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Kalle Vaaramo

ALCOHOL AFFECTS THE OUTCOME AFTER HEAD TRAUMA

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Abstract

Traumatic brain injury can be a catastrophe for an individual and a huge economic burden for a society. Such injuries are common especially among young men and as many as half of the patients are under the influence of alcohol at the time of injury. Traumatic brain injuries can also frequently cause epileptic seizures. On the other hand, epileptic seizures are often caused by alcohol. A significant reduction in the tax on alcohol in Finland in 2004 led to a 10% increase in its consumption at the population level and a considerable increase in mortality rate among patients with alcoholic liver diseases. The risk of subsequent epileptic seizures and traumatic brain injuries among intoxicated head trauma subjects has not been evaluated before.

The present cohort consists of all subjects who were admitted to the emergency room at Oulu University Hospital in 1999 on account of head trauma. These subjects were then followed-up for 10 years, which enabled the effect of the tax reduction on the long-term outcome to be observed. The effect of being under the influence of alcohol at the time of the index head trauma on the onset of a new epileptic seizure problem and further traumatic brain injuries was investigated.

The mortality rate among head trauma subjects with harmful drinking increased significantly after the reduction in the alcohol tax, and the subjects with recorded alcohol-related seizure problems experienced an increased risk of death after the price reduction. Head trauma under the influence of alcohol predicted both new-onset seizure problems and traumatic brain injury during the follow-up.

The results are in accordance with the previous observations of a rapid increase in mortality among heavy drinkers following a sharp reduction in alcohol prices. Inebriated head trauma subjects have an increased risk of subsequent traumatic brain injury and epileptic seizure.

Keywords: alcohol drinking, alcohol price reduction, alcohol-related seizure, epidemiology, epilepsy, follow-up studies, head trauma, mortality, traumatic brain injury

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Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta, Kliinisen lääketieteen laitos, Neurologia; Oulun yliopistollinen sairaala
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Tiivistelmä

Traumaattinen aivovamma voi olla potilaalle katastrofi ja yhteiskunnalle valtava taloudellinen tappio. Aivovammat ovat yleisiä erityisesti nuorilla miehillä, ja jopa puolet niistä tapahtuu alkoholin vaikutuksen alaisena. Aivovammat aiheuttavat usein epileptisiä kohtauksia, jotka toisaalta usein johtuvat alkoholista. Vuonna 2004 Suomessa tapahtunut mittava alkoholiveron alennus lisäsi väestötasolla alkoholin kokonaiskulutusta 10 % vuoden aikana. Kuolleisuus erityisesti alkoholimaksasairauksiin lisääntyi voimakkaasti. Aiemmin ei ole tiedetty humalassa ilmaantuneen pään vamman vaikutuksesta potilaan riskiin saada uusi aivovamma tai uusi epileptinen kohtaus.

Tutkimuskohortin muodostivat vuonna 1999 Oulun yliopistollisen sairaalan päivystyksessä hoidetut päähän vammautuneet potilaat. Heitä seurattiin rekisteritietojen avulla vuoden 2009 loppuun, minkä ansiosta voitiin tutkia veronalennuksen vaikutusta potilaiden pitkäaikaisennusteeseen. Tutkimuksessa havainnoitiin humalassa tapahtuneen pään vamman vaikutusta epileptisen kohtauksen ja uuden aivovamman ilmaantumiseen seuranta-aikana.

Haitallisesti alkoholia käyttävien päähän vammautuneiden potilaiden kuolleisuus lisääntyi merkitsevästi alkoholiveron alennuksen jälkeen. Myös alkoholiin liittyvän epileptisen kouristuksen sairastaneilla kuolleisuus lisääntyi merkitsevästi. Alkoholin vaikutuksen alaisena tapahtunut pään vamma oli riskitekijä uudelle epileptiselle kohtaukselle sekä uudelle aivovammalle seuranta-aikana.

Tulokset vahvistavat aiempia havaintoja siitä, että alkoholin hinnan voimakas lasku lisää nopeasti alkoholin suurkuluttajien kuolleisuutta. Humalassa päätään loukanneella on lisääntynyt riski saada uusi aivovamma sekä uusi epileptinen kohtaus.

Asiasanat: alkoholi, alkoholiin liittyvä kouristus, alkoholiveron alennus, epidemiologia, epilepsia, epileptinen kohtaus, kuolleisuus, pään vamma, seurantatutkimus, traumaattinen aivovamma

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Vaasa archipelago, October 2013 Kalle Vaaramo

Abbreviations

ACRM	American Congress of Rehabilitation Medicine
AED	antiepileptic drug
ARS	alcohol-related seizure
AWS	alcohol withdrawal seizure
BAC	blood alcohol concentration
CNS	central nervous system
CPP	cerebral perfusion pressure
CT	computed tomography
CTE	chronic traumatic encephalopathy
CVD	cardiovascular disease
DAI	diffuse axonal injury
DALY	disability-adjusted life-year
DC	decompressive craniectomy
EDH	epidural haemorrhage
EFNS	European Federation of Neurological Societies
ER	emergency room
GCS	Glasgow Coma Scale
ICD	International Classification of Diseases
ICP	intracranial pressure
ILAE	International League Against Epilepsy
LOC	loss of consciousness
MAP	mean arterial pressure
MRI	magnetic resonance imaging
NHD	National Hospital Discharge Register
PTA	post-traumatic amnesia
PTE	post-traumatic epilepsy
SAH	subarachnoidal haemorrhage
SDH	subdural haemorrhage
SFCD	Statistics Finland Causes-of-Death Register
TBI	traumatic brain injury
WHO	World Health Organization

List of Original Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2012) Mortality of harmful drinkers increased after reduction of alcohol prices in northern Finland: a 10-year follow-up of head trauma subjects. Neuroepidemiology 39(3–4): 156–162. DOI: 10.1159/000341241.

II Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2014) Mortality of subjects with alcohol-related seizures increased after alcohol cheapening. Acta Neurol Scand 129(1): 56–60. DOI: 10.1111/ane.12150.

III Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2013) Predictors of new-onset seizures: a 10-year follow-up of head trauma subjects with and without traumatic brain injury. J Neurol Neurosurg Psychiatry. In press. DOI:10.1136/jnnp-2012-304457.

IV Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2013) Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: a long-term follow-up study. Eur J Neurol. In press. DOI: 10.1111/ene.12302.

Contents

1 Introduction

Traumatic brain injury (TBI) is a huge health problem worldwide, and its global incidence is rising (Maas *et al*. 2008). The vast majority of TBIs are mild, but a more severe TBI may be a catastrophe for an individual, frequently leading to permanent disability or death. In addition, TBI is an enormous economic burden for society, partly because it is most common among young men (Jennett 1996). It has been estimated that 3.7 million Europeans sustain such an injury each year and that the economic costs exceed 33 billion euros (Olesen *et al.* 2012).

The relationship between heavy alcohol drinking, traumatic brain injuries and acute symptomatic seizures is a multifaceted one. Seizures are typical health problems caused by alcohol abuse (Hillbom 1980), and the risk of seizures increases after TBI, depending on the severity and the type of the trauma (Annegers *et al*. 1998). Alcohol abuse and TBI frequently co-occur, and alcohol abuse is common both before and after injury (Kolakowsky-Hayner *et al*. 1999, Dikmen *et al.* 1995, Kreutzer *et al*. 1996, Bombardier *et al*. 2003, Horner *et al*. 2005). As many as one half of all TBI subjects are intoxicated on admission (Corrigan 1995, Parry-Jones *et al*. 2006), and TBI recurrence is more common among subjects with alcohol abuse than among others (Hillbom & Holm 1986). Furthermore, a first TBI that is related to alcohol predicts future TBI incidents (Winqvist *et al*. 2008).

Because of its huge potential to cause harm, alcohol should not be considered an ordinary commercial commodity (Babor *et al.* 2010). Political decisions concerning alcohol can greatly improve (Leon *et al*. 1997, Nemtsov 2002) or impair (Mäkelä & Österberg 2009) public health. The decisions made by the public authorities in this respect often take other aspects into account than those related to public health (Chenet *et al*. 1997). For example, alcohol taxation in Finland was lowered by an average of 33% in March 2004, as a result of which alcohol consumption increased by 10% at the population level within one year (Mäkelä & Österberg 2009) and there was a dramatic increase in alcohol-related deaths and hospitalisations (Koski *et al*. 2007, Herttua *et al.* 2008a, Herttua *et al.* 2011). The reduction in alcohol prices had the greatest effect on people in the lower social categories, those already known to bear the heaviest burden of alcohol-related problems (Herttua *et al*. 2008a).

This thesis is concerned with the effects of alcohol on the outcome after head trauma. The cohort consists of all subjects admitted to the ER at Oulu University Hospital in 1999 because of acute head trauma. The follow-up lasted until the end

of 2009. The aim was to assess factors predictive of new-onset posttraumatic seizures and new TBI incidents during the follow-up. The alcohol price reduction that occurred in the middle of the follow-up period made it possible to explore the effects of this reduction on mortality in a rare natural experimental setting.

2 Review of the literature

2.1 Traumatic brain injury (TBI)

2.1.1 Definition and classification

The definition and terminology of TBI has varied considerably, and previous terms such as head trauma or head injury are still sometimes used to mean TBI. Head injury does not always imply TBI, however, as the latter is a more specific term that refers to the fact that crucial damage has been done to the brain tissue irrespective of the presence or absence of scalp or skull trauma. In the Finnish guidelines (Aivovammojen käypä hoito 2008), which are modified from the ACRM recommendations (Kay *et al*. 1993), TBI is defined as traumatically induced physiological disruption of brain function that is manifested by at least one of the following:

1. any period of loss of consciousness,
2. any loss of memory for events immediately before or after the accident,
3. any alteration in mental state at the time of the accident (e.g. feeling dazed, disoriented or confused),
4. focal neurological deficits that may or may not be transient, or
5. abnormal intracranial CT/MRI findings due to trauma.

More recently and concisely, TBI has been defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon *et al*. 2010). Although TBI is a diverse disorder with various forms of presentation, the unifying factor is that external forces cause brain damage (Maas *et al*. 2008).

Traditionally, TBI has been classified in terms of the mechanism involved, the degree of clinical severity and an assessment of the structural damage incurred (Maas *et al*. 2008, Saatman *et al*. 2008). Mechanistically, it can be classified as a closed, penetrating or crash or blast injury, while classification by clinical severity is typically based on GCS (Teasdale & Jennett 1974), which is useful for the clinical management of TBI and for establishing a prognosis (Saatman *et al*. 2008). TBI is usually classified as being severe if GCS $\leqslant$8 and mild if GCS=13–15 (Vos *et al*. 2012). Patients with moderate TBIs have GCS=9–12 (Vos *et al*. 2012). GCS has a relatively high inter-observer reliability and in most cases good

prognostic capabilities when assessed by appropriately qualified personnel (Narayan *et al*. 1981, Rowley & Fielding 1991, Saatman *et al*. 2008) although the traditional correlation between GCS on admission and outcome may have diminished (Balestreri *et al*. 2004). As a marker of level of consciousness, however, GCS does not provide specific information on the pathophysiological mechanisms responsible for the neurological deficits (Saatman *et al*. 2008). Furthermore, it is prone to confounding factors such as intoxication (Brickley & Shepherd 1995), although alcohol intoxication does not seem reduce the GCS significantly among subjects with TBI (Stuke *et al*. 2007). These confounding factors do not influence a classification performed by means of neuroimaging, which is based on structural changes in the brain, e.g. swelling, midline shift, a mass lesion and obliteration of basal cisterns (Marshall *et al*. 1992, Maas *et al*. 2008, Bratton *et al*. 2007). There are four main pathoanatomical sequelae of TBI: brain contusion, traumatic subarachnoid haemorrhage (SAH), subdural (SDH), epidural (EDH) and intraparenchymal haematomas and diffuse axonal injury (DAI) (Saatman *et al*. 2008). Many of these sequelae often coincide, especially among subjects with severe TBI (Saatman *et al*. 2008).

