Traumatic Brain Injury

Epidemiology, risk factors and decision making

Crispijn van den Brand

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COLOFON

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Traumatic Brain Injury

Epidemiology, risk factors and decision making

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Epidemiologie, risicofactoren en beslismodellen

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Trust in dreams for in them is hidden the gate to eternity (Kahlil Gibran)

In herinnering aan mijn ouders

Voor Joanne, Josephine en Mathilde

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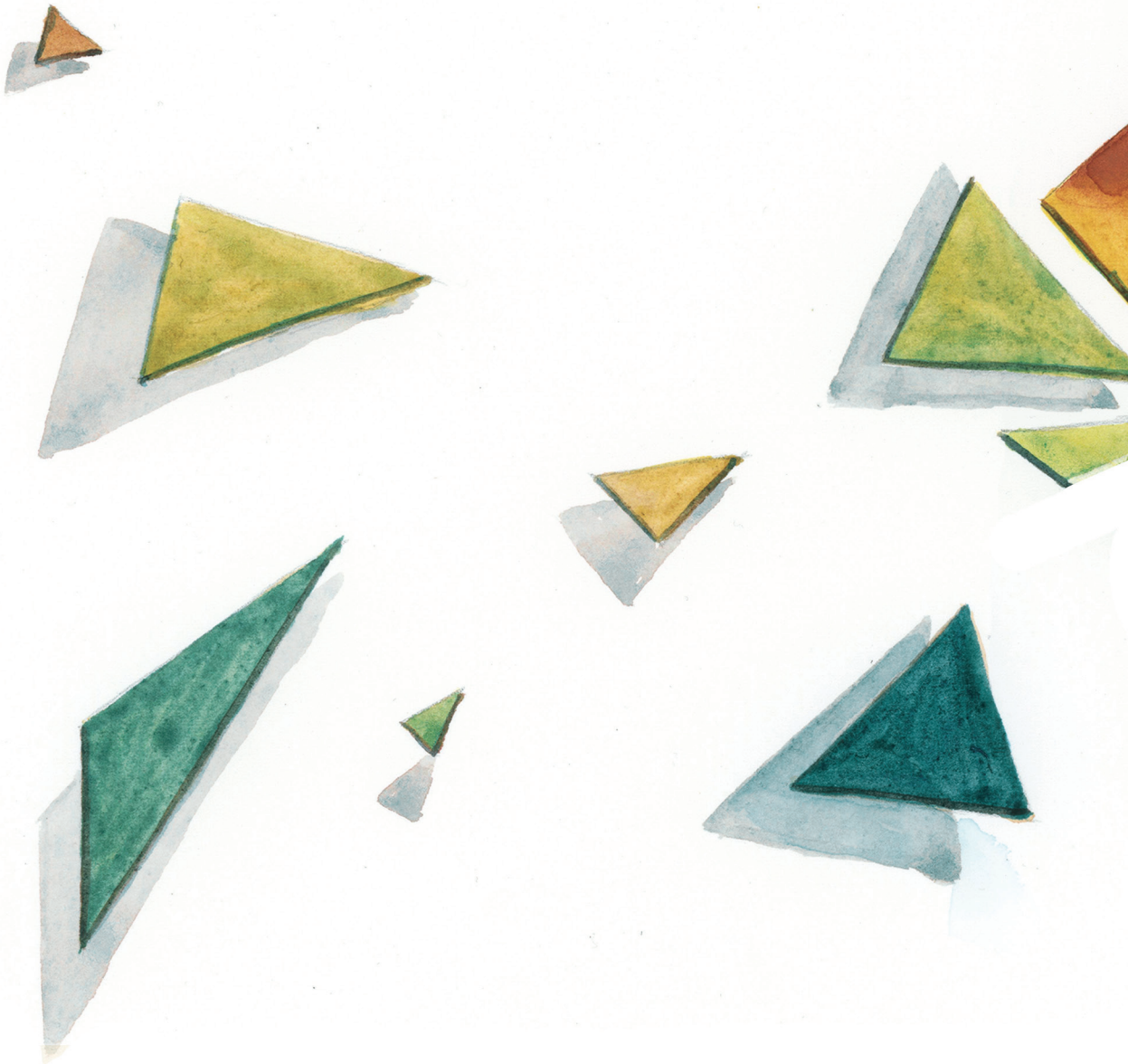

