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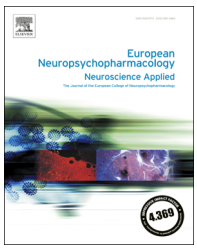

REVIEW

Amphetamine-type stimulant use and the risk of injury or death as a result of a road-traffic accident: A systematic review of observational studies

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Abstract
Amphetamine-type substances are frequently detected among drivers injured or killed due to road-trauma. However, the role of this substance in crash causation remains equivocal. We performed a systematic review to evaluate existing evidence regarding the association between amphetamine use and the risk of injury or death due to road traffic accidents. A bibliographical search of PubMed, SafetyLit, Scopus, and Science Direct literature databases from 01 January 1980 until May 2015 was performed. The quality of included studies was assessed using the Newcastle-Ottowa Scale (NOS) (cut-off of ≥ 7 indicated high quality). Inter-rater reliability between three independent reviewers for the NOS was calculated using Cohens kappa (κ) statistic, and best-evidence synthesis was performed. A total of 182 articles were found. Nine studies met eligibility criteria for inclusion for review, and seven studies were included for best-evidence synthesis. Best-evidence synthesis demonstrated a conflicting level of evidence for associations between the use of-amphetamine-type substances and the risk of sustaining an injury, and a moderate level of evidence between amphetamine use and the risk of death due to road trauma. This is the first review to synthesise evidence regarding the association between amphetamine-type substance use and the risk of injury or death due to a road traffic accident. More conclusive evidence of death due to road trauma among amphetamine users

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may reflect significant and global deficits in functioning associated with effective vehicular control under the influence of this substance. Additional high quality, sufficiently powered studies are required to elucidate the magnitude of these associations.

1. Introduction

Driving under the influence of alcohol is known to result in a significantly increased risk for being severely injured or killed as a result of road traffic accident. Conversely, considerably less is known about the role of substances other than alcohol, particularly psychoactive substances such as amphetamines, and the relative risk of injury or death as a result of traffic accidents due to intoxication. Some limited and conflicting experimental studies have indicated that the consumption of amphetamine-type substances produce significant deficits in behavioural and cognitive domains associated with driving ability, translating to increased accident risk; however, other studies have observed no significant association (Brookhuis et al., 2004). Although a few systematic and narrative reviews exist which assess the relative role of illicit drugs in accident risk (Asbridge et al., 2012), there are currently no systematic evaluations explicitly assessing the role of amphetamine-type substances in attenuating this association.

Extant research has demonstrated that a linear, dose-response relationship exists between alcohol consumption and the relative risk of being involved in a road traffic accident. Substantial numbers of observational (Drummer et al., 2004; Movig et al., 2004), laboratory-based (Gawron and Ranney, 1988; Mets et al., 2011) and on road experimental (Ramaekers et al., 2000), review (Ogden and Moskowitz, 2004) and meta-analytic studies (Taylor et al., 2010) have described the strength of the association between alcohol consumption and the risk of sustaining severe or fatally injury as a result of a traffic incident. Conversely, substantially less is known about the relative risk of being involved in a road traffic accident as a direct result of illicit drugs. Although limited systematic review articles are available evaluating the role of some classes of illicit substances, such as barbiturates (Rapoport et al., 2009; Thomas, 1998) and cannabanoids (Asbridge et al., 2012; Li et al., 2012) and the risk of injury or death due to traffic accidents, inferences regarding the collective role of new-class psychoactive substances, such as amphetamines, and relative risk of injury or death as a result of a road traffic accident are currently equivocal.

Limited lab-based experimental simulation (Silber et al., 2005; Stough et al., 2012) and observational (Drummer et al., 2004; Gjerde et al., 2011) studies have indicated a significantly increased accident risk following the consumption of amphetamine-type substances, however, this finding is not universal, with some studies reporting no such association (Brookhuis et al., 2004; Silber et al., 2012). Although restricted observational research has suggested an increased risk of being involved in a vehicular accident due to amphetamine use, these findings are often impeded by the concurrent detection of other psychoactive substances among injured or killed drivers, such as cocaine (Bogstrand et al., 2012; Sharwood et al., 2013), or by lack of distinction between illicit substances (Ramli et al., 2014). Thus it is difficult to draw conclusive arguments regarding the relative impact of amphetamine consumption alone. Indeed, there is paucity of systematic assessments collating and evaluating the magnitude of these reported associations in isolation, and thus it is problematic to reconcile whether the use of these substances represents a true independent risk factor for sustaining serious injury or being killed in a road traffic accident, particularly beyond a lab-based environment. Elvik (2013) reviewed observational studies that assessed the risk of accidents associated with the use of drugs whilst driving. Here it was reported that amphetamine use was associated with an increased risk of being injured or killed as a result of a traffic accident, or for incurring property damage as a result of the incident. When stratified by fatal-only studies as a function of study quality, although significant, a negative relationship was observed between study quality and accident risk. Despite these assertions, several areas of investigation remain. Inferences from available reviews regarding the extent of the reported associations are often impeded by inherent methodological flaws, such as small study numbers included for analyses and omission of evaluation of study quality, lack of distinction between the types of drugs assessed, and as the use of non-standardised subgroup analyses assessing peripheral crash indices.

Preliminary observational and experimental research, coupled with limited review articles and meta-analytic studies have indicated that the use of amphetamine-type substances is associated with an increased risk of being involved in a road-traffic accident (Brookhuis et al., 2004; Gawron and Ranney, 1988; Mets et al., 2011; Movig et al., 2004). Despite this, there is currently no research explicitly and systematically reconciling the observations provided from observational research, and thus it is unclear whether the magnitude of these associations are truly representative of an increased risk. Therefore, the aim of current study is to collate extant data regarding the use of amphetamine-type substances and the relative risk of being injured or killed as a result of a road-traffic accident. Such assessments have potential to inform both legislative and preventative approaches.

2. Experimental procedures

This systematic review adheres to the guidelines addressed in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement 2009 (Moher et al., 2009)

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(Additional File 1). Methods of analysis, inclusion and exclusion criteria were performed using a standardized protocol, and are outlined below.

2.1. Eligibility criteria for considering studies for this review

Studies were eligible for inclusion if: (1) the article was available as a full text article; (2) the study investigated the association between the presence of amphetamines and amphetamine-type substances and the risk for injury or death as a result of single or multiple road-traffic accidents. Substances evaluated included; amphetamine, methamphetamine, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA), mephentermine, (MDEA), paramethoxyamphetamine (PMA), ephedrine, dexamphetamine, phentermine and pseudoephedrine. Road traffic accidents were defined as a 'collision or incident that may or may not lead to injury or death, occurring on a public road and involving at least one moving vehicle'. Where appropriate, relevant negative driving behaviours and driver safety behaviours were described according to the original study designs of the included studies. Vehicles were inclusive of cars, vans, sport utility vehicles, light or heavy trucks, buses, motorcycles or scooters, all-terrain vehicles, and/or snowmobiles; and (3) employed epidemiological observational cohort, case-control, cross-sectional, culpability, case cross-over or sample survey design.

2.2. Criteria for excluding studies

Studies were excluded if they: (1) were published in languages other than English; (2) did not explicitly assess amphetamines and accident risk (i.e. assessed other substances or presented exposure only); (3) the study did not report sufficient statistical indication of risk to be included (such as OR and/or RR); or (4) if the study was a review article or book.

2.3. Search strategy for identification of studies

A computerised search strategy was implemented using PubMed, SafetyLit, Scopus, and Science Direct literature databases for citations of relevant articles, which were restricted to January 1980 to 31st May 2015. The following medical subject headings (MeSH) were applied: "Amphetamines" AND "accident" AND "Driv*" AND "risk", and additional key words included "road traffic" or "collision" or "crash" or "transport* or "trauma" or "drug". Three reviewers confirmed the search strategy (ACH LAD and CS) and one reviewer performed the computerised search (ACH). The complete search strategy can be obtained from the corresponding author.

The reference lists of all articles selected were also manually searched (ACH). Two reviewers (ACH and LAD) then confirmed the selection of articles according to the above set of criteria based on the reading of the full text article. In case of disagreement, two reviewers (ACH, and LAD) tried to achieve consensus; if disagreements were not resolved, a third reviewer (CS) was consulted to achieve a final judgment.