Structural brain damage can be assessed on both a macroscopic and a microscopic level. Macroscopically, it includes shearing of white matter tracts, focal contusions, microhaemorrhages due to the tearing of vessels, haematomas and diffuse swelling (Maas *et al.* 2008), while at the cellular level, neurotrauma includes microporation of membranes, ion channel leakages and protein reformation (Maas *et al*. 2008). DAI is a condition with damaged axonal anatomy due to traumatic shear forces that occur when the head is rapidly accelerated or decelerated, e.g. in an automobile crash (Smith *et al*. 2003). DAI was previously thought to be always a severe condition, typically leading to profound coma and often carrying a poor prognosis (Saatman *et al*. 2008), but improved MRI techniques have meant that DAI can now also be seen in patients with milder injuries (Saatman *et al*. 2008). Indeed, it is important to note that a normal CT scan does not preclude the presence of structural damage to the brain (Maas & Menon 2012). Focal contusions are common traumatic lesions in the brain, and they are more frequent in older patients, having usually arisen from contact impact such as a fall (Maas *et al.* 2008).

Along with GCS, PTA is commonly used to evaluate the severity of TBI. Amnesia is divided into retrograde and anterograde amnesia, of which the former is defined as a partial or total loss of the ability to recall events that have occurred

immediately preceding TBI (Cantu 2001). However, no TBI severity score at the moment takes retrograde amnesia into account (Marshman *et al*. 2013). Anterograde amnesia, i.e. PTA, refers to the period from the injury until the time when the patient is able to form continuous new memories and later retrieve them (Meares *et al*. 2011). It has been shown that PTA is a better predictor of the long-term outcome than GCS (Sherer *et al*. 2008), but its predictive accuracy is limited by wide variability in outcome (Walker *et al.* 2010). Some controversy remains, however, over which method for defining the severity of TBI on the basis of PTA duration is the best (Nakase-Richardson *et al*. 2011), and it has also been suggested that the term PTA should be redefined as post-TBI confusion (Marshman *et al*. 2013). In the seminal work on this topic TBI is classified as mild if PTA is <1 hour, moderate if it is 1-24 hours, severe if it is 1-7 days and very severe if it exceeds 7 days (Russell & Smith 1961). The classification of the severity of TBI on the basis of the duration of PTA is different in the guidelines used in Finland: mild TBI <24h, moderate TBI 1–7 days, severe TBI 7–28 days and very severe TBI > 4 weeks (Aivovammojen käypä hoito 2008).

TBI can also be divided into primary and secondary damage (McIntosh *et al.* 1996). Primary injury usually refers to unavoidable and immediate parenchymal damage occurring at the time of injury as a result of shearing, tearing and stretching (Kumar & Loane 2012), while secondary damage may develop over hours and weeks after the acute phase of TBI, and may incorporate events that are thought to account for the development of many post-traumatic neurological deficits (McIntosh *et al*. 1996). These include neurotransmitter release (Faden *et al.* 1989), deregulation of ionic homeostasis (Gentile & McIntosh 1993) and inflammatory responses, for instance, the last-mentioned being an important component of TBI that can have both beneficial and harmful effects (Kumar & Loane 2012). The secondary damage is potentially avoidable, but pharmacological studies have failed to find a neuroprotective treatment so far, despite considerable research efforts (Kumar & Loane 2012, Maas *et al*. 2010, Saatman *et al*. 2008). Secondary injury responses are so complex that neuroprotection cannot be achieved by a panacea and focus has turned to multipotential therapeutic strategies (Kumar & Loane 2012). As no neuroprotective medication has been found, the prevention of secondary damage in clinical practice is based on maintaining adequate cerebral perfusion pressure (CPP) and oxygenation (Bratton *et al*. 2007). CPP incorporates mean arterial pressure (MAP) and intracranial pressure (ICP), both of which have to be continuously monitored (Bratton *et al*. 2007). Sometimes the conservative

methods employed to maintain adequate CPP are not enough because of swelling of the brain and increased ICP, and then decompressive craniectomy (DC) may provide additional space for the swollen brain and efficiently reduce ICP (Bor-Seng-Shu *et al*. 2012). An early neuroprotective DC nevertheless carries an increased risk of severe complications and is not superior to medical management in the case of patients with diffuse TBI (Cooper *et al*. 2011, Kolias *et al*. 2013). DC may be beneficial as a life-saving procedure among TBI subjects, but this is under investigation (Hutchinson *et al*. 2006, Kolias *et al*. 2013). Corticosteroids should not be used for improving the outcome or reducing ICP after TBI (Edwards *et al*. 2005).

Although TBI is often seen as an event, it is really a permanent condition caused by non-reversible pathological alterations, and one that often requires a long period of rehabilitation and should therefore be considered to be a chronic disease process rather than an event (Masel & DeWitt 2010).

2.1.2 Epidemiology

TBI includes a wide range of severity, from patients who die before admission to hospital to those with injuries so mild they do not even seek medical attention (Jennett 1996). It has been evaluated that only one fourth of all TBI subjects attend hospitals (Sosin *et al*. 1996). This means that the accuracy of incidence rates is limited. The annual incidence of ER visits for TBI in the USA is 403 per 100 000 (Langlois *et al*. 2006), and it has been estimated that at least 5.3 million persons (2% of the population) have a long-lasting or persistent disability on account of TBI (Thurman *et al*. 1999). A recent study has shown, however, that the true incidence of TBI can be as high as 790 cases per 100 000 people per year, and that the vast majority of cases are mild (Feigin *et al*. 2013). The global incidence of TBI is rising because of increasing motor vehicle use in low and middle-income countries (Maas *et al*. 2008), and the incidence of TBI caused by falls is increasing as the population becomes older (Maas *et al*. 2008). TBI is more common among young male adults (Jennett 1996), but the male/female ratio declines with increasing age (Mosenthal *et al*. 2002, Tokutomi *et al*. 2008). Also, head injuries are more common among people from more deprived areas (Dunn *et al*. 2003).

2.1.3 Symptoms and diagnosis

The symptoms following TBI can vary substantially. Severe TBI is a common cause of death and disability among trauma patients. However, the majority of TBIs are mild and the symptoms are not usually persistent. The symptoms experienced after mild traumatic brain injury can be categorised as follows (Kay *et al*. 1993):

1. physical symptoms such as nausea, headache or fatigue that cannot be attributed to peripheral injury or other causes,
2. cognitive symptoms such as deficits in memory, concentration and executive functions that cannot be completely attributed to emotional states or other causes, or
3. behavioural symptoms such as irritability and emotional lability that cannot be attributed to psychological reactions to stress or other causes.

The diagnosis of TBI can be a challenging process, as there are factors other than TBI that may be responsible for the symptoms present in the acute phase, e.g. alcohol intoxication, post-traumatic shock, pain and medication. These confounders are commonly associated with documented TBI, however, so that their presence does not preclude a TBI diagnosis (Menon *et al*. 2010).

Sometimes symptoms and clinical manifestations such as neuropsychiatric disorders (depression, apathy etc.) are delayed and the diagnosis of TBI may require neuroradiological imaging after the acute event (Menon *et al*. 2010). In any case, although TBI may cause neuropsychiatric disorders, it would not be appropriate to establish a diagnosis using only these as criteria (Kay *et al.* 1993). Traumatic haematomas, especially epidural haematomas, can bring about a delayed onset of LOC after a lucid interval (Ganz 2013), and therefore a further assessment may be indicated.

2.1.4 Outcome

TBI is a major health problem that frequently causes premature mortality or long-term disability and is closely associated with various post-injury neurological or psychiatric disorders (Bazarian *et al*. 2009, Hesdorffer *et al.* 2009b, Bombardier *et al.* 2010). Most patients with severe TBI either die or recover to pursue an independent lifestyle, but severe disability or a vegetative state can also ensue (Maas *et al*. 2008). The vast majority of all TBI cases are mild (Feigin *et al*.

2013), and the outcome is then generally good, but a minor proportion even of mild TBI cases lead to distressing and even persistent symptoms after the injury (Cancelliere *et al.* 2012). The reasons why individuals respond differently to similar injuries are largely unknown, but the differing outcomes may be partly genetically determined (Lingsma *et al*. 2010), e.g. it has been observed that recovery is poorer among TBI subjects with the APOE ε4 allele (Alexander *et al*. 2007). Mild TBI may be followed by a combination of physical (e.g. headache), emotional (depression) and cognitive (memory problems) symptoms collectively known as post-concussion syndrome (Belanger & Vanderploeg 2005, Levin & Robertson 2013), while repeated mild TBIs may lead to chronic traumatic encephalopathy (CTE) (Baugh *et al*. 2012), the manifestation of which was earlier referred to in boxing as *dementia pugilistica* (Jordan 2013).

It has been noted that approximately 85% of recoveries occur within 6 months of TBI, but further recovery can occur later (Maas *et al*. 2008). Patients hospitalized on account of severe TBI have a high early mortality rate (Jennett 1996), the highest incidence occurring in the first 60 days after TBI (Cameron *et al.* 2008). One study has shown the most powerful independent prognostic factors on admission to be age, GCS motor score, pupil response and CT characteristics (Murray *et al*. 2007). Patients with TBI also have a significantly higher long-term mortality rate than the general population (Lewin *et al*. 1979, Baguley *et al*. 2000, Shavelle *et al*. 2001, Ratcliff *et al.* 2005, Cameron *et al*. 2008), with an average life expectancy reduction of 4–6 years (Harrison-Felix *et al*. 2009, Ventura *et al*. 2010), although the excess risk of death after TBI decreases as time elapses (Ventura *et al*. 2010). The mortality risk after head injury has been shown to increase as early as 30 years of age, and the greatest increases occur after the age of 60 (Harris *et al*. 2003), the major mechanism probably being the more destructive progression of secondary brain injury (Tokutomi *et al.* 2008). Long-term mortality relative to the general population is nevertheless significantly higher among young adults with head injury (McMillan *et al*. 2011), with the ratio of the raw death rate to the expected death rate decreasing towards older age groups (Colantonio *et al.* 2008). Age is a significant predictor of post-acute death (Harrison-Felix *et al*. 2009), others being pre-existing comorbidities such as psychosocial and psychiatric problems, including alcohol abuse (Ratcliff *et al*. 2005, Colantonio *et al*. 2008, Baguley *et al*. 2012). Variables related to the severity of the injury appear to be poor predictors in this respect (McMillan & Teasdale 2007), although not for all observers (Cameron *et al*. 2008). Women

may show better outcomes after TBI, but reports on this are again contradictory (Farace & Alves 2000). It is important to note that follow-up studies may be systematically biased, especially since subjects who are socioeconomically disadvantaged often have a history of substance abuse and are difficult to trace (Corrigan *et al*. 2003).

2.2 Alcohol

2.2.1 Patterns of alcohol abuse

Alcohol may cause medical and social burdens in three ways. First, it is a toxic substance that directly and indirectly affects organs and tissues; and second, intoxication may lead to acute social problems and to physical injuries; and third, recurrent bouts of intoxication may lead not only to social, psychological and biological complications but also to alcohol dependence (Babor *et al.* 2010).

Drinking patterns influence the detrimental impacts of alcohol consumption in different ways (Wetterling *et al*. 1999), but it should be remembered, too, that drinking patterns do not exclude each other. Binge drinking, usually defined as taking 4–5 drinks per occasion or drinking that results in a BAC of 0.8‰ or higher (Fillmore & Jude 2011), often referred to as heavy episodic drinking (Nazareth *et al*. 2011), causes alcohol intoxication and predisposes subjects to traumas and poisoning. This is a common drinking pattern in Finland, with a reported mean frequency in Finland of approximately 11 times a year (Mäkelä *et al*. 2001). Hazardous drinking is defined as a pattern of alcohol consumption that increases the risk of harmful consequences for the drinker and is recognized by the WHO as a distinct disorder, although it does not serve as a diagnosis (Babor *et al*. 1994). Harmful drinking (ICD-10 code F10.1) is a pattern of alcohol use that is causing damage to either physical or mental health (Babor *et al*. 1994). Finally, regular daily drinking causes chronic diseases such as liver cirrhosis (Corrao *et al*. 1999) and digestive tract cancers (Baan *et al*. 2007) and predisposes subjects to alcohol dependence, which as a psychiatric diagnosis (ICD-10 code F10.2), presupposes that three or more of the following have been present together at some time during the previous year (‘substance’ refers here to alcohol) (WHO 1992):

1. a strong desire or sense of compulsion to take the substance,
2. difficulties in controlling substance-taking behaviour,

3. a physiological withdrawal state when substance use has ceased or been reduced,
4. evidence of tolerance,
5. progressive neglect of alternative pleasures or interests because of psychoactive substance use, and
6. persisting with substance use despite clear evidence of overtly harmful consequences.

