds ratio	Lab analysis	AG	No	No
16	Neutel	1995	Canada	Cohort (pros)	6	Injury	Odds ratio	Prescriptions	L	Yes	Yes
17	Hemmelgarn et al.	1997	Canada	Case–control	6	Injury	Odds ratio	Prescriptions	ADGIR	Yes	Yes
18	Barbone et al.	1998	Great Britain	Case-crossover	4-6-10-12	Injury, PDO	Odds ratio	Prescriptions	AEGIMOPR	Yes	Yes
19	Neutel	1998	Canada	Cohort	4-6	Injury	Odds ratio	Prescriptions	ADG	No	No
20	Longo et al.	2000	Australia	Culpability	6-7	Injury	Odds ratio	Lab analysis	None	Yes	Yes
21	McGwin et al.	2000	United States	Case–control	4-10	Mostly PDO	Odds ratio	Self report	AGMP	No	No
22	Swann	2000	Australia	Culpability	7	Fatal	Odds ratio	Lab analysis	None	No	No
23	Fergusson	2001	New Zealand	Sample survey	7	Mostly PDO	Odds ratio	Self report	ABGMVX	Yes	Yes
24	Lowenstein	2001	United States	Culpability	7	Injury	Odds ratio	Lab analysis	None	No	No
25	Chipman et al.	2002	Canada	Case–control	7-8	Mostly PDO	Relative risk	Self report	AGDX	No	No
26	Dussault et al.	2002	Canada	Case–control	1-6-7-8-9	Fatal	Odds ratio	Lab analysis	Not clear	No	No
27	Gerberich et al.	2003	United States	Sample survey	7	Serious injury	Relative risk	Self report	ACEFGIJO	Yes	Yes
28	Mura et al.	2003	France	Case–control	6-7-9	Injury	Odds ratio	Lab analysis	AG	No	No
29	Wadsworth et al.	2003	Great Britain	Sample survey	4	Injury	Odds ratio	Self report	ACGIJOQW	No	No
30	Brault et al.	2004	Canada	Case–control	1-6-7-8-9	Fatal	Odds ratio	Lab analysis	AGTW	No	No
31	Drummer et al.	2004	Australia	Culpability	1-6-7-9	Fatal	Odds ratio	Lab analysis	ADGJKR	Yes	Yes
32	Etminam et al.	2004	Canada	Case–control	4	Injury	Odds ratio	Prescriptions	ADGIRW	Yes	Yes
33	Movig et al.	2004	Netherlands	Case–control	1-6-7-8-9	Injury	Odds ratio	Lab analysis	ADGJTY	No	No
34	Macdonald et al.	2004	Canada	Cohort (bef-aft)	7-8	Mostly PDO	Odds ratio	Self report	AG	No	No
35	Asbridge et al.	2005	Canada	Sample survey	7	Mostly PDO	Odds ratio	Self report	AEGJNX	Yes	Yes
36	Assum	2005	Norway	Case–control	1-6-7-8-9	Mostly fatal	Odds ratio	Lab analysis	N	No	No
37	Blows et al.	2005	New Zealand	Case–control	7	Injury	Odds ratio	Self report	AEGJMPST	No	No
38	Delaney et al.	2005	Canada	Case–control	12	Injury	Odds ratio	Prescriptions	ADGIW	No	No
39	French et al.	2005	United States	Cohort	6	Injury	Odds ratio	Prescriptions	AFGIOW	No	No
40	Lam et al.	2005	New Zealand	Case–control	4	Injury	Odds ratio	Self report	AEGJOQT	No	No
41	Laumon et al.	2005	France	Culpability	1-7-8-9	Fatal	Odds ratio	Lab analysis	AJT	Yes	Yes
42	Mathijssen	2005	Netherlands	Case–control	6-7-9	Injury	Odds ratio	Lab analysis	None	No	No
43	Tamblyn et al.	2005	Canada	Cohort	6	Injury	Odds ratio	Prescriptions	ADGIW	No	No
44	Wadsworth et al.	2005	Great Britain	Sample survey	4	Injury	Odds ratio	Self report	ACDEGHIJQ	No	No
45	Hemmelgarn et al.	2006	Canada	Case–control	12	Injury	Odds ratio	Prescriptions	AGRW	No	No
46	Sagberg	2006	Norway	Culpability	4	Mostly PDO	Odds ratio	Self report	AM	No	No
47	Bramness et al.	2007	Norway	Cohort (registry)	3-6-12	Injury	Relative risk	Prescriptions	AG	No	No
48	Engeland et al.	2007	Norway	Cohort (registry)	3-6-9-11-12	Injury	Relative risk	Prescriptions	AG	No	No
49	Hebert	2007	Canada	Case–control	6	Injury	Odds ratio	Prescriptions	ADGIW	No	No
50	Mann et al.	2007	Canada	Sample survey	7	Injury	Odds ratio	Self report	AEGNOW	Yes	Yes
51	Bramness et al.	2008	Norway	Cohort (registry)	4	Injury	Relative risk	Prescriptions	AG	No	No
52	Fergusson et al.	2008	New Zealand	Sample survey	7	Mostly PDO	Relative risk	Self report	BJM	Yes	Yes
53	Gustavsen et al.	2008	Norway	Cohort (registry)	6-10	Injury	Relative risk	Prescriptions	AG	No	No
54	Hours et al.	2008	France	Culpability	4-6-11	Injury	Odds ratio	Self report	AJW	No	No

55	Rapoport et al.	2008	Canada	Case-crossover	4-6	Mostly PDO	Odds ratio	Prescriptions	AEGIMOPR	No	No
56	Vingilis and Wilk	2008	Canada	Sample survey	2-4-6-9	Injury	Odds ratio	Self report	QAGIJPQ	Yes	Yes
57	Bachs et al.	2009	Norway	Cohort (registry)	9	Injury	Relative risk	Prescriptions	AGHY	Yes	Yes
58	Gibson et al.	2009	Great Britain	Case-crossover	2-4-5-6-9-10	Injury	Relative risk	Prescriptions	AEGIMOPR	Yes	Yes
59	Majdzadeh et al.	2009	Iran	Case-crossover	9	Injury	Relative risk	Lab analysis	AEGIMOPR	Yes	No
60	Richer et al.	2009	Canada	Sample survey	7	Mostly PDO	Odds ratio	Self report	ABGJM	No	No
61	Woratanarat et al.	2009	Thailand	Case–control	1-4-5-7-9	Injury	Odds ratio	Lab analysis	None	No	No
62	Orriols et al.	2010	France	Cohort (registry)	2-5-12	Injury	Odds ratio	Prescriptions	ADGIJNTW	No	No
63	Pulido et al.	2010	Spain	Sample survey	7-8	Injury	Odds ratio	Self report	ADEGJMPW	Yes	Yes
64	Yang et al.	2011	Taiwan	Case-crossover	6-10	Injury	Odds ratio	Prescriptions	D	Yes	Yes
65	Gjerde et al.	2011	Norway	Case–control	1-6-7-9-10	Fatal	Odds ratio	Lab analysis	AGTY	No	No
66	Orriols et al.	2011	France	Cohort (registry)	6-10-12	Injury	Odds ratio	Prescriptions	ADGIJTW	Yes	Yes

7. Measure of drug use. Three indicators of drug use have been applied: self-reported use, records of prescriptions, and results of laboratory analyses.
8. Confounders controlled. Potentially confounding factors were identified by letters. A total of 24 potentially confounding factors were coded, see Table 1.
9. Dose-response pattern assessed. This refers to whether a study tested for a dose-response relationship between the dose taken of a drug and its effect on accident risk.
10. Dose-response pattern found. This refers to whether a study found a dose-response relationship between a drug and the risk of accident involvement.

These variables are listed in Table 1.

2.3. Main characteristics of available studies

A total of 66 studies were included in the systematic review and meta-analysis. Table 2 lists these studies. Most of the studies are recent. 47 of the studies have been published between 2000 and 2011. The 66 studies contain a total of 264 estimates of the risk of accident involvement associated with the use of drugs. The most common study design is the case–control design, which was used in 20 studies. This design normally involves comparing a sample of accident victims treated at a medical facility to a group of drivers not involved in accidents with respect to various risk factors of interest. Sample surveys, i.e. questionnaires mailed to a sample of the population were used in 12 studies. A cohort design, which includes both prospective and retrospective studies, was applied in 15 studies. Fourteen studies were culpability studies, i.e. studies relying on the induced exposure approach (Chandraratna and Stamatiadis, 2009), comparing a group of drivers involved in accidents at fault to a group of drivers involved in accidents not-at-fault. The remaining five studies were case-crossover studies. A case-crossover study is a study in which the same subjects serve both as cases and controls. Thus, a person would be a case when using a certain drug and a control when not using it. To save space, a further description of the study designs will not be given in this paper.

Thirty studies assessed the effect on accident risk of a single drug. Thirty-six studies assessed the effects of more than one drug, although these drugs were not necessarily used in combination at the same time. No study assessed the effects of more than six of the drugs identified in this review. An advantage of trying to assess the effects of multiple drugs is that it is then, in principle, possible to control for exposure to another drug when assessing the effects of a specific drug. This, however, is not possible when several drugs are used at the same time. In such cases, an estimate of risk can only show the combined effects of the drugs that were used together, not the specific effect of any one of these drugs. When deciding which results to include from studies reporting multiple results, results that referred to use of a single drug were included, whereas results that referred to combined use of many drugs were not included. As an example, from the study by Gjerde et al. (2011), two estimates of accident risk were given for benzodiazepines, diazepam, zopiclone, cannabis and amphetamine. For these drugs the estimates of risk that stated “only benzodiazepines”, “only diazepam”, and so on were included, whereas those that did not state explicitly that the estimate of risk applied to the use of a single drug only were not included. Unfortunately, not all studies state explicitly that the estimate of risk applied to a single drug only, hence some estimates may refer to the combined use of more than one drug.

A majority of the studies (44) assessed the association between the use of drugs and involvement in injury accidents. Ten studies assessed the risk of fatal accidents and twelve studies assessed the risk of property damage only accidents. Nearly all studies (54) applied the odds ratio of accident involvement as the estimator of

Table 3
Studies not included in meta-analysis.