2.4. Data analysis

The reported odds ratio (OR), risk ratio or culpability ratio provided within the eligible studies were obtained. Where appropriate, both the crude values and those values adjusted for potentially confounding variables were assessed and reported. The culpability ratio provided in one study (Poulsen et al., 2014) was converted to derive a point estimate odds ratio by dividing the culpability ratio of the particular portion of the driver population culpable by the culpability ratio of the control group. Heterogeneity between studies was initially evaluated with the I^2 statistic as a measure of the proportion of total variation in estimates due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity, respectively. Initial assessment of the uniformity of the included studies using meta analytic software (RevMan) (Collaboration, 2003) revealed significant heterogeneity between a sub-set of four eligible case-control studies (Gjerde et al., 2013; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004) ($Chi^2=12.00$, $df=3$ ($p=0.007$); $I^2=75\%$). Assessment of heterogeneity of the remaining four case-control studies (Bernhoft et al., 2012; Bogstrand et al., 2015; Gadegbeku et al., 2011; Gjerde et al., 2011) was not performed due to missing information (such as specific exposure rates between cases and controls for amphetamines), and assessment of study heterogeneity of the $n=1$ cohort study was not appropriate (Poulsen et al., 2014). As a result, we decided to apply a 'best evidence synthesis' approach to all case-control and cohort studies, which comprised a modified version of that previously outlined by Lievense and colleagues (see Table 1) (Lievense et al., 2001). Using this method we performed two separate assessments of the impact of amphetamine consumption on non-fatal or fatal outcomes.

We were unable to assess publication bias using traditional quantitative methods such as a funnel plot as the total number of studies included for analysis fell below the recommended threshold for acceptable sample size

Table 1 Criteria for ascertainment of evidence level for best-evidence synthesis, adapted from Lievense et al., 2001.

Level of evidence	Criteria for inclusion in best evidence synthesis
Strong evidence	Generally consistent findings in: Multiple high-quality case-control studies
Moderate evidence	Generally consistent findings in: One high-quality case-control study and >2 high quality cohort studies
Limited evidence	Generally consistent findings in: Single case control study One or two cohort studies or Multiple cross-sectional studies
Conflicting evidence	Inconsistent findings in <75% of the trials
No evidence	No studies could be found

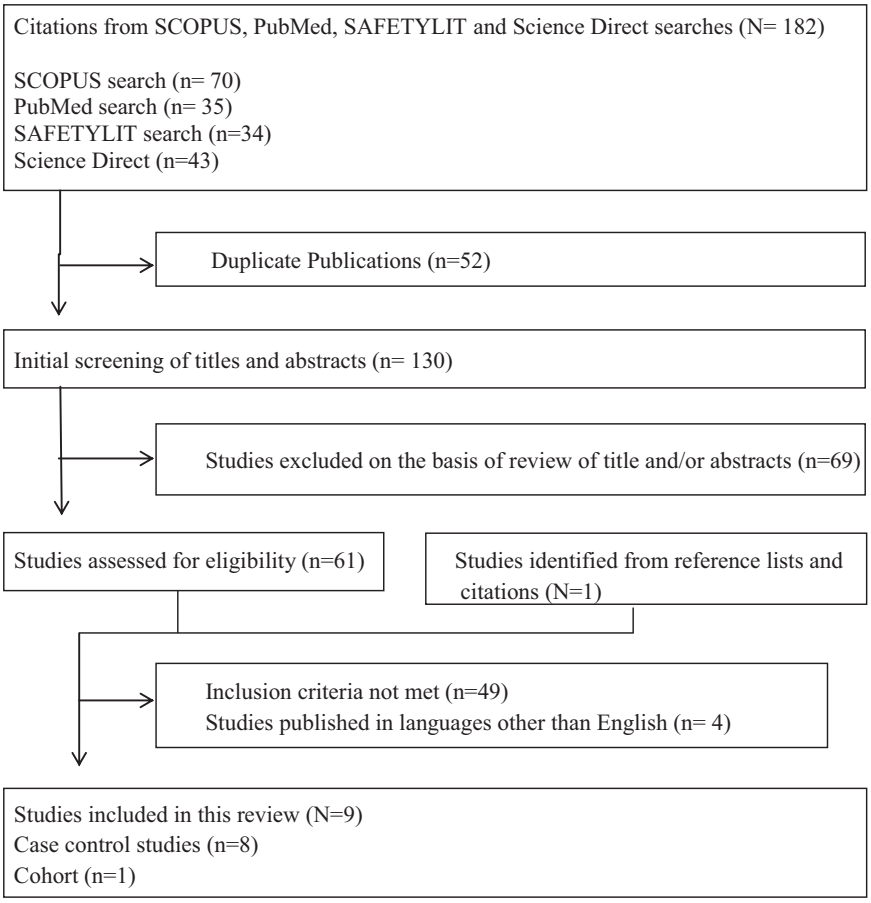

Figure 1 Summary of the systematic search presented as an adapted consort diagram.

($N = \geq 10$ studies) (Macaskill et al., 2001).

2.5. Assessment of study quality

2.5.1. Newcastle-Ottowa Scale

To assess the quality of the included studies, a modified version of the Newcastle-Ottowa Scale for both case-control and cohort studies was applied (Wells et al., 2000). The instrument evaluates observational studies based on three criteria, whereby a quality score is calculated on the basis of three major components: (i) selection of the groups of study (0-4 points), (ii) quality of the adjustment for confounding (0-2 points) and (iii) ascertainment of the exposure or outcome of interest in the case-control or cohorts, respectively (0-3 points), and is intended to assess for selection and attrition bias on the basis of the selection, applicability and comparability of study groups. We chose to assess for the confounding factors of (i) age and (ii) gender, as these are consistently reported in studies of this nature. Scale criteria were independently scored by three authors (ACH, LAD and BS). Each of the nine criteria items were scored as follows for analyses: positive (1), negative (0), or unclear (0). A fourth reviewer (CS) provided a final judgment where the reviewers' agreement could not be reconciled. Inter-rater reliability and consistency between scorers was assessed. Inter-rater reliability consensus was satisfied when 100% agreement was met on all criteria. At present there is no universally applied cut off score to indicate study quality using the NOS (Wells et al., 2000). We specified *a priori* that a score of seven or more indicated high methodological quality, a score of six indicated moderate quality, and a score of five or less indicated low quality (out of a possible nine).

2.5.2. Lievense method for best-evidence synthesis

Only high-quality studies (NOS score ≥ 7) were included in the best evidence synthesis. For the current study, the 'best-evidence synthesis' consisted of five levels of evidence ranging from strong evidence (1), moderate evidence (2), limited evidence (3), conflicting evidence (4), to no evidence (5), which reflected the type of study design used (see Table 1). Due to the nature of the research area and the type of studies often observed in this field of research, the optimal design was considered to be case-control studies, followed by cohort studies, and, finally, cross-sectional study designs.

3. Results

3.1. Identification and selection of the included manuscripts

Utilising using PubMed, SafetyLit, Scopus, Science Direct and the TRANSOPT literature database, the computer-assisted search generated a total of 182 articles, 52 of which were duplicates. The title and/or abstracts of the remaining 130 articles were screened for eligibility, of

Table 2 Study characteristics of eligible studies included in this review, grouped by study design, year of publication, and author.