Alcohol abuse is one of the leading preventable causes of disability and death (Leon *et al*. 1997, Rehm *et al*. 2009), with detrimental effects at the population level that closely reflect changes in *per capita* alcohol consumption (Leon *et al*. 1997, Edwards 1997). Injuries account for the largest proportion of socio-medical burden attributable to alcohol, but its consumption is also related to many other diseases such as liver cirrhosis, cerebrovascular diseases (Hillbom *et al*. 1999, Rantakömi *et al*. 2009, Hillbom *et al*. 2011), pancreatitis (Opie & Meakins 1909), cardiomyopathy (Pintar *et al*. 1965), depressive disorders (Regier *et al*. 1990) and breast cancer (Baan *et al*. 2007). It has been estimated that globally 3.8% of all deaths and 4.6% of DALYs are attributable to alcohol (Rehm *et al*. 2009). In addition, alcohol consumption is a major risk factor for social problems (Klingemann & Gmel 2001). Since acute conditions mostly involve younger people, it has been observed that the average number of years of life lost through untimely deaths is more than twice that from chronic causes (Chikritzhs *et al*. 2001). In addition, the economic costs of excessive alcohol consumption are enormous. It has been estimated that the cost of excessive drinking in the USA in 2006 was $223.5 billion, or approximately $745 *per capita*, three quarters of which was due to binge drinking (Bouchery *et al*. 2011).

2.2.2 Alcohol and TBI

The signs of acute alcohol intoxication have long been known: they include muscular incoordination, sluggishness and alteration in behaviour (Bogen 1927). The proportion of blood alcohol positives among trauma subjects is approximately one half (Rivara *et al*. 1993, Savola *et al*. 2005), and the risk of head trauma specifically increases with increasing BAC (Savola *et al*. 2005). It is easy to understand that alcohol intoxication may increase the risk of trauma, and there is strong evidence to support this (Borges *et al*. 1998, Borges *et al.* 2004, Cherpitel *et al*. 1995, Honkanen *et al*. 1975, Li *et al*. 2001, Lowenfels & Miller

1984, McLeod *et al*. 1999, Taylor *et al*. 2010, Watt *et al*. 2004). Taylor *et al*. (2010) found that the risk of injury increased non-linearly with increasing alcohol consumption, while Borges *et al*. (2004) found that the risk of injury was highest within an hour after the last drink, especially among inexperienced drinkers. The risk of injury is more than three-fold after consuming 60 grams of alcohol in a 6-hour period (McLeod *et al*. 1999). Similarly, Paljärvi *et al*. (2005) found that the risk of fatal injury was highest among subjects with the highest annual number of binge episodes, and Puljula *et al*. (2007) that there was a significant increase in the admission of head trauma patients at weekends, caused by alcohol-related traumas. It has been estimated that alcohol abuse and/or problem drinking is the most common chronic illness in trauma patients (Jurkovich *et al*. 1993), to the extent that trauma itself is sometimes seen as a marker of alcohol abuse or alcoholism (Maull 1982).

Alcohol abuse is a common feature among patients with TBI (Kolakowsky-Hayner *et al*. 1999, Dikmen *et al*. 1995) and it seems to be present both before and after TBI (Kreutzer *et al*. 1996, Bombardier *et al*. 2003, Horner *et al*. 2005). Pre-injury alcohol abuse is associated with a poorer outcome (Dikmen *et al*. 1995, Kelly *et al*. 1997, Ratcliff *et al*. 2005, Baguley *et al*. 2012). There are indications that approximately two thirds of subjects with TBI have a history of substance abuse before the injury and as many as half of the subjects are intoxicated on admission (Corrigan 1995, Parry-Jones *et al*. 2006), which in turn is a significant indicator of both pre-injury and post-injury abuse (Rivara *et al*. 1993, Dikmen *et al*. 1995, O´Dell *et al*. 2012). Three fourths of a series of acutely intoxicated trauma patients were found to be chronic alcohol abusers (Rivara *et al*. 1993), and it has been suspected that perhaps a quarter of all head trauma subjects with no alcohol in their blood on admission may have had pre-injury alcohol problems (Rivara *et al*. 1993, Dikmen *et al*. 1995). One study has shown the frequency of alcohol use disorders during the year preceding TBI to be 34.8% (Jorge *et al*. 2005), and it has been found elsewhere that young adult men have the highest incidences of both TBI (Jennett 1996) and substance abuse (Pirkola *et al*. 2005). There is one study with demographically matched controls, however, in which no significant difference in pre-injury alcohol abuse was found between TBI subjects and controls (Ponsford *et al*. 2007).

It has been suggested that alcohol intoxication is a significant risk factor for more severe trauma (Waller *et al*. 1986, Pories *et al*. 1992, Cunningham *et al*. 2002, Fabbri *et al*. 2002, Puljula *et al*. 2013), but this remains controversial (Nath *et al*. 1986, Ward *et al*. 1982, Brickley & Shepherd 1995, Sperry *et al*. 2006,

Andelic *et al*. 2010, Talving *et al*. 2010). Some experimental animal investigations suggest that a low to moderate dose of alcohol can have a neuroprotective effect in instances of TBI (Kelly *et al*. 1997, Tureci *et al*. 2004) whereas a high dose of alcohol seems to worsen the outcome (Kelly *et al*. 1997, Yamakami *et al*. 1995). In fact, several clinical studies have suggested decreased mortality among intoxicated TBI subjects (O´Phelan *et al*. 2008, Salim *et al*. 2009a, Salim *et al*. 2009b, Shandro *et al*. 2009, Talving *et al*. 2010), and one found decreased mortality specifically among subjects with severe TBI and low-to-moderate BAC levels (Tien *et al*. 2006). These studies have usually been concerned with hospital mortality, and it is important to note that a substantial proportion of trauma deaths occur in pre-hospital settings (Sauaia *et al*. 1995, Masella *et al*. 2008). In addition, subjects with more severe TBI are more likely to be tested for BAC (Kraus *et al*. 1989). Furthermore, it is important to distinguish acute intoxication from chronic alcoholism, because these patient groups may differ in their outcome following TBI (Opreanu *et al*. 2010). Acute alcohol intoxication does not seem to increase mortality or morbidity following trauma in general (Ward *et al*. 1982, Jurkovich *et al*. 1993), whereas chronic alcoholism seems to increase the risk of complications following trauma (Jurkovich *et al*. 1993). There is nevertheless only a limited amount of congruent evidence available to show whether the mortality rate among intoxicated TBI subjects is lower than that among sober subjects (Opreanu *et al*. 2010), and prospective clinical trials are needed (Talving *et al*. 2010). When considering alcohol for the treatment of TBI, it is important to note that every publication on this topic has observed the outcome in subjects who had consumed alcohol prior to the injury and the effect of alcohol may be different if used as a therapeutic agent after TBI (Bourdeaux & Marsh 2010).

Pre-injury alcohol abuse predicts heavy drinking after the trauma (Horner *et al*. 2005). Bombardier *et al*. (2003) observed that only a minority of subjects without pre-injury alcohol abuse (3.5%) developed alcohol-related problems after the injury. The risk for post-injury heavy drinking was 10.9 times higher among subjects with preceding alcohol-related problems than among those without, and approximately one quarter of all TBI survivors are heavy drinkers 1–2 years after injury (Bombardier *et al.* 2003, Ponsford *et al*. 2007), a proportion that may increase further with time (Ponsford *et al*. 2007). One study showed that nearly a half of its series of hospitalized TBI patients reported at least one binge drinking occasion per month a year after TBI, i.e. 50% more than in an age and gender-

matched general population (Horner *et al*. 2005). Little is known about whether TBI alone increases substance abuse, however (Bjork & Grant 2009), and it has been suggested that TBI is more often a consequence of heavy drinking than a cause (Rogers & Read 2007). On the other hand, alcohol abuse following TBI may be a coping response to the psychosocial stress of disability (Bjork & Grant 2009). Psychiatric illnesses in general tend to increase after TBI (Fann *et al*. 2004), which may disrupt incentive motivation patterns in the neurocircuitry and thereby predispose the individual to substance abuse (Bjork & Grant 2009). Furthermore, TBI may lead to an organic personality disorder that may increase alcohol consumption (Bjork & Grant 2009). All the same, it has been proved that alcohol abuse following TBI impairs recovery (Corrigan 1995, Jorge *et al*. 2005), and that in general alcohol consumption tends to decline at first after TBI but it often increases again after a relatively short interval and regains the pre-injury level (Corrigan *et al*. 1998, Bombardier *et al*. 2003, Kreutzer *et al*. 1996, Dikmen *et al*. 1995). Patients who relapse into alcohol abuse after TBI are less educated and have a greater frequency of focal lesions involving the frontal and temporal lobes (Jorge *et al*. 2005). On the other hand, severely injured patients have been observed to reduce their drinking more than those with a mild injury (Dikmen *et al*. 1995), while among a series of hospitalized patients previous heavy drinkers seemed to reduce their consumption more than did light-to-moderate drinkers (Bombardier *et al*. 2003).

Alcohol seems to increase the risk of a recurrent TBI (Salcido & Costich 1992). A first TBI occurring under the influence of alcohol has been found to be a significant predictor of recurrent TBI (Winqvist *et al*. 2008), although it has been suggested on the basis of one retrospective cohort that pre-existing alcohol abuse is not a significant independent predictor of a repeat TBI (Saunders *et al*. 2009). There are only a few studies of recurrent TBIs among general populations, and most of them report only on cases among young male athletes (Zemper 2003, Guskiewicz *et al.* 2003).

Brief intervention

The course of alcohol abuse can be effectively altered by brief interventions (Bien *et al*. 1993). It has been shown that interventions for alcohol abuse reduce the risk of both injuries and deaths from injuries (Dinh-Zarr *et al*. 1999). The availability of modern facilities and prompt care means that significant future decreases in the rate of deaths from injuries will depend primarily on progress in injury prevention

(Gentilello *et al*. 1999). In view of the significant role of alcohol abuse in traumas, it will be essential to reduce hazardous drinking to prevent traumas (Gentilello *et al*. 1999), and reductions could indeed be achieved in alcohol consumption (Smith *et al*. 2003) and trauma recurrence (Gentilello *et al*. 1999) using brief interventions for subjects who are injured while under the influence of alcohol. In general, trauma patients are willing to discuss their alcohol consumption while hospitalized for their injury (Schermer *et al*. 2003), and although it has long been thought that patients under-report their drinking levels, one study has pointed to a significant concordance between patients´ and relatives´ reports with regard to drinking behaviour following TBI (Sander *et al*. 1997). Most patients think physicians should be interested in their lifestyle behaviour, but only a minority report having received advice about their habits (Richmond *et al*. 1996). Emergency departments and trauma centres have a unique opportunity to perform brief interventions (Dikmen *et al*. 1995, Babor & Kadden 2005).

Brain damage may reduce the efficacy of a brief intervention. Assessments of brief interventions for injury patients have systematically neglected those with more severe TBIs and those too confused to provide informed consent (Corrigan *et al*. 2010). One evaluation of an experiment with relatively few participants provided evidence that a brief intervention has the potential to influence expectations regarding the consequences of alcohol misuse after TBI (Sander *et al*. 2012). It must be admitted, however, that only a non-significant effect of brief intervention for problem alcohol use following TBI (Tweedly *et al*. 2012), or no effect at all (Sander *et al*. 2012), has been reported so far, and there is a lack of randomized controlled trials with sufficient sample sizes (Tweedly *et al*. 2012).

2.2.3 Alcohol policy

Alcohol policy can be defined as covering all the policy decisions made by public authorities that influence alcohol-related social and health issues. The main purpose of alcohol policy is to serve the interests of public health and social well-being, but it also affects alcohol manufacturing, taxation, availability, marketing legislation and education (Babor *et al*. 2010).

Alcohol is an intoxicant that has many detrimental effects, and alcohol policy should aim at keeping these effects to a minimum. The measures concerned are not equally effective, however.

It has been shown that public information campaigns and classroom-based education are ineffective methods of reducing the negative effects of alcohol consumption (Babor *et al*. 2010), whereas brief advice aimed at people with hazardous and harmful consumption habits is effective (Kaner *et al*. 2007). Lowering the established legal BAC for drivers is effective in reducing drink-and-drive road casualties (Mann *et al*. 2001). It is hard to evaluate the interaction between advertising and alcohol consumption, but there is evidence showing that marketing affects the initiation of drinking and the patterns of drinking among young people (Anderson *et al*. 2009a). An increased density of alcohol outlets is associated with increased consumption by young people (Huckle *et al*. 2008), but where the network of outlets is relatively dense, small changes in density are unlikely to affect consumption levels (Livingston *et al*. 2007). A reduction in the numbers of hours or days for which outlets are open may lead to fewer alcohol-related problems (Duailibi *et al*. 2007), and all in all, restricting the availability of alcohol is a highly cost-effective strategy for reducing its harmful effects (Anderson *et al*. 2009b).

