Project No. TREN-05-FP6TR-S07.61320-518404-DRUID

DRUID
Driving under the Influence of Drugs, Alcohol and Medicines

Integrated Project
1.6. Sustainable Development, Global Change and Ecosystem
1.6.2: Sustainable Surface Transport

6th Framework Programme
Deliverable D2.3.5

Risk of injury by driving with alcohol and other drugs

Due date of deliverable: 14.04.2011
Actual submission date: 28.11.2011
Revision 2.0 date: 14.09.2012

Start date of project: 15.10.2006
Duration: 60 months
Organisation name of lead contractor for this deliverable: DTU
Revision 2.0

Project co-funded by the European Commission within the Sixth Framework Programme (2002-2006)		
Dissemination Level		
PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services)	

Deliverable 2.3.5

Risk of injury by driving with alcohol and other drugs

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Project funded by the European Commission under the Transport RTD Programme of the 6th Framework Program

Executive summary

The objective of this deliverable is to assess the risk of driving with alcohol, illicit drugs and medicines in various European countries. In total nine countries participated in the study on relative risk of serious injury/fatality while positive for psychoactive substances. Six countries contributed to the study on the relative risk of getting seriously injured: Denmark, Finland, Lithuania, Italy, Belgium and the Netherlands. Four countries contributed to the study on the relative risk of getting killed: Finland, Norway, Sweden and Portugal.

The risk for a driver of getting seriously injured or killed in an accident while positive for a given substance was calculated as the ratio between the odds for a driver of being seriously injured/killed in an accident while positive for a given substance and the odds of being seriously injured/killed while negative. The odds ratios were calculated by means of logistic regression using the SAS 9.2 procedure *proc logistic*.

Data from the case study population consisted of samples from the hospital studies of seriously injured drivers and those of killed drivers (Isalberti et al., 2011). In total, 2,490 seriously injured drivers and 1,112 killed drivers were included. Data from the control population came from the roadside surveys in the same countries, in total, 15,832 drivers participated in the control sample of the seriously injured drivers and 21,917 drivers participated in the control samples of killed drivers; data were weighted for the national distribution of traffic in each of eight time periods of the week (Houwing et al., 2011). The relative risk estimates were adjusted for age and gender.

An estimation of the overall relative risk by substance group is given. These risk estimates are based on the odds ratios estimated separately for each country, together with aggregated odds ratios estimated on the basis of all countries' data together or a subset of countries. In the estimate is also taken into account the imprecision of the odds ratios of getting seriously injured and killed as expressed by the confidence intervals of the odds ratio estimates.

The main finding of this report is that the highest risk of getting seriously injured or killed is associated with driving with high alcohol concentrations (above 1.2 g/L) and alcohol combined with other psychoactive substances. These two groups indicate extremely high risks of about 20-200 times that of sober drivers. Other high risk groups are drivers with medium blood alcohol concentrations (between 0.8 g/L and 1.2 g/L), multiple drug use and amphetamines. The risks indicated for this group are about 5-30 times that of sober drivers. Medium increased risk was found for alcohol concentrations between 0.5 and 0.8 g/L, for cocaine, benzoylecgonine, illicit opiates and medicinal opioids. Risk for this group was estimated to about 2-10 times that of sober drivers. The risk associated with benzoylecgonine that is not an active agent might be caused by sleep deprivation after cocaine consumption. The risk associated with cannabis seems to be similar to the risk when driving with a low alcohol concentration (between 0.1 g/L and 0.5 g/L), which is slightly increased of about 1-3 times that of sober drivers.

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1 Introduction

1.1 General background

DRUID (Driving under the Influence of Drugs, Alcohol and Medicines) aimed to combat the problem of driving under the influence of psychoactive substances by providing a solid scientific base for European policy makers. It brought together experienced organisations in Europe to assemble a co-ordinated set of data resources and measures. DRUID is an integrated European research project which consisted of different sub-projects (Work Packages) that were aimed at different topics such as the prevalence and risk of psychoactive substances, enforcement, classification of medicines, rehabilitation of offenders and withdrawal of driving licenses.

The main objective of WP2 of DRUID is to assess the situation in Europe regarding the prevalence and risk of the use of illicit drugs, alcohol and psychoactive medicinal drugs by drivers.

The prevalence of drugs in accidents with personal injuries has been estimated in DRUID Deliverable 2.2.5 (Isalberti et al. 2011) by means of hospital surveys of seriously injured and/or killed drivers and the prevalence of drug driving has been estimated in DRUID Deliverable 2.2.3 (Houwing et al., 2011) by means of roadside surveys.

1.2 Objectives

The objectives of this deliverable is to determine the relation between psychoactive substance use by car drivers and their risk of being seriously injured or killed in a road accident by means of calculating the odds-ratios of being seriously injured or killed. The data collected in the hospital studies (Isalberti et al. 2011) serve as the case samples and the data collected in the road side surveys (Houwing et al., 2011) serve as the control samples for the calculation of the odds-ratios.

1.3 Participating countries

In the following **table 1** the countries are shown that are included in the case-control study of drivers being seriously injured in an accident while positive for alcohol and other drugs and the case-control study of drivers being killed in an accident while positive for alcohol and other drugs. **Table 1** also shows for each country and study population when the data collection took place.

Table 1 Participating countries and study period

	Control samples	**Case samples**	
Country	**Road side survey**	**Seriously injured drivers**	**Killed drivers**
Belgium (BE)	2008-2009	2008-2010	
Denmark (DK)	2008-2009	2007-2010	
Finland (FI)	2007-2009	2008-2010	2006-2008
Italy (IT)	2008-2009	2008-2009	
Lithuania (LT)	2008-2009	2008-2010	
Norway (NO)	2008-2009		2006-2008
Portugal (PT)	2008-2009		2009
Sweden (SE)	2008-2009		2008
The Netherlands (NL)	2007-2009	2008-2010	

The regions for the data collection of controls and cases are shown in **table 2**. Ideally, control samples from the roadside surveys and case samples from the hospital studies should be collected from the same regions in a country in order to meet the assumptions of a case-control study. Roadside survey data were collected in one or more regions of a country, depending on various factors, e.g. the cooperation with police and cooperation with hospitals within these regions and thus enabling also collection of data on seriously injured drivers from the road side survey regions.

Table 2 Participating countries and regions

	Control samples	**Case samples**	
Country	**Road side survey**	**Seriously injured drivers**	**Killed drivers**
Belgium	1. Brussels 2. Flanders 3. Wallonia	1. Brussels 2. Flanders 3. Wallonia	
Denmark	1. Ålborg and Viborg 2. Kolding, Vejle and Odense 3. Roskilde	1. Ålborg and Viborg 2. Kolding, Vejle and Odense	
Finland	1. Uusimaa 2. Pohjois-Savo	1. Uusimaa	1. Uusimaa 2. Pohjois-Savo 3. Rest of Finland
Italy	1. Padova 2. Venezia 3. Vicenza 4. Treviso 5. Rovigo	1. Padova 2. Venezia 4. Treviso 5. Rovigo	
Lithuania	1. Vilnius 2. Kaunas 3. Klaipeda 4. Alytus	1. Vilnius 2. Kaunas 3. Klaipeda 4. Alytus	
Norway	1. Hedmark & Romerike and Buskerud & Asker-Bærum (Part of South-east Norway) 2. Hordaland and Haugaland (Part of South-west Norway) 3. Trøndelag and Troms (Part of Middle-north Norway)		1. South-east Norway 2. South-west Norway 3. Middle-north Norway
Portugal	1. Porto 2. Coimbra (Part of Centre Branch of INML) 3. Lisboa (Part of South Branch of INML)		2. Centre Branch of INML 3. South Branch of INML
Sweden	1. Södermanlands, Örebro and Östergötlands län		Whole Sweden
The Netherlands	1. Hollands-Midden 2. Tilburg 3. Amsterdam Amstelland 4. Groningen 5. Twente 6. Gelderland-Zuid	2. Tilburg (Tilburg hospital) 5. Twente (Enchede hospital) 6. Gelderland-Zuid (Nijmegen hospital)	

The information on which substances the drivers were positive for were based on toxicological confirmation analyses of body fluids collected from drivers included in the case study samples and drivers included in the control study samples. **Table 3** shows which body fluids were collected in each country for the various study populations.

Table 3 Participating countries and body fluid collected

	Control samples	**Case samples**	
Country	**Road side survey**	**Seriously injured drivers**	**Killed drivers**
Belgium	Saliva, whole blood	Whole blood	
Denmark	Saliva	Whole blood	
Finland	Saliva	Whole blood	Whole blood
Italy	Saliva, whole blood	Whole blood	
Lithuania	Whole blood	Whole blood	
Norway	Saliva		Whole blood
Portugal	Saliva		Whole blood
Sweden	Saliva		Whole blood
The Netherlands	Saliva, whole blood	Whole blood	

2 Method

The design of the case-control study is population based, that is both the case study sample and the control study sample reflects the driving population. The strenghts of a population based study are the following:

- A population based design gives an estimation of the overall risk of, e.g. alcohol, including the confounding factors, like, for example time. Alcohol is consumed more often at night, accidents risk is higher at night, and thus alcohol risk as calculated with the population based design is the sum of the pure alcohol effect and the night effect.
- One can separate the effects by including confounding risk factors like, for example age, in a logistic regression analysis.
- Thus, this design enables to evaluate risk aspects separately compared to the usual case-control design which focuses on the pure effect.

As mentioned in chapter 1, cases were collected in hospital studies and studies of killed drivers and controls were collected in road side surveys. Cases were drivers of passenger cars (no more than eight passengers) and small vans who have been seriously injured or killed in traffic accidents (Isalberti et al., 2011). Controls were drivers of passenger cars (no more than eight passengers) and small vans who had been stopped from the general traffic at randomly selected sites and times (Houwing et al., 2011).

In the following, the two types of case samples will be described separately in this report. Drivers of passenger cars (no more than eight passengers) and small vans will be referred to as “car drivers”.

2.1 Selection of cases of seriously injured drivers

Cases of seriously injured drivers were defined as car drivers injured in traffic accidents (MAIS ≥ 2 or equivalent). Information on case drivers was collected, and a blood sample was taken for subsequent toxicological analyses. Cases were obtained from the Emergency Department of one or more hospitals where the drivers had been admitted after a road traffic accident in the following countries: Belgium, Denmark, Finland, Italy, Lithuania and the Netherlands.

Since MAIS is not implemented in Italian hospitals, the criterion to be applied was: prognosis ≥ 20 days of hospitalisation (Ferrara et al., 2011b). In Denmark drivers were included based on admission to hospital because of traumatological reasons (based on the Danish trauma score, including unconsciousness, paralysation, open lesions and multiple fractures) (Bernhoft et al., 2011).

Cases consisted of all seriously injured car drivers from the selected trauma centres. A list of inclusion criteria that all countries needed to comply with was decided upon in order to increase homogeneity across the participating countries. However, due to practical and legal issues national differences could not be avoided. For further information we refer to DRUID Deliverable 2.2.5 (Isalberti et al., 2011).

In principle, the case samples should consist of all seriously injured drivers that fulfilled the criteria for inclusion. However, due to various reasons, i.e. time pressure in the emergency room, doctors’ focusing on the treatment instead of the inclusion in the study or simply loss of the blood sample or the blood sample tube broken, although the collection of blood/urine is part of a routine during emergency procedure by medical staff, we know that there was a certain underreporting. However, the presence

of non-inclusion is difficult to evaluate in those countries where the patients that were not included are not known.

Furthermore, in three of the six countries involved in the injured drivers study, an informed consent had to be signed by the driver or a relative. The need for such a written informed consent can be expected to have a negative influence on the response rate. However looking at the data of Belgium, Finland and Italy, where informed consent was needed, non response was limited to a maximum of 8.5%.

The non response in the six countries varies between 0% and 8.5% for the surveys on the injured drivers, as shown in **table 4** (Isalberti et al., 2011).

Table 4 Factors related to non-inclusion of seriously injured drivers

INJURED DRIVERS		
Country	**Problems encountered**	**Non response percentage**
Belgium	No blood sample was available for toxicological analysis in some cases For some drivers a patient form was filled in, but they refused to give a blood sample for toxicological analysis	5.4%
Denmark	Blood sample or patient sheet went missing For some drivers a patient form was available but no blood sample; these drivers make up the non-response percentage. For other patients, only a blood sample was available, but no patient form. Those patients were considered not fulfilling the inclusion criteria of the study.	5%
Finland	No problems reported	8.5%
Italy	Accident information from the police could not be obtained	0%
Lithuania	No problems reported	0%
The Netherlands	Drug and alcohol intoxicated patients were less likely to be blood sampled than sober patients	Unknown

(Source: Isalberti et al., 2011)

2.2 Selection of cases of killed drivers

Cases of killed drivers were all drivers from the participating countries during a period of 2-3 years for whom toxicological analyses had been performed in connection to the fatal accident.

Cases consisted of killed car drivers in the following countries: Finland, Norway and Sweden. In addition to this, Portugal also participated with a case sample of killed drivers. However, in the Portuguese data material, it was not possible to exclude drivers that were not car drivers from the study sample. Drivers other than car drivers (a.o. motor cycle drivers, cyclists) are assumed to amount to 5% of the total number of drivers in the sample. Since this is a small fraction made up of other road users than car drivers, it was decided to include the Portuguese study sample as well. For further information we refer to DRUID Deliverable 2.2.5 (Isalberti et al., 2011).

The study samples of killed drivers are retrospective. Thus, the blood samples were taken in connection to the fatality, and not as part of the DRUID study. In principle, blood samples should have been taken from all fatally injured drivers, but it was reported that missing cases varied between 5.7 and 41% for the studies on the killed drivers (Isalberti et al., 2011). Furthermore, the analyses that were performed, did not always meet the DRUID criteria, see **table 5**.

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Table 5 Factors related to non-inclusion of killed drivers

KILLED DRIVERS		
Country	**Problems encountered**	**Non response percentage**
Finland	No problems reported	5.7%
Norway	No analysis was done for following reasons - Probability of finding alcohol or drugs was low - Practical matters such as economy - Transportation over long distances to obtain an autopsy	41%
Portugal	If analysis was performed for only alcohol or only for alcohol and illicit drugs, the case was excluded from the study	21%
Sweden	Lack of blood sample to do extra analysis Missing values for some substances or drivers	6%

(Source: Isalberti et al., 2011)

2.3 Selection of controls

Controls were random samples of car drivers drawn from moving traffic on main urban and rural roads from the general traffic at selected sites and times (Houwing et al., 2011).

The general hypothesis of DRUID is that drug use increases accident risk. Consequently, the roadside surveys should cover drug use among road users who may cause road accidents. Ideally, all active road users, in all regions of each country, on all roads, in all vehicles, at all times of the year, week and day should be represented in the survey, in order to have the road traffic in each country surveyed in a representative way. For practical reasons, among others because roadside surveys usually require co-operation between the police and researchers, deviations from the ideal principle have been necessary.

The survey sample was collected in a systematic way, covering a variety of research locations and times of the day and week. It was the intention that the survey sample should be representative of traffic on all roads at all times. At the selected research locations, drivers were stopped at random from the moving traffic and all selected drivers were tested for alcohol and drugs in a uniform way. For more information we refer to Houwing et al. (2011).

The aim of the roadside surveys was two-fold:

1. To provide data for calculation of the prevalence of alcohol and other psychoactive substances in the driving population (Houwing et al., 2011)
2. To form a representative sample of controls for the case-control study

To this latter aim, eight sample periods over the week were defined.

- The controls were sampled over all eight time periods
- The controls were then weighted according to the naional distribution of traffic in each time period in order to represent general traffic.
- The weighted controls were used for the odds ratio estimates.

In order to meet the assumptions of a case-control design, roadside surveys were to be conducted in the catchment areas of the trauma centre(s) (where cases were recruited).

Week and weekend – day and night were defined in eight time intervals of the week, as shown in **table 6**. In The Netherlands, time periods 1-3 and 5-7 were merged resulting in four time intervals.

Table 6 Eight time intervals of the week

Weekdays			Weekend		
1	Monday – Friday	04:00-09:59	5	Saturday and Sunday	04:00-09:59
2	Monday – Friday	10:00-15:59	6	Saturday and Sunday	10:00-15:59
3	Monday –Thursday	16:00-21:59	7	Friday – Sunday	16:00-21:59
4	Monday – Thursday Tuesday – Friday	22:00-23:59 00:00-03:59	8	Friday – Sunday Saturday – Monday	22:00-23:59 00:00-03:59

The principle that the results of the survey should be representative for the general traffic in each time period in each country was not met, partly due to national principles of collecting control drivers, partly because of other limitations on national levels such as long travel distances or very low traffic volumes in sparsely populated areas. Therefore, to adjust for the skewness in the sampling, the data for each driver in road side survey sample were weighted by the traffic fraction of the general driving population in the specific time period and country where the driver was stopped as recommended by Mathijssen and Houwing (2005).

The traffic fractions of car drivers for each time period and each country that were used for the weighting are shown in **table 7**.

Table 7 Distribution of traffic over the week

Time period	Weekday morning	Weekday daytime	Weekday afternoon	Weekday evening/night	Weekend morning	Weekend daytime	Weekend afternoon	Weekend evening/night	In total
BE	0.1870	0.2515	0.2515	0.0580	0.0630	0.0818	0.0818	0,0254	1.000
DK	0.2230	0.3050	0.1710	0.0240	0.0310	0.1130	0.1080	0.0250	1.000
FIN	0.1860	0.2890	0.1970	0.0330	0.0570	0.0880	0.1300	0.0200	1.000
IT*	0.2100	0.2600	0.2400	0.0300	0.0400	0.1100	0.0900	0.0200	1.000
LT*	0.2100	0.2600	0.2400	0.0300	0.0400	0.1100	0.0900	0.0200	1.000
N	0.1500	0.2700	0.2300	0.0600	0.0100	0.0800	0.1500	0.0500	1.000
NL	0.2200	0.2360	0.2690	0.0350	0.0270	0.1110	0.0800	0.0220	1.000
PT*	0.2100	0.2600	0.2400	0.0300	0.0400	0.1100	0.0900	0.0200	1.000
S	0.2100	0.2600	0.2500	0.0200	0.0400	0.1200	0.0800	0.0200	1.000

* Based on international estimates

2.4 Non-response bias of controls

Non-response and non-response bias are common problems in epidemiological studies (Berghaus et al., 2007). Non-response bias occurs in the case of people not responding to the survey, differ from those who do respond with regard to drug and/or alcohol use. In this case, the calculated prevalence becomes erroneously high or low. The higher the non-response rate, the higher the possibility for a non-response bias (Houwing et al., 2011).

The non-response rate of the road side surveys in the countries in this case-control study varied between 0% and 52% and were divided into two groups: countries with a high non-response rate (above 20%): Belgium (52%), Finland (48%), Sweden (38%), Lithuania (24%) and Czech Republic (23%), and countries with a low non-response rate (10% or below): Hungary (10%), Norway (6%), The Netherlands (5%), Denmark (5%), Portugal (3%), Spain (2%), Poland (1%), Italy (0%). In this study, non-response bias was tested for by comparing the distribution of age and gender of the response control study samples to the non-response samples. If the distributions did not differ significantly, it was concluded that there was no non-response bias.

The Belgian roadside survey suffered from a high non-response rate (Van der Linden et al., 2011). Age and gender were significantly differently distributed in the response and non-response group (age: N=6,060, df=3, χ^2=37.5, p<0.0001; gender: N=6,087, df=1, χ^2=11.3, p<0.001). There was an

overrepresentation of responding female drivers compared to responding male drivers, an overrepresentation of non-respondents in the age group 25-34, and finally an underrepresentation of non-respondents in the youngest and oldest age group. This pattern may have lead to non-response bias.

The non-response rate of the Finnish study was 48% (Engblom et al., 2011). Due to judicial limitations – for ethical reasons interviewers were not allowed to collect information about refusers - no comparison was possible between the response and non-response groups. Comparison of the respondents in the road side survey with a recently conducted study on the Finnish traffic distribution showed that the demographic profile of the respondents was representative of the Finnish general driving population (Ministry of Transport and Communications Finland et al.) which is an indication of the non-respondents not being systematically different from the respondents in demographic profile. However, the police in Finland allowed only a(n) (unknown) fraction of the alcohol positives to be sampled, so prevalence of alcohol and alcohol-drug combinations are underestimated to an unknown degree.

Non-response rate in the Swedish roadside survey was 38% (Forsman et al., 2011). No information was collected about the non-respondents. However, in a similar study, where participation was mandatory (Forsman et al., 2007), gender distribution was similar to this study (χ^2=0.06, df=1, p>>0.05), but age distribution was not (χ^2=67.13, df=3, p<0.01). There was an overrepresentation of drivers aged 50+ in the DRUID sample and a corresponding underrepresentation of younger age groups who are probably more inclined to refuse participation. Furthermore, no data on alcohol above the legal limit of 0.2 g/L BAC were collected because of the Swedish legislation.