Author, country of study, year.	*N* subjects (% female)	Age, years, (±SD) or range, yr, or age group, yr, *n* (%)	Population description	Drug assessment			Accident assessment	
				Tool	Drug classes assessed	Threshold for detection of amphetamines	Tool	Type assessed
Case control								
Movig et al., The Netherlands, 2004	*N*=916 (26) Cases: 110 (26) Control: 816 (26)	38.6 ([a]), [a], Age group 18-25: 31 (28) 25-34: 35 (32) 35-49: 28 (26) ≥50: 16 (14)	Cases: Injured car or van drivers admitted to the emergency department of St. Elizabeth Hospital, Denmark from May 2000 until August 2001. Control: Drivers randomly selected from traffic during 20 roadside sessions, for a duration of 6-h/session, located along main roads of the Tilburg district, which covers the area of St. Elizabeth Hospital	Urine and blood sample, with confirmatory analyses using gas chromatography mass spectrometry (GC-MS) techniques (all participants.	Alcohol, amphetamines, barbiturates, benzodiazepine, cannabis, methadone, opiates, tricyclic antidepressants	[a]	Hospital records, ISS	Driver injury
Laumon et al., France, 2005	*N*=9772 (15.1), [a] Cases: 6766 ([a]) Control: 3006 ([a])	[a] Age group (all drivers)	Cases: Drivers located in France from October 2001 to September 2003, and who were involved in fatal crashes resulting in immediate death and who were deemed to be at fault Control: Drivers located in France	Urine, with confirmatory blood sample (all participants)	Cannabis, amphetamines, opiates, cocaine	50 ng/ml	Hospital records	Fatality

Table 2 (*continued*)

Author, country of study, year.	*N* subjects (% female)	Age, years, (±SD) or range, yr, or age group, yr, *n* (%)	Population description	Drug assessment			Accident assessment	
				Tool	Drug classes assessed	Threshold for detection of amphetamines	Tool	Type assessed
		≤24: 2339 (24.5), 25-34: 2379 (24.3), 35-69: 4436 (45.4), ≥70: 558 (5.7).	from October 2001 to September 2003 who were involved in fatal crashes resulting in immediate death and who were deemed to not be at fault.					
Gjerde et al., Norway, 2011	*N*= 10,744 ([a])	[a], (cases- total)	Cases: Persons injured or killed in a road traffic accident in Norway (data collected as part of the Norwegian Road Accident Registry).	Blood sample (cases), oral fluid sample (controls)	Alcohol (ethanol), Alprazolam, Amphetamines, Carisoprodol, Clonazepam, Cocaine, Codeine, Diazepam, Flunitrazepam, Methadone, methamphetamine, Morphine, Nordiazepam, Nitrazepam, Oxazepam, Tetrahydrocannabinol, Zolpidem, Zopiclone, 3,4-methylenedioxy-N-methylamphetamine	Amphetamine: 20 ng/ml Methamphetamine: 22 ng/ml	Toxicology database of the Norwegian Institute for Public health (NIPH)	Severe injury or fatality
	Cases: 204 (21.1) Control: 10,540 (30.5)	<25: 39 (19.1), 25-34: 43 (21.1), 45-54 (38 (18.6), 55-64: 24 (11.8), >64 (35 (17.2). (Cases- single vehicle accident) <25: 21 (30.9), 25-34: 12 (17.6), 35-44: 14 (20.6), 45-54: 6 (8.8), 55-64 : 7 (10.3), >64: 8 (11.8). (Controls) <25: 980 (9.43), 25-34: 1809 (17.2), 35-44: 2443 (23.2), 45-	Control: Car and van drivers included in a roadside survey among random drivers performed in South-eastern Norway from April 2005-March 2006.					

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		54: 2365 (22.4), 55-64: (1940 (18.4), >65: 1001 (9.5)						
Gadegbeku et al., France, 2011	*N*=6932 ([a]) Cases: 4946 ([a]) Control: 1986 ([a])	[a]	Cases: Drivers involved in traffic accidents between October 2001 and September 2003 and who are considered responsible. Control: Drivers involved in traffic accidents between October 2001 and September 2003 and are not considered responsible.	Alcohol: Breath test with blood test if breath test refused/unable to obtain Illicit substances: Urine test with confirmatory blood test	Cannabis, Amphetamines, Opiates, Alcohol.	20 ng/ml	Hospital records	Severe injury, fatality
Bernhoft et al. Europe, 2012	*N*=48, 542 ([a]) 1.) Injured drivers, total *N*=1118.	[a]	Cases: Injured or killed car or van drivers assessed as part of the DRUID project between 2007 and 2010.	Blood test (cases), saliva and/or blood test (controls)	Alcohol (ethanol), 6-AM, Amphetamines (MDEA, MDA, MDMA, Methamphetamine), Benzodiazepines (Benzoylecgonine, Clonazepam, Diazepam, Flunitrazepam, Lorazepam, Nordiazepam, Oxazepam), Cocaine, Medicinal Opiates (Codeine, Methadone, Morphine, Tramadol), THC, Z-drugs (Zolpidem, Zopiclone),	20 ng/ml (blood), 360 ng/ml (saliva)	Hospital records	Severe injury (DK, FI, LT, IT, BE, NL) or fatality (FI, NO, S and PT)
	(i) Northern Europe: DK: *N*=3841 (Cases:839 Control 3002); FI: *N*=2760 (Cases:54, Control: 2706); NO: *N*=9429 Cases: 193, Control: 9236); S: *N*=6355 (Cases: 156, Control): 6199). (ii) Eastern Europe: LT: *N*=1652 (Cases:	Age group (negative for substances) Missing: 4 (2.3), 18-24: 31 (17.6). 25-24 (28.4), 35-49 (22.1), >50: 29.5) (positive for any substances)	Control: Drivers of passenger cars or vans aged ≥18 years approached at roadside surveys.					

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Table 2 (*continued*)

Author, country of study, year.	*N* subjects (% female)	Age, years, (±SD) or range, yr, or age group, yr, *n* (%)	Population description	Drug assessment			Accident assessment	
				Tool	Drug classes assessed	Threshold for detection of amphetamines	Tool	Type assessed
	385, Control: 1267). (iii) Southern Europe: IT: *N*=1782 (Cases 676, Control: 1086). (iv) Western Europe: BE: *N*=3297 (Cases: 348, Control: 2949); NL: *N*=5010 (Cases: 188, Control: 4822). 2.) Killed drivers, total *N*=2492. (i) Northern Europe: FI: *N*=4319 (Cases: 378, Control: 3841); NO: *N*=9429 (Cases: 193, Control: 9236); S: *N*=6355 (Cases: 156, Control: 6199). (ii) Eastern Europe: LT: *N*=1652 (Cases: 385, Control: 1267). (iii) Southern Europe: PT: *N*=2296 (Cases: 285, Control: 2641).	Missing: 3 (2.6), 18-24: 22 (18.8), 25-34: 38 (32.5), 35-49:33 (28.2), >50: 20 (17.1)						
Kuypers et al., Belgium, 2012	*N*=2601	Age group (all)	Cases: Car and van drivers involved in an accident and who were hospitalised	Blood sample (cases) saliva and blood sample (controls- only	Alcohol, amphetamines (amphetamine, methamphetamine or	20 ng/ml	Hospital records, MAIS score ≥ 2	Driver injury

			in one of five Belgian Hospitals (University Hospitals of Brussels, Ghent, Leuven, and Liege, and regional Hospital of Namur.	blood used)	samples	methamphetamine+ amphetamine, MDMA or MDMA+MDA, MDEA or MDEA +MDA, MDA), Benzodiazepines (Diazepam+Nordiazepam, or Diazepam+Oxazepam or Diazepam + Nordiazepam+ Oxazepam, Nordiazepam or Nordiazepam+ Oxazepam, Oxazepam, Lorazepam, Alprazolam, Flunitrazepam or Flunitrazepam +7- aminoflunitrazepam), cannabis (THC or THC+THCCOOH), Cocaine (Cocaine +Benzoylecgonine or Cocaine), Illicit opiates (6-acetylmorphine or 6-AM+Codeine or 6-AM+Morphine or 6AM+Codeine +Morphine or (Morphine +Codeine and Morphine concentration. = Codeine), medicinal opiates and opioids (Morphine, Codeine or (Codeine+Morphine and Codeine

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Table 2 (*continued*)