Study number	Authors	Year	Country	Design	Reason for not including study in meta-analysis
1	MacPherson et al.	1984	United States	Sample survey	Standard errors of estimates of risk are not reported
2	Beylich et al.	1994	Norway	Cohort	Estimates of risk are hypothetical and imprecise; standard errors are not stated
3	Marowitz	1995	United States	Cohort	Standard errors of estimates of risk are not stated
4	Meulemans et al.	1998	Belgium	Not clear	Study report was not retrieved
5	Thomas	1998	Canada	Review	Study is a literature review and does not contain original estimates of risk
6	Bates and Blakely	1999	New Zealand	Review	Study is a literature review and does not contain original estimates of risk
7	Río and Alvarez	2000	Spain	Cohort	Study does not contain any estimates of risk
8	Zador et al.	2000	United States	Case–control	Study deals only with alcohol
9	Longo et al.	2001	Australia	Culpability	Standard errors of estimates of risk given only in a difficult-to-read figure
10	Río et al.	2002	Spain	Cohort	Study does not contain any estimates of risk
11	Vernon et al.	2002	United States	Case–control	Study does not deal with risk associated with drug use
12	Lardelli-Claret et al.	2003	Spain	Case–control	Study does not deal with risk associated with drug use
13	Keall et al.	2004	New Zealand	Case–control	Study deals only with alcohol
14	Ramaekers et al.	2004	Netherlands	Review	Study is a literature review and does not contain original estimates of risk
15	Cunradi et al.	2005	United States	Cohort	Type of drug on which estimates of risk are based is not stated
16	Lagarde et al.	2005	France	Cohort	Study does not deal with risk associated with drug use
17	Smink et al.	2005	Netherlands	Cohort	Study deals with injury severity only, not risk of accident involvement
18	Oyefeso et al.	2006	Great Britain	Cohort (registry)	Definition of risk not relevant for the purpose of this study
19	Sheridan et al.	2006	New Zealand	Review	Study is a literature review and does not contain original estimates of risk
20	Alvarez and Fierro	2007	Spain	Cohort	Study does not deal with risk associated with drug use
21	Bédard et al.	2007	Canada	Case–control	Study does not use accident involvement as dependent variable
22	Baldock	2008	Australia	Review	Study is a literature review and does not contain original estimates of risk
23	Dubois et al.	2008	Canada	Culpability	Study does not use accident involvement as dependent variable
24	Far et al.	2008	Spain	Sample survey	Type of drug used while driving is not stated, only type of drug used in general consumption
25	Hingson et al.	2008	United States	Sample survey	Type of drug on which estimates of risk are based is not stated
26	Lenguerrand et al.	2008	France	Case–control	Duplicates a paper included (paper 34 on the list in Table 2 above)
27	Blomberg et al.	2009	United States	Case–control	Study deals only with alcohol
28	Davey and Freeman	2009	Australia	Cohort	Study presents exposure only; no estimates of risk
29	Lia et al.	2009	Norway	Review	Study is a literature review and does not contain original estimates of risk
30	Orriols et al.	2009	France	Review	Study is a literature review and does not contain original estimates of risk
31	Pasnin et al.	2009	Norway	Case series	Study contains only a case series, no control group to enable risks to be estimated
32	Rapoport	2009	Canada	Review	Study is a literature review and does not contain original estimates of risk
33	Smink	2010	Netherlands	Review	Study is a literature review and does not contain original estimates of risk
34	Dubois et al.	2010	Canada	Cohort (registry)	Study does not use accident involvement as dependent variable
35	Dassanayake et al.	2011	Australia	Review	Study is a literature review and does not contain original estimates of risk
36	Asbridge et al.	2012	Canada	Review	Study is a literature review and does not contain original estimates of risk

risk. In the studies that permitted a comparison of the odds ratio and relative risk as estimators of accident risk, there was only a small difference between them. In the meta-analysis all estimators of risk (odds ratio, relative risk and standardized incidence ratio) have therefore been treated as equivalent.

Twenty studies relied on self reports of drug use. Obviously, such reports are likely to be inaccurate with respect both to the amount and time of drug use. Twenty-six studies relied on data regarding prescriptions. Prescriptions are usually specific with respect to the dose to be taken and the duration of the use of a drug. Patient compliance with prescribed use is, however, always an issue. Twenty studies assessed drug use in terms of the results of laboratory analyses, usually analyses of a sample of blood or saliva. This is clearly the most reliable method for determining whether a drug was used when driving.

Studies vary greatly with respect to how many potentially confounding factors they have controlled for. Twenty-three studies evaluated the presence of a dose-response relationship between the dose taken of a drug and the size of the increase in accident risk; twenty-two of these studies confirmed a dose-response relationship, one did not. The other 43 studies did not probe for a dose-response relationship.

Thirty-six studies were neither included in the systematic review nor in the meta-analysis. The reason for omitting these studies was in all cases related to the possibility of including them in the meta-analysis. Some studies could in principle have been included in a systematic review, but excluded from meta-analysis. Table 3 lists the studies that were excluded from the systematic review and the meta-analysis and states for each study the reason for its exclusion.

The reasons for excluding studies were many, but three reasons were the most important: (1) The study dealt with a different topic, such as the risk associated with alcohol; (2) The study did not report sufficient information to be included in meta-analysis; (3) The study was a review, i.e. a secondary source not reporting original results of research.

2.4. Study quality assessment

It is clear that the studies that could be included in the meta-analysis are very different in a number of important respects. It was therefore decided to summarize study characteristics in terms of a numerical measure of study quality. While assessing study quality is certainly not an exact science (Elvik, 2008, 2011), it is widely regarded as a useful part of meta-analysis (Borenstein et al., 2009). The quality score was based on four study characteristics:

1. How drug use was measured. A distinction was made between five methods of determining drug use. Listed in order from the most reliable to the least reliable, these were: (a) Laboratory analysis of blood samples; (b) Laboratory analysis of saliva samples or a mixture of blood and saliva; (c) Laboratory analysis of urine samples or a mixture of urine and other body fluids; (d) Prescribed dose of a drug according to prescriptions given by physicians; (e) Self-reported drug use.

2. How accident severity was specified. A distinction was made between three levels (fatal, injury, property damage only), and a study rated as best if it included estimates of risk for all levels of accident severity.
3. Control for confounding factors. A checklist was made of nine important potentially confounding factors and studies rated according to how many of these factors they controlled for. Up to two additional points could be earned if a study controlled for other potentially confounding factors in addition to the nine that were listed.
4. Confirmation of the presence of a dose-response relationship between the dose taken of a drug and its effect on accident risk.

These variables were selected because they are consistently reported in studies, thus avoiding the problem of basing quality scores on missing data. Table 4 shows how studies were scored according to these characteristics.

Control for confounding represented 55% of the maximum score (11 out 20 points) and was thus regarded as by far the most important element of study quality. Quality scores were stated on a scale ranging from 0 to 1. Fig. 1 shows the quality scores of the 264 estimates of risk in chronological order.

As can be seen from Fig. 1, no estimate scored higher for study quality than 0.65. The majority of estimates scored less than 0.50, which is the midpoint of the scale. A tendency can be seen for study quality to improve over time. The main reason why so many studies score comparatively low for quality is poor control for potentially confounding variables. No study scored more than 7 points for control for confounding factors. The maximum score was 11.

3. Meta-analysis

3.1. Study inclusion criteria and statistical weighting

Estimates of the risk of accident involvement associated with the use of drugs were included in the meta-analysis if the standard error of the estimate was stated or could be derived. Each estimate of risk was assigned a statistical weight which was inversely proportional to its sampling variance (standard error squared). Most estimates of risk were odds ratios, which were converted to log odds ratios in order to apply the normal distribution for statistical testing and estimation of confidence intervals. The statistical weight assigned to each estimate of risk was defined as follows:

$$w_i = \frac{1}{v_i}$$

$$\text{Variance of logarithm of odds ratio}: \quad v_i = \frac{1}{A} + \frac{1}{B} + \frac{1}{C} + \frac{1}{D}$$

A, B, C, and D are the four numbers that enter the calculation of the odds ratio. In case relative risk was used to measure accident involvement, variance was estimated as:

$$\text{Variance of logarithm of relative risk} = \frac{1}{A} + \frac{1}{B} - \frac{1}{A+C} - \frac{1}{B+D}$$

In studies not stating the numbers used to estimate the odds ratio or relative risk, the statistical weight was derived from the 95% confidence interval for the estimate of risk as follows:

$$\text{Statistical weight} = \frac{1}{((\ln(\text{upper } 95\%) - \ln(\text{lower } 95\%))/3.92)^2}$$

All these statistical weights are fixed-effects weights, i.e. they account only for the sampling variance of each estimate of risk (Borenstein et al., 2009). When there is systematic variation between estimates of risk, a random-effects model of meta-analysis should be used. To determine if estimates of risk vary systematically (i.e. more than random sampling variation), the following test statistic is computed:

$$Q = \sum_{i=1}^{g} w_i y_i^2 - \frac{\left(\sum_{i=1}^{g} w_i y_i\right)^2}{\sum_{i=1}^{g} w_i}$$

where y_i is the logarithm of estimate of risk i and w_i is the fixed-effects weight of estimate i. This test statistic has a Chi-square distribution with $g-1$ degrees of freedom, where g is the number of estimates of risk that have been combined. If this test statistic is statistically significant, a random effects model of meta-analysis is more adequate than a fixed effects model. In a random effects model, the statistical weights are modified to include a component reflecting the systematic variation of estimates of risk between studies. This component is estimated as follows (Shadish and Haddock, 1994):

$$\tau^2 = \frac{Q - (g-1)}{C}$$

Q is the test statistic described above, g is the number of estimates and C is the following estimator:

$$C = \sum_{i=1}^{g} w_i - \left[\frac{\sum_{i=1}^{g} w_i^2}{\sum_{i=1}^{g} w_i}\right]$$

The variance of each result now becomes:

$$v_i^* = \tau^2 + v_i$$

The corresponding statistical weight becomes the inverse of the variance. The weighted mean estimate of risk is

$$\bar{y} = \exp\left(\frac{\sum_{i=1}^{g} w_i y_i}{\sum_{i=1}^{g} w_i}\right)$$

Exp is the exponential function (that is 2.71828 raised to the power of the expression in parenthesis), y_i is the logarithm of each estimate of risk and w_i is the statistical weight (fixed-effects or random-effects) of each estimate of effect. A 95% confidence interval for the weighted mean estimate of risk is obtained according to the following expression: 95% confidence interval (upper/lower limit) = $\exp\left[\left(\sum_{i=1}^{g} w_i y_i / \sum_{i=1}^{g} w_i\right) \pm 1.96 \cdot 1/\sqrt{\sum_{i=1}^{g} w_i}\right]$

The weights in this expression are either the fixed effects weights or the random effects weights, depending on the model of analysis adopted.