The Lithuanian roadside survey had a non-response rate of 24% (Caplinskiene et al., 2011). The non-respondents were between 18 and 31 years of age, and women were significantly overrepresented (N=1,731, χ^2=511, df=1, p<<0.001). This indicates that there is a bias in gender the study sample for the two youngest age groups. The main reason of refusal appeared to be lack of time, and no signs of impairment were observed in this group.

In the Norwegian study, the non-response rate was 6% (Gjerde et al., 2011). Due to Norwegian laws of protection of individual rights it was not allowed to collect any information about the non-respondents. Norwegian researchers hypothesize that prevalence of both alcohol and drugs might have been higher in the non-response group, and thus the prevalence estimate is underestimated (Houwing et al., 2011).

In The Netherlands, the overall non-response rate was 5% (Houwing et al., 2011). Male drivers were significantly overrepresented among the non-respondents (N=5,064, χ^2=17.66, df=1, p<<0.001), and so were younger drivers (N=5,046, χ^2=19.08, df=3, p=0.0003). There was no significant difference in distribution of BAC level between the respondents and the non-respondents (N=5,064, χ^2=5.35, df=4, p=0.25) which is an indication of no non-response bias. On the other hand, the self-reported use of psychoactive substances was higher for the non-response group (6.5%) than for the response group (3.6%) (Houwing et al., 2011).

The Danish non-response rate was 5% (Hels et al., 2011). There was no non-response bias in distribution of gender (N=3,163, χ^2=0.41, df=1, p=0.52) or age (N=3,163, χ^2=6.32, df=3, p=0.10).

The Portuguese non-response rate was 3% (Dias et al., 2011). No information was obtained on the non-respondents.

Italy had the lowest non-response rate possible, i.e. 0% (Ferrara et al., 2011a). Although participation in the study was voluntary, refusal to do so could be followed by a formal charge for driving under the influence. Thus, participation was in a way forced. However, in Italy there was skewness in the driving population sampled towards drivers exhibiting signs of alcohol impairment (Favretto, personal communication). This most probably has overestimated alcohol prevalence in the driving population.

It is not possible to control for the bias in the road side surveys, but the above information is necessary when interpreting the results of this report.

2.5 Toxicological methods

As mentioned in table 3, saliva and/or blood was collected in the road side surveys and blood was collected in the studies of seriously injured drivers and the studies of killed drivers. The time between accident and sampling was maximum 3h for injured drivers and up to one day for killed drivers. However, one day might be more than 24h. During this period the concentration of some drugs might have declined significantly, especially 6-AM, THC, cocaine, zopiclone, zolpidem, flunitrazepam. For detailed information on the sample collection, see Isalberti et al. (2011) and Houwing et al. (2011).

The criteria for blood samples were:

- 5-10 mL whole blood collected in vacuum tubes containing sodium fluoride and potassium oxalate
- Transported at 4°C (max. 48 hours)
- Stored in laboratory at -20°C

The criteria for saliva samples were:

- 1 mL oral fluid collected using Statsure Saliva Sampler.
- Collected according to guidelines by manufacturer
- Transported at 2-8°C (max. 48 hours)
- Stored in the laboratory at -20°C

The Statsure Saliva sampler was not used in the Netherlands because the study in the Netherlands already started before the decision was taken on which saliva sampler should be used in the DRUID road side surveys. The drivers in the Netherlands spitted in a cup. However, the concentrations in saliva, analysed by means of pure saliva do not differ from the concentrations analysed by means of the saliva from the Statsure Samplers that were diluted by the buffer in the sampler (Langel et al., 2008).

Within the DRUID partners, it was decided which core substances should be analysed for in order to be able to compare the results from all countries. The list of substances, as shown in **table 8** was agreed upon except for the last three substances that were analysed for in most of the countries and were therefore added to the list of core substances. In addition to the substances shown in the table, the blood samples were also analysed for THCCOOH, but because THCCOOH cannot be detected in saliva with commonly available methods, no equivalent cut-off was needed for this substance. All samples were analysed with confirmation methods.

All blood- and saliva samples were analysed by means of fully validated methods for the same number of substances in all countries, c.f**. table 8**. Whole blood samples were extracted using solid phase extraction (SPE) or liquid-liquid (LLE) extraction. Chromatographic separation was performed by gas chromatography (GC), High Performance liquid chromatography (HPLC) or Ultra Performance liquid chromatography (UPLC). Saliva samples were extracted using solid phase extraction (SPE) or liquid-

liquid (LLE) extraction. Chromatographic separation was performed by gas chromatography (GC), High Performance liquid chromatography (HPLC), Ultra Performance liquid chromatography (UPLC) or liquid chromatography (LC). Detection was done by mass spectrometry (MS) or tandem mass spectrometry (MSMS). Proficiency test analyses of saliva and whole blood were carried out by all participating laboratories, resulting in a high quality of toxicological analyses in all countries.

If both a blood and a saliva sample were taken, the toxicological analysis of the blood sample was always used as the result. For the calculations of risk, it was necessary to be able to compare the concentrations of the substances in the cases with the concentrations of the substances in the controls for those countries that had collected blood from the case study population and saliva from the control study population, as well as for the comparison of risk for countries that had collected different body fluids. For this purpose, equivalent cut-off values for the concentrations in blood and saliva for each tested substance were developed for the DRUID project by a team of toxicologists (Verstraete et al., 2011).

Concentrations at and above these equivalent cut-offs were used as an indication for whether a sample was positive for the substance in question. **Table 8** shows the substances as well as the equivalent cut-offs.

Table 8 Recommended equivalent cut-offs in blood and saliva for the DRUID core substances

Substance	**Recommended equivalent cut-off in whole blood (ng/mL)**	**Recommended equivalent cut-off in oral fluid (ng/mL)**
Ethanol	0.1 (g/L)	0.082 (g/L)
6-acetylmorphine	10	16[1]
Alprazolam	10	3.5
Amphetamine	20	360
Benzoylecgonine	50	95
Clonazepam	10	1.7
Cocaine	10	170
Codeine	10	94
Diazepam	140	5.0[2]
Flunitrazepam	5.3[1]	1.0[2]
Lorazepam	10	1.1
MDA	20	220[1]
MDEA	20	270[3]
MDMA	20	270[1]
Methadone	10	22
Methamphetamine	20	410
Morphine	10	95
Nordiazepam	20	1.1
Oxazepam	50	13
Cannabis	1.0	27
Zolpidem	37	10[2]
Zopiclone	10	25[1]
Tramadol	50	480
7-amino-clonazepam	10	3.1[1]
7-amino-flunitrazepam	8.5[1]	1.0[2]

[1] data based on less than 10 individual cases

[2] recommended cut-off for OF lower than the original DRUID cut-off in oral fluid, therefore the cut-off of blood has been raised

[3] no positive cases; cut-off of MDMA used for MDEA

Ten substance groups were developed (**table 9**), based on the analytical findings of positive concentrations at and above the equivalent cut-offs, see **table 8**. The analytical findings in the samples were evaluated according to table 9.

It was decided that samples with positive concentrations of the substance THCCOOH alone that could only be detected in blood are considered to be belonging to the negative samples, both for controls and for cases for the following reasons:

- THCCOOH was very seldom found in the road side surveys, because it cannot be detected in saliva
- Samples positive for THCCOOH are considered negative in the prevalence calculations (Houwing et al., 2011)
- Relative risk calculations cannot be carried out for the countries that have collected saliva, and there are so few positive samples in the control populations from the remaining countries
- There are numerous other substances that were not analysed for in the survey which might be found in the samples, although they are considered negative
- THCCOOH is a metabolite and is not supposed to impair driving when found alone

Table 9 Substance groups for calculating relative risk

Type	Group	Analytical findings
Alcohol	alcohol	ethanol
Illicit drugs	amphetamines	amphetamine methamphetamine or methamphetamine + amphetamine MDMA or MDMA + MDA MDEA or MDEA + MDA MDA
	benzoylecgonine	benzoylecgonine
	cocaine	cocaine + benzoylecgonine or cocaine
	THC	THC or THC+THCCOOH
	illicit opiates	6-acetylmorphine or 6-AM + codeine or 6-AM + morphine or 6-AM + codeine + morphine or (morphine + codeine and morphine>= codeine)
Medicinal drugs	benzodiazepines and Z-drugs	diazepam or diazepam + nordiazepam or diazepam + oxazepam or diazepam + nordiazepam + oxazepam nordiazepam or nordiazepam + oxazepam oxazepam lorazepam alprazolam flunitrazepam or flunitrazepam + 7-aminoflunitrazepam clonazepam or clonazepam + 7-aminoclonazepam zolpidem zopiclone
	medicinal opioids	morphine codeine or (codeine + morphine and codeine> morphine) methadone tramadol
Various combinations	alcohol-drugs	all combinations
	multiple drugs	all combinations

2.6 Representativeness of the case and control samples

The study design was aimed to be a population base case-control study. To this aim, controls were sampled at all timepoints, but in a sampling scheme similar to that of the cases. Then, a weighting procedure was used to estimate the prevalence in the general driving population. These data were also used for the risk calculations.

Controls consisted of a sample stratified with respect to time of the general driving population in the catchment area(s) of the trauma centre(s) – typically large hospitals. The samples were stratified according to time of day and week and road type. Within the strata, samples were taken randomly. The control sample was weighted with the traffic fractions by time period.

In the case of injured drivers, case drivers consisted of drivers who were severely injured (MAIS≥2 or equivalent) and admitted to hospitals in pre defined regions of the following countries: Belgium, Denmark, Finland, Italy, Lithuania and The Netherlands.

In the case of killed drivers, case drivers consisted of drivers who were killed from the whole countries in the following countries: Finland, Norway, Portugal and Sweden.

In a population case control design, cases and controls have to match on a population level (reference). Along this line two questions were asked:

1. In the case that a country had a higher number of road side survey regions (RSSR) than hospital survey regions (HSR), it was tested (χ^2-tests) if age and gender distributions of the sampled drivers were significantly different in the road side survey regions that were matched by a hospital catchment area and the road side survey regions that were not matched. The results of these tests are presented in **table 10** (injured drivers) and **table 11** (killed drivers). If either age, gender or both distributions differed significantly, the RSSRs that were not matched by HSRs were not included. If they did not differ, they were included in order to have large sample sizes
2. In the case that a country had one or more hospital catchment areas that extended geographically beyond the road side survey area(s), it was tested (χ^2-tests) whether there was a significant difference between the injury score distribution of the sampled injured driving population inside and outside of the road side survey area(s). The results of these tests are presented in **table 10**. This answers the question if the injured sampled population inside and outside of the road side survey area was injured to the same degree, generally. One hypothesis of this not being so would be that the longer the distance to the hospital, the more serious the injury for a driver would have to be for the driver to be brought to that particular hospital. If so, the distribution of the injury scores would be skewed towards more serious injuries outside of the road side survey area, and the resulting relative risk would be wrong.

Table 10 Answers to questions about representativeness for injured drivers

Country	**Question 1:** Do road sample regions match hospital catchment areas geographically? If not, is there a significant different age- and gender distribution in the road sample regions that have matching hospital catchment areas and the road side sample regions that do not?
BE	Three road sample regions that match the hospital catchment areas by design. Consequently, all data from the roadside survey were included as controls in the relative risk calculations.
DK	One road sample region out of the three, Roskilde, was not matched by a hospital catchment area. This one, Roskilde (no. 3), was tested against the two other road sample region: 1+2 (cf. Table p. 2) with regard to potential differences in age- and gender distribution. No difference was found, either in age (N=2,995, df=3, χ^2=3.27, p=0.99) or gender (N=2,998, df=1, χ^2=0, p=1) Consequently, all data from the roadside survey were included as controls in the relative risk calculations.
FI	One road side sample region out of two, Pohjois-Savo, was not matched by a hospital catchment area. This one, Pohjois-Savo (no.2) was tested against the other (Uusimaa) with regard to potential differences in age- and gender distribution. Significant differences were found, both in distributions of age (N=3,835, df=3, χ^2=408.64, p<0.0001) and in gender (N=3,827, df=1, χ^2=151.64, p<0.0001). Consequently, road side survey data from Pohjois-Savo were left out in the relative risk calculations.
IT	One road side sample region out of five, Vicenza, was not matched by a hospital catchment area. This one, Vicenza, was tested against the other four areas with regard to potential differences in age- and gender distribution. Significant difference was found in gender distribution (N=1,310, df=1, χ^2=73.25, p=0.007),

	but not in age distribution (N=1,310, df=3, χ^2=20.12, p=0.57). Consequently, road side survey data from Vicenza region were left out in the relative risk calculations.
LT	Four road sample regions that match the hospital catchment areas by design. Consequently, all data from the roadside survey were included as controls in the relative risk calculations.
NL	Three road side sample regions out of six (i.e. Hollands-Midden, Amsterdam Amstelland, Groningen) were not matched by a hospital catchment area. Thus, these three regions were tested against the other three regions (with matching hospital catchment areas) with regard to potential differences in age- and gender distribution. No difference was found, either in age (N=4,817, df=3, χ^2=16.81, p=0.64) or gender (N=4,817, df=1, χ^2=12.45, p=0.26). Consequently, all data from the roadside survey were included as controls in the relative risk calculations.

Country	**Question 2:** Do one or more hospital catchment areas extend geographically beyond the corresponding road side survey region(s)? If so, is there a significant difference in injury severity score of the injured population within and outside of the road side survey region(s)?
BE	Hospital catchment areas match road side survey regions exactly by design. Consequently, all hospital study data were used in relative risk calculations.
DK	Hospital catchment area Kolding, Vejle and Odense (no. 2, cf. **table 2**) was extended beyond the corresponding road side survey region. Trauma score for all injured drivers in this area were grouped into four groups, split into two groups: within and outside the road side survey region and subsequently tested for potential difference in injury score distribution. No significant difference was found (N=530, df=3, χ^2=7.03, p=0.07). Consequently, all hospital study data were included in the relative risk calculations.
FI	Data from one of the road side survey regions, Pohjois-Savo, were left out, cf. question 1 above The hospital catchment area of the Uusimaa region match road side survey region exactly by design. Consequently, all hospital data from Uusimaa region were used in relative risk calculations.
IT	Data from the fifth road side survey area, Vicenza, were left out of the calculations, cf. question 1 above. The other hospital catchment areas match road side survey regions exactly by design (Padova and Rovigo regions) or road side survey regions are larger than hospital catchment areas (Venezia and Treviso). Consequently, all hospital study data from these four regions were used in relative risk calculations.
LT	Hospital catchment areas match road side survey regions exactly by design. Consequently, all hospital study data were used in relative risk calculations.
NL	In the Netherlands, three out of six road side survey regions were matched by hospital catchment areas. In region no. 2, Tilburg, the hospital catchment area was larger than the road side survey region; in region no. 5, Twente, the hospital catchment area and the road side survey region matched each other quite well; and in region no. 6, Gelderland-Zuid, there was a certain overlap between the two. Since the regions and catchment areas were not defined exactly, matching calculations could not be carried out. Consequently, all hospital study data were used in relative risk calculations.

Table 11 Answers to questions about representativeness for killed drivers

Country	**Question 1:** Do road sample regions match catchment areas for collecting samples from killed drivers geographically? If not, is there a significant different age- and gender distribution in the road sample regions that have matching killed driver catchment areas and the road side sample regions that do not?
FI	Two road side survey regions corresponded geographically exactly to two killed driver catchment areas. Besides these two, samples were taken from killed drivers from the rest of Finland. Consequently, all road side survey data were used in relative risk calculations.
N	All three road side survey regions were contained in three killed driver catchment areas. Consequently, all road side survey data were used in relative risk calculations.

PT	Two road side survey regions were contained in two killed driver catchment areas. One other road side survey region, Porto, was not matched by a killed driver catchment area. Thus, Porto was tested against the other two regions (with matching killed driver catchment areas) with regard to potential differences in age- and gender distribution. No difference was found in gender distribution (N=3,907, df=1, χ^2=18.7, p=0.17), but a significant difference was found in age distribution (N=3,907, df=3, χ^2=103.9, p=0.02). Consequently, road side survey data from Porto region were left out in the relative risk calculations.
SE	Both road side survey regions were contained in the killed driver catchment areas, which latter consisted of the whole of Sweden. Consequently, all road side survey data were included in the relative risk calculations.

As for the case samples, question 2 was not relevant for the killed driver sample, since there is no difference in severity score (all cases MAIS=6).

Based on the answers in t**able 10** and **11**, Table 12 summarises the regions from which data were included in the risk calculations.

Table 12 Participating countries and regions in the calculations of relative risk

	Control samples	**Case samples**	
Country	**Road side survey**	**Seriously injured drivers**	**Killed drivers**
Belgium	1. Brussels 2. Flanders 3. Wallonia	1. Brussels 2. Flanders 3. Wallonia	
Denmark	1. Ålborg and Viborg 2. Kolding, Vejle and Odense 3. Roskilde	1. Ålborg and Viborg 2. Kolding, Vejle and Odense	
Finland	1. Uusimaa (both for seriousluy injured and killed drivers) 2. Pohjois-Savo (for killed drivers)	1. Uusimaa	1. Uusimaa 2. Pohjois-Savo 3. Rest of Finland
Italy	1. Padova 2. Venezia 4. Treviso 5. Rovigo	1. Padova 2. Venezia 4. Treviso 5. Rovigo	
Lithuania	1. Vilnius 2. Kaunas 3. Klaipeda 4. Alytus	1. Vilnius 2. Kaunas 3. Klaipeda 4. Alytus	
Norway	1. Hedmark & Romerike and Buskerud & Asker-Bærum (Part of South-east Norway) 2. Hordaland and Haugaland (Part of South-west Norway) 3. Trøndelag and Troms (Part of Middle-north Norway)		1. South-east Norway 2. South-west Norway 3. Middle-north Norway
Portugal	2. Coimbra (Part of Centre Branch of INML) 3. Lisboa (Part of South Branch of INML)		2. Centre Branch of INML 3. South Branch of INML
Sweden	1. Södermanlands, Örebro and Östergötlands län		Whole Sweden

The Netherlands	1. Hollands-Midden 2. Tilburg 3. Amsterdam Amstelland 4. Groningen 5. Twente 6. Gelderland-Zuid	 2. Tilburg (Tilburg hospital) 5. Twente (Enchede hospital) 6. Gelderland-Zuid (Nijmegen hospital)	

2.7 Relative risk and odds ratio

In case-control studies, data is often presented at as shown in the contingency **table 13**.

Table 13 Contingency table for case-control study

	Cases (acc=1)	Controls (acc=0)	Sum
Exposed (subst=1)	a	b	a+b
Non-exposed (subst=0)	c	d	c+d

In this study, the event is getting seriously injured/killed as a driver in a road accident (acc=1) or not (acc=0) while positive for a given substance group (subst=1) or not positive for any substances (subst=0). The variables in the table represent numbers, that is:

- a: the number of cases (here seriously injured drivers/killed drivers) positive for a given substance group
- b: the number of controls positive for a given substance group
- c: the number of cases (here seriously injured drivers/killed drivers) negative for all substances
- d: the number of controls negative for all substances

From this type of contingency table it is possible to set up a calculation for both the relative risk and the odds ratio, as explained below.

2.7.1 Relative risk

Relative risk is the ratio of two risks, the risk of the event occurring in the group of exposed subjects and the risk of the event occurring in the group of non-exposed subjects. The risks are measured by their probabilities, or in mathematical terms:

$$RR = \frac{p(acc = 1|subst = 1)}{p(acc = 1|subst = 0)}$$

From table 1, it is possible to express this in terms of a, b, c and d:

$$RR = \frac{p(acc = 1|subst = 1)}{p(acc = 1|subst = 0)} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

This expression computes the relative risk based on the numbers from the contingency table.

2.7.2 Odds ratio

Odds ratio is a measure which is often used in epidemiological studies. The odds ratio is a ratio between two odds, that is - in this study - between the odds of having the event among subjects who were positive for a given substance group (exposed) and the odds of having the event among non-exposed subjects. Odds is the ratio between the risk of having the event and the risk of not having the event.

Odds is defined as:

$$Odds = \frac{p}{1-p}$$

From **table 12**, it is clear that the probability of having the event (acc=1) given that the person is positive for a given substance group (subst=1) is a/a+b, and the probability of not having the event given that the person is positive for a given substance group is 1 - a/a+b

Odds of having the event (acc=1), given that the subject is positive for a given substance group is:

$$Odds(subst = 1) = \frac{p(acc = 1|\, subst = 1)}{1 - p(acc = 1|\, subst = 1)} == \frac{\frac{a}{a+b}}{1 - \frac{a}{a+b}} = \frac{a}{b}$$

Similarly, the probability of having the event (acc=1) given that the person is negative for a given substance group (subst=0) is c/c+d, and the probability of not having the event, given that the person is not positive for a given substance group is 1 - c/c+d

Consequently, odds of having the event (acc=1) given that the subject is negative for a given substance group (subst=0) is:

$$Odds(subst = 0) = \frac{p(acc = 1|\, subst = 0)}{1 - p(acc = 1|\, subst = 0)} = \frac{\frac{c}{c+d}}{1 - \frac{c}{c+d}} = \frac{c}{d}$$

Finally, the odds ratio (*OR),* that is the ratio between the odds of the event among exposed subjects and the odds of the event among non-exposed subjects is:

$$OR = \frac{Odds(subst = 1)}{Odds(subst = 0)} = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$$

This expression gives the odds ratio from the numbers given in the contingency table.