One fundamental law of economics states that as the price of a product rises, the quantitative demand for the product falls. This is a question of affordability, which in this case is determined by alcohol prices and consumers' incomes. There is extensive literature that shows clearly that alcohol consumption and the consequent harmful effects of alcohol are inversely related to the price of alcoholic beverages, suggesting that the pricing should be the key policy for limiting total alcohol consumption (Anderson *et al*. 2009b, Wagenaar *et al*. 2009).Young people have traditionally appeared to be more affected by the price of alcohol (Heeb *et al*. 2003, Kuo *et al*. 2003), although recent results from Finland are contrary to this (Helakorpi *et al*. 2010). In reality, however, alcohol affordability has increased in the EU member states during recent decades (Österberg 2011), as also in the United States (Chaloupka *et al*. 2002) and this effect has been driven primarily by increases in income (Österberg 2011). Increases in the customer prices of alcoholic beverages are an effective means of reducing drinking and driving and its consequences, and of reducing diseases, injuries and deaths related to alcohol (Chaloupka *et al*. 2002). They may also

reduce violence (Sivarajasingam *et al*. 2006), including wife abuse (Markowitz 1999) and child abuse (Markowitz & Grossman 2000), but this effect has not been definitely proved (Herttua *et al*. 2008b). Wagenaar *et al*. (2009) has suggested six key policy approaches for countries with normal alcohol availability: taxation, governmental monopolies with age restrictions, advertising bans, the legal BAC for drivers, widespread simple help in primary care and educational programmes to reinforce awareness of the problems involved. Trends in nominal and real prices of alcohol in Finland are shown in Figure 1, where the nominal price means the price actually paid for the commodity, while the real price is adjusted for the effect of inflation. The figure shows that the real price of alcohol has remained relatively stable for the last thirty years.

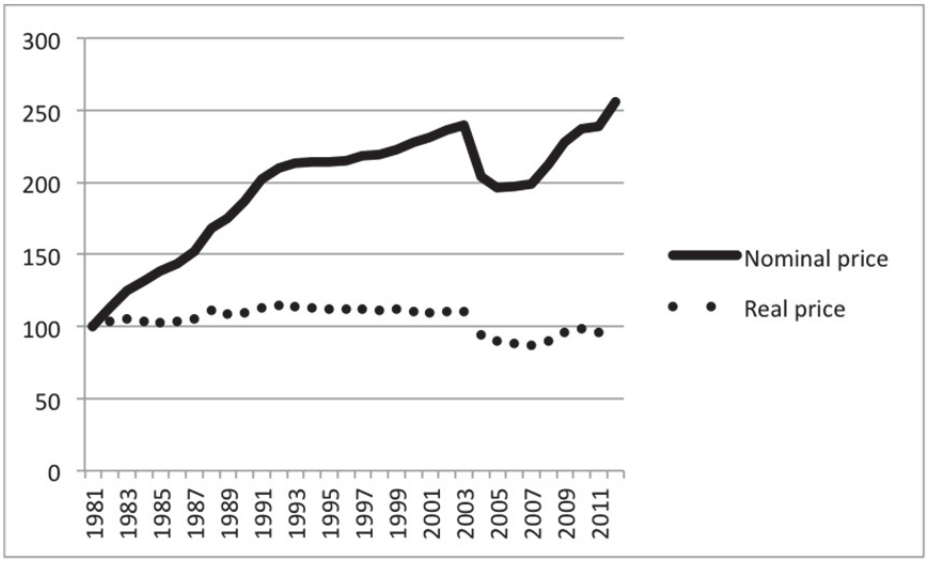

Fig 1. Nominal and real prices of alcoholic beverages in Finland in 1981–2012 (1981=100). Source of data: Statistics Finland.

Alcohol policy in Finland

Finland has a long history of restrictive alcohol policy. Total prohibition was in force in 1919–1932, and after that the production of alcohol (manufacture, imports, exports and sales) was for the most part in the hands of a monopoly, the state company Alko, which handled all sales, so that retail trading on and off the

premises was permitted only in towns, where only a minority of the population lived at that time (Herttua 2010). The recorded alcohol consumption in Finland over the period 1871–1968 was among the lowest in Europe, namely 1.1–2.9 litres of absolute ethanol *per capita* per year (Peltonen 1997, Alkoholikysymys 1976). At the beginning of 1969 more liberal legislation came into effect, and medium-strength beer could be sold in cafeterias and grocery stores from then onwards. This meant that the countryside was no longer "dry" (Herttua 2010).

The second turning point in the liberalisation process occurred at the beginning of 1995, when Finland joined the European Union. The resulting legislative changes included abolition of the state monopoly over the production, imports, exports and wholesale trading in alcoholic beverages and minor changes in travellers' import quotas. The state monopoly over retail sales of beverages with an alcohol content of 4.7% or more was retained, however (Herttua 2010).

The alcohol tax cut in 2004 – a natural experiment

The year 2004 can be regarded as a milestone in Finnish alcohol policy (Herttua *et al*. 2008a). First, tax-free import quotas within the EU were removed on 1 January, and second, taxes on alcohol were reduced by an average of 33% on 1 March. This was done because Estonia was joining the EU on 1 May and the Finnish government wished to intervene to prevent the problems likely to be caused by the expected growth in the volumes of alcoholic drinks brought back from there by travellers (Koski *et al*. 2007, Mäkelä & Österberg 2009). The tax cut in fact precipitated an estimated 10% increase in the total alcohol consumption *per capita* in 2004 (Stakes 2007), creating the circumstances for a "natural experiment" with regard to the effects of alcohol consumption (Herttua 2010). Trends in total alcohol consumption in Finland over the period 1960–2012 are shown in Figure 2.

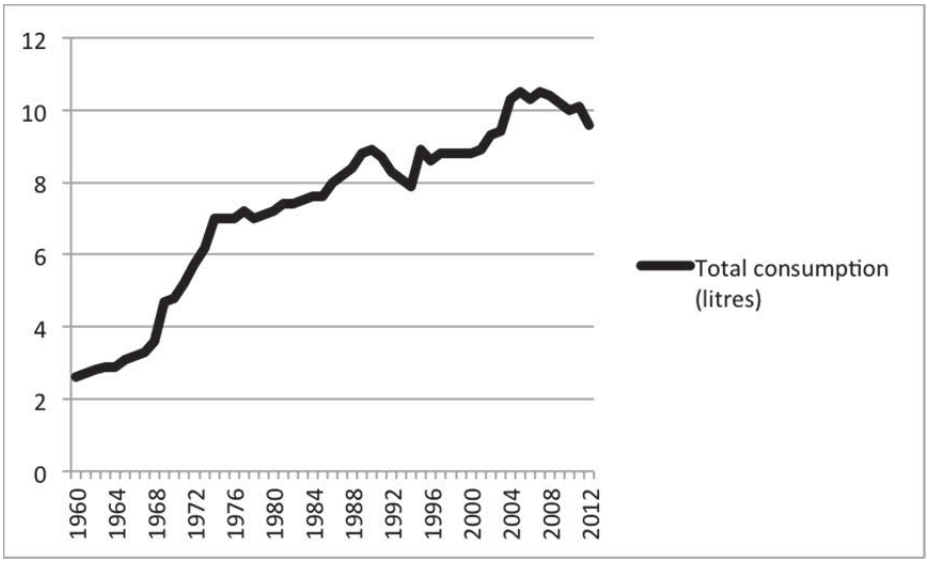

Fig. 2. Consumption of pure alcohol *per capita* in Finland in 1960–2012. Source of data: THL.

As a result of this new situation, i.e. a rapid increase in *per capita* alcohol consumption among the Finnish population, alcohol-related mortality increased by 16% among men and 31% among women, the majority of the increase (82%) being due to chronic causes, particularly liver diseases (Herttua *et al*. 2008a). The number of deaths caused by alcoholic liver diseases in 2004–2006 was 46% higher than in the early 2000s (Mäkelä & Österberg 2009), while alcohol-positive sudden deaths (not known to be due to an illness) increased by 17% within a year of the price reduction (Koski *et al*. 2007). Similarly, alcohol-related hospitalizations increased after the price reduction, mostly among men aged 50–69 and attributable to mental and behavioural disorders brought on by alcohol (Herttua *et al*. 2011). These findings are in line with previous studies that show how sharp increases in consumption and related problems reflect reductions in alcohol prices (Chaloupka *et al*. 2002, Cook & Moore 1993, Kuo *et al*. 2003, Room *et al*. 2005, Wagenaar *et al*. 2009).

2.3 Seizures

2.3.1 Acute symptomatic seizures and epilepsy

Some disagreement exists with regard to the terms "seizure" and "epilepsy". The ILAE defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires at least one epileptic seizure, but this is not required to be "unprovoked". An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in brain (Fisher *et al*. 2005).

Acute symptomatic seizures are events occurring in close temporal relationship with an acute CNS insult, which may be metabolic, toxic, structural, infectious or due to inflammation (Beghi *et al*. 2010). The specific causes of acute symptomatic seizures include TBI and alcohol, for example (Powell & McLauchlan 2012). Provoked seizures and situation-related seizures are synonyms for acute symptomatic seizures (Beghi *et al*. 2010). Unprovoked and acute symptomatic seizures can be of the same aetiology, i.e. static brain lesions, but their prognoses are different. The cumulative risk of subsequent unprovoked seizures is higher after a first unprovoked seizure than after a first acute symptomatic seizure, and it is hard to say when there is an enduring predisposition to further epilepsy. It has therefore been suggested that first acute symptomatic seizures caused by static brain lesions should not be included in the diagnosis of epilepsy (Hesdorffer *et al*. 2009a).

2.3.2 Seizures and TBI

The increased risk of seizures after head injury has long been known (Jennett & Lewin 1960). The overall risk is very high after skull-penetrating war injuries, for instance (Salazar *et al*. 1985), and lower in civilian populations comprising mild, moderate and severe TBIs with or without penetrating injuries (Annegers *et al*. 1980). In general, TBI does not contribute greatly to the overall burden of epilepsy, as head trauma has been shown to be the aetiology of the seizures in approximately 3% of epilepsy patients (Chadwick 2000, Sander *et al.* 1990). There is a strong positive correlation between the severity of TBI and the risk of subsequent unprovoked seizures, however (Annegers *et al*. 1998). Post-traumatic

seizures can be divided into early types, occurring within 7 days of the injury, and late types, occurring after 7 days (Jennett & Lewin 1960, Annegers *et al*. 1998). There is some evidence for a seizure-free interval after an early seizure, and therefore the two types may be the results of different epileptogenic processes (Angeleri *et al*. 1999). Chronic alcohol abuse, brain contusion and subdural haematoma seem to predict early post-traumatic seizures (Wiedemayer *et al*. 2002), while late post-traumatic seizures have been shown to be associated with factors that correlate with severity, the extent of tissue loss and the penetrating nature of the brain trauma, such as a depressed skull fracture, an initial focal deficit, brain contusion and/or subdural haematoma, and with the presence of early seizures (Hillbom 1959, Jennett & Lewin 1960, Pohlmann-Eden & Bruckmeir 1997, Asikainen *et al*. 1999, Annegers *et al*. 1998, Ferguson *et al*. 2010). Annegers *et al*. (1998) nevertheless found that early seizures are not an independent risk factor for late post-traumatic seizures, and maintained that they should rather be regarded as a marker of injuries severe enough to cause late seizures (Chadwick 2000). Ferguson *et al*. (2010) found that a history of depression increases the risk of post-traumatic seizures, and Haltiner *et al.* (1997) showed that altogether 86% of patients with a single late post-traumatic seizure develop a second seizure within 2 years. The risk of developing late seizures after severe TBI falls rapidly, but remains elevated for at least 20 years (Annegers *et al*. 1998). It was found in one prospective study following TBI subjects for 24 months that over 90% of the late post-traumatic seizures occurred during the first 18 months post injury, suggesting this to be the highest risk time (Englander *et al*. 2003). It is nevertheless clear that subjects with severe TBI in particular, but also some with milder TBI, have an elevated risk of seizures for a much longer period (Annegers *et al*. 1998 Christensen *et al.* 2009).