3.2. Exploratory analysis

To prepare for meta-analysis, a funnel plot of all estimates of the risk of accident involvement associated with the use of drugs while driving was prepared. In total, the 66 studies included in the meta-analysis contained 264 estimates of risk. Fig. 2 shows the funnel plot. The scales used for the axes are as recommended by Sterne and Egger (2001).

The horizontal axis shows the logarithm of the estimate of risk; positive values indicate an increase of risk, negative values indicate a reduction of risk. The vertical axis shows the standard error of each estimate of risk. The scale has been inverted, so that estimates that have a small standard error are located at the top of the diagram.

Ideally speaking, the outer contours of the data points should resemble a funnel turned upside down. Contours have been indicated in Fig. 2; some data points are located outside the contour lines, suggesting either the presence of outlying data points or large heterogeneity in estimates of risk. Nevertheless, it is evident that

Table 4
Study quality assessment.

Study characteristic	Scores assigned	Maximum possible score
Measure of drug use	5 = laboratory analysis of blood samples for all subjects (cases and controls); 4 = laboratory analysis of samples of saliva or mix of blood and saliva; 3 = laboratory analysis of samples of urine or mix of urine and other body fluids; 2 = prescriptions; 1 = self report	5 (25% of total score)
Specification of accident severity	2 = at least two levels of accident or injury severity included in the same study; 1 = accidents at a specific level of severity (fatal, injury, property damage) included; 0 = a mix of injury accidents and property damage accidents included	2 (10% of total score)
Control for confounding factors	9 = if all the following potentially confounding factors are controlled for: Age, gender, km driven, drug use history, dose of drug, use of other drugs, use of alcohol, health status (co-morbidity), place of residence 2 = additional points if multiple other potentially confounding factors are controlled for 1 = additional point if one other potentially confounding factor is controlled for	11 (55% of total score)
Test of dose-response	2 = tested and found; 1 = tested but not found; 0 = not tested or not relevant **Scoring of studies** Points counted and divided by maximum possible score (20 = 5 + 2 + 11 + 2). Expressed as relative score, e.g. 12/20 = 0.60	2 (10% of total score)

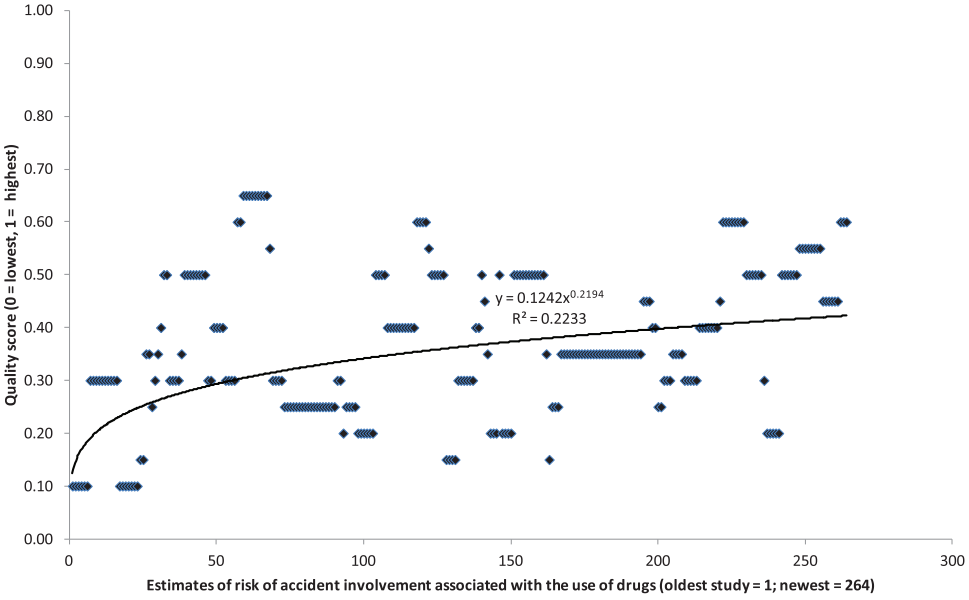

Fig. 1. Quality scores of 264 estimates of risk associated with the use of drugs while driving.

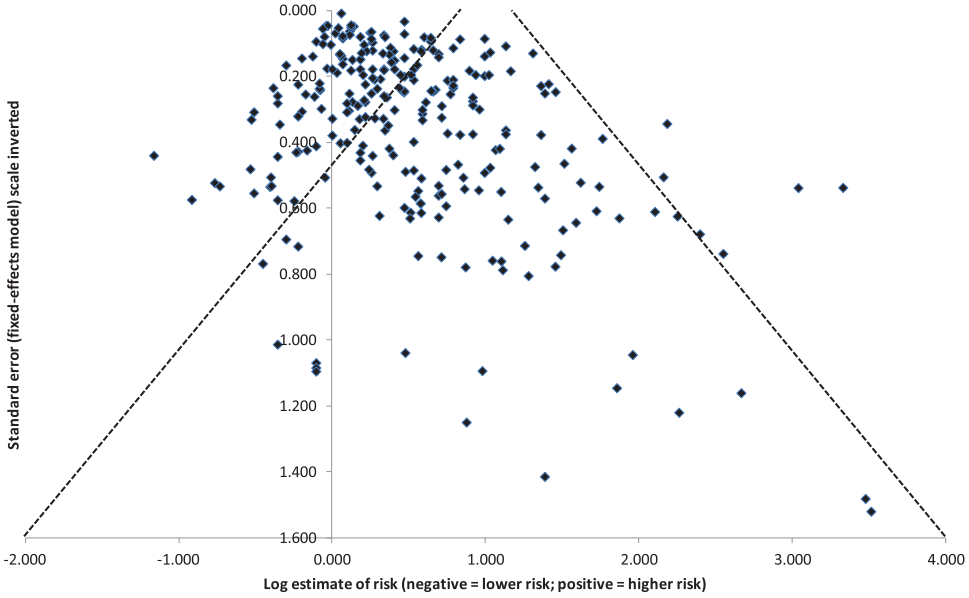

Fig. 2. Funnel plot of all estimates of relative risk associated with the use of drugs while driving.

Table 5
Design of meta-analysis with respect to model of analysis (fixed-effects versus random-effects) and test for publication bias (by means of the trim-and-fill technique).

Drug	Accident severity	Number of estimates	Test for heterogeneity	Model of analysis	Trim-and-fill analysis	Data points added
Amphetamine	Fatal	8	Positive	Random effects (RE)	Performed	3 (FE); 1(RE)
	Injury	2	Not applicable	Fixed effects (FE)	Not performed	0
	Property damage	1	Not applicable	Fixed effects	Not performed	0
Analgesics	Injury	8	Positive	Random effects	Performed	2 (FE); 2 (RE)
Anti-asthmatics	Injury	6	Negative	Fixed effects	Performed	1 (FE)
Anti-depressives	Injury	20	Positive	Random effects	Performed	1 (FE); 2 (RE)
	Property damage	5	Positive	Random effects	Performed	0
Anti-histamines	Injury	7	Negative	Fixed effects	Performed	0
Benzodiazepines	Fatal	10	Positive	Random effects	Performed	0
	Injury	51	Positive	Random effects	Performed	34 (FE); 26 (RE)
	Property damage	4	Negative	Fixed effects	Not performed	0
Cannabis	Fatal	10	Positive	Random effects	Performed	0 (FE); 1 (RE)
	Injury	15	Positive	Random effects	Performed	1 (FE); 2 (RE)
	Property damage	17	Positive	Random effects	Performed	14 (FE); 7 (RE)
Cocaine	Fatal	4	Positive	Random effects	Not performed	0
	Injury	3	Positive	Random effects	Not performed	0
	Property damage	4	Positive	Random effects	Not performed	0
Opiates	Fatal	7	Positive	Random effects	Performed	5 (FE); 2 (RE)
	Injury	18	Positive	Random effects	Performed	3 (FE); 1 (RE)
	Property damage	1	Not applicable	Fixed effects	Not performed	0
Penicillin	Injury	5	Positive	Random effects	Performed	0
Zopiclone	Fatal	1	Not applicable	Fixed effects	Not performed	0
	Injury	4	Positive	Random effects	Not performed	0
	Property damage	1	Not applicable	Fixed effects	Not performed	0

the data points located near the top of the diagram are less dispersed than those located closer to the bottom. Most of the data points indicate an increase in risk, but the left part of the diagram appears to be less populated by data points than the right, suggesting the possible presence of publication bias. Publication bias denotes the tendency not to publish studies if their findings are not statistically significant, go in the opposite direction of what was expected (e.g. indicating lower risk when drugs are used) or are otherwise regarded as difficult to interpret.

Based on Fig. 2, it was decided to continue the meta-analysis. Summary estimates of risk were developed if at least five estimates of risk were available in the original studies. All levels of accident severity were initially aggregated; subsequently different summary estimates of risk were obtained for each level of accident severity; some of these estimates were based on less than five source estimates. It was possible to obtain summary estimates of risk for eleven different drugs. When three or more estimates of risk were available, it was tested whether there was systematic between-study variation in the estimates of risk. If there was systematic variation (heterogeneity), a random-effects model of meta-analysis was adopted (Borenstein et al., 2009).