2.7.3 Relation between relative risk and odds ratio

By comparing the expressions for relative risk and odds ratio

$$RR = \frac{p(acc=1|subst=1)}{p(acc=1|subst=0)} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

$$OR = \frac{Odds(subst = 1)}{Odds(subst = 0)} = \frac{\frac{a}{b}}{\frac{c}{d}} = \frac{ad}{bc}$$

it is seen that if *a* and *c* are small numbers, then OR will approximate RR. As *a* and *c* are the numbers of accidents, this approximation holds, since the numbers of accidents are usually small compared to the numbers of controls. This is convenient as the odds ratio can be generalised to more than two binary variables using logistic regression.

2.7.4 Generalization of odds ratio using logistic regression

Logistic regression relates a number of independent variables to the probability of an event, in this case the probability of a driver in the driving population of being seriously injured/killed in an accident. Besides the probability, *P(y)*, a confidence interval is estimated.

The logistic function is given by

$$P(y) = \frac{\exp(y)}{1+\exp(y)} \quad (1)$$

Here, *P(y)* denotes the probability of being in an accident which is confined to a number between 0 and 1. The logit, *y*, is a linear expression of x on the form:

$$y = \beta_0 + \beta_{agegrp}x_{agegrp} + \beta_{gender}x_{gender} + \beta_{subst}x_{subst} \quad (2)$$

where $x_{agegrp}, x_{gender}, x_{subst}$ denote the three independent variables, age group, gender and the presence of a substance, respectively. The three independent variables are all categorical. β_0 is the intercept and $\beta_{agegrp}, \beta_{gender}, \beta_{subst}$ are scaling coefficients for the three independent variables.

By a little rearranging, the formula (1) can be put on the form

$$\exp(y) = \frac{P(y)}{1-P(y)} \quad (3)$$

This means that each of the odds can be found by means of logistic regression. Then the odds ratio between the two odds can also be found by logistic regression.

An odds ratio is significantly different from 1 if its confidence interval does not include the value 1. The confidence intervals in this report are all computed with a risk equal to 5%. In other words, the confidence intervals have 95% chance of containing the true value of the odds ratio.

2.8 Statistical analysis

The main aim of this study was to calculate odds ratios which approximate relative risk in the case of a rare event, such as a road accident for a car driver of getting injured in an accident when driving under the influence of various psychoactive substances.

Two odds ratios have been calculated for car drivers:

- The odds ratio for a driver of getting seriously injured in a road accident while positive for a certain substance group compared to a driver getting seriously injured while negative for all substances
- The odds ratio for a driver of getting killed in a road accident while positive for a certain substance group compared to a driver getting killed while negative for all substances

The odds ratios have been calculated by means of logistic regression for the following substance groups: Alcohol, amphetamines, cocaine, cannabis, illicit opiates, benzodiazepines and z-drugs, as well as medicinal opioids. Furthermore, two extra groups, alcohol-drugs and multiple drugs, were included, as some observations were positive for both alcohol and drugs or multiple drugs.

Negative samples, that is samples for which no substances have been found in concentrations above or equal to the equivalent cut off, form the reference group irrespective of the substance group in question. The description of the categorical variables can be found in **table 14**.

Table 14 Categorical variables used in the logistic regression

Categorical variable	Number of categories	Categories
Age	4	18-24 25-34 35-49 50+
Gender	2	Male Female
Alcohol	5	Samples negative for all substances, that is concentration below cut-off (reference group) 0.1-0.49 g/L 0.5-0.79 g/L 0.8-1.19 g/L 1.2+ g/L
Amphetamines Benzoylegonine Cocaine Cannabis Illicit opiates Benzodiazepines and Z-drugs Medicinal opioids Alcohol-drug(s) Multiple drugs	2	Samples negative for all substances, that is concentration below cut-off (reference group) Positive, concentration above or equal to cut-off: – positive for one drug: positive for one drug group only – positive for alcohol-drug(s): positive for alcohol plus one or more drugs – positive for multiple drugs: positive for more than one drug, but not for alcohol

Both crude odds ratios and adjusted odds ratios were calculated for the various substance groups.

Both for the calculation of crude odds ratio and adjusted odds ratio, a weighting of the controls was done as the estimates of the odds ratios must reflect the driving population as a whole, and therefore weighting of the controls have been done according to traffic volume (Mathijssen and Houwing, 2005). This means that more weight has been given to controls in time periods with a higher fraction of traffic volume than the fraction of controls in the same time period, and at the other end of the spectrum: less weight has been given to controls in time periods with a lower fraction of traffic volume than the fraction of controls in the same time period. The weighting was based on the distribution of traffic volume over the eight time periods, as can be seen in **table 7** in section 2.3.

All cases were assigned the weight 1.

The reference group consisted of samples negative for all substances, that is below the cut-off as agreed upon in the study and shown in section 2.5, **table 8**. The reference group was constant irrespective of the substance group in question for the calculation. For alcohol, the odd ratio estimate for each interval of alcohol concentration was considered.

Crude odds ratios were calculated for each country separately as described in section 2.7.2. If in a country, any of the four categories:

- negative controls
- positive controls
- negative cases
- positive cases

was equal to zero, 0.5 was added to each of the four categories (following Greenland et al., 2000).

Odds ratios adjusted for age and gender were calculated for the various substance groups for countries with enough positive cases and controls in the substance group in question. In the logistic regression, the adjustment for age and gender was done by incorporating them as independent variables in the model.

The logistic regression analysis was computed by means of SAS 9.2, using the procedure *proc logistic*.

2.8.1 Odds ratio calculations based on data from more than one country

In order to get more reliable relative risk results, one could argue that data from all countries be pooled and odds ratio estimates should be calculated based on data from all countries in the survey.

However, the number of subjects with positive concentrations of substances is sparse in both the case samples and the control samples. Even though this is fortunate from at road safety point of view, it results in imprecise odds ratio estimates with broad confidence intervals.

This chapter includes three different sets of criteria for pooling data from various countries. Each of the methods is correct in its own right; still they produce different results. Therefore, in the result chapter, three different sets of odds ratios are presented based on the pooling of data following the three sets of criteria one by one. Finally, the recommended set of results is included in the concluding chapter.

Method 1
Data from all countries were included in common risk estimates, irrespective of differences in the various countries' odds ratio estimates and their precision (measured by the size of the confidence intervals).

The controls of each country were weighted by traffic before they were merged. All cases were assigned the weight 1. Odds ratios were estimated both as crude odds ratios and odds ratios adjusted for age and gender.

Method 2
The rationale of the second method was to pool data from countries with similar odds ratio estimates and leave out data from countries with odds ratio estimates that were very different. This rationale was implemented as follows (all three criteria should be met for the data to be pooled):

- The highest odds ratio estimate among the countries which data were pooled was as a maximum four times higher than the lowest one.
- The confidence intervals of the odds ratio estimates for all the countries which data were pooled overlapped.
- If there were several solutions of pooling countries' data, the one which included most countries was chosen.

The controls of each country were weighted by traffic before they were merged. All cases were assigned the weight 1. Odds ratios adjusted for age and gender were calculated.

Method 3

The rationale of the third method was to include data from countries where the odds ratio estimates were most precise and leave out data from countries where the odds ratio estimates were very imprecise. The precision of the odds ratio estimates for each country is evaluated as follows:

The evaluation is based on the crude odds ratio: *OR = (a*d)/(b*c)* (cf. section 2.7, t**able 13**)
The procedure is to find the smallest value in any of the cells *a,b,c,d* and compute the modified odds ratio estimate when 1 is either added ('OR+1') or subtracted ('OR-1') from the value in the cell. The rationale is that the smallest value of the four *(a,b,c,d)* will be the one where a change has the largest effect on the size of the odds ratio estimate.

If the value of 'OR+1' is at least twice as big as 'OR-1', it is a sign that the odds ratio estimate is too susceptible to be influenced by very small changes in the data, and data from that country were left out of the pooled odds ratio estimate.

The controls of each country were weighted by traffic before they were merged. All cases were assigned the weight 1. Odds ratios adjusted for age and gender were calculated.

Fictitious example:

a=4, *b*=8, *c*=400, *d*=2000 (for the meaning of a,b,c,d, please cf. section 2.7, **table 13**)

OR = (4*2000)/(8*400) = 2.5
'OR-1' = (3*2000)/(8*400) = 1.9
'OR+1' = (5*2000)/(8*400) = 3.1

Since 'OR+1' (=3.1) is not greater than twice the value of 'OR-1' (2x1.9=3.8), data from this (fictitious) country should be included in the pooled odds ratio estimate.

3 Results

3.1 Odds ratio for drivers of getting seriously injured in a road accident

3.1.1 Data material

The distribution of the study samples from the case and control studies by substance group is shown in **table 15**. Categories are mutually exclusive, so a sample negative was negative for all substances. A sample positive for alcohol-drug(s) was considered positive in this category only – not in the alcohol category and neither in the drug(s) category. This principle holds for the risk calculations as well.

Table 15 Number of cases and controls for the study of seriously injured drivers by country and substance group

Belgium	**Cases**	**Controls**	
		Unweighted	Weighted for traffic
Negative samples	171	2597	2634.85
0.1 g/L ≤ alcohol < 0.5 g/L	8	140	125.80
0.5 g/L ≤ alcohol < 0.8 g/L	6	47	39.11
0.8 g/L ≤alcohol < 1.2 g/L	11	16	12.33
Alcohol ≥ 1.2 g/L	83	17	12.02
Amphetamine	3	0	0.00
Benzoylecgonine	0	4	5.03
Cocaine	0	2	0.75
All cannabis concentrations	5	15	10.35
Illicit opiates	0	3	2.69
Benzodiazepines and Z-drugs	8	62	65.94
Medicinal opioids	6	23	22.12
All alcohol-drug combinations	40	12	9.02
All multiple drug combinations	7	11	8.99
In total	348	2949	2949

Denmark	**Cases**	**Controls**	
		Unweighted	Weighted for traffic
Negative samples	599	2858	2867.36
0.1 g/L ≤ alcohol < 0.5 g/L	15	58	57.15
0.5 g/L ≤ alcohol < 0.8 g/L	16	16	13.05
0.8 g/L ≤alcohol < 1.2 g/L	17	5	4.13
Alcohol ≥ 1.2 g/L	81	2	1.51
Amphetamine	9	1	0.50
Benzoylecgonine	0	0	0.00
Cocaine	1	0	0.00
All cannabis concentrations	5	7	5.97
Illicit opiates	0	0	0.00
Benzodiazepines and Z-drugs	16	22	23.65
Medicinal opioids	21	26	23.75
All alcohol-drug combinations	36	5	3.05
All multiple drug combinations	23	2	1.87
In total	839	3002	3002

Finland	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	32	2627	2625.91
0.1 g/L ≤ alcohol < 0.5 g/L	1	13	11.58
0.5 g/L ≤ alcohol < 0.8 g/L	1	3	2.36
0.8 g/L ≤alcohol < 1.2 g/L	1	1	1.01
Alcohol ≥ 1.2 g/L	10	4	4.77
Amphetamine	0	1	1.73
Benzoylecgonine	0	1	1.28
Cocaine	0	0	0.00
All cannabis concentrations	1	2	1.61
Illicit opiates	0	0	0.00
Benzodiazepines and Z-drugs	1	32	32.96
Medicinal opioids	1	16	16.07
All alcohol-drug combinations	4	2	2.29
All multiple drug combinations	2	4	4.44
In total	54	2706	2706

Italy	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	464	924	906.65
0.1 g/L ≤ alcohol < 0.5 g/L	15	25	43.54
0.5 g/L ≤ alcohol < 0.8 g/L	9	23	27.03
0.8 g/L ≤alcohol < 1.2 g/L	15	27	20.23
Alcohol ≥ 1.2 g/L	88	27	11.46
Amphetamine	0	0	0.00
Benzoylecgonine	5	4	3.84
Cocaine	5	7	11.56
All cannabis concentrations	11	10	14.58
Illicit opiates	2	4	3.99
Benzodiazepines and Z-drugs	2	5	13.22
Medicinal opioids	16	1	3.32
All alcohol-drug combinations	29	17	9.89
All multiple drug combinations	15	12	16.69
In total	676	1086	1086

Lithuania	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	282	1192	1198.71
0.1 g/L ≤ alcohol < 0.5 g/L	6	29	19.99
0.5 g/L ≤ alcohol < 0.8 g/L	4	7	5.52
0.8 g/L ≤alcohol < 1.2 g/L	7	7	4.88
Alcohol ≥ 1.2 g/L	43	23	17.07
Amphetamine	1	2	2.71
Benzoylecgonine	1	0	0.00
Cocaine	1	0	0.00
All cannabis concentrations	1	0	0.00
Illicit opiates	0	0	0.00
Benzodiazepines and Z-drugs	6	6	17.77
Medicinal opioids	22	0	0.00
All alcohol-drug combinations	8	1	0.35
All multiple drug combinations	3	0	0.00
In total	385	1267	1267

The Netherlands	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	125	4426	4537.08
0.1 g/L ≤ alcohol < 0.5 g/L	3	141	82.11
0.5 g/L ≤ alcohol < 0.8 g/L	4	20	13.43
0.8 g/L ≤alcohol < 1.2 g/L	9	14	8.11
Alcohol ≥ 1.2 g/L	32	15	11.31
Amphetamine	2	13	8.78
Benzoylecgonine	3	11	6.02
Cocaine	0	9	9.54
All cannabis concentrations	1	104	82.63
Illicit opiates	0	1	0.68
Benzodiazepines and Z-drugs	1	15	20.58
Medicinal opioids	1	7	8.69
All alcohol-drug combinations	7	22	14.11
All multiple drug combinations	0	24	18.92
In total	188	4822	4822

The distributions of the study samples from the case and control studies by gender, age and time periods in the six countries involved are shown in **Appendix 1, tables 8.1-8.6.**

In The Netherlands, the Ethics Committee did not allow recording the exact time of the accident, neither could information about the distribution of accidents in eight time periods be recorded. Therefore, time period 1-3 and time period 5-7 were merged for the Dutch data.

3.1.2 Odds ratios for drivers in various European countries of getting seriously injured

The odds ratios of getting seriously injured estimated by logistic regression are presented below separately for each country. Crude OR and OR adjusted for age and gender have been calculated.

Odds ratios are estimated on the basis of drug and/or alcohol content in the samples from seriously injured drivers and drivers in the general traffic, some of which were saliva and some of which were blood (**table 3**).

The effect of gender and age on the odds ratio for the various substance groups is shown in **Appendix 2, tables 9.1-9.6** separately for each country.

3.1.2.1 Belgium

Table 16 Crude and adjusted odds ratios of getting seriously injured while positive for various substance groups in Belgium. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	8.79	*6.63-11.66*	8.76	*6.53-11.74*
0.1 g/L ≤ alcohol < 0.5 g/L	0.98	*0.47-2.04*	1.03	*0.49-2.15*
0.5 g/L ≤ alcohol < 0.8 g/L	2.36	*0.99-5.66*	2.27	*0.94-5.49*
0.8 g/L ≤alcohol < 1.2 g/L	13.75	*6.01-31.45*	13.23	*5.61-31.21*
Alcohol ≥ 1.2 g/L	106.41	*56.99-198.68*	108.68	*57.50-205.43*
Amphetamine	107.57*	*5.53-2090.81*	n.a.	
Benzoylecgonine	1.39*	*0.08-25.21*	n.a.	
Cocaine	6.14*	*0.23-163.46*	n.a.	
Cannabis	7.44	*2.53-21.89*	4.88	*1.60-14.84*
Illicit opiates	2.41*	*0.12-47.58*	n.a.	
Benzodiazepines and Z-drugs	1.87	*0.88-3.96*	2.30	*1.07-4.94*
Medicinal opioids	4.18	*1.67-10.44*	4.33	*1.58-11.89*
All alcohol-drug combinations	68.33	*32.64-143.05*	58.16	*27.05-125.07*
All multiple drug combinations	12.00	*4.41-32.61*	9.99	*3.61-27.68*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or too few positive cases

Table 16 shows an elevated risk by driving with alcohol in concentrations above 0.8 g/L in Belgium. The risk increased drastically by alcohol concentrations above 1.2 g/L. The odds ratios of driving with amphetamine, cannabis, medicinal drugs, alcohol-drug and multiple drug combinations were higher than one. The odds ratio of driving with amphetamine in Belgium was very high, 107.6, but due to the small number of observations, the confidence interval is very large. There is an elevated odds ratio (7.4) of driving with cannabis with a very large confidence interval. However, Driving with alcohol-drug combinations in Belgium had very high odds ratio (68.3), far higher than driving with multiple drug combinations (12.0). The adjusted odds ratios were of similar magnitude as the crude odds ratios.

There was no significant effect of gender whereas the odds ratio was higher for the age groups 18-24 and 25-34 compared to the age group 50 and above, see **Appendix 2, table 9.1**. The effects were the same for all substance groups.

One weakness in the Belgian study is the very high non-response rate, i.e. 52% in the controls. Female drivers were overrepresented among the respondents, and so were the youngest and oldest drivers. One strength of the study is the fact that in 93% of the cases; blood was sampled at the road side and only in 7%; the specimen sampled was oral fluid. Since the specimen from injured drivers was blood in nearly all cases, the comparison of alcohol and drug presence between injured and not injured drivers needed no conversion and was thus error free.

3.1.2.2 Denmark

Table 17 Crude and adjusted odds ratios of getting seriously injured while positive for various substance groups in Denmark. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	8.13	*6.04-10.94*	9.17	*6.63-12.68*
0.1 g/L ≤ alcohol < 0.5 g/L	1.25	*0.71-2.23*	1.47	*0.79-2.74*
0.5 g/L ≤ alcohol < 0.8 g/L	5.86	*2.81-12.24*	5.66	*2.50-12.82*
0.8 g/L ≤alcohol < 1.2 g/L	19.67	*6.69-57.85*	14.32	*4.68-43.87*
Alcohol ≥ 1.2 g/L	255.96	*51.11-1282.01*	296.99	*58.84-Inf.*
Amphetamine	86.43	*4.97-1502.29*	49.94	*2.80-891.67*
Benzoylecgonine	n.a.		n.a.	
Cocaine	14.33*	*0.58-352.13*	n.a.	
Cannabis	4.00	*1.22-13.17*	2.17	*0.61-7.79*
Illicit opiates	n.a.		n.a.	
Benzodiazepines and Z-drugs	3.23	*1.70-6.13*	4.37	*2.18-8.75*
Medicinal opioids	4.22	*2.33-7.65*	5.72	*3.06-10.67*
All alcohol-drug combinations	56.35	*17.46-181.84*	52.68	*16.01-173.35*
All multiple drug combinations	58.75	*13.21-261.34*	57.54	*12.66-261.53*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Table 17 shows an elevated risk in Denmark of driving with alcohol concentrations above 0.5 g/L; the odds ratio increased drastically with increasing alcohol concentration. The crude odds ratios of driving with different concentrations of alcohol were very similar to the odds ratios adjusted for gender and age. The odds ratio of driving with amphetamine in Denmark was very high, i.e. 86.4, but with a large confidence interval. Although the adjusted odds ratio was much lower, i.e. 49.9, the confidence intervals overlapped to a large extent. There was also an elevated risk of driving with cannabis, benzodiazepines and z-drugs, and medicinal opioids in Denmark, and the odds ratios were similar – around 3-4. The crude odds ratios of driving with alcohol-drug combinations or multiple drug combinations in Denmark were very high and similar, 56.4 and 58.8, respectively. Their values were similar when adjusting for age and gender.

The odds ratio for men was significantly higher than for women, and the odds ratio was higher for all three age groups compared to the age group 50 and above, see **Appendix 2, table 9.2**. Especially the age group 18-24 had a very high risk. The effects were the same for all substance groups.

The Danish case-control study used oral fluid (controls) and blood (cases). This is a source of error in the results, since alcohol and drug presence in oral fluid were converted to presence in blood (cf. section 2.5). One strength of the Danish study is the relatively low degree of non-response of the control sample; a non-response that had neither gender nor age bias (cf. section 2.4).