Author, country of study, year.	*N* subjects (% female)	Age, years, (±SD) or range, yr, or age group, yr, *n* (%)	Population description	Drug assessment			Accident assessment	
				Tool	Drug classes assessed	Threshold for detection of amphetamines	Tool	Type assessed
	Cases: 176 (40.3), Control: 2425 (33.6)	<20: 140 (13.4) 20-29: 241 (23) 30-39: 191 (18.3) 40-49: 205 (19.6) 50-59: 121 (11.6) >60 148 (14.1)	Control: Random sample of drivers on Belgian roads, conducted in five regions corresponding to catchment areas of the hospitals		concentration>-Morphine concentration), Methadone, Tramadol), Z-drugs (Zolpidem, Zopiclone).			
Gjerde et al., Norway, 2013	*N*=9769 ([a]) Cases: 508 (18.3)	Age groups (cases)	Cases: Car and van drivers who were killed in road traffic accident in Norway between the years 2003-2010.	Blood sample (cases), oral fluid (controls)	Alcohol (ethanol), Medicinal drugs (Alprazolam, Clonazepam, Codeine, Diazepam, Flunitrazepam, Methadone, Morphine, Nitrazepam, Nordiazepam, Oxazepam, Zolpidem, Zopiclone), Illigal drugs (Amphetamine, Cocaine, MDMA, Methamphetamine, THC)	41 ng/ml (Amphetamines), 48 ng/ml (MDMA), 45 ng/ml (Methamphetamine)	Forensic Toxicology Database at the NIPH.	Fatality
	Control: 9261 (28.9)	<25: 137 (27.0), 25-34: 109 (21.5), 35-44: 76 (15.0), 45-54: 58 (11.4), 55-64: 73 (14.4). (controls) <25: 969 (10.5), 25-34: 1656 (17.9), 35-44: 2222 (24.0), 45-54: 1961 (21.2), 55-64: 1575 (17.0), >64: 870 (9.4), unknown: 8 (0.1)	Control: Drivers randomly selected from police districts from April 2008-March 2009.					
Bogstrand et al., 2015	*N*=350 ([a]) Cases: 127 (7.9) Control: 223 (25.6)	[a] Age group (sober) 17-21 (16.6), 22-29: (17.0), 30-39: (14.3), 40-59:	Cases: drivers fatally injured in RTC in Norway during 2005-2010.	Blood samples with confirmatory GS-MS or LS-MS (all participants)	Alcohol, Alprazolam, Amphetamine, Clonazepam, Cocaine, Diazepam, MDMA (ecstasy) ,	Amphetamine: 41 μg/L	(a)The Norwegian Road Accident (NRA) Registry operated by Statistics Norway, (b) The Forensic	Fatality

		(25.1), >60: (26.9). (Impaired) (23.6), 22–29: (27.6), 30–39: (24.4), 40–59: (18.9), >60 (5.5)	Control: Drivers fatally injured RTC in Norway during 2005–2010 who were considered 'sober' (BAC ≤ 0.05 g/L or any drug concentration below 0.05 g/L) at the time of the accident.		Flunitrazepam, Methadone, Methamphetamine, Morphine, Nitrazepam, Oxazepam, Tetrahydocannabinol, Zolpidem, Zopiclone	Methamphetamine: 45 μg/L	Toxicology (FT) database, operated by the Norwegian Institute of Public Health (NIPH) and (c) the Crash Investigation team (CIT) database, operated by the Norwegian Public Road Administration (NPRA)	
Cohort								
Poulsen et al., New Zealand, 2014	1046 (23.8)	39 ([a]), (14–92)	Drivers killed as a result of a road traffic accident in New Zealand from the 1st July 2004 until 30th June 2009	Blood samples, confirmatory analyses using LC-MSMS	Stimulants (Methamphetamine, MDMA, Amphetamine, Pseudoephedrine, Methylphenidate, Benzylpiperazine), Sedative drugs -(Benzodiazepines and Zopiclone), Opioids (Morphine, Codeine, Oxycodone, Methadone, Tramadol, Dextropropyphene), Cannabis, Kava, Solvents (toluene), Lysergic acid Diethylamide, Antihistamines, Antipsychotics, Tricyclics Antidepressants.	0.05 mg/L	Police reports	Fatality

Abbreviations: *BAC* Blood Alcohol Content, *DRUID* Driving Under the influence of Drugs, Alcohol and Medicines, *ISS* Injury Severity Scale, MAIS Maximum Abbreviated Injury Scale, *MDMA* 3,4-methylenedioxy-methamphetamine, *THC* Tetrahydrocannabinol, *DK* Denmark, *FI* Finland, *IT* Italy, *BE* Belgium, *NL* Netherlands, *LT* Lithuania, *NO* Norway, *S* Sweden, *PT* Portugal.

[1] Only crude OR available for amphetamines.

[2] Multivariable analyses did not include amphetamines.

[a]Data not provided.

which 69 were excluded due to failing to meet preliminary eligibility criteria, and four were excluded as they were printed only in languages other than English. A further 48 articles were excluded failing to meet eligibility criteria, based on a concise reading of the full articles. One author repeated data published in one paper in a second (Hels et al., 2013), and so only the earlier version of the study has been included in this review (Bernhoft et al., 2012). One additional article was identified when searching the reference lists of articles meeting inclusion criteria. The final number of studies to be included in the review was nine, which included eight case control studies and one cohort design (Figure 1).

Studies most frequently failed to meet eligibility criteria for inclusion for the following reasons (i) study presented exposure only and gave no estimate of risk, (ii) study did not explicitly assess amphetamine use (i.e. grouped illicit drugs together), and (iii) study does not use accident risk as the dependent variable.

3.2. Characteristics of available studies

An overview of the reviewed studies ($n=9$) is presented in Table 2. Eight of the eligible studies utilised case-control design (Bernhoft et al., 2012; Bogstrand et al., 2015; Gadegbeku et al., 2011; Gjerde et al., 2011, 2013; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004), with the remaining study using cohort design (Poulsen et al., 2014). The majority of studies were published from 2011 onwards ($n=7$, 77.7%), with precise publication years being; 2004 (Movig et al., 2004), 2005 (Laumon et al., 2005), 2011 (Gadegbeku et al., 2011; Gjerde et al., 2011), 2012 (Bernhoft et al., 2012; Kuypers et al., 2012), 2013 (Gjerde et al., 2013), 2014 (Poulsen et al., 2014) and 2015 (Bogstrand et al., 2015). Eight of the 9 studies were conducted in Europe (Bernhoft et al., 2012; Bogstrand et al., 2015; Gadegbeku et al., 2011; Gjerde et al., 2011, 2013; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004). Of these, three studies were conducted in Norway (Bogstrand et al., 2015; Gjerde et al., 2011, 2013), two in France (Gadegbeku et al., 2011; Laumon et al., 2005), one in the Netherlands (Movig et al., 2004), one in Belgium (Kuypers et al., 2012), and one which covered various regions of Europe (Denmark, Finland, Norway, Sweden, Czech Republic, Hungary, Lithuania, Poland, Spain, Italy, Portugal, Belgium, The Netherlands) (Bernhoft et al., 2012). The remaining study was conducted in New Zealand (Poulsen et al., 2014).

The sample sizes of the included case-control studies ranged from $N=350$ (Bogstrand et al., 2015) to $N=48{,}542$ (Bernhoft et al., 2012), and the remaining cohort study citing a sample size of $N=1046$ (Poulsen et al., 2014), with the total number of participants examined by this review summing $N=90{,}694$. Age ranges varied from as young as 17 years in one case-control study (Bogstrand et al., 2015), however the majority of the studies classified the youngest tertile of individuals as being aged <20 (Kuypers et al., 2012), <24 years (Bernhoft et al., 2012; Laumon et al., 2005) or <25 years (Gjerde et al., 2011, 2013; Movig et al., 2004), to a maximum of >70 years (Laumon et al., 2005). One study provided the mean age of the whole sample only, which was reported as 39 (range 14-92) years (Poulsen et al., 2014), and one study provided no information about participant age (Gadegbeku et al., 2011).