3.3. Testing and adjusting for publication bias

If at least five individual estimates of risk were available, a trim-and-fill analysis (Duval and Tweedie, 2000a, 2000b; Duval, 2005) was performed to test and adjust for the possible presence of publication bias. The trim-and-fill technique is based on the assumption that in the absence of publication bias, the data points in a funnel plot ought to be symmetrically distributed around the summary estimate. The technique detects the possible presence of publication bias by testing for asymmetry in the funnel plot by means of three estimators that are based on ranks. Duval and Tweedie (2000a, 2000b) label these estimators *R*, *L* and *Q*; the simpler and more widely used estimators are *R* and *L* and the testing made in this paper was confined to those estimators.

To perform a trim-and-fill analysis, estimates of risk are sorted from the lowest to the highest. A summary estimate of risk is obtained and the differences between the individual estimates of risk and the summary estimate are computed. These differences are then ranked from the smallest to the largest. Ranks are signed. Thus, any estimate of risk lower than the mean gets a negative rank. Any estimate higher than the mean gets a positive rank. The estimator *R* is based on the length of the rightmost number of ranks associated with positive effects, i.e. the number of positive ranks larger than the absolute value of any of the negative ranks. Denoting this length with γ, the estimator is defined by $R_0 = \gamma - 1$. The second estimator is based on the sum of ranks for the positive effects. Denoting the ranks by r_i, the sum of positive ranks is defined by $T_n = \sum_{r_i>0} r_i$, an estimator of the number of missing studies is defined by: $L_0 = \frac{4T_n - n(n+1)}{2n-1}$.

A more detailed technical description of how to perform a trim-and-fill analysis is given in the publications quoted above as well as Høye and Elvik (2010).

Table 5 summarizes the design of the meta-analysis. It shows the groups that were formed and the tests performed in each group. A total of 24 groups were formed by combining type of drug and accident severity. A test for heterogeneity (systematic variation) in estimates of risk was performed for 19 groups. The test was positive in 16 cases. A trim-and-fill analysis was applied in 14 groups. It indicated publication bias in ten cases. Results are presented both with and without adjusting for publication bias.

3.4. Main analysis

Table 6 reports the results of analysis. The risk associated with the use of drugs is stated in terms of a summary odds ratio. The summary odds ratio in each cell of Table 6 is based on between 1 and 51 individual estimates. Estimates that are statistically significant at the 5% level are shown in bold.

Summary estimates of risk based on less than five studies must be regarded as highly uncertain. The largest number of estimates

Table 6
Summary estimates of relative risk of accident involvement associated with the use of various drugs. Based on meta-analysis.

Drug	Accident severity	Number of estimates	Best estimate of odds ratio[a]	95% confidence interval	Best estimate adjusted for publication bias[a]	95% confidence interval
Amphetamine	Fatal	8	**5.61**	(2.74, 11.49)	**5.17**	(2.56, 10.42)
	Injury	2	**6.19**	(3.46, 11.06)	**6.19**	(3.46, 11.06)
	Property damage	1	**8.67**	(3.23, 23.32)	**8.67**	(3.23, 23.32)
Analgesics	Injury	8	1.06	(0.92, 1.21)	1.02	(0.89, 1.16)
Anti-asthmatics	Injury	6	**1.33**	(1.09, 1.62)	**1.31**	(1.07, 1.59)
Anti-depressives	Injury	20	**1.39**	(1.17, 1.70)	**1.35**	(1.11, 1.65)
	Property damage	5	1.28	(0.90, 1.80)	1.28	(0.90, 1.80)
Anti-histamines	Injury	7	**1.12**	(1.02, 1.22)	**1.12**	(1.02, 1.22)
Benzodiazepines	Fatal	10	**2.30**	(1.59, 3.32)	**2.30**	(1.59, 3.32)
	Injury	51	**1.65**	(1.49, 1.82)	**1.17**	(1.08, 1.28)
	Property damage	4	**1.35**	(1.04, 1.76)	**1.35**	(1.04, 1.76)
Cannabis	Fatal	10	1.31	(0.91, 1.88)	1.26	(0.88, 1.81)
	Injury	15	1.26	(0.99, 1.60)	1.10	(0.88, 1.39)
	Property damage	17	**1.48**	(1.28, 1.72)	**1.26**	(1.10, 1.44)
Cocaine	Fatal	4	**2.96**	(1.18, 7.38)	**2.96**	(1.18, 7.38)
	Injury	3	1.66	(0.91, 3.02)	1.66	(0.91, 3.02)
	Property damage	4	1.44	(0.93, 2.23)	1.44	(0.93, 2.23)
Opiates	Fatal	7	**2.13**	(1.23, 3.72)	**1.68**	(1.01, 2.81)
	Injury	18	**1.94**	(1.51, 2.50)	**1.91**	(1.48, 2.45)
	Property damage	1	**4.76**	(2.10, 10.80)	**4.76**	(2.10, 10.80)
Penicillin	Injury	5	1.12	(0.91, 1.39)	1.12	(0.91, 1.39)
Zopiclone	Fatal	1	2.60	(0.89, 7.56)	2.60	(0.89, 7.56)
	Injury	4	1.42	(0.87, 2.31)	1.42	(0.87, 2.31)
	Property damage	1	**4.00**	(1.31, 12.21)	**4.00**	(1.31, 12.21)

[a] Estimates shown in bold are statistically significant at the 5% level.

of risk was found for benzodiazepines. There were 65 estimates of risk in total, of which 10 for fatal accidents, 51 for injury accidents and 4 for property damage only accidents. All summary estimates indicate an increase in the odds ratio of accident involvement associated with using benzodiazepines. The increase in accident risk displays a severity gradient; the increase in risk is largest for fatal accidents, smaller for injury accidents and still smaller for property damage only accidents.

The trim-and fill analysis indicated the presence of substantial publication bias in the estimates of the risk of injury accident associated with using benzodiazepines. Twenty-six new data points were added according to the random-effects analysis. Fig. 3 shows these data points in addition to the original 51 data points.

Adjusting for publication bias by means of the trim-and-fill method reduced the summary odds ratio for involvement in injury accidents from 1.65 to 1.17. The adjusted estimate remains statistically significant at the 5% level.

The second largest number of estimates of risk (42) refers to the use of cannabis. The summary odds ratio indicates that the risk of becoming involved in an accident at any level of severity increases moderately (by about 25–50%) when using cannabis. Evidence of publication bias was found in summary estimates of risk at all levels of accident severity. Adjusting for publication bias lowered all summary estimates of risk. Fig. 4 shows the new data points added by the trim-and-fill analysis of estimates of risk referring to property damage only accidents.

Adjusting for publication bias reduced the summary estimate of the odds ratio of becoming involved in a property damage only accident when using cannabis from 1.48 to 1.26. The adjusted estimate was, however, statistically significant at the 5% level.

As far as the other drugs are concerned, a severity gradient with respect to the increase in risk is seen for cocaine. However, the confidence intervals of the odds ratios for injury accidents and property-damage-only accidents overlap almost completely, which indicates that the small difference in the summary estimates of risk is not statistically significant. For opiates and zopiclone, the pattern is irregular. There is a somewhat greater increase in the risk of a fatal accident than in the risk of an injury accident, but then again a larger increase in the risk of a property-damage-only accident. For both these drugs, however, the differences between fatal accidents and injury accidents with respect to summary estimates of risk are not statistically significant. For amphetamine, an adverse pattern is observed: risk increases more for injury accidents and property damage accidents than for fatal accidents. Again, it should be noted that this trend is not statistically significant.

Some summary estimates of risk are not statistically significant at the 5% level. This applies to the risks associated with analgesics and penicillin. The summary estimate of the risk of property damage only accidents associated with the use of anti-depressives also failed to reach statistical significance.

By and large, the increase in the risk of accident involvement associated with the use of drugs must be regarded as modest. This applies particularly to some of the medicinal drugs. Thus, the odds ratio for accident involvement is 1.06 for analgesics, 1.33 for anti-asthmatics, 1.28–1.39 for anti-depressives, and 1.12 for penicillin. Fifteen of the summary estimates indicate less than a doubling of risk. Compared to the huge increase in accident risk associated with alcohol, as well as the high accident rate among young drivers (Elvik, 2010), the increases in risk associated with the use of drugs are surprisingly small. It should be noted, however, the several of the summary estimates of risk presented in Table 6 are highly uncertain. Thus, nine of the twenty-four summary estimates of risk in Table 6 were not statistically significant at the 5% level.

3.5. Sensitivity analysis

The results of a meta-analysis partly depend on analytic choices made by the analyst (Elvik, 2005). It is important to assess the sensitivity of results of meta-analysis with respect to these choices.

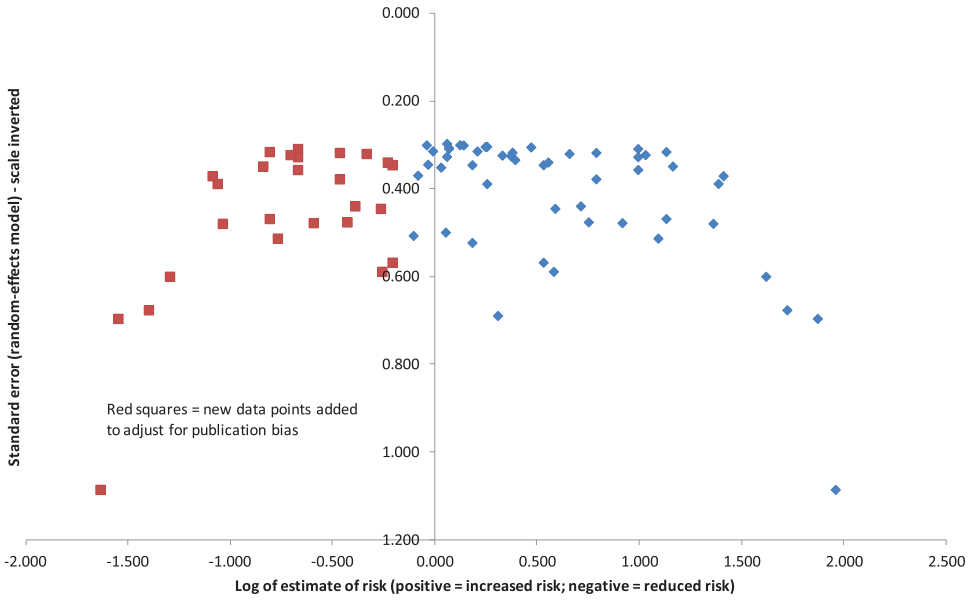

Fig. 3. Funnel plot of estimates of risk associated with use of benzodiazepines – adjusted for publication bias (random-effects model).