3.1.2.3 Finland

Table 18 Crude and adjusted odds ratios of getting seriously injured while positive for various substance groups in Finland. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	54.11	*24.75-118.29*	43.66	*19.29-98.81*
0.1 g/L ≤ alcohol < 0.5 g/L	7.09	*0.89-56.30*	6.55	*0.81-53.25*
0.5 g/L ≤ alcohol < 0.8 g/L	34.81	*3.27-370.46*	36.01	*3.14-413.06*
0.8 g/L ≤alcohol < 1.2 g/L	81.11	*5.00-1314.90*	55.07	*2.74-inf.*
Alcohol ≥ 1.2 g/L	172.11	*54.76-540.91*	128.84	*38.69-429.03*
Amphetamine	18.10*	*0.83-396.08*	n.a.	
Benzoylecgonine	22.72*	*0.97-533.61*	n.a.	
Cocaine	n.a.		n.a.	
Cannabis	51.02	*4.10-634.29*	25.38	*1.86-345.78*
Illicit opiates	n.a.		n.a.	
Benzodiazepines and Z-drugs	2.49	*0.33-18.77*	2.59	*0.34-19.86*
Medicinal opioids	5.11	*0.66-39.67*	5.40	*0.68-42.97*
All alcohol-drug combinations	143.33	*27.22-754.67*	148.70	*26.84-823.94*
All multiple drug combinations	40.00	*6.72-203.60*	45.86	*7.92-265.38*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Table 18 shows an elevated risk in Finland of driving with blood alcohol concentration above 0.5 g/L. The Finnish odds ratios for alcohol are much higher than those of the other participating countries. This is a result of the sampling procedure of the controls, where the police in Finland allowed only a(n) (unknown) fraction of the alcohol positives to be sampled (Engblom et al., 2011). This may have skewed the odds ratio of the alcohol-drug combinations as well; this odds ratio was very high and with a very large confidence interval in Finland. Only driving with cannabis, alcohol-drug and multiple drug combinations were associated with an elevated risk besides alcohol. When adjusting for gender and age, the odds ratio of driving with cannabis got halved, suggesting a sample population skewed towards young men.

There was no significant effect of gender whereas the odds ratio was higher for the age group 18-24 compared to the age group 50 and above, see **Appendix 2, table 9.3**. The effects were the same for all substance groups.

Quite a few of the odds ratio calculations suffered from having neither positive controls, nor positive cases. Regarding the positive controls, this probably stems from the high Finnish non-response rate of 48% which most probably has resulted in an underestimation of drug prevalence in the driving population and consequently overestimation of the odds ratios.

In Finland, the specimen sampled from the driving population was oral fluid whereas those from injured drivers were blood samples. This is a source of error in the results, since alcohol and drug presence in oral fluid were converted to presence in blood (cf. section 2.5).

Because of the sampling procedure in Finland, Finnish results were not included in the aggregated alcohol and alcohol-drugs odds ratio calculations (section 3.1.3).

3.1.2.4 Italy

Table 19 Crude and adjusted odds ratio of getting seriously injured while positive for various substance groups in Italy. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	2.43	*1.83-3.22*	2.47	*1.84-3.31*
0.1 g/L ≤ alcohol < 0.5 g/L	0.67	*0.37-1.22*	0.56	*0.29-1.06*
0.5 g/L ≤ alcohol < 0.8 g/L	0.67	*0.3-1.40*	0.58	*0.26-1.29*
0.8 g/L ≤alcohol < 1.2 g/L	1.45	*0.74-2.85*	1.53	*0.76-3.10*
Alcohol ≥ 1.2 g/L	15.01	*8.02-28.06*	16.55	*8.80-31.15*
Amphetamine	n.a.		n.a.	
Benzoylecgonine	2.54	*0.67-9.66*	3.24	*0.85-12.38*
Cocaine	0.85	*0.29-2.43*	1.17	*0.40-3.40*
Cannabis	1.47	*0.67-3.25*	1.88	*0.85-4.17*
Illicit opiates	0.98	*0.18-5.38*	1.38	*0.25-7.62*
Benzodiazepines and Z-drugs	0.30	*0.07-1.31*	0.20	*0.04-1.00*
Medicinal opioids	9.41	*2.87-30.84*	11.16	*3.38-36.88*
All alcohol-drug combinations	5.73	*2.76-11.89*	7.30	*3.49-15.27*
All multiple drug combinations	1.76	*0.87-3.56*	2.29	*1.12-4.66*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

The results from Italy are highly atypical compared to the results of the other participating countries. The odds ratios for alcohol and alcohol-drug combinations were very low and only high concentrations of alcohol (≥ 1.2 g/L) and alcohol-drug combinations were associated with increased risk of injury (odds ratios 15.0 and 5.7, respectively), as shown in t**able 19**. The low risk connected to alcohol is most probably due to skewness in the control sampling procedure. In Italy, there was skewness in the driving population sampled towards drivers exhibiting signs of alcohol impairment (Favretto, personal communication). This way, there was a tendency of oversampling of alcohol positives. Thus, alcohol prevalence among the controls was artificially inflated and the odds ratios correspondingly deflated. Moreover, controls were preferentially sampled in periods of the week where alcohol intake was known to be highest, cf. table 18 (Favretto, personal communication). The odds ratios were low for the BACs higher than 0.5 g/L in particular – corresponding to the lower limit of showing signs of alcohol impairment.

The odds ratio estimate in Italy for medicinal opioids (9.4) was high compared to those of Belgium (4.2), Denmark (4.2) and The Netherlands (4.2 – not significant) and the confidence interval large compared to the countries mentioned. Surprisingly, multiple drug combinations were not associated with an elevated risk of injury as in all other participating countries except The Netherlands.

The odds ratio for men was significantly lower than for women, and the odds ratio was lower for all three age groups compared to the age group 50 and above, see **Appendix 2, table 9.4.** The effects were the same for all substance groups, except concerning alcohol, where there was no gender effect.

In Italy, 1310 (57%) of the control sample specimens were oral fluid and 987 (43%) were blood. All the case sample specimens were blood. This is a source of error in the results, since in a little more than half of the control samples, alcohol and drug presence in oral fluid were converted to presence in blood (cf. section 2.5).

3.1.2.5 Lithuania

Table 20 Crude and adjusted odds ratio of getting seriously injured while positive for various substance groups in Lithuania. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	5.37	*3.59-8.04*	6.35	*4.06-9.93*
0.1 g/L ≤ alcohol < 0.5 g/L	1.28	*0.51-3.21*	1.49	*0.54-4.13*
0.5 g/L ≤ alcohol < 0.8 g/L	3.08	*0.85-11.23*	3.69	*0.91-15.02*
0.8 g/L ≤alcohol < 1.2 g/L	6.09	*1.90-19.49*	10.82	*3.03-21.22*
Alcohol ≥ 1.2 g/L	10.71	*6.02-19.04*	11.42	*6.14-21.22*
Amphetamine	1.57	*0.16-15.59*	0.50	*0.04-6.88*
Benzoylecgonine	12.73*	*0.52-313.43*	n.a.	
Cocaine	12.73*	*0.52-313.43*	n.a.	
Cannabis	12.73*	*0.52-313.43*	n.a.	
Illicit opiates	n.a.		n.a.	
Benzodiazepines and Z-drugs	1.43	*0.56-3.65*	1.02	*0.36-2.87*
Medicinal opioids	191.02*	*11.55-3158.43*	n.a.	
All alcohol-drug combinations	96.51	*3.30-2823.70*	127.32	*4.22-inf.*
All multiple drug combinations	29.71*	*1.53-576.90*	n.a.	

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Unlike in Denmark and The Netherlands, in Lithuania there was no elevated risk associated with blood alcohol concentrations below 0.8 g/L, see **table 20**. The odds ratio estimates for alcohol concentrations at and above 1.2 g/L were well below those of Belgium, Denmark, Finland and the Netherlands. In Lithuania there was a high non-response rate (24%), which had a significant bias towards women, and all the non-respondents were between 18 and 31 years of age. None of the non-respondents showed signs of impairment (cf. Section 2.4). As a consequence of this, alcohol prevalence in the driving population may have been overestimated and odds ratios thus underestimated. For both benzoylecgonine, cocaine and cannabis there was only one positive case and no positive controls in the Lithuanian sample, which is the reason for the large confidence interval. The odds ratio estimate for medicinal opioids was associated with an elevated risk and it was very high compared to the other participating countries, i.e. 191.0.

The odds ratio for men was significantly lower than for women, and the odds ratio was lower for the age group 18-24 compared to the age group 50 and above, see **Appendix 2, table 9.5.** The effects were the same for all substance groups.

3.1.2.6 The Netherlands

Table 21 Crude and adjusted odds ratios and their confidence intervals of getting seriously injured in the Netherlands while positive for various substance groups. The reference group was negative for all substances

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	15.16	*10.36-22.18*	15.98	*10.70-23.87*
0.1 g/L ≤ alcohol < 0.5 g/L	1.33	*0.41-4.25*	1.58	*0.49-5.12*
0.5 g/L ≤ alcohol < 0.8 g/L	10.81	*3.49-33.49*	9.40	*2.89-30.61*
0.8 g/L ≤alcohol < 1.2 g/L	40.30	*15.34-105.82*	31.37	*11.34-86.83*
Alcohol ≥ 1.2 g/L	102.69	*50.95-206.98*	108.09	*52.45-222.75*
Amphetamine	8.27	*1.76-38.81*	8.87	*1.84-42.86*
Benzoylecgonine	18.08	*4.47-73.05*	12.23	*2.86-52.34*
Cocaine	1.80*	*0.10-30.99*	n.a.	
Cannabis	0.44	*0.06-3.18*	0.29	*0.04-2.11*
Illicit opiates	15.28*	*0.56-418.81*	n.a.	
Benzodiazepines and Z-drugs	1.76	*0.24-13.23*	2.56	*0.34-19.36*
Medicinal opioids	4.17	*0.52-33.34*	5.96	*0.73-48.84*
All alcohol-drug combinations	18.00	*7.15-45.32*	12.55	*4.76-33.12*
All multiple drug combinations	0.93*	*0.06-15.51*	n.a.	

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Table 21 shows an elevated odds ratio associated with driving with blood alcohol concentrations above 0.5 g/L, like in the Danish and Finnish data. The odds ratios in the Netherlands increased drastically with blood alcohol concentration. There was indication of no alcohol concentration bias in the non-response population in the Netherlands (cf. Section 2.4).

The odds ratio estimate for amphetamine in the Netherlands was lower than that of the other participating countries (where it was significantly different from 1).

The Netherlands was the only participating country where the odds ratio estimate for benzoylecgonine was higher than one. This estimate is based on the highest number of positives among the participating countries (3 cases, 11 controls) and is thus considered a reliable estimate. When adjusted for age and gender, the odds ratio estimate decreased, which is probably due to the fact that cocaine – the parent drug to benzoylecgonine – is prevalent among young male drivers.

There was no significant effect of gender whereas the odds ratio was higher for the age group 18-24 compared to the age group 50 and above, see **Appendix 2, table 9.3**. The effects were the same for all substance groups, except for alcohol, where there was also a higher odds ratio for the age group 25-34 concerning alcohol.

In the control population in the Netherlands, the self-reported use of psychoactive substances was higher among the non-respondents than among the respondents (cf. Section 2.4). This may have artificially inflated the odds ratio estimates, but probably only to a small extent.

3.1.3 Aggregated odds ratios for drivers of getting seriously injured

By merging data from all participating countries using the three different aggregation methods described in the methods section 2.8.1, odds ratio estimates based on data from several countries give added value to the discussion of the most reliable risk estimates. Because of serious bias in the

control sampling procedure in Finland and Italy (see section 3.1.2.3 and 3.1.2.4), data from these countries have been excluded from the calculations of odds ratios of getting seriously injured while positive for alcohol and for alcohol in combination with other drugs.

Table 22 includes both crude odds ratios and odds ratios adjusted by age and gender based on data from all countries (except Finland and Italy for alcohol and alcohol combined with other drugs).

Table 23 and 24 include adjusted odds ratios based on data from a number of countries according to aggregation methods 2 resp. 3, cf. section 2.8.1. Weighted controls from each country form the control samples.

Table 22 Crude and adjusted odds ratios including confidence intervals of getting seriously injured when driving with various substances, based on data from all countries. The reference group was negative for all substances

Substance	**Crude OR**	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1		1	
All alcohol concentrations	7.55	*6.47-8.80*	8.27	*7.03-9.74*
0.1 g/L ≤ alcohol < 0.5 g/L	1.05	*0.73-1.53*	1.18	*0.81-1.73*
0.5 g/L ≤ alcohol < 0.8 g/L	3.8	*2.48-5.82*	3.64	*2.31-5.72*
0.8 g/L ≤alcohol < 1.2 g/L	13.97	*8.75-22.29*	13.35	*8.15-21.88*
Alcohol ≥ 1.2 g/L	55.27	*39.52-77.31*	62.79	*44.51-88.58*
All illicit drugs	2.87	*2.12-3.89*	2.35	*1.72-3.21*
Amphetamine	9.66	*4.80-19.46*	8.35	*3.91-17.83*
Benzoylecgonine	5.36	*2.53-11.34*	3.70	*1.60-8.57*
Cocaine	3.41	*1.61-7.21*	3.30	*1.40-7.79*
Cannabis	1.86	*1.20-2.88*	1.38	*0.88-2.17*
Illicit opiates	4.03	*1.32-12.32*	2.47	*0.50-12.10*
All medicines	3.6	*2.84-4.57*	4.13	*3.22-5.28*
Benzodiazepines and Z-drugs	1.73	*1.19-2.51*	1.99	*1.36-2.91*
Medicinal opioids	7.99	*5.73-11.15*	9.06	*6.40-12.83*
All alcohol-drug combinations	31.97	*20.76-49.25*	28.82	*18.41-45.11*
All multiple drug combinations	8.64	*5.85-12.75*	8.01	*5.34-12.01*

Table 23 Adjusted odds ratios including confidence intervals of getting seriously injured when driving with various substances, based on data from a number of countries according to aggregation method 2, cf. section 2.8.1. The reference group was negative for all substances

Substance	Countries method 2	Adjusted OR	*C.I.*
Negative (ref.)		1	
All alcohol concentrations	BE, DK, LT, NL	8.27	*7.03-9.74*
0.1 g/L ≤ alcohol < 0.5 g/L	BE, DK, LT, NL	1.18	*0.81-1.73*
0.5 g/L ≤ alcohol < 0.8 g/L	BE, DK, LT, NL	3.64	*2.31-5.72*
0.8 g/L ≤alcohol < 1.2 g/L	BE, DK, LT, NL	13.35	*8.15-21.88*
Alcohol ≥ 1.2 g/L	BE, DK, LT, NL	62.79	*44.51-88.58*
Amphetamine		n.a.	
Benzoylecgonine	IT, NL	5.93	*2.29-15.31*
Cocaine		n.a.	
Cannabis	BE, DK, IT	2.41	*1.36-4.28*
Illicit opiates		n.a.	
Benzodiazepines and Z-drugs	BE, DK, FI, LT, NL	3.04	*2.04-4.52*
Medicinal opioids	BE, DK, FI, IT, NL	6.96	*4.72-10.26*
All alcohol-drug combinations	BE, DK	36.75	*19.96-67.65*
All multiple drug combinations	DK, FI	35.01	*14.25-86.03*

n.a.: no positive controls and/or no positive cases, or too few positive cases.

Table 24 Adjusted odds ratios including confidence intervals of getting seriously injured when driving with various substances, based on data from a number of countries according to aggregation method 3, cf. section 2.8.1. The reference group was negative for all substances

Substance	Countries method 3	Adjusted OR	*C.I.*
Negative (ref.)		1	
All alcohol concentrations	BE, DK, LT, NL	8.27	*7.03-9.74*
0.1 g/L ≤ alcohol < 0.5 g/L	BE, DK, LT, NL	1.18	*0.81-1.73*
0.5 g/L ≤ alcohol < 0.8 g/L	BE, DK, LT, NL	3.64	*2.31-5.72*
0.8 g/L ≤alcohol < 1.2 g/L	BE, DK, LT, NL	13.35	*8.15-21.88*
Alcohol ≥ 1.2 g/L	BE, DK, LT, NL	62.79	*44.51-88.58*
Amphetamine		n.a.	
Benzoylecgonine	IT, NL	5.93	*2.29-15.31*
Cocaine		n.a.	
Cannabis	BE, DK, IT	2.41	*1.36-4.28*
Illicit opiates		n.a.	
Benzodiazepines and Z-drugs	BE, DK, LT	2.41	*1.58-3.70*
Medicinal opioids	BE, DK	5.14	*3.08-8.57*
All alcohol-drug combinations	BE, DK, NL	29.05	*18.38-45.90*
All multiple drug combinations	BE IT	4.48	*2.51-8.00*

n.a.: no positive controls and/or no positive cases, or too few positive cases.

Obviously, more data were included in this analysis compared to the analysis of separate countries, and this has, as expected, resulted in generally narrower confidence intervals **(table 22**). Adjustment for age and gender only resulted in minor changes in the odds ratios. Results of the aggregated data indicate that only for drivers with a BAC of 0.5 g/L and above there was a significantly increased odds ratio of getting seriously injured in an accident. Furthermore, the results indicate that the risk increased exponentially with increasing alcohol concentration up to an extremely increased risk for drivers with a BAC of 1.2 g/L and above.

For amphetamines, data could not be merged according to method 2 because of very different odds ratio estimates from the single countries (see section 2.8.1). Neither according to method 3 due to all odds ratios from the single countries being very imprecise (see section 2.8.1). Therefore, there is only

one aggregated odds ratio estimate based on all six participating countries. This odds ratio of getting seriously injured while positive for amphetamine was significantly increased, as was also the case for Belgium, Denmark and the Netherlands separately. Based on all results, the overall risk is expected to be significantly increased of the order of at least 5. This indicates that driving with amphetamines is a risky endeavour.

For benzoylecgonine, data from Italy and the Netherlands were merged using the methods 2 and 3 described in section 2.8. The odds ratio estimate of getting seriously injured while positive for benzoylecgonine was significantly higher than 1 both based on data from all countries and data from Italy and the Netherlands. Positive findings of benzoylecgonine were sparse in the other four countries, but contribute to the result including all six countries. Based on all results, the estimate is assessed to be of the order of around 5 indicating that driving some hours after using cocaine is risky.

Odds ratios of getting seriously injured while positive for cocaine varied among the participating countries and the numbers of positive samples were generally low. Therefore, odds ratios could neither be estimated based on method 2, nor on method 3. However, when merging data from all participating countries, the odds ratios of getting seriously injured were significantly above 1 which indicates an increased risk of injury while positive for cocaine.

For cannabis, data from Belgium, Denmark and Italy could be merged using both method 2 and 3, described in section 2.8.1. The resulting odds ratio estimate was significantly higher than 1, which was also the case for the crude odds ratio estimate based on data from all countries, but not the adjusted estimate based on data from all countries. Some of the estimates based on the single countries' data were significantly above 1, while others were not.

The odds ratio of getting seriously injured when driving positive for benzodiazepines and z-drugs was estimated with data from Belgium, Denmark, Finland, Lithuania and the Netherlands using method 2, and data from Belgium, Denmark and Lithuania using method 3. Moreover, data from all countries were merged following method 1. All odds ratio estimates were significantly higher than 1. However, not all odds ratios based on single countries were significantly higher than 1, which is assumed to be caused by low numbers of positive cases and controls in the single countries. Based on all results, the odds ratio estimate is nevertheless assessed to be significantly above 1 and of the order of about 2-3.

The common odds ratio of getting seriously injured when driving while positive for medicinal opioids was estimated with data from all countries (method 1), with data from Belgium, Denmark, Finland, Italy and The Netherlands (method 2) and data from Belgium and Denmark (method 3). All odds ratio estimates were significantly higher than 1. As for the single countries, all showed significantly increased risks except Finland and the Netherlands. Based on all results, the estimate is assessed to be significantly above 1 and of the order of about 5-8.

The common odds ratio estimates for getting seriously injured when positive for a combination of alcohol and drug(s) included data from Belgium, Denmark, Lithuania and the Netherlands (method 1), data from Belgium and Denmark (method 2) and from Belgium, Denmark and the Netherlands (method 3). All odds ratio estimates were significantly and much higher than 1. All countries except Lithuania separately showed significantly increased risks. Based on all results, the estimate is assessed to be significantly higher than 1 and of the order of at least 20. These odds ratios were by far the highest of the merged odds ratios indicating a synergetic effect of alcohol and drugs and also indicating that driving with a combination of alcohol and drugs is a very risky endeavour.

The common odds ratio estimates for getting seriously injured when positive for a combination of drugs included data from all countries (method 1), data from Denmark and Finland (method 2) and data from Belgium and Italy (method 3). The odds ratio estimates were all significantly and very much higher than 1. As for the countries separately, all but the Netherlands indicated significantly increased risks. Based on all results, the risk estimate is assessed to be significantly higher than one and of the order of at least 5-10. This indicates that driving with a combination of different drugs is a very risky endeavour.

3.2 Odds ratio for drivers of getting killed in a road accident

3.2.1 Data material

The distribution of the study samples from the case and control studies by substance group is shown in **table 25**. Categories are mutually exclusive, so a sample negative was negative for all substances. A sample positive for alcohol-drug(s) was considered positive in this category only – not in the alcohol category and neither in the drug(s) category. This principle holds for the risk calculations as well.