Chronic alcohol abuse has been shown to predict early post-traumatic seizures in one study (Wiedemayer *et al*. 2002), but in another there was no association between the development of PTE and reported earlier episodes of substance abuse (Ferguson *et al*. 2010). Abuse of alcohol after the injury may predispose TBI patients to post-injury seizures, however (Heikkinen *et al*. 1990, De Reuck 2011).

Antiepileptic drugs (AED) started as soon as possible after TBI reduce the risk of early post-traumatic seizures. The efficacy of phenytoin is well documented (Temkin *et al*. 1990) and levetiracetam is increasingly being used as an alternative (Kruer *et al*. 2013). There is no evidence, however, that any AED

intervention, in spite of preventing early seizures, actually reduces mortality or the development of late seizures (Temkin *et al.* 1990, Chadwick 2000, Temkin 2009, Kharatishvili & Pitkänen 2010). Furthermore, the drugs that arrest epileptogenesis may be different from those that suppress seizures in a patient who has already developed epilepsy (Temkin 2009). The current Brain Trauma Foundation guideline recommends prescribing anticonvulsants to reduce the incidence of early post-traumatic seizures, but routine seizure prophylaxis is not recommended later than 7 days after TBI (Bratton *et al*. 2007).

Seizures can cause injuries, including TBIs. The head is in fact the most commonly injured part of the body in persons with epilepsy/seizure disorders (Neufeld *et al.* 2000). Seizure-related injuries are infrequent, however, they are generally minor ones and the risk of sustaining them can be efficiently reduced by AEDs (Lawn *et al*. 2004).

2.3.3 Seizures and alcohol

Alcohol-related seizures have been recognized since Hippocratic times (Lloyd 1978). The Romans even spoke of *morbus convivialis* or "disorder related to partying" (Lennox 1941). There has been a constant debate regarding the definitions in this field, i.e. how to define seizures that are provoked by alcohol consumption.

Alcoholic epilepsy

"Alcoholic epilepsy" refers to different things in different contexts. Some authors use the term to define subjects with seizures following abrupt cessation of chronic daily abuse of alcohol (Victor & Brausch 1967), while others reserve it for recurrent seizures in alcohol-abusing subjects who are not epileptics nor suffer from other diseases that can trigger seizures and have not had alcohol withdrawal seizures (Devetag *et al*. 1983). There are studies in which alcoholic epilepsy refers to seizures directly caused by alcohol ingestion (Yamane & Katoh 1981), while others have recommended not using the term if alcohol is still being consumed at the time of the seizure onset (Tartara *et al*. 1983). "Rum fits" is sometimes used as a synonym for alcoholic epilepsy (Victor & Brausch 1967) or for alcohol withdrawal seizures (AWS) (Menken *et al*. 1977). In conclusion, alcoholic epilepsy is a term with a broad spectrum of definitions and should be avoided (Bråthen 2001).

Alcohol-related seizures (ARS)

An alcohol-related seizure is one that occurs as a complication of alcohol abuse or chronic alcohol dependence (Bråthen *et al*. 1999, Rathlev *et al*. 2002, Rathlev *et al*. 2006). More precisely, ARS may refer at least to alcohol withdrawal seizures, post-traumatic epilepsy secondary to alcohol abuse, alcohol-induced seizures, or latent or pre-existing epilepsy unmasked or complicated by alcohol use (Bråthen 2001). There is a powerful association between heavy drinking and a first generalized tonic-clonic seizure (Ng *et al*. 1988, Leone *et al*. 1997), but not between chronic alcohol use and a first symptomatic seizure (Leone *et al.* 2002).

Seizures due to alcohol abuse have been reported to be the most common single cause of an acute seizure problem (Earnest & Yarnell 1976, Hillbom 1980). Alcohol-related seizures have also been observed to be more common among men than among women, but seizures unrelated to alcohol have not shown any sex difference (Hillbom *et al*. 2003). The observed sex differences in alcohol-related seizures reflect the sex difference in alcohol consumption within the population concerned. Alcohol usually acts in the brain like a CNS depressant, i.e. increasing the seizure threshold, and seizures appear as a rebound phenomenon after the abrupt cessation of prolonged intoxication (Hillbom *et al*. 2003). Alcohol withdrawal seizure is a part of alcohol withdrawal syndrome, which may include tremulousness, hallucinosis and delirium (Victor & Laureno 1978). The vast majority of alcohol-related seizures occur 6 to 48 hours after cessation of heavy prolonged drinking (Victor & Brausch 1967), hence they are called alcohol withdrawal seizures, and they are usually a rather late complication of alcoholism (Bråthen *et al*. 1999) and can occasionally result in *status epilepticus* (Hughes 2009). The proportion of alcohol withdrawal seizures among seizure patients varies in different populations, but approximately 40% of seizures in alcohol-dependent patients are related to alcohol withdrawal (Rathlev *et al*. 2002), whereas the corresponding proportion among consecutive seizure problem patients is approximately one fourth (Earnest & Yarnell 1976, Hillbom 1980). Seizure patients are frequently admitted on Mondays, whereas alcohol consumption peaks occur on Saturdays, but the phenomenon may partly be due to other weekend behaviour factors such as early rising following irregular sleeping hours (Hillbom 1980, Bråthen *et al*. 2000). Long-term mortality among patients with alcohol withdrawal seizures is high (Pieninkeroinen *et al*. 1992). On the other hand, Ng *et al*. (1988) challenged the concept of alcohol withdrawal

seizures, suggesting that alcohol withdrawal is not a significant predictor of a seizure problem but that a seizure is induced by the ingestion of alcohol.

Alcohol-dependent patients may also have seizures that are not related to alcohol withdrawal. Occasionally, acute alcohol intoxication with a rising BAC may also precipitate seizures because of the excitatory effects of alcohol (Yamane & Katoh 1981). Cerebral traumas and haemorrhagic strokes are commonly associated with alcoholism and can lead to seizures (Jennett 1996, Feigin *et al*. 2005, Ariesen *et al*. 2003, Chan 1985). Furthermore, there are suggestions that the long-term neurotoxic effects of alcohol could also induce seizures (Hauser *et al*. 1988). Sometimes it is hard to say whether a seizure problem is alcohol-related. A cerebral infection can cause seizures, for instance, and infections are common among alcoholics, but a seizure caused by an infectious disease in an alcoholic is not necessarily alcohol-related (Bråthen 2001).

The prevalence of epilepsy among alcohol-dependent patients has been assessed to be at least triple that in the general population (Chan 1985), but the prevalence of alcoholism is only slightly higher among epileptics than in the general population (Hillbom *et al*. 2003). It has been suggested that if a cerebral process (neoplasm, scar, etc.) simultaneously lowers the seizure threshold, smaller amounts of alcohol are needed to trigger epileptogenic activity (Hillbom 1980). One report, however, found no evidence of an association between alcohol use and a first symptomatic seizure caused by stroke, head trauma or a cerebral tumour (Leone *et al*. 2002).

3 Purpose of the research

The purpose of the present research was to evaluate the effects of alcohol on the outcome after head trauma. The following questions were addressed:

1. Did the reduction in the price of alcohol influence mortality among harmful drinkers?
2. Did the reduction in the price of alcohol influence mortality among subjects with alcohol-related seizures?
3. Does an alcohol-related index head trauma predict new-onset seizures?
4. Does an alcohol-related index head trauma predict future TBI?

4 Subjects and methods

4.1 Study design

A series of observational longitudinal studies was designed to determine the effect of the reduction in alcohol prices on mortality among harmful drinkers and those experiencing alcohol-related seizures and to demonstrate predictors for new-onset seizures and TBIs in a cohort of head trauma patients. The baseline data were collected during 1999 and the cohort was followed up prospectively until the end of 2009.

4.2 Subjects

4.2.1 Cohort

The cohort included all 827 subjects, including children and elderly people, who were admitted to the ER at Oulu University Hospital during 1999 (from 1st January to 31st December) on account of acute head trauma. All subjects with head trauma, ranging from scalp wounds to severe TBIs, were included. The catchment area for our hospital is the Northern Ostrobothnia region (population 365 689 in 1999 and 392 110 in 2009). The persons admitted are mainly residents of the area, but may also come from other parts of Finland. Our cohort included 745 residents of Northern Ostrobothnia and 82 people from elsewhere in Finland. In paper III the subjects with previous seizures and other neurological diseases that are known to entail a predisposition to seizures, such as brain infarction and TBI, were excluded from the cohort. This was done because we wanted to investigate the occurrence and predictors of new-onset seizures. After these exclusions, the series considered in paper III comprised 739 subjects who were followed up until the end of 2009.

All patients with head trauma admitted during 1999 were included in the cohort independent of age and trauma severity. Acute head traumas were identified from the checklist kept in the emergency room by a nurse who inspected the list and the ER records daily and picked out any notes suggestive of acute head trauma for further assessment by one of the research team. Furthermore, the hospital discharge register was checked weekly to identify any head trauma subjects who had not been noticed on the basis of the checklist. This

method maximized the possibilities for identifying every single acute head trauma subject admitted during 1999. Further data gathered from the hospital charts for 1999 included information on age, sex, place of residence, time of the index head trauma, severity of the index head trauma and alcohol involvement. Previous diseases and lifestyle factors such as TBIs, psychiatric illnesses and alcohol consumption were also ascertained.

4.2.2 Follow-up

The subjects in the cohort were followed-up from their ER visit in 1999 until death or the end of 2009 by linking their social security numbers to the data obtained from National Hospital Discharge Register (NHD). All Finnish citizens and permanent residents have their own unique social security number, which makes it possible to link various registers. We also checked the available hospital records. The NHD data included all diagnoses recorded on discharge from any hospital in Finland after an in-patient, out-patient or emergency room visit, and also all diagnoses for in-patient visits to Finnish health centres (but not for out-patient or emergency room visits to health centres). We gathered data especially on alcohol abuse, TBIs and seizures. We did not contact the subjects themselves.

All 827 subjects were searched for in the Statistics Finland Causes-of-Death Register (SFCD) for possible death. Altogether 160 subjects had died during the follow-up period, for which we obtained data from the register on the time of death, direct, underlying and contributory causes and whether the causes had been determined by medico-legal autopsy, medical autopsy or clinical examination.

4.3 Definitions

4.3.1 TBI

The head traumas were divided into three categories modified from the EFNS guideline (Vos *et al*. 2002). Subjects with a Glasgow Coma Scale (GCS) score of 15 on admission and no loss of consciousness (LOC) or no post-traumatic amnesia (PTA) were classified as having head trauma without TBI (category 0 according to the EFNS guideline), mild TBIs included subjects with GCS scores of 13–15 on admission, LOC for less than 30 min, PTA for less than 1 hour and an absence of traumatic intracranial findings in brain CT/MRI (categories 1–3),

subjects without a brain CT/MRI also being classified as having mild TBI if any of the other criteria for mild TBI were fulfilled, while the category with most severe injuries, i.e. with moderate-to-severe TBIs, included all subjects who presented with GCS <13 and also subjects with brain contusion, diffuse axonal injury, traumatic subarachnoid haemorrhage or traumatic intracranial haematomas regardless of their GCS score or need for surgery.

4.3.2 Alcohol parameters

Harmful drinking

World Health Organization (WHO) has defined the harmful use of alcohol as a pattern of alcohol drinking that causes damage to either physical or mental health (WHO 1992). A subject was defined here as a harmful drinker if he or she had at least one diagnosis of an alcohol-related disease (including mental and behavioural disorders caused by alcohol, alcoholic hepatitis, acute and chronic alcohol liver cirrhosis and acute and chronic alcohol pancreatitis) in the NHD register or if there were any diagnostic or otherwise reliable notes on the hospital charts pointing to acute alcohol intoxication or harmful consumption of alcohol immediately preceding admittance to an ER, health centre or hospital during the follow-up (i.e. after the index trauma). An alcohol-related index trauma as such was excluded because it served as a separate parameter in the analyses. The category of harmful drinkers was not taken to include subjects who had an alcohol-related disease or intoxication as a direct, underlying or contributory cause of death unless they had had an alcohol-related visit to a hospital or health centre during the follow-up period.

Alcohol-related index trauma

Blood and/or breath alcohol concentration is usually measured of all head trauma subjects with impaired consciousness. Informed consent is not required for this in our hospital. An alcohol-related index trauma was recorded if the subject had at least 10 mg/dl (0.1‰) alcohol in his/her blood or breath. In the absence of an alcohol measurement a trauma was defined as alcohol-related if the subject had been found by a nurse or physician to be under the influence of alcohol. In such cases, the criteria were based on a smell of alcohol on the breath combined with

signs suggesting alcoholic intoxication, such as unsteady gait, slurred speech or aggressive behaviour.