CHAPTER 1

General introduction

General introduction

Traumatic Brain Injury (TBI) is a major health and socio-economic problem worldwide. Although society is largely unaware of the magnitude of the problem, TBI is a growing epidemic.[1,2] Each year over 50 million people will have a TBI and it is estimated that approximately 50% of the world's population will have at least one TBI in their lifetime. TBI is a leading cause of mortality and disability in all age groups, for young adults it is even the leading injury-related cause of death. Not only the health impact of TBI is huge, also the economic impact is substantial. An estimate of total costs of TBI for the global economy is about US$ 400billion annually, which is approximately 0.5% of the entire global output.[3,4]

TBI severity classification

Fortunately, not all head trauma leads to TBI. Only patients with head trauma *and* evidence of brain pathology are classified as TBI.[5] The exact percentage of patients with head trauma that have TBI is unknown because many individuals with head injury do not seek medical care.

The Glasgow Coma Scale (GCS) is the most widely used score to classify the severity of TBI. The GCS was originally published in 1974 to objectively describe the extent of impaired consciousness.[6] Nowadays the GCS is, in combination with other factors, also used to assess TBI severity. However, the GCS has some limitations, mainly because other factors such as alcohol intoxication may alter consciousness regardless of TBI.

Based on GCS on arrival at hospital TBI is classified as follows:[7]

- Mild TBI: GCS 13-15; mortality ~ 0.2-0.4%
- Moderate TBI: GCS 9-12; mortality ~ 10%
- Severe TBI: GCS 3-8; mortality ~ 40%

The vast majority of TBI can be classified as mild TBI and this thesis will mainly focus on that group. However, this is actually a misnomer because a substantial part of patients with mild TBI still have complaints 6-12 months after the trauma, moreover some (0.2-0.4%) individuals even die as a result of 'mild' TBI.[8-11]

Epidemiology

The incidence of TBI is rising globally, both in low- and middle-income countries and in high income countries.[1,3] Although rough estimates of the incidence of TBI exist, the exact incidence is unknown.[1] Causes of uncertainty and poor comparability

of incidence estimates are various. First, many individuals with mild TBI probably do not seek medical help and may not be registered as such. Second, definitions of TBI and head trauma are subject of debate and different definitions are used in different registries, complicating international use and comparison. Third, the source of information may cause substantial variation in incidence estimates. Sources of information can be either routinely registered information, such as International Classification of Disease (ICD) codes, or specifically collected data such as national trauma registries, which may result in differences in estimates.

The incidence of TBI is not only rising, the epidemiology of TBI is also changing. A distinction has to be made between low- and middle-income countries and high-income countries. Globally, two leading causes of TBI can be identified: motor vehicle accidents and falls. In low- and middle- income countries motor vehicle accidents are the leading cause of TBI and the increasing use of motorized vehicles in combination with poor road safety leads to more TBI.[3,12] In contrast, in high income countries, with an ageing population and increased road safety, falls are the main cause of TBI nowadays.[13-15] For example in the USA falls are the leading cause of TBI-related emergency department (ED) visits (48% in 2014) and hospitalizations (52% in 2014). However, in the USA intentional self-harm (33% in 2014, mostly due to fire arms) followed by falls (28% in 2014) were the overall leading causes of death from TBI.[2,16]