Table 25 Number of cases and controls for the study of killed drivers by country and substance group

Finland	**Cases**	**Controls**	
		Unweighted	Weighted for traffic
Negative samples	282	3730	3731.67
0.1 g/L ≤ alcohol < 0.5 g/L	7	16	14.70
0.5 g/L ≤ alcohol < 0.8 g/L	0	5	3.98
0.8 g/L ≤alcohol < 1.2 g/L	6	1	0.92
Alcohol ≥ 1.2 g/L	104	4	4.82
Amphetamine	3	1	2.07
Benzoylecgonine	0	1	1.26
Cocaine	0	0	0.00
All cannabis concentrations	0	2	1.64
Illicit opiates	0	0	0.00
Benzodiazepines and Z-drugs	32	52	50.61
Medicinal opioids	7	22	21.49
All alcohol-drug combinations	31	3	3.09
All multiple drug combinations	6	4	4.77
In total	478	3841	3841

Norway	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	120	8960	8961.12
0.1 g/L ≤ alcohol < 0.5 g/L	3	25	23.66
0.5 g/L ≤ alcohol < 0.8 g/L	2	6	3.75
0.8 g/L ≤alcohol < 1.2 g/L	5	1	1.50
Alcohol ≥ 1.2 g/L	26	1	0.91
Amphetamine	2	7	5.20
Benzoylecgonine	0	6	5.99
Cocaine	0	0	0.00
All cannabis concentrations	3	46	44.04
Illicit opiates	0	1	0.99
Benzodiazepines and Z-drugs	8	137	143.96
Medicinal opioids	1	15	15.10
All alcohol-drug combinations	13	7	6.31
All multiple drug combinations	10	24	23.46
In total	193	9236	9236

Portugal	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	152	2364	2361.61
0.1 g/L ≤ alcohol < 0.5 g/L	26	102	107.11
0.5 g/L ≤ alcohol < 0.8 g/L	16	10	13.70
0.8 g/L ≤alcohol < 1.2 g/L	7	9	12.85
Alcohol ≥ 1.2 g/L	70	9	7.96
Amphetamine	0	0	0.00
Benzoylecgonine	0	0	0.00
Cocaine	0	2	0.85
All cannabis concentrations	0	41	39.96
Illicit opiates	0	5	3.34
Benzodiazepines and Z-drugs	2	79	67.13
Medicinal opioids	2	3	4.06
All alcohol-drug combinations	9	10	15.91
All multiple drug combinations	1	7	6.55
In total	285	2641	2641

Sweden	Cases	Controls	
		Unweighted	Weighted for traffic
Negative samples	110	6110	6115.77
0.1 g/L ≤ alcohol < 0.5 g/L	3		
0.5 g/L ≤ alcohol < 0.8 g/L	4		
0.8 g/L ≤alcohol < 1.2 g/L	2		
Alcohol ≥ 1.2 g/L	14		
Amphetamine	4	3	4.12
Benzoylecgonine	0	0	0.00
Cocaine	0	0	0.00
All cannabis concentrations	1	3	1.91
Illicit opiates	0	0	0.00
Benzodiazepines and Z-drugs	5	29	31.36
Medicinal opioids	2	50	38.80
All alcohol-drug combinations	6		
All multiple drug combinations	5	4	7.04
In total	156	6199	6199

The distribution of the study samples from the case and control studies by gender, age and time periods that were used in the four countries involved (FI, NO, PT and SE) are shown in **Appendix 1, tables 8.7-8.10,** respectively.

3.2.2 Odds ratios for drivers in various European countries of getting killed

The odds ratios of getting killed estimated by logistic regression are presented below separately for each country. Crude OR and OR adjusted for age and gender have been calculated.

Odds ratios are estimated on the basis of drug and/or alcohol content in the blood samples from killed drivers and saliva samples from drivers in the general traffic (**table 3**).

3.2.2.1 Finland

Table 26 Crude and adjusted odds ratio estimates including confidence intervals of getting killed while positive for various substance groups in Finland. The reference group was negative for all substance groups

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	63.43	*40.34-99.73*	57.41	*36.02-91.51*
0.1 g/L ≤ alcohol < 0.5 g/L	6.30	*2.54-15.63*	5.91	*2.34-14.97*
0.5 g/L ≤ alcohol < 0.8 g/L	1.47*	*0.08-27.48*	n.a.	
0.8 g/L ≤alcohol < 1.2 g/L	86.69	*9.59-784.00*	63.22	*6.78-589.57*
Alcohol ≥ 1.2 g/L	285.55	*113.66-717.40*	267.25	*105.34-678.00*
Amphetamine	19.16	*3.25-113.01*	18.39	*2.83-119.72*
Benzoylecgonine	3.76*	*0.16-87.06*	n.a.	
Cocaine	n.a.		n.a.	
Cannabis	3.09*	*0.14-67.43*	n.a.	
Illicit opiates	n.a.		n.a.	
Benzodiazepines and Z-drugs	8.37	*5.29-13.24*	7.97	*4.99-12.74*
Medicinal opioids	4.31	*1.82-10.20*	3.82	*1.60-9.16*
All alcohol-drug combinations	132.72	*40.97-429.92*	160.31	*48.90-525.53*
All multiple drug combinations	16.66	*4.97-55.79*	20.10	*5.84-69.15*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Table 26 indicates a highly elevated risk associated with driving with alcohol in Finland (including alcohol-drug combinations), and the odds ratios increase drastically with blood alcohol concentration. The odds ratios are high compared to other participating countries (except Norway, see below), and they are of the same magnitude as those of getting seriously injured when driving with alcohol in Finland (cf. **Table 18**). As mentioned in section 3.1.2.3., this is most probably due to under sampling of controls positive for alcohol and thus artificially inflating the odds ratio estimate.

There was an elevated risk of getting killed associated with driving with amphetamine in Finland, and the odds ratio was almost identical when adjusted for age and gender. The numbers of cases and controls positive for benzoylecgonine, cocaine, cannabis and illicit opiates were very low in Finland (**Table 25**), and this resulted in no meaningful odds ratio estimates. In contrast to getting seriously injured in Finland when driving with benzodiazepines and z-drugs and medicinal drugs, there was an elevated risk of getting killed when positive for these substances. The odds ratio estimate of getting killed when driving with benzodiazepines and z-drugs in Finland (8.4) was similar to that of getting killed in Sweden (8.9), but considerably higher than the odds ratio estimates of getting killed in Norway

and Portugal. The odds ratio of getting killed when driving with medicinal drugs (4.3) is similar to that of Norway (4.9) which, however, is not significant.

Finally, there was an elevated risk associated of getting killed with driving with multiple drug combinations in Finland. This odds ratio is difficult to interpret since it contained all kinds of drug-drug combinations.

The odds ratio for men was significantly higher than for women, and the odds ratio was higher for the age group 18-24 and lower for the age groups 25-34 and 35-49 compared to the age group 50 and above, see **Appendix 2, table 9.7.** The effects were the same for all substance groups.

Finland suffered from a high non-response rate among the controls (48%) which may have underestimated the prevalence of both alcohol and other drugs in the driving population and consequently overestimated the odds ratio estimates. Another source of error is the conversion of alcohol and drug concentrations in oral fluid (sampled in the control population) to concentration in blood (sampled in the case population), cf. section 2.5.

3.2.2.2 Norway

Table 27 Crude and adjusted odds ratio estimates including confidence intervals of getting killed in Norway while positive for various substance groups. The reference group was negative for all substance groups

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	90.14	*53.72-151.25*	92.89	*53.89-160.11*
0.1 g/L ≤ alcohol < 0.5 g/L	9.47	*2.81-31.89*	9.35	*2.71-32.21*
0.5 g/L ≤ alcohol < 0.8 g/L	39.88	*7.10-224.00*	46.10	*7.76-273.96*
0.8 g/L ≤alcohol < 1.2 g/L	248.76	*39.78-1555.45*	278.70	*40.96-inf.*
Alcohol ≥ 1.2 g/L	2123.20	*261.80-17218.96*	n.a.	
Amphetamine	28.71	*5.57-148.10*	22.99	*4.12-128.44*
Benzoylecgonine	5.73*	*0.32-102.30*	n.a.	
Cocaine	n.a.		n.a.	
Cannabis	5.09	*1.56-16.61*	3.91	*1.17-13.08*
Illicit opiates	24.95*	*1.01-617.21*	n.a.	
Benzodiazepines and Z-drugs	4.15	*1.99-8.65*	4.47	*2.11-9.47*
Medicinal opioids	4.94	*0.65-37.72*	5.64	*0.73-43.82*
All alcohol-drug combinations	153.84	*58.45-404.95*	104.67	*38.29-286.16*
All multiple drug combinations	31.83	*14.86-68.18*	35.18	*15.99-77.40*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

As **Table 27** shows, there was an elevated risk of getting killed in Norway by driving with any concentration of alcohol above the cut off (0.1 g/L). As expected, the odds ratios increased dramatically with increasing blood alcohol concentration, and the Norwegian odds ratios for alcohol were the highest in the entire data set, including odds ratios based on data from seriously injured drivers. The odds ratio estimates were of the same magnitude when adjusted for age and gender.

In Norway, there was an elevated risk associated with driving with amphetamine (28.7), cannabis (5.1), illicit opiates (25.0), benzodiazepines and z-drugs (4.2), alcohol-drug (153.8) and multiple drug (31.8) combinations. Norway was the only country among the four participating countries with a crude odds ratio above one for illicit opiates. And yet, the confidence interval is close to one and very wide.

There was no significant effect of gender whereas the odds ratio was higher for the age group 18-24 and lower for the age group 35-49 compared to the age group 50 and above, see **Appendix 2, table 9.8**. The effects were the same for all substance groups.

In Norway, there was a non-response rate among the drivers of 6%, and as stated in section 2.4, alcohol and drug prevalence may have been higher among the non-respondents resulting in an underestimation of drug and alcohol prevalence in the driving population and consequently an overestimation of odds ratios. Another source of error is the conversion of alcohol and drug concentrations in oral fluid (sampled in the control population) to concentration in blood (sampled in the case population), cf. section 2.5.

3.2.2.3 Portugal

Table 28 Crude and adjusted **o**dds ratio estimates including confidence intervals of getting killed in Portugal while positive for various substance groups. The reference group was negative for all substance groups

	Crude OR	***C.I.***	**Adjusted OR**	***C.I.***
Negative (ref.)	1.0		1.0	
All alcohol concentrations	13.06	*9.73-17.51*	12.06	*8.85-16.42*
0.1 g/L ≤ alcohol < 0.5 g/L	3.77	*2.38-5.97*	3.26	*2.03-5.23*
0.5 g/L ≤ alcohol < 0.8 g/L	18.14	*8.66-38.01*	19.16	*8.87-41.37*
0.8 g/L ≤alcohol < 1.2 g/L	8.47	*3.32-21.57*	8.21	*2.92-23.07*
Alcohol ≥ 1.2 g/L	136.65	*64.47-289.66*	144.43	*64.60-322.89*
Amphetamine	n.a.		n.a.	
Benzoylecgonine	n.a.		n.a.	
Cocaine	5.75*	*0.22-148.43*	n.a.	
Cannabis	0.19*	*0.01-3.13*	n.a.	
Illicit opiates	2.02*	*0.11-38.57*	n.a.	
Benzodiazepines and Z-drugs	0.46	*0.11-1.91*	0.55	*0.13-2.32*
Medicinal opioids	7.66	*1.40-41.97*	8.93	*1.52-52.45*
All alcohol-drug combinations	8.79	*3.82-20.24*	8.22	*3.46-19.52*
All multiple drug combinations	2.37	*0.29-19.59*	2.35	*0.27-20.24*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000).
n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

As in other participating countries, **Table 28** shows an elevated risk of getting killed in Portugal when driving with alcohol. Like in Norway, there was an elevated risk for any blood concentration of alcohol above the cut off (0.1 g/L), but the odds ratio estimates are far lower than those from Norwegian data.

Apart from alcohol and unlike other participating countries, in Portugal there was an elevated risk associated with driving with medicinal drugs and alcohol-drug combinations only.

The odds ratio for men was significantly higher than for women, and the odds ratio was lower for the age groups 25-34 and 35-49 compared to the age group 50 and above, see **Appendix 2, table 9.9.** The effects were the same for all substance groups.

Portugal had a low non-response rate of 3%. Oral fluid was sampled in the control population and blood in the case population; thus another source of error is the conversion of alcohol and drug concentrations in oral fluid to concentration in blood, cf. section 2.5.

3.2.2.4 Sweden

Table 29 Crude and adjusted odds ratio estimates including confidence intervals of getting killed in Sweden while positive for various substance groups. The reference group was negative for all substance groups

	Crude OR	*C.I.*	Adjusted OR	*C.I.*
Negative (ref.)	1.0		1.0	
Amphetamine	53.94	*13.46-216.19*	63.65	*15.16-267.27*
Benzoylecgonine	n.a.		n.a.	
Cocaine	n.a.		n.a.	
Cannabis	29.17	*2.57-330.45*	28.88	*2.17-384.87*
Illicit opiates	n.a.		n.a.	
Benzodiazepines and Z-drugs	8.86	*3.39-23.21*	9.06	*3.43-23.93*
Medicinal opioids	2.87	*0.68-12.02*	2.85	*0.68-12.03*
All multiple drug combinations	39.47	*12.35-126.10*	47.33	*14.42-155.29*

n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

In **Table 29**, results for alcohol and alcohol in combination with other drugs were omitted, because nothing was known about alcohol prevalence in the driving population (cf. section 2.4).

In Sweden, there was an elevated risk associated with driving with amphetamine. The odds ratio estimate for amphetamine (54.0) was the highest among the four countries participating in the study of killed drivers, whereas in the study of injured drivers, two odds ratio estimates were higher: the Belgian one (110.3) and the Danish one (86.4). The same was true for cannabis (OR=29.2) where only the Finnish estimate for getting injured was higher (51.0). The Swedish odds ratio estimate for benzodiazepines and z-drugs was the highest in the entire data set (8.9).

There was no significant effect of gender whereas the odds ratio was higher for the age group 18-24 compared to the age group 50 and above, see **Appendix 2, table 9.10**. The effects were the same for all substance groups

In Sweden there was a substantial non-response rate among the controls, i.e. 38%. Nothing is known about the non-respondents, but it may be that drug prevalence is underestimated with this high non-response rate, and this may be the reason for the high odds ratio estimates. In Sweden, like in most other countries, oral fluid was sampled at the road side while blood was sampled among the killed drivers. This is another source of error due to conversion of concentrations between oral fluid and blood.

3.2.3 Aggregated odds ratios for drivers of getting killed

As it appears from the results in section 3.2.2, odds ratios of getting killed while positive for a substance and their confidence intervals differ among countries like the odds ratios of getting seriously injured. Again, this may partly be due to a limited number of positive samples from each of the involved countries, partly to bias in the data collection and partly to differences in odds ratios in the various countries because of confounding factors not adjusted for, e.g. differences between countries in the general accident risk.

However, by merging data from all countries, under the assumptions described in the method section 2.8.1, odds ratio estimates based on aggregated data give added value to the discussion of the most reliable risk estimate. But, as earlier described there was a known control sampling bias in Finland (see section 3.1.2.3), and the road side survey in Sweden did not include alcohol positive drivers, see section 3.2.2.4). Therefore, Finland and Sweden were excluded from the estimation of aggregated

odds ratios of getting killed while positive for alcohol and for alcohol in combination with other drugs (**table 30**).

Table 30 includes both crude odds ratios and odds ratios adjusted by age and gender based on data from Norway and Portugal. Furthermore, **Table 31 and 32** include adjusted odds ratios based on data from a number of countries according to aggregation methods 2 resp. 3, cf. section 2.8.1. Weighted controls from each country form the control samples.

Table 30 Crude and adjusted odds ratios including confidence intervals of getting killed when driving with various substances, based on data from all countries (method 1). The reference group was negative for all substances

Substance	Crude OR	*C.I.*	Adjusted OR	*C.I.*
Negative (ref.)	1		1	
All alcohol concentrations	37.64	*29.36-48.24*	34.9	*27.00-45.11*
0.1 g/L ≤ alcohol < 0.5 g/L	9.23	*6.07-14.05*	8.01	*5.22-12.29*
0.5 g/L ≤ alcohol < 0.8 g/L	42.94	*21.99-83.86*	45.93	*23.02-91.66*
0.8 g/L ≤alcohol < 1.2 g/L	34.81	*16.02-75.65*	35.69	*15.68-81.22*
Alcohol ≥ 1.2 g/L	450.37	*224.06-905.25*	500.04	*238.07-inf.*
All illicit drugs	3.85	*2.17-6.80*	3.55	*1.97-6.42*
Amphetamine	25.44*	*10.81-59.90*	24.09	*9.72-59.71*
Benzoylecgonine	6.87*	*1.49-31.76*	n.a.	
Cocaine	22.34*	*3.66-136.53*	n.a.	
Cannabis	1.8*	*0.73-4.44*	1.33	*0.48-3.67*
Illicit opiates	10.04*	*2.04-49.32*	n.a.	
All medicines	5.05	*3.80-6.72*	5.29	*3.95-7.08*
Benzodiazepines and Z-drugs	5.11	*3.72-7.02*	5.40	*3.90-7.46*
Medicinal opioids	4.82	*2.61-8.88*	4.82	*2.60-8.93*
All alcohol-drug combinations	41.22	*22.59-75.24*	31.52	*16.83-59.05*
All multiple drug combinations	16.77	*9.95-28.27*	18.51	*10.84-31.63*

*: In the case of 0 counts in one of the categories a, b, c, d (cf. Table 12), 0.5 was added to all four cells to be able to calculate crude OR (Greenland et al., 2000). n.a.: no positive controls and/or no positive cases or (adjusted OR only) too few positive cases

Table 31 Adjusted odds ratios including confidence intervals of getting killed when driving with various substances, based on data from a number of countries according to aggregation method 2, cf. section 2.8.1. The reference group was negative for all substances

Substance	Countries method 2	Adjusted OR	*C.I.*
Negative (ref.)		1	
All alcohol concentrations	N	92.89	*53.89-160.11*
0.1 g/L ≤ alcohol < 0.5 g/L	N	9.35	*2.71-32.21*
0.5 g/L ≤ alcohol < 0.8 g/L	N	46.10	*7.76-273.96*
0.8 g/L ≤alcohol < 1.2 g/L	N	278.70	*40.96-inf.*
Alcohol ≥ 1.2 g/L	N	n.a.	
Amphetamine	FI, N, S	28.15	*11.30-70.14*
Benzoylecgonine		n.a.	
Cocaine		n.a.	
Cannabis		n.a.	
Illicit opiates		n.a.	
Benzodiazepines and Z-drugs	FI, N, S	7.42	*5.29-10.41*
Medicinal opioids	FI, N, PT, S	4.82	*2.60-8.93*
All alcohol-drug combinations	N	104.67	*38.29-286.16*
All multiple drug combinations	FI, N, S	24.86	*14.20-43.52*

n.a.: no positive controls and/or no positive cases or too few positive cases

Table 32 Adjusted odds ratios including confidence intervals of getting killed when driving with various substances, based on data from a number of countries according to aggregation method 3, cf. section 2.8.1. The reference group was negative for all substances

Substance	Countries method 3	Adjusted OR	*C.I.*
Negative (ref.)		1	
All alcohol concentrations	PT	12.06	*8.85-16.42*
0.1 g/L ≤ alcohol < 0.5 g/L	PT	3.26	*2.03-5.23*
0.5 g/L ≤ alcohol < 0.8 g/L	PT	19.16	*8.87-41.37*
0.8 g/L ≤alcohol < 1.2 g/L	PT	8.21	*2.92-23.07*
Alcohol ≥ 1.2 g/L	PT	144.43	*64.60-322.89*
Amphetamine		n.a.	
Benzoylecgonine		n.a.	
Cocaine		n.a.	
Cannabis		n.a.	
Illicit opiates		n.a.	
Benzodiazepines and Z-drugs	FI, N, S	7.42	*5.29-10.41*
Medicinal opioids		n.a.	
All alcohol-drug combinations	N, PT	31.52	*16.83-59.05*
All multiple drug combinations	FI, N, PT	15.05	*8.23-27.53*

n.a.: no positive controls and/or no positive cases or too few positive cases

One effect of merging data is that this way, there are enough data to estimate a more precise risk of driving when positive for various substances. This is indicated by the fact that every single odds ratio estimate for various alcohol concentrations is significantly above 1. It is indicated to be extremely risky to drive when positive for alcohol in higher concentrations and when positive for the combination of alcohol with another drug.

Results of the merged data indicate that for drivers with a BAC of 0.1 g/L and above there is a significantly increased odds ratio of getting killed in an accident. However, this is not in line with the literature, but the result cannot be explained further. Moreover, it is extremely risky to drive when positive for alcohol in higher concentrations.