The sensitivity of summary estimates of risk has been tested with respect to:

1. How drug use was measured (self report, prescription, laboratory analysis).
2. Study quality.
3. The possible presence of outlying data points.

In the summary estimates of risk presented in Table 6, all estimates were combined, irrespective of how the use of a drug was measured. One may suspect, however, that the imprecision associated with self reported use of drugs, and to some extent use inferred from prescription data might "water down" estimates of risk. The only objective evidence of drug use comes from laboratory analyses of body fluids, which show both the type of drug used and dose present in the body.

A comparison was made of estimates of the odds ratio of accident involvement based on self reported drug use, drug use as known from prescriptions and drug use as inferred from laboratory analyses. To make the comparison as stringent as possible, it was based only on injury accidents and the odds ratio estimator of risk. With these restrictions, the different measures of drug use could only be compared for analgesics, anti-depressives, benzodiazepines, cannabis and cocaine. The results are reported in Table 7.

There is a weak tendency for estimates of risk based on drug use determined by means of laboratory analysis to be higher than estimates of risk based on self reported drug use. The differences are small and the confidence intervals surrounding estimates of risk are very wide. Still, it cannot be ruled out that the increase in accident risk associated with the use of drugs has been slightly underestimated by not relying exclusively on studies that determined drug use by means of laboratory analysis.

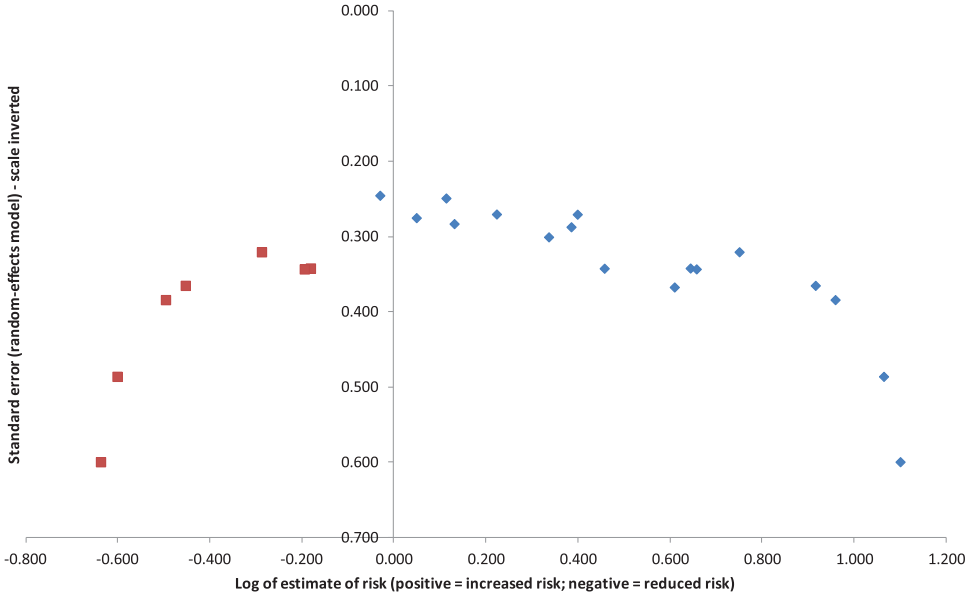

Fig. 4. Funnel plot of estimates of risk associated with use of cannabis – adjusted for publication bias (random-effects model).

Table 7
Comparison of estimates of risk based on different measures of drug use.

Drug	Odds ratio of involvement in injury accident based on three measures of drug use					
	Self reported drug use		Drug use based on prescriptions		Drug use determined by laboratory analysis	
	Best estimate	95% confidence interval	Best estimate	95% confidence interval	Best estimate	95% confidence interval
Analgesics	1.30	(0.92, 1.84)	1.14	(0.91, 1.44)		
Anti-depressives	1.99	(1.28, 3.08)	1.10	(0.77, 1.59)	3.10	(0.54, 17.75)
Benzodiazepines	1.64	(0.96, 2.78)	1.37	(1.20, 1.56)	1.96	(1.34, 2.87)
Cannabis	1.31	(0.80, 2.15)			1.16	(0.79, 1.71)
Cocaine	1.56	(0.79, 3.08)			2.04	(0.58, 7.13)

On the other hand, other sources of error may pull in a different direction. In particular, poor studies tend to be associated with exaggerated estimates of risk, attributable above all to poor control for potentially confounding variables. Houwing et al. (2009) show that poor control for confounding variables in case–control studies is associated with highly misleading estimates of risk, often considerably exaggerating the risk associated with the use of a drug. To test if a similar tendency can be found in the studies included in the meta-analysis, weighted regression analyses were run for all cases in which summary estimates of risk were based on at least five individual estimates. Each individual estimate was assigned its fixed- or random-effect statistical weight, and regressions run with study quality score as independent variable and estimate of risk as dependent variable. The following functions were fitted to the scatter plots: linear, logarithmic, inverse, power, exponential and quadratic. The results are presented in Table 8.

Five of the six functions have a single parameter and will therefore not have a turning point. The quadratic function has two parameters, allowing for one turning point. In the majority of cases, a quadratic function fitted the data best, but the function was rejected as nonsensical in most of these cases. The quadratic functions usually implied negative estimates of risk for studies scoring either high or low for study quality. This is logically impossible, and strongly suggests that the function fitted best simply because it had an additional parameter compared to the single-parameter functions. However, the quadratic functions were accepted if they did not imply negative estimates of risk. To illustrate the relationships found, fitted estimates of risk were calculated for studies scoring 0.20, 0.50 and 0.80 on the quality scale (which ranged from 0 to 1). Due to the small variation of quality scores for studies of the risk associated with the use of penicillin (four studies scored 0.35, the fifth scored 0.30), no meaningful relationship between study quality and the estimate of risk could be found.

As can be seen from Table 8, there is in many cases a tendency for estimates of risk to be higher in poor studies than in good studies. This pattern is not universal, however. Cases can also be found in which there is a positive relationship between study quality and estimate of risk. However, in the majority of cases, high study quality appears to be associated with lower estimates of risk.

Finally, the presence of outlying estimates of risk was assessed. This assessment was made by successively omitting one estimate of risk at a time and re-estimating the summary estimate of risk based on the remaining $N-1$ individual estimates. If the estimate based on $N-1$ individual estimates stayed inside the 95% confidence interval of the summary estimate of risk based on all individual estimates, no individual estimate was classified as outlying. The possible presence of outlying estimates of risk was only tested if there were at least five estimates.

Only one outlying estimate of risk was found. It referred to studies evaluating the risk of fatal accident associated with the use of benzodiazepines. The 95% confidence interval for studies that have evaluated the relationship between use of benzodiazepines and risk of becoming involved in a fatal accident ranges from 1.59 to 3.32. When one of the estimates in the study of Brault et al. (2004) was omitted, the summary estimate of risk dropped from 2.30 (based on N estimates) to 1.58 (based on $N-1$ estimates). This single estimate (3.90) therefore exerts a decisive influence on the summary estimate of risk. The estimate is above the upper 95% confidence limit, but it is not highest reported estimate of risk among the studies included, which was the estimate of 14.40 in the study of Assum (2005). The latter estimate, however, had a smaller statistical weight than the estimate presented by Brault et al. (2004).

4. Discussion

Is the use of drugs while driving associated with an increase in the risk of accident involvement? That was the question that motivated the study reported in this paper. Based on available evidence, the answer to this question is yes. Summary estimates of risk were developed for eleven different drugs. For most of the drugs,

Table 8
Relationship between study quality score and estimates of risk.

Drug	Accident severity	Sign of relationship between quality score and estimate of risk	Best fitting function	Assessment of best fitting function	Alternative function	Summary estimate of risk for all studies	Fittedestimate of risk for quality score of 0.2	Fitted estimate of risk for quality score of 0.5	Fitted estimate of risk for quality score of 0.8
Amphetamines	Fatal	Negative	Exponential	Accepted	None	5.61	7.02	4.71	3.16
Analgesics	Injury	Negative	Quadratic	Rejected	Exponential	1.06	1.19	1.06	0.85
Anti-asthmatics	Injury	Positive	Quadratic	Rejected	Power	1.33	1.05	1.60	1.99
Anti-depressives	Injury	Negative	Quadratic	Rejected	Exponential	1.39	2.03	1.30	0.84
Anti-depressives	PDO[a]	Negative	Quadratic	Rejected	Linear	1.28	1.64	1.28	0.92
Anti-histamines	Injury	Positive	Exponential	Accepted	None	1.12	0.95	1.08	1.23
Benzodiazepines	Fatal	Negative	Quadratic	Rejected	Linear	2.30	3.21	2.57	1.93
Benzodiazepines	Injury	Negative	Exponential	Accepted	None	1.65	2.88	1.43	0.71
Cannabis	Fatal	Curvilinear	Quadratic	Accepted	None	1.31	2.26	1.58	7.03
Cannabis	Injury	Positive	Quadratic	Rejected	Power	1.26	1.04	1.36	1.55
Cannabis	PDO[a]	Curvilinear	Quadratic	Accepted	None	1.48	1.46	3.47	12.08
Opiates	Fatal	Positive	Quadratic	Rejected	Power	2.13	1.63	2.62	3.34
Opiates	Injury	Curvilinear	Quadratic	Accepted	None	1.94	16.16	0.73	21.18

[a] PDO = property damage only.

it was possible to stratify estimates of risk according to accident severity. The summary estimates indicate that the odds ratio of accident involvement increases when drugs are used, but only fifteen of the estimates show a statistically significant increase in risk. The estimates are consistent in the sense that all of them indicate that accident risk increases. On the other hand, estimates of risk vary considerably and some of the variations, if taken at face value, appear difficult to explain.