Guidelines for diagnostics

The large majority of individuals with head injury have no intracranial complications and many do not even need professional care. Nonetheless, a small but important group does have traumatic (intra)cranial lesions and these lesions can lead to severe disability or even death. The most used technique to reliably rule out (intra)cranial lesions is head computed tomography (CT), which is available in all Dutch hospitals. However, there are important disadvantages of scanning all patients with head injury. First and most important, scanning all patients with head trauma would lead to many more ED visits and prolonged ED throughput times and crowding as result.[17] Second, CT scanning exposes the patient to (a limited) radiation risk.[18,19] Third, the price of CT varies substantially and can be up to US$2200 for a non-contrast head CT.[19,20] Therefore, CT should be used selectively for those patients that benefit most and several guidelines have been developed for this purpose. Globally, the guidelines that are most widely used are the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC).[21,22] These guidelines are suitable for patients with mild traumatic brain injury that have loss of consciousness, amnesia or confusion. However, many patients with head trauma do not have any of these and are still at risk for (intra) cranial lesions.[23,24] Therefore the CT in Head Injury Patients (CHIP) decision rule

was developed in the Netherlands.[25] The CHIP decision rule is applicable for almost all patients with head injury and a GCS between 13 and 15. However, until the study included in this thesis, the CHIP had not been externally validated.

The Dutch situation

In the Netherlands the general practitioner is traditionally the gatekeeper for secondary healthcare and is available 24/7. However, in emergency situations patients can come directly to the ED or (in more serious situations) call the national emergency number '112'. For head trauma, as for many other conditions, there is a grey area which patient should call 112, who should come to the ED, who should go to the general practitioner and who does not need any medical care. Some EDs have a joint triage with the out-of-hours general practitioners service. The triage determines which patients should be seen in the ED or by the general practitioner. This thesis will focus on ED care for patients with head injury.

In the ED patients with (minor) head trauma can, depending on local agreements, be treated by either emergency physicians or neurologists or residents of other specialties.

The Dutch guideline for minor head injury (MHI) was introduced in 2010 and partially revised in 2017.[26-28] According to the current Dutch guideline, minor head injury is defined as:

Head injury is any trauma to the head, other than superficial injuries to the face. For minor head injury the following criteria apply:

- *GCS at first examination 13-15*
- *In case of loss of consciousness: no more than 30 minutes*
- *In case of posttraumatic amnesia: no more than 24 hours*

The guideline formulated criteria for adults and children with minor head injury regarding: referral to a hospital; examination at the ED; performance of a CT; and admission to a hospital. Regarding indications for CT scanning in MHI, the guideline is with some adjustments based on the CHIP decision rule. The guideline has major and minor criteria for a head CT. In case of at least 1 major or 2 minor criteria a CT-scan of the head is indicated.

In the 2017 update antiplatelet therapy was added as a major risk factor and criteria for minimal head injury were formulated, for which a CT scan is, under circumstances, *not* indicated.[26]

Table 1. The Dutch guideline for CT scanning following MHI in adults

Major criteria	Minor Criteria
Pedestrian or cyclist versus vehicle	Fall from any elevation
Ejected from vehicle	Posttraumatic amnesia 2-4 hours
Vomiting	Visible injury to the head, excluding the face (without signs of fracture)
Posttraumatic amnesia (PTA) ≥ 4h	Loss of consciousness
Clinical signs of skull(base) fracture	GCS deterioration of 1 point (1 hour after presentation)
GCS < 15 on presentation (including persisting PTA)	Age ≥ 40
GCS deterioration ≥ 2 points (1 hour after presentation)	
Use of anticoagulants*	
Posttraumatic seizure	
Focal neurologic deficit	
Suspicion of intracranial injury after focal "high impact" injury	

*In 2017 antiplatelet therapy, other than acetylsalicylic acid monotherapy, was added as a major risk factor.

After introduction of the guideline in 2010 the authors expected a decrease in the number of CTs with approximately 30%.[27] However, several healthcare professionals feared that the guideline would lead to more rather than less diagnostics and referrals.[29-31] The evaluation of the guideline was the starting point of this thesis. We performed a simple 'before-after' study and concluded that the number of CTs increased in our hospital after the introduction of the guideline.[32] An extended version of that study has been included in this thesis in chapter 3. Another Dutch study that was subsequently published confirmed the conclusion of our before-after study: "The number of CTs performed for head trauma gradually increased over two decades, while the yield decreased. In 2011, despite implementation of a guideline aiming to improve selective use of CT in minor head injury, utilization significantly increased."[33]

Aim of the thesis

This thesis aims to study changing trends, risk factors, preventive measures and decision rules for diagnostics in patients with head trauma and TBI in emergency departments in the Netherlands.