For amphetamines, it was possible to estimate an odds ratio based on aggregated data from all four countries (method 1) and an estimate based on data from Finland, Norway and Sweden (method 2). Method 3 did not allow merging of data from several countries due to the single country estimates being too imprecise (see section 2.8.1). Both aggregated odds ratio estimates of getting killed in an accident when positive for amphetamine indicated a highly increased risk, as was also the case for Finland, Norway and Sweden alone. Based on these results, the odds ratio estimate for amphetamines is assumed to be around 25, indicating that there is a highly increased fatality risk while driving with amphetamines.

For benzoylecgonine, data from all countries were merged (method 1) while no countries could be merged according to method 2 and 3 (section 2.8.1). The odds ratio estimate of getting killed while positive for benzoylecgonine was significantly higher than 1 based on data from all countries; this was not the case for odds ratios based on data from the countries separately. Positive findings of benzoylecgonine were sparse in Portugal and Sweden, but data from these countries contributed to the aggregated estimate including all four countries. Based on this result, the odds ratio estimate is assumed to be around 5, indicating that there is an increased fatality risk while driving with benzoylecgonine.

Odds ratios of getting killed while positive for cocaine could neither be calculated based on method 2, nor method 3. However, when merging data from all countries, the odds ratio estimate of getting killed

while positive for cocaine was significantly higher than 1. This gives rise to assume that there is an increased fatality risk when positive for cocaine.

For cannabis, like for cocaine, odds ratios of getting killed while positive could neither be calculated based on method 2, nor method 3. When merging data from all four countries, the odds ratio estimate was not significantly higher than 1, while this was the case for the estimates based on Norway and Sweden alone. Based on the various estimates, it is assumed that the fatality risk while driving with cannabis is slightly increased.

The aggregated odds ratio of getting killed when positive for benzodiazepines and z-drugs was estimated with data from Finland, Norway and Sweden using both method 2 and 3. Together with the estimate based on all countries (method 1), all odds ratio estimates were significantly higher than 1. All odds ratios based on single countries except Portugal were also significantly higher than 1. Low numbers of positive cases and controls in Portugal are believed to be the reason for no significant estimate in Portugal. Based on all results, the risk estimate is assessed to be significantly increased of about 2-3.

The aggregated odds ratio of getting killed when positive for medicinal opioids was estimated with data from all four countries using method 2 but method 3 did not allow for merging any countries' data due to imprecise estimates for the single countries. The odds ratio estimate based on all countries was significantly higher than 1. As for the single countries, data from Finland and Portugal indicated significantly increased risks, but those from Finland and the Netherlands did not. Based on all results, the estimate is assessed to be significantly increased of about 5-8.

The aggregated odds ratio estimates for getting killed when positive for a combination of alcohol and drug(s) included Norway and Portugal (method 1 and 3), whereas method 2 included only Norway. The aggregated odds ratio estimate was significantly very much higher than 1. As for the single countries, data from all indicated significantly increased risks. Based on all results, the estimate is assessed to be significantly increased of at least 20. These odds ratios were by far the highest of the various odds ratios indicating that driving with a combination of alcohol and drugs or different drugs is an extremely risky endeavour.

The odds ratio estimate for getting killed when positive for a combination of drugs based on all countries (method 1) was significantly higher than 1. The aggregated odds ratio estimates included data from Finland, Norway and Sweden when using method 2 and data from Finland, Norway and Portugal when using method 3. These aggregated odds ratio estimates were also significantly higher than 1. As for the single countries, this was also the case except for Portugal. Based on all results, the estimate is assumed to be significantly increased of at least 5-10. These estimates indicate that driving with a combination of different drugs is very risky.

4 Overall conclusion on relative risk

Based on the assessments of the aggregated odds ratios in section 3.1.3 (seriously injured drivers) and 3.2.3 (killed drivers), together with odds ratios estimated for each of the countries separately, an overall and general assessment of the magnitude of the relative risk by substance group is shown in **table 33**. The confidence intervals have been included in the overall assessment of the relative risk.

Table 33 Relative risk level of getting seriously injured or killed for various substance groups. Assessment based on the preceding estimates and their confidence intervals

Risk level	Risk	Substance group
Slightly increased risk	1-3	0.1 g/L ≤ alcohol in blood < 0.5 g/L Cannabis
Medium increased risk	2-10	0.5 g/L ≤ alcohol in blood < 0.8 g/L Benzoylecgonine Cocaine Illicit opiates Benzodiazepines and Z-drugs Medicinal opioids
Highly increased risk	5-30	0.8 g/L ≤ alcohol in blood < 1.2 g/L Amphetamines Multiple drugs
Extremely increased risk	20-200	Alcohol in blood ≥ 1.2 g/L Alcohol in combination with drugs

Cannabis and amphetamines: due to very different single country estimates, the risk estimate must be treated with caution.
Benzoylecgonine, cocaine and illicit opiates: due to few positive cases and controls, the risk estimates must be treated with caution

As indicated in **table 33,** the highest risk is associated with driving with high blood alcohol concentration and alcohol combined with other psychoactive substances. Other problem groups are medium alcohol concentrations, multiple drug use and driving with amphetamines. However, the risk associated with amphetamine use is very much related to the dose and time period of use, and also related to the type of amphetamines, cf. discussion.

Medium increased risk was assessed for alcohol concentrations between 0.5 and 0.8 g/L, for cocaine and for the medicinal opioids included in the study. The risk associated with benzoylecgonine that is not an active agent but merely a metabolite of cocaine, might be caused by sleep deprivation after cocaine consumption. The risk associated with cannabis was assessed to be similar to the risk of driving with a low alcohol concentration. However, it should be noted that the risk estimates for illicit drugs were based on small number of positive samples and/or very different estimates for the single countries. They should therefore be handled with care.

High blood alcohol concentrations and the combination of alcohol and other drugs indicate the highest risk of getting killed and reflect that in contrast to the driving population, alcohol was found in high concentrations in accident involved drivers. Multiple drug use was also associated with very high risk.

5 Discussion

5.1 Strengths and weaknesses of the study

In case-control studies a high number of both cases and controls is a prerequisite for obtaining reliable risk estimates. Within the field of driving under the influence of alcohol and/or other drugs, a high number of samples is even more crucial because drug and alcohol prevalence in the driving population is fairly low (from a statistical point of view). One obvious strength of this study is the high number of both control and case samples. The base of the injury risk estimates is 2,490 case samples and 15,832 control samples, and for the killed risk estimates 1,112 case samples and 21,917 controls. The samples are distributed over nine European countries which makes the study unique in an international context.

With so many countries participating in the study, it is difficult to pool the results. The strength of this study is a high standardisation of the data collection and analysis. Proficiency testing was organised during the study to guarantee conformity between the laboratories. Besides standardisation every country strived for a high representativeness of the sampled drivers. The uniform study design across the countries makes it possible to compare data and to examine inter-country differences.

This having been mentioned, there are a number of drawbacks of the study as well: In some of the countries, the non-response rates of the control samples were very high, and in most countries, the non-response rate for the control drivers was higher than the prevalence of alcohol and other psychoactive substances in the general driving population.

It is also highly questionable whether data from this study form a representative basis for common European risk estimates as far from all European countries participated in the study. However, we think that the risk estimates represent the countries involved in this study in a fair way.

In some countries, the number of cases was rather low. For injured drivers this was Finland (54 cases) and the Netherlands (188 cases). For killed drivers the number of cases was relatively low in Norway (193) and Sweden (156). Although very satisfactory from a road safety point of view, few case samples result in more imprecise risk estimates.

In Denmark and Italy, the MAIS≥2 criterion was not used to include injured drivers in the study, since the MAIS scale is not applied in these countries. Instead, an equivalent assessment was done. This is a source of error since the scales may not be completely concordant.

Inclusion of the injured drivers into the study was supposed to be done regardless of a suspicion of them being positive for alcohol and other psychoactive drugs. In practice, there may have been skewness with patients more likely to be positive for alcohol and other drugs included more readily. If this was the case, it would result in an overestimation of risk.

In the study, not all opioids and benzodiazepines were analysed for, neither in the case or the control samples, so prevalence of these drugs are an underestimation. It is not possible to assess the consequence of this for the risk estimate.

It is questionable whether the hospitals selected for cooperation were indeed representative for the country. No test has been carried out to check this. It is not possible to assess the consequence of this for the risk estimate.

Although post-accident administration of benzodiazepines and opioids in the hospital should have been noted to be corrected for, we have no certainty that this was always the case.

If the samples were stored for a long time, some degradation of analytes could have occurred, especially for. zopiclone, cocaine and some benzodiazepines.

No back calculation was made to account for the delay between the accident and sampling. Some drugs have a rapid half-life, and after three hours, cannabis concentrations are approximately 25% of the original concentration. Substance blood concentrations from hospital data have been underestimated because of metabolism in the time between the accident and sampling, whereas concentrations from fatal cases have been overestimated because of post-mortem redistribution. This may have slightly overestimated the risk estimate of getting killed and underestimated that of getting injured.

Despite the sources of error mentioned above we believe that the risk estimates presented in this report is a best risk estimate of the participating countries. Due to the various sources of error in the study, specific risk estimates must be interpreted with caution, whereas general trends as presented in **table 33** are considered reliable.

5.2 Risk of getting seriously injured or killed

The risk of getting seriously injured and killed increased exponentially with increasing blood alcohol concentration in every participating country (seriously injured: DK, FI, LT, IT, BE, NL; killed: FI, NO, PT). This is in accordance with earlier findings (reviewed by Elvik and Vaa (2004), Assum (2005)). The actual values of increased risk of getting seriously injured fits quite well with Borkenstein's probabilities of involvement in single vehicle accidents; however, the relative risk in this study associated with driving with very high BAC, 1.2 g/L or higher (99.45), was considerably higher than the one in Borkenstein et al. (1974). Here, the relative risk is from 22 at BAC 1.2 g/L and upwards at higher BACs. The relative risk of getting seriously injured with a BAC between 0.1 and 0.5 g/L did not deviate significantly from one – neither for the single participating countries or the common estimate. This is consistent with the findings that actual impairment/increased risk starts at 0.5 g/L (empirical findings: Assum et al. (2005), Schnabel et al. (2010), findings summarised in Elvik and Vaa (2004); experimental results with 0.5 g/L and 0.8 g/L in Veldstra et al. (2011)).

The relative risks of getting injured at different BACs were similar for the participating countries except for FI where the relative risk was higher by most alcohol concentrations. This is probably due to the sample procedure in Finland: Not all drivers positive for alcohol were allowed by the police to take part in the road side survey recruiting the control samples, because they were taken into police custody (Engblom et al., 2011). Thus, alcohol prevalence in the Finnish driving populations was underestimated and relative risk consequently overestimated, since there was not the same bias in the case population of injured drivers. Moreover, Finnish risk estimates of getting seriously injured were calculated on the basis of few cases which resulted in very large confidence intervals and less reliable estimates.

The relative risk of getting killed fluctuated considerably among the participating countries and was surprisingly enough generally higher than the relative risk of getting injured at the same BAC level.

Fujita and Shibata (2006) report an OR of getting killed after the use of alcohol (any BAC level) to be 4.08 which is lower than the result from this study. Robertson and Drummer (1994) evaluated 341 driver fatalities and determined the relative risk of getting killed with increasing BAC. Their relative risk estimate is 1.75 for BAC levels between 0.5 and 1.0 g/L and about 5 for BAC levels between 1.0 and 1.5 g/L which is far lower than relative risk estimates from this study.

In this study, risk of getting killed was generally higher than risk of getting injured at similar BAC levels. Smink et al. (2005) analysed the association between the use of drugs and the severity of the accident and found no clear association between the two.

The amphetamine drugs group consisted of amphetamines, metamphetamines, MDMA (ecstasy), MDA and MDEA. Amphetamines are designer drugs that have a stimulating effect on mental and physical performance which affect the degree of attention and concentration on driving negatively (OECD, 2010 and references therein). Based on metaanalyses of experimental studies no negative influence of stimulants on the fitness to drive could be stated (Berghaus et al., 2011). In summary there are more findings of performance improvements than of performance impairments. Most experimental studies indicate that effects of stimulant drugs on driving performance are generally small and do not affect road safety. Therapeutic doses of stimulant drugs produce neutral or even stimulating effects on a range of psychomotor functions and driving skills. Stimulants are generally safe for driving when taken alone at regular doses (e.g. as in medicinal use), but stimulant effects are less safe when taken in combination with sleep loss or alcohol intoxication as is often the case in drug abusers.

Negative effects of stimulants can be found by performing more complex driving tasks; moreover, driving behaviour tends to be more impulsive. When the stimulant effect is gone, users become very tired which may affect their driving behaviour (OECD, 2010, Houwing et al., 2011). OECD (2010) state that stimulants (including cocaine) are often the second most frequently detected drug class in the driving population; in this study, this was not so with amphetamine prevalence in the driving population (even together with cocaine) being far below prevalence of cannabis, benzodiazepines and medicinal opioids (Houwing et al., 2011). The odds ratio of getting injured when driving with amphetamine was quite different in the three countries where the number of positive drivers was high enough to get an estimate (DK, LT, NL), and only the estimates from DK and NL were significantly above one. However, the confidence intervals were large and included estimates from all three countries. The common odds ratio of getting killed was somewhat lower than the estimate from DK of getting injured, i.e. 28.2. It includes data from three Nordic countries: FI, NO and SE. The Swedish odds ratio of getting killed was substantially higher than in FI and NO. It must be noted, however, that all odds ratio estimates have been calculated on the basis of quite small numbers which is also reflected in the large confidence intervals.

Studies assessing the enhanced risk of driving with amphetamines are sparse, but the OR-estimate for Denmark (50.0) is very close to the OR found in a similar study in Norway (47.8) (Assum et al., 2005). The literature is not convincing in establishing an elevated risk of driving with amphetamines/stimulants. Walsh et al. (2004) conclude that laboratory investigations have failed to document negative effects of traditional performance tests; however, they attribute this to small doses administered in the experimental situation. In a responsibility study of drivers killed in crashes in Australia, Drummer et al. (2004) found an OR of 2.3 for driving with stimulants – an OR, however, that was not significantly different from 1. Brault et al. (2004) in a case-control set up of 512 fatally injured drivers and 5,931 drivers tested at the roadside in Quebec concluded an elevated risk when driving with amphetamines, but their cases included drivers positive for other drugs as well which is believed to clearly elevate the risk. Finally, Ogden and Moskowitz (2004) conclude that more laboratory

experiments have to be carried out to clarify the effect of stimulants under conditions where they are frequently used on driving behaviour.

In this study, there was a clearly highly elevated risk of getting killed an injured when positive for amphetamines. Due to relatively low prevalence of amphetamines in the samples, it was not possible to estimate risk at various amphetamine concentrations.

The risk of getting killed or injured when driving positive for amphetamines was assessed by the present epidemiological studies to be highly increased (5-30). This is very different from the outcome of the DRUID experimental studies where a significantly elevated risk was not indicated (Ramaekers, 2011). Bosker et al. (2011) find the same lack of negative effects of MDMA on driving performance with doses administered within the therapeutic range (Ramaekers, pers. com.).This rather substantial difference in outcome may primarily be caused by two factors:
1) In the present studies of injured or killed drivers where amphetamine was found, the median concentrations were very high, i.e. 102 and 420 ng/mL respectively, with maximum concentrations of 1095 and 120000 ng/mL. For methamphetamine in injured and killed drivers, the median concentrations were 125 and 411 ng/mL, respectively, and maximum concentrations were 240 and 2939 ng/mL (Isalberti et al, 2011). High concentrations of amphetamine may have harmful effects on self-perception, critical judgement and risk taking, while when the stimulating effects are disappearing, a period associated with fatigue, anxiety and irritability may occur. The risk for involvement in traffic accidents might be increased both during the stimulated and fatigue periods when taking high doses.
2) In the present studies, it is probably not a random sample of drivers who choose to drive positive for (large concentrations of) amphetamines. Probably those who do are more risk taking than the average road user as opposed to the experiments where test persons were ‘healthy volunteers’.

Cocaine like amphetamines is considered a central nervous system stimulant drug with effects similar to the amphetamines. Cocaine has similar acute effects as amphetamines. From a metaanalysis of experimental studies no negative influence on the fitness to drive could be stated. Only some case-reports and non-experimental publications revealed negative effects (Berghaus et al., 2011). But overall there is a lack of studies focusing on impairments during the post acute phase. In this study rather low cocaine prevalence was found both in the injured driver population and in the control population. Despite an overall prevalence in the driving population that was somewhat higher than prevalence of amphetamines (0.42% and 0.08%, respectively (Houwing et al., 2011)) it was not possible to estimate general odds ratios for driving with cocaine. Positive cases and controls were concentrated in Italy, where the odds ratio for getting injured was calculated to be 1.17, yet not significantly over 1.0. This result reflects the fact that the number of positive cases and controls (7 and 18, respectively) out of 2490 cases and 15832 controls sampled across the articipating countries unfortunately is too small to estimate a valid odds ratio. The result should be handled with care.

Benzoylecgonine (BZE) is an inactive metabolite of cocaine and has thus no psychoactive properties. Still in this study, BZE like cocaine was associated with a medium increased risk. The risk associated with benzoylecgonine may be caused by sleep deprivation after cocaine consumption. Benzoylecgonine may also be caused by degradation during storage of samples, and may be a result of cocaine present in the sample when it was collected.

Cannabis has hallucinogenic and central nervous system depressant properties (OECD 2010). Its hallucinogenic properties are distracting in the driving task, and its depressant properties result in impaired coordination, difficulty in thinking and problems with learning and memory (Ramaekers et al., 2006). Cannabis is the most frequently encountered drug in European and North America driving populations (OECD, 2010), and this study confirms that position of the drug: 1.32% of the driving

population in this study were positive for cannabis (alone – not in combination with other drugs or alcohol). Only alcohol was more frequent in the driving population with a prevalence of 3.48% (Houwing et al., 2011).

In this study, the crude odds ratios of a driver of getting seriously injured with cannabis in the blood varied from 0.49 (NL) to 51.02 (FI), and the odds ratio of getting killed varied from 0.19 (PT) to 29.17 (SE). Apart from the high odds ratio in Finland, the level of odds ratios of getting injured in this study is equal to the level reported in the literature (reviewed in OECD, 2010). The odds ratio of getting killed with cannabis in the blood in PT was within the range reported in the literature (OECD, op. cit.), but in SE it was very high. The number of controls sampled at the road side positive for cannabis may have been underestimated in DK, SE, NO, FI and LT because oral fluid was sampled at the road side, and it was not possible to test for the cannabis metabolite THCCOOH in oral fluid. This results in a potential underestimation of positive controls (but not cases) and thus in an inflated risk estimate. This may be the reason for the high odds ratio estimate for getting injured in Finland and the high odds ratio estimate of getting killed in Sweden. Moreover, the numbers of cases and controls positive for cannabis were small in Finland (1 and 2, respectively) and Sweden (1 and 3, respectively) which is reflected in the large confidence interval around the odds ratio estimate.

In this study, benzodiazepines (BZD) and sedative hypnotics (z-drugs) were grouped. Unlike the stimulants amphetamine and cocaine, benzodiazepines and z-drugs are central nervous system depressants. They are therapeutic drugs with the effect of treating anxiety, produce muscle relaxation, control seizures and promoting sleep. Their effect on driving is weaving and decreased alertness (OECD, 2010).

Benzodiazepines and z-drugs are relatively often detected among drivers in the general European driving population; in this study it was the third most frequently used drug with a prevalence of 1.02%, exceeded only by alcohol (3.48%) and cannabis (1.32%) (Houwing et al., 2011).

In this study, the risk of getting seriously injured when driving with BZD and z-drugs varied from insignificantly different from one (BE, FI, LT, IT, NL) to 3.2 (DK). The common European estimate was 2.0 (significantly different from one). Prevalence of benzodiazepines and z-drugs vary quite a lot among participating countries, and the odds ratios which are insignificantly different from one mostly stem from countries where few cases and/or controls were found positive (cf. Table 14). Thus, the most reliable result is believed to be the estimate from Denmark. These results correspond quite well with results from the literature, although the estimate for DK is to the higher end of the spectrum. Assum et al. (2005) found an odds ratio of 2.98 in a case-control design in The Netherlands (injured drivers, BZD's only); Brault et al. (2004) reported an odds ratio of 3.9 in a case-control responsibility analysis (fatally injured drivers, BZP's only); Dussault et al. (2002) reported an odds ratio of 2.5 in a similar set up, Movig et al. (2004) reported an odds ratio of 5.1 in a case-control study (injured drivers, BZD's only), and finally, Mura et al. (2003) reported an odds ratio of 1.7 in a case control study (injured drivers, BZD's only).

The risk of getting killed when driving with BZD was generally found to be higher than the risk of getting injured. This was so for all participating countries' estimates except that of PT which was based on only 2 cases. We see no obvious explanation for this.
Generally we consider the use of BZD to be associated with a medium risk of getting killed or injured.

Medicinal opioids (in this study morphine, codeine, methadone and tramadol) like BZD and z-drugs belong to the central nervous system depressants. Opioids produce analgesia and reduced sensitivity to pain, but also euphoria, central nervous system and respiratory depression, sedation and sleep

(OECD, 2010). These effects have obvious negative implications for safe driving causing various sorts of driving impairment.