Seven of the reviewed studies examined mixed populations of males and females (Bogstrand et al., 2015; Gjerde et al., 2011, 2013; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004; Poulsen et al., 2014) and two studies did not report sex distribution (Bernhoft et al., 2012; Gadegbeku et al., 2011). Of the seven studies that reported sex distribution, two studies- one case-control and one cohort- provided the sex distribution for the whole sample only (Laumon et al., 2005; Poulsen et al., 2014), and two studies provided complete information regarding the sex distribution for the whole sample as well both the exposed and unexposed groups (case-control studies only) (Kuypers et al., 2012; Movig et al., 2004). Three studies reported gender distribution among the exposed and unexposed groups only (i.e. no information available regarding the whole sample sex distribution) (Bogstrand et al., 2015; Gjerde et al., 2011, 2013). Among the case-control studies which assessed gender distribution among both the exposed and unexposed group, all examined studies reported a higher proportion of males compared to females in the exposed group, with the distribution of exposed females ranging from 7.9% (Bogstrand et al., 2015) to 40.3% (Kuypers et al., 2012).

All studies included for assessment comprised individuals who had been injured or killed as a result of road traffic accident. Data for these studies were derived primarily from hospital and/or medical records (Bernhoft et al., 2012; Gadegbeku et al., 2011; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004), however, data was also sourced from a combination of forensic toxicology databases and accident/crash registries (Bogstrand et al., 2015; Gjerde et al., 2011, 2013) and police reports (Poulsen et al., 2014). One study examined the relative cause of death with regard to drug use as a function of safety behaviours such as wearing a seatbelt and speeding (Bogstrand et al., 2015), one study assessed driver culpability as a function of drug use (Poulsen et al., 2014), and one study assessed driver responsibility (Gadegbeku et al., 2011).

Tools employed to ascertain drug use were predominantly homogenous between studies, with most studies utilising blood samples, or a combination of blood and/or saliva to test for the presence of drugs; however, the order of assessment differed between studies. In all case-control studies assessed, blood samples were used to assess for the presence of drugs among exposed individuals. Two studies employed a blood sample screen alone for both exposed and unexposed groups (Bogstrand et al., 2015; Kuypers et al., 2012), three studies used initial urine screening with confirmatory blood screen for both exposed and unexposed individuals (Gadegbeku et al., 2011; Laumon et al., 2005; Movig et al., 2004). Two studies employed different methods for screening drugs between exposed (blood) and unexposed (urine or oral fluid) individuals (Gjerde et al., 2011, 2013), and the exact method of assessment in unexposed individuals was unclear (stated saliva and/or blood) in one study (Bernhoft et al., 2012)

3.3. Study groupings

Due to the substantial heterogeneity of the study designs, particularly in relation to measures of outcomes measured and assessment methods, subjective decisions were required regarding the way studies were grouped for analyses. As such, studies were grouped with regard to the outcome of the traffic

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Table 3 Summary of associations between amphetamine-type substance use and the risk of injury as a result of road traffic accidents, presented by year of publication and author. Results presented as crude and adjusted Odds Ratio (OR) or Culpability Ratio (CR) and (95% CI).

Author, country, year	Measure of drug use	Adjusted for cofounders	Results (C=category)	*P* for trend	Summary of associations
Movig et al., The Netherlands, 2004	Urine and/or blood sample, with confirmatory analyses using gas chromatography mass spectrometry (GC-MS) techniques (all participants)	Age, gender, blood alcohol concentration, concomitant drug exposure, season, time of day (10:00 a.m-10:00 p.m) or night 10:00 p.m-10:00 a.m)	C1: Referent Adjusted OR=2.10 (0.66-6.73)	NS[a]	Amphetamine-type substance use associated with an increased risk of being injured in a road traffic accident; however this is not statistically significant.
Bernhoft et al., Europe, 2012	Blood test (cases), saliva and/or blood test (controls)	Age, gender and country	C1: Referent Injury: DK, FI, IT, LT, BE, NL Crude OR=9.66 (4.80-19.46), Adjusted OR=14.15 (5.82-34.42)	<0.05	Amphetamine-type substance use is associated with an increased risk for a driver being seriously injured in a road traffic accident.
Kuypers et al., Belgium, 2012	Blood sample (cases) saliva and blood sample (controls- only blood samples used)	Age, gender time period[b,c]	Crude OR[c]= 54.82 (6.09-493.12)	<0.001	Amphetamine-type substance use is associated with an increased risk for a being injured in a road traffic accident.

Abbreviations: DK Denmark, FI Finland, IT Italy, LT Lithuania, BE Belgium, NL Netherlands.
[a]Data not provided, NS not significant.
[b]Only crude OR available for amphetamines.
[c]Observation added to each of the four cells.

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Table 4 Summary of associations between amphetamine-type substance use and the risk of death as a result of road traffic accidents, presented by year of publication and author. Results presented as crude and adjusted Odds Ratio (OR).

Author, country, year	Measure of drug use	Adjusted for cofounders	Results (C=category)	*P* for trend	Summary of associations
Laumon et al., France, 2005	Urine, with confirmatory blood sample (for all participants)	Age, gender, concomitant drug exposure, vehicle type crash time (day of week, daytime or nigh-time)	Crude OR 1.96 (0.73-5.27)[a]	<0.05	Amphetamine-type substance use associated with increased risk of being responsible for a fatal road traffic accident
Gjerde et al., Norway, 2011	Blood sample (cases), oral fluid sample (controls)	Age, gender, time period and season	(i). Fatal road traffic accident (any): Crude OR=26.7 (9.9-71.9) Adjusted OR=20.9 (7.3-60.0). (ii). Fatal single vehicle accident: Crude OR=13.3 (1.7-103.7.7) Adjusted OR= 10.8 (1.3-93.5)	Both <0.05	Use of amphetamines-type substances without other substances is independently associated with increased risk for both fatal accident (any) and single vehicle fatal accident
Gadegbeku et al., France, 2011	Alcohol: Breath test with blood test if breath test refused/unable to obtain Illicit substances: Urine test with confirmatory blood test	Age, gender, cannabis use	Crude OR=2.71 (1.22-6.01) Adjusted OR=1.54 (0.66-3.56)	<0.05 for Crude OR only	Amphetamine-type substance use is associated with increased responsibility for fatal accident (unadjusted); however this is no longer significant after adjustment for confounders.
Bernhoft et al., Europe, 2012	Blood test (cases), saliva and/or blood test (controls)	Age, gender and country	(ii) Death FI, N, S, PT: Crude OR 25.44 (10.81-59.90), Adjusted OR=34.34 (13.18-89.49)	Both <0.05	Amphetamine- type substance use is independently associated with an increased risk of fatality in a road traffic accident
Gjerde et al., Norway, 2013	Blood sample (cases), oral fluid (controls)	Time period, region, season, road type, gender, age group.	Crude OR= 23.4 (8.7-62.8) Adjusted OR= 41.6 (12.6-137.1)	<0.05	The use of amphetamine-type substances without other substances is independently associated with increased risk of road being fatally injured in a road traffic accident

Bogstrand et al., 2014	Blood samples with confirmatory GS-MS or LS-MS (all participants)	Age group and gender	(i) Fatally injured due to no seat-belt use: C1: Referent Adjusted OR 3.5 (1.2-9.9) (ii) Fatally injured due to speeding: C1: Referent Adjusted OR= 2.9 (1.0-8.3)	(i) 0.018 (ii) 0.045	Amphetamine-type substance use is independently associated with increased risk for death due to no seatbelt use, and a trend towards significance was noted for amphetamine use and an increased risk of death due to speeding.
Poulsen et al., New Zealand, 2014	Blood samples, confirmatory analyses using LC-MSMS	Age group, gender, licence status, type of vehicle, BAC, drug use other than alcohol or cannabis[a]	Culpability of driver: (i) CR=12.3 (*) (ii) OR=2.46[b] (*)	NS	Not indicated	

Abbreviations: *DK* Denmark, *FI* Finland, *IT* Italy, *BE* Belgium, *NL* Netherlands, *LT* Lithuania, *NO* Norway, *S* Sweden, *PT* Portugal.
NS= not significant or unable to be computed.
[a]Adjustments for multivariable culpability analyses only, crude culpability ratio presented here.
[b]Point estimate odds ratio derived by dividing the culpability ratio of the particular portion of the driver population (12.3) culpable by the culpability ratio of the control group (5.0).
*Refers to data not provided.

accident; (i) incident resulting in driver injury or (ii) incident resulting in driver fatality.