There is, therefore, reason to remain sceptical to many of the findings reported in this paper. In the first place, it is not always clear that drugs were actually used while driving. Most studies provide no information regarding the situation or circumstances in which drugs were used. However, when a drug has been prescribed, it is likely that it will be taken and that its effects may be present when the user is driving. Moreover, a prescribed drug taken in an excessive dose may affect accident risk more strongly than when only the prescribed dose was taken. Laboratory analyses of blood samples provide the best evidence of drug use. Such analyses provide objective evidence that a drug was actually used and may give a fairly good indication of the dose taken of the drug. Thus, it is likely that most estimates of risk refer to driving that took place while the drug still had an effect, although it may not have been taken when the driver was behind the wheel.

In the second place, to claim that a certain risk factor is causally related to an increase in risk, one must rule out the possibility that the increase in risk was caused by one or more different risk factors. In practice, it is never possible to attain complete control for all confounding factors in observational (i.e. non-experimental) studies. Many of the studies reviewed in this paper did not control very well for confounding factors. It is likely that the estimates of risk in these studies are influenced by residual confounding, i.e. they show an increase in risk which is attributable to a set of correlated risk factors, not just the single risk factor of drug use. A tendency, albeit somewhat inconsistent, was found for well-controlled studies to report lower increases in risk than poorly controlled studies. One should, of course, take this as indicative only. Nevertheless, the evidence is not strong enough to conclude that the use of drugs is causally related to the increases in accident risk. There are fairly consistent statistical associations, but on the whole, control for potentially confounding factors remains too poor to rule out the possibility that these factors may have influenced estimates of risk.

In the third place, there is great heterogeneity in estimates of risk. This study cannot offer any explanation of this heterogeneity. Part of it may be related to study design and the quality of data and statistical analysis; part of it may be real. For most drugs, there are too few studies to compare the results obtained by means of different study designs. Such a comparison was made for benzodiazepines. The weighted mean odds ratio for accident involvement was 1.31 in case–control studies, 1.33 in culpability studies, 1.91 in cohort studies and 1.26 in case-crossover studies. With the exception of cohort studies, these estimates are very close to each other and the confidence intervals overlap considerably.

One potential source of error in meta-analysis is an undetected time trend in estimates of risk. If, over time, estimates of risk show a consistent tendency in a certain direction, failure to account for this may produce summary estimates of risk that are not representative of current knowledge. A test was run for estimates of the risk associated with benzodiazepines. Studies reporting on the risk associated with benzodiazepines span the period from 1976 to 2011. A statistically significant tendency was found for estimates of risk to increase over time (the fitted estimate of risk was 1.33 for the year 1976 and 1.72 for the year 2011). For most of the drugs covered by this study, any test for a time trend would be weak because there are few data points that cover a rather short period of time. As an example, there are eleven estimates of risk for cocaine, covering the period from 1992 to 2010. This period may be too short for any trend to emerge. Extensive testing for the possible presence of trends over time was therefore not performed.

In the fourth place, the practical implications of the findings remain largely unknown. To estimate the contribution that driving under the influence of drugs makes to accidents, it is not enough to know the risk associated with the drugs. One should also know the share of traffic that takes place under the influence of the drugs. If that share is minor, the contribution will be small. But very few roadside studies have been made to determine how common it is to drive after taking drugs.

5. Conclusions

The main conclusions of the research reported in this paper can be summarized as follows:

1. A meta-analysis has been performed of 66 studies reporting a total of 264 estimates of the risk of accident involvement associated with the use of drugs while driving.
2. Summary estimates of risk were developed for eleven different drugs. All these estimates indicate that the use of drugs is associated with an increase in the odds ratio of becoming involved in an accident.
3. The increase in accident risk associated with the use of a drug is in most cases fairly modest; a majority of estimates indicate that the increase in risk is less than 100% (i.e. less than a doubling of the risk).
4. The trim-and-fill test indicates the presence of publication bias for some drugs. Adjusting for publication bias lowers the estimates of risk associated with the use of drugs.
5. Many studies are of modest quality, in particular with respect to the control for potentially confounding factors. A numerical index of study quality was developed; it was found that studies scoring high on this index sometimes reported lower estimates of risk than studies scoring low on the index for study quality.
6. The associations between the use of drugs and accident risk presented in his paper cannot be interpreted as causal relationship. There is a need for more research, embodying better control of confounding factors than past studies and more careful attention to how drug use is measured, preferably relying on laboratory analyses.

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References

Alvarez, F.J., Fierro, I., 2008. Older drivers, medical condition, medical impairment and crash risk. Accident Analysis and Prevention 40, 55–60.

Asbridge, M., Hayden, J.A., Cartwright, J.L., 2012. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. British Medical Journal 344, 1–9, http://dx.doi.org/10.1136/bmj.e536.

Asbridge, M., Poulin, C., Donato, A., 2005. Motor vehicle collision risk and driving under the influence of cannabis: evidence from adolescents in Atlantic Canada. Accident Analysis and Prevention 37, 1025–1034.

Assum, T., 2005. The prevalence and relative risk of drink and drug driving in Norway. Report 805. Institute of Transport Economics, Oslo.

Bachs, L.C., Engeland, A., Mørland, J.G., Skurtveit, S., 2009. The risk of motor vehicle accidents involving drivers with prescriptions for codeine or tramadol. Clinical Pharmacology and Therapeutics 85, 596–599.

Baldock, M.R.J., 2007. Review of the literature on cannabis and crash risk. Case Report Series, CASR010. Centre for Automotive Research, The University of Adelaide, Adelaide.