In this study, medicinal opioids were about as prevalent in the driving population as benzodiazepines and z-drugs (0.96% and 0.99%, respectively (Houwing et al., 2011)). The odds ratio of getting seriously injured with medicinal opioids ranged from insignificantly different from one (FI, NL) to 4.2 (BE and DK), 9.4 (IT) and 186.6 (LT). The common European estimate was 8.0 (including all countries). The estimate for Italy is based on 16 cases (injured drivers) and only one control, and this is reflected in the relatively large – yet not including 1 – confidence interval (2.7-30.8). Thus, the most reliable results were the ones from BE and DK which are to the high end of the relative risks reported in the literature. In the literature, both significant and insignificant relative risks are reported: Brault et al. (2004) find in a case-control responsibility study of fatally injured drivers an odds ratio of 3.1, whereas Drummer (1995) in a similar set up report an odds ratio of 2.0 – an estimate insignificantly different from one. Movig et al. (2004) also report in a case-control set up of injured drivers an odds ratio insignificantly different from one.

The risk of getting killed when driving with medicinal opioids ranged from odds ratios insignificantly different from one (NO, SE) to 4.3 (FI), 7.7 (PT) with a common estimate of 4.8 (including FI, NO, SE, PT). The Portuguese estimate is based on 2 cases (killed drivers) and 3 controls only, whereas the Finnish estimate is believed to be more reliable with more cases (7) and controls (22). The Finnish estimate is fairly close to the estimate for killed drivers of Brault et al. (2004) of 3.1 cited above.

The use of medicinal opioids, like BZD are considered to result in medium increased risk of getting killed or injured.

The risk of getting injured when driving with alcohol combined with another psychoactive substance was generally higher than the risk of driving with alcohol or other drugs alone. This is in accordance with the fact that alcohol and (most) drugs have a synergetic, not an additive effect (however, see Veldstra et al. (2011) for the combined effect of alcohol and ecstasy). The combined risk of alcohol and other drugs was higher than the risk of other drugs combined with other drugs. This pattern was seen both for injury risk and risk of getting killed. This finding is consistent with the finding of Assum et al. (2005). It does not make sense to interpret the risk of combined use more into detail since the combined use of alcohol and other drugs and drugs with other drugs represents many different combinations of drugs that are probably different among countries.

From the results of this study it can be concluded that the highest risk of getting seriously injured or killed comes from driving with high concentrations of alcohol in the blood. Driving with high concentrations of alcohol in blood (1.2 g/L and upwards) alone or in combination with other drugs is riskier than driving with any other drug. The second most risky category contained various drug-drug combinations, amphetamines and alcohol in blood concentrations between 0.8 g/L and 1.2 g/L. Medium increased risk was associated with medicinal opioids, benzodiazepines and z-drugs, cocaine, benzoylecgonine and alcohol in lower blood concentrations (0.5 g/L to 0.8 g/L). The least risky drug seemed to be cannabis and alcohol in concentrations below the legal limit in most countries, i.e. 0.5 g/L.

6 Acknowledgements

We thank Professor Bjarne Kjær Ersbøl and statistician Helle Mølgaard Sommer, DTU Data Analysis section and Klaus Kaae Nielsen, former assistant professor at DTU Informatics for informative and valuable discussions of data and methods. Moreover, we thank Dr. Volker Hargutt, University of Würzburg, for valuable discussions.

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8 Appendix 1 Number of samples

8.1 Studies of seriously injured drivers

Table 8.1 Number of cases and controls for the odds ratio calculation of getting seriously injured in Belgium, by gender, age and time period

By gender	**Cases**		**Controls**	
Male	243	*69.83%*	1983	*67.24%*
Female	104	*29.89%*	965	*32.72%*
Unknown	1	*0.29%*	1	*0.03%*
In total	**348**	***100%***	**2949**	***100%***
By age group	**Cases**		**Controls**	
18-24	71	*20.40%*	336	*11.39%*
25-34	106	*30.46%*	611	*20.72%*
35-49	88	*25.29%*	1097	*37.20%*
50+	70	*20.11%*	885	*30.01%*
Unknown	13	*3.74%*	20	*0.68%*
In total	**348**	***100%***	**2949**	***100%***
By time period	**Cases**		**Controls**	
1	51	*14.66%*	278	*9.43%*
2	57	*16.38%*	765	*25.94%*
3	38	*10.92%*	632	*21.43%*
4	45	*12.93%*	95	*3.22%*
5	35	*10.06%*	171	*5.80%*
6	23	*6.61%*	228	*7.73%*
7	38	*10.92%*	521	*17.67%*
8	52	*14.94%*	259	*8.78%*
Unknown	9	*2.59%*	0	*0%*
In total	**348**	***100%***	**2949**	***100%***

Table 8.2 Number of cases and controls for the odds ratio calculation of getting seriously injured in Denmark, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	546	*65.64%*	1977	*65.86%*
Female	293	*34.36%*	1021	*34.01%*
Unknown	0	*0%*	4	*0.13%*
In total	**839**	***100%***	**3002**	***100%***
By age group	**Cases**		**Controls**	
18-24	269	*32.06%*	257	*8.56%*
25-34	203	*24.20%*	499	*16.62%*
35-49	215	*25.63%*	1061	*35.34%*
50+	146	*17.40%*	1178	*39.24%*
Unknown	6	*0.72%*	7	*0.23%*
In total	**839**	**100%**	**3002**	**100%**
By time period	**Cases**		**Controls**	
1	149	*17.76%*	496	*16.52%*
2	183	*21.81%*	684	*22.78%*
3	170	*20.26%*	506	*16.86%*
4	39	*4.65%*	203	*6.76%*
5	34	*4.05%*	187	*6.23%*
6	58	*6.91%*	247	*8.23%*
7	120	*14.30%*	434	*14.46%*
8	68	*8.10%*	245	*8.16%*
Unknown	18	*2.15%*	0	*0%*
In total	**839**	***100%***	**3002**	***100%***

Table 8.3 Number of cases and controls for the odds ratio calculation of getting seriously injured in Finland, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	43	*79.63%*	1756	*64.89%*
Female	11	*20.37%*	940	*34.74%*
Unknown	0	*0%*	10	*0.37%*
In total	**54**	***100%***	**2706**	***100%***
By age group	**Cases**		**Controls**	
18-24	17	*31.48%*	307	*11.35%*
25-34	11	*20.37%*	555	*20.51%*
35-49	10	*18.52%*	876	*32.37%*
50+	16	*29.63%*	964	*35.62%*
Unknown	0	*0%*	4	*0.15%*
In total	**54**	***100%***	**2706**	***100%***
By time period	**Cases**		**Controls**	
1	6	*11.11%*	424	*15.67%*
2	11	*20.37%*	773	*28.57%*
3	7	*12.96%*	417	*15.41%*
4	5	*9.26%*	212	*7.83%*
5	6	*11.11%*	184	*6.80%*
6	2	*3.70%*	362	*13.38%*
7	11	*20.37%*	203	*7.50%*
8	6	*11.11%*	131	*4.84%*
Unknown	0	*0%*	0	*0%*
In total	**54**	***100%***	**2706**	***100%***

Table 8.4 Number of cases and controls for the odds ratio calculation of getting seriously injured in Italy, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	520	*76.92%*	839	*77.26%*
Female	156	*23.08%*	247	*22.74%*
Unknown	0	*0%*	0	*0%*
In total	**676**	***100%***	**1086**	***100%***
By age group	**Cases**		**Controls**	
18-24	126	*18.64%*	257	*23.66%*
25-34	208	*30.77%*	404	*37.20%*
35-49	204	*30.18%*	365	*33.61%*
50+	138	*20.41%*	60	*5.52%*
Unknown	0	*0%*	0	*0%*
In total	**676**	***100%***	**1086**	***100%***
By time period	**Cases**		**Controls**	
1	47	*6.95%*	63	*5.80%*
2	100	*14.79%*	85	*7.83%*
3	117	*17.31%*	68	*6.26%*
4	71	*10.50%*	275	*25.32%*
5	37	*5.47%*	88	*8.10%*
6	55	*8.14%*	13	*1.20%*
7	122	*18.05%*	71	*6.54%*
8	89	*13.17%*	423	*38.95%*
Unknown	38	*5.62%*	0	*0%*
In total	**676**	***100%***	**1086**	***100%***

Table 8.5 Number of cases and controls for the odds ratio calculation of getting seriously injured in Lithuania, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	238	*61.82%*	1156	*91.24%*
Female	134	*34.81%*	111	*8.76%*
Unknown	13	*3.38%*	0	*0%*
In total	385	*100%*	1267	*100%*
By age group	**Cases**		**Controls**	
18-24	104	*27.01%*	206	*16.26%*
25-34	95	*24.68%*	333	*26.28%*
35-49	104	*27.01%*	441	*34.81%*
50+	58	*15.06%*	275	*21.70%*
Unknown	24	*6.23%*	12	*0.95%*
In total	385	*100%*	1267	*100%*
By time period	**Cases**		**Controls**	
1	67	*17.40%*	36	*2.84%*
2	97	*25.19%*	183	*14.44%*
3	75	*19.48%*	379	*29.91%*
4	11	*2.86%*	26	*2.05%*
5	9	*2.34%*	0	*0%*
6	31	*8.05%*	412	*32.52%*
7	45	*11.69%*	220	*17.36%*
8	24	*6.23%*	11	*0.87%*
Unknown	26	*6.75%*	0	*0%*
In total	385	100%	1267	100%

Table 8.6 Number of cases and controls for the odds ratio calculation of getting seriously injured in the Netherlands, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	150	*79.79%*	3400	*70.51%*
Female	37	*19.68%*	1422	*29.49%*
Unknown	1	*0.53%*	0	*0%*
In total	**188**	***100%***	**4822**	***100%***
By age group	**Cases**		**Controls**	
18-24	55	*29.26%*	628	*13.02%*
25-34	51	*27.13%*	1106	*22.94%*
35-49	46	*24.47%*	1653	*34.28%*
50+	35	*18.62%*	1430	*29.66%*
Unknown	1	*0.53%*	5	*0.10%*
In total	**188**	***100%***	**4822**	***100%***
By time period	**Cases**		**Controls**	
1-3	91	*48.40%*	1977	*41.00%*
4	46	*24.47%*	674	*13.98%*
5-7	23	*12.23%*	1539	*31.92%*
8	28	*14.89%*	632	*13.11%*
Unknown	0	*0%*	0	*0%*
In total	**188**	***100%***	**4822**	***100%***

8.2 Studies of killed drivers

Table 8.7 Number of cases and controls for the odds ratio calculation of getting killed in Finland, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	387	*80.96%*	2566	*66.81%*
Female	91	*19.04%*	1261	*32.83%*
Unknown	0	*0%*	14	*0.36%*
In total	**478**	***100%***	**3841**	***100%***
By age group	**Cases**		**Controls**	
18-24	115	*24.06%*	425	*11.06%*
25-34	74	*15.48%*	735	*19.14%*
35-49	102	*21.34%*	1184	*30.83%*
50+	187	*39.12%*	1491	*38.82%*
Unknown	0	*0%*	6	*0.16%*
In total	**478**	***100%***	**3841**	***100%***
By time period	**Cases**		**Controls**	
1	78	*16.32%*	605	*15.75%*
2	114	*23.85%*	1212	*31.55%*
3	73	*15.27%*	601	*15.65%*
4	41	*8.58%*	279	*7.26%*
5	37	*7.74%*	254	*6.61%*
6	23	*4.81%*	501	*13.04%*
7	62	*12.97%*	241	*6.27%*
8	50	*10.46%*	148	*3.85%*
Unknown	0	*0%*	0	*0%*
In total	**478**	***100%***	**3841**	***100%***

Table 8.8 Number of cases and controls for the odds ratio calculation of getting killed in Norway, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	152	*78.76%*	6570	*71.13%*
Female	41	*21.24%*	2664	*28.84%*
Unknown	0	*0%*	2	*0.02%*
In total	**193**	***100%***	**9236**	***100%***
By age group	**Cases**		**Controls**	
18-24	56	*29.02%*	963	*10.43%*
25-34	37	*19.17%*	1651	*17.88%*
35-49	42	*21.76%*	3238	*35.06%*
50+	58	*30.05%*	3376	*36.55%*
Unknown	0	*0%*	8	*0.09%*
In total	**193**	***100%***	**9236**	***100%***
By time period	**Cases**		**Controls**	
1	30	*15.54%*	923	*9.99%*
2	48	*24.87%*	2326	*25.18%*
3	34	*17.62%*	1325	*14.35%*
4	10	*5.18%*	746	*8.08%*
5	10	*5.18%*	380	*4.11%*
6	9	*4.66%*	1632	*17.67%*
7	33	*17.10%*	1399	*15.15%*
8	19	*9.84%*	505	*5.47%*
Unknown	0	*0%*	0	*0%*
In total	**193**	***100%***	**9236**	***100%***

Table 8.9 Number of cases and controls for the odds ratio calculation of getting killed in Portugal, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	265	*92.98%*	1800	*68.16%*
Female	20	*7.02%*	830	*31.43%*
Unknown	0	*0%*	11	*0.42%*
In total	**285**	***100%***	**2641**	***100%***
By age group	**Cases**		**Controls**	
18-24	45	*15.79%*	394	*14.92%*
25-34	71	*24.91%*	854	*32.34%*
35-49	77	*27.02%*	823	*31.16%*
50+	85	*29.82%*	517	*19.58%*
Unknown	7	*2.46%*	53	*2.01%*
In total	**285**	***100%***	**2641**	***100%***
By time period	**Cases**		**Controls**	
1	37	*12.98%*	236	*8.94%*
2	43	*15.09%*	769	*29.12%*
3	34	*11.93%*	291	*11.02%*
4	24	*8.42%*	269	*10.19%*
5	19	*6.67%*	159	*6.02%*
6	15	*5.26%*	291	*11.02%*
7	35	*12.28%*	335	*12.68%*
8	25	*8.77%*	291	*11.02%*
Unknown	53	*18.60%*	0	*0%*
In total	**285**	***100%***	**2641**	***100%***

Table 8.10 Number of cases and controls for the odds ratio calculation of getting killed in Sweden, by gender, age and time period

	Number	*Percentage*	Number	*Percentage*
By gender	**Cases**		**Controls**	
Male	119	*76.28%*	4348	*70.14%*
Female	37	*23.72%*	1844	*29.75%*
Unknown	0	*0%*	7	*0.11%*
In total	**156**	***100%***	**6199**	***100%***
By age group	**Cases**		**Controls**	
18-24	34	*21.79%*	421	*6.79%*
25-34	18	*11.54%*	830	*13.39%*
35-49	35	*22.44%*	1851	*29.86%*
50+	69	*44.23%*	3092	*49.88%*
Unknown	0	*0%*	5	*0.08%*
In total	**156**	***100%***	**6199**	***100%***
By time period	**Cases**		**Controls**	
1	20	*12.82%*	394	*6.36%*
2	44	*28.21%*	3065	*49.44%*
3	32	*20.51%*	565	*9.11%*
4	7	*4.49%*	225	*3.63%*
5	8	*5.13%*	299	*4.82%*
6	14	*8.97%*	1316	*21.23%*
7	14	*8.97%*	208	*3.36%*
8	17	*10.90%*	127	*2.05%*
Unknown	0	*0%*	0	*0%*
In total	**156**	***100%***	**6199**	***100%***

9 Appendix 2 Gender and age effect

9.1 Odds ratios of getting seriously injured

Table 9.1 Adjusted odds ratios of getting seriously injured when driving with various substances in Belgium. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	0.96	*0.72-1.28*
	Age	18-24 vs. 50+	2.69	*1.78-4.07*
		25-34 vs. 50+	1.96	*1.36-2.82*
		35-49 vs. 50+	0.97	*0.67-1.40*
Amphetamine	Gender	Male vs. female	0.82	*0.59-1.14*
	Age	18-24 vs. 50+	2.06	*1.27-3.32*
		25-34 vs. 50+	1.52	*1.00-2.30*
		35-49 vs. 50+	0.69	*0.44-1.06*
Benzoylecgonine	Gender	Male vs. female	0.82	*0.59-1.14*
	Age	18-24 vs. 50+	2.06	*1.27-3.32*
		25-34 vs. 50+	1.52	*1.00-2.30*
		35-49 vs. 50+	0.69	*0.44-1.06*
Cocaine	Gender	Male vs. female	0.82	*0.59-1.14*
	Age	18-24 vs. 50+	2.06	*1.27-3.32*
		25-34 vs. 50+	1.52	*1.00-2.30*
		35-49 vs. 50+	0.69	*0.44-1.06*
Cannabis	Gender	Male vs. female	0.81	*0.59-1.12*
	Age	18-24 vs. 50+	2.00	*1.24-3.23*
		25-34 vs. 50+	1.54	*1.01-2.33*
		45-49 vs. 50+	0.68	*0.44-1.06*
Illicit opiates	Gender	Male vs. female	0.82	*0.59-1.14*
	Age	18-24 vs. 50+	2.06	*1.27-3.32*
		25-34 vs. 50+	1.52	*1.00-2.30*
		35-49 vs. 50+	0.69	*0.44-1.06*
Benzodiazepines and Z-drugs	Gender	Male vs. female	0.80	*0.58-1.09*
	Age	18-24 vs. 50+	2.08	*1.29-3.36*
		25-34 vs. 50+	1.51	*1.00-2.29*
		45-49 vs. 50+	0.72	*0.47-1.10*
Medicinal opioids	Gender	Male vs. female	0.83	*0.60-1.14*
	Age	18-24 vs. 50+	2.08	*1.28-3.36*
		25-34 vs. 50+	1.65	*1.09-2.49*
		35-49 vs. 50+	0.71	*0.46-1.10*
All alcohol-drug combinations	Gender	Male vs. female	0.81	*0.58-1.11*
	Age	18-24 vs. 50+	2.14	*1.33-3.44*
		25-34 vs. 50+	1.62	*1.07-2.47*
		35-49 vs. 50+	0.77	*0.50-1.18*
All multiple drug combinations	Gender	Male vs. female	0.82	*0.59-1.13*
	Age	18-24 vs. 50+	1.99	*1.23-3.22*
		25-34 vs. 50+	1.61	*1.06-2.42*
		35-49 vs. 50+	0.70	*0.45-1.08*

Table 9.2 Adjusted odds ratios of getting seriously injured when driving with various substances in Denmark. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	0.75	*0.62-0.90*
	Age	18-24 vs. 50+	11.00	*8.41-14.40*
		25-34 vs. 50+	3.28	*2.52-4.28*
		35-49 vs. 50+	1.67	*1.30-2.14*
Amphetamine	Gender	Male vs. female	0.74	*0.61-0.90*
	Age	18-24 vs. 50+	10.09	*7.66-13.28*
		25-34 vs. 50+	2.83	*2.15-3.74*
		35-49 vs. 50+	1.56	*1.20-2.02*
Benzoylecgonine	Gender	Male vs. female	0.74	*0.61-0.90*
	Age	18-24 vs. 50+	10.08	*7.65-13.27*
		25-34 vs. 50+	2.84	*2.15-3.74*
		35-49 vs. 50+	1.56	*1.20-2.02*
Cocaine	Gender	Male vs. female	0.74	*0.61-0.90*
	Age	18-24 vs. 50+	10.08	*7.65-13.27*
		25-34 vs. 50+	2.84	*2.15-3.74*
		35-49 vs. 50+	1.56	*1.20-2.02*
Cannabis	Gender	Male vs. female	0.74	*0.61-0.89*
	Age	18-24 vs. 50+	10.08	*7.65-13.26*
		25-34 vs. 50+	2.82	*2.14-3.72*
		35-49 vs. 50+	1.56	*1.21-2.03*
Illicit opiates	Gender	Male vs. female	0.74	*0.61-0.90*
	Age	18-24 vs. 50+	10.08	*7.65-13.27*
		25-34 vs. 50+	2.84	*2.15-3.74*
		35-49 vs. 50+	1.56	*1.20-2.02*
Benzodiazepines and Z-drugs	Gender	Male vs. female	0.73	*0.61-0.89*
	Age	18-24 vs. 50+	9.98	*7.60-13.11*
		25-34 vs. 50+	2.83	*2.15-3.73*
		35-49 vs. 50+	1.53	*1.19-1.98*
Medicinal opioids	Gender	Male vs. female	0.76	*0.63-0.92*
	Age	18-24 vs. 50+	10.11	*7.69-13.28*
		25-34 vs. 50+	2.80	*2.12-3.68*
		35-49 vs. 50+	1.59	*1.23-2.05*
All alcohol-drug combinations	Gender	Male vs. female	0.74	*0.61-0.90*
	Age	18-24 vs. 50+	10.03	*7.62-13.20*
		25-34 vs. 50+	2.80	*2.13-3.70*
		35-49 vs. 50+	1.54	*1.19-2.00*
All multiple drug combinations	Gender	Male vs. female	0.74	*0.61-0.89*
	Age	18-24 vs. 50+	9.93	*7.54-13.07*
		25-34 vs. 50+	2.84	*2.15-3.74*
		35-49 vs. 50+	1.56	*1.21-2.02*