3.4. Results of the studies

Results of the nine reviewed studies are presented in Tables 3 and 4. Table 3 presents findings from studies assessing the association between the use of amphetamine-type substances and the risk of injury as a result of road-traffic accidents, and Table 4 presents studies assessing the association between the use of amphetamine-type substances and the risk of death. Where possible, results are presented in the form of odds ratio (OR) with 95% confidence intervals (95% CI), or beta coefficient and standard error (SE) or 95% CI; *p* values are provided where available. One of the studies (Bernhoft et al., 2012) presented data for both injury and death, and so are counted twice in the sub-group analyses and in Tables 3 and 4. A summary of plotted adjusted OR and 95% CI for case-control studies assessing the association between the use of amphetamine-type substances and the risk of injury or death as a result of road traffic accidents are presented in Figure 2.

3.4.1. Amphetamine-type stimulant use and the risk of injury as a result of road-traffic accidents

Two of the three case-control studies assessing the use of amphetamine-type substances and the risk of being injured as a result of a road-traffic accident present adjusted OR values (Bernhoft et al., 2012; Movig et al., 2004), with the remaining study presenting crude values only (Kuypers et al., 2012). One of the case-control studies (Movig et al., 2004) found an increased risk of being injured in a road traffic accident following adjusted for age, gender, blood alcohol concentration, concomitant drug exposure, season, time of day; however this is not statistically significant. One study (Bernhoft et al., 2012) reported that following adjustment for age, gender and country, amphetamine-type substance use is associated with an independently increased risk for a driver being seriously injured in a road traffic accident. The remaining study (Kuypers et al., 2012) reported an increased risk for a being injured in a road traffic accident as a result of amphetamine-type substance use, however this is unadjusted OR values and reflect imputed data. A summary of the plotted crude and adjusted odds ratio and 95% CI for amphetamine-type substance use and the risk of injury (only) as a result of road-traffic accidents are presented in Figure 3.

3.4.2. Amphetamine-type stimulant use and the risk of death as a result of road-traffic accidents

Six of the seven studies showed a positive association between the use of amphetamine-type studies and the risk of being killed as a result of a road traffic accident (Bernhoft et al., 2012; Bogstrand et al., 2015; Gadegbeku et al., 2011; Gjerde et al., 2011, 2013; Laumon et al., 2005). Four of these six studies that indicated a positive association employed adjusted risk values (Bernhoft et al., 2012; Bogstrand et al., 2015; Gjerde et al., 2011, 2013), with the remaining study presenting crude values only (Laumon et al., 2005), and one study (Gadegbeku et al., 2011) reported an association among crude values only. Of the studies that presented the adjusted risk values, one study (Gjerde et al., 2011) reported that after controlling for age, gender, time period and season, the use of

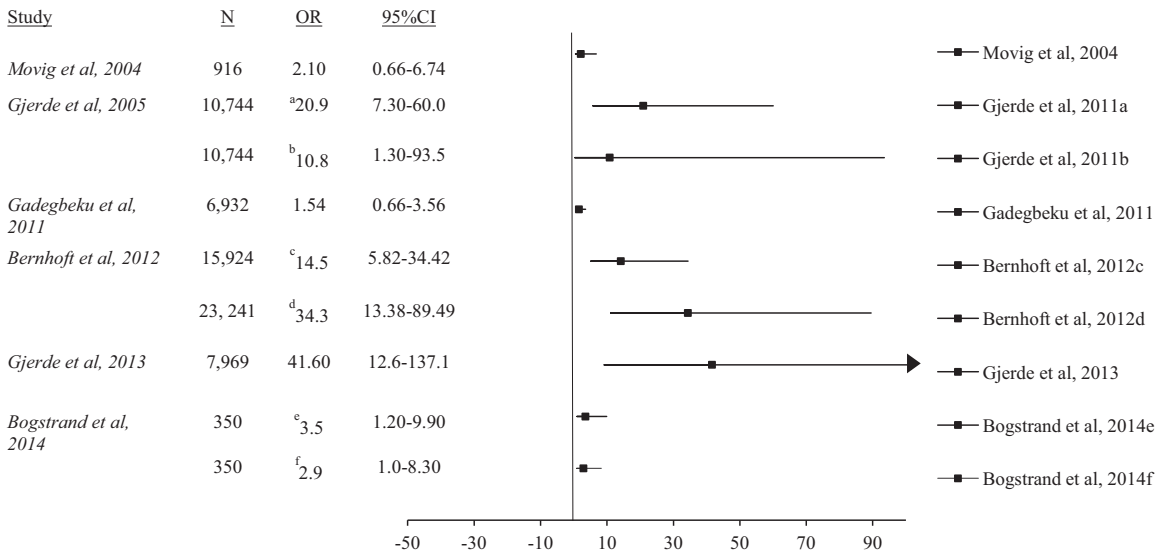

Figure 2 Adjusted odds ratio and 95% CI for amphetamine-type substance use and the risk of being involved in a road traffic accident resulting in death or injury; a summary of cross-sectional studies. OR=Odds Ratio, 95% CI=95% Confidence Interval, [a] Fatal road traffic accident (any), [b] Fatal single vehicle accident, [c] Serious injury (includes data from DK, FI, IT, LT, BE, NL), [d] Death (includes data from FI, N, S and PT), [e] Death due to no seat-belt use, [f] Death due to speeding.

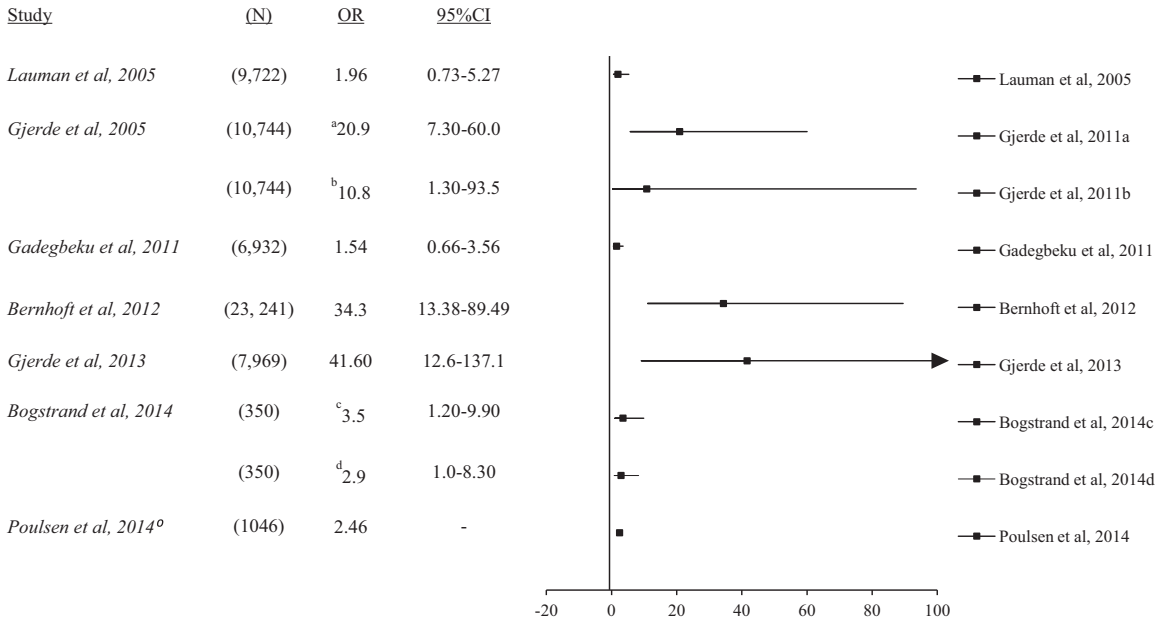

Figure 3 Crude and adjusted odds ratio and 95% CI for amphetamine-type substance use and the risk of being involved in a road traffic accident resulting in death. OR=Odds Ratio, 95% CI=−95% Confidence Interval, [a] Fatal road traffic accident (any), [b] Fatal single vehicle accident, [c] Death due to no seat-belt use, [e] Death due to speeding, [o] Point estimate odds ratio derived by dividing the culpability ratio of the particular portion of the driver population (12.3) culpable by the culpability ratio of the control group (5.0).

amphetamines-type substances is independently associated with increased risk for both fatal accident (any) and single vehicle fatal accident. Another study (Bogstrand et al., 2015) reported that following adjustment for age group and gender, amphetamine-type substance use is independently associated with increased risk for death due to no seatbelt use, and a trend towards significance was noted for amphetamine use and an increased risk of death due to speeding. One other study (Gjerde et al., 2013) reported that the use of amphetamine-type substances is independently associated with increased risk of road being fatally injured in a road traffic accident, following adjustment for time period, region, season, road type, gender and age group. One study presenting the crude risk ratio only (Laumon et al., 2005) indicated that amphetamine-type substance use associated with increased risk of being responsible for a fatal road traffic accident, and one study (Gadegbeku et al., 2011) indicated that although the use of amphetamine-type substances is associated with increased responsibility for fatal accident (unadjusted); this is no longer significant after adjustment for age, gender and cannabis use. The relative risk

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of being killed as a result of being involved in a road traffic accident was unable to be computed for one cohort study (Poulsen et al., 2014). Figure 4 presents a summary of the plotted crude and adjusted odds ratio and 95% CI for amphetamine-type substance use and the risk of being fatally injured (only) a result of road-traffic accidents.