Outline of the thesis

Part I Changing trends in traumatic brain injury

In **Chapter 2** epidemiological changes in TBI related ED visits, hospitalizations and mortality in the Netherlands are assessed. The results are put into context of the ageing population and increased traffic safety. In **Chapter 3** the association between implementation of the minor head injury guideline in 2010 and CT and hospital admission rate is described.

Part II Prevention of- and risk factors for traumatic brain injury

Chapter 4 reviews the association between the pre-injury use of antiplatelet therapy and traumatic intracranial hemorrhage. The association between the use of bicycle helmets and (prevention of) traumatic brain injury in the Netherlands is presented in **Chapter 5**.

Part III Decision rules for patients with minor head injury and mild traumatic brain injury

In **Chapter 6** several decision rules for minor head injury are validated and compared in a multicenter study in the Netherlands. The evaluated decision rules are the CHIP-rule, the NOC, the CCHR and the National Institute for Health and Care Excellence (NICE) clinical guideline for head injury. **Chapter 7** describes a possible adjustment of the CHIP-rule. This update aims to improve the identification of patients that require a head CT to identify traumatic lesions.

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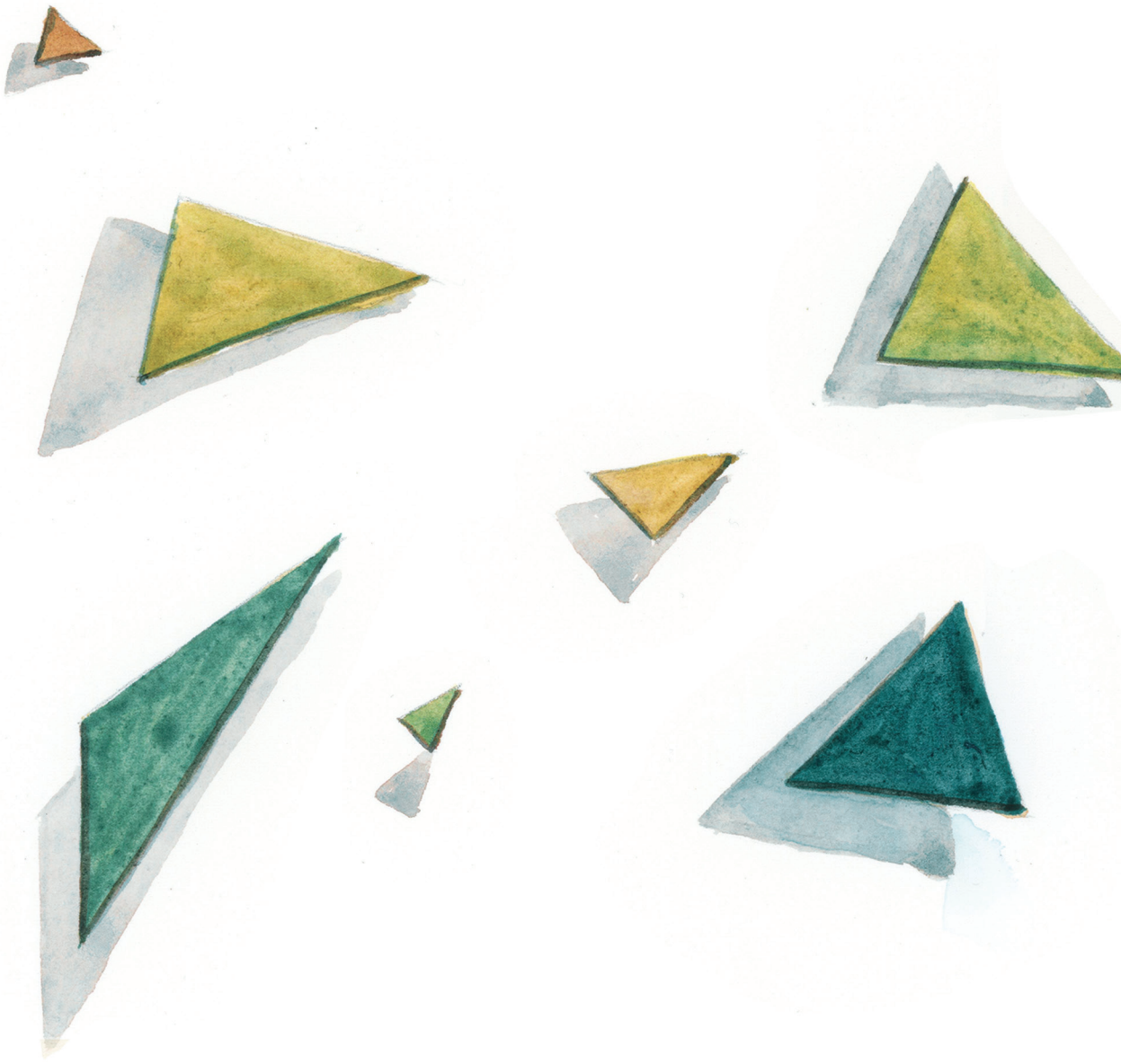
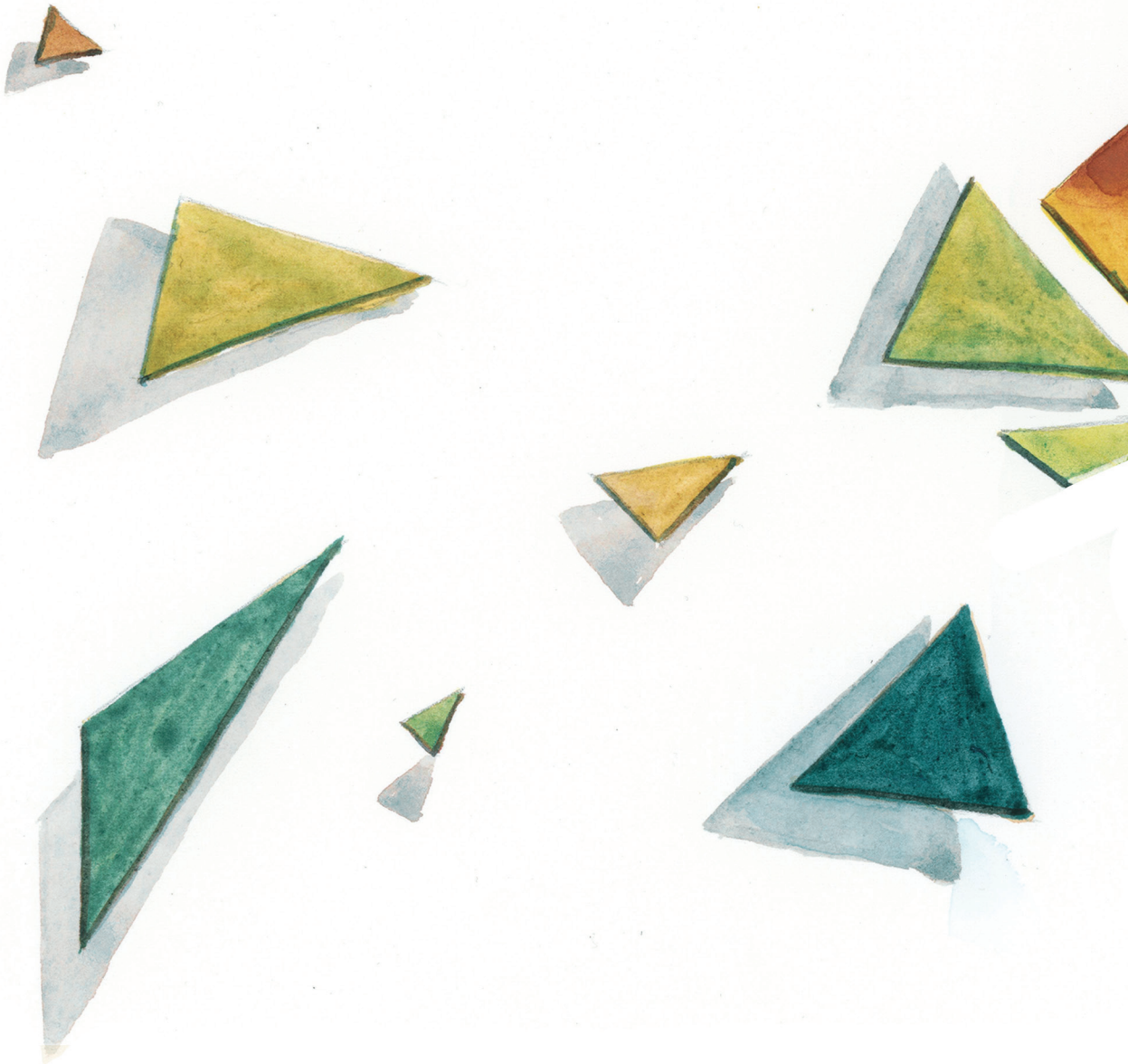