Barbone, F., McMahon, A.D., Davey, P.G., Morris, A.D., Reid, I.C., McDevitt, D.G., MacDonald, T.M., 1998. Association of road-traffic accidents with benzodiazepine use. Lancet 352, 1331–1336.
Bates, M.N., Blakely, T.A., 1999. Role of cannabis in motor vehicle crashes. Epidemiologic Reviews 21, 222–232.
Bédard, M., Dubois, S., Weaver, B., 2007. The impact of cannabis on driving. Canadian Journal of Public Health 98, 6–11.
Benzodiazepine/Driving collaborative group, 1993. Are benzodiazepines a risk factor for road accidents? Drug and Alcohol Dependence 33, 19–22.
Beylich, K.-M, Bjørneboe, A., Christophersen, A.S., Fosser, S., Glad, A., Mørland, J., 1994. Forekomsten av alkohol og andre rusmidler i blodprøver fra førere innblandet i trafikkulykker. Rapport 248. Transportøkonomisk institutt, Oslo.
Blomberg, R.D., Peck, R.C., Moskowitz, H., Burns, M., Fiorentino, D., 2009. The Long Beach/Fort Lauderdale relative risk study. Journal of Safety Research 40, 285–292.
Blows, S., Ivers, R.Q., Connor, J., Ameratunga, S., Woodward, M., Norton, R., 2005. Marijuana use and car crash injury. Addiction 100, 605–611.
Borenstein, M., Hedges, L.V., Higgins, J.P.T., Rothstein, H.R., 2009. Introduction to Meta-analysis. John Wiley & Sons, Chichester.
Borkenstein, R.F., Crowther, R.F., Shumate, R.P., Ziel, W.B., Zylman, R., 1964. The Role of the Drinking Driver in Traffic Accidents. Department of Police Administration, Indiana University, Bloomington, IN.
Bramness, J.G., Skurtveit, S., Mørland, J., Engeland, A., 2007. The risk of traffic accidents after prescriptions of carisoprodol. Accident Analysis and Prevention 39, 1050–1055.
Bramness, J.G., Skurtveit, S., Neutel, C.I., Mørland, J., Engeland, A., 2008. Minor increase in risk of road traffic accidents after prescriptions of antidepressants: a study of population registry data in Norway. Journal of Clinical Psychiatry 69, 1099–1103.
Brault, M., Dussault, C., Bouchard, J., Lemire, A.M., 2004. The contribution of alcohol and other drugs among fatally injured drivers in Quebec: final results. Paper presented at ICADTS Conference, Glasgow.
Chandraratna, S., Stamatiadis, N., 2009. Quasi-induced exposure: evaluation of not-at-fault assumption. Accident Analysis and Prevention 41, 308–313.
Chipman, M., Macdonald, S., Mann, R., 2002. Interactions between alcohol, cannabis and cocaine in risks of traffic violations and traffic crashes. In: Proceedings of 16th International Conference on Alcohol, Drugs and Traffic Safety, Montreal, pp. 59–64.
Cunradi, C.B., Ragland, R.R., Greiner, B., Klein, M., Fisher, J.M., 2005. Attributable risk of alcohol and other drugs for crashes in the transit industry. Injury Prevention 11, 378–382.
Currie, D., Hashemi, K., Fothergill, J., Findlay, A., Harris, A., Hindmarch, I., 1995. The use of anti-depressants and benzodiazepines in the perpetrators and victims of accidents. Occupational Medicine 45, 323–325.
Davey, J., Freeman, J., 2009. Screening for drugs in oral fluid: drug driving and illicit drug use in a sample of Queensland motorists. Traffic Injury Prevention 10, 231–236.
Dassanayake, T., Michie, P., Carter, G., Jones, A., 2011. Effects of benzodiazepines, antidepressants and opioids on driving. Drug Safety 34, 125–156.
Delaney, J.A.C., Opatrny, L., Suissa, S., 2005. Warfarin use and the risk of motor vehicle crash in older drivers. British Journal of Clinical Pharmacology 61, 229–232.
Drummer, O.H., 1995. Drugs and accident risk in fatally-injured drivers. In: Proceedings of 14th International Conference on Alcohol, Drugs and Traffic Safety, Adelaide.
Drummer, O.H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J., Robertson, M.D., Swann, P., 2004. The involvement of drugs in drivers of motor vehicles killed in Australian road traffic crashes. Accident Analysis and Prevention 36, 239–248.
Dubois, S., Bédard, M., Weaver, B., 2008. The impact of benzodiazepines on safe driving. Traffic Injury Prevention 9, 404–413.
Dubois, S., Bédard, M., Weaver, B., 2010. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. Accident Analysis and Prevention 42, 30–37.
Dussault, C., Brault, M., Bouchard, J., Lemire, A.M., 2002. The contribution of alcohol and other drugs among fatally injured drivers in Quebec: some preliminary results. In: Proceedings of 16th International Conference on Alcohol, Drugs and Traffic Safety, Montreal, pp. 423–430.
Duval, S., Tweedie, R., 2000a. Trim and fill: a simple funnel plot based method of testing and adjusting for publication bias in meta-analysis. Journal of the American Statistical Association 95, 89–98.
Duval, S., Tweedie, R., 2000b. A non-parametric trim and fill method of assessing publication bias in meta-analysis. Biometrics 56, 455–463.
Duval, S., 2005. The trim and fill method. In: Rothstein, H., Sutton, A.J., Borenstein, M. (Eds.), Publication Bias in Meta-analysis: Prevention, Assessment and Adjustments. John Wiley & Sons, Chichester, pp. 127–144.
Elvik, R., 2005. Can we trust the results of meta-analyses? A systematic approach to sensitivity analysis in meta-analyses. Transportation Research Record 1908, 221–229.
Elvik, R., 2008. Making sense of road safety evaluation studies. Developing a quality scoring system. Report 984. Institute of Transport Economics, Oslo.
Elvik, R., 2010. Why some road safety problems are more difficult to solve than others. Accident Analysis and Prevention 42, 1089–1096.
Elvik, R., 2011. A framework for a critical assessment of the quality of epidemiological studies of driver health and accident risk. Accident Analysis and Prevention 43, 2047–2052.
Engeland, A., Skurtveit, S., Mørland, J., 2007. Risk of road traffic accidents associated with the prescription of drugs: a registry-based cohort study. Annals of Epidemiology 17, 597–602.
Etminam, M., Hemmelgarn, B., Delaney, J.A.C., Suissa, S., 2004. Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case–control study nested within a cohort. British Medical Journal 328, 558–559.
Far, A.C., Roig, D.A., Jerez, M.J., Franzke, N.T.B., 2008. Relación del consumo de alcohol y drogas de los jóvenes españoles con la siniestralidad vial durante la vida recreativa nocturna en tres comunidades autónomas en 2007. Revista Español Salud Publica 82, 323–331.
Fergusson, D.M., Horwood, L.J., 2001. Cannabis use and traffic accidents in a birth cohort of young adults. Accident Analysis and Prevention 33, 703–711.
Fergusson, D.M., Horwood, L.J., Boden, J.M., 2008. Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. Accident Analysis and Prevention 40, 1345–1350.
French, D.D., Chirikos, T.N., Spehar, A., Campbell, R., Means, H., Bulat, T., 2005. Effect of concomitant use of benzodiazepines and other drugs on the risk of injury in a veterans population. Drug Safety 28, 1141–1150.
Gerberich, S.G., Sidney, S., Braun, B.L., Tekawa, I.S., Tolan, K.K., Quesenberry, C.P., 2003. Marijuana use and injury events resulting in hospitalization. Annals of Epidemiology 13, 230–237.
Gibson, J.E., Hubbard, R.B., Smith, C.J.P., Tata, O.J., Britton, J.R., Fogarty, A.W., 2009. Use of self-controlled analytical techniques to assess the association between use of prescription medications and the risk of motor vehicle crashes. American Journal of Epidemiology 169, 761–768.
Gjerde, H., Normann, P.T., Christophersen, A.S., Samuelsen, S.O., Mørland, J., 2011. Alcohol, psychoactive drugs and fatal road traffic accidents in Norway: a case–control study. Accident Analysis and Prevention 43, 1197–1203.
Gustavsen, I., Bramness, J.G., Skurtveit, S., Engeland, A., Neutel, I., Mørland, J., 2008. Road traffic accident risk related to prescriptions of the hypnotics zopiclone, zolpidem, flunitrazepam and nitrazepam. Sleep Medicine 9, 818–822.
Hebert, C., Delaney, J.A.C., Hemmelgarn, B., Lévesque, L.E., Suissa, S., 2007. Benzodiazepines and elderly drivers: a comparison of pharmacoepidemiological study designs. Pharmacoepidemiology and Drug Safety 16, 845–849.
Hemmelgarn, B., Lévesque, L.E., Suissa, S., 2006. Anti-diabetic drug use and the risk of motor vehicle crash in the elderly. Canadian Journal of Clinical Pharmacology 13, 112–120.
Hemmelgarn, B., Suissa, S., Huang, A., Boivin, J.-F., Pinard, G., 1997. Benzodiazepine use and the risk of motor vehicle crash in the elderly. Journal of the American Medical Association 278, 27–31.
Hingson, R.W., Heeren, T., Edwards, E.M., 2008. Age at drinking onset, alcohol dependence, and their relation to drug use and dependence, driving under the influence of drugs, and motor-vehicle crash involvement because of drugs. Journal of Studies on Alcohol and Drugs 69, 192–201.
Hingson, R., Heeren, T., Mangione, T., Morelock, S., Mucatel, M., 1982. Teenage driving after using marijuana or drinking and traffic accident involvement. Journal of Safety Research 13, 33–37.
Honkanen, R., Etama, L., Linnoila, M., Alha, A., Lukkari, I., Karlsson, M., Kiviluoto, O., Puro, M., 1980. Role of drugs in traffic accidents. British Medical Journal 281, 1309–1312.
Hours, M., Fort, E., Charnay, P., Bernard, M., Martin, J.-L., Boisson, D., Sancho, P.-O., Laumon, B., 2008. Diseases, consumption of medicines and responsibility for a road crash: a case–control study. Accident Analysis and Prevention 40, 1789–1796.
Houwing, S., Mathijssen, R., Brookhuis, K.A., 2009. Case–control studies. In: Verster, J.C., Pandi-Perumal, S.R., Ramaekers, J.G., de Gier, J.J. (Eds.), Drugs, Driving and Traffic Safety. Birkhäuser Verlag, Switzerland, pp. 107–120.
Høye, A., Elvik, R., 2010. Publication bias in road safety evaluation. How can it be detected and how common is it? Transportation Research Record 2147, 1–8.
Jick, H., Hunter, J.R., Dinan, B.J., Madsen, S., Stergachis, A., 1981. Sedating drugs and automobile accidents leading to hospitalization. American Journal of Public Health 71, 1399–1400.
Keall, M.D., Frith, W.J., Patterson, T.L., 2004. The influence of alcohol, age and number of passengers on the night-time risk of driver fatal injury in New Zealand. Accident Analysis and Prevention 36, 49–61.
Lagarde, E., Chastang, J.-F., Lafont, S., Coeuret-Pellicer, M., Chiron, M., 2005. Pain and pain treatment were associated with traffic accident involvement in a cohort of middle-aged workers. Journal of Clinical Epidemiology 58, 524–531.
Lam, L.T., Norton, R., Connor, J., Ameratunga, S., 2005. Suicidal ideation, antidepressive medication and car crash injury. Accident Analysis and Prevention 37, 335–339.
Lardelli-Claret, P., Luna-del-Castillo, J., Jimenez-Moleon, J.J., Rudea-Dominguez, T., Garcia-Martin, M., Femia-Marzo, P., Bueno-Cavanillas, A., 2003. Association of main driver-dependent risk factors with the risk of causing a vehicle collision in Spain, 1990–1999. Annals of Epidemiology 13, 509–517.
Laumon, B., Gadegbeku, B., Martin, J.-L., Biecheler, M.-B., 2005. Cannabis intoxication and fatal road crashes in France: population based case–control study. British Medical Journal 331, 1371–1376.
Lenguerrand, E., Martin, J.-L., Moskal, A., Gadegbeku, B., Laumon, B., 2008. Limits of the quasi-induced exposure method when compared with the standard case–control design. Application to the estimation of risks associated with driving under the influence of cannabis or alcohol. Accident Analysis and Prevention 40, 861–868.
Leveille, S.G., Buchner, D.M., Koepsell, T.D., McCloskey, L.W., Wolf, M.E., Wagner, E.H., 1994. Psychoactive medications and injurious motor vehicle collisions involving older drivers. Epidemiology 5, 591–598.