3.5. Assessment of study quality

3.5.1. Newcastle-Ottowa Scale (NOS)

Three reviewers (ACH, LAD and BS) independently scored 81 criteria over the nine studies, resulting in an inter-rater reliability of 95% (Cohens κ=0.95). The conflicts between reviewers (ACH, LAD and BS) on the remaining 9.9% (n=8) of the 81 items was resolved a second meeting (final consensus results presented in Table 5). The mean quality score for all included studies was 7.10 (range 5-9). Using these criteria, we judged seven studies to be of high methodological quality (Bernhoft et al., 2012; Gadegbeku et al., 2011; Gjerde et al., 2011; Kuypers et al., 2012; Laumon et al., 2005; Movig et al., 2004; Poulsen et al., 2014), and the remaining two studies to be of moderate quality (Bogstrand et al., 2015; Gjerde et al., 2013). No studies were judged to be of low quality. Only high-quality studies were included in the best evidence synthesis.

3.6. Best evidence synthesis

3.6.1. Amphetamine-type stimulant use and the risk of injury as a result of road-traffic accidents

Two high-quality case-control studies (Bernhoft et al., 2012; Kuypers et al., 2012) reported a significant association between the use of amphetamine-type substances and an increased risk of being seriously injured in a road traffic accident, presenting a crude OR of 54.82 (95% CI= 6.09-493.12) and an adjusted OR of 14.15 (95% CI=5.82-34.42) respectively. One high quality case-control study (Movig et al., 2004) identified no association between amphetamine-type substance use and the risks of being injured in a road-traffic accident, with an OR of 2.10 (95% CI= 0.66-6.73). Given that two high-quality case-control studies reported an increased risk of sustaining serious injury as a result of amphetamine-type substance use, whilst one high-quality case-control study reported no association, we report that a conflicting level of evidence exists.

3.6.2. Amphetamine-type stimulant use and the risk of death as a result of road-traffic accidents

Four high quality case-control studies (Bernhoft et al., 2012; Gadegbeku et al., 2011; Gjerde et al., 2011; Laumon et al., 2005) reported a significant association between use of amphetamine-type substances and an increased risk of being killed in a road traffic accident. One study (Gjerde et al., 2011) presented OR the adjusted ORs for both (i) risk of death (any) OR=20.9 (95% CI= 7.3-60.0) and (ii) risk of death due to single vehicle accident OR=10.8 (95% CI=1.3-93.5). One study (Laumon et al., 2005) presented a crude OR of 1.96 (95% CI=0.73-5.27), and another (Gadegbeku et al., 2011) presented a significant result for the crude values only, OR=2.71 (95% CI=1.22-6.01). The remaining high-quality case-control study (Bernhoft et al., 2012) presented an adjusted OR= 34.34 (95% CI=13.18-89.49) for amphetamine-type substance use and the risk of being killed as a result of a traffic accident. One high-quality cohort study (Poulsen et al., 2014) presented a computed odds ratio of OR=2.46, however, confidence intervals and significance levels were unable to be ascertained. Therefore for the purpose of this analysis, it was inferred that no association was present. Given that four high-quality case-control studies reported an increased risk of sustaining serious injury as a result of amphetamine-type substance use, whilst one high-quality cohort study reported no association, we report that a moderate level of evidence exists.

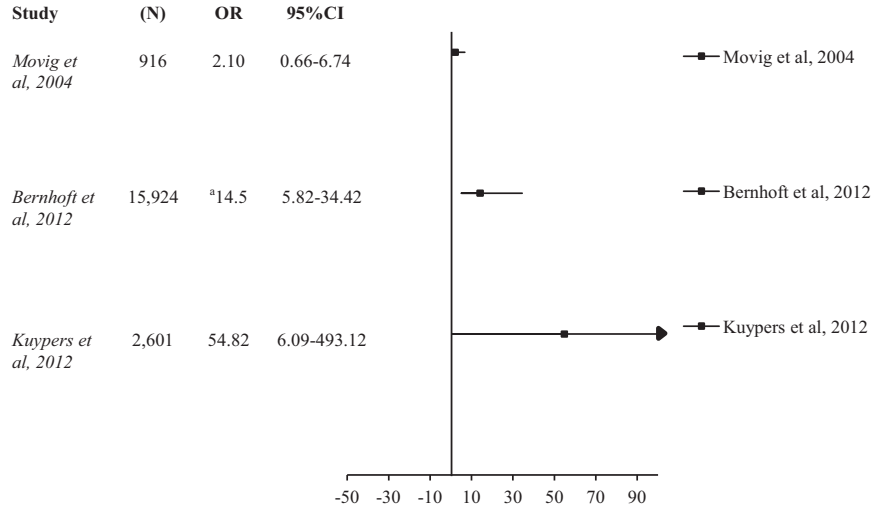

Figure 4 Crude and adjusted odds ratio and 95%CI for amphetamine-type substance use and the risk of being injured as a result a road traffic accident. OR=Odds Ratio, 95% CI=95% Confidence Interval, a Serious injury (includes data from DK, FI, IT, LT, BE, NL).

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Table 5 Quality of included studies as assessed by the Newcastle-Ottowa Scale (NOS).

Study	NOS items									
	Adequate definition	Representative cases	Selection controls	Definition controls	Comparability (important factor, age)	Comparability (additional factor, gender)	Exposure ascertained	Same method ascertained	Non-response rate	NOS Score (0-9)
Case control										
Movig et al. (2004)	1	1	1	1	1	1	1	1	1	9
Laumon et al. (2005)	1	1	1	0	1	0	1	1	1	7
Gjerde et al. (2011)	1	1	1	0	1	1	1	0	1	7
Gadegbeku et al. (2011)	1	1	1	0	1	1	1	1	1	8
Bernhoft et al. (2012)	1	1	1	1	1	1	1	0	0	7
Kuypers et al. (2012)	1	1	1	0	1	1	1	1	0	8
Gjerde et al. (2013)	1	1	1	0	1	1	1	0	0	6
Bogstrand (2014)	1	1	0	0	1	1	1	1	0	6
Cohort										
Poulsen et al. (2014)	1	1	1	0	1	1	1	1	0	7

4. Discussion

This review identified and summarised the limited number of observational research examining the association between the use of amphetamine-type substances and the relative risk of sustaining a serious injury or being killed in a road-traffic accident. A best-evidence synthesis was conducted on seven studies deemed to be of high methodological quality. On the basis of this reviewed literature, we conclude that a conflicting level of evidence exists for amphetamine-type substance use and the risk of being injured as a result of a traffic accident, and a moderate level of evidence exists for the association between the use of amphetamine-type substances and the relative risk of being killed as a result of a road traffic accident.