Table 9.3 Adjusted odds ratios of getting seriously injured when driving with various substances in Finland. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	1.55	*0.73-3.27*
	Age	18-24 vs. 50+	3.42	*1.53-7.62*
		25-34 vs. 50+	0.93	*0.35-2.43*
		35-49 vs. 50+	0.79	*0.33-1.92*
Amphetamine	Gender	Male vs. female	1.55	*0.69-3.48*
	Age	18-24 vs. 50+	2.52	*1.05-6.05*
		25-34 vs. 50+	0.76	*0.27-2.17*
		35-49 vs. 50+	0.58	*0.22-1.55*
Benzoylecgonine	Gender	Male vs. female	1.55	*0.69-3.48*
	Age	18-24 vs. 50+	2.52	*1.05-6.05*
		25-34 vs. 50+	0.76	*0.27-2.17*
		35-49 vs. 50+	0.58	*0.22-1.55*
Cocaine	Gender	Male vs. female	1.55	*0.69-3.48*
	Age	18-24 vs. 50+	2.52	*1.05-6.05*
		25-34 vs. 50+	0.76	*0.27-2.17*
		35-49 vs. 50+	0.58	*0.22-1.55*
Cannabis	Gender	Male vs. female	1.55	*0.69-3.48*
	Age	18-24 vs. 50+	2.68	*1.14-6.34*
		25-34 vs. 50+	0.78	*0.27-2.24*
		35-49 vs. 50+	0.59	*0.22-1.60*
Illicit opiates	Gender	Male vs. female	1.55	*0.69-3.48*
	Age	18-24 vs. 50+	2.52	*1.05-6.05*
		25-34 vs. 50+	0.76	*0.27-2.17*
		35-49 vs. 50+	0.58	*0.22-1.55*
Benzodiazepines and Z-drugs	Gender	Male vs. female	1.62	*0.72-3.62*
	Age	18-24 vs. 50+	2.43	*1.02-5.77*
		25-34 vs. 50+	0.73	*0.26-2.06*
		35-49 vs. 50+	0.55	*0.21-1.47*
Medicinal opioids	Gender	Male vs. female	1.37	*0.63-2.97*
	Age	18-24 vs. 50+	2.46	*1.03-5.86*
		25-34 vs. 50+	0.70	*0.25-1.99*
		35-49 vs. 50+	0.55	*0.21-1.48*
All alcohol-drug combinations	Gender	Male vs. female	1.54	*0.69-3.47*
	Age	18-24 vs. 50+	2.60	*1.08-6.24*
		25-34 vs. 50+	0.95	*0.36-2.46*
		35-49 vs. 50+	0.53	*0.19-1.45*
All multiple drug combinations	Gender	Male vs. female	1.64	*0.73-3.68*
	Age	18-24 vs. 50+	2.64	*1.09-6.35*
		25-34 vs. 50+	0.81	*0.29-2.24*
		35-49 vs. 50+	0.65	*0.25-1.69*

Table 9.4 Adjusted odds ratios of getting seriously injured when driving with various substances in Italy. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	0.80	*0.62-1.03*
	Age	18-24 vs. 50+	0.18	*0.12-0.28*
		25-34 vs. 50+	0.17	*0.12-0.25*
		35-49 vs. 50+	0.17	*0.11-0.24*
Amphetamine	Gender	Male vs. female	0.70	*0.53-0.92*
	Age	18-24 vs. 50+	0.16	*0.10-0.25*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.09-0.21*
Benzoylecgonine	Gender	Male vs. female	0.69	*0.53-0.91*
	Age	18-24 vs. 50+	0.16	*0.10-0.24*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.10-0.22*
Cocaine	Gender	Male vs. female	0.70	*0.53-0.92*
	Age	18-24 vs. 50+	0.16	*0.10-0.25*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.09-0.22*
Cannabis	Gender	Male vs. female	0.71	*0.54-0.94*
	Age	18-24 vs. 50+	0.17	*0.11-0.26*
		25-34 vs. 50+	0.14	*0.09-0.22*
		35-49 vs. 50+	0.14	*0.09-0.21*
Illicit opiates	Gender	Male vs. female	0.70	*0.53-0.92*
	Age	18-24 vs. 50+	0.16	*0.10-0.25*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.09-0.21*
Benzodiazepines and Z-drugs	Gender	Male vs. female	0.69	*0.52-0.91*
	Age	18-24 vs. 50+	0.15	*0.10-0.24*
		25-34 vs. 50+	0.14	*0.09-0.20*
		35-49 vs. 50+	0.14	*0.09-0.21*
Medicinal opioids	Gender	Male vs. female	0.68	*0.52-0.90*
	Age	18-24 vs. 50+	0.16	*0.10-0.25*
		25-34 vs. 50+	0.14	*0.09-0.22*
		35-49 vs. 50+	0.14	*0.09-0.21*
All alcohol-drug combinations	Gender	Male vs. female	0.72	*0.55-0.95*
	Age	18-24 vs. 50+	0.16	*0.11-0.25*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.10-0.22*
All multiple drug combinations	Gender	Male vs. female	0.72	*0.55-0.95*
	Age	18-24 vs. 50+	0.16	*0.11-0.25*
		25-34 vs. 50+	0.14	*0.09-0.21*
		35-49 vs. 50+	0.14	*0.09-0.21*

Table 9.5 Adjusted odds ratios of getting seriously injured when driving with various substances in Lithuania. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	0.15	*0.11-0.20*
	Age	18-24 vs. 50+	2.47	*1.61-3.79*
		25-34 vs. 50+	1.03	*0.67-1.57*
		35-49 vs. 50+	0.94	*0.63-1.41*
Amphetamine	Gender	Male vs. female	0.16	*0.11-0.22*
	Age	18-24 vs. 50+	2.26	*1.45-3.53*
		25-34 vs. 50+	0.96	*0.62-1.50*
		35-49 vs. 50+	0.93	*0.61-1.42*
Benzoylecgonine	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.31	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*
Cocaine	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.31	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*
Cannabis	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.31	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*
Illicit opiates	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.30	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*
Benzodiazepines and Z-drugs	Gender	Male vs. female	0.17	*0.12-0.23*
	Age	18-24 vs. 50+	2.48	*1.58-3.87*
		25-34 vs. 50+	1.09	*0.70-1.69*
		35-49 vs. 50+	1.00	*0.65-1.52*
Medicinal opioids	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.31	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*
All alcohol-drug combinations	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.33	*1.49-3.64*
		25-34 vs. 50+	0.97	*0.62-1.51*
		35-49 vs. 50+	0.93	*0.61-1.42*
All multiple drug combinations	Gender	Male vs. female	0.15	*0.11-0.21*
	Age	18-24 vs. 50+	2.31	*1.47-3.60*
		25-34 vs. 50+	0.96	*0.61-1.49*
		35-49 vs. 50+	0.92	*0.60-1.40*

Table 9.6 Adjusted odds ratios of getting seriously injured when driving with various substances in the Netherlands. Confidence intervals included. Effect of gender or various age groups.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	1.41	*0.95-2.08*
	Age	18-24 vs. 50+	5.64	*3.54-9.00*
		25-34 vs. 50+	1.98	*1.23-3.17*
		35-49 vs. 50+	1.22	*0.76-1.95*
Amphetamine	Gender	Male vs. female	1.25	*0.83-1.87*
	Age	18-24 vs. 50+	4.59	*2.78-7.59*
		25-34 vs. 50+	1.55	*0.90-2.66*
		35-49 vs. 50+	1.12	*0.67-1.88*
Benzoylecgonine	Gender	Male vs. female	1.31	*0.87-1.97*
	Age	18-24 vs. 50+	4.42	*2.67-7.33*
		25-34 vs. 50+	1.49	*0.86-2.58*
		35-49 vs. 50+	1.21	*0.73-2.01*
Cocaine	Gender	Male vs. female	1.29	*0.85-1.94*
	Age	18-24 vs. 50+	4.63	*2.80-7.65*
		25-34 vs. 50+	1.47	*0.85-2.56*
		35-49 vs. 50+	1.16	*0.69-1.94*
Cannabis	Gender	Male vs. female	1.29	*0.86-1.94*
	Age	18-24 vs. 50+	4.56	*2.76-7.54*
		25-34 vs. 50+	1.53	*0.88-2.63*
		35-49 vs. 50+	1.15	*0.69-1.93*
Illicit opiates	Gender	Male vs. female	1.29	*0.85-1.94*
	Age	18-24 vs. 50+	4.63	*2.80-7.65*
		25-34 vs. 50+	1.47	*0.85-2.56*
		35-49 vs. 50+	1.16	*0.69-1.94*
Benzodiazepines and Z-drugs	Gender	Male vs. female	1.31	*0.87-1.97*
	Age	18-24 vs. 50+	4.53	*2.76-7.45*
		25-34 vs. 50+	1.44	*0.83-2.48*
		35-49 vs. 50+	1.12	*0.67-1.86*
Medicinal opioids	Gender	Male vs. female	1.31	*0.87-1.97*
	Age	18-24 vs. 50+	4.72	*2.86-7.81*
		25-34 vs. 50+	1.51	*0.87-2.62*
		35-49 vs. 50+	1.21	*0.72-2.02*
All alcohol-drug combinations	Gender	Male vs. female	1.26	*0.84-1.89*
	Age	18-24 vs. 50+	4.61	*2.80-7.60*
		25-34 vs. 50+	1.54	*0.90-2.64*
		35-49 vs. 50+	1.14	*0.68-1.91*
All multiple drug combinations	Gender	Male vs. female	1.29	*0.85-1.94*
	Age	18-24 vs. 50+	4.63	*2.80-7.65*
		25-34 vs. 50+	1.47	*0.85-2.56*
		35-49 vs. 50+	1.16	*0.69-1.94*

9.2 Odds ratios of getting killed

Table 9.7 Adjusted odds ratios of getting killed when driving with various substances in Finland, including confidence intervals. Gender and age effect.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	1.52	*1.16-2.01*
	Age	18-24 vs. 50+	1.62	*1.18-2.23*
		25-34 vs. 50+	0.62	*0.43-0.88*
		35-49 vs. 50+	0.56	*0.41-0.77*
Amphetamine	Gender	Male vs. female	1.58	*1.18-2.10*
	Age	18-24 vs. 50+	1.49	*1.07-2.06*
		25-34 vs. 50+	0.56	*0.39-0.82*
		35-49 vs. 50+	0.49	*0.35-0.69*
Benzoylecgonine	Gender	Male vs. female	1.55	*1.16-2.07*
	Age	18-24 vs. 50+	1.48	*1.06-2.05*
		25-34 vs. 50+	0.58	*0.40-0.84*
		35-49 vs. 50+	0.49	*0.36-0.69*
Cocaine	Gender	Male vs. female	1.55	*1.16-2.07*
	Age	18-24 vs. 50+	1.48	*1.06-2.05*
		25-34 vs. 50+	0.58	*0.40-0.84*
		35-49 vs. 50+	0.49	*0.36-0.69*
Cannabis	Gender	Male vs. female	1.55	*1.16-2.07*
	Age	18-24 vs. 50+	1.48	*1.06-2.05*
		25-34 vs. 50+	0.58	*0.40-0.84*
		45-49 vs. 50+	0.49	*0.36-0.69*
Illicit opiates	Gender	Male vs. female	1.55	*1.16-2.07*
	Age	18-24 vs. 50+	1.48	*1.06-2.05*
		25-34 vs. 50+	0.58	*0.40-0.84*
		35-49 vs. 50+	0.49	*0.36-0.69*
Benzodiazepines and Z-drugs	Gender	Male vs. female	1.55	*1.17-2.04*
	Age	18-24 vs. 50+	1.51	*1.09-2.09*
		25-34 vs. 50+	0.58	*0.41-0.84*
		45-49 vs. 50+	0.52	*0.38-0.72*
Medicinal opioids	Gender	Male vs. female	1.59	*1.20-2.12*
	Age	18-24 vs. 50+	1.50	*1.08-2.08*
		25-34 vs. 50+	0.56	*0.39-0.82*
		35-49 vs. 50+	0.50	*0.36-0.70*
All alcohol-drug combinations	Gender	Male vs. female	1.54	*1.16-2.05*
	Age	18-24 vs. 50+	1.49	*1.08-2.08*
		25-34 vs. 50+	0.60	*0.41-0.86*
		35-49 vs. 50+	0.50	*0.36-0.70*
All multiple drug combinations	Gender	Male vs. female	1.56	*1.17-2.07*
	Age	18-24 vs. 50+	1.49	*1.07-2.07*
		25-34 vs. 50+	0.57	*0.39-0.82*
		35-49 vs. 50+	0.51	*0.36-0.70*

Table 9.8 Adjusted odds ratios of getting killed when driving with various substances in Norway, including confidence intervals. Gender and age effect.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	1.33	*0.89-1.99*
	Age	18-24 vs. 50+	2.70	*1.73-4.22*
		25-34 vs. 50+	1.09	*0.66-1.80*
		35-49 vs. 50+	0.62	*0.39-0.99*
Amphetamine	Gender	Male vs. female	1.25	*0.82-1.90*
	Age	18-24 vs. 50+	2.42	*1.54-3.80*
		25-34 vs. 50+	0.86	*0.51-1.46*
		35-49 vs. 50+	0.49	*0.29-0.81*
Benzoylecgonine	Gender	Male vs. female	1.23	*0.81-1.87*
	Age	18-24 vs. 50+	2.43	*1.54-3.82*
		25-34 vs. 50+	0.88	*0.52-1.50*
		35-49 vs. 50+	0.47	*0.28-0.79*
Cocaine	Gender	Male vs. female	1.23	*0.81-1.87*
	Age	18-24 vs. 50+	2.43	*1.54-3.82*
		25-34 vs. 50+	0.88	*0.52-1.50*
		35-49 vs. 50+	0.47	*0.28-0.79*
Cannabis	Gender	Male vs. female	1.25	*0.82-1.89*
	Age	18-24 vs. 50+	2.40	*1.53-3.78*
		25-34 vs. 50+	0.93	*0.56-1.56*
		45-49 vs. 50+	0.47	*0.28-0.79*
Illicit opiates	Gender	Male vs. female	1.23	*0.81-1.87*
	Age	18-24 vs. 50+	2.43	*1.54-3.82*
		25-34 vs. 50+	0.88	*0.52-1.50*
		35-49 vs. 50+	0.47	*0.28-0.79*
Benzodiazepines and Z-drugs	Gender	Male vs. female	1.19	*0.80-1.77*
	Age	18-24 vs. 50+	2.49	*1.60-3.90*
		25-34 vs. 50+	0.87	*0.52-1.47*
		45-49 vs. 50+	0.50	*0.31-0.83*
Medicinal opioids	Gender	Male vs. female	1.20	*0.79-1.81*
	Age	18-24 vs. 50+	2.52	*1.61-3.96*
		25-34 vs. 50+	0.89	*0.53-1.52*
		35-49 vs. 50+	0.47	*0.28-0.79*
All alcohol-drug combinations	Gender	Male vs. female	1.25	*0.83-1.90*
	Age	18-24 vs. 50+	2.58	*1.65-4.02*
		25-34 vs. 50+	0.93	*0.55-1.55*
		35-49 vs. 50+	0.48	*0.28-0.80*
All multiple drug combinations	Gender	Male vs. female	1.27	*0.84-1.92*
	Age	18-24 vs. 50+	2.34	*1.48-3.69*
		25-34 vs. 50+	0.92	*0.55-1.53*
		35-49 vs. 50+	0.53	*0.33-0.87*

Table 9.9 Adjusted odds ratios of getting killed when driving with various substances in Portugal, including confidence intervals. Gender and age effect.

Substance	Effect		Adjusted OR	*C.I.*
All alcohol concentrations	Gender	Male vs. female	4.17	*2.57-6.76*
	Age	18-24 vs. 50+	0.65	*0.42-1.01*
		25-34 vs. 50+	0.53	*0.36-0.78*
		35-49 vs. 50+	0.54	*0.37-0.77*
Amphetamine	Gender	Male vs. female	3.33	*1.98-5.61*
	Age	18-24 vs. 50+	0.85	*0.53-1.38*
		25-34 vs. 50+	0.42	*0.26-0.67*
		35-49 vs. 50+	0.41	*0.26-0.64*
Benzoylecgonine	Gender	Male vs. female	3.33	*1.98-5.61*
	Age	18-24 vs. 50+	0.85	*0.53-1.38*
		25-34 vs. 50+	0.42	*0.26-0.67*
		35-49 vs. 50+	0.41	*0.26-0.64*
Cocaine	Gender	Male vs. female	3.33	*1.98-5.61*
	Age	18-24 vs. 50+	0.85	*0.53-1.38*
		25-34 vs. 50+	0.42	*0.26-0.67*
		35-49 vs. 50+	0.41	*0.26-0.64*
Cannabis	Gender	Male vs. female	3.33	*1.98-5.61*
	Age	18-24 vs. 50+	0.85	*0.53-1.38*
		25-34 vs. 50+	0.42	*0.26-0.67*
		45-49 vs. 50+	0.41	*0.26-0.64*
Illicit opiates	Gender	Male vs. female	3.33	*1.98-5.61*
	Age	18-24 vs. 50+	0.85	*0.53-1.38*
		25-34 vs. 50+	0.42	*0.26-0.67*
		35-49 vs. 50+	0.41	*0.26-0.64*
Benzodiazepines and Z-drugs	Gender	Male vs. female	3.46	*2.05-5.82*
	Age	18-24 vs. 50+	0.85	*0.53-1.39*
		25-34 vs. 50+	0.43	*0.27-0.69*
		45-49 vs. 50+	0.41	*0.26-0.64*
Medicinal opioids	Gender	Male vs. female	3.36	*1.99-5.65*
	Age	18-24 vs. 50+	0.85	*0.52-1.37*
		25-34 vs. 50+	0.43	*0.27-0.68*
		35-49 vs. 50+	0.39	*0.25-0.61*
All alcohol-drug combinations	Gender	Male vs. female	3.32	*1.97-5.59*
	Age	18-24 vs. 50+	0.76	*0.47-1.24*
		25-34 vs. 50+	0.42	*0.27-0.67*
		35-49 vs. 50+	0.44	*0.29-0.69*
All multiple drug combinations	Gender	Male vs. female	3.34	*1.98-5.61*
	Age	18-24 vs. 50+	0.84	*0.51-1.36*
		25-34 vs. 50+	0.43	*0.27-0.69*
		35-49 vs. 50+	0.40	*0.26-0.63*

Table 9.10 Adjusted odds ratios of getting killed when driving with various substances in Sweden, including confidence intervals. Gender and age effect.

Substance	Effect		Adjusted OR	*C.I.*
Amphetamine	Gender	Male vs. female	0.98	*0.65-1.49*
	Age	18-24 vs. 50+	2.24	*1.35-3.72*
		25-34 vs. 50+	0.51	*0.26-1.02*
		35-49 vs. 50+	0.67	*0.42-1.07*
Benzoylecgonine	Gender	Male vs. female	0.98	*0.65-1.49*
	Age	18-24 vs. 50+	2.21	*1.33-3.70*
		25-34 vs. 50+	0.50	*0.24-1.01*
		35-49 vs. 50+	0.69	*0.43-1.11*
Cocaine	Gender	Male vs. female	0.98	*0.65-1.49*
	Age	18-24 vs. 50+	2.21	*1.33-3.70*
		25-34 vs. 50+	0.50	*0.24-1.01*
		35-49 vs. 50+	0.69	*0.43-1.11*
Cannabis	Gender	Male vs. female	0.98	*0.65-1.49*
	Age	18-24 vs. 50+	2.26	*1.36-3.76*
		25-34 vs. 50+	0.48	*0.24-0.98*
		45-49 vs. 50+	0.69	*0.43-1.10*
Illicit opiates	Gender	Male vs. female	0.98	*0.65-1.49*
	Age	18-24 vs. 50+	2.21	*1.33-3.70*
		25-34 vs. 50+	0.50	*0.24-1.01*
		35-49 vs. 50+	0.69	*0.43-1.11*
Benzodiazepines and Z-drugs	Gender	Male vs. female	1.01	*0.67-1.53*
	Age	18-24 vs. 50+	2.26	*1.35-3.77*
		25-34 vs. 50+	0.50	*0.25-1.02*
		45-49 vs. 50+	0.73	*0.46-1.16*
Medicinal opioids	Gender	Male vs. female	1.01	*0.67-1.54*
	Age	18-24 vs. 50+	2.19	*1.31-3.66*
		25-34 vs. 50+	0.49	*0.24-1.00*
		35-49 vs. 50+	0.68	*0.42-1.09*
All multiple drug combinations	Gender	Male vs. female	1.03	*0.68-1.57*
	Age	18-24 vs. 50+	2.27	*1.36-3.80*
		25-34 vs. 50+	0.54	*0.28-1.06*
		35-49 vs. 50+	0.73	*0.45-1.16*