Lia, K., Spigset, O., Slørdal, L., 2009. Kjøring under påvirkning av amfetamin og metamfetamin. Tidsskrift for Den norske legeforening 129, 105–108.
Longo, M.C., Hunter, C.E., Lokan, R.J., White, J.M., White, M.A., 2000. The prevalence of alcohol, cannabinoids, benzodiazepines and stimulants amongst injured drivers and their role in driver culpability. Part II: The relationship between drug prevalence and drug concentration, and driver culpability. Accident Analysis and Prevention 32, 623–632.
Longo, M.C., Lokan, R.J., White, J.M., 2001. The relationship between blood benzodiazepine concentration and vehicle crash culpability. Journal of Traffic Medicine 29, 36–43.
Lowenstein, S.R., Koziol-McLain, J., 2001. Drugs and traffic crash responsibility: a study of injured motorists in Colorado. Journal of Trauma: Injury, Infection, and Critical Care 50, 313–320.
Macdonald, S., Mann, R.E., Chipman, M., Anglin-Bodrug, K., 2004. Collisions and traffic violations of alcohol, cannabis and cocaine abuse clients before and after treatment. Accident Analysis and Prevention 36, 795–800.
MacPherson, R.D., Perl, J., Starmer, G.A., Homel, R., 1984. Self-reported drug-usage and crash-incidence in breathalyzed drivers. Accident Analysis and Prevention 16, 139–148.
Majdzadeh, R., Feiz-Zadeh, A., Rajabpour, Z., Motevalian, A., Hosseini, M., Abdollah, M., Ghadirian, P., 2009. Opium consumption and the risk of traffic injuries in regular users: a case-crossover study in an emergency department. Traffic Injury Prevention 10, 325–329.
Mann, R.E., Adlaf, E., Zhao, J., Stoduto, G., Ialomiteanu, A., Smart, R.G., Asbridge, M., 2007. Cannabis use and self-reported collisions in a representative sample of adult drivers. Journal of Safety Research 38, 669–674.
Marowitz, L.A., 1995. Drug arrests and driving risks. Alcohol, Drugs and Driving 11, 1–22.
Mathijssen, M.P.M., Houwing, S., 2005. The risk of drink and drug driving – results of a case–control study conducted in the Netherlands. In: Proceedings of Drugs and Traffic: A Symposium, 22–35. Transportation Research Circular, E-circular E-C096, Transportation Research Board, Washington, DC.
McGwin, G., Sims, R.V., Pulley, L., Roseman, J.M., 2000. Relations among chronic medical conditions, medications, and automobile crashes in the elderly: a population-based case–control study. American Journal of Epidemiology 152, 424–431.
Meulemans, A., Hooft, P., Camp, L., van, 1998. Belgian toxicology and trauma study (BTTS): a study on alcohol, medication and illicit drugs in drivers/victims of road traffic accidents. Report 1998: NK-101.
Movig, K.L.L., Mathijssen, M.P.M., Nagel, P.H.A., van Egmond, T., de Gier, J.J., Leufkens, H.G.M., Egberts, A.C.G., 2004. Psychoactive substance use and the risk of motor vehicle accidents. Accident Analysis and Prevention 36, 631–636.
Mura, P., Kintz, P., Ludes, B., Gaulier, J.M., Marquet, P., Martin-Dupont, S., Vincent, F., Kaddour, A., Goullé, J.P., Nouveau, J., Moulsma, M., Tilhet-Coartet, S., Pourrat, O., 2003. Comparison of the prevalence of alcohol, cannabis and other drugs between 900 injured drivers and 900 control subjects: results of a French collaborative study. Forensic Science International 133, 79–85.
Neutel, C.I., 1995. Risk of traffic accident injury after a prescription for a benzodiazepine. Annals of Epidemiology 5, 239–244.
Neutel, I., 1998. Benzodiazepine-related traffic accidents in young and elderly drivers. Human Psychopharmacology Clinical Experiments 13, 115–123.
Orriols, L., Delorme, B., Gadegbeku, B., Tricotel, A., Contrand, B., Laumon, B., Salmi, L.-R., Lagarde, E., 2010. Prescription medicines and the risk of road traffic crashes: a French registry-based study. Public Library of Science Medicine 7 (11), 1–9.
Orriols, L., Philip, P., Moore, N., Gadegbeku, B., Delorme, B., Mallaret, M., Lagarde, E., 2011. Benzodiazepine-like hypnotics and the associated risk of road traffic accidents. Clinical Pharmacology and Therapeutics (advanced online publication).
Orriols, L., Salmi, L.-R., Philip, P., Moore, N., Delorme, B., Castot, A., Lagarde, E., 2009. The impact of medicinal drugs on traffic safety: a systematic review of epidemiological studies. Pharmacoepidemiology and Drug Safety 18, 647–658.
Oster, G., Russell, M.W., Huse, D.M., 1987. Accident- and injury-related health-care utilization among benzodiazepine users and nonusers. Journal of Clinical Psychiatry 48 (12, supplement), 17–21.
Oster, G., Huse, D.M., Adams, S.F., Imbimbo, J., Russell, M.W., 1990. Benzodiazepine tranquilizers and the risk of accidental injury. American Journal of Public Health 80, 1467–1470.
Oyefeso, A., Schifano, F., Ghodse, H., Cobain, K., Dryden, R., Corkery, J., 2006. Fatal injuries while under the influence of psychoactive drugs: a cross-sectional exploratory study in England. BMC Public Health 6, 148–159.
Pasnin, L.T., Løsnæs, S., Smedstad, G., Moe, D., Nordtømme, M.E., 2009. Hvem fortjener politiets oppmerksomhet? En studie av dødsulykkene i trafikken i 2004 og 2005. Utrykningspolitiets temahefte 2/2009. Utrykningspolitiet, Stavern.
Pulido, J., Barrio, G., Lardelli, P., Bravo, M.J., Regidor, E., de la Fuente, L., 2010. Association between cannabis and cocaine use, traffic injuries and use of protective devices. European Journal of Public Health (e-publication November 10).
Ramaekers, J.G., Berghaus, G., van Laar, M., Drummer, O.H., 2004. Dose related risk of motor vehicle crashes after cannabis use. Drug and Alcohol Dependence 73, 109–119.
Rapoport, M.J., Molnar, F., Rochon, P.A., Juurlink, D.N., Zagorski, B., Seitz, D., Morris, J.C., Redelmeier, D.A., 2008. Psychotropic medications and motor vehicle collisions in patients with dementia. Journal of the American Geriatrics Society 56, 1968–1970.
Rapoport, M.J., Lanctôt, K.L., Streiner, D.L., Bédard, M., Vingilis, E., Murray, B., Schaffer, A., Shulman, K.I., Herrmann, N., 2009. Benzodiazepine use and driving: a meta-analysis. Journal of Clinical Psychiatry 70, 663–673.
Ray, W.A., Fought, R.L., Decker, M.D., 1992. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. American Journal of Epidemiology 136, 873–883.
Richer, I., Bergeron, J., 2009. Driving under the influence of cannabis: links with dangerous driving, psychological predictors, and accident involvement. Accident Analysis and Prevention 41, 299–307.
del Río, M.C., Alvarez, F.J., 2000. Presence of illegal drugs in drivers involved in fatal road traffic accidents in Spain. Drug and Alcohol Dependence 57, 177–182.
del Río, M.C., Gómez, J., Sancho, M., Alvarez, F.J., 2002. Alcohol, illicit drugs and medicinal drugs in fatally injured drivers in Spain between 1991 and 2000. Forensic Science International 127, 63–70.
Sagberg, F., 2006. Driver health and crash involvement: a case–control study. Accident Analysis and Prevention 38, 28–34.
Shadish, W.R., Haddock, C.K., 1994. Combining estimates of effect size. In: Cooper, H., Hedges, L.V. (Eds.), The Handbook of Research Synthesis. Russell Sage Foundation, New York, pp. 261–281 (Chapter 18).
Sheridan, J., Bennett, S., Coggan, C., Wheeler, A., McMillan, K., 2006. Injury associated with metamphetamine use: a review of the literature. Harm Reduction Journal 3, 14–21.
Skegg, D.C.G., Richards, S.M., Doll, R., 1979. Minor tranquillisers and road accidents. British Medical Journal 1, 917–919.
Smart, R.G., Fejer, D., 1976. Drug use and driving risk among high school students. Accident Analysis and Prevention 8, 33–38.
Smink, B.E., Egberts, A.C.G., Lusthof, K.J., Uges, D.R.A., de Gier, J.J., 2010. The relationship between benzodiazepine use and traffic accidents. A systematic literature review. Central Nervous System Drugs 24, 639–653.
Smink, B.E., Ruiter, B., Lusthof, K.J., de Gier, J.J., Uges, D.R.A., Egberts, A.C.G., 2005. Drug use and the severity of a traffic accident. Accident Analysis and Prevention 37, 427–433.
Sterne, J.A.C., Egger, M., 2001. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of Clinical Epidemiology 54, 1046–1055.
Swann, P., 2000. The real risk of being killed when driving whilst impaired by cannabis. In: Paper presented at ICADTS conference 2000, Stockholm.
Tamblyn, R., Abrahamowicz, M., du Berger, R., McLeod, P., Bartlett, G., 2005. A 5-year prospective assessment of the risk associated with individual benzodiazepines and doses in elderly users. Journal of the American Geriatrics Society 53, 233–241.
Terhune, K.W., 1983. An evaluation of responsibility analysis for assessing alcohol and drug crash effects. Accident Analysis and Prevention 15, 237–246.
Terhune, K.W., Ippolito, C.A., Hendricks, D.L., Michalovic, J.G., Bogema, S.C., Santinga, P., Blomberg, R., Preusser, D.F., 1992. The incidence and role of drugs in fatally injured drivers. Report DOT HS 808 065. U.S. Department of Transportation, National Highway Traffic Safety Administration, Washington, DC.
Thomas, R.E., 1998. Benzodiazepine use and motor vehicle accidents. Systematic review of reported associations. Canadian Family Physician 44, 799–808.
Vernon, D.D., Diller, E.M., Cook, L.J., Reading, J.C., Suruda, A.J., Dean, J.M., 2002. Evaluating the crash and citation rates of Utah drivers licensed with medical conditions, 1992–1996. Accident Analysis and Prevention 34, 237–246.
Vingilis, E., Wilk, P., 2008. The effects of health status, distress, alcohol and medicinal drug use on subsequent motor vehicle injuries. Accident Analysis and Prevention 40, 1901–1907.
Wadsworth, E.J.K., Moss, S.C., Simpson, S.A., Smith, A.P., 2003. Preliminary investigation of the association between psychotropic medication use and accidents, minor injuries and cognitive failures. Human Psychopharmacology Clinical Experiments 18, 535–540.
Wadsworth, E.J.K., Moss, S.C., Simpson, S.A., Smith, A.P., 2005. Psychotropic medication use and accidents, injuries and cognitive failures. Human Psychopharmacology Clinical Experiments 20, 391–400.
Williams, A.F., Peat, M.A., Crouch, D.J., Wells, J.K., Finkle, B.S., 1985. Drugs in fatally injured young male drivers. Public Health Reports 100, 19–25.
Woratanarat, P., Ingsathit, A., Suriyawongpaisal, P., Rattanasiri, S., Chatchaipun, P., Wattayakorn, K., Anukarahanonta, T., 2009. Alcohol, illicit and non-illicit psychoactive drug use and road traffic injury in Thailand: a case–control study. Accident Analysis and Prevention 41, 651–657.
Yang, Y.-H., Lai, J.-N., Lee, C.-H., Wang, J.-D., Chen, P.-C., 2011. Increased risk of hospitalization related to motor vehicle accidents among people taking Zolpidem: a case-crossover study. Journal of Epidemiology, 2010 (on-line publication October 23).
Zador, P.L., Krawchuk, S.A., Voas, R.B., 2000. Relative risk of fatal and crash involvement by BAC, age and gender. Report DOT HS 809 050. U.S. Department of Transportation, National Highway Traffic Safety Administration, Washington, DC.