4.3.3 Seizure

Data on seizures were gathered from the NHD and SFCD registers. If these registers included any diagnosis of seizures, the nature of the events was checked from the available hospital records.

Alcohol-related seizure

A seizure problem was defined as alcohol-related differently in papers II and III. In paper II a seizure was said to be alcohol-related if the NHD register contained such a diagnosis of seizure and/or the notes on our hospital charts indicated the same, while in paper III we defined a seizure as alcohol-related if it was indicated in the NHD register and/or our hospital discharge data as being due to acute withdrawal of heavy alcohol drinking.

4.4 Methods

4.4.1 Statistical analyses

All the data were analysed using IBM SPSS Statistics, version 20.0 for Windows (IBM Corp, Armonk, NY, USA). Fisher´s exact test and Pearson´s χ^2 test were used to compare categorical variables. Continuous variables were compared between groups with Student´s t-test. Cumulative survival rates and cumulative rates of developing seizures or TBI were estimated by the Kaplan-Meier product-limit method, and the curves for the groups were compared using the log-rank test. Predictors of death, new-onset seizure and subsequent TBI were investigated by means of the Cox proportional-hazards regression model. The assumption of proportionality was checked. The test for significance was based on changes in log (partial) likelihood. A two-tailed p value of less than 0.05 was considered to be statistically significant.

5 Results

5.1 Mortality among harmful drinkers (paper I)

Of the 827 subjects admitted to the ER at Oulu University Hospital on account of acute head trauma in 1999 and followed up until the end of 2009, 295 (35.7%) were found to be under the influence of alcohol on admission. 202 subjects had the alcohol concentration in their blood or breath measured. Altogether 160 subjects out of the 827 (19%) died during the follow-up. According to the NHD register and hospital charts, there were altogether 101 harmful drinkers recorded until the end of 2009.

Significantly more deaths occurred among the harmful drinkers than among the subjects who were not recorded as such ($p<0.001$), and alcohol was much more often recorded as an underlying or contributing cause of death among harmful drinkers than among the others ($p<0.001$). The harmful drinkers also more often died while being under the influence of alcohol ($p<0.001$). Life-table analysis demonstrated that the death rate among harmful drinkers markedly increased after the price of alcoholic beverages was reduced on March 1st 2004. This original life-table is shown in Fig. 3.

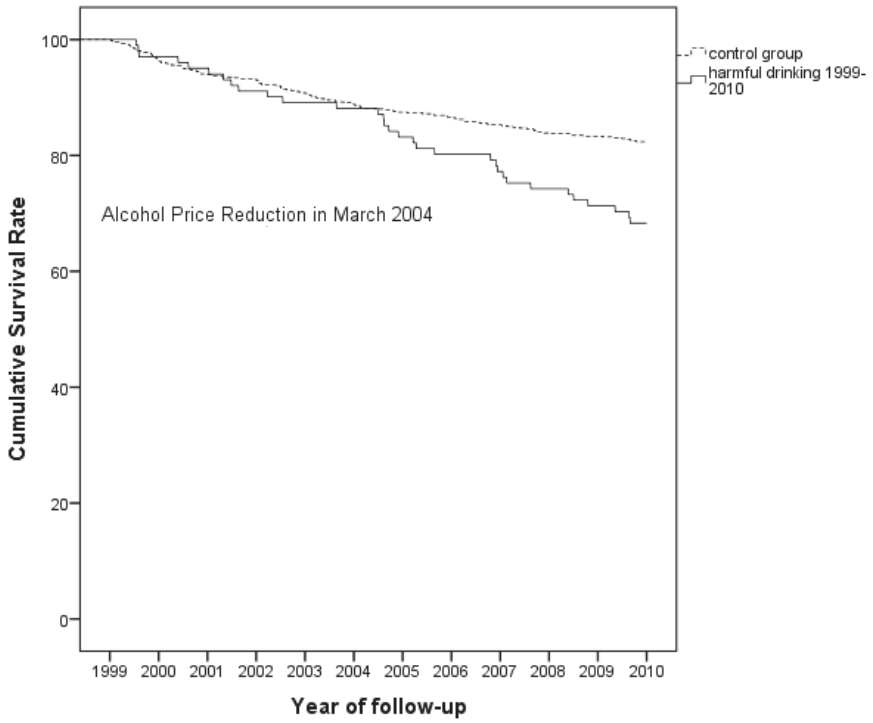

Fig. 3. Cumulative survival rate for subjects recorded as harmful drinkers between 1999 and the end of 2009 (n=101), showing the abrupt change in the trend associated with the reduction in alcohol prices on 1 March 2004. (Paper I and Jussi Puljula: Alcohol-related traumatic brain injuries before and after the reduction of alcohol prices. Observations from Oulu Province and Northern Ostrobothnia. Acta Universitatis Ouluensis D 1176, 2012, University of Oulu. Published by permission of Karger, Jussi Puljula and Acta Universitatis Ouluensis).

As there were 16 subjects whose diagnosis of harmful drinking was recorded after the price reduction, we performed a separate analysis in which these 16 subjects were considered non-harmful drinkers. Even then the survival rate for harmful drinkers was significantly lower than that among non-harmful drinkers (Fig. 4).

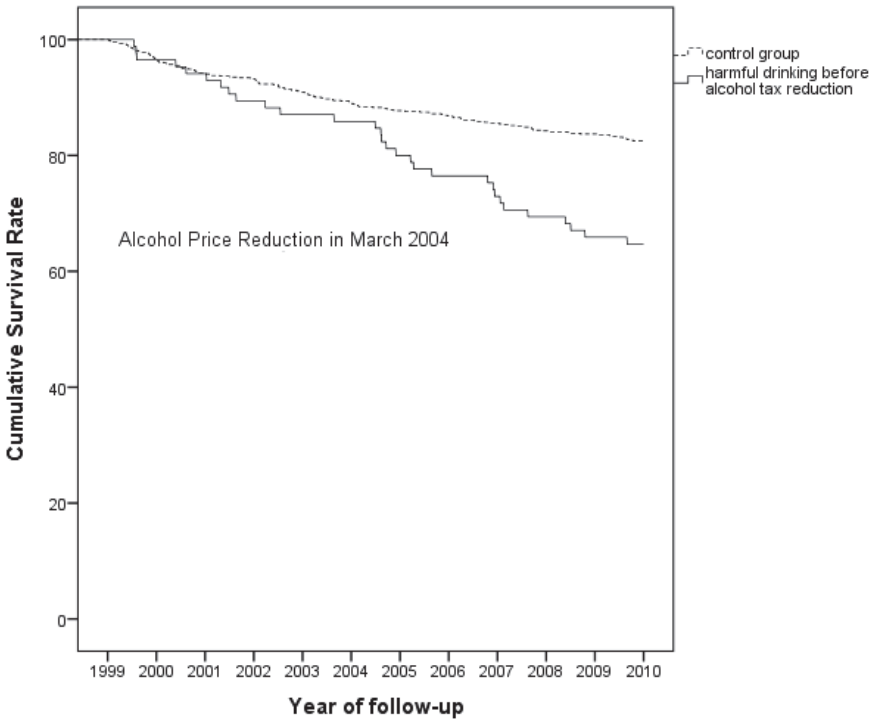

Fig. 4. Cumulative survival rate for subjects classified as harmful drinkers before the alcohol price reduction (n=85). (Jussi Puljula: Alcohol-related traumatic brain injuries before and after the reduction in alcohol prices. Observations from Oulu Province and Northern Ostrobothnia. Acta Universitatis Ouluensis D 1176, 2012, University of Oulu. Published by permission of Jussi Puljula and Acta Universitatis Ouluensis).

Figure 5 demonstrates a much greater ($p<0.001$) mortality among subjects with moderate-to-severe TBI as the index trauma compared with others during the follow-up. Among the subjects with moderate-to-severe TBI there were 6 who had already been observed to be harmful drinkers before the index trauma. Three others were observed to be harmful drinkers later on.

Follow-up of the total cohort showed that there was no significant difference in mortality between the subjects who were and were not under the influence of alcohol at the time of the index trauma. Lack of the difference was partly due to the fact that there were many subjects with moderate-to-severe TBI among those who were not under the influence of alcohol while getting the index head trauma.

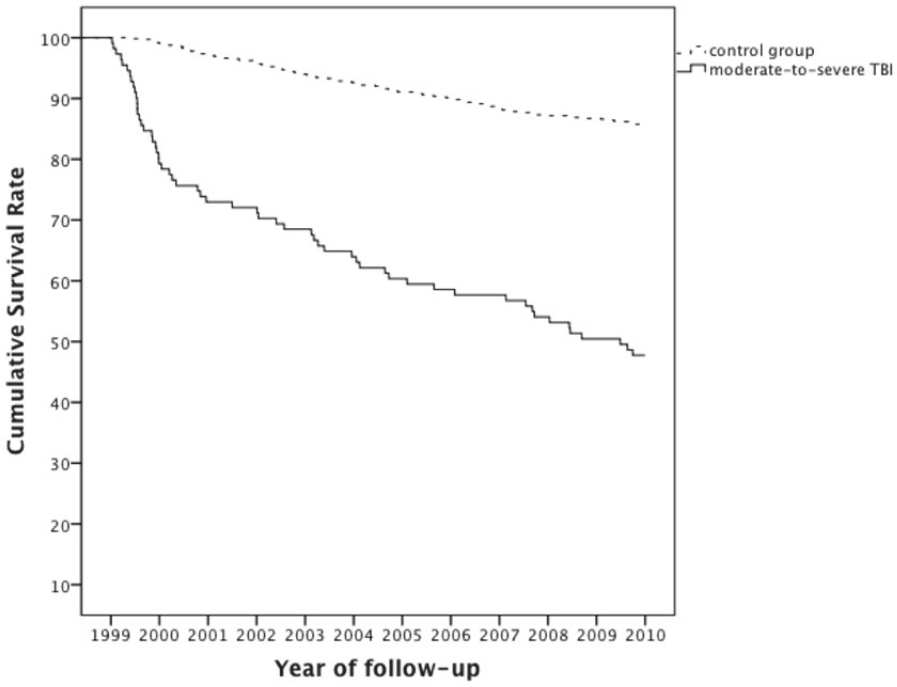

Fig. 5. Cumulative survival rates for subjects with and without moderate-to-severe TBI as the index trauma.

The Cox proportional-hazards model identified age and moderate-to-severe TBI as significant independent predictors of death. An alcohol-related index trauma was not a predictor of death, but being a harmful drinker was a powerful predictor (Table 1).

Table 1. Cox proportional hazards model for variables predicting death during the 10-year follow-up. (Paper I, published by permission of Karger)

Predictors of death	Hazard ratio (95% CI)	P value
Age (per year)	1.06 (1.05–1.07)	<0.001
Sex (men vs. women)	1.12 (0.77–1.61)	
Index trauma was alcohol-related	1.06 (0.70–1.59)	
Harmful drinking recorded after the index trauma	2.59 (1.62–4.62)	<0.001
Severity of index head trauma (vs. no brain injury)		
Mild TBI	0.76 (0.49–1.16)	
Moderate-to-severe TBI	2.39 (1.59–3.60)	<0.001
History of (recorded before the index trauma)		
Seizures	2.07 (1.15–3.72)	0.015
TBI	0.84 (0.48–1.48)	
Psychiatric disease	1.47 (0.76–2.84)	

5.2 Mortality among subjects with alcohol-related seizures (paper II)

There were altogether 79 subjects with seizure problems in the cohort, of whom 32 (40.5%) were recorded as having alcohol-related seizures and 25 of these (78.1%) had developed alcohol-related seizures before the reduction in alcohol prices. The mortality rate for these 25 subjects was similar to that of the subjects without alcohol-related seizures up to the time of the alcohol price reduction, but after the reduction their mortality curve became significantly steeper (p=0.015). Mortality among the subjects with alcohol-related seizures, however, did not significantly differ from that among other harmful drinkers or from that of other subjects with seizures. Age, a moderate-to-severe index TBI and alcohol-related seizures were significant predictors of death during the follow-up (Table 2). Each subject who died and was recorded as having a history of at least one alcohol-related seizure was also recorded as having an alcohol-related cause of death.