Limited observational research has indicated that amphetamines use is associated with an increased-risk of sustaining an injury as a result of a road traffic accident (Dussault et al., 2002); however, estimations vary significantly as a function of region (Bernhoft et al., 2012), and an inverse relationship often exists with regard to the relative risk and year of ascertainment (Gjerde et al., 2011; Movig et al., 2004). Prospective case-control studies have cited risk ratios ranging between 0.3 (Smink et al., 2005) and 12.8 (Dussault et al., 2002), and a negative relationship is often observed between study size and relative risk (for example ratios provided by Bernhoft et al. (2012) and Bogstrand et al. (2015)). Our findings indicate that when collated, a conflicting level of evidence exists between the use of amphetamine-type substances and the relative risk of injury as a result of a road traffic accident. One high quality case-control study performed by Movig et al. (2004) reported that although a twofold increased risk was observed, this was not deemed statistically significant. Small sample size and/or unequal cell allocation for multivariable binary regression analyses restrict inferences regarding the magnitude of the associations due to an inflated likelihood of statistical bias; and are not uncommon in this type of research (Mura et al., 2003). This limitation was similarly reflected in results presented by Kuypers et al. (2012), where, due to missing observations, cell/data imputation was used to indicate a positive association between amphetamine-type substance use and the relative increased risk for a being injured in a road traffic accident was presented in univariate analysis only. It is possible that these limitations are somewhat reflective of the specific population sampled, due to the reported variation in the prevalence of drug use among divers in different regions and between counties (Bernhoft, 2011), and are not necessarily indicative of a true lack of association. Indeed, the study conducted by Bernhoft et al. (2012) indicated a strong and positive association between the use of amphetamine-type substances and an increased risk for a driver being seriously injured in a road traffic accident.

The risk of being fatally injured whilst driving under the influence of drugs is somewhat proportional to the substance used and blood concentration levels detected. Although no reviews exist that explicitly evaluate the association between amphetamine use and the risk of being killed in a road-traffic accident, sub-analyses available in one review study has indicated that the risk of being fatally injured as a result of ingesting this substance yields higher risk ratios when compared to other commonly abused illicit and prescribed substances (Elvik, 2013). Our best-evidence synthesis of high quality studies suggests that at present, a moderate relationship exists between the use of amphetamine-type substances and the relative risk of being fatally injured in a road-traffic accident. Indeed, statistically significant adjusted risk estimates for the risk of death due to amphetamine consumption were typically inflated among high quality studies, with the reported adjusted OR ranging from 3.5 (Bogstrand et al., 2015) to 24.4 (Bernhoft et al., 2012). Accidental death as a result of road traffic accidents are the most common cause of fatality for individuals under the influence of amphetamines (Logan et al., 1998). Deficits in numerous domains associated with effective vehicular control following acute amphetamine consumption, such as neurocognitive (Scott et al., 2007) and neurobehavioural (Silber et al., 2005) functioning, combined with the observed increase in risk taking behaviours (Aitken et al., 2000) and reduced risk perceptions (Darke et al., 2004; Kelly et al., 2004), likely act to inflate the risk of death as a result of an accident.

It is difficult to ascertain whether the risk of being injured or killed as a result of a road traffic accident is directly attributable to the blood concentration of amphetamine, given that there was a notable degree of variation in detection threshold levels observed between studies (ranging from 20 to 45 ng/ml), and no standardised or recommended therapeutic dose exists. Several well-designed, placebo controlled driving simulator studies have indicated a dose-dependent association between some amphetamine-type substances, such as methamphetamine (Stough et al., 2012) and dexamphetamine (Silber et al., 2005) and accident risk, however other studies have noted no association for other amphetamine derivatives (Brookhuis et al., 2004). Other on-road studies have similarly noted deficits in measures of lane deviation and speed maintenance abilities after administration of 3,4-methylenedioxymethamphetamine (MDMA) (Ramaekers et al., 2006), and behavioural assessments of impairments have yielded similar deficits for this substance (Downey et al., 2012).

A large proportion of the studies examined was deemed to be of high quality, as assessed by the NOS. Indeed, all studies included for analysis derived driver statistics from secure hospital records, governmental data-bases and/or forensic/toxicology databases, and generally employed large sample sizes. For the case-control studies, control participants were generally representative of the general driving population and detection rates of substances among these drivers was characteristically low. Assessment methods for substance detection were typically homogenous and of high quality, comprising of blood, saliva and urine analysis. The most common factors reducing the scores of the evaluated studies on the NOS were due to insufficient description of amphetamine exposure among control participants, and non-reporting or unequal study response rates between cases and control (case-control studies) or between exposed/unexposed individuals (cohort). It is likely that the generally high quality of the studies included for analysis are reflective of the methodology employed in these types of assessments, as they are often performed in

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conjunction with medical organisations and law-enforcement agencies, utilising secure and reliable methods. It is acknowledged that this increased proportion of high quality studies included for analysis may similarly be attributed to the *a priori* threshold applied.

Due to the relatively small pool of eligible studies, we were unable to assess for study bias using conventional methods, such as a funnel plot. We therefore concede that it is possible that some degree bias is present within the extracted studies. As this data is unavailable, we are unable to comment on this in any great detail. Where applicable, we present both the crude and unadjusted risk estimates, which negate some degree of sample and methodological bias in our reporting. Moreover, we addressed the issue of bias within our quality assessments, whereby two common confounders were require to be accounted for in order to fulfil criteria on two items for that measure. Due to the heterogeneous nature of the included studies, we were unable to perform meta-regression analyses, and thus we are unable to comment on the magnitude of the pooled variance of the presented relationships. We systematically assessed study quality and utilised previously validated methods to infer study quality metrics, and thus provide alternative, albeit tentative interpretations of the observed associations. It is acknowledged that assessment of defined amphetamine-type substances was limited to those which are frequently detected in populations of drivers (such as MDMA, MDEA and methamphetamine), which differs from the list of theoretically possible (e.g. Khat), and thus analysis was limited to the data available and these factors may have influenced the reported findings. Despite this, is likely that the prevalence of use of these substances in countries where road-side drug testing occurs is low, and therefore rates of use would similarly reflect this. Thus, we do not anticipate that these factors significantly attenuated our reported findings. Lastly, as the studies evaluated were largely derived from European cohorts, with the exception of one study conducted in New Zealand, it is unclear whether these associations are similarly observed among different geographical locations and among different populations. Additional studies are therefore urgently required if these associations are to be effectively and systematically evaluated, and if definite conclusions are to be drawn regarding the magnitude of these associations. High detection rates of amphetamine type-substances among injured and killed drivers, coupled with indication of an independent risk for injury or death due to road trauma due to the use of this substance highlight the importance multi-platform preventative strategies to curb this behaviour among motorists. Facilitation of multi-component programs targeting aspects of driver behaviour, community attitude, and subsequent legal and healthcare implications are required if effective mobilisation of such initiatives is to be achieved.

This systematic review presents the first evaluation of the magnitude of collated results assessing the association between the use of amphetamine-type substances and the risk of being injured or killed as a result of a road-traffic accident. Although limited observational research has proposed that an independent association exists between the use of this substance and accident risk, this review revealed that at present, very few well-controlled, sufficiently powered studies are available. Results of a best-evidence synthesis suggest that a conflicting level of evidence exists for the risk of serious injury, and a moderate level of evidence exists for the risk of death in a road-traffic accident due to the use of these substances; however inferences regarding the strength of the reported associations are impeded by several methodological limitations. This review provides a consolidated evaluation of currently available observational literature, which should be complimented by additional enquiry to facilitate the reduction of the personal and societal burden of severe injury and death which results from drug-driving incidents. Driving under the influence of amphetamines represents a growing area of concern, and effective, multi-component and targeted prevention strategies are urgently required if adequate legislative and healthcare focussed programs are to be utilised.

Author contributions

ACH, LAD and CS were involved in the development and design of the study. ACH collected the data, and ACH, LAD, CS and BS constructed variables for this paper and analysed the data. ACH interpreted the data and wrote the manuscript. ACH, LAD, CS and BS were involved in drafting, editing and critical appraisal of the manuscript. All authors have approved the manuscript for submission.

Conflict of interest declaration

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Prof Con Stough and Ms Brook Shiferaw have no conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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No study sponsors were involved in the study design; collection, analysis and interpretation of data; the writing of the manuscript; or in the decision to submit the manuscript for publication.

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