PART I

Changing trends in traumatic brain injury



CHAPTER 2

Traumatic brain injury in the Netherlands
Trends in emergency department visits, hospitalization and mortality between 1998 and 2012

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ABSTRACT

Background
Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide. The effects of epidemiological changes such as ageing of the population and increased traffic safety on the incidence of TBI are unknown.

Objective
The objective of this study was to evaluate trends in TBI related emergency department (ED)-visits, hospitalization and mortality in the Netherlands between 1998 and 2012. Design This was a retrospective observational, longitudinal study.

Main outcome measures
The main outcome measures were TBI-related ED-visits, hospitalization and mortality.

Results
Between 1998 and 2012 there were 500,000 TBI related ED visits in the Netherlands. In the same period there were 222,000 TBI related admissions and 17,000 TBI related deaths. During this period there was a 75% increase in ED visits for TBI, a 95% increase for TBI related hospitalization; overall mortality due to TBI did not change significantly. Despite the overall increase in TBI related ED visits this increase was not evenly distributed among age groups or trauma mechanisms. In patients younger than 65 years, a declining trend in ED visits for TBI caused by road traffic accidents was seen. Among patients 65 years or older, ED visits for TBI caused by a fall increased markedly. TBI related mortality shifted from mainly young (67%) and middle-aged people (< 65 years) to mainly elderly (63%) individuals (≥65 years) between 1998 and 2012. The conclusions of this study did not change when adjusting for changes in age, gender and overall population growth.

Conclusions
The incidence of TBI-related ED visits and hospitalization increased markedly between 1998 and 2012 in the Netherlands. TBI-related mortality occurred at an older age. These observations are probably the result of a change in aetiology of TBI, specifically a decrease in traffic accidents and an increase in falls in the ageing population. This hypothesis is supported by our data. However, ageing of the population is not the only cause of the changes observed; the observed changes remained significant when correcting for age and sex. The higher incidence of TBI with a relative stable mortality rate highlights the importance of clinical decision rules to identify patients with a high risk of poor outcome after TBI.

Introduction

Traumatic brain injury (TBI) is a major cause of mortality and morbidity worldwide affecting ~ 10 million individuals annually.[1,2,3] Although several definitions of TBI exist, the most frequently used definition is 'an alteration in brain function, or other evidence of brain pathology, caused by an external force'.[1,4,5]

In the USA TBI accounts for ~2.5 million emergency department (ED) visits, hospitalizations and deaths annually; of these, ~ 53,000 individuals die as a result of TBI.[1] The exact incidence for the Netherlands and many other European countries is unknown.[5]

TBI used to be most prevalent in young men. However, in most industrialized countries, TBI is predominantly a disease of the elderly nowadays