Table 2. Cox proportional-hazards multivariable model for variables predicting death within 10 years after head trauma. (Paper II, published by permission of Wiley)

Predictors of death	Hazard ratio (95% CI)	P value
Age (per year)	1.06 (1.05–1.07)	0.000
Sex (men vs. women)	1.25 (0.88–1.78)	0.211
Preceding TBI	0.96 (0.56–1.66)	0.893
Severity of index TBI (vs. no brain injury)		
Mild TBI	0.70 (0.46–1.07)	0.098
Moderate-to-severe TBI	2.04 (1.37–3.04)	0.000
New TBI	1.41 (0.85–2.32)	0.182
Presence of alcohol-related seizures (n=25)	3.02 (1.48–6.16)	0.002

5.3 Alcohol consumption as a predictor of new-onset seizures in patients with head trauma (paper III)

Out of the 739 subjects with acute head trauma in 1999 who did not have a preceding neurological disease, including seizures, 362 had a head trauma without TBI, 297 mild TBI and 80 moderate-to-severe TBI. 42 of these subjects developed seizure problems during the follow-up, and 19 of these (45.2%) had alcohol-related seizures. The baseline data for the cohort are shown in Table 3.

Table 3. Baseline data on the head injury cohort. (Paper III, published by permission of BMJ Publishing Group Ltd.)

Variable	No TBI (n=362)	Mild TBI (n=297)	Moderate-to-severe TBI (n=80)	Total (n=739)
Age, mean (range)*	38.0 (0–90)	32.1 (0–90)	46.1 (1–86)	36.5 (0–90)
Sex (men) (%)**	271 (74.9)	178 (59.9)	56 (70.0)	505 (68.3)
History of psychiatric disease	11 (3.0)	7 (2.4)	3 (3.8)	21 (2.8)
Alcohol-related index injury**	175 (48.3)	80 (26.9)	17 (21.2)	272 (36.8)
New-onset seizure, total*	22 (6.1)	9 (3.0)	11 (13.8)	42 (5.7)
New-onset seizure, alcohol-related	14 (3.9)	3 (1.0)	2 (2.5)	19 (2.6)
New TBI before new-onset seizure	4 (1.1)	2 (0.7)	1 (1.2)	7 (0.9)
Death during follow-up**	52 (14.4)	27 (9.1)	33 (41.2)	112 (15.2)

*$p<0.01$ and **$p<0.001$ for difference between groups.

TBI, traumatic brain injury

The significant independent risk factors for new-onset seizures identified by means of the Cox proportional-hazards model are shown in Table 4. When subjects with different degrees of severity of the head trauma were analysed separately, an alcohol-related index head trauma was shown to be a significant independent risk factor for new-onset seizures among subjects with a head trauma without TBI or with mild TBI. Subjects having a head trauma without TBI developed alcohol-related seizures significantly more often than those with TBI.

Table 4. Risk factors for new-onset seizures among 739 head injury subjects. (Paper III, published by permission of BMJ Publishing Group Ltd.)

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)
Age per year	1.01 (0.99–1.02)	1.00 (0.98–1.02)
Male sex	1.72 (0.82–3.59)	1.33 (0.62–2.83)
History of psychiatric disease	4.05 (1.45–11.35)**	3.23 (1.13–9.21)*
Moderate-to-severe TBI as index trauma	2.42 (1.17–4.98)*	3.13 (1.46–6.71)**
Alcohol-related index injury	2.57 (1.39–4.76)**	2.50 (1.30–4.82)**

Subjects without a risk factor served as a reference category for the significant independent factors.

*P<0.05, **p<0.01

TBI, traumatic brain injury

5.4 Head trauma under the influence of alcohol is a predictor of future TBI (paper IV)

Altogether there were 52 subjects who sustained a TBI during the follow-up, this being mild in 29 cases (55.8%) and moderate-to-severe in 23 (44.2%). The risk of sustaining a TBI during the follow-up was significantly higher among the subjects who were intoxicated at the time of the index trauma. This finding was particularly prominent when observing those subjects who had initially sustained a head trauma without TBI (n=396).

Cox regression models identified age, moderate-to-severe TBI as an index trauma, preceding TBI, preceding harmful drinking and an alcohol-related index trauma as predictors associated with an increased risk of TBI in the univariable analysis. As there was a strong positive correlation between the alcohol parameters, two separate multivariable analyses were conducted, each including one of the alcohol parameters, to avoid multicollinearity: model 1, which included an alcohol-related index trauma together with preceding TBI, with both parameters appearing to be significant independent predictors of future TBI, and model 2, in which the alcohol-related index trauma variable was replaced with a

preceding history of harmful drinking, which now appeared to be the only significant predictor of TBI ($p<0.001$) (Table 5). In the subset of 396 patients with a head trauma without TBI, an alcohol-related index trauma was also a highly significant risk factor for future TBI after adjustment for sex, age and history of TBI (adjusted HR 3.54, 95% CI 1.36–9.18, $p=0.009$).

Table 5. Predictors of traumatic brain injury. (Paper IV, published by permission of Wiley-Blackwell).

Variable	Univariable HR (95% CI)	Multivariable HR (95% CI)	
		Model 1	Model 2
Age per year	1.02 (1.00–1.03)*	1.01 (1.00–1.03)	1.01 (1.00–1.03)
Male sex	1.02 (0.57–1.84)	0.88 (0.47–1.64)	0.78 (0.42–1.46)
Severity of head trauma			
Head trauma without TBI	1.00	1.00	1.00
Mild brain injury	1.02 (0.55–1.86)	1.24 (0.67–2.32)	1.23 (0.66–2.27)
Moderate-to-severe brain injury	2.22 (1.06–4.67)*	1.97 (0.84–4.65)	2.12 (0.95–4.75)
Preceding:			
Traumatic brain injury	4.63 (1.97–10.85)**	3.39 (1.32–8.72)*	1.94 (0.77–4.90)
Harmful drinking	10.02 (5.59–17.96)**		10.37 (5.53–19.43)**
Alcohol-related index trauma	2.06 (1.19–3.55)*	2.51 (1.38–4.56)**	

*p<0.05, **p<0.01

6 Discussion

6.1 The alcohol price reduction and mortality

Finnish taxes on alcohol were lowered by an average of 33% on March 1st 2004, on account of Estonia joining the EU on May 1st 2004, the import quotas for alcoholic beverages having been abolished within the EU as of January 1st 2004. As a consequence of these changes, the total estimated *per capita* alcohol consumption in Finland increased by about 10% within a year (Mäkelä & Österberg 2009). This finding confirms previous observations that higher prices of alcohol are related to a lower level of consumption and lower prices to a higher level (Wagenaar *et al*. 2009). Other studies making use of a comparable natural experiment have led to similar conclusions (Ponicki *et al*. 1997, Kuo *et al*. 2003).

We found that the mortality rates of the harmful drinkers and subjects with alcohol-related seizures in the cohort increased after the price reduction. Harmful drinking and alcohol-related seizures were also powerful predictors of death during the follow-up. Alcohol was significantly more common as an underlying or contributing cause of death among the harmful drinkers and subjects with alcohol-related seizures than it was among the other members of the cohort.

Alcohol-related seizures usually occur after prolonged heavy drinking and are typically a clear sign of alcohol dependence (Bråthen *et al.* 1999, Victor & Brausch 1967). It has also been found that persons with alcohol dependence have a significantly higher mortality rate than the general population (Moos *et al*. 1994, John *et al*. 2013). Our findings are in line with this, suggesting that an alcohol-related seizure can be considered a warning sign pointing to alcoholism and an increased risk of premature death.

It has also been observed in other studies carried out in Finland that alcohol-related hospitalisation rates (Herttua *et al*. 2011) and the alcohol-related mortality rate (Herttua *et al*. 2008a) increased after the reduction in alcohol prices, the increase in the mortality rate being most prominent among subjects in the lower social categories (Herttua *et al*. 2008a). Deaths from alcohol-induced liver disease increased most, by 46% in 2004–2006 compared with 2001–2003 (Mäkelä & Österberg 2009). As alcohol liver cirrhosis takes years or even decades to develop (Bellentani *et al*. 1997), this observation indicates that the alcohol price reduction had a powerful effect on previous heavy drinkers (Mäkelä & Österberg 2009). Our findings are in accordance with this.

6.2 Alcohol and the risk of seizures after head trauma

The main finding in paper III was that an alcohol-related head trauma predicts new-onset seizures. We observed that nearly one half of the cases of new-onset seizure problems were alcohol-related and that alcohol-related seizures were more common among subjects with head trauma but without traumatic brain injury. It has been shown previously that the risk of post-traumatic seizures depends on the severity of the head trauma and is slightly increased in subjects with mild TBI (Annegers *et al*. 1998). Annegers *et al*. (1998) suggested that the increased incidence of post-traumatic seizures in mild TBI cases may have been due to the characteristics of these subjects and not to the injuries themselves. Our finding supports this notion. Since the prevalence of alcohol problems is high among head injury subjects, it is plausible to suggest that the risk of subsequent seizure problem after minor head trauma depends on the individual's alcohol consumption pattern and not on the trauma. A seizure problem after a minor head trauma may reflect an underlying alcohol problem rather than being a structural consequence of the head trauma itself (Welch & Derry 2013).

The mortality rate among the subjects with a new-onset seizure problem was significantly higher than that among the others, as shown by the fact that 33% of the 42 new-onset seizure subjects died during the follow-up. Similarly, the corresponding figure of 34% among the subjects with alcohol-related seizures in general suggests that a post-traumatic seizure problem, which is often alcohol-related, is a powerful predictor of premature death, and that the mortality rate can be affected by influencing people's drinking patterns.

6.3 Alcohol and the risk of TBI after head trauma

The subjects with a history of alcohol-related head trauma had a significantly higher risk of future TBI than those without. This finding was particularly clear among the subjects with an index head trauma without TBI. This indicates that an alcohol-related head trauma is a more powerful predictor of subsequent TBI than is the severity of the index trauma itself. An alcohol-related head trauma should be taken as a warning sign of later TBI, and interventions should be targeted at subjects with the habit of hazardous drinking.

Some researchers have seen the trauma itself as a marker of alcohol abuse or alcoholism (Maull 1982), and our findings tend to confirm this. More than one third of the cohort subjects were intoxicated on admission, and the proportion

could well have been even higher if all the subjects had been tested. Other studies have estimated the proportion of intoxicated subjects among head trauma populations to vary from 1/3 to 2/3 (Corrigan 1995, Savola *et al*. 2005).

Binge drinking, i.e. taking 4–5 drinks per occasion or drinking that results in a BAC of 0.8‰ or higher (Fillmore & Jude 2011), is a growing problem in the developed countries (Mäkelä *et al*. 2001, Naimi *et al*. 2003) and is a characteristic drinking pattern among trauma patients (Savola *et al*. 2005). Binging significantly increases the risk of a fatal injury (Paljärvi *et al*. 2005) and appears to specifically increase the risk of head trauma (Savola *et al*. 2005). If no intervention against binge drinking is performed, the habit will be likely to continue. Health care professionals need to try to influence drinking habits among those attending the ER. Although this topic is not specific to the head injury population, there is strong evidence that a physician can affect the pattern of drinking by means of a brief intervention (Bien *et al*. 1993, Fleming *et al*. 1997, Gentilello *et al*. 1999, Smith *et al*. 2003). It is therefore important that this useful tool for preventing hazardous drinking should be taken into use.

One efficient method of identifying subjects with alcohol dependence among trauma patients is to perform breath or blood alcohol measurements as a screening instrument for each trauma patient (Ryb *et al*. 1999). An easy-to-use method for identifying a subject with an elevated risk of an alcohol-related outcome has recently been validated (Paljärvi *et al*. 2012). This is based on asking three questions, whereupon any hazardous drinkers are to be found among those who admit to having been drunk or having experienced a hangover at least once a week or having passed-out on account of alcohol inebriation at least once during the previous year (Paljärvi *et al*. 2012). Such subjects need a brief intervention.

The intervention itself is simple and consists of three phases. First, the patient needs to be informed of his/her BAC level, second, the connection between inebriation and trauma has to be made clear, and finally, an encouraging discussion should follow aimed at reducing alcohol consumption and binge drinking in the future. It would be appropriate for the intervention to take place in the ER, assuming that the BAC is at a level that does not interfere with cognition. There is often a shortage of time for performing brief interventions in the ER, but mostly the reason for not doing so is cynicism.

