Using Data from Primary Care to Investigate the Epidemiology of Motor Vehicle Crashes

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Abstract

Background Motor Vehicle Crashes (MVCs) are a major cause of morbidity and mortality worldwide. This thesis explores the potential use of large databases of primary care medical records to investigate the epidemiology of MVCs in the United Kingdom and to supplement the data available from national statistics, which are believed to understate both the number of crashes, and the number of injuries which occur as a result.

Methods Details of all individuals enrolled in The Health Improvement Network (THIN) database whose primary care records indicated involvement in a MVC were used to calculate a series of summary measures describing the burden and consequences of MVCs. These were compared with data available from police accident reports and from hospital admissions. Data from THIN were used to conduct a series of studies of the impact of health and healthcare-related factors on the risk of involvement in MVCs. Specifically: a case-control study of the impact of modifiable lifestyle factors on the risk of MVC; case-crossover and self-controlled case-series studies of the effect of exposure to prescribed medications on the risk of MVC; a case-control study investigating the impact of disordered sleep on the risk of MVC; a case-control study of the risk of involvement in MVC among individuals with diabetes relative to the general population; and; a cohort study assessing whether there is evidence to suggest that involvement in a MVC may indicate the presence of undiagnosed disease which may impair driving performance.

Results The socio-demographic characteristics of individuals involved in MVCs recorded in THIN differ markedly from those recorded in police accident reports and hospital admissions data. There was no evidence of consistent trends in MVC incidence over time in the three data sources. Differences in data collection methodology and the severity and scope of crashes recorded may account for these variations. Evidence was found of an association between having a high Body Mass Index and involvement in MVCs, and between past (but not current) smoking and involvement in MVCs, however the recording of data on lifestyle-related exposures such as smoking and alcohol consumption in the age-groups most likely to be involved in MVCs was poor, complicating interpretation of these results. Current exposure to benzodiazepines and preparations containing opioid analgesics was found to increase the risk of involvement in MVCs, as was longer-term use of non-benzodiazepine hypnotics, selective serotonin reuptake inhibitors and antihistamines. No increased risk of MVC was observed with exposure to beta-blockers or tricyclic antidepressants. Individuals reporting insomnia or snoring to their primary care practitioner were found to be at increased risk of MVC, as were individuals with diagnosed sleep apnoea. This association was independent the use of sedative or antidepressant medications. Individuals with diabetes were not found to be at an increased risk of MVC compared with the general population, and there was no difference in risk between those receiving different forms of treatment. Involvement in a MVC was associated with an increased risk of being diagnosed with cardiac disease in the two years following the crash.

Conclusions Current sources of data about MVCs in the UK use different data collection methodologies, none of which is likely to accurately describe the overall burden of MVCs in the population. Primary care data remain a useful resource for those wishing to study the epidemiology of MVCs, but care must be taken to ensure that the uses to which the data are put are appropriate. Studies investigating lifestyle-related exposures are unlikely to produce reliable results as primary care recording of such factors is poor in the age-groups most likely to be involved in MVCs. Primary care data are more useful when studying the time course of pharmacological effects, or the effects of diagnosed illness, and can successfully detect previously observed associations. Primary care data is currently of little use in the study of injuries associated with involvement in MVCs as it is rare for both an injury and its proximate cause to be recorded. The investigation of methods by which this problem might be resolved is an important avenue for future research.

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1. INTRODUCTION

Overview

Motor vehicle crashes are a leading cause of mortality and morbidity worldwide. The World Health Organization estimates that in 2002, road traffic injuries accounted for 2.1% of all global deaths, killing approximately 1.2 million people and injuring between 20 and 50 million more. Road traffic injuries were the leading cause of injury mortality worldwide, and the 11th leading cause of overall global mortality (at approximately 19.0 deaths per 100,000 population) (1). The United Kingdom Department for Transport (DfT) reports that, in 2005, 3,201 people were killed in motor vehicle crashes in the UK and a further 271,017 were injured. Motor vehicle crashes also represent a considerable economic burden: the estimated total value of prevention of road traffic injuries in 2005 was estimated to be £12.8bn, corresponding to an average of £44,930 per casualty (2). A further £5bn was associated with non-injury costs (such as damage to property and police and insurance administration).

DfT statistics are based entirely on police-reported accidents. Police officers in the UK are required to complete a Road Accident Report Form (form STATS19) (3) for each accident "*involving human death or personal injury occurring on the Highway and notified to the police within 30 days of occurrence, and in which one or more vehicles are involved*" (defined in the accompanying instructions). In practice, it is recognised that there is significant under-reporting (4). This is thought to be due to a combination of ignorance of the legal obligation of members of the public to report such accidents to the police, the unwillingness of intoxicated or unlicensed drivers to involve the police, and the fact that

injuries resulting from involvement in a reportable accident may not be immediately apparent. A 2006 DfT report investigating the impact of such factors on reporting of MVCs found that published studies comparing police and hospital records estimated that between 28% and 50% of casualties were not reported to the police (4).

The same report compared specific hospital records from the Gloucester Royal Hospital with local police accident reports and found that in the years 1996 to 2000, between 42% and 48% of accidents were not reported to the police. Furthermore, it was found that 50% of minor injuries and 38% of serious injuries recorded by the police could not be identified in the hospital records. This suggests that a large proportion of those injured in accidents seek treatment elsewhere – perhaps from their General Practitioner (GP) – or do not sustain injuries serious enough to require medical attention. Given that hospital data were found to omit casualties recorded by the police and *vice versa*, it seems likely that there are a further group of casualties unrecorded by both.

On the basis of this evidence it can reasonably be concluded that the official UK figures considerably underestimate the true overall human and financial costs of road traffic accidents in the United Kingdom. It is clear, then, that there is a need to investigate alternate sources of data which may be used (or combined with existing sources) to produce more robust measures of the burden of road traffic accidents in the United Kingdom.

One possible source of such data is the primary care medical record. In the United Kingdom National Health Service (NHS), General Practitioners occupy a "gatekeeper" position and are the normal first point of contact for non-emergency patients requiring advice or treatment. The GP is responsible for treating minor injuries and ailments and for the routine management of chronic conditions. Patients are referred onward to specialist secondary care practitioners for further investigations or for specialist treatments where necessary. Secondary care institutions routinely send back summaries of the investigations undertaken and treatments given along with details of any required changes to the patient's medication and management. Patients who present directly to secondary care institutions (for instance at Accident & Emergency Departments) are normally asked to give the contact details of their GP in order that they may be notified of the reason for attendance, and the nature of any treatment given. Each patient's primary care records therefore contain a comprehensive summary of their medical history and their use of NHS services.

In recent years, there has been a drive to computerise the storage and maintenance of medical records, culminating in the ongoing NHS national programme for IT, which is intended to eventually provide a centralised, nationally networked, records storage system allowing detailed patient information to be accessed and updated by practitioners throughout the NHS. Whilst this work has yet to be completed, mature computerised practice management systems have been available in primary care settings for many years, simplifying the management of large practices and to reducing the need

to safely store and maintain large quantities of paper-based records, This has led to the creation of research databases which aggregate data extracted from the medical records storage systems at large numbers of primary care practices. These databases contain vast quantities of prospectively collected medical and lifestyle data for millions of people around the UK and are of tremendous value in the field of epidemiological research, allowing large-scale observational studies to be conducted without the need for time-consuming and expensive data collection.

The use of such primary care databases offers a number of potential benefits to the field of road safety research. The large samples of the UK population for whom data are available may permit the calculation of far more inclusive estimates of the burden of road traffic accidents in the UK. Furthermore, the availability of data on many clinically relevant lifestyle factors, as well as on medical treatments and diagnoses permits the study of their impact on the risk of involvement in MVCs. This thesis uses data from The Health Improvement Network (THIN), one such database, to describe the recording of road traffic accidents in primary care records and to examine the effects of a number of lifestyle and healthcare related factors on the risk of road traffic accident.

The Health Improvement Network

Data Collection

The Health Improvement Network (THIN) is a large database of primary care records from General Practices around the United Kingdom. THIN data may be divided into three broad classes – vision data, other computerised data and historical data. Vision data are extracted from the Vision patient management system, a software package produced by In Practice Systems (London, UK), which is used to electronically store patient records at all participating practices. Patient records (stripped of identifying details) are extracted on a regular basis by means of a secure internet connection and collected by EPIC (London, UK), the company responsible for assimilating the raw data into the final THIN database. Vision data contain basic demographic details of all currently and previously registered patients, all diagnoses and clinically relevant recordings made by (or reported to) the practitioner, all prescriptions issued and in more recent records, details of tests ordered (and the results), details of occupation and information regarding a range of lifestyle factors which may affect health.

Practices are recruited via the partnership between EPIC and In Practice Systems, and are paid for the use of their data. In order to join THIN, each practice must meet minimum quality control standards for data entry as laid down by EPIC. These standards are regularly updated to reflect changes in NHS requirements for data collection and storage. The recording of information relating to a series of key conditions and exposures is regularly audited to

ensure that each practice's recording falls within the normal range. Where there is cause for concern about the quality of recording in a particular practice, that practice may be suspended from the database until the problem is corrected or removed altogether if issues persist.

Where practices have used other computerised patient management or prescribing systems prior to the installation of Vision, other computerised data may be available. The quality and scope of this data varies according to the system previously in use and the ease with which records may be converted and transferred to Vision. Historical data, derived from paper records or entered in the course of routine care, may also be present. These data are of somewhat limited use as not all practices choose to systematically transfer older, paper-based records into Vision, introducing a risk of bias. Such information may be omitted altogether, may only be present for currently registered patients, or may include only those diagnoses and events considered relevant to each patient's ongoing care.

A number of different iterations of THIN are available, reflecting different stages of the project's development. Major versions are named according to the number of participating practices at the time of data assimilation. For example, THIN 255 contains data from 255 practices throughout the UK. Within each major version, there may be a number of sub-versions relating arising from periodic updates to the collected data. For example, THIN 255 (November 2004) contains data from 255 practices, where the latest date of data extraction was in November 2004.

THIN data are supplied in the form of five tables; the patient table, the medical table, the therapy table, the additional health details (AHD) table and the postcode variable indicators (PVI) table. Each row of each table contains a unique practice identification code and a unique (per practice) patient identification code, which together form a unique identifier for individuals within the database. It should be noted that there is currently no mechanism by which patients transferring from one THIN practice to another may be tracked, so certain individuals may appear multiple times within the database. This is not a major concern when carrying out analyses dealing exclusively with data relating to incident events and diagnoses, but may complicate the interpretation of historical data.

Data Format

The patient table (Table 1) contains basic demographic and registration details about each patient, including (where applicable) the practice[A] and patient[B] identifiers, year of birth[D] (and month, for patients aged 16 or younger), sex[F], a unique (per practice) household identifier[E], date of registration[G], a code indicating registration status[H] (e.g. active, inactive, transferred out) date of transfer out of practice[I], a code indicating the reason for registration or transfer[J], date of death[K], the date of practice computerisation[L], the date of introduction of Vision at the practice[M], the date of last data collection from the practice[N] and a quality-control flag indicating the integrity of the data for that patient[C] (a minority of patient records exhibit problems with the dating of entries, such as consultations recorded after death, death or transfer dates earlier than registration date, long periods without any data recording, which

are identified by this flag, allowing researchers to decide to include or exclude them from study as appropriate to the investigation in question). It is important to note that household identifiers relate to individual addresses, rather than dwellings. Individuals living in different flats or apartments within the same building may therefore have the same household identifier, despite not forming part of the same household. The date of computerisation is the date from which the practice began routinely issuing prescriptions using Vision or a previously installed system.

Table 1: Sample extract from the patient table

prac[A]	patid[B]	patflag[C]	yobstring[D]	famnum[E]	gender[F]	regreal[G]	regstat[H]	xferreal[I]	regrea[J]	deathreal[K]	compdate[L]	visdate[M]	lastdate[N]
a1234	02Gh	A	19710000	12317	1	19761201	2		0		19980901	19992804	20041102
a1234	02Dy	A	19740000	12183	2	19761202	2		0		19980901	19992804	20041102
a1234	02CG	A	19680000	12091	1	19761203	5	20030114	30		19980901	19992804	20041102
a1234	02LS	A	19630000	12552	1	19761204	2	20031209	99	20031209	19980901	19992804	20041102
a1234	005i	A	19670000	2865	2	19761205	2				19980901	19992804	20041102
a1234	001F	A	19460000	587	2	19761206	5				19980901	19992804	20041102
a1234	001Q	A	19720000	587	1	19761207	5				19980901	19992804	20041102
a1234	001W	A	19640000	4167	1	19761208	2				19980901	19992804	20041102
a1234	00?M	A	19430000	1463	2	19761209	2				19980901	19992804	20041102
a1234	00@S	A	19460000	1527	1	19761210	2				19980901	19992804	20041102
a1234	00?I	A	19280000	2344	2	19761211	2				19980901	19992804	20041102
a1234	00aM	A	19610000	3889	1	19761212	2				19980901	19992804	20041102
a1234	00aW	A	19760000	880	2	19761213	5				19980901	19992804	20041102
a1234	00AY	A	19740000	4520	2	19761214	2				19980901	19992804	20041102
a1234	00B0	A	19720000	3695	1	19761215	2				19980901	19992804	20041102
a1234	00b2	A	19640000	3303	1	19761216	5				19980901	19992804	20041102

The medical table (Table 2) contains details of each observation or diagnosis made by, or reported to the general practitioner. Records are classified using Read Clinical Terms (5), a coded, hierarchical list of terms used in medical records. Practitioners can search the Read Term list within Vision using keywords and attach appropriate codes to each consultation record. In addition, some codes are generated automatically by Vision when practitioners use specialised data collection dialogs to record information about certain exposures and conditions (for example, Vision has a specialised dialog for

recording information about height, weight and body mass). The codes entered for each patient form the basis of the medical table. Each row of the table contains the practice[A] and patient[B] identifiers, a record quality indicator[E], a Read Term code[D] and an associated date[C]. The table contains one row per Read Term. Each consultation may therefore result in the addition of multiple rows of data.

Table 2: Sample extract from the medical table

prac[A]	patid[B]	evdate[C]	medcode[D]	medflag[E]	source[F]	episode[G]	nhsspec[H]	locate[I]
a1234	a123	20020300	G55..00	R	0	4	0	I
a1234	a123	19761001	7E04900	R	0	4	0	O
a1234	a123	19890601	7D19400	R	0	4	0	O
a1234	a123	19910410	K510200	R	0	4	0	O
a1234	a123	19980304	5372.00	R	0	4	0	O
a1234	a123	19990611	T1...00	R	0	4	0	I
a1234	a123	19991109	424..00	R	0	4	0	I
a1234	a123	20000118	7L17.00	R	0	4	0	A
a1234	a123	20000411	7L17.00	R	0	4	0	I
a1234	a123	20000518	7L17.00	R	0	4	0	A
a1234	a123	20000804	863..12	R	0	4	0	I
a1234	a123	20001121	G730.00	R	0	4	0	A
a1234	a123	20010115	9N1S.00	R	0	4	0	N
a1234	a123	20010220	9N1S.00	R	0	4	0	N
a1234	a123	20010622	9N1S.00	R	0	4	0	O
a1234	a123	20011219	1....00	R	0	4	0	I

By default, Vision applies the current date to any new entries made in a patient's record. Where an observation or diagnosis was made prior to the date of entry, it is necessary to change adjust the date manually. In practice, this is not always done. The date of any recording in the medical table may reflect either the date of entry or the date on which the observation was made. Dates of medical recordings may not, therefore, always be accurate. A study of data entry patterns in the General Practice Research Database (GPRD), the forerunner of THIN, found that the numbers of diagnoses apparently made in the first year

after registration are far higher than the numbers made subsequently, suggesting that recordings made during this period may reflect back-entry of data obtained from previous practitioners or from previous (computerised or paper-based) recording systems, rather than incident events (6). It is important to consider this issue when using THIN data for epidemiological studies.

Each row of the medical table also contains a set of codes indicating the source[F], location[I] and specialty[H] associated with each recording. Source codes indicate whether each observation or diagnosis derives from a consultation, a telephone conversation, a letter received by the GP (or a number of other possibilities). Location codes indicate where the observation or diagnosis was made (e.g. Within the practice, at the patient's home, at a hospital or clinic) and specialty codes indicate the medical specialty of the individual or service responsible (e.g. Oncology, renal, respiratory, mental health). Finally, there is code indicating whether the recording relates to a new event or an ongoing condition[G]. Each of these codes is only meaningful if the data are correctly entered into Vision, and may not be available where recordings derive from earlier computer systems. Their usefulness may therefore be somewhat limited.

The therapy table (Table 3) contains details of all prescriptions issued to each patient by the practitioner. Each row of the table contains the practice[A] and patient[B] identifiers, a quality control flag[E] and a multilex[D] code which uniquely identifies the preparation prescribed, the unit dose and the number of doses per packet. Vision, in common with some other systems previously in use at participating practices, is capable of producing printed prescriptions.

Preparations can be selected from a searchable list, and directions and quantities can be entered either through the prescribing interface or as free text. Where quantities and directions are entered through the interface, or the free text can be decoded automatically by EPIC, a series of codes are available describing the quantity prescribed[G], the daily unit dosage[M] (e.g. number of tablets, measures or injections) the length of prescription[H] (i.e. number of days treatment) and the directions for use[F] (e.g. 3 times a day, with food, on an empty stomach). Each row also contains the date of prescription[C], which is likely to be more accurate than the dates of other recordings in THIN owing to the convenience of using Vision to print prescriptions.

Table 3: Sample extract from the therapy table

prac[A]	patid[B]	rxdate[C]	drugcode[D]	therflag[E]	doscode[F]	rxqty[G]	rxdays[H]	rxtype[I]	opno[J]	seqnoiss[K]	maxnoiss[L]	dosgval[M]
a1234	ab12	19920107	97130998	Y	16	20	0	1	0	0	0	-1
a1234	ab12	19920902	97464998	Y	1	6	0	1	0	0	0	-1
a1234	ab12	19940113	97464998	Y	1	3	0	1	0	0	0	-1
a1234	ab12	19941228	97110997	Y	16	20	0	1	0	0	0	-1
a1234	ab12	19980806	94851997	Y	8	20	0	1	0	0	0	-1
a1234	ab12	19991110	93304998	Y	55	90	0	1	0	0	0	-1
a1234	ab12	20010619	93304998	Y	139	90	0	1	0	0	0	2
a1234	ab12	20011204	97110997	Y	48	20	0	1	0	0	0	4
a1234	ab12	20021113	98617998	Y	963	13	0	1	0	0	0	3
a1234	ab12	20040726	96974998	Y	1GZz	25	0	1	0	0	0	-1
a1234	c345	19990823	96379998	Y	4943	30	0	0	0	1	3	3
a1234	c345	19990923	97227998	Y	03mW	28	0	0	0	1	4	-1
a1234	c345	19990927	97227998	Y	03ns	84	0	0	0	1	84	-1
a1234	c345	19991007	96379998	Y	958	21	0	0	0	3	4	3
a1234	c345	19991014	97227998	Y	03mg	28	0	0	0	4	4	-1
a1234	c345	19991028	96379998	Y	743	21	0	0	0	2	4	3

The therapy table also contains a code indicating whether the prescription is novel, or part of an ongoing course of treatment[I]. Where the prescription is repeated, another code represents the number of times, in total, that the prescription has been issued[K]. Where preparations may be considered harmful or addictive in prolonged use, another code may be present indicating the maximum number of times the prescription may be issued[L]. These codes may

not always be reliable, as they depend on each subsequent prescription being issued specifically as a repeat in Vision. Where a prescription is only slightly modified (e.g. from one brand name to another), or an identical prescription is written afresh within Vision, the counter is reset and must be manually changed to reflect the true issue number. A final code indicates the identity of the practitioner responsible for issuing the prescription[J].

The AHD table (Table 4) is perhaps the most complicated of the THIN data tables. It is used to hold recordings which necessarily comprise multiple pieces of information; typically, measurements, test results, quantities and death certification data. Each row contains patient[A] and practice[B] identifiers, a quality-control indicator[E], an AHD code[D] indicating the record type, an associated Read Term code[H], a record date[C], and one or two AHD values[F,G] which contain explanatory data. The AHD table may be used to store measurements, in which case the first AHD value may indicate the units of measurement, and the second the measurement itself. Where an AHD record contains the result of a biochemical test, the values might relate to the unit of measurement and the measurement, or the measurement and the interpretation (e.g. normal/abnormal). The associated Read Terms may add contextual information to the record; for example, an AHD record for tobacco consumption might carry a Read Term indicating whether the recorded daily quantity relates to cigarettes or cigars, or whether the record relates to current or past tobacco consumption.

Table 4: Sample extract from the additional health details (AHD) table

prac[A]	patid[B]	evdate[C]	ahdcode[D]	ahdflag[E]	ahdval1[F]	ahdval2[G]	medcode[H]	nhsspec[I]	locate[J]
a1234	01ab	19940512	1003050000	R	0	0	1362.12	0	I
a1234	01ab	19960801	1003040000	R	0	0	137L.00	0	I
a1234	01ab	19990525	1002000010	R	4000	0	6584.00	0	O
a1234	01ab	20010914	1005010500	R	134	80	246..00	0	I
a1234	02cd	19921014	1003040000	R	0	0	137L.00	0	I
a1234	02cd	19930825	1005010200	R	56	23.3	22A..00	0	I
a1234	02cd	19950221	1005010500	R	128	74	246..00	0	I
a1234	02cd	19951011	1002550000	R	0	0	61L..00	0	I
a1234	02cd	20001220	1052000000	R	N	0	9N7..11	0	I
a1234	02cd	20020328	1001400152	R	0	0	4672.00	0	I
a1234	02cd	20020328	1005010200	R	59	24.5	22A..00	0	I
a1234	02cd	20020402	1001400289	R	0	0	4J...00	0	P
a1234	02cd	20030801	1005010200	R	59	24.5	22A..00	0	I
a1234	01AA	19960219	1002000001	R	4000	0	6564.00	0	I
a1234	01AA	19960219	1005010500	R	190	100	246..00	0	I
a1234	01AA	19991130	1005010100	R	1.67	0	229..00	0	I

Dates within the AHD table are subject to the same type of uncertainty as those within the medical table. For example, details of height, weight and tobacco and alcohol consumption might be collected on a form at the time of registration, but not entered until later. The date in the AHD record might reflect either the date that the form was completed, or the date on which the data were entered into the computer. The AHD table also contains details of the location[I] and specialty[J] associated with each record. These are subject to similar concerns to their medical table equivalents.

The PVI table (Table 5) contains information about the sub-postcode area (e.g. NG5-5 for NG5 5UE) in which each patient lives. Each line contains practice[A] and patient[B] identifiers, a 6-level indicator of building density[C] (e.g. 1=urban, 6=rural), a set of values[D-H] indicating the ethnicity of the local population (e.f. if percw[D]=1, the postcode falls into the quintile of national postcodes with the lowest proportion of white residents), a variable indicating the quintile of

postcodes with ascending levels of limiting long term illness among the local population[I], a set of values indicating levels of air pollution (quintiles of postcodes with ascending levels of nitrogen dioxide[J], particulate matter[K], sulphur dioxide[L] and nitrous oxides[M]), a value indicating into which quintile of postcodes with ascending levels of deprivation (as measured by Townsend Index (7)) the area falls[N], and the date on which the information was last updated[O]. All the variables are based on 2001 classifications.

Table 5: Sample extract from the postcode variable indicators (PVI) table

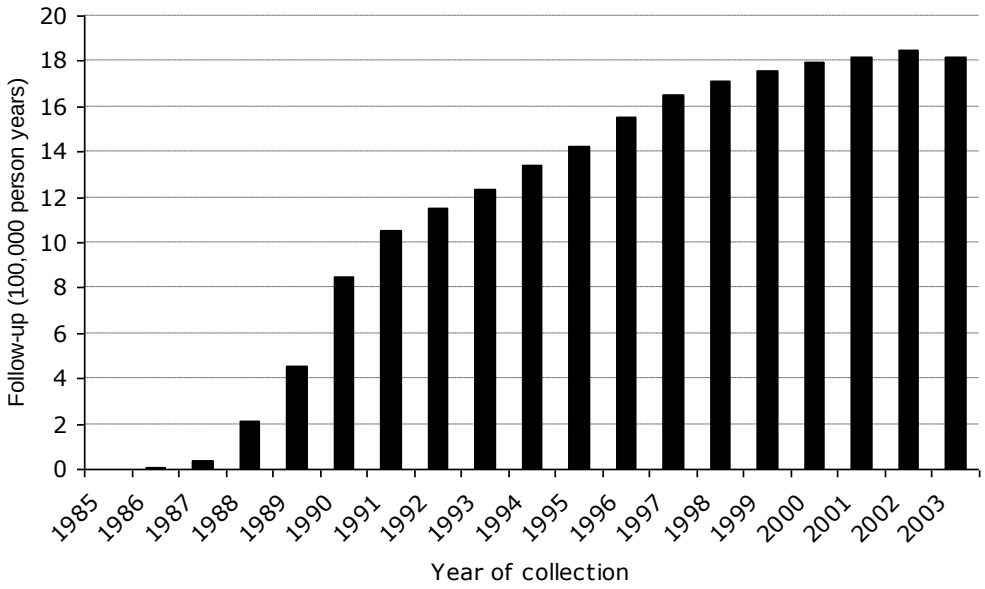
prac[A]	patid[B]	urbanrural[C]	percw[D]	percm[E]	percas[F]	bercb[G]	perco[H]	llti[I]	no211[J]	pm1012[K]	so2[L]	nox[M]	townsend[N]	date[O]
a1234	abc0	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc1	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc2	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc3	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc4	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc5	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc6	5	1	5	5	5	5	2	4	4	3	4	5	20060330
a1234	abc7	5	1	5	5	5	5	2	4	4	3	4	3	20060330
a1234	abc8	5	1	5	5	5	5	2	4	4	3	4	3	20060330
a1234	abc9	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abc9	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abca	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abcb	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abcc	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abcd	5	1	5	5	5	5	2	4	4	3	4	4	20060330
a1234	abce	4	1	5	5	5	5	2	5	4	4	5	3	20060330
a1234	abcf	5	1	5	5	5	5	2	4	4	3	4	2	20060330
a1234	abcg	4	1	5	5	5	5	2	5	4	4	5	3	20060330

The THIN Population

The earliest recordings in THIN date back to the first quarter of the 20th century. As discussed previously, such data are of limited value; of far greater importance are those recordings made after the introduction of computerised patient management systems. The earliest computerised data available in THIN 255 (November 2004), the version used for much of this project, date back to 1985. The amount of data available from this time is small, as only one participating practice had a computerised data-collection system in place at this

time. Figure 1 shows the increase in the available follow-up in each subsequent year.

Figure 1: Availability of computerised follow-up data in THIN 255 (November 2004), by year of collection



The available data increase steadily with each subsequent year of collection, reaching a plateau in the year 2000. A similar pattern is observed in later major versions of THIN (THIN 300 and THIN 314) as most practices nationwide had (THIN compatible) computerised data recording systems in place by this time. Data for the year 2004 are not presented here as they are incomplete in this revision of THIN-255.

Figure 2 shows the equivalent graph for data collected using the Vision system. The plateau occurs much later (2002) in these data. This is due to practices switching from other systems to Vision. The plateau occurs later in each

subsequent major version of THIN for the same reason. The plateau typically occurs approximately two years before the date of first release of each major version as EPIC stipulate that Vision must have been in productive use for more than one year before a practice may join THIN. Once again, data from the year 2004 are excluded as they are incomplete in this revision.

Figure 2: Availability of follow-up data collected using Vision in THIN 255 (November 2004), by year of collection

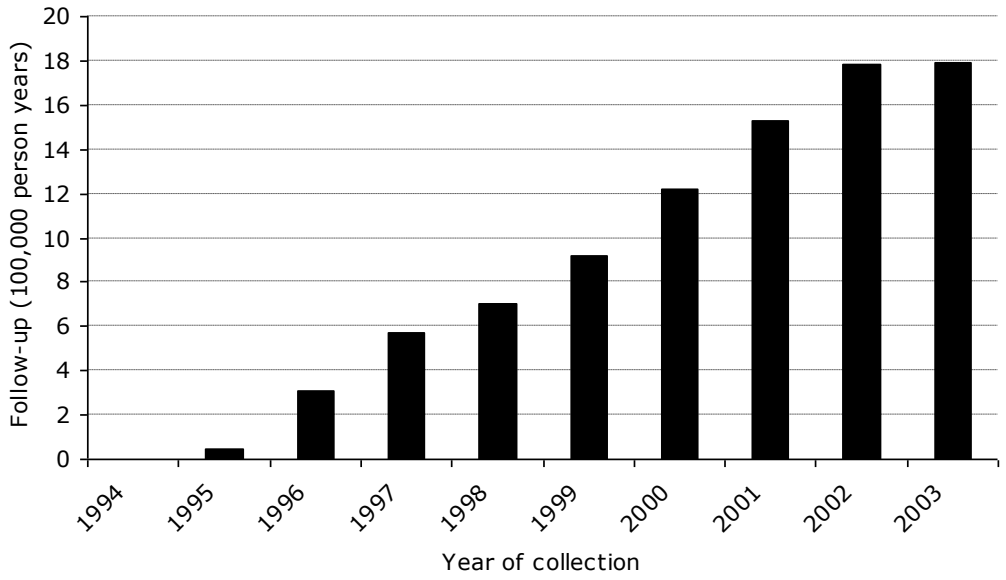


Table 6 shows the composition of the 2003 THIN-255 (November 2004) population and the 2003 United Kingdom general population broken down by age and sex. The age structure of both populations is approximately vertical up to age 59, with a slow decline thereafter. There are approximately equal proportions of males and females within each population up to age 69, with a decline in the proportion of males thereafter (due to the greater longevity of

women in general). There is minimal difference in the observed proportions between data derived from Vision, and the combined computerised data. Some slight differences exist between the structures of the THIN population(s) and the general population, but these are very small. Overall, it can be concluded that the THIN population reflects closely the age-structure of the United Kingdom population.

Table 6: Comparison between THIN 255 (November 2004) population and the United Kingdom population by age and sex, 2003

Age (years)	Percent Population in each 5 year age band			Percent Males in each 5 year age band		
	General Population*	THIN Population**		General Population*	THIN Population**	
		All computerised data	Vision data only		All computerised data	Vision data only
0 to 4	5.66%	5.31%	5.32%	51.23%	51.07%	51.06%
5 to 9	6.10%	5.91%	5.91%	51.20%	51.07%	51.06%
10 to 14	6.50%	6.42%	6.42%	51.27%	51.23%	51.24%
15 to 19	6.43%	5.98%	5.98%	51.43%	51.33%	51.34%
20 to 24	6.23%	5.98%	5.99%	50.17%	49.86%	49.84%
25 to 29	6.14%	6.32%	6.34%	50.03%	49.90%	49.91%
30 to 34	7.41%	7.67%	7.69%	49.61%	50.67%	50.68%
35 to 39	7.92%	8.15%	8.16%	49.59%	51.23%	51.25%
40 to 44	7.39%	7.54%	7.54%	49.55%	51.33%	51.35%
45 to 49	6.50%	6.63%	6.63%	49.51%	51.04%	51.04%
50 to 54	6.30%	6.44%	6.43%	49.50%	50.77%	50.79%
55 to 59	6.42%	6.60%	6.59%	49.44%	50.51%	50.52%
60 to 64	4.95%	5.06%	5.05%	48.90%	50.05%	50.10%
65 to 69	4.48%	4.46%	4.44%	48.15%	49.00%	49.00%
70 to 74	3.96%	3.91%	3.89%	45.84%	46.21%	46.22%
75 and over	7.61%	7.62%	7.60%	37.40%	37.53%	37.48%

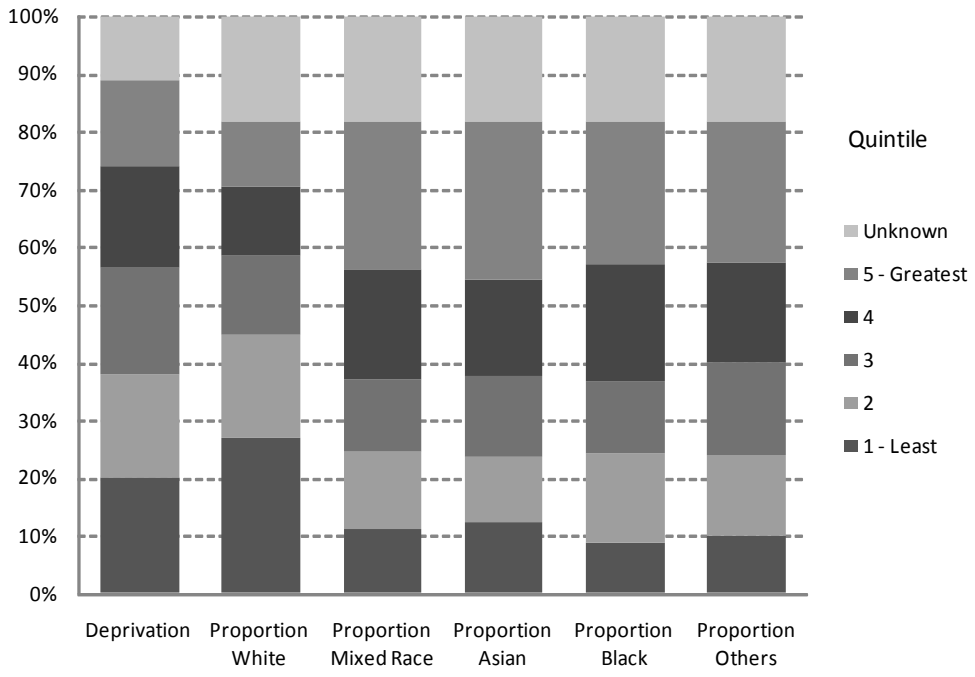
* Source: UK Office of National Statistics, mid-year population estimate.

** Based on available follow-up time in THIN-255 (November 2004) population

Figure 3 shows the proportions of the THIN population living in postcode which fall into each quintile of deprivation (as measured by Townsend Index) and local area ethnicity. In a completely nationally representative population the lower 5 segments of each column would be expected to be of equal size. This is not the case in the THIN population – the graph suggests that whilst the proportions falling into the mid-quintiles are similar, the most deprived quintile of the UK population is slightly under-represented in THIN 255, whilst the least

deprived quintile is slightly over-represented. The ethnicity data suggest that the white population is substantially under-represented, whilst the ethnic minority populations are substantially over-represented, although the large proportion of the population for whom ethnicity data are not available (~20%) make it difficult to form firm conclusions.

Figure 3: Proportion of THIN 255 (November 2004) population living in postcode areas falling into UK national quintiles of deprivation and ethnicity



Aims and Objectives

The specific aims and objectives of this thesis are:

- To use data from The Health Improvement Network to describe the incidence and severity of motor vehicle crashes in the United Kingdom, stratified by socio-demographic group.
- To compare the estimates obtained using THIN data with those available from police accident reports and from hospital reports.
- To use data from THIN to investigate the effect of modifiable lifestyle factors on the risk of involvement in MVCs.
- To investigate the effects of taking prescribed medications on the risk of involvement in MVCs
- To explore the impact of diagnosed illnesses on the risk of MVCs and to test the hypothesis that involvement in a MVC may predict the subsequent development of diseases which may impair driving ability.

Role of Candidate

The candidate was provided with an initial extract of THIN data containing the records of all individuals involved in an MVC at any time. The candidate carried out all analyses, literature reviews and designed all the studies reported in this thesis, with assistance from other members of the Division of Epidemiology & Public Health as described in Appendix III.

2. MOTOR VEHICLE CRASH RECORDING IN THIN

Clinical Coding of Motor Vehicle Crashes in THIN

The Read Term list contains a large number of terms relating to MVCs. The more detailed terms contain information about the type of road user and vehicle involved, whether each individual was driving or a passenger (in the case of car occupants or motorcyclists) and where they were seated in or on the vehicle. The Read Term list was searched to obtain all terms relating to accidents involving motor vehicles which have been used in THIN records. The list of codes obtained, and the number of recordings associated with them in THIN-255 (November 2004) are given in Table 7. In practice, the highly specific terms are rarely used (presumably because selecting the correct term can be somewhat time-consuming). The vast majority of crashes recorded in THIN are described simply as "Motor Vehicle Traffic Accident (MVTA)". In most cases it is therefore impossible to determine whether an individual involved in a MVC was driving, a passenger, a pedestrian or another road user. This is an important limitation of the THIN data.

Table 7: Numbers of occurrences of MVC recordings in THIN 255 (November 2004)

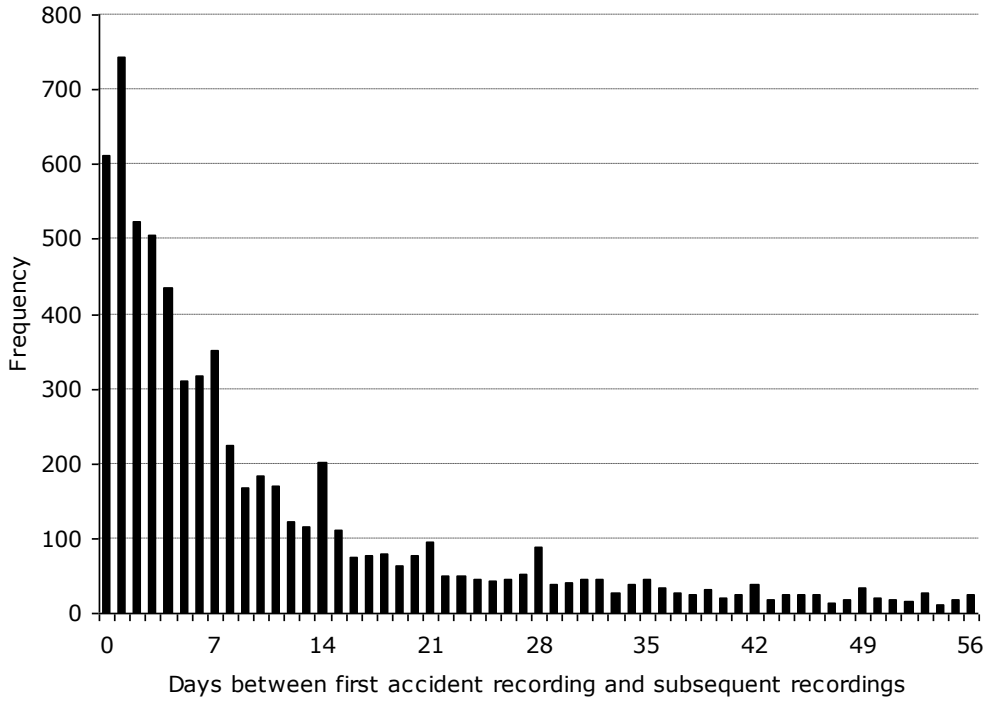
Read Term	Number of Uses
Motor Vehicle Traffic Accidents (MVTA)	101,016
Other road vehicle accidents	21,267
Motor vehicle accident NOS	2,162
[X]RTA - Road Traffic and other transport accidents	1,017
Road vehicle accident NOS	165
MVTA involving collision with other vehicle	84
Other motor vehicle traffic accident with collision on road	74
MVTA+Coll+other vehicle NOS - motor vehicle driver injured	43
[X]Traffic and other transport accidents	21
MVTA due to loss of control, without collision, on the road	19
Other MVTA involving collision with another motor vehicle	19
Motor vehicle traffic accident of unspecified nature	17
Motor vehicle traffic accident, unspecified	16
MVTA - motor vehicle out of control - driver falling asleep	16
Motor vehicle collision NOS	15
MVTA involving collision with other vehicle NOS	13
MVTA involving collision with pedal cycle	13
MVTA involving collision - motor vehicle + road boundary	10
Total	**125,987**

A minority of individuals have multiple accidents on record (Table 8). There are, however, a number of reasons to suspect that most of these do not truly reflect new accidents. Firstly, a large number of these multiple recordings are made on the same day as the first accident, or the day after (Figure 4) – possibly due to accidental double entry, or the practitioner using multiple Read Terms to describe the circumstances of each accident. Secondly, the majority of these subsequent recordings are made in the four weeks immediately after the first accident – it is somewhat implausible that accidents would occur in such quick succession. Finally, there are peaks in the number of recordings at weekly intervals following the first recording, suggesting that these relate to follow-up appointments.

Table 8: Numbers of individuals with single and multiple MVC recordings in THIN 255 (November 2004)

Number of Accident recordings per individual	Frequency	%
1	94,815	87.33%
2	11,275	10.38%
3	1,825	1.68%
4	421	0.39%
5	146	0.13%
6	44	0.04%
7	13	0.01%
8	10	0.01%
9	8	0.01%
10	5	0.00%
11	3	0.00%
12	1	0.00%
15	1	0.00%
16	1	0.00%
18	1	0.00%
22	1	0.00%
28	1	0.00%
32	1	0.00%
Total	**108,572**	**100.00%**

Figure 4: Length of interval between first MVC recording and subsequent recordings in THIN 255 (November 2004)



As a consequence of these concerns, second and subsequent accident recordings are excluded from the analyses in this thesis, in order to avoid potential bias due to these spurious multiple recordings.

Comparison of summary statistics derived from THIN data with other UK data sources

The records of all individuals in THIN-255 (November 2004) with a recorded motor vehicle accident were extracted and cleaned. Records with no useable date of accident were excluded, as were records where the accident occurred within one year of the individual's registration at their practice, or where the

accident occurred prior to the introduction of computerised records at their practice. The raw numbers of accident records obtained are given in Table 9. The period of computerised follow-up was determined for each patient in the complete THIN population. The period was defined as starting on the latest of date of birth, date of patient registration and date of practice computerisation and as ending on the earliest of date of transfer to another practice, date of death and date of last data collection at the relevant practice. This information was used to calculate the sex-specific yearly total computerised follow-up (in persion-years) available in THIN, using STATA 9 (STATA Corp. TX, USA) for Windows XP. Patients whose records were flagged as incomplete or corrupt in the patient table were excluded from the calculation. These data were used as denominators in order to calculate crude yearly incidence rates of MVCs in THIN (Table 10 & Figure 5).

Table 9: Number of recorded MVCs in THIN 255 (November 2004) computerised follow-up, by gender (1990 to 2003)

Year	Number of accidents		
	males	females	**total**
1990	774	694	**1,468**
1991	1,365	1,260	**2,625**
1992	1,593	1,551	**3,144**
1993	1,778	1,639	**3,417**
1994	1,877	1,827	**3,704**
1995	1,991	1,927	**3,918**
1996	2,151	2,256	**4,407**
1997	2,398	2,423	**4,821**
1998	2,533	2,663	**5,196**
1999	2,799	3,004	**5,803**
2000	3,302	3,399	**6,701**
2001	3,584	3,648	**7,232**
2002	4,009	4,182	**8,191**
2003	4,162	4,115	**8,277**

Table 10: Incidence rates of MVCs in THIN 255 (November 2004) computerised follow-up, by gender (1987 to 2003)

Year	Incidence rate per 100,000 person years		
	Males	Females	Total
1987	289	269	**279**
1988	257	296	**277**
1989	293	257	**274**
1990	353	299	**325**
1991	330	292	**310**
1992	309	290	**299**
1993	315	281	**298**
1994	308	291	**299**
1995	302	284	**293**
1996	305	312	**309**
1997	313	309	**311**
1998	311	319	**315**
1999	331	348	**340**
2000	379	382	**381**
2001	403	403	**403**
2002	**444**	455	**450**
2003	455	441	**448**

Figure 5: Incidence rates of MVCs in THIN 255 (November 2004) computerised follow-up, by gender (1990 to 2003)

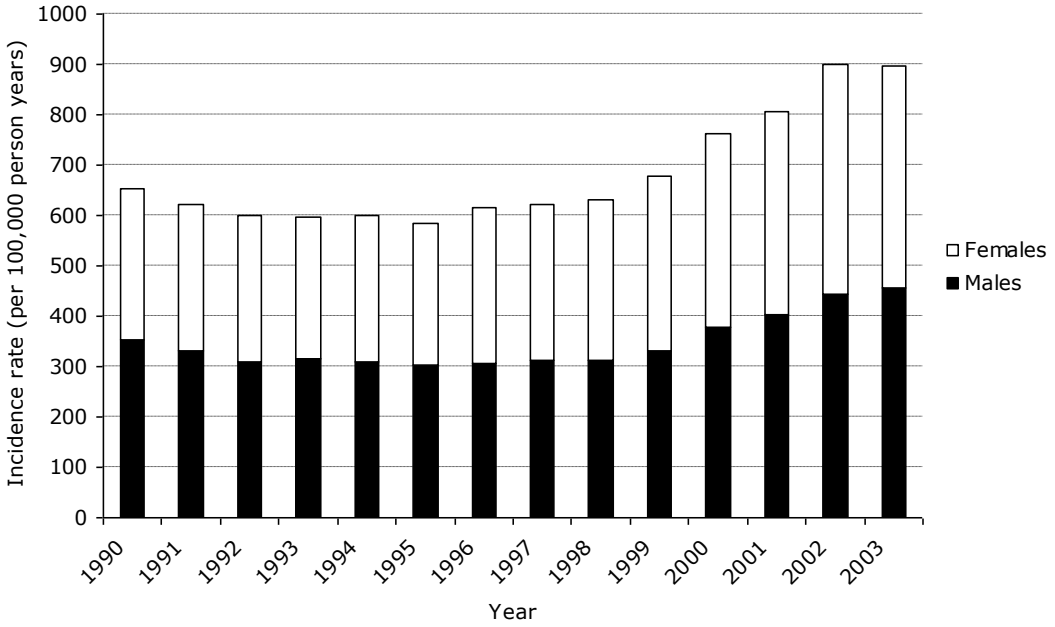


Table 11 and Figure 6 show the estimated incidence of road traffic accident casualties in Great Britain in the same time period. As discussed in the previous chapter, these data are based on written police accident reports (which are routinely passed to the UK Department for Transport) and therefore represent those crashes serious enough to warrant police attendance or which are voluntarily reported to the police by those involved. There is no specific definition of injury in the guidelines for completion of the STATS 19 accident report form; the decision as to whether the injuries sustained by those involved in a crash are serious enough to warrant the submission of a report is at the discretion of the officer responsible. It remains uncertain whether this results in under-reporting of minor injuries or internal injuries which may not be immediately apparent. Conversely, very minor contusions may be

inappropriately recorded as injuries. It is also unclear whether reporting practice may vary between forces or jurisdictions.

Two things are particularly notable; firstly, the incidence is far higher in the national statistics than in the THIN data (suggesting that police data may indeed record details of individuals with injuries not serious enough to warrant subsequent medical attention). Secondly, the national data show a continual declining trend not apparent in the THIN data.

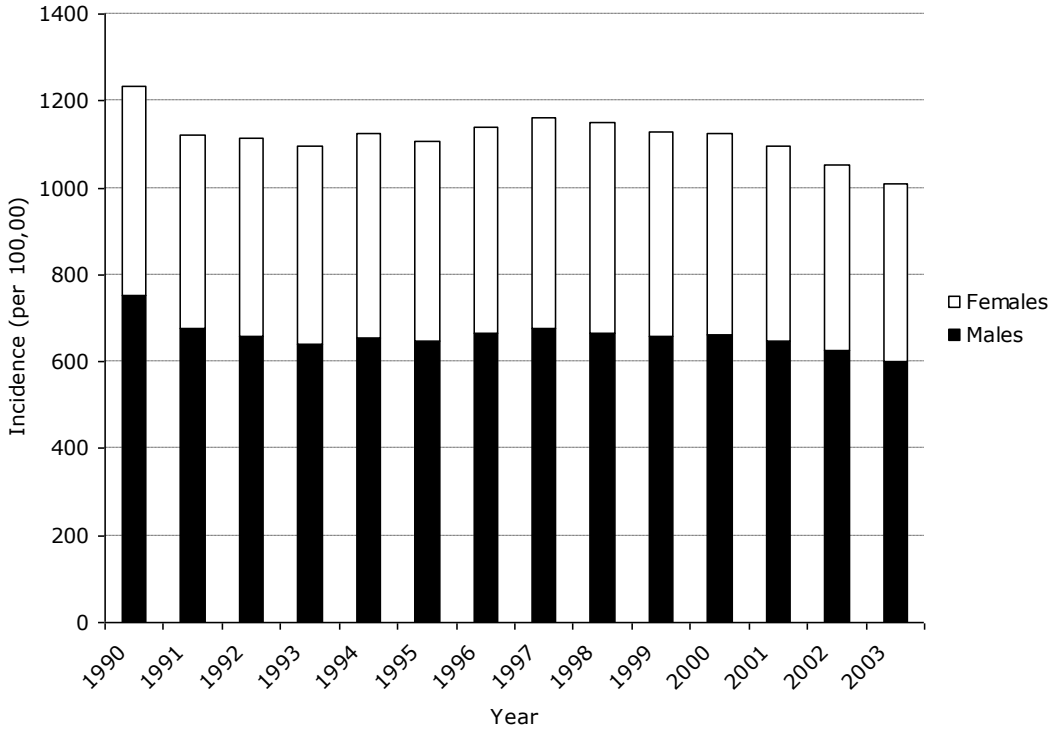
Table 11: Estimated incidence of MVCs resulting in injury, by gender (police reports, Great Britain 1990 to 2003)

Year	Road traffic casualties*			Mid-year population estimate**			Incidence (per 100,000)		
	males	females	total	males	females	total	males	females	total
1990	203,865	137,207	**341,141**	27,040,655	28,601,243	**55,641,898**	754	480	613
1991	183,224	128,063	**311,368**	27,125,852	28,705,511	**55,831,363**	675	446	558
1992	179,419	131,225	**310,753**	27,184,733	28,776,534	**55,961,267**	660	456	555
1993	174,619	131,424	**306,135**	27,241,061	28,837,276	**56,078,337**	641	456	546
1994	178,914	136,319	**315,359**	27,306,385	28,912,053	**56,218,438**	655	471	561
1995	177,365	133,221	**310,687**	27,399,687	28,975,981	**56,375,668**	647	460	551
1996	182,577	137,859	**320,578**	27,476,797	29,025,826	**56,502,623**	664	475	567
1997	186,398	141,282	**327,803**	27,555,516	29,087,472	**56,642,988**	676	486	579
1998	184,277	140,819	**325,212**	27,639,691	29,157,483	**56,797,174**	667	483	573
1999	182,392	137,727	**320,310**	27,759,976	29,245,445	**57,005,421**	657	471	562
2000	184,259	135,803	**320,283**	27,869,972	29,333,149	**57,203,121**	661	463	560
2001	181,167	131,631	**313,309**	28,007,991	29,416,187	**57,424,178**	647	447	546
2002	175,706	126,583	**302,605**	28,134,242	29,490,803	**57,625,045**	625	429	525
2003	169,492	121,001	**290,607**	28,275,201	29,575,930	**57,851,131**	599	409	502

*Source: UK Department for Transport

**Source: UK Office of National Statistics

Figure 6: Estimated incidence of MVCs resulting in injury, by gender (police reports, Great Britain 1990 to 2003)



To compare the recorded incidence of MVCs in primary care and police reports with data from secondary care, summaries of Hospital Episode Statistics (HES) data were obtained from the NHS Information Centre, UK. HES data derive from the admission forms and discharge forms (or, in recent years, their computerised equivalents) completed by the attending physician for each patient admitted as an in-patient to secondary care. The admissions and discharge records contain basic demographic details (such as age and sex and home postcode) of each patient, the reasons for admission and a brief summary of diagnoses made during the stay. HES data will therefore only record the most

serious crashes; those resulting in injuries severe enough to warrant in-patient admission to hospital.

Diagnostic data are recorded in the form of one or more International Classification of Diseases (ICD) (8) codes which may be directly selected by the physician (in the case of computerised records) or alternatively selected by the administrator responsible for compiling data from paper records, based on the physician's summary. The ICD code list was searched for all entries relating to MVCs and detailed summaries, broken down by year, age, gender and socio-economic status were requested from the Information Centre. The estimated incidences of MVC-related admissions, by age and gender, in these data are given in Table 12 and Figure 7.

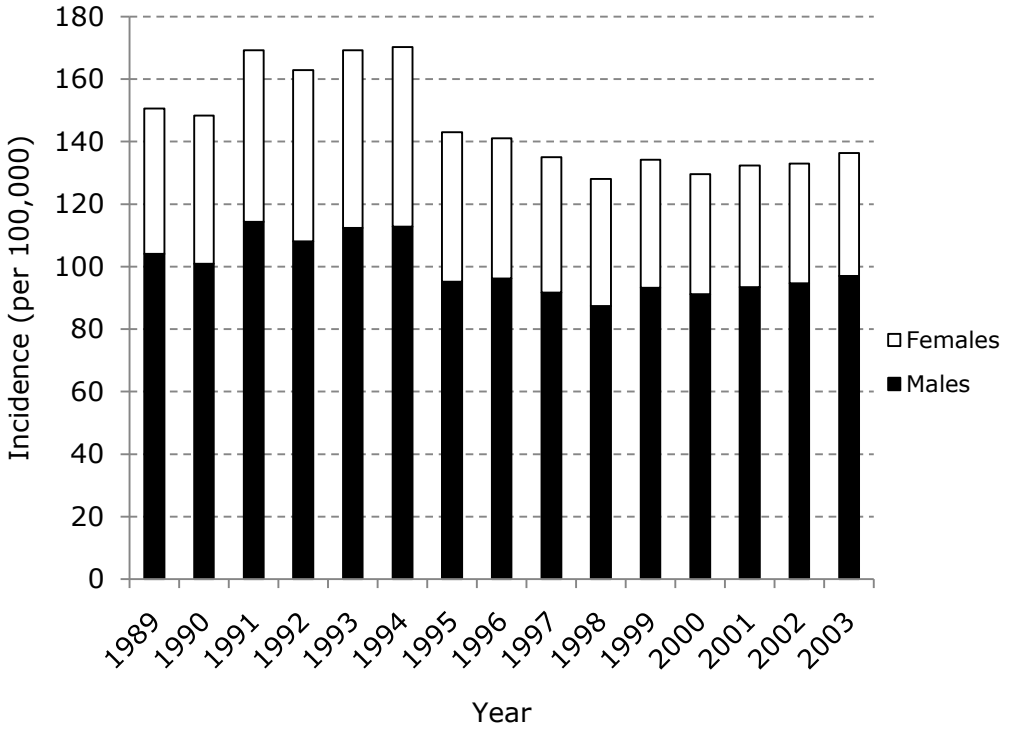
Table 12: Estimated incidence of MVCs resulting in hospital admission, by gender (England 1989 - 2003)

Year	MVC-related admissions*			Mid-year Population Estimate**			Incidence (per 100,000)		
	males	females	total	males	females	total	males	females	total
1989	24219	11353	**35572**	23,276,000	24,414,000	**47,690,000**	104	47	**75**
1990	23569	11630	**35199**	23,367,000	24,480,000	**47,847,000**	101	48	**74**
1991	26819	13482	**40301**	23,458,000	24,547,000	**48,005,000**	114	55	**84**
1992	25454	13486	**38940**	23,547,000	24,611,000	**48,158,000**	108	55	**81**
1993	26578	14008	**40586**	23,639,000	24,678,000	**48,317,000**	112	57	**84**
1994	26764	14240	**41004**	23,734,000	24,746,000	**48,480,000**	113	58	**85**
1995	22667	11877	**34544**	23,829,000	24,814,000	**48,643,000**	95	48	**71**
1996	23011	11158	**34169**	23,925,000	24,882,000	**48,807,000**	96	45	**70**
1997	22221	10851	**33072**	24,247,470	25,031,115	**49,278,585**	92	43	**67**
1998	21282	10195	**31477**	24,347,183	25,093,107	**49,440,290**	87	41	**64**
1999	22774	10307	**33081**	24,438,022	25,148,433	**49,586,455**	93	41	**67**
2000	22374	9672	**32046**	24,527,772	25,202,548	**49,730,320**	91	38	**64**
2001	22993	9850	**32843**	24,615,940	25,255,263	**49,871,203**	93	39	**66**
2002	23390	9684	**33074**	24,702,085	25,306,463	**50,008,548**	95	38	**66**
2003	24045	9975	**34020**	24,786,014	25,356,260	**50,142,274**	97	39	**68**

* Source: Hospital Episode Statistics © The Information Centre, UK

** Source: UK Government Actuary's Department

Figure 7: Estimated incidence of MVCs resulting in hospital admission, by gender (England 1989 - 2003)



The incidence of MVCs recorded in the HES data is considerably lower than that in both the THIN and the police report data, reflecting the fact that only serious injuries require hospitalisation. Similarly, the low incidence in THIN compared with the police report data suggest that many injuries recorded by the police may be very minor and not require medical attention. An alternative possibility is that injuries sustained in MVCs are not always recorded as such by general practitioners. Examination of a sample of 100,000 randomly selected patient records revealed that over 90% of consultations recorded in THIN carry only one Read Term (i.e. a single entry in the medical or AHD table on each unique date). It is therefore possible that injuries which require specific treatment may

be coded directly, but without an associated MVC-related Read Term. This explanation is supported by the low incidence of coded injuries associated with MVCs in the THIN population: when the records of all individuals involved in MVCs during the computerised follow-up period were searched for Read Terms indicating fractures or whiplash injuries within 14 days before and after the date of MVC, fewer than 200 such injuries were identified.

When entering information into Vision (and earlier data-collection systems) practitioners have the option of entering supplementary details of a consultation in text format. It is not currently possible for researchers to obtain full access to these additional data. It is possible, therefore, that injuries sustained in MVCs are typically referred to in the text portion of the record, but not coded separately (especially if there are multiple injuries). Conversely, it is possible that injuries may be coded directly and the cause of the injury (the MVC) may be referred to in the text. Depending on whether there is a systematic bias towards coding more severe injuries directly (something which it is not currently possible to adequately assess), Read Term coded MVCs in THIN may represent either a random sample of a greater overall number of MVCs reported to primary care practitioners, or may represent mostly comparatively minor incidents. This issue, and means by which such deficiencies in recording might be addressed, are discussed in greater detail in the concluding chapter.

In common with the THIN data, the HES data do not show the declining trend in recent years apparent in the police reports. This suggests that either the

proportion of accidents resulting in injuries serious enough to warrant medical attention is increasing, or that changes in the quality of MVC recording in one or more of these datasets have occurred in recent years. The increase in incidence of MVCs recorded in THIN approximately coincides with the introduction of the Vision software at participating practices, so it is possible that improvements in recording associated with the use of this more advanced system may have obscured any true declining trend, although the smaller increase in MVCs recorded in HES (a much more stable and longer established reporting system) over the same period suggests that this may, at least in part, reflect a true increase.

Figure 8 shows the breakdown of motor vehicle crash incidence rates by age and sex in the THIN population in 2003. These follow a similar overall trend to the equivalent DfT (Figure 9) and HES (Figure 10) data, rising to a peak by age 25 and declining steadily thereafter. There are two notable differences – in the police report and HES data, the peak occurs by age 20, and the incidence of road traffic injury among males is considerably greater than among females. In the THIN data this is reversed, suggesting either that women are more prone to accidents of the sort most likely to be recorded in THIN, or that women may be more likely to report minor accidents to their GP.

Figure 8: MVC incidence rate by age and sex in the THIN 255 (November 2004) population, 2003.

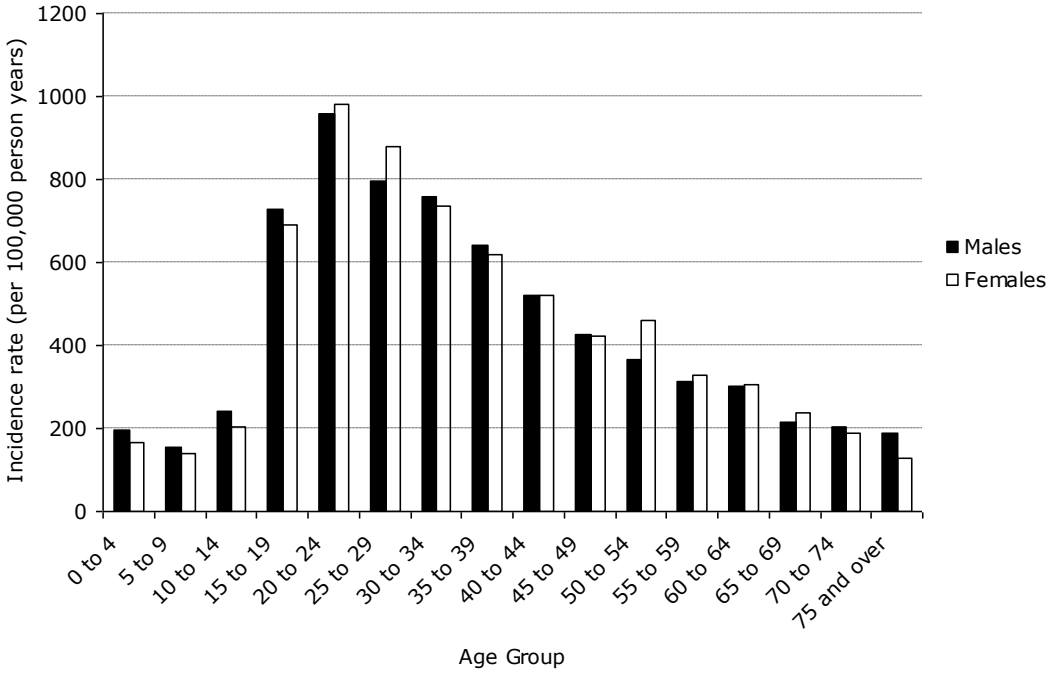


Figure 9: MVC incidence by age and sex in the Great Britain population, 2003

(Source: DfT)

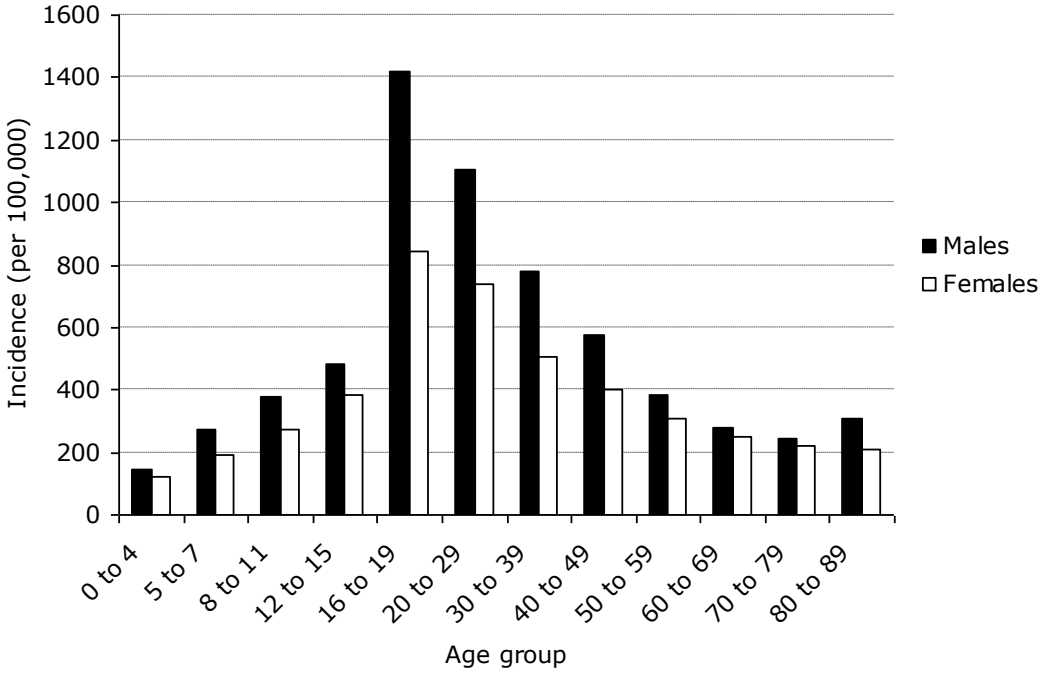


Figure 10: Incidence of MVCs leading to hospital admission in England by age and sex, 2003 (Source: NHS Information centre)

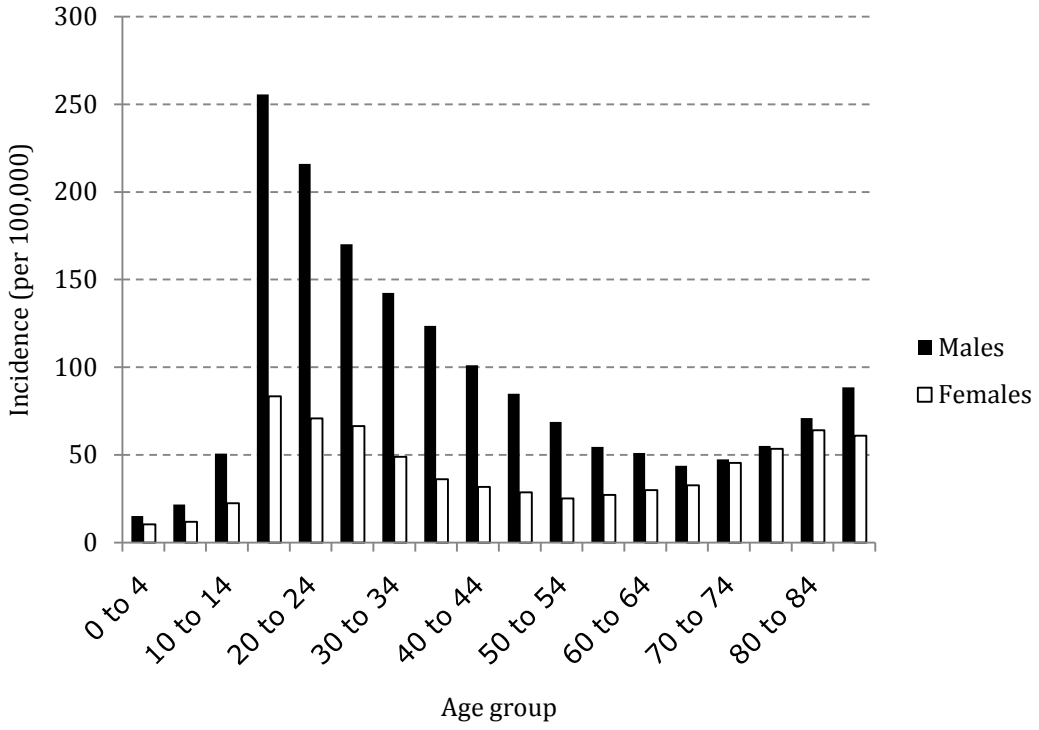


Figure 11 shows the breakdown of MVC recordings in THIN 2005 by quintile of Townsend Index of deprivation. MVCs appear most common in the least deprived quintile of the population in these data, with the lowest levels recorded in the most deprived quintile. This trend is reversed in the incidence data from hospital recordings broken down by quintiles of IMD2000 (9) score. (Figure 12). Both Townsend Indices and IMD2000 scores are calculated at area level (and matched to individual patients by postcode of residence). Townsend Indices are calculated based on area-specific unemployment rates, non-car ownership rates, non-home ownership rates and levels of household overcrowding in each area. IMD2000 scores are calculated using a greater range

of (33 different) metrics describing typical income, employment, housing conditions, geographic access to basic amenities, education levels and levels of disability in each area. Given that the IMD2000 score incorporates information similar to that used to calculate the Townsend Index, it is likely that the two measures will be broadly comparable, although the greater range of information included in the IMD2000 score may result in important differences in quintile-level classification between the two measures.

The DfT do not provide detailed breakdowns of MVC incidence by socio-economic status for a police report comparison, but the findings of a study (10) carried out in Lothian for the Scottish Executive, which linked police reports to census data, suggest MVC incidence is highest in the most and the least deprived groups (a U-shaped distribution). Neither of the healthcare datasets appears to capture this trend, although the population of Lothian may not be representative of the UK as a whole, so it is difficult to draw inferences from these discrepancies.

Figure 11: Breakdown of MVC recordings in THIN 255 by quintile of postcode-level Townsend deprivation index, 2003

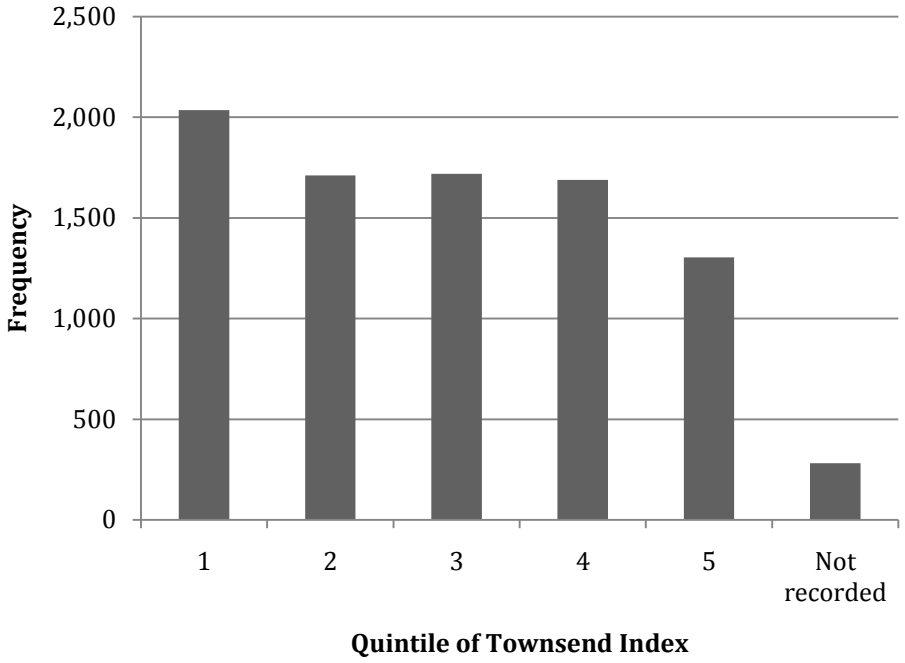
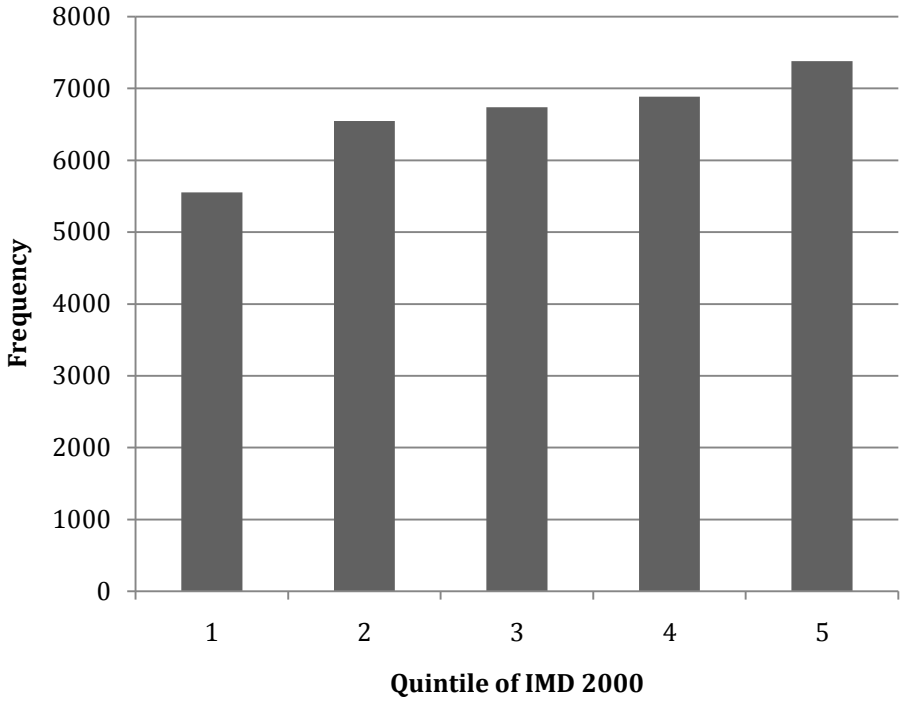


Figure 12: Breakdown of MVCs recorded in Hospital Episode Statistics by quintile of Indices of Multiple Deprivation 2000 score, 2003



Overall, the lack of consistency between the three data sources is striking. It is likely that the discrepancies described are in large part due to the differing methods of data collection. Police accident reports are likely to capture the largest proportion of all MVCs as they do not depend on the existence of an injury serious enough to warrant medical attention, however the lack of a proper definition of injury in the guidance for officers means that trends and patterns in these data should be viewed cautiously – there is no guarantee that MVCs are reported consistently over time, or even within different geographic areas over the same period. The probability of a given MVC being recorded in these data will depend upon its seriousness, police practice or manpower in the area in which it occurred (which, due to differences in the population structure

of different areas, may bias the demographic breakdowns of MVC incidence) and upon police priorities at the time it occurred. Data from general practice may provide a more consistent definition of MVCs over time and in different areas, but are effectively dependent on self-reporting are therefore likely to over-represent those groups most likely (or most easily able) to consult their GP. Data from Hospital Episode Statistics are the least likely to be affected by such biases as (a physician assessed) injury serious enough to warrant admission to hospital must be sustained for an individual to appear in these data, but consequently exclude information about the vast majority of individuals injured in less serious MVCs. None of these three data sources is likely to provide an accurate description of the overall burden of MVCs, or of trends over time. An additional problem, especially when attempting to investigate factors which affect the probability of involvement in a MVC, is that none of the three data sources reliably differentiate between drivers, passengers and other road users.

Whilst the comparisons between MVC recording in THIN and other data sources tend to suggest that neither is suitable for monitoring the incidence of MVCs, it is important to note that this does not preclude the use of THIN data to assess which factors may affect the risk of MVC. Such assessments depend entirely on the adequacy of the comparison made: provided the THIN population contains a reasonable cross section of the MVC types observed in the general population (even if they are not proportionally representative), comparative studies of the effects of potential risk factors should produce generalisable results so long as the referent group for any comparison is chosen so as to mitigate or eliminate

the effect of systematic distortions in the THIN population. For example, the differences in the age and sex-specific breakdowns of MVC incidence between the THIN population and other sources of data are not problematic provided that each age group and sex is well represented in the THIN population and any studies of comparative risk use appropriate statistical adjustment or matching processes to eliminate any potential distortions due to these factors.

3. The Effects of Modifiable Lifestyle Factors on the Risk of Involvement in Motor Vehicle Crashes – a Case-Control Study

Abstract

***Background*:** Previous research suggests that smoking and high body mass index (BMI) may increase the risk of MVC (Motor Vehicle Crash). This study investigated the individual and combined effects of these factors on the risk of involvement in MVCs.

***Methods*.** Data from THIN were used to conduct a nested case-control study. Cases were all individuals aged between 18 and 75 whose records indicated involvement in a MVC. 5 controls per case were selected from those individuals who had no recorded MVC and were matched to the cases by age, sex and general practice. The medical records of all participants were searched for recordings of smoking status and BMI.

***Results*:** After adjustment for potential confounding factors, having a BMI greater than 30 kg m^{-2} was associated with involvement in a MVC (OR=1.15, 95% CI 1.03-1.29 compared with those having a BMI of between 20 and 25 kg $m^{-2)}$. Being an ex-smoker was also associated with involvement in a MVC (OR=1.16, 95% CI 1.02-1.32 compared with non-smokers). No significant associations were found between current smoking and involvement in MVC.

***Conclusions*:** Being an ex-smoker and having a BMI greater than 30 kg m-2 were associated with an increased risk of involvement in a MVC, but these results may not be reliable due to poor recording of lifestyle related factors in the THIN dataset.

Introduction

Consumption of alcohol is a recognised risk factor for involvement in MVCs, but several studies have produced evidence which suggests that other modifiable lifestyle factors such as smoking (11-21) and having a high Body Mass Index (BMI) (18, 22) may also increase the risk of MVC. A high BMI has also been found to be associated with an increase in the severity of injuries due to involvement in MVCs (23-27). These factors are interrelated, as smokers are more likely to have extreme BMI measurements than non-smokers (28), and smoking and a high BMI both increase the risk of serious cardiovascular illnesses which may modify the risk of involvement in MVC. In addition, a high BMI can lead to the development of obstructive sleep apnoea syndrome, which is a recognised risk factor for MVCs (29). This study uses data from THIN to investigate the combined effects of smoking and BMI on the risk of involvement in MVCs, with adjustment for alcohol consumption and the presence of cardiovascular disease and/or obstructive sleep apnoea.

Initial methods and problems with exposure recording

Study population

Data from THIN 255 (November 2004) were used to construct a case-control population. Cases were defined as all individuals with a first recorded MVC dated on or after the 1st of January 1991, at least one year after the start of the computerised medical record and whilst they were aged between 18 and 75 years. MVCs recorded prior to 1991 were excluded as incidence rates of MVCs recorded in THIN increase steeply from nearly nil in the early years of the

computerised data to a relatively steady level by the end of 1990. Since incidence rates should be mostly unaffected by increases in population size over this period, it is likely that this increase is due to changes in quality of data entry during this period as practitioners become more adept at maintaining electronic records, or progressively move away from paper-based recording. The exclusion of events prior to 1991 helps to mitigate any potential bias or random error that might be caused by these trends.

The exclusion of events in the first year of each patient's computerised record helps to ensure that MVC (and other) recordings during the study period relate to incident events. As discussed earlier, recordings of diagnoses and events with the potential to impact patient health over a long period of time are most frequent in the early portion of a each patient's record, suggesting that early recordings may reflect back entry of paper records or records received from previous practitioners, rather than incident events or diagnoses.

Individuals aged less than 18 were excluded as the minimum age for driver licensing in the UK is 17 years. THIN records only indicate the year of birth of each patient over the age of 16, necessitating the assignment of an estimated month and day of birth for calculations involving age (1st July throughout this thesis). In view of the inaccuracy inherent in this approach individuals calculated to be aged 17 on the date of MVC were excluded as a substantial proportion might in fact have been 16 years of age. Individuals aged over 75 were excluded as they were felt to be the least likely to be involved in MVCs as

drivers (especially given that entitlement to drive requires medical review at age 70 in the UK).

SearchRC – a tool to simplify creation of Read Term lists describing exposures and illnesses in THIN

The Read Clinical Terms list is a hierarchical catalogue of terms used in medical records. The majority of data in THIN are stored using a system of codes which identify individual Read Terms. In order to identify the presence of a given medical condition (or other type of recording) in a patient's record, it is first necessary to define a complete list of the Read Terms which may be used by practitioners to describe that condition. This is a somewhat complicated process as the Read Term list is extremely long (~100,000 terms) and contains many duplicate codes, synonymous terms, typographical errors and abbreviations which might not be immediately obvious to a researcher attempting to create a list.

In view of the size and complexity of the Read Term list, identifying relevant codes by manual inspection alone is impractical for studies involving multiple conditions or exposures, and highly susceptible to oversights. Entirely automated keyword searching is also ineffective as it requires the researcher to anticipate every possible variation of terminology or abbreviation prior to running the search. The most practical approach is to take advantage of the hierarchical structure of the Read Term list, which groups similar terms together. Automatic searching can be used to identify likely terms, and the other terms in the same category can then be manually inspected to identify

variations which might also be relevant. Unfortunately, this is extremely time-consuming in practice, generally involving loading the Read Term list into a database application and using the "find next" function to work through all the possible matches (and surrounding terms for each match) for each individual keyword. It is also very easy to accidentally omit potentially important codes using this approach, as a simple "slip of the mouse" may lead to a match being skipped.

In order to address this issue I created SearchRC, a new command for STATA (STATA Corp. TX, US). SearchRC performs keyword searches on the Read Term list, and includes additional options to permit inspection of related terms.

SearchRC accepts queries in the following format:

```
searchrc keywords, [file() keepcat keeptree csen current]
```

SearchRC searches the Read Term list for the specified keyword(s). Either ***file()*** or ***current*** must be specified. ***File()*** allows the filename of the Read Term list to be specified. ***Current*** searches within the current loaded dataset. When using multiple keywords, searchRC will find all Read Terms containing one or more of the keywords. If a keyword contains a space, it should be enclosed in quotes. For example:

```
searchrc occupations "Medical History", current
```

Asterisks can be used to search within a description, rather than for the entire description. For example:

```
searchrc *ed, file("C:\data\readcodes.dta")
```

will find all Read terms ending in the letters "***ed***";

```
searchrc q*, file("C:\data\readcodes.dta")
```

will find all Read terms beginning with the letter "***q***"; and;

```
searchrc *heart*, file("C:\data\readcodes.dta")
```

will find all Read terms containing the word "***heart***".

The option ***current*** allows searching within previous results (AND searching). For example, to find codes for heart disease and Parkinson's disease one might use:

```
searchrc *heart* "*parkinson*", file("C:\data\readcodes.dta")

searchrc *disease*, current
```

The option ***keepcat*** additionally returns all other Read Terms in any category where a match is found. The option ***keeptree*** additionally includes all the Read Terms directly above each keyword-matched term in the Read hierarchy. The option ***csen*** activates case-sensitive keyword searching.

Using SearchRC to perform keyword searches with the keepcat option activated allows the complete Read Term list to be quickly cut down to a much shorter list which can be manually inspected to identify the relevant terms for a given

diagnosis, event or exposure, or to help identify additional keywords which should be included in the search. This considerably simplifies the process of compiling Read Term lists, and this software is now in widespread use in the Division of Epidemiology and Public Health.

In the remainder of this thesis, whenever SearchRC was used in the compilation of a Read Term list, the keywords used are listed.

Exposure definitions

The Read Term dictionary was searched using (a primitive prototype of) SearchRC to identify all terms relating to smoking (*smok*, *cigar*, *tobacco*), alcohol consumption (*alcoh*, *drink*) and body mass index (*mass*, *body*, *weigh*, *bmi*). The completed lists were used to extract all medical and AHD table records containing these terms for each patient. In addition, AHD table records describing daily cigarette and alcohol consumption and BMI and / or separate height and weight measurements were extracted.

Individuals were classed as smokers, former smokers and non-smokers according to the content of the relevant records. Although a substantial number of AHD table records (which should indicate levels of smoking) were obtained, the overwhelming majority of these contained a string of zeroes (the default value) in the ahdval1 field, and were therefore discarded. Records indicating a daily cigarette consumption of nil were interpreted as indicating a non-smoker. Records indicating that one or more cigarettes were smoked daily were interpreted as indicating a smoker.

Data from Read Terms indicating a specific level of alcohol consumption were combined with direct numerical recordings of alcohol consumption from the AHD table to create a categorical representation of daily alcohol consumption (based on the categories used by the relevant Read Terms). Records indicating only a subjective general level of consumption (light, moderate, heavy etc.) were discarded. The following categories were obtained: none; <1 unit / day; 1-2 units /day; 3-6 units/day; 7-9 units/day; and >9 units/day.

Data from Read Terms indicating a specific BMI range were combined with direct recordings of BMI from the AHD table and estimated values based on AHD recordings of height and weight to create a categorical representation of BMI. Records indicating only a subjective assessment of body mass (underweight, normal, overweight etc.) were discarded. The following categories were obtained: <20 kg m^{-2}; 20 to <25 kg m^{-2}; 25 to <30 kg m^{-2}; and ≥30 kg m^{-2}. Since the majority of BMI measurements eventually derived from numerical recordings, the use of BMI as a continuous measure was also explored.

Each of these main exposures was defined using the most recent recording prior to the date of MVC, but other possibilities were investigated, including using the record closest to the date of MVC (whether before or after), the earliest recording, or the recording nearest to the date of registration.

Read Term lists defining cardiac disease (*cardi* *angi* *heart* *ischae*), cerebrovascular disease (*cva* *stroke* *tia* *cerebrov*) and obstructive sleep

apnoea (*apne*, *apnoe*, *osa*, *obstructive*, *sleep*) were also created. Individuals were defined as suffering from each condition of interest if their AHD or medical records contained a relevant entry at any time more than 14 days prior to the date of MVC.

Frequencies of GP consultation were calculated for each individual to permit adjustment for the possibility that smokers, heavy drinkers and those with very high or low body mass may visit their GP more often (due to poorer general health) and therefore be more likely to report a minor MVC. The frequency of consultation was defined as the number of dates on which data were entered in each individual's AHD or medical table records prior to the date of MVC, and more than one year after the start of the computerised record, divided by the duration of this period. Recordings in the therapy table were excluded as repeat prescriptions may be issued without a formal consultation.

Statistical analysis

The data were analysed using conditional logistic regression models in STATA 9.1 for Windows XP. Univariate analyses were conducted to estimate the odds ratios (OR) of association between smoking and BMI exposure and MVC. Likelihood Ratio tests were used to determine whether categorical or continuous recordings of BMI provided the best fit. Where complete data for individuals were available, two further analyses were used to assess the combined effects of the lifestyle factors of interest on the risk of MVC. The first investigated the combined effects of smoking and BMI with adjustment for alcohol consumption, and the second additionally adjusted for the presence of

concurrent illnesses and any differences in consultation frequency (transformed to a loglinear scale due to non-normal distribution).

Problems with this method

A major problem was encountered when attempting to obtain useable measures of smoking status in this population. Individuals in the case population were considerably more likely to have a recording of smoking status than those in the control population (regardless of the timing of the records used). The proportions of smokers in the two populations were similar (approximately 25%), but the proportion of recorded non-smokers was approximately twice as large among the cases as controls. This pattern of data entry suggests a bias towards "positive recording". In effect, that practitioners are more motivated to note the presence of a clinically-relevant exposure than its absence. Cases had a higher average frequency of consultation than controls, so the observed differences in the proportion of non-smokers were presumably due to cases having more opportunities to have their non-smoking status recorded than controls. The net result was a substantial ascertainment bias, with an over-representation of non-smokers in the case population.

When attempting to analyse the data in this form, smoking appeared to have a strong and highly significant protective effect against involvement in MVC, however if all individuals with no recorded smoking status were classed as non-smokers, or if the "unknowns" were included as a separate category in the model, a small but significant positive effect was observed. Neither of these two alternative methods was felt to be particularly satisfactory, so the effects of

varying the exclusion criteria were investigated in the hope of equalising the probability of having a smoking status recorded in the two groups, minimising the effects of ascertainment bias.

Further analyses revealed that by restricting the population to individuals registered after the introduction of Vision at each practice, the proportions with known smoking status in the case and control groups could be approximately equalised. This is presumably a consequence of the fact that smoking status is requested as part of the process of adding a new patient to the Vision system, leading practitioners to enquire about smoking at the time of registration. Unfortunately, restricting the population in this way dramatically reduced the number of patients available, and broke the matching process, leading to many cases having no matched control due to the controls having been registered earlier. At this point it was decided to abandon the analysis and obtain a new case-control population properly incorporating this additional criterion.

Revised methods

A revised case-control population was obtained using data from the larger THIN 300 (July 2005) dataset in an attempt to mitigate the loss of statistical power due to the exclusion of pre-Vision patients. This version of THIN contains data from 300 general practices (including 1.49 million patients registered after the introduction of Vision at their practice) around the UK, collected up to July 2005. Cases were defined as individuals registered after the introduction of Vision at their practice whose records indicated involvement in a MVC whilst aged between 18 and 75 years. Individuals with a MVC recorded within 1 year

of the date of registration were excluded. The control population was randomly selected from those individuals with no recorded MVC, matched by age (±3 years), sex and practice. Each control was required to have a minimum of 1 year of computerised medical recording before the date of MVC of their associated case, to have been registered after the introduction of Vision at their practice, and to be living in a different household to the case. Where possible, 5 controls were matched to each case.

Data extraction

The most recent recordings of smoking status, BMI and alcohol consumption recorded more than 14 days prior to the date of MVC were extracted for each individual in the study population. Individuals were defined as suffering from cardiac disease, cerebrovascular disease or obstructive sleep apnoea at the time of MVC if their record contained any record contained a diagnosis of that condition in the same time period.

The treatment of BMI and smoking records in this analysis was exactly as before, but unfortunately the alcohol consumption data were far poorer in this population than previously (presumably due to the reduced duration of follow-up). Very few individuals (~30%) had a recording of alcohol consumption indicating a specific range or amount, so individuals were classed only as consumers or non-consumers of alcohol.

Frequencies of GP consultation were calculated for each individual to permit adjustment for the possibility that individuals visiting their GP regularly due to

ill health caused by smoking, alcohol consumption or high or low body mass may be more likely to report a MVC. The frequency of consultation was defined as the number of dates on which data were entered in each individual's medical and AHD table records more than 14 days before the date of MVC, and more than one year after the start of the computerised record, divided by the duration of this period.

Analysis

The data were analysed using conditional logistic regression models in STATA 9.1 for Windows XP. As before, univariate analyses were conducted to estimate the odds ratios (OR) of association between smoking and BMI exposure and MVC. Likelihood Ratio tests were used to determine whether categorical or continuous recordings of BMI provided the best fit. Where complete data for individuals were available, two further analyses were used to assess the combined effects of the lifestyle factors of interest on the risk of MVC. The first investigated the combined effects of smoking and BMI with adjustment for alcohol consumption, and the second additionally adjusted for the presence of concurrent illnesses and any differences in consultation frequency (transformed to a loglinear scale due to non-normal distribution).

A power calculation performed using Egret SIZ for MS-DOS (Cytel Software, Cambridge, MA) suggested that a population of 3,653 case-control sets would have 90% power to detect an Odds Ratio of 1.15 at the 5% significance level,

assuming a population of 57% males and 43% females, with 24% of women and 28% of men being current smokers, and a 3:1 control:case ratio.

Results

The basic characteristics of the study population are shown in Table 13. Cases and controls were well matched for socio-economic status. Smoking status at registration was available for 60% of the study population and data on the number of cigarettes smoked per day were available for 66% of smokers. Data on BMI were available for 79% of the population and data on alcohol consumption were available for 82%.

Table 13: Socio-demographic characteristics and lifestyle exposures of MVC cases and controls in THIN 300 (July 2005)

Characteristic	Cases		Controls	
	Male	Female	Male	Female
	(n=3383)	*(n=3760)*	*(n=16364)*	*(n=18386)*
Age at time of crash				
Years, median (interquartile range)	34 (27 – 41)	32 (25 – 40)	34 (28 – 42)	32 (26-40)
Quintile of Townsend deprivation index				
1st; least deprived, n (%)	716 (21.2%)	902 (24.0%)	3508 (21.4%)	4253 (23.1%)
2nd, n (%)	586 (17.3%)	684 (18.2%)	2783 (17.0%)	3394 (18.5%)
3rd, n (%)	595 (19.6%)	693 (18.4%)	3136 (19.2%)	3403 (18.5%)
4th, n (%)	628 (18.6%)	611 (16.3%)	2839 (17.4%)	3147 (17.1%)
5th; most deprived, n (%)	508 (15.0%)	486 (12.9%)	2462 (15.0%)	2401 (13.1%)
Not available, n(%)	350 (10.4%)	384 (10.2%)	1636 (10.0%)	1788 (9.7%)
*Body mass index (BMI)**				
BMI<20 kg m^{-2}, n (%)	199 (5.9)	392 (10.4)	931 (5.7)	1983 (10.8)
20≤BMI<25 kg m^{-2}, n (%)	1025 (30.3)	1501 (39.9)	5161 (31.5)	7245 (39.4)
25≤BMI<30 kg m^{-2}, n (%)	943 (27.9)	784 (20.9)	4504 (27.5)	3711 (20.2)
BMI≥30 kg m^{-2}, n (%)	455 (13.5)	556 (14.8)	1602 (9.8)	2281 (12.4)
not recorded, n (%)	761 (22.5)	527 (14.0)	4166 (25.5)	3166 (17.2)
*Smoking status**				
non-smoker, n (%)	605 (17.9)	974 (25.9)	3041 (18.6)	4926 (26.8)
ex-smoker, n (%)	249 (7.4)	298 (7.9)	966 (5.9)	1267 (6.9)
smoker, n (%)	1169 (34.6)	1153 (30.7)	5289 (32.3)	5300 (28.8)
not recorded, n (%)	1360 (40.2)	1335 (35.5)	7068 (43.2)	6893 (37.5)
*Alcohol consumption**				
non-consumers of alcohol, n (%)	222 (6.6)	316 (8.4)	980 (6.0)	1682 (9.2)
consumers of alcohol, n (%)	2509 (74.2)	2958 (78.7)	11859 (72.5)	13907 (75.6)
not recorded, n (%)	652 (19.3)	486 (12.9)	3525 (21.5)	2797 (15.2)
Consultation rate†				
uniquely dated GP recordings per year, median (IQR)	2.9 (0.8-6.3)	7.0 (3.5-12.4)	1.5 (0.0-4.6)	4.9 (1.6-10.0)
*Medical conditions**				
cardiac disease, n (%)	138 (4.1)	92 (2.5)	496 (3.0)	379 (2.1)
cerebrovascular disease, n (%)	17 (0.5)	13 (0.4)	78 (0.5)	68 (0.4)
obstructive sleep apnoea, n (%)	9 (0.3)	0 (0)	27 (0.2)	6 (0.0)

* *recorded up to 14 days prior to MVC*

† *based on period between 365 days after registration and 14 days before MVC*

The unadjusted analysis showed significantly increased risks of involvement in a MVC among individuals with a BMI of 30 kg m^{-2} or greater (OR=1.27 | 95% Confidence Interval CI: 1.17-1.38) relative to those with BMI of 20 to 25 kg m^{-2} Current smokers (OR=1.08 | 95% CI: 1.00-1.17)and ex-smokers (OR=1.24 | 95% CI: 1.10-1.39) were also at an increased risk of involvement in MVC relative to non-smokers (Table 14), as were individuals with a diagnosis of cardiac disease (OR=1.33 | 95% CI 1.14-1.56).

Table 14: Univariate and multivariate analysis of lifestyle-related risk factors for MVC in THIN 300 (July 2005)

Risk Factor	Unadjusted Model OR (95% confidence interval)	p	Adjusted Model A OR (95% confidence interval)	p	Adjusted model B OR (95% confidence interval)	p
smoking status						
non-smoker	1.00	-	1.00	-	1.00	-
ex-smoker	1.24 (1.10-1.39)	<0.01	1.23 (1.08-1.39)	<0.01	1.16 (1.02-1.32)	0.02
current smoker	1.08 (1.00-1.17)	0.05	1.05 (0.96-1.15)	0.27	1.02 (0.93-1.12)	0.67
	n=4,308		n=3,762		n=3,762	
body mass index (by category)						
BMI<20 kg m^{-2}	0.98 (0.88-1.08)	0.65	0.96 (0.84-1.10)	0.55	0.95 (0.83-1.09)	0.50
20≤BMI<25 kg m^{-2}	1.00	-	1.00	-	1.00	-
25≤BMI<30 kg m^{-2}	1.04 (0.97-1.11)	0.30	0.98 (0.89-1.07)	0.61	0.96 (0.87-1.05)	0.34
BMI≥30 kg m^{-2}	1.27 (1.17-1.38)	<0.01	1.25 (1.11-1.39)	<0.01	1.15 (1.03-1.29)	0.01
	n=5,815		n=3,762		n=3,762	

n=number of cases with complete data with at least one matched control with complete data

Model A : Adjusted for smoking status + BMI + alcohol consumption

Model B : Additionally adjusted for concurrent illnesses and frequency of consultation

In the multivariate analysis, after mutual adjustment for smoking status, alcohol consumption and BMI, having a BMI of 30 kg m^{-2} or greater (OR=1.25 | 95% CI: 1.11-1.39) and being an ex-smoker (OR=1.23 | 95% CI: 1.08-1.39) remained statistically significant, but there was no association between involvement in a MVC and current smoking (OR=1.05 | 95% CI: 0.96-1.15). Following adjustment for the effects of concurrent illnesses and for differences in frequency of

consultation, the associations between having a BMI>30 (OR=1.15 | 95% CI: 1.03-1.29) and being an ex-smoker (OR=1.16 | 95% CI: 1.02-1.32), and involvement in a MVC persisted.

Discussion

This is the first population-based study in the UK investigating the associations between smoking, BMI and alcohol consumption and involvement in a MVC. The results suggest that, following adjustment for potential confounding factors, having a BMI of greater than 30 kg m^{-2} is associated with a 15% increased risk of involvement in a MVC compared with those with a BMI between 20 and 25 kg m^{-2}, and being an ex-smoker is associated with a 16% increased risk of involvement in a MVC compared with a non-smoker. Current smoking was not found to be associated with an increased risk of involvement in a MVC.

The strengths of this analysis are the large size of the study population (covering 1.49 million individuals), the prospective nature of the data collection and the comprehensive coverage of significant medical events due to the universal coverage of health care in the UK and the gatekeeper role of primary care providers in implementing this system. The data used in this study were collected between 1994 and 2005 and are therefore relevant to the current driving conditions in the UK.

The analysis has two important limitations. The outcome indicator is specific for MVC, but the exact nature of each crash is unclear and it is not possible to determine whether those involved were driving, passengers or pedestrians. The

presence of non-drivers in the population would tend to introduce random error and reduce the magnitude of the observed associations. A more serious problem is the poor recording of lifestyle-related exposures in THIN. Data on smoking status, alcohol consumption and BMI were unavailable for 40%, 18%, and 21% of individuals respectively. Complete data on all exposures of interest were available for fewer than 50% of cases and controls, so there is much potential for distortion of the results due to ascertainment bias.

A number of previous epidemiological studies have reported associations between involvement in a MVC and smoking, predominantly in drivers, suggesting that smoking may impair the ability to drive safely, but none of these studies adjusted for alcohol use, BMI, and concurrent disease simultaneously. Case-control studies have found that smokers have an increased risk of involvement in a MVC (12, 13) and an increased risk of death due to involvement in a MVC compared with non-smokers (30), that those who routinely smoke whilst driving have an increased risk of involvement in a MVC compared with those who do not (18), and that smoking is more common amongst those who have had crashes, traffic code violations and licence suspensions than amongst those reporting no crashes or violations (11). Cross-sectional studies have also reported associations between smoking and increased risk of involvement in a MVC (15, 19) and traffic violations (15). Most recently, a cross-sectional study of 1,214 drivers attending health centres in the city of Zaragoza, Spain, found that the number of recorded MVCs was significantly higher amongst smokers when compared with non-smokers (OR=2.2), regardless of whether smokers smoked whilst driving or not (14).

Cohort studies have also produced similar findings. Analysis of surveillance data from a cohort of 7,863 petrochemical workers across the United States found that male smokers were 75% more likely to be involved in MVCs resulting in over 5 days absence from work between 1985 and 1987, but found no excess risk among ex-smokers (20). The risk of death due to MVC amongst smokers in a cohort of 82,461 participants in the United States National Health Interview Survey followed up between 1990 and 1995 was found to be 2.1 times that of non-smokers following adjustment for age, race, gender, level of education, marital status and level of alcohol consumption, but no adjustments were made for the presence of pre-existing medical conditions (17). Similarly, the risk of death due to MVC among smokers in a cohort of 64,319 Taiwanese males between 1982 and 2001 was found to be 1.9 times that of non-smokers after adjustment for age and alcohol use (21).

The observations in THIN, which suggest that being an ex-smoker but not a current smoker is associated with involvement in MVC, is at odds with those of earlier studies, which consistently demonstrate an association between being a smoker and involvement in MVC. In addition, the results obtained from THIN are implausible – it is difficult to conceive of a reason why ex-smokers should be more at risk of involvement in MVCs than current smokers.

The THIN population is very large, and should provide sufficient power to detect an association of the size suggested by previous findings, By far the most likely explanation for the absence of an association with current smoking is the poor quality of exposure recording in the THIN data. Surveys in primary care

also suggest that recordings of smoking status in GP records are often inaccurate (31). It is also likely that some of the discrepancy is a result of selecting cases solely as a consequence of having been involved in a MVC, while most of the existing literature has specifically focussed on drivers. This uncertainty over the precise nature of each MVC – in particular as to whether the case was driving or not - would tend to reduce the magnitude of any observed association towards unity if the effect was only present in drivers who smoke.

Explaining the presence of an association among ex-smokers in the absence of an association among smokers is more difficult. It is possible that a significant proportion of ex-smokers are in fact misclassified current smokers. Alternatively, the association between being an ex-smoker and involvement in MVAs may be a true one. Ex-smokers are, by definition, older on average than current smokers. Older individuals are more likely to have a record of smoking status. This may have made it possible to detect an association in this group whilst the poor ascertainment among younger individuals may have obscured any association among current smokers. Ex-smokers may have stopped smoking due to deteriorating health that may not have led to overt disease, but that may have impaired driving ability such as impaired vision (32), subclinical cardiac disease or respiratory problems (33). In addition, ex-smokers are likely to share behavioural characteristics with current smokers which may lead to an increased risk of MVC. Alternatively, this may simply be a chance (incorrect) finding.

The results of this study are consistent with previous findings that a high BMI is associated with an increased risk of MVC. A high BMI has also been linked with an increased risk of Obstructive Sleep Apnoea (OSA), which is an established risk factor for MVC (29), and although the results are adjusted for the presence of a diagnosis of OSA, it is likely that there is a significant prevalence of undiagnosed OSA in the THIN population (34). The association between increased BMI and involvement in a MVC may be a consequence of the presence of other subclinical health problems such as cardiovascular disease amongst those with high BMI (35). Alternatively, the relation between BMI and risk of involvement in MVC may be confounded by greater annual mileage amongst those with high BMI due to an inability to walk long distances, or to a tendency to gain weight amongst those who routinely make short journeys by car. Nonetheless, if a raised BMI is a risk factor for involvement in a MVC, this raises the possibility that regular medical surveillance for common treatable diseases in obese adults who drive may be one approach that has potential to reduce risk of involvement in MVCs.

Conclusions

The results of this study suggest that previously having smoked and having a high BMI may both be associated with an increased risk of involvement in MVCs. There was no evidence of an increased risk among current smokers. These findings should be interpreted cautiously as the recording of lifestyle related exposures in the study population is poor, and the statistical analysis is based on only a small portion of the overall population. The results with regard to smoking contradict several previous findings from studies with more robust

data collection, suggesting that THIN is not ideally suited to studying the effects of such factors in a population with a young age structure. Further analyses should concentrate on those areas where THIN data can be considered more reliable.

4. META-ANALYSIS OF OBSERVATIONAL STUDIES OF THE ASSOCIATION BETWEEN SMOKING AND INVOLVEMENT IN MVCS

Introduction

In recognition of the problems with using THIN data to produce an adequately adjusted analysis of the risk of MVC associated with smoking, and in order to provide a more balanced perspective on this issue, a meta-analysis of existing epidemiological studies in this area was carried out.

Methods

Identification of relevant studies

A systematic search of the published literature was performed to identify studies reporting risks of involvement in, or death or injury due to MVCs in smokers compared with non-smokers. EMBASE (1980 to week 31 2007), Medline and "old" Medline (1950 to week 31 2007), CINAHL (1982 to week 31 2007), AMED (1985 to week 31 2007) and the British Nursing Index (1985 to week 31 2007) were searched using the following keyword query:

```
(smok$ OR cigar$ OR tobacc$ OR pipe OR nicotin$) AND (motor OR
vehic$ OR road OR crash$ or automobi$ OR collision OR driv$)
```

In addition, conference abstracts from the Society for Research on Nicotine and tobacco in the last 3 years were searched for relevant reports. Attempts were made to contact the lead authors of all potentially relevant papers published since 1990 in order to identify any additional relevant research.

Data extraction

Three researchers independently read and extracted data from each identified study. In the small number of instances where studies subdivided smoking status into more than two levels, data were extracted describing the comparative risk of MVC among smokers vs. non-smokers. Each study was assessed for quality using the Newcastle Ottawa Scale (NOS) (36). All discrepancies were resolved by consensus.

Analysis

Data were analysed using the Cochrane Collaboration Reviews Manager v5 for Windows Vista. Cohort studies were analysed separately from case-control and cross-sectional studies. Fixed effects models were used to calculate pooled estimates and 95% confidence intervals in view of the small number of studies available. Funnel plots were created to assess the potential for publication bias.

Results

After initial inspection of the abstracts and titles of the 17,463 papers identified by the electronic search, 27 full papers were obtained for review. Of these, 8 were eventually included in the meta-analysis. Figure 13 outlines the search process. The papers included in the analysis are listed in Table 15. Data from the analysis in THIN were excluded in view of the problems with exposure recording outlined previously.

Figure 13: Search process for meta-analysis

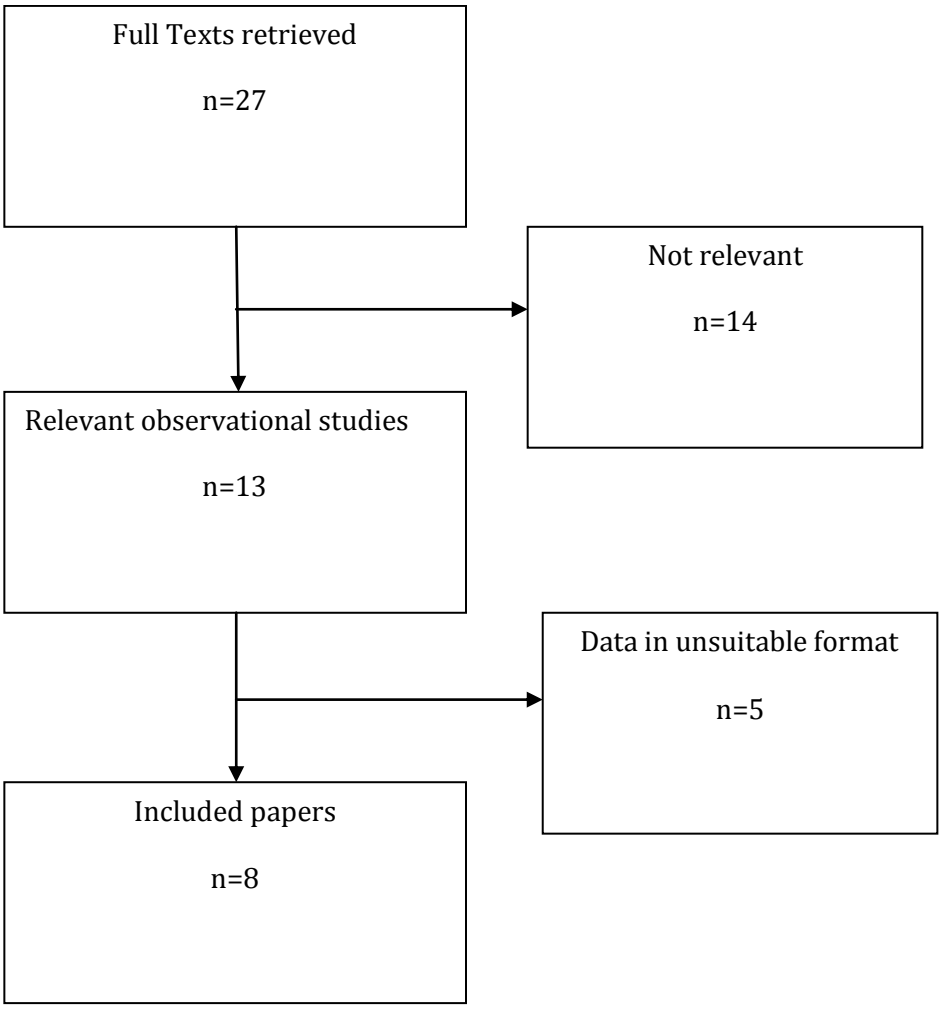


Table 15: Studies included in meta-analysis

Lead Author	Year	Design	n	Exposure Definition	Outcome definition	Confirmed Drivers?	Quality Score*
Liddell (18)	1982	Case-control	694	Any smoking whilst driving y/n	Crash	Yes	6
Grout (16)	1983	Case-control	127	Any Smoking y/n	Injury	Yes	6
DiFranza (15)	1986	Cross-sectional	3,714	Cigarette smoking y/n	Crash	Yes	4
Tsai (20)	1990	Cross-sectional	7,863	Any Smoking y/n	Injury	No	5
Leistikow (17)	2000	Cohort	82,461	Cigarette smoking y/n	Death	No	9
Avi (12)	2001	Case-control	29,212	Cigarette smoking y/n	Injury	Yes	7
Bunuel-Granados (14)	2003	Cross-sectional	1,214	Any Smoking y/n	Crash	Yes	6
Wen (21)	2005	Cohort	64,319	Cigarette smoking y/n	Death	No	8

* Newcastle-Ottawa scale

Forest plots illustrating the individual study estimates and pooled results are given in Figure 14 and Figure 15. The pooled results from the two cohort studies suggest that the relative risk of a fatal MVC among smokers is 1.87 (95% CI 1.46 to 2.41). There was no evidence of heterogeneity between these two studies. The pooled results from the case-control and cross-sectional studies suggest that the odds ratio for involvement in MVC among smokers (compared to non-smokers is 1.68 (1.49 to 1.98). There was clear evidence of heterogeneity between these studies.

Figure 14: Forest plot of relative risk of involvement in a fatal MVC for smokers relative to non-smokers

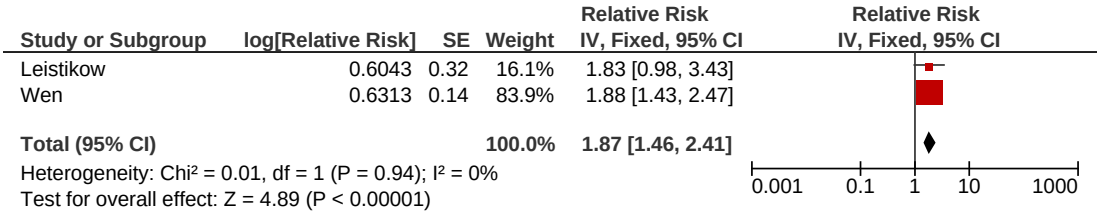
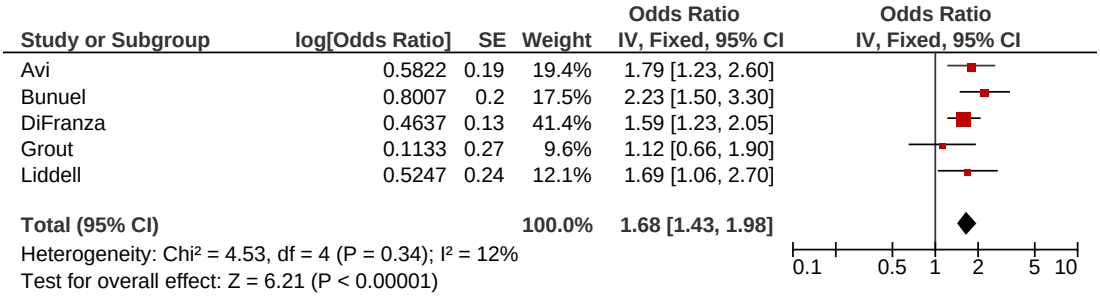


Figure 15: Forest plot of odds ratio of association between current smoking and involvement in MVC



Funnel plots for the cohort and case-control/cross-sectional studies are given in Figure 16 and Figure 17 respectively. There was no evidence of publication bias in either group.

Figure 16: Funnel plot for cohort studies of association between smoking and death due to MVC

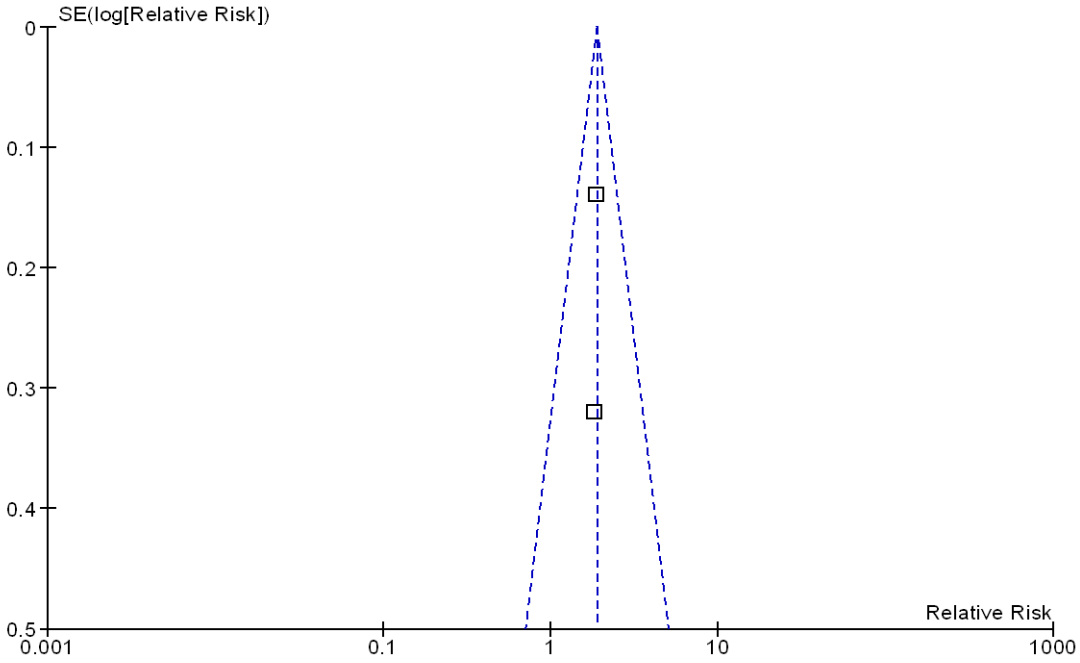
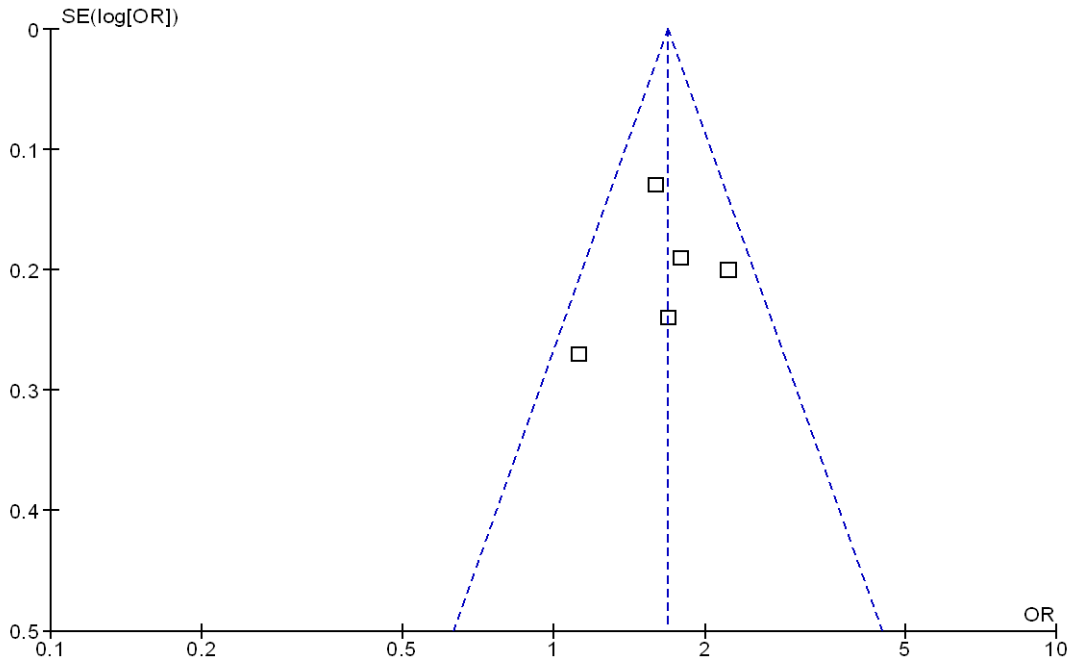


Figure 17: Funnel plot for case-control and cross-sectional studies of association between smoking and involvement in MVC



Discussion

The pooled estimates from the meta-analysis suggest that smoking is associated with a 70 to 90 percent increase in the risk of MVC. The two cohort studies were methodologically very similar and produced similar individual estimates of the magnitude of association, suggesting that the pooled analysis is appropriate. The observed effects in the case-control and cross-sectional studies were less consistent and there was evidence of heterogeneity between the studies. This is unsurprising given the diverse range of data sources and outcomes (Table 15 and discussion in previous chapter).

The Newcastle-Ottawa scores suggest that the overall methodological quality of the included studies was fair, although only one study achieved the highest

possible score (9 marks), and it should be noted that there is currently no widely-agreed threshold for distinguishing between "good-" and "poor-quality" studies. The Newcastle Ottawa scale assesses study quality in three main areas – the appropriateness of the case selection method (up to 4 marks), the comparability of the control or unexposed group (up to 2 marks) and the assessment of exposure status and major confounders (up to 3 marks). Other quality assessment schema exist, but the Newcastle Ottawa score was chosen for this study as it is the Cochrane Collaboration's preferred measure for nonrandomised studies. Newcastle Ottawa scores can be used to assess the impact of study design quality on the observed size of effect (by dividing studies into ranges of NOS score), but this was not considered worthwhile in this case in view of the small number of qualifying studies.

Overall, in spite of the small number of useable studies, it seems reasonable to conclude that smoking is indeed associated with an increased risk of MVC. Unfortunately, it is not possible to derive any firm conclusions about the mechanisms underlying this association from the current literature. Two studies have compared the risk of MVC between individuals who habitually smoke whilst driving and non-smokers (14, 18), but none has attempted to compare the risks between smokers who habitually smoke whilst driving and other smokers who do not. It is not, therefore, possible to determine whether the increase in risk is due to smoking in general or smoking whilst driving in particular.

There are a number of possible mechanisms which may explain the observed association. A smoky atmosphere within a vehicle may reduce visibility, as may residues deposited on the windscreen (13). The act of smoking may distract drivers' attention from the road; research involving direct observation of drivers suggests that drivers are distracted when lighting cigarettes, although there was no evidence of an overall deterioration in performance (37). Similarly, dropping a hot cigarette within a vehicle might lead to a loss of control. Alternatively, the short term effects of smoking may impair co-ordination or response times – high blood carbon monoxide levels have been shown to impair performance in driving simulation studies, and changes in blood nicotine levels have been demonstrated to affect (but not necessarily impair) drivers' responses to stress (38, 39).

A particular complication of this association is the behaviour of smokers. Smoking is associated with a range of risk-taking behaviours, including drunk-driving and other forms of dangerous driving (40, 41), and failure to wear seat belts (16, 42, 43). These behavioural characteristics make smokers inherently more likely to be involved in a MVC, and it is unlikely that any study which did not involve direct observation of the circumstances surrounding a crash would be able to disentangle this effect from the more mechanical and physiological processes which may also contribute to an increased risk.

Conclusions

The available body of research provides clear evidence that the risk of MVCs is higher among smokers than among non-smokers, but it is not possible to

determine either whether this effect is limited to those who smoke whilst driving, or whether the association is confounded by the behavioural characteristics of smokers.

5. The Effects of Prescribed Medications on the Risk of Motor Vehicle Crashes – a Self-Controlled Case-Series Study

Abstract

***Background*.** Previous studies have reported inconsistent associations between use of certain medications and involvement in a motor vehicle crash (MVC).

Study design and methods. This study investigated the impact of taking benzodiazepines, non-benzodiazepine hypnotics, beta-blockers, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, opioids and antihistamines on the risk of MVC, using data from THIN. The self-controlled case series method was used to compare the incidence of a MVC when exposed to each medication with the incidence when unexposed.

Results. 49,821 individuals aged 18-74 had documented involvement in a MVC. The first four weeks of treatment with a combined acetaminophen and opioid preparation was associated with an increased risk of MVC (Incidence Rate Ratio=2.06, 99% Confidence Interval 1.84, 2.32) as was the use of an opioid alone (IRR=1.70, 99% CI 1.39, 2.08). The use of SSRIs (IRR=1.16, 99% CI 1.06, 1.28), non-benzodiazepine hypnotics (IRR=1.37, 99% CI 1.05, 1.79) and antihistamines (IRR=1.21, 99% CI, 1.04, 1.41) for more than 4 weeks was associated with MVC but shorter term use was not. The use of beta-blockers and tricyclic antidepressants was not associated with an increased risk of MVC.

Conclusions. The use of benzodiazepines and preparations containing opioid analgesics is associated with an increased risk of involvement in MVCs. Longer term use of SSRIs, antihistamines and non-benzodiazepine hypnotics may also increase the risk of MVC. There was no evidence of any increased risk among users of beta-blockers or tricyclic antidepressants.

Introduction

Studies describing the effects of prescribed medications suggest that driving performance may be impaired by the use of benzodiazepines (44), tricyclic antidepressants (45), opioids (46), beta-blockers (46), antihistamines (47) and non benzodiazepine sedatives such as zopiclone (48). Users of these medications may be at increased risk of MVC, but controlled epidemiological studies assessing the actual effect of taking medication on the risk of MVC are scarce. Available data suggest that the risk of MVC involvement is increased by the use of sedatives such as zopiclone (49) and the benzodiazepines (49-55) but studies of the effects of taking tricyclic antidepressants (49, 51, 55) and opioids (49, 55) have produced inconsistent results.

This study uses data from THIN to assess the risk of MVC among individuals taking a selection of medications which may affect co-ordination or alertness.

Methods I – Case crossover analysis and problems with this approach

The largest and most often cited study of the effects of taking prescribed medications on the risk of MVCs to date was published in 1998 by Barbone et al (49). This study linked data from police accident records with information from the prescription pricing authority (PPI) listing all the medications used by the drivers in the year prior to the date of MVC. To avoid the difficulty and expense of recruiting a suitable control population, the study used a case-crossover method, whereby the odds of having received a prescription for a medication of interest in the month immediately prior to the date of MVC was compared with the odds in different control periods of equal length earlier in each patient's

record. In effect, a case-crossover study is analogous to a case control study, where case individuals and control individuals are replaced with at-risk ("case") and not at-risk ("control") periods of time within the record of a single individual. The data are then analysed using logistic regression conditioned on the individual. The initial aim of the work described in this chapter was to update the earlier study, using the same methods to investigate the association between medication use and involvement in MVCs in the larger population and longer follow-up available in THIN.

Study population and selection of time periods for comparison

The study population comprised all individuals with a first recorded MVC dated at least 1 year after the start of their computerised THIN record who were aged 18-74 at the time. Individuals whose MVC records indicated that they were not driving at the time were excluded. In line with the previous study, the at-risk period was defined as the four-week period immediately prior to (and excluding) the date of MVC. The not at-risk period was defined as the four-week period immediately prior to the at-risk period.

A key assumption of the case-crossover method is that the risk of exposure in the not-at-risk period is should appropriately reflect the backround risk of exposure (56). That is, that the results should be independent of the choice of not at-risk period. To test this assumption in the THIN population, three additional not at-risk periods were defined (each 4 weeks in length, successively extending back to 16 weeks prior to the beginning of the at-risk

period), so that the degree of variation in the results with differing choices of control period could be assessed.

Exposure ascertainment

The therapy table records for each individual in the study population were searched for recordings indicating the prescription of any benzodiazepine, non-benzodiazepine hypnotic, beta-blocker, opioid, compound analgesic (acetaminophen + opioid), tricyclic antidepressant, selective serotonin reuptake inhibitor (SSRI) or anti-histamine preparation dated prior to the date of MVC. Individuals were considered exposed or unexposed to each class of medication whilst at-risk or not at-risk of MVC according to the presence or absence of a suitable prescription record within the relevant time periods.

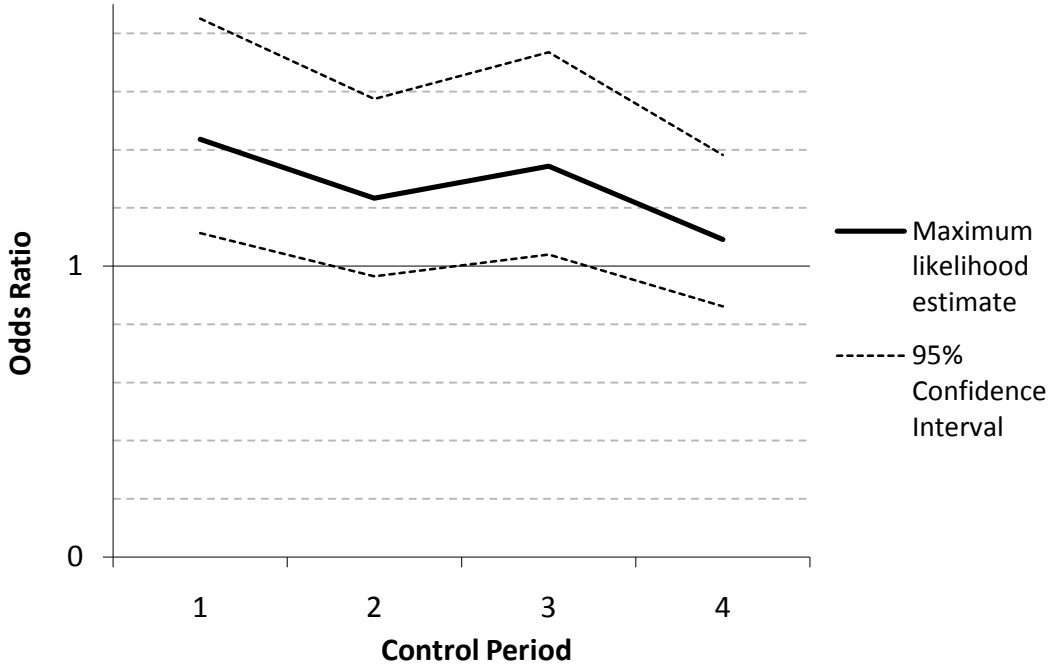
Analysis

The data were analysed using conditional regression models in StataSE v9.1 (Stata Corp. TX, USA) for Windows XP. The use of case-only methods has the advantage of implicitly controlling for the effects of fixed (per individual) confounding. In effect, the effects of any potential confounding factors which vary between individuals but which do not vary substantially for any single individual during the period of study are removed. For this reason, and to maintain consistency with the "template" study, no further adjustments were made.

Results I – failure to meet necessary assumptions

When the results were obtained, it quickly became apparent that the assumption of equivalency of control periods was not met in the THIN data. The results for all categories of medication were unstable, leading to substantially differing estimates of effect size and of statistical significance. Figure 18 shows the differing results obtained with successive not-at risk periods for opioid medications. Depending on the choice of not at-risk period, the estimated Odds Ratio varies by over 20%, and the result may or may not be statistically significant. Similar instabilities were observed for each of the categories of medication under investigation, making use of the case-crossover method inappropriate in these data.

Figure 18: Odds ratio of association between involvement in MVC and receipt of a prescription for an opioid using 4 successive 4-week control periods prior to the at-risk period



It is interesting to note that while the THIN data fail to comply with the necessary assumption, experimentation with different control periods in the earlier study did not reveal similar instability. One possible explanation is the likely presence of non-drivers in the THIN population, which may have reduced the magnitude of the observed associations sufficiently that relatively small variations in probability of exposure with different not at-risk periods may have constituted a larger proportion of the overall odds ratio, making the instabilities more obvious. Alternatively, the reliance on issued prescriptions as a measure of exposure in the THIN data, rather than collected prescriptions in the PPI data, may have magnified any variations if a substantial proportion of prescriptions

are not collected. Whatever the explanation, the failure of this technique to produce stable results in the THIN data prevents robust conclusions from being drawn from the results.

Methods II – The self-controlled case-series approach

In view of the failure of the case-crossover method to produce stable results, the decision was taken to repeat the analysis using the more complicated self-controlled case-series approach. The case series method was originally developed to permit study of adverse reactions to childhood vaccinations (56, 57) but has been applied successfully in a variety of other situations, including several pharmacoepidemiological studies using THIN data (58-61). The case-series method is similar in principle to the case-crossover method; if the case-crossover method is analogous to a case-control study, the case-series method is analogous to a cohort study. The case-series method divides individual patient follow-up time into exposed and unexposed periods, between which the incidence rates of the outcome of interest are compared. Like the case-crossover method, the case-series approach implicitly controls for the effects of fixed (per individual) confounding factors, but does not require a constant probability of exposure outside the time period immediately prior to the outcome, so the variations observed in the THIN data do not prevent use of this method. The case-series method additionally permits exploration of changes in risk with duration of exposure, and has been shown to approach cohort methodologies in terms of statistical power (56).

Study population

As before, the study population comprised all individuals with a first recorded MVC dated at least 1 year after the start of their computerised THIN record who were aged 18-74 at the time. Individuals whose MVC records indicated that they were not driving at the time were excluded.

Exposure ascertainment, and a note about the exposures investigated

The therapy table records for each individual in the study population were searched for prescriptions for any benzodiazepine, non-benzodiazepine hypnotic, beta-blocker, opioid, compound analgesic (paracetamol + opioid), tricyclic antidepressant, selective serotonin reuptake inhibitor (SSRI) anti-histamine or protein pump inhibitor (PPI) preparation. Although the therapy table includes variables which either directly indicate, or can be used to calculate the duration of a given prescription, in practice, these are rarely used in data recorded prior to the introduction of Vision (and even then, a substantial proportion are missing). To avoid restricting the population and losing statistical power, the therapy table records for each class of medication, and also for each medication, were grouped into estimated courses of treatment based on the interval between prescription dates. The modal interval between prescription dates within each category of medication was found to be 4 weeks, with further discernable peaks at 8, 12 and 16 weeks and a steady baseline thereafter, in line with normal prescribing practice in the United Kingdom. The conservative assumption was therefore made that prescriptions were part of an ongoing course of treatment if they were dated within 16 weeks of a prior prescription for a drug in the same class. Prescriptions issued prior to the start

of follow-up were examined in order to determine the correct exposure status of each individual at the start of follow-up, but no person-time from this period was included in the analysis. Prescription records in THIN do not exhibit the patterns of recording associated with back entry of historical data which are observed in the diagnostic data.

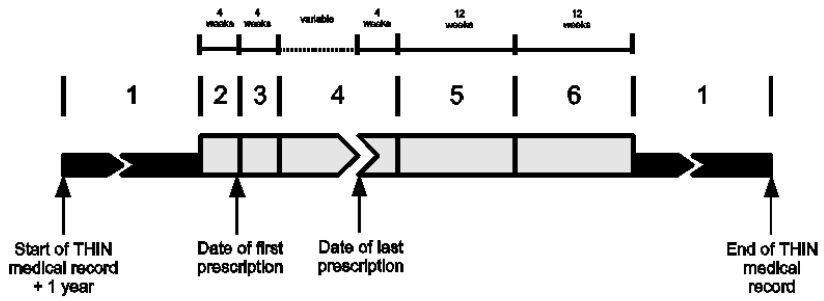
It is important at this point to explain the reasoning behind the final selection of medications investigated in this study. The original intention was to study the effects of the benzodiazepines, non-benzodiazepine hypnotics, SSRIs, opioid and combined paracetamol and opioid analgesics, and the tricyclic antidepressants as these medications are only available on prescription in the UK and are normally prescribed for a limited period of time. The beta-blockers were included at the insistence of the ethics committee which approved the study, however the results obtained for this class of medication should be interpreted cautiously, as a key assumption of the case series method is that exposure is only temporary, and should be of short duration compared with the overall period of follow-up. Beta-blockers are normally prescribed as "rest-of-life" medications for the treatment of chronic cardiovascular conditions and cannot reasonably be expected to meet this requirement. The anti-histamines were included at the request of a Lancet peer-review panel. Again, the results for these medications should be interpreted cautiously as many are available over the counter, and can often be obtained more cheaply in this way for individuals who are not exempt from UK prescription charges. Given the age structure of the population of individuals involved in MVCs, it is unlikely that a substantial proportion of the population is exempt from charging, so the exposure

ascertainment is likely to be inaccurate for this group of medications. The PPIs were also included at the request of the review panel in order to provide a "negative control" (as they would be unlikely to lead to impaired driving performance) to determine whether spurious positive associations might arise due to the choice of exposure periods (see next section).

Statistical analysis

For each class of medication, and for each individual compound within each class, a separate dataset was created for analytical purposes, dividing the follow-up time for each exposed case into different periods according to exposure status. 6 different categories were defined (Figure 19):

Figure 19: Exposure-time categories for case-series analysis



1 – Unexposed time
2 – 4 week pre-exposure period, up to and including date of first prescription
3 – First 4 weeks following first prescription
4 – Remainder of course of treatment
5 – First 12 weeks after end of course of treatment
6 – Second 12 weeks after end of course of treatment

1. Time when unexposed to the medication of interest (baseline).

2. A four week period up to and including the date of the start of each course of treatment.

3. The four weeks immediately following the start of a course of treatment (starting the day after the date of first prescription).

4. The remainder of that course of treatment, ending 4 weeks after the last prescription.

5. The first 12 weeks after the end of each course of treatment

6. The second 12 weeks after the end of each course of treatment

The first category represents baseline time, to which other exposure-time categories are compared. Since many of the medications of interest could be used to treat anxiety or pain caused by a MVC it is necessary to include the second category, a pre-exposure time period which removes any MVCs which might have led to the issue of a prescription from the calculation of the baseline incidence rate, thus preventing any spurious inflation of this quantity. The number of prescriptions for any medication of interest issued on each day subsequent to the date of accident was inspected graphically and found to decline, from a peak on the day of accident, to a steady baseline within 4 weeks, hence this was the duration chosen for this category.

The time during which individuals were exposed to each medication of interest was divided into two categories to investigate whether any changes in the risk of MVC are short-lived (while patients adjust to their medication), develop over

time (only become apparent with extended use) or are constant. The fifth and sixth periods were included to investigate withdrawal effects; most individuals would have discontinued their use of the medication by the start of the fifth period, whilst those on 8, 12 or 16-week prescriptions would have discontinued use by the start of the sixth period. In cases where a new course of treatment began during either of these last two periods, the exposure statuses associated with the new course took preference.

Data were analysed using Stata 9SE for Windows XP. Fixed-effects Poisson regression models were used to calculate incidence rate ratios (IRRs) comparing the incidence rates of MVC in each exposure category with the incidence rate during the baseline period. Within each drug class, the effects of taking individual medications on the risk of MVC were assessed where a minimum of 450 exposed cases were available.

Whilst the case-series method controls for confounding by factors which are constant within each individual, it does not reduce confounding due to risk factors which vary over time. Since the risk of MVC is strongly age-dependent, and the period of available follow-up for some individuals was long (up to approximately 15 years) the data were further stratified by three-year age group, by which the analysis was adjusted. The choice of three-year age bands was purely pragmatic – the xtpoisson estimator in STATA can only operate on a maximum of 500,000 lines of data and any finer subdivision would have exceeded this limit. Consideration was also given to the possibility of adjusting by calendar year as MVC rates were known to vary over time, and prescribing practice for the medications of interest might also have changed over the period

of follow-up, however a time adjustment would be collinear with age for each individual, so the age-adjustment would implicitly account for most such changes. In addition, further stratification of the datasets would have breached the limits described previously. 99 percent confidence intervals were calculated for each incidence rate ratio in view of the multiple hypotheses being tested.

Using a sample size formula based on the signed root likelihood ratio (proposed by Musonda et al (62)) it was estimated that 3,169 exposed cases would be required in order to detect an incidence rate ratio of 1.2 in the first 28 days after prescription, with 95 percent power and at the 5 percent significance level.

Results

49,821 individuals with a first recording of involvement in a MVC during the qualifying period of follow-up were identified (Figure 20). The median duration of follow-up in this population was 9.6 years. Table 16 shows the results of the case-series analyses, adjusted for age. All categories of medication show a marked association with involvement in a MVC in the 28 days up to and including the date of first prescription of a course of treatment, consistent with the issue of prescriptions as a consequence of involvement in a MVC.

Figure 20: Age and sex-specific breakdown of the case-series population

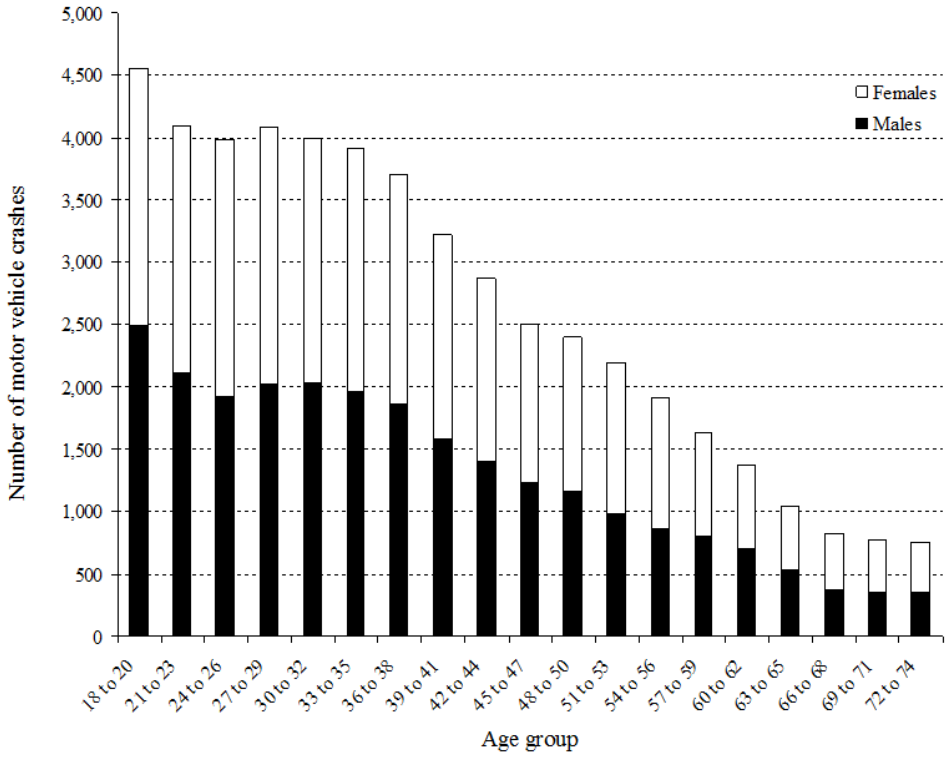


Table 16: Age-adjusted incidence rate ratios for involvement in motor vehicle crashes, by use of medication

Medication	Number of exposed cases *	Incidence rate ratio; 99% Confidence interval †				
		Period 2	Period 3	Period 4	Period 5	Period 6
Benzodiazipenes (all)	**10,667**	**16.44; 15.29, 17.67**	**1.94 ; 1.62, 2.32**	**2.38 ; 2.01, 2.81**	**1.22 ; 1.07, 1.40**	**1.07 ; 0.92, 1.24**
Diazepam	7,337	21.02; 19.35, 22.82	1.93 ; 1.54, 2.43	2.77 ; 2.20, 3.48	1.17 ; 0.99, 1.40	1.08 ; 0.89, 1.30
Temazepam	3,917	8.71 ; 7.49, 10.14	1.56 ; 1.12, 2.17	1.36 ; 1.02, 1.80	1.16 ; 0.93, 1.46	0.89 ; 0.67, 1.17
Nitrazepam	610	3.90 ; 2.18, 6.95	1.66 ; 0.72, 3.86	1.55 ; 0.89, 2.70	1.17 ; 0.64, 2.13	1.07 ; 0.54, 2.10
Chlordiazepoxide	538	3.42 ; 2.00, 5.85	1.45 ; 0.65, 3.21	1.36 ; 0.62, 2.99	0.45 ; 0.19, 1.03	1.45 ; 0.87, 2.43
Non-benzodiazipene hypnotics (all) ‡	**3,899**	**6.97 ; 5.96, 8.16**	**1.06 ; 0.73, 1.54**	**1.37 ; 1.05, 1.79**	**0.95 ; 0.75, 1.21**	**1.11 ; 0.88, 1.41**
Zopiclone	3,280	6.93 ; 5.83, 8.24	1.03 ; 0.68, 1.55	1.40 ; 1.04, 1.87	0.92 ; 0.70, 1.20	1.21 ; 0.94, 1.55
Zolpidem	774	5.31 ; 3.55, 7.95	1.04 ; 0.43, 2.48	1.16 ; 0.60, 2.25	1.13 ; 0.67, 1.89	0.71 ; 0.36, 1.39
Beta-blockers (all)	**7,852**	**2.10 ; 1.74, 2.52**	**1.00 ; 0.77, 1.30**	**0.97 ; 0.87, 1.10**	**0.94 ; 0.79, 1.12**	**0.97 ; 0.80, 1.17**
Propranolol	4,344	2.63 ; 2.09, 3.31	1.05 ; 0.73, 1.49	0.89 ; 0.70, 1.14	0.96 ; 0.77, 1.20	0.95 ; 0.74, 1.20
Atenolol	3,405	1.67 ; 1.21, 2.30	0.99 ; 0.66, 1.49	0.96 ; 0.82, 1.11	0.83 ; 0.61, 1.12	0.92 ; 0.65, 1.30
Opioids (all)	**8,603**	**10.90 ; 9.96, 11.93**	**1.70 ; 1.39, 2.08**	**1.29 ; 1.08, 1.54**	**1.02 ; 0.87, 1.20**	**0.90 ; 0.75, 1.08**
Dihydrocodeine	3,735	11.73 ; 10.21, 13.49	1.60 ; 1.14, 2.25	1.05 ; 0.78, 1.42	1.15 ; 0.91, 1.47	1.03 ; 0.79, 1.35
Tramadol	3,153	9.17 ; 7.81, 10.77	1.46 ; 1.02, 2.11	1.34 ; 1.02, 1.76	0.92 ; 0.69, 1.22	0.91 ; 0.67, 1.24
Codeine Phosphate	3,081	10.90 ; 9.33, 12.74	1.61 ; 1.11, 2.32	1.33 ; 0.88, 2.00	0.93 ; 0.69, 1.24	0.85 ; 0.62, 1.18
Morphine	484	3.14 ; 1.60, 6.15	1.16 ; 0.39, 3.45	0.87 ; 0.43, 1.75	1.10 ; 0.49, 2.47	1.42 ; 0.63, 3.16
Compound analgesics (all) §	**21,787**	**21.22 ; 20.27, 22.20**	**2.06 ; 1.84, 2.32**	**2.66 ; 2.40, 2.95**	**1.10 ; 1.00, 1.21**	**0.94 ; 0.85, 1.05**
Co-proxamol	11,775	17.41 ; 16.27, 18.64	1.78 ; 1.49, 2.13	2.24 ; 1.93, 2.59	1.18 ; 1.04, 1.34	0.98 ; 0.85, 1.14
Co-dydramol	9,942	20.44 ; 19.06, 21.92	1.76 ; 1.44, 2.15	2.02 ; 1.67, 2.45	0.97 ; 0.83, 1.14	0.84 ; 0.70, 1.00
Co-codamol	8,734	15.50 ; 14.30, 16.80	1.62 ; 1.30, 2.01	1.76 ; 1.40, 2.20	0.90 ; 0.76, 1.07	0.93 ; 0.78, 1.11
SSRIs (all)	**11,301**	**1.71 ; 1.47, 1.99**	**0.92 ; 0.75, 1.12**	**1.16 ; 1.06, 1.28**	**1.03 ; 0.92, 1.16**	**1.02 ; 0.89, 1.16**
Fluoxetine	5,980	1.31 ; 1.02, 1.69	0.77 ; 0.56, 1.07	1.18 ; 1.02, 1.37	1.00 ; 0.84, 1.19	0.98 ; 0.81, 1.18
Citalopram	3,933	1.73 ; 1.26, 2.38	1.02 ; 0.68, 1.53	1.18 ; 0.97, 1.45	0.94 ; 0.72, 1.23	1.14 ; 0.88, 1.49
Paroxetine	3,102	1.84 ; 1.38, 2.46	1.01 ; 0.69, 1.48	1.18 ; 0.98, 1.42	1.08 ; 0.86, 1.35	0.88 ; 0.68, 1.14
Tricyclic antidepressants (all)	**9,984**	**2.89 ; 2.52, 3.30**	**0.92 ; 0.73, 1.16**	**1.04 ; 0.91, 1.18**	**0.93 ; 0.81, 1.07**	**0.95 ; 0.81, 1.10**
Amitryptyline	5,426	3.35 ; 2.81, 3.99	0.86 ; 0.62, 1.20	0.94 ; 0.77, 1.14	0.85 ; 0.69, 1.05	1.00 ; 0.82, 1.23
Doselupin	4,066	2.60 ; 2.03, 3.33	0.98 ; 0.66, 1.45	1.03 ; 0.83, 1.28	0.94 ; 0.74, 1.20	0.78 ; 0.59, 1.02
Lofepramine	1,719	1.53 ; 0.91, 2.58	1.09 ; 0.59, 2.01	1.11 ; 0.76, 1.61	1.10 ; 0.76, 1.57	1.07 ; 0.73, 1.56
Trazodone	612	2.00 ; 0.96, 4.15	0.61 ; 0.17, 2.24	1.06 ; 0.62, 1.82	0.85 ; 0.43, 1.69	1.13 ; 0.60, 2.11
Antihistamines (all)	**14,333**	**1.16 ; 1.00, 1.35**	**1.01 ; 0.86, 1.19**	**1.21 ; 1.04, 1.41**	**1.02 ; 0.92, 1.12**	**1.13 ; 1.03, 1.25**
Loratadine	4,910	1.21 ; 0.90, 1.62	1.00 ; 0.73, 1.38	1.20 ; 0.88, 1.64	1.08 ; 0.90, 1.30	1.13 ; 0.94, 1.36
Cetirizine	4,304	1.00 ; 0.72, 1.38	1.06 ; 0.78, 1.44	1.04 ; 0.77, 1.39	0.95 ; 0.78, 1.15	0.93 ; 0.75, 1.14
Terfenadine	3,827	0.98 ; 0.65, 1.50	1.02 ; 0.68, 1.53	0.91 ; 0.56, 1.48	0.98 ; 0.77, 1.24	1.07 ; 0.85, 1.35
Chlorphenamine	3,092	0.89 ; 0.56, 1.44	0.65 ; 0.37, 1.13	0.92 ; 0.45, 1.87	0.99 ; 0.76, 1.30	1.15 ; 0.88, 1.48
Fexofenadine	1,845	1.11 ; 0.69, 1.78	0.92 ; 0.55, 1.53	1.17 ; 0.73, 1.85	1.02 ; 0.76, 1.37	1.39 ; 1.05, 1.83
Desloratidine	1,688	1.38 ; 0.90, 2.12	0.93 ; 0.56, 1.55	1.12 ; 0.72, 1.74	0.87 ; 0.63, 1.20	1.25 ; 0.93, 1.68
Hydroxyzine	743	2.58 ; 1.44, 4.61	0.74 ; 0.25, 2.13	1.33 ; 0.63, 2.81	1.23 ; 0.74, 2.02	1.36 ; 0.82, 2.23
Levocitirizine	480	0.99 ; 0.37, 2.68	2.11 ; 1.06, 4.19	1.14 ; 0.42, 3.11	1.08 ; 0.60, 1.97	0.76 ; 0.35, 1.66
Brompheniramine Maleate	474	1.55 ; 0.61, 3.92	1.31 ; 0.49, 3.53	1.62 ; 0.50, 5.19	1.68 ; 0.99, 2.85	1.34 ; 0.73, 2.44
Astemizole	451	1.82 ; 0.71, 4.65	1.55 ; 0.57, 4.22	2.45 ; 0.82, 7.34	0.85 ; 0.39, 1.84	1.54 ; 0.86, 2.78

* - Individual medication totals do not equate to the category total as some subjects received more than one medication in each category.

† - Exposure-time periods:
2) 4 week period up to and including date of prescription
3) 4 week period following 1st prescription of a course of treatment
4) remainder of exposed time
5) 12-week period following end of exposure
6) second 12 week period following end of exposure

‡ - Zopiclone, zolpidem, chlormezanone, zaleplon.

§ - Co-codamol, co-proxamol & co-dydramol.

Table 17 shows the equivalent results for individuals exposed to PPIs. No significant increased risk of MVCs was observed in any time period for any

medication in this class, suggesting that there is no systematic bias inherent in the choice of exposure categories.

Table 17: Age adjusted incidence rate ratios for involvement in motor vehicle crashes among individuals prescribed proton pump inhibitors

Medication	Number of exposed cases[α]	Incidence rate ratio (99% Confidence interval)[β] Period 2	Period 3	Period 4	Period 5	Period 6
Proton pump inhibitors (all)	**8,391**	**1.79 (1.50 - 2.14)**	**0.91 (0.72 - 1.16)**	**1.11 (0.97 - 1.26)**	**1.11 (0.96 - 1.28)**	**0.99 (0.84 - 1.18)**
Lansoprazole	4,957	1.93 (1.53 - 2.44)	0.69 (0.47 - 1.01)	1.03 (0.86 - 1.23)	1.01 (0.82 - 1.23)	0.93 (0.74 - 1.18)
Rabeprazole	4,165	0.95 (0.46 - 1.97)	0.66 (0.28 - 1.56)	1.26 (0.86 - 1.85)	0.71 (0.42 - 1.20)	0.91 (0.55 - 1.50)
Pantoprazole	1,144	2.33 (1.22 - 4.45)	1.51 (0.68 - 3.35)	1.51 (0.91 - 2.50)	1.09 (0.60 - 1.99)	0.70 (0.32 - 1.56)
Omeprazole	633	1.42 (1.05 - 1.92)	0.95 (0.66 - 1.37)	1.04 (0.86 - 1.27)	1.28 (1.05 - 1.57)	1.04 (0.82 - 1.33)
Esomeprazole	629	2.19 (1.16 - 4.12)	1.94 (0.99 - 3.78)	1.06 (0.65 - 1.73)	0.95 (0.51 - 1.77)	1.10 (0.57 - 2.10)

α - Individual medication totals do not equate to the category total as some subjects received more than one medication in each category.

β - Exposure-time periods:
2) 4 week period up to and including date of prescription
3) 4 week period following 1st prescription of a course of treatment
4) remainder of exposed time
5) 12-week period following end of exposure
6) second 12 week period following end of exposure

Discussion

This is the largest study to date, with the longest period of follow-up, of the effect of taking a selection of prescribed medicines on the risk of involvement in a motor vehicle crash. The results suggest that the risk of MVC may be increased by the use of benzodiazepines, opioids such as codeine phosphate, dihydrocodeine and tramadol, and compound analgesic preparations containing paracetamol and an opioid for the duration of their usage, but not by the use of morphine. In addition, there was a modest association between involvement in a MVC and the use of non-benzodiazepine hypnotics, SSRIs and antihistamines for longer than four weeks. No evidence was found of any increased risk of MVC among users of tricyclic antidepressants or beta-blockers, or following withdrawal from any of the medications under investigation.

Adequately powered studies of the effect of taking prescribed medicines on the risk of MVC are scarce, possibly due to the difficulty of obtaining a sufficiently large number of MVC cases and detailed information on their use of medication. The use of primary care data in this study provides considerable statistical power to investigate these associations, above and beyond that which would be available from any other source. The use of the self-controlled case series method circumvents the problem of selecting an appropriate control group and eliminates the effect of fixed (per individual) confounding (63). An additional benefit is the ability to explore temporal changes in risk during exposure to the medications of interest, or following the cessation of treatment; factors which have not been investigated before.

This study is subject to a number of limitations which must be considered when interpreting the results. A substantial number of hypotheses have been investigated, increasing the risk that spurious associations might have been observed, although the use of 99% confidence intervals mitigates against this possibility. The use of the case-series analysis in large healthcare datasets establishes the temporal relation between the prescription of a medication and an outcome e.g. MVC, but cannot distinguish between the clinical impact of the disease which necessitated the prescription of the medication and the side-effects of the drug itself. In either case, the observed increased risks are useful in informing practitioners and patients of the potential consequences of driving whilst using, or needing to use, the medications in question. The lack of regularly updated information on lifestyle exposures in the THIN data makes it impossible to exclude confounding by factors which accompany the issue of a

prescription; for example an increase in alcohol consumption might occur in patients suffering depressive illness and therefore confound the observed association with the use of SSRIs. It is also impossible to determine whether patients collected their medication or took it as prescribed, so the results give a guide to the consequences of receiving a prescription, rather than taking the medication per se.

The lack of detailed information on the duration of treatment is also problematic, and may have led to misclassification of exposed time periods. For example, some prescriptions may be for as short a period as one to two weeks, leading to an underestimate of the risks associated with short term use. For similar reasons, it was also impossible to investigate whether dose-response relationships were present in this population.

A further issue, inherent in all studies of MVCs in THIN, is the quality of recording of these events in primary care. The inability to differentiate between drivers, passengers and pedestrians tends to dilute the observed effects, and the possibility (discussed earlier) that accidents resulting in injury may not be coded as MVCs raises the possibility that the observed associations describe the risks of involvement in a subset of more minor MVCs, rather than the overall population-level risk.

It is possible that patients seeking treatment for other illnesses for which the medications of interest are eventually prescribed may report some minor events which would not otherwise have been recorded, however if this were a

serious issue one would expect to observe increased incidences of MVC for all medications. In fact, there was no increased incidence of MVC among users of beta-blockers and tricyclic antidepressants (although interpretation of the result for the beta-blockers is problematic, as discussed earlier). Finally, it is not possible to account for the impact of patient behaviour following the receipt of a prescription. Some patients may refrain from driving whilst taking the medications of interest, leading to an underestimate of the associated risk. This is consistent with the observation that morphine use was not associated with an increased risk of injury when all other opioids investigated were, as morphine is generally reserved for the management of severe pain, and those receiving such treatment may therefore be more likely to be incapable of driving, or to have been advised not to drive.

The four week period prior to drug prescription (Period 2) was designed to exclude any MVCs that may have led to a drug prescription for pain control or relief from anxiety from the baseline person time. The high rate ratios observed in this period unsurprisingly suggest that some of these medications are prescribed in response to a MVC. Data were not available on the provision of prescriptions from sources other than the primary care centres so there may be some misclassification is medication was obtained from other places such as emergency doctors or family members. However, this would be expected to introduce random error to the analysis which would tend to reduce the size of effect seen.

The results of previous studies investigating the effect of opioid use on the risk of MVC are conflicting. Ray et al (55) found no evidence of an increased risk of MVC associated with oral opioid use in a study of 495 injurious crashes among 16,262 elderly drivers, although as the exact medications concerned are not specified, it is possible that the patients concerned may have been using only mild or low-dose opioids. By contrast, Leveille et al (51) found that opioid (primarily codeine and oxycodone) use was associated with an increased risk of MVC (adjusted risk ratio = 1.8) in a case-control study of 681 elderly drivers. The observation that the use of these medications is associated with a 70 percent to 100 percent increased incidence of MVC in the THIN population support the latter result and are congruent with previous reports of driving impairment due to opioid use (46) and with serological studies which show that opioids are commonly detected in the blood of fatally injured drivers (64).

In common with the study by Barbone et al (49), the THIN data suggest an increased incidence of MVC among those taking zopiclone, but in this population the effect was only observed following prolonged exposure. There was also a modest increased incidence among longer term users of SSRIs which was not observed in the earlier study. This could be explained in terms of the larger population and longer duration of follow-up (and resultant increased statistical power) available in THIN. The use of antihistamines had no immediate effect on the risk of MVC, although a small effect was seen after longer term use of these drugs, however, the availability of many antihistamines without prescription in the UK makes it difficult to derive firm conclusions from this result. There was no evidence of an increase in risk of MVC among users of

tricyclic depressants. Studies of elderly drivers (51, 55) have shown an increase in the risk of MVC in users of these medications, but a larger study in a more representative population did not (49).

The findings in relation to benzodiazepines are consistent with those of previous studies (49-55) which suggest that current use of these medications approximately doubles the risk of MVC. In the THIN data there was a much larger association between diazepam use and MVC than with the use of other benzodiazepines. Diazepam is commonly prescribed as an anxiolytic (65) and taken during the daytime when individuals are more likely to drive, whereas temazepam and nitrazepam are more likely to be used as night-time hypnotics.

Conclusions

The results of this study suggest that there is a substantially increased incidence of MVC among those taking opioids such as dihydrocodeine, codeine phosphate and tramadol and among those taking combined acetaminophen and opioid analgesics. There was also some evidence of an increased incidence of MVC among those taking SSRIs and antihistamines for long periods, which merits further investigation. In addition, this work confirms previous findings of an association between the use of benzodiazepines and zopiclone and an increased risk of MVC. There was no evidence of an association between the therapeutic use of tricyclic antidepressants or beta-blockers and MVC.

The results of this study suggest that a substantial number of injuries could be prevented if users of certain medications were to refrain from driving. Further work is required to explore these relationships further, with particular emphasis on the mechanisms involved.

6. The Impact of Disordered Sleep on the Risk of Motor Vehicle Crashes – a Case-Control Study

Abstract

Background. Sleep apnoea syndromes are an established risk factor for involvement in motor vehicle crashes (MVCs), but the potential impact of other sleep disorders has received little attention in the literature.

Study design and methods. Data from THIN were used to conduct a nested case-control study of the effects of snoring, sleep apnoea syndromes and insomnia on the risk of MVC

Results Insomnia was associated with an increased risk of involvement in MVC (Odds Ratio =1.57; 99% Confidence Interval: 1.45 to 1.69), as were snoring (OR=1.91; 99%CI: 1.52 to 2.40) and sleep apnoea syndromes (OR=1.68; 99%CI: 1.08 to 2.61). These associations were independent of the effects of alcohol consumption and the use of sedative and antidepressant medications.

Conclusions. The results of this study suggest that insomnia is a potential risk factor for involvement in MVCs, and confirm previous findings that snoring and sleep apnoea syndromes are associated with an increased crash risk.

Introduction

Research in the UK suggests that up to 23% of MVCs in the United Kingdom may be caused by drivers falling asleep whilst driving (66). Sleep apnoea syndromes are an established risk factor for involvement in MVCs (67), and there is limited evidence to suggest that non-apnoeic snorers may also be at increased risk (68). In addition, an association between irregular sleep patterns and an increased risk of involvement in MVCs among occupational drivers has been reported (69), but the effect of insomnia on the risk of MVC in the general population has received relatively little attention in the literature. A 1991 telephone survey in the United States reported that 5% of individuals with symptoms of insomnia had been involved in a MVC due to sleepiness compared with 2% in the wider population, suggesting that difficulty sleeping may more than double the risk of such crashes (70), however these figures were not adjusted for the use of sedative or antidepressant medications, which have been demonstrated to increase the risk of involvement in MVCs (see pp. 78 to 102). This study uses data from THIN to investigate the association between sleeping disorders recorded in primary care records and subsequent involvement in MVCs, adjusting for the effects of current treatment with sedative or antidepressant medications, and of alcohol consumption.

Methods

Study design and population

Data from THIN were used to construct a nested case-control population. Cases were defined as all individuals with a first Read Term recording indicating involvement in a MVC dated after the 1st January 1991, at least one year after the start of their computerised medical record and whilst they were aged between 18 and 75 years. MVCs recorded prior to 1991 were excluded as MVC incidence rates in THIN rise steeply from approximately nil to a relatively steady level between the start of computerised follow-up and 1990, indicating that MVCs may not be consistently recorded within each practice prior to this time. As before, the age range was chosen to minimise the proportion of cases who are unlikely to be drivers, and recordings in the first year of computerised follow-up were excluded to minimise the number of "historical" events. The control population was randomly selected from those individuals with no recorded MVC, matched by age (±2 years), sex and practice. Each control was required to have a minimum of 1 year of computerised medical recording before the date of MVC of their associated case, and to be from a different household. Where possible, 2 controls were matched to each case.

Exposure definitions

The Read Term dictionary was searched using SearchRC to identify all terms and categories containing the terms *insom*, *snor*, *sleep*, *apnoe* and *apne*. The resulting list was hand searched to identify relevant terms. Terms relating to past, but potentially resolved illness or symptoms ("history of"

terms) were excluded. Individuals were defined as suffering from sleep apnoea syndromes (including both obstructive and neurological apnoeas), insomnia or snoring if their medical or AHD table records contained a relevant record at any time prior to the date of MVC.

Exposure to sedative medication was defined as the presence or absence of therapy table entry indicating a prescription for any benzodiazepine or other hypnotic (zopiclone, zolpidem, chlormezanone or zaleplon) dated up to 16 weeks prior to the date of MVC, but not on the date of MVC (the rationale for choosing this time period is the same as in the preceding chapter). Exposure to antidepressant medication was defined as the presence or absence of a prescription for any tricyclic antidepressant or selective serotonin reuptake inhibitor within the same period.

Levels of alcohol consumption were determined using records from both the medical and AHD tables. The Read Term list was searched (using SearchRC) to identify all terms and categories containing the keywords *alcoh* or *drink*. The resulting list was manually searched to identify those terms indicating a specific level of alcohol consumption. The medical and AHD table records for all individuals were searched to identify the most recent record prior to the date of MVC containing any of these codes. In addition, the AHD table records were searched to identify the most recent (but prior to the date of MVC) directly entered (numeric) recordings of alcohol consumption for each individual. These data were transformed into categories equivalent to those indicated by the Read Terms for alcohol consumption and combined with the Read Term based

records to allow the most recent overall recordings to be identified. The categories obtained were: none; <1 unit / day; 1-2 units /day; 3-6 units/day; 7-9 units/day; and >9 units/day.

In order to determine whether any observed association between disordered sleep and MVC might occur as a consequence of individuals with poor general health consulting their GP more often (and therefore being more likely to report both the existence of sleep-related symptoms, or involvement in a MVC), frequencies of consultation were calculated for each individual in the study population. The frequency of consultation was defined as the number of dates on which data were entered in each individual's AHD or medical table records prior to the date of MVC (excluding those on which recordings relating to the presence of any of the sleep disorders of interest were entered), and more than one year after the start of the computerised record, divided by the duration of this period. Recordings in the therapy table were excluded as repeat prescriptions may be issued without a formal consultation.

Statistical methods

The data were analysed using conditional logistic regression models in STATA 9.1 (STATA Corp. TX, United States) for Windows XP. Three analyses were conducted; a univariate analysis of the association between each sleep disorder and MVC, an analysis adjusted for the current use of sedative or antidepressant medications, and an analysis adjusted for medication use and alcohol consumption (for those individuals with a recording of alcohol consumption). The adjusted results were also stratified according to consultation frequency

(above vs. below or equal to the median frequency)_to investigate the impact of consulting behaviour on the results. In view of the multiple hypotheses being tested, 99% confidence intervals were calculated to reduce the probability of observing positive associations due to chance.

A power calculation using PS (71) for Windows XP indicated that 14,000 cases would provide over 95% power at the 1% significance level to detect a 30% increase in the risk of MVC due to insomnia (well below the level in the US survey), assuming a background prevalence of insomnia of 3% (72).

Results

The basic demographic characteristics of the study population are given in Table 18. The case and control populations were similar in terms of age and socioeconomic status. 5.3%, 0.6% and 0.2% of cases had diagnoses of insomnia, snoring and sleep apnoea syndromes respectively recorded in the THIN database.

Insomnia was associated with an increased risk of involvement in a MVC (OR=1.57; 99% CI: 1.45 to 1.69). Adjustment for the use of sedative and antidepressant medications (OR=1.49; 99% CI: 1.38 to 1.62) and alcohol consumption (OR=1.41; 99%CI: 1.26 to 1.57) slightly reduced the observed effects, but the association remained significant (Table 19). Snoring (OR=1.91; 99% CI: 1.52 to 2.40) and sleep apnoea syndromes (OR=1.68; 99% CI: 1.08 to 2.61) were associated with increased risks of MVC, which were unaffected by adjustment for medication use and alcohol consumption.

Table 18: Socio-demographic characteristics and prevalence of sleep disorders among individuals involved in MVCs and age & gender matched controls in THIN 255 (November 2004)

Characteristic	Cases		Controls	
	males n =19,954	females n =20,155	males n =37,908	females n =38,490
Age at time of MVC, median (interquartile range)	36 (27 - 48)	36 (27 - 49)	36 (27 - 49)	37 (27 - 50)
Quintile of Townsend deprivation index, n (%)				
1st; least deprived	4,641 (23.3)	5,107 (25.3)	8,569 (22.6)	9,152 (23.8)
2nd	4,058 (20.3)	4,196 (20.8)	7,191 (19.0)	7,505 (19.5)
3rd	3,941 (19.8)	3,989 (19.8)	7,291 (19.2)	7,498 (19.4)
4th	3,678 (18.4)	3,606 (17.9)	6,841 (18.1)	6,851 (17.8)
5th; most deprived	3,006 (15.1)	2,638 (13.1)	6,265 (16.5)	5,808 (15.1)
not available	630 (3.2)	619 (3.0)	1,751 (4.6)	1,676 (4.4)
Sleep disorders recorded prior to MVC, n (%)				
insomnia	777 (3.9)	1,343 (6.7)	1,048 (2.8%)	1,645 (4.3)
snoring	199 (1.0)	54 (0.3)	184 (0.5%)	74 (0.2)
sleep apnoea syndromes	53 (0.3)	11 (0.1)	58 (0.2)	15 (0.0)
Medication use up to 112 days prior to MVC, n (%)				
benzodiazepines	401 (2.0)	735 (3.7)	657 (1.7)	1,050 (2.7)
non-benzodiazepine hypnotics	112 (0.6)	194 (1.0)	209 (0.6)	314 (0.8)
Alcohol consumption prior to MVC, n (%)				
none	1,604 (8.0)	2,647 (13.1)	2,742 (7.2)	4,844 (12.6)
<1 unit / day	4,610 (23.1)	8,543 (42.4)	8,193 (21.6)	14,914 (38.8)
1-2 units / day	3,805 (19.1)	2,313 (11.5)	7,280 (19.2)	4,873 (12.7)
3-6 units / day	1,680 (8.4)	367 (1.8)	3,176 (8.4)	793 (2.1)
7-9 units / day	36 (0.2)	10 (0.1)	84 (0.2)	13 (0.0)
>9 units / day	8 (0.0)	1 (0.0)	26 (0.1)	2 (0.0)
not recorded	8,211 (41.2)	6,274 (31.1)	16,407 (43.3)	13,051 (33.9)

Table 19: Crude and adjusted associations between involvement in MVCs and sleep disorders in THIN 255 (November 2004)

Condition	Unadjusted model	Adjusted for use of sedative and/or antidepressant medications	Adjusted for medication use* and alcohol consumption
	OR (99% Confidence Interval)		
Insomnia	1.57 (1.45 - 1.69)	1.49 (1.38 - 1.62)	1.41 (1.26 - 1.57)
Sleep Apnoea	1.68 (1.08 - 2.61)	1.67 (1.07 - 2.59)	1.61 (0.90 - 2.87)
Snoring	1.91 (1.52 - 2.40)	1.90 (1.51 - 2.39)	1.85 (1.37 - 2.49)
	n_{cases}=40,109 $n_{controls}$=76,318	n_{cases}=40,109 $n_{controls}$=76,318	n_{cases}=21,810 $n_{controls}$=33,441

* Sedative and/or antidepressant medications

Table 20 shows the results of the adjusted analysis, stratified by consultation frequency. Effect sizes for insomnia and sleep apnoea were similar in both groups, but the effect size for snoring was greatest among those with below median consultation frequencies.

Table 20: Association between involvement in MVCs and sleep disorders in THIN 255 (November 2004), adjusted by use of sedative and antidepressant medications and alcohol consumption and stratified by consultation frequency

Condition	Odds Ratio (99% Confidence interval)	
	Below median consultation frequency	Above median consultation frequency
Snoring	2.54 (1.11 to 5.80)	1.29 (0.85 to 1.95)
Insomnia	1.10 (0.69 to 1.75)	1.27 (1.10 to 1.46)
Sleep Apnoeas	1.49 (0.26 to 8.54)	1.65 (0.75 to 3.67)

Discussion

The results of this study indicate that practitioner-recorded insomnia is associated with a 1.5-fold increase in the risk of MVC, and that this effect is not explained by the use of sedative medications amongst affected individuals. The observed associations between both snoring and sleep apnoea syndromes and subsequent involvement in MVCs are consistent with previous reports in the literature (67, 68) suggesting that the use of THIN data to investigate the impact of disordered sleep on the risk of MVC is appropriate.

The results of the analysis stratified by consultation frequency suggest that the association between snoring and MVC was largely driven by those consulting their GP the least frequently, whilst the associations between sleep apnoea and insomnia and MVC were broadly similar in both groups. This may have occurred because snoring is more likely to be the primary reason for a consultation among those who do not consult their GP frequently, and the severity (and any consequent effects on driving ability) may be greater in this group. The absence of such a marked difference in effect sizes for insomnia and sleep apnoea suggests that these conditions are more likely to be the primary reasons for a consultation and that bias due to opportunistic recording during consultations for other conditions or problems is minimal.

As before, the major strength of this study is the considerable statistical power provided by the use of THIN; this is the largest study to date of these effects in the UK population. The study population contained a reasonable spread of socio-demographic characteristics, and the case and control populations were well matched in terms of age, sex and deprivation, suggesting that the results should be generalisable to the overall UK population. In addition, the availability of prescription data permits adjustment for the effects of sedative and antidepressant medications which may also affect MVC risk. Fortunately, in this population, a substantial proportion of individuals experiencing disordered sleep did not receive medication so the effects were not completely co-linear and the adjustment should be adequate.

The major limitation of this study is the uncertainty as to whether individuals involved in MVCs in the study population were driving at the time. Assuming that passengers and / or pedestrians are not also more likely to be involved in MVCs as a consequence of disordered sleep, their presence in the study population would tend to lead to underestimation of the true magnitude of association. It is also likely that the recording of sleep disorders in THIN under-represents the true prevalence in the UK population, as approximately only one in four individuals with insomnia inform their physician (51), and the prevalence of sleep apnoea syndromes in the UK may be as high as 3.8% (73) - well above the observed level in this study (although this may be in part due to the relative youth of individuals involved in MVCs compared with the general population). It is likely that those individuals who consult their physician regarding sleep disorders are those with more severe symptoms, so the observed effects may overestimate the risk of MVC associated with these conditions as a whole, whilst underestimating the absolute number of individuals affected. The poor recording of alcohol consumption in this population is problematic as it prevents full adjustment for any potential confounding effect of higher consumption of alcohol among individuals with sleep disorders, although the similarity of the adjusted effects in the sub-population with a record of alcohol consumption to those in the wider population is reassuring.

Sleep apnoea syndromes cause daytime hypersomnolence (74), and are an established risk factor for involvement in MVCs, with estimates of the odds ratio of association ranging from 1.3 to 13.3 (67). The observation that sleep apnoea

syndromes are associated with a 1.6-fold increased risk of MVC in the THIN population is consistent with these findings, but at the lower end of the range, suggesting that the presence of non-drivers in the population may indeed dilute the observed effects somewhat. Treatment with continuous positive airway pressure has been demonstrated to reduce the risk of MVC among affected individuals (67), providing strong evidence that the association is causal.

The results of this study support the limited available evidence suggesting that snoring is associated with an increased risk of involvement in MVC (68). Snoring is associated with daytime hypersomnolence (75), and as many as 36% of adults aged 30 to 60 years may be habitual snorers (75). The emergence of snoring as a potential risk factor for involvement in MVCs is of concern and merits further investigation given the high prevalence of snoring in the general population. It is likely that some of the association between snoring and involvement in MVCs in this study is due to the presence of individuals with undiagnosed sleep apnoea syndromes presenting with the symptom of snoring, but regardless of the causal pathways involved snoring appears to be an important risk factor for MVCs.

Individuals with insomnia report a range of daytime symptoms with the potential to affect driving performance, including hypersomnolence, irritability and impaired memory and cognitive function (69, 76-78). It is therefore plausible that the association between insomnia and involvement in MVCs in the THIN population is causal. The only previous report in the literature on the association between insomnia and risk of involvement in a MVC in the general

population is from a telephone survey in the United States (70). This suggested that individuals with insomnia had a 2.5-fold increased risk of involvement in a MVC although the absence of both formal statistical analysis and adjustment of for potential confounding factors such as the use of sedative medication makes interpretation of these results problematic.

Conclusion

The findings of this study corroborate previously observed associations between snoring and sleep apnoea syndromes and an increased risk of involvement in MVCs. In addition, they demonstrate an increased risk of involvement in MVCs among individuals reporting insomnia to their physician, which is independent of the effect of the use of sedative medications. If these associations are causal, effective management of these heterogeneous sleep disorders may reduce the risk of involvement in MVCs.

7. The Risk of Motor Vehicle Crashes Among Individuals with Diabetes Mellitus – a Case-Control Study

Abstract

Background. Individuals with diabetes may be subject to driving restrictions in the United Kingdom (UK), but few studies have assessed the impact of diabetes on the risk of involvement in motor vehicle crashes (MVCs) in the UK population.

Study design and methods. Data from THIN were used to conduct a nested case-control study of the effect of diabetes on the risk of MVC, stratified by treatment group.

Results. 40,109 individuals aged 18-75 years with a first recorded motor vehicle crash on or after 1st Jan 1991 and 76,398 controls (matched by age, sex and primary care provider)were identified. Following adjustment for frequency of GP consultation, a diagnosis of diabetes was associated with a decreased risk of involvement in a MVC (Odds Ratio – 0.78; 95% Confidence Interval, 0.72 to 0.85). The risk of involvement in a MVC was similar for individuals receiving insulin treatment, oral antidiabetics and for those receiving no medication.

Conclusions. A population-based assessment suggests that the risk of involvement in MVC is lower among individuals with diabetes than in the general UK population.

Introduction

Diabetes mellitus affects over 170 million individuals worldwide, and demographic changes are projected to double the number of cases by 2030 (79). Hypoglycaemia due to diabetes is often cited as a cause of motor vehicle accidents (80), and as a consequence many drivers with diabetes are charged higher premiums by their motor insurers (81).

The evidence base supporting an effect of diabetes mellitus on the risk of involvement in MVC in the UK is limited. Two comparative studies in the UK found no significant increase in the risk of motor vehicle crashes (MVCs) among individuals with insulin-treated diabetes (82, 83); however both were based on very small numbers of crashes among drivers with diabetes and may have lacked sufficient power to detect any real association. By contrast, the largest study to date, an audit of United States (US) police records, suggests that drivers with diabetes are 44% more likely than other drivers to be involved in an accident where they are found to be at fault (84). Studies elsewhere in the world have produced conflicting results, with some suggesting that drivers with diabetes are at an equal or even decreased risk of MVC relative to the general population (85-87), whilst others suggest that the risk is increased (88-90). These inconsistencies are at least partly due to methodological issues (91), but may also reflect differences in driving conditions, behaviours and regulations in different jurisdictions.

Current United Kingdom driving regulations impose restrictions on individuals who use insulin treatment, but do not apply to those using oral antidiabetic

medications or diets to control their condition unless they also suffer from complications which may impair driving performance. This is a potential concern, as hypoglycaemia may also occur among individuals using oral antidiabetic medications (92), and chronic hyperglycaemia (which may occur in those with diet controlled diabetes) may result in cognitive impairment (93-95). This study uses data from THIN to assess whether whether individuals with diabetes, stratified by treatment group, are at increased risk of involvement in motor vehicle crashes (MVCs) compared with the general population.

Methods

Study population

Data from THIN were used to construct a nested case-control population. Cases were defined as all individuals with a first Read Term indicating involvement in a MVC dated after the 1st January 1991, at least 1 year after the start of their computerised medical record and whilst aged 18-75 years. The reasons for these criteria were the same as in the previous chapter. The control population was randomly selected from those individuals with no recorded MVC, matched by age (±2 years), sex and practice. Each control was required to have a minimum of 1 year of computerised medical recording before the date of MVC of their associated case, and to be living in a different household to the case. Where possible, 2 controls were matched to each case.

Exposure ascertainment

The Read Term dictionary was searched using SearchRC to identify all terms and categories containing the terms *diab* and *glycae*. The resulting list was manually inspected to identify all terms indicating the presence of chronic diabetes. Terms relating to gestational diabetes were excluded as this condition normally resolves post partum. The medical table records of all individuals in the study population were searched to identify relevant diagnoses dated prior to the date of MVC. The therapy table records of all individuals were searched to identify prescriptions for insulin or antidiabetic medications up to 1 year prior to the date of MVC. Individuals were defined as currently insulin dependent if they were diagnosed with diabetes and were treated with insulin. Individuals were classified as on antidiabetic therapy if they were diagnosed with diabetes and treated with antidiabetic drugs, but not insulin (in line with the categorisation used by the UK licensing authority (96)). Those with diagnosed diabetes but with no prescribed treatment within one year prior to the date of MVC were classified as untreated. To obtain an objective marker of glucose control, the AHD records of all individuals with a diagnosis of diabetes were searched to identify the results of glycosylated haemoglobin (HbA1c) measurements within 1 year prior to the date of MVC. Individuals were classified as controlling their diabetes well if the most recent HbA1c measurement was 7% or lower, and as controlling their diabetes poorly if their HbA1c was greater than 7% (97). Where multiple recordings were available, the most recent recording prior to the date of MVC was used.

Frequencies of GP consultation were calculated for each individual to permit adjustment for the possibility that individuals visiting their GP regularly due to chronic disease may be more likely to report a MVC. The frequency of consultation was defined as the number of dates on which data were entered in each individual's AHD or medical table records prior to the date of MVC, and more than one year after the start of the computerised record, divided by the duration of this period. Recordings in the therapy table were excluded as repeat prescriptions may be issued without a formal consultation. Area level Townsend indices were extracted from individuals' PVI table records where available to allow the socio-economic status of cases and controls to be compared.

Statistical analysis

The data were analysed using conditional logistic regression models in STATA 9.1 (STATA Corp. TX, United States) for Windows XP. Three analyses were conducted. The first compared the risk of involvement in MVC for all individuals with diabetes with that in the general population. Two further analyses subdivided individuals with diabetes by the type of treatment prescribed and by their level of diabetic control, respectively. In each case unadjusted odds ratios, and odds ratios adjusted by quintile of consultation frequency were calculated. In order to further investigate the impact of consulting behaviour the association between diabetes and involvement in MVC was also calculated stratified according to consultation frequency (above vs. below or equal to the median frequency).

A power calculation using PS for WindowsXP suggested that 45,000 MVC cases would provide over 95% power at the 5% significance level to detect a 15% increased risk of involvement in MVC, assuming a background prevalence of a diagnosis of diabetes of 3.7% (98).

Results

The basic demographic characteristics of the study population are given in Table 21. The case and control populations were similar in terms of age and socioeconomic status. The prevalence of diabetes (recorded prior to the date of MVC) in the population was 2.8%. 24.4% of individuals with diabetes received a prescription for insulin within 1 year prior to the date of MVC, 33.2% received only antidiabetic medications, and 42.4% received no prescription. According to the most recent available glycosylated haemoglobin measurement, 17.2% of individuals with diabetes were controlling their condition well prior to the date of MVC (HbA1C≤7%), 25.5% were poorly controlled (HbA1C>7%), and 57.3% had no recording in the year prior to MVC. Individuals involved in MVCs consulted their GP more regularly than controls (median numbers of consultations per year 2.9 and 1.6 respectively) and women consulted their GP more frequently than men (3.1 versus 1.3 consultations per year).

In the unadjusted analysis, diagnosed diabetes was associated with a small increased risk of involvement in MVC (Table 22: OR = 1.12; 95% Confidence interval, 1.04 to 1.21). Similar effects were observed in each of the three treatment categories, but only the untreated group showed a significantly raised risk of involvement in MVC (OR=1.15; 95% CI, 1.03 to 1.29). There was

little difference between those with well controlled diabetes and poorly controlled diabetes. Following adjustment by quintile of GP consultation frequency, diagnosed diabetes was associated with a decreased risk of MVC (OR=0.78; 95% CI, 0.72 to 0.85). There was little difference in risk between those prescribed insulin (OR = 0.71, 95% CI, 0.61 to 0.83) and those taking oral antidiabetics (OR = 0.73; 95% CI, 0.64 to 0.84) and those receiving no treatment (OR = 0.87; 95% CI, 0.77 to 0.98). Stratification by level of diabetic control (as indicated by glycosylated haemoglobin levels) showed similar risks of involvement in MVCs among individuals with good control (OR = 0.81; 95% CI, 0.68 to 0.97) and individuals with poor control (OR = 0.77; 95% CI 0.66 to 0.90).

Table 21: Socio-demographic characteristics and prevalence of diabetes among individuals involved in motor vehicle crashes and age & gender matched controls in THIN 255 (November 2004)

Characteristic	Cases		Controls	
	males	females	males	females
	n =19,954	n =20,155	n =37,908	n =38,490
Age at time of MVC, median (interquartile range)	36 (27 - 48)	36 (27 - 49)	36 (27 - 49)	37 (27 - 50)
Quintile of Townsend deprivation index, n (%)				
1st; least deprived	4,641 (23.3)	5,107 (25.3)	8,569 (22.6)	9,152 (23.8)
2nd	4,058 (20.3)	4,196 (20.8)	7,191 (19.0)	7,505 (19.5)
3rd	3,941 (19.8)	3,989 (19.8)	7,291 (19.2)	7,498 (19.4)
4th	3,678 (18.4)	3,606 (17.9)	6,841 (18.1)	6,851 (17.8)
5th; most deprived	3,006 (15.1)	2,638 (13.1)	6,265 (16.5)	5,808 (15.1)
not available	630 (3.2)	619 (3.0)	1,751 (4.6)	1,676 (4.4)
Individuals with a recordiing of diabetes prior to MVC, n (%)	659 (3.3)	539 (2.7)	1075 (2.8)	1004 (2.6)
prescribed insulin*	161 (0.8)	130 (0.7)	276 (0.7)	233 (0.6)
prescribed antidiabetics*	240 (1.2)	150 (0.7)	389 (1.0)	310 (0.8)
untreated*	258 (1.3)	259 (1.3)	410 (1.1)	461 (1.2)
Level of diabetic control, n (%)				
good control (HbA1c level <=7%) †	120 (0.6)	93 (0.5)	173 (0.5)	179 (0.5)
poor control (HbA1c level >7%) †	186 (0.9)	127 (0.6)	278 (0.7)	243 (0.6)
with diabetes, but no HbA1c recording *	353 (1.8)	319 (1.6)	624 (1.7)	582 (1.5)
GP consultation frequency ‡ (visits per year), median (IQR)	1.9 (0.9 - 3.6)	4.1 (2.3 - 7.0)	0.9 (0.0 - 2.4)	2.5 (0.9 - 4.9)

* in 1 year prior to MVC

† most recent recording up to 1 year prior to MVC

‡ Prior to MVC and >1 year after start of computerised record.

Table 22: Crude and adjusted associations between involvement in motor vehicle crashes in THIN 255 (November 2004), by treatment category and glycosylated haemoglobin level

Exposure	Unadjusted Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)*
All diabetes	1.12 (1.04 to 1.21)	0.78 (0.72 - 0.85)
By treatment type:†		
- prescribed insulin	1.11 (0.96 to 1.28)	0.71 (0.61 - 0.83)
- prescribed antidiabetics	1.09 (0.96 to 1.24)	0.73 (0.64 - 0.84)
- untreated	1.15 (1.03 to 1.29)	0.87 (0.77 - 0.98)
By level of control: ‡		
- good control (HbA1c < =7%)	1.19 (1.00 to 1.41)	0.81 (0.68 - 0.97)
- poor control (HbA1c >7%)	1.17 (1.02 to 1.35)	0.77 (0.66 - 0.90)
- not recorded	1.08 (0.98 to 1.19)	0.78 (0.70 - 0.86)

* adjusted by quintile of GP consultation frequency
† in 1 year prior to MVC
‡ most recent recording in 1 year prior to MVC

The association between diabetes and MVC was considerably smaller among those who consulted their GP infrequently (OR=0.74, 95% CI 0.56 to 0.97) than among those with above-median consultation frequencies (OR=0.90, 95% CI 0.82 to 1.00).

Discussion

This is the largest study of the association between diabetes and involvement in MVC in the UK population to date. The results suggest that once differences in frequency of GP consultation (and hence ascertainment bias) are taken into account, individuals with diabetes are less likely to be involved in MVCs than the general population (OR=0.78; 95% CI, 0.72 to 0.85). There was no

substantial difference in risk of MVC after stratification by treatment regime, or by level of blood glucose control. The results of the analysis stratified by consulting frequency suggest that any potential increased risk of MVC among individuals with diabetes may be largely confined to those who consult most frequently. These individuals are likely to be those with more severe disease, or those with other health problems.

The major strength of this study is the large population available in THIN, which provides sufficient power to detect even a small increased risk of MVC among individuals with diabetes. The 2.8% prevalence of diabetes in the population is reassuring as it is within the range suggested by national prevalence data (98), allowing for the demographic characteristics of the population. This suggests that the method of exposure ascertainment and the recording of diabetes in primary care are sufficiently robust to permit the study of this condition in THIN.

The major limitation of the study is, as ever, the inability of THIN records to effectively distinguish between drivers and other road users. Some of the observed reduction in risk of MVC among individuals with diabetes in the adjusted analysis may be due to the presence of a substantial proportion of individuals with diabetes who have modified their driving behaviour, refrain from driving, or are not permitted to drive. For this reason, the results provide a population level estimate of the risk of involvement in MVC among all individuals with diabetes, rather than the individual risk among drivers with diabetes.

Previous studies of the association between diabetes and involvement in MVCs have produced inconsistent results, partly due to differing sources of data, selections of control groups and differing treatment of potential confounding factors (91). The largest to date, published in 2000 and involving 66,870 drivers involved in MVCs in the US found a relative risk for at-fault MVCs of 1.44 ($p<0.05$) among diabetic patients with unrestricted driving licenses, compared with the general population (84). It is unlikely that such a large effect would be possible in the UK population as driver behaviour varies significantly between countries; the results of a recent international survey suggest that drivers in the US are more likely to experience episodes of hypoglycaemia whilst driving than those in Europe, and are more likely to continue driving during an episode (88). In addition, European and UK licensing regulations with respect to diabetes are stricter than those in force in many US states, some of which impose no restrictions on drivers with diabetes (91).

There has been little comparative epidemiological research into the impact of diabetes on MVC risk in the UK to date. A 1989 study of drivers involved in MVCs in Belfast found that 81 drivers with insulin-treated diabetes reported 7.9 accidents per million miles driven, compared with 7.8 in a control population of 76 non-diabetic drivers (83). A 2002 study in the Scottish Trauma Audit Group reported no increased risk of MVC leading to death or serious injury among individuals with diabetes (82). Both studies were based on comparatively small numbers of MVCs among individuals with diabetes and consequently have limited statistical power to detect any difference in risk of involvement in MVC among individuals with diabetes. The results in the THIN poplation do not

support these findings, possibly reflecting differences in the type and severity of accidents in these heterogeneous populations, or as a consequence of our inability to definitively identify drivers.

Current UK driving regulations require that only individuals with insulin-treated diabetes inform the licensing authority of their condition, and licenses are issued only to those with awareness of the onset of hypoglycaemia and in the absence of other conditions likely to impair driving performance. Individuals taking oral antidiabetics or controlling their condition with diet alone are not required to inform the licensing authority of their condition unless their driving may be impaired by complications of diabetes. The findings of this study suggest that, at population level and under the current system of regulation, diabetes is not associated with any increase in the risk of MVC and that there is little or no difference in the risk between the different treatment groups. On the contrary, the combined deterrent effects of the current regulations and raised insurance premiums may result in a lower risk of MVC among diabetics than in the general population. These findings do not appear to justify the charging of higher motor insurance premiums for drivers with diabetes in the current system, although it is possible that our population-level estimates do not reflect individual-level risks. Whether relaxation of restrictions on driving would result in a marked increase in MVCs is not clear.

Conclusions

The results of this study suggest that, once differences in consulting behaviour are taken into account, rates of involvement in MVCs are lower among

individuals with diabetes than in the general population, and that this lower risk is consistent between individuals receiving different treatments for diabetes. Further work is required to determine whether this reduction in risk is attributable to changes in driving behaviour arising from the current regulations or perceptions of increased risk among drivers with diabetes, or whether indeed at individual level, people with diabetes are less likely to crash.

8. Motor Vehicle Crashes as a Marker of Undiagnosed Disease – a Cohort Study

Abstract

Background. Common diseases that involve the neurological, visual and cardiovascular systems may impair driving ability and increase the risk of involvement in motor vehicle crashes (MVCs). This study tests the hypothesis that involvement in a MVC may predict a subsequent increased risk of being diagnosed with common diseases involving cardiovascular, neurological and visual symptoms.

Study design and methods. Data from THIN were used to conduct a cohort study. The exposed cohort comprised all individuals aged over 18 years whose records indicated involvement in a MVC. A control cohort was selected from those individuals who had no recorded MVC and was matched to the MVC cohort by age, sex and general practice. The medical records of all participants were searched for subsequent diagnoses of dementia, Parkinson's disease, cataracts, glaucoma, cardiac disease, cerebrovascular disease and diabetes in the two years after the MVC.

Results. Data were obtained on 42230 individuals involved in MVCs and 80555 matched "controls". After adjustment for consultation frequency, there was an increased incidence of a new diagnosis of cardiac disease (incidence rate ratio 1.20; 99% confidence intervals: 1.10 to 1.32) in the two years after the MVC. There was no excess risk of receiving a diagnosis of dementia, Parkinson's disease, cataracts, glaucoma, cerebrovascular disease or diabetes in the two years after the MVC.

Conclusions: Involvement in a MVC may predict subsequent development of cardiac disease.

Introduction

The causes of Motor Vehicle Crashes (MVCs) are multifactorial, but the majority of incidents can be attributed to sub-optimal driving performance (99). It has long been recognised that a range of illnesses may contribute to impaired driving ability, and individuals suffering from such conditions may be subject to legal restrictions or prohibited from driving altogether (96). Driver impairment can be caused by even comparatively mild symptoms involving the neurological, visual and cardiovascular systems. For example, drivers with Alzheimer's disease exhibit impaired ability to perform simple tasks of visual search and recognition of roadside targets even in the early stages of illness (100). Many diseases have a subclinical period prior to formal diagnosis when sensory or motor impairment may be present, leading to an increased risk of MVC. Involvement in a MVC may therefore constitute a sentinel event indicating the possible presence of an undiagnosed disease. If true, this may help in the earlier diagnosis of diseases that are amenable to interventions; over 50 million individuals are injured in MVCs each year worldwide (1), many of whom have contact with medical services as a result. This study uses data from THIN to investigate whether involvement in a MVC predicts subsequent development of common diseases involving visual, cardiovascular and neurological symptoms, excluding those (such as epilepsy) which could be directly caused by involvement in a crash.

Methods

Study population

Data from THIN were used to construct a cohort population. The database was searched to obtain details of all individuals whose records noted that they were involved in a first recorded MVC after 1st January 1991, at least one year after the start of their computerised medical record, and whilst aged 18 years or over. The upper age limit used in previous studies was dropped in view of the nature of the illnesses under investigation (see below). The date of entry into the study was defined as the date of the MVC. A control cohort of individuals, matched by age (±2 years), sex and primary care centre was randomly selected from those individuals with no recorded involvement in a MVC. Where possible, two control individuals were selected for each case. Individuals in the non-MVC cohort were defined as entering the study on the same date as their associated case, and were similarly required to have at least 1 year of computerised follow-up data available prior to this date.

Exposure ascertainment

As in previous studies, SearchRC and manual inspection were used to create Read Term lists defining the conditions of interest. The medical and AHD table records of each individual were then searched for recordings of Parkinson's disease (SearchRC term: *Parkinson*), non-alcoholic or substance abuse related dementias (*dement* *senil* *alzheim*), cerebrovascular disease (*cva* *stroke* *tia* *cerebrov*), cataracts (*cataract*), glaucoma (*glauc*), cardiac disease (*cardi* *angi* *heart* *ischae*) or non-gestational diabetes (using the

list defined previously). In each case, individuals diagnosed with the condition of interest on or prior to the date of entry were excluded from the population before analysis. The end of follow-up for each individual was defined as the date of diagnosis with the condition of interest, the date of death or of transfer to another primary care centre or two years from the date of MVC, as appropriate for the primary statistical analysis. The duration of two years was chosen as this was the median period of time data were available after the MVC.

Frequencies of GP consultation prior to the date of MVC were calculated for each participant to permit adjustment for the possibility that those who visit their GP most regularly may be more likely to report involvement in a minor MVC, and that individuals in the MVC cohort may consequently be diagnosed with other illnesses at an earlier stage than those in the non-MVC cohort. The frequency of consultation was defined in the same manner as in the previous study. Frequencies prior to the date of MVC were used as it was considered likely that involvement in a MVC might temporarily or permanently affect consultation frequency, and that the prior level would better reflect the innate tendency of each individual to consult their GP for an incident illness. Postcode level Townsend indices were obtained where possible to allow the socio-economic status of the MVC and non-MVC cohorts to be compared.

Preliminary analysis

The initial analytical approach used Cox's proportional hazards models in STATA SE version 10 for Windows Vista to compare time to diagnosis or exit in the MVC and non-MVC cohorts. In each case, Schoenfeld residuals were

calculated and the phtest postestimation command was used to test the assumption of proportional hazards between the two cohorts. Whilst this assumption was met (at the 5% significance level) for cardiac and cerebrovascular disease, this was not the case for the other conditions under investigation. Experimentation with subdividing the follow-up time did not allow the assumption to be met for all conditions, so the decision was taken to use an alternative method with less strict assumptions for all conditions for the sake of analytical consistency.

Revised statistical analysis

Poisson regression models were used to estimate crude incidence rate ratios (IRRs) of each condition of interest in the MVC cohort relative to the non-MVC cohort. A second series of analyses was conducted to estimate IRRs adjusted by quintile of GP consultation frequency. In both cases, 99% confidence intervals were calculated in view of the risk of detecting spurious associations due to the large number of hypotheses being tested.

Results

The basic demographic characteristics of the study population are given in Table 23. The median duration of follow-up data post MVC was 2.1 years (interquartile range 0.7 to 4.8). The MVC and non-MVC cohorts were similar in terms of both age and socioeconomic status. Individuals involved in MVCs consulted their GP more regularly than those in the non-MVC cohort (median numbers of consultations per year 2.9 and 1.6 respectively) and women

consulted their GP more frequently than men (3.1 versus 1.3 consultations per year).

Table 23: Socio-demographic characteristics of the cohort population

Characteristic	Involved in MVC		Not involved in MVC	
	males	females	males	females
	n =20,966	n =21,264	n =39,898	n =40,657
Age at time of MVC, median (interquartile range)	36 (27 - 49)	36 (27 - 50)	37 (28 - 49)	37 (28 - 50)
Quintile of Townsend deprivation index, n (%)				
1st; least deprived	4644 (22.2)	5126 (24.1)	8571 (21.5)	9171 (22.6)
2nd	4060 (19.4)	4209 (19.8)	7193 (18.0)	7502 (18.5)
3rd	3953 (18.9)	4000 (18.8)	7304 (18.3)	7538 (18.5)
4th	3692 (17.6)	3607 (17.0)	6857 (17.2)	6872 (16.9)
5th; most deprived	3003 (14.3)	2629 (12.4)	6265 (15.7)	5777 (14.2)
not available	1614 (7.7)	1693 (8.0)	3708 (9.3)	3797 (9.3)
Incident diagnoses up to 2 years after date of MVC, n (%)				
Parkinson's disease	20 (0.1)	16 (0.1)	42 (0.1)	26 (0.1)
Dementia	36 (0.2)	31 (0.1)	44 (0.1)	68 (0.2)
Cerebrovascular disease	193 (0.9)	176 (0.8)	262 (0.7)	242 (0.6)
Cataract	205 (1.0)	258 (1.2)	219 (0.5)	367 (0.9)
Glaucoma	73 (0.3)	89 (0.4)	121 (0.3)	156 (0.4)
Heart disease	1950 (9.3)	2174 (10.2)	1679 (4.2)	1896 (4.7)
Diabetes mellitus	664 (3.2)	810 (3.8)	680 (1.7)	868 (2.1)
GP consultation frequency* (visits per year), median (IQR)	1.9 (0.9 - 3.6)	4.2 (2.3 - 7.0)	0.9 (0.0 - 2.4)	2.5 (0.8 - 4.9)

* Prior to MVC and >1 year after start of computerised record.

In the unadjusted analysis, individuals involved in MVCs were at significantly increased risk of being diagnosed with diabetes (IRR=1.22; 99% Confidence Interval CI: 1.05-1.44) and cardiac disease (IRR=1.40; 99% CI: 1.29-1.53) compared with those in the non-MVC cohort. There was no evidence of a significant difference in the incidence of Parkinson's disease, dementia,

cataracts, glaucoma or cerebrovascular disease between the two groups (Table 24).

Table 24: Association between involvement in MVCs and diagnosed disease in the subsequent two years

Condition	Unadjusted Incidence Rate Ratio (99% Confidence Interval)	Adjusted Incidence Rate Ratio (99% Confidence Interval)*
Dementia	0.79 (0.38-1.65)	0.67 (0.32-1.39)
Parkinson's Disease	0.88 (0.32-2.47)	0.71 (0.25-1.99)
Cataract(s)	1.10 (0.82-1.49)	0.89 (0.66-1.21)
Glaucoma	0.70 (0.45-1.09)	0.59 (0.38-0.93)
Cardiac Disease	1.40 (1.29-1.53)	1.20 (1.10-1.32)
Cerebrovascular Disease	0.84 (0.62-1.13)	0.69 (0.51-0.93)
Diabetes	1.22 (1.05-1.44)	1.04 (0.88-1.22)

* Adjusted by quintile of GP consultation frequency.

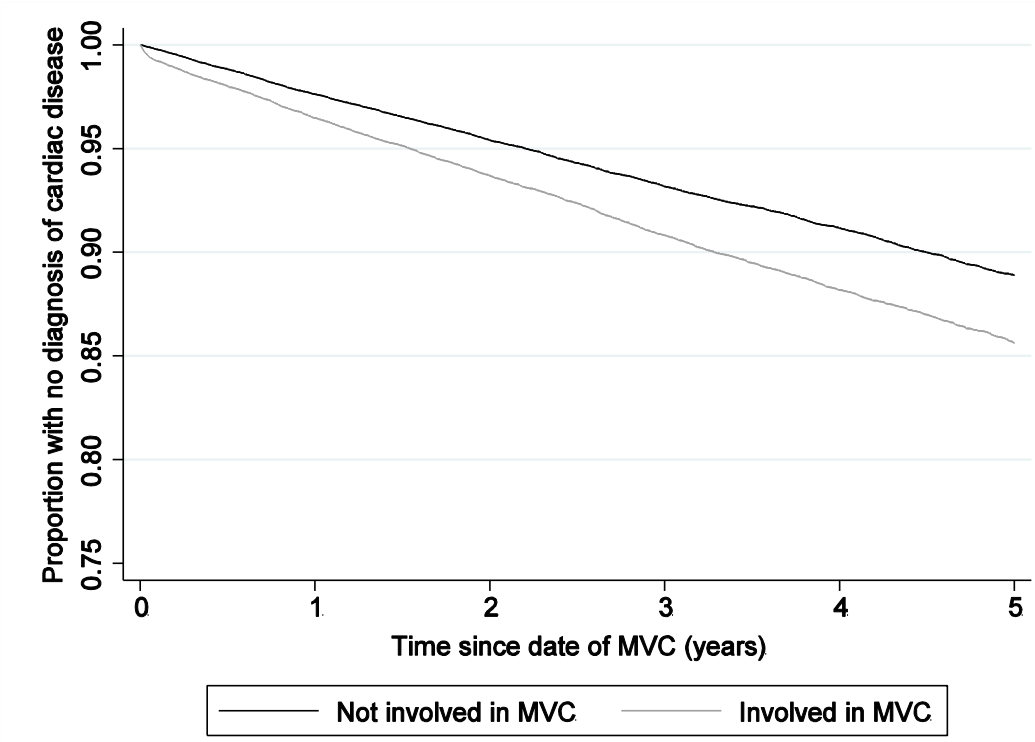
Following adjustment by quintile of GP consultation frequency, involvement in MVCs continued to be associated with an increased incidence of cardiac disease (IRR=1.20; 99% CI: 1.10-1.32). The time course of this effect in the five years after the date of MVC is presented in Figure 1. Involvement in a MVC was no longer associated with an increased incidence of diabetes (IRR=1.04; 99% CI: 0.88-1.22). Individuals involved in MVCs were at significantly decreased risk of being diagnosed with glaucoma (IRR=0.59; 99% CI: 0.38-0.93) and cerebrovascular disease (0.69; 99% CI: 0.51-0.93) compared with those in the control cohort. There was no evidence of a significant difference in the incidence of Parkinson's disease, dementia or cataracts between the two groups.

Discussion

This is the first study to test the hypothesis that involvement in a motor vehicle crash (MVC) may predict the risk of receiving a diagnosis of a common disease in the subsequent two years. There was a 20% excess of cardiac disease in those who had had a MVC compared to controls, but no difference for dementia, Parkinson's disease, cataracts or diabetes. Individuals in the MVC cohort were less likely be diagnosed with glaucoma or cerebrovascular disease in the two years following an MVC, perhaps indicating that the early symptoms of these conditions constitute a stronger deterrent to driving than for other diseases, or that these diseases are most common among those who already refrain from driving for other reasons.

The major strengths of the analysis are the large size of the study population, which affords considerable statistical power, and the prospective nature of data collection in THIN. The data used in this study were collected between 1984 and 2004 and are therefore relevant to contemporary health care systems and driving regulations in the UK. The cases and controls have a similar demographic structure as measured by the Townsend deprivation index and hence our results are unlikely to be a consequence of confounding by socio-economic status. Figure 21 demonstrates that the increased incidence of cardiac disease in cases compared to controls is constant over time, which suggests that this is a true effect rather than an artefact caused by increased diagnostic pick-up as a consequence of recent exposure to the health care system.

Figure 21: The incidence of cardiac disease in individuals involved in a motor vehicle crash compared with individuals not involved in MVCs



The effect of adjusting for consulting behaviour in this analysis raises some interesting questions. In previous chapters, adjustments by consulting frequency were used to avoid or investigate the possibility of bias due to coincident reporting of exposure or outcome events during consultations for a different problem or condition. In this case, the intention was to adjust for the possibility that individuals who consult their GP very frequently may simply tend to be diagnosed with one of the outcome conditions earlier than those who consult infrequently, and that there may in fact be no real difference in the prevalence of underlying disease between individuals involved in MVCs and the comparison group. In practice, however, this may have been an over-

adjustment. The Kaplan-Meier plot suggests that differences in rates of diagnosis of cardiovascular disease are sustained over a long period; if consulting behaviour was a major confounding factor, one might expect to observe an increasing trend towards convergence, which is not apparent in these data. Adjustment by consultation frequency also implicitly adjusts for the possibility that MVCs may be more likely to be recorded among individuals with poor general health (and a greater likelihood of developing the illnesses of interest) during attendance for other conditions. This may also be undesirable – if involvement in a MVC is an indicator of possible subclinical disease (regardless of whether this is causal or due differences in recording), adjusting by consultation frequency may lead to underestimation of the usefulness of such indicators in clinical practice.

The main limitation of the analysis is the inability to definitively identify drivers in THIN data. If, as hypothesised, the link between the MVC and the subsequent diagnosis of disease is causal, the presence of non-drivers in the MVC cohort would tent to reduce the observed effects. This provides alternative explanation for the absence of a positive association between involvement in an MVC and cerebrovascular disease, dementia, Parkinson's disease, cataracts, glaucoma or diabetes.

If replicated elsewhere, these findings have important implications for public policy. According to present trends in the United States, half of healthy 40-year-old males will develop coronary heart disease in the future, as will one in three healthy 40-year-old women (101). The Screening for Heart Attack Prevention

and Education Task Force from the USA recommended early screening of the asymptomatic at-risk population (102), and the identification of new risk factors or precursors may help target individuals who may benefit from early diagnosis and intervention. Whilst the 20% increased risk of cardiac disease in the MVC cohort is relatively small, it is of the same order of magnitude as the increased risk of breast cancer among women taking hormone replacement therapy (103) and is therefore sufficiently large to be considered clinically significant. In addition, certain groups of society are difficult to identify and engage with health care services. All of the MVC cases in this study population had to make contact with the health care system to have their details of involvement in a MVC recorded in THIN. This provides an opportunity to identify and make contact with individuals who are high risk of developing cardiac disease, and to introduce appropriate interventions at an early stage.

This prospective observational study is primarily hypothesis generating as it is not possible to identify the precise mechanism responsible for the observed association between involvement in a MVC and subsequent diagnosis of cardiac disease in these data. Potential explanations include cognitive impairment due to subclinical cardiovascular disease (104) or confounding by associated lifestyle factors such as smoking and obesity which may increase MVC risk. The findings with respect to chronic diseases are generally reassuring as the absence of any positive association suggests that patients may refrain from driving soon after the onset of symptoms. Further work is required to investigate the association between MVC and subsequent cardiac disease in other datasets and to investigate the mechanisms underlying these results.

Conclusions

Involvement in a MVC may be associated with the presence of sub-clinical cardiac disease. If this finding can be independently verified, routine screening by primary care practitioners of individuals involved in MVCs may aid in the early identification of cardiac disease.

9. CONCLUDING REMARKS

Summary of findings.

A considerable number of MVCs are recorded in THIN, but the characteristics of the individuals involved, and the trends in incidence over time are inconsistent with data from other sources. The odds of having a Body Mass Index over 30 kg m^{-2} was greater among individuals involved in MVCs than among age and sex matched controls (OR=1.15, 95% CI 1.03-1.29), individuals involved in MVCs were more likely to be past (but not current) smokers than to be ex-smokers (OR=1.16, 95% CI 1.02-1.32) . Current exposure to benzodiazepines (IRR=1.94, 99% CI 1.82 – 2.32) and preparations containing opioid analgesics (Combined with paracetamol: IRR=2.06, 99% CI 1.84 - 2.32, Opioid alone: IRR=1.70, 99% CI 1.39 to 2.08) was associated with an increased incidence of MVCs, as was longer-term use of non-benzodiazepine hypnotics (IRR=1.37, 99% CI 1.05, 1.79), selective serotonin reuptake inhibitors (IRR=1.16, 99% CI 1.06, 1.28) and antihistamines (IRR=1.21, 99% CI, 1.04, 1.41). No increased incidence of MVC was observed with exposure to beta-blockers or tricyclic antidepressants. Individuals involved in MVCs were more likely to have a diagnosis of snoring (OR=1.91; 99%CI: 1.52 to 2.40), insomnia (OR=1.57; 99% CI: 1.45 to 1.69) or sleep apnoea (OR=1.68; 99%CI: 1.08 to 2.61) than age and sex matched controls. Individuals involved in MVCs were (following adjustment for consultation frequency) less likely to have diagnosed diabetes (OR=0.78; 95% CI; 0.72 to 0.85) than controls, and there was no difference in risk between those receiving different forms of treatment. Involvement in a MVC was associated with an increased risk of being diagnosed with cardiac disease in the two years following the crash (adjusted IRR=1.20; 99% CI: 1.10 to 1.32).

Commentary on findings and avenues for further research

The main advantages of using THIN to investagate factors associated with involvement in MVCs are the large populations available, and the wide variety of individual-level data recorded in primary care records. Using THIN data it is possible to carry out analyses which would otherwise require extremely time-consuming and expensive prospective data collection, or for which it would not be feasible to collect information on a sufficiently large population. The main disadvantages of using THIN data are the lack of detailed information on individual MVCs, and poor or biased recording of some exposures – particularly those related to lifestyle. The work presented in this thesis illustrates these characteristics well.

The results of the study investigating the impact of lifestyle factors on the risk of involvement in MVCs demonstrates a particular weakness of primary care data. Lifestyle-related exposures are poorly recorded overall, and there is considerable potential for ascertainment bias, as these factors are more important clinically among those with poorer health. Whilst the findings that having a high BMI and being an ex-smoker are associated with involvement in MVCs are plausible, the absence of an association with current smoking is not (especially in light of the consistency of previous published studies on this topic), and simply highlights the poor recording of smoking status among younger individuals (who are most likely to be involved in MVCs). In any case, it is questionable whether the previously observed findings are the result of a causal association as there are a number of other factors (such as a tendency towards risk-taking behaviour among smokers) which may confound this

association, and which have not been adequately addressed in the published literature. It is, however, difficult to conceive of a study design which could feasibly address these issues.

Primary care data appear to perform better when investigating the effects of medications as the quality of recording of prescriptions issued is strong; most practice management systems have (automatically updated) formularies built in, simplifying the process of issuing a prescription for the practitioner, and issuing prescriptions through the computer systems allows the level of prescribing within each practice (and the budgetary consequences) to be monitored closely. Indeed, the computerised issue of prescriptions is mandated by the NHS in most circumstances. The results of the study investigating the impact of medication use on the incidence of MVCs demonstrates this well. The results are consistent with previous findings, and whilst it is not possible to disentangle the effects of medication use from those of the underlying indication in these data, in the context of the published literature on this subject it is likely that the findings do represent causal associations. The use of the case-series analytical technique provides additional information about the time course of changes in the risk of MVC with differing durations of medication use. An interesting avenue for future research would be to apply this technique to some of the data sources used in previous studies of this topic to determine whether the patterns observed in THIN correctly describe these changes, and to more accurately estimate the magnitude of the observed effects.

Primary care data also work well when studying events and conditions which are easily entered into the management software using single, simple clinical codes. As discussed in Chapter 1, over 90% of consultations recorded in THIN carry only a single Read Term. The findings of the studies investigating the impact of medical conditions on the risk of MVC demonstrate this. The observed prevalence of diabetes in the THIN population closely approximates the prevalence from national surveys, and the associations between sleep disorders and involvement in MVCs are consistent with previous findings. Overall, it is likely that the findings in relation to the medical conditions investigated are accurate, although it is probable that the inability to distinguish drivers from other road users has diluted the observed effect sizes somewhat. The plausibility of the results relating to diabetes and sleep disorders inspires some confidence in the results of the analysis investigating the association between MVC and subsequent disease, although this work remains rather speculative. This issue could be addressed more definitively by screening individuals involved in MVCs (and an appropriate control cohort) for early signs of the conditions of interest, although it is likely that a large study population would be required to provide adequate statistical power.

A major concern with all the analyses presented in this thesis is the possibility that there may be many MVCs which are not recorded as such in THIN due to coding of consultations according to the injuries sustained rather than their cause. Ongoing efforts by the NHS to improve coding of medical record data through defined recording quality standards and incentives (105), and improvements to the interfaces of practice management software packages may

help to improve this situation in the future, but it will be some time before these higher quality data comprise the majority of the research datasets. In the mean time, there is a clear need to develop means to retrospectively improve the utility of existing resources.

As discussed in Chapter 1, the software packages used by primary care practitioners to maintain patient records allow the entry of text-based information to supplement the coded recordings. A primitive system allowing some of the text component of THIN records to be investigated was released shortly before the completion of the work for this thesis. This system lists and codes the most common text comments held in THIN records. Using this information it was possible to identify over 5,000 whiplash injuries in the MVC records, compared with around 100 which were coded using Read Terms. It is likely that this still represents an underestimate - The list of common text entries is only capable of identifying those which contain the term "whiplash" with no additional text or allowance for different phraseology, so any entries containing equivalent, but differently expressed, recordings (e.g. "whip-lash", "whip lash", "whiplash injury", "neck pain due to whiplash" etc.) will still have been missed. It is also interesting to note that the list of common text entries also contains the term "RTA" (presumably indicating a "road traffic accident") lending credence to the earlier suggestion that the low incidence of MVCs in THIN compared with national statistics may be a consequence of a large number of crashes being Read coded only according to the injury sustained. The extent to which the absence of these additional recordings from the datasets used in this thesis may have biased or otherwise affected the results is

unknown. Another worthwhile avenue for future research would be to investigate whether these text data could be converted to Read Terms. If this were possible, it would enable more robust analyses of the impact of medication use and medical conditions of the risk of MVCs (and other accidents or causes of injury) to be carried out without considerable additional work. In addition, such data would increase the populations available for study, permitting investigation of rarer exposures and the calculation of more accurate estimates. Access to such data might also permit the use of primary care records to accurately quantify the incidence of MVCs at population level and allow more meaningful comparisons with data from other sources to be made.

In conclusion, it is clear that there is considerable uncertainty as to the accuracy of many of the findings presented in this thesis, although it is likely that the analyses of the associations between medication use and medical conditions and MVCs are representative of the direction of any true effects, if not the magnitude. The studies presented demonstrate important strengths and weaknesses of using primary care data for research, and describe designs and analytical techniques which could be used to effectively address the issues investigated in more appropriate datasets or in improved primary care datasets which may become available in the future.

10. APPENDICES

Appendix I – Ethical Approval

Confirmation of Approval

NHS

National Research Ethics Service

West Midlands Research Ethics Committee

27 Highfield Road
Edgbaston
Birmingham
B15 3DP

Tel: 0121 245 2544 or 2521
Fax: 0121 245 2519

Please reply to Acting Chair:

Acting Chair: **Dr Ronald Jubb**
Co-ordinator: **Mrs A McCullough**

12 December 2007

Mr Jack Gibson
Division of Epidemiology & Public Health
University of Nottingham
Clinical Sciences Building
City Hospital
Hucknall Road
Nottingham NG5 1PB

Dear Mr Gibson

Study title: **Smoking and road traffic accidents.**
REC reference: **04/MRE07/63**
Amendment ref: **AM02**
Amendment number: **3**
Amendment date: **26 October 2006**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 03 December 2007.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	5	
Notice of Substantial Amendment (non-CTIMPs)		

Membership of the Committee

The members of the Committee who were present at the meeting are listed below:

- Dr Ronald Jubb, Acting Chair – Consultant Rheumatologist
- Mrs Pat Moseley, Lay Member

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE07/63:	**Please quote this number on all correspondence**

Yours sincerely

Mrs Anne McCullough
Committee Co-ordinator

E-mail: anne.mccullough@westmidlands.nhs.uk

Copy to: *R & D Department*
City Hospital
Hucknall Road
Nottingham NG5 1PB

NHS

West Midlands Multi-centre Research Ethics Committee

27 Highfield Road
Edgbaston
Birmingham
B15 3DP

Tel: 0121 245 2544
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24 November 2006

Dr Andrew Fogarty
Division of Epidemiology & Public Health
University of Nottingham
Clinical Sciences Building
City Hospital
Hucknall Road
Nottingham NG5 1PB

Dear Dr Fogarty

Study title: **Smoking and road traffic accidents.**
REC reference: **04/MRE07/63**
Amendment ref: **AM01**
Amendment number: **3**
Amendment date: **25 September 2006**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 21 November 2006.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	4	25 September 2006
Notice of Substantial Amendment (non-CTIMPs)		25 September 2006

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed below:-

- *Dr Robert Hawker, Retired Clinical Scientist – Chairman*
- *Mrs Ros Salter, Expert Member*

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/MRE07/63:	Please quote this number on all correspondence

Yours sincerely

Anne McC

Mrs Anne McCullough
Committee Co-ordinator

E-mail: anne.mccullough@westmidlands.nhs.uk

Please ask for: Graeme Docherty

Ref: GD/04RM11

16 December, 2004

Research and Development
Hucknall Road
Nottingham
NG5 1PB

Direct Dial: 0115 9627913
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Dr AW Fogarty
Research Fellow
Division of Respiratory Medicine
Nottingham City Hospital

Dear Dr Fogarty

Smoking and Road Traffic Accidents: A Case Control Study
Project Registration Number: 04RM11 Ethics Committee Number: 04/MRE07/63

The above project has been approved by the Director of Research and Development, subject to the conditions listed below and Ethical Committee approval when required.

YOUR PROJECT CANNOT START AND DOES NOT HAVE INDEMNITY UNTIL YOU HAVE AGREED THE CONDITIONS OF APPROVAL. PLEASE COMPLETE AND RETURN THE FORM ATTACHED TO THIS LETTER CONFIRMING YOUR COMPLIANCE WITH THE CONDITIONS OF APPROVAL.

Conditions of Approval

That you have read and agree to abide with the Research Governance Framework for Health and Social Care, and comply with all reporting requirements, systems and duties of action put in place to deliver Research Governance including:

- All projects are liable to be monitored by the Trust.
- That a system for recording, reporting and reviewing all adverse events and adverse drug reactions in research is in place. This is in addition to the reporting to the approved Research Ethics Committee and the agreed sponsor.
- Honorary contracts for all non Nottingham City Hospital NHS Trust employees, involved in the project are obtained from Human Resources.
- That R&D are notified of the Research Ethics Committee 'favourable opinion' (approval) and that a copy of the letter and all approved documents (if different from those originally submitted) are forwarded to R&D with the attached Registration Details.
- All research which is discontinued temporarily or permanently should be reported to R&D.
- All changes to the project protocol including amendments, changes in study personnel and change in duration/timescale of the project should be referred to R&D as well as the appropriate ethics committee.
- That R&D are notified when project findings are published or disseminated in any way.
- To complete yearly/final reports as requested.

DJH/04RM11

The University of Nottingham

17th November 2004

Title: **Smoking and road traffic accidents: a case control study.**

Researcher: **Dr A Fogarty, Division of Respiratory Medicine**

Re: Sponsorship Statement

The following statement is the formal acceptance of the University of Nottingham, to act as Research Sponsor as set out in the Research Governance Framework.

'The University of Nottingham accepts the role of Research Sponsor as set out in the Research Governance Framework for Health and Social Care 2001'.

Paul Cartledge
Head of Research Grants and Contracts

world-changing research
from The University of Nottingham

NHS

West Midlands Multi-centre Research Ethics Committee

27 Highfield Road
Edgbaston
Birmingham
B15 3DP

Tel: 0121 245 2544
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4 October 2004

Dr A Fogarty
Lecturer in Respiratory Medicine
University of Nottingham
Respiratory Medicine – Clinical Science Building
Nottingham City Hospital
Hucknall Road
Nottingham
NG5 1PB

Dear Dr Fogarty

Full title of study: Smoking and Road Traffic Accidents: A Case Control Study
REC reference number: 04/MRE07/63

The Research Ethics Committee reviewed the above application at the meeting held on 22 September 2004.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion to the above research on the basis described in the application form, protocol and supporting documentation.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The documents reviewed and approved at the meeting were:

- ***Covering Letter, dated 27 August 2004***
- ***Application Form signed and dated 23 August 2004***
- ***Chief Investigators CV, dated 23 August 2004***
- ***Additional Sheet relating to Question A10 of the application form, dated 23 August 2004***
- ***Protocol, dated 23 August 2004***

Management approval

You should arrange for all relevant host organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

1/...

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance *(from 1 May 2004)*

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/MRE07/63. Please quote this number on all correspondence

Yours sincerely,

Anne McCullough [Mrs]
On behalf of
Dr J Rao]
Chairman

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions [SL-AC2]

2/...

Latest approved protocol

Smoking and Road Traffic Accidents: A Case Control Study

Department of Respiratory Medicine
University of Nottingham
Nottingham City Hospital
Hucknall Rd
Nottingham
NG5 1PB

Background

It is well recognised that smoking is a cause of many health problems, especially respiratory diseases, cardiovascular disease, and several forms of cancer. In 1990 tobacco and road traffic accidents (RTA) were the first and eighth highest causes of death causing 400, 000 deaths (19% to total) and 25, 000 deaths (1% of total) respectively, in an assessment of environmental causes of mortality in the United States (1). It is important to understand any potentially reversible risk factors which contribute to the complex aetiology of RTA as these are a significant cause of death in young people, in whom 40% of all deaths were caused by motor vehicles (1).

It is biologically plausible that car drivers who smoke will have an increased risk of RTAs compared to those who do not smoke, as a consequence of the decreased concentration on the task of driving while lighting and smoking a cigarette, smoking related medical conditions and direct toxicity from inhaling the cigarette fumes. Very few studies have directly addressed this question, as it is methodologically difficult and few datasets possess sufficient data to do so. As a consequence the majority of the literature consists of small studies which are

vulnerable to bias. A case-control study from Canada demonstrated that smokers have a 50% excess risk of having been at fault for an RTA compared to non-smokers (2). Smokers in a cohort study of 80 000 adults from the USA have a risk of 1.83 times that of non-smokers of having a RTA over a five year period (3). Similar associations have been shown for using a mobile phone when driving and increased risk of RTA (4). This activity is now illegal in England and Wales. To our knowledge, there have been no studies of the risk of smoking on RTA in England and Wales, or in any countries which drive on the left hand side of the road. If those who smoke do have a 50% excess risk of a RTA then the estimated societal cost in terms of property damage, injuries, deaths and health care costs in 1988 has been estimated to be over seven billion dollars Sacks (5).

We propose a case-control study to investigate the risk of smoking on road traffic accidents. If this demonstrates that, in an English population, smoking is a risk factor for road traffic accidents, we will pursue this area of research using quantitative and qualitative research methodology. The ultimate aim is to develop and evaluate public health interventions which will reduce the impact of this problem.

As the usage of medication with sedative properties (benzodiazepines, anti-histamines, other sleeping tablets) and other drugs which are known to impair performance such as beta-blockers may also reduce concentration while driving, we will also use this opportunity to assess the effect of the regular usage of these medications on the risk of having a RTA.

We also propose to use the study population to determine whether having a RTA may be an early indicator of undiagnosed or subclinical disease, and to identify which existing medical conditions may increase the risk of RTA.

Methods

Study population

The THIN Research Database is a longitudinal database of general practice records established in 1987 that covers nearly 4 million patients in England and Wales. It is not possible to identify individuals from this database. Over this period, a provision search has revealed that 86 361 patients have been coded as having had a RTA. We aim to randomly select 10 000 of these along with 2 controls for each case. Controls will not have had a RTA in the time period covered by the study and will be matched for gender, age and general practitioner. Data on potential confounding factors such as alcohol intake, socio-economic status, epilepsy, as well as factors that may be confounding or on the causal pathway such as a diagnosis of ischaemic heart disease, cerebro-vascular disease or diabetes will be collected.

Statistical analysis

Statistical analysis will use logistic regression to ascertain the effect of smoking status (never, ex-smoker, current smoker) on the risk of being involved in an RTA. We will also proceed to see if there is a dose-response relationship between the number of daily cigarettes consumed and the risk of an RTA. If an

effect is seen for smoking on the risk of RTA, this will be explored for potential confounding factors by adjusting for these. As the consumption of alcohol is an important confounding factor, we will repeat the analysis using a limited subpopulation of those who do not drink alcohol. The same analytical approach will be used to assess the effect of sedative medication and other drugs known to impair performance on the risk of having a RTA.

We will use cohort methods to compare the rates of subsequent diagnosis of conditions which might impair driving performance including dementia, Parkinson's disease, stroke, cardiovascular disease and epilepsy between RTA cases and controls in the time period after the date of accident. We will also use case-control methods to investigate the impact of conditions diagnosed prior to the date of accident.

Reference List

(1) McGinnis J, Foege W. Actual causes of death in the United States. JAMA 1993; 270:2207-2212.

(2) Brison J. Risk of automobile accidents in cigarette smokers. Can J Pub Health 1990; 81:102-106.

(3) Leistikow B, Martin B, Samuels S. Injury death excesses in smokers: a 1990-95 United States national cohort study. Injury prevention 2000; 6:277-280.

(4) Redelmeier D, Tibshirani R. Association between cellular-telephone calls and motor vehicle collisions. New Eng J Med 1997; 336:453-458.

(5) Sacks J, Nelson D. Smoking and injuries: An overview. Preventive Medicine 1994; 23:515-520.

Appendix II: SearchRC Source code

Note: SearchRC is installed as an .ado file. The data file containing the Read Term dictionary must comprise two variables labelled “medcode” (containing the Read Term Code) and “description” (containing the Read Term in text format).

```
program define searchrc



                version 9.0
                syntax anything [,csen keepcat keeptree current file(string asis)]

                capture {
                        if "`current'"!="current" {
                                use `file', clear
                        }

                        gen _keep=0
                        gen _testdes=trim(description)

                        foreach a of local anything {

                                if strpos("`a'","*")==0 & "`csen'"=="csen" {
                                        replace _keep=1 if _testdes=="`a'"
                                }

                                if strpos("`a'","*")==0 & "`csen'"!="csen" {
                                        replace _keep=1 if lower(_testdes)==lower("`a'")
                                }

                                if strpos("`a'","*")==1 & strpos(reverse("`a'"),"*")==1 {
                                        if "`csen'"=="csen" {
                                                replace _keep=1 if
strpos(_testdes,substr("`a'",2,length("`a'")-2))!=0
                                        }
                                        else {
                                                replace _keep=1 if
strpos(lower(_testdes),lower(substr("`a'",2,length("`a'")-2)))!=0
                                        }
                                }

                                if strpos("`a'","*")==1 & strpos(reverse("`a'"),"*")!=1 {

                                        if "`csen'"=="csen" {
                                                replace _keep=1 if
strpos(reverse(_testdes),reverse(substr("`a'",2,length("`a'")-1)))==1
                                        }
                                        else {
                                                replace _keep=1 if
strpos(reverse(lower(_testdes)),reverse(lower(substr("`a'",2,length("`a'")-1))))==1

                                        }
                                }

                                if strpos("`a'","*")!=1 & strpos(reverse("`a'"),"*")==1 {
                                        if "`csen'"=="csen" {
                                                replace _keep=1 if
strpos(_testdes,substr("`a'",2,length("`a'")-1))==1
                                        }
                                        else {
                                                replace _keep=1 if
strpos(lower(_testdes),lower(substr("`a'",2,length("`a'")-1)))==1

                                        }
                                }


                        }

                        gen int _kcn=0
```

```
                        sort _keep
                        by _keep: replace _kcn=_n if _keep==1
                        gsort -_kcn
                        local total=_kcn[1]
                        local runner=1
                        gen lv=strpos(medcode,".")
                        if "`keepcat'"=="keepcat" {

                                while `runner'<=`total' {
                                        gsort -_kcn
                                        display medcode[`runner']
                                        local level=strpos(medcode[`runner'],".")
                                        if `level'>3 {
                                                replace _keep=1 if
strpos(medcode,substr(medcode[`runner'],1,`level'-2))==1 &lv==`level'
                                        }
                                        if `level'==0 {
                                                replace _keep=1 if
strpos(medcode,substr(medcode[`runner'],1,4))==1 &lv==0
                                        }
                                        local latest=`runner'
                                        local runner=`latest'+1
                                }

                        }

                        if "`keeptree'"=="keeptree" {
                                while `runner'<=`total' {
                                        gsort -_kcn
                                        local level=strpos(medcode[`runner'],".")
                                        if `level'==5 {
                                                local
match=substr(medcode[`runner'],1,`level'-2)+".."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local
match=substr(medcode[`runner'],1,`level'-3)+"..."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local
match=substr(medcode[`runner'],1,`level'-4)+"...."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                        }
                                        if `level'==4 {
                                                local
match=substr(medcode[`runner'],1,`level'-2)+"..."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local
match=substr(medcode[`runner'],1,`level'-3)+"...."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                        }

                                        if `level'==3 {
                                                local
match=substr(medcode[`runner'],1,`level'-2)+"...."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)

                                        }
                                        if `level'==0 {
                                                local match=substr(medcode[`runner'],1,4)+"."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local match=substr(medcode[`runner'],1,3)+".."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local
match=substr(medcode[`runner'],1,2)+"..."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                                local
match=substr(medcode[`runner'],1,1)+"...."
                                                replace _keep=1 if
"`match'"==substr(medcode,1,5)
                                        }
                                        local latest=`runner'
                                        local runner=`latest'+1
                                }
                        }
                        keep if _keep==1
                        keep medcode description
                        sort medcode
        }
        display "Found `total' Read descriptions containing search term(s)"
        local extra=string(_N-`total')
```

```
        display "Retained `extra' additional codes from same category or tree"


end
```

Appendix III: List of Postgraduate Training Courses Attended

1.	Exploiting the Power of MS Word	2 credits
2.	Preparing and Presenting an Effective CV	2 credits
3.	Visual Basic for Applications	2 credits
4.	Finishing Your Thesis and Preparing for the Viva	2 credits
5.	Getting Going on Your Thesis and Getting Your Work Published	2 credits
6.	Building a Bibliography 2005 (an Online Learning Course)	1 credit
7.	Clinical Trials 1 & 2	2 credits
8.	Scientific Abstracts and First Year Reports	1 credit
9.	Critical Analysis of Scientific Literature Coursework	2 credits
10.	Postgraduates who Teach: Communication Skills	1 credit
11.	Faculty Postgraduate Research Forum	3 credits
	Total	20 credits

Appendix IV: List of Abbreviations

AHD	Additional Health Details
BMI	Body Mass Index
bn	Billion - short scale
CI	Confidence Interval
DfT	The United Kingdom Department for Transport
e.g.	*Exempli gratia*
GATE	General Architecture for Text Engineering
GP	General Practitioner
GPRD	The General Practice Research Database
HbA1c	Glycosylated Haemoglobin level
HES	Hospital Episode Statistics
i.e.	*Id est*
ICD	International Classification of Diseases

IMD2000	Indices of Multiple Deprivation 2000
IRR	Incidence Rate Ratio
IT	Information Technology
kg	Kilogram
m	Metre
MRC	The Medical Research Council
MVC	Motor Vehicle Crash
MVTA	Motor Vehicle Traffic Accident
N.B.	*Nota bene*
NHS	The United Kingdom National Health Service
NOS	The Newcastle Ottawa Scale
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea Syndrome
pp	Pages

PPA	The Prescription Pricing Authority
PPI	Proton Pump Inhibitor
PVI	Postcode Variable Indicators
RTA	Road Traffic Accident
SE	Standard Error
SSRI	Selective Serotonin Reuptake Inhibitor
THIN	The Health Improvement Network
UK	The United Kingdom of Great Britain and Northern Ireland
US	The United States of America
y/n	Yes or no

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