6.4 Alcohol policy and public health

Alcohol policy in Finland has for a long time been rather restrictive, but some liberalisation has taken place during recent decades. Consumption was at a relatively low level before the alcohol legislation was revised in 1968 (Herttua 2010), and nowadays it is at an average European level (Anderson *et al.* 2012). A wide spectrum of detrimental health consequences of alcohol drinking has been identified, and it has been estimated that globally 3.8% of all deaths are attributable to alcohol (Rehm *et al*. 2009). It should be remembered, however, that alcohol may also have some beneficial effects on health. Thus the relation of alcohol to total mortality among middle-aged and elderly people is J-shaped, the reduced risk among light drinkers being due to the lower incidence of cardiovascular deaths (Rehm & Sempos 1995, Klatsky & Udaltsova 2007, Di Castelnuovo *et al*. 2002, Mukamal *et al*. 2010). However, even in regions where the net effect of alcohol on CVDs is beneficial, the overall effect of alcohol on the burden of disease is detrimental (Rehm *et al*. 2009). It has also been noted that research into alcohol and cardiovascular mortality may entail methodological problems (Naimi *et al.* 2005, Stockwell *et al*. 2012). It has even been suggested that the consumption of alcohol should never be encouraged on health grounds (Beaglehole & Bonita 2009). Alcohol may have some positive effects in terms of people´s social lives, and therefore on their mental health, but these effects are difficult to measure.

The deleterious effects of alcohol are inversely related to the unit price of alcohol drinks, and therefore adjustment of the latter can be an effective means of influencing these effects (Anderson *et al*. 2009b). It has been pointed out in Finland that approximately 10% of the population drink about one half of all the alcohol consumed (Huhtanen *et al*. 2011), and some people may consider a price-oriented alcohol policy to be unfair because it is implemented on terms dictated by the problem drinkers (Herttua 2010). It is important to remember, however, that the drinker is doing damage not only to him/herself and other drinkers but also to innocent bystanders and others´ property (Babor 2011). Maladaptive family dynamics, fetal alcohol syndrome and physical and emotional violence are some of the consequences of alcohol abuse that affect the whole community and can be referred to as collateral damage (Babor 2011). It has been reported from Australia that 70% of the population considered that they had been affected by strangers´ drinking within the last year and 30% that drinking by someone close to them had had negative effects on them (Laslett *et al*. 2011). Furthermore,

governments try to restrict people´s usage of other potentially harmful, legally produced consumer products and services such as automobiles, tobacco products and gambling facilities and thereby reduce their harmful effects on public health despite the fact that majority of the population behave in a non-detrimental manner even without restrictions. There have also been suggestions that if alcohol was cheaper problem drinkers would have a little more money to buy food and other basics (Herttua 2010). There is no evidence, however, that problem drinkers would live healthier lives if alcohol was cheaper, but contrary observations do exist (Herttua *et al*. 2008a, Koski *et al*. 2007). The potential beneficial effects of alcohol are restricted to light drinkers, who may consider the price-oriented policy unfair but will not be seriously affected financially because of the small amounts of alcohol they consume. If an individual can´t afford to buy the same amount of alcohol as before a price increase, the reason may not be the price but more likely the person's relatively high level of alcohol consumption. On the other hand, the use of taxation for price regulation purposes is not a straightforward matter because sharp increases in alcohol prices may lead to increased importation from the neighbouring countries, an increased risk of black market trading and increased amounts of homemade alcohol. Also, the alcoholic beverages industry is a significant employer and reduced consumption of its products may lead to redundancies.

Free movement of goods lies at a core of the European Union legislation, but since alcohol prices differ significantly between EU countries, this principle has far-reaching public health dimensions. Public health issues in the EU are usually regulated by means of "soft laws" such as guidelines and recommendations, while economic issues are controlled by "hard laws", i.e. binding legislation (Mäkelä & Österberg 2009). Because of the lobbying power of the alcoholic beverages industry, the EU has chosen to adopt only legislation that causes little or no damage to that industry´s profits (Greer *et al*. 2013). In view of the pharmacological power of alcohol and its huge detrimental impact on public health, it is nevertheless justifiable to ask whether the categorical acceptance of the free movement of goods is truly a reasonable option.

It has been suggested that liberalising alcohol policy by lowering prices and removing the availability restrictions would steer the culture of alcohol drinking in a more responsible direction (Herttua 2010), and this is also the agenda pursued by the alcohol industry (McCambridge *et al*. 2013). However, there is little evidence to support the mechanisms behind this concept. At least the evolution of a more responsible alcohol drinking culture would take a great deal of time and

would entail sacrificing those individuals who are prone to develop alcohol dependence or are already suffering from such a dependence. It is important to understand that alcohol drinkers are consumers of alcoholic beverages and alcohol industry is profiting from the sale of its products. The commercial interests often prompt the alcohol industry to misrepresent the strong evidence and promote the weak evidence concerning alternative means for tackling alcohol problems (McCambridge *et al*. 2013). The results of the present study are in accordance with previous observations of a rapid increase in mortality among heavy drinkers following a sharp reduction in alcohol prices. Political decisions can greatly affect public health.

6.5 Strengths and limitations

Since Oulu University Hospital is the only hospital with neurosurgical facilities in Northern Ostrobothnia, all subjects with symptoms and signs suggestive of at least moderate-to-severe TBI are usually admitted to this hospital. In addition, the majority of the subjects in the cohort were living in the hospital's catchment area. Also, the hospital charts were easily available and all the relevant hospital records could be consulted when compiling the data. The baseline data were gathered systematically from the hospital charts in 1999 using a standard protocol, and the subjects were followed up prospectively until the end of 2009.

The NHD registration system made it possible to search through all the diagnoses recorded anywhere in Finland for the whole follow-up period. Likewise, comprehensive mortality data for Finland were available in the SFCD register. Even so, we also checked hospital records for further relevant follow-up data, as we wanted to minimize the bias that is always possible in register-based studies. The coding in registers can sometimes be inaccurate or deficient. There is also a risk that not all visits due to seizures or TBIs are recorded. Hospital records were available for the vast majority of the cohort subjects (90%), i.e. those living in the catchment area.

The 10 years of follow-up meant that we could observe the outcome for the head injury subjects over a relatively long period. In this case it also meant that we could make use of a natural experiment setting, which is relatively rarely possible in the field of alcohol studies.

The sample size is rather small, however, and therefore the statistical power may be modest and the results should be interpreted with caution. The cohort consisted of 827 subjects and we only had 42 subjects who developed new-onset

seizures and 52 subjects who sustained a TBI during the follow-up. Furthermore, we presumably missed some future TBIs and new-onset seizures because the study was register-based.

The inclusion of children and elderly people in the cohort may have caused some bias in the results. The purpose of the present research was to evaluate the effect of alcohol on the outcome after head trauma, and children and the elderly do not usually engage in alcohol abuse as often as young adults and middle-aged people do. Our cohort included altogether 127 subjects who were under 16 years of age at the time of the index trauma, and a further 47 subjects who were aged 80 years or older at the time.

As we did not measure the BAC systematically in all the head trauma cases, some subjects who had been under the influence of alcohol may have remained unnoticed. Furthermore, some head trauma subjects may have escaped notice, especially if they had multiple traumas or the main reason for their attending hospital was something other than trauma. The majority of TBIs are mild (Feigin *et al*. 2013) and many subjects with mild TBI do not even seek medical attention. Thus the real incidence figures for mild TBI and head trauma without TBI in our area are not known. In addition, because the severity of the head trauma was based on notes in the hospital records, the accuracy of the data should be interpreted with caution.

A harmful drinker was defined as a subject having at least one diagnosis of alcohol-related disease (including mental and behavioural disorders attributable to alcohol, alcoholic hepatitis, acute or chronic alcohol liver cirrhosis and acute or chronic alcohol pancreatitis) recorded during the follow-up or if there was any diagnosis of harmful use of alcohol or alcohol intoxication immediately preceding admittance to ER, health centre or hospital during the follow-up. We certainly missed some harmful drinkers because the NHD coding is not accurate enough to identify all such cases, and there may have been some coding errors. We excluded the alcohol-related index trauma in 1999 from the definition of harmful drinking because these two parameters were used separately. Mortality among harmful drinkers was observed in paper I, to have increased significantly after the alcohol price reduction, but since the category of harmful drinkers in that analysis included 16 subjects who were recorded as harmful drinkers only after the price reduction, we performed another analysis with these 16 subjects relocated in the control group. Even in this analysis, however, the harmful drinkers still showed increased mortality after the price reduction.

6.6 Future aspects

This thesis is concerned with the effect of alcohol abuse on the outcome after head trauma. The cohort was an unselected series of head trauma patients including subjects with injuries ranging from minor bruises to severe TBI and of all ages: from children to elderly people. One problem with TBI research is that the spectrum of the traumas is wide and it is hard to reach general conclusions concerning patient care and outcomes. Traumatic epidural haematoma (EDH), for instance, is an emergency usually requiring neurosurgical intervention and is traditionally placed in the category of severe TBI. The head trauma that causes EDH, however, may be relatively minor and have no impact on the brain tissue, so that the outcome for these subjects is usually excellent. The field of TBI research lacks studies of the specific outcomes associated with different types of TBI, which is an important aspect when trying to develop medications for TBI subjects because DAI and EDH, for example, may involve different responses to the same medication.

McMillan *et al*. (2011) found that the risk of death is increased until 13 years after TBI, especially among young subjects with mild TBI, but admitted that the reason for this increased vulnerability remains unclear. Our study indicates that alcohol consumption is a potential risk factor for long-term mortality among subjects with head trauma, and this needs further investigation.

7 Conclusions

1. The mortality rate among harmful drinkers increased after the alcohol price reduction.
2. The mortality rate among subjects with alcohol-related seizures increased after the alcohol price reduction.
3. Alcohol-related head trauma was predictive of new-onset seizures, especially alcohol-related seizures, among subjects with an index head trauma without TBI or with mild TBI.
4. Subjects with alcohol-related head trauma had an elevated risk of TBI during the follow-up.

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Original Publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2012) Mortality of harmful drinkers increased after reduction of alcohol prices in northern Finland: a 10-year follow-up of head trauma subjects. Neuroepidemiology 39(3–4): 156–162. DOI: 10.1159/000341241.

II Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2014) Mortality of subjects with alcohol-related seizures increased after alcohol cheapening. Acta Neurol Scand 129(1): 56–60. DOI: 10.1111/ane.12150.

III Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2013) Predictors of new-onset seizures: a 10-year follow-up of head trauma subjects with and without traumatic brain injury. J Neurol Neurosurg Psychiatry. In press. DOI:10.1136/jnnp-2012-304457.

IV Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M (2013) Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: a long-term follow-up study. Eur J Neurol. In press. DOI: 10.1111/ene.12302.

Original publications are not included in the electronic version of the dissertation.

1216. Malo, Elina (2013) The role of low birth weight and resistin in metabolic syndrome

1217. Karjalainen, Jaana (2013) Cardiovascular autonomic function in coronary artery disease patients with and without type 2 diabetes : significance of physical activity and exercise capacity

1218. Peurala, Emmi (2013) Regulators of hypoxia response and the cell cycle in breast cancer

1219. Koskela, Sanna (2013) Granulosa cell anti-Müllerian hormone secretion in ovarian development and disease

1220. Soini, Heidi (2013) Mitochondrial DNA sequence variation in Finnish patients with maternally inherited type 2 diabetes, epilepsy and mitochondrial disease: risk and novel mutations

1221. Sinikumpu, Juha-Jaakko (2013) Forearm shaft fractures in children

1222. Vuorela, Mikko (2013) Role of the *RNF8*, *UBC13*, *MMS2* and *RAD51C* DNA damage response genes and rare copy number variants in hereditary predisposition to breast cancer

1223. Äijälä, Meiju (2013) Studies about contribution of leptin receptor in cardiovascular risk

1224. Turunen, Pauliina (2013) Natural antibodies to malondialdehyde adducts in atherosclerosis

1225. Aikio, Mari (2013) Novel roles for basement membrane collagens : isoform-specific functions of collagen XVIII in adipogenesis, fat deposition and eye development, and effects of the collagen IV-derived matricryptin arresten on oral carcinoma growth and invasion

1226. Turk, Eva (2013) Patient reported outcomes in elderly patients with Diabetes Mellitus Type 2 in Slovenia

1227. Niinimäki, Tuukka (2013) High tibial osteotomy and unicompartmental knee arthroplasty : The treatment of isolated medial osteoarthritis of the knee – A registry-based study in Finland

1228. Niinimäki, Riitta (2013) Osteonecrosis in children, adolescents and young adults treated for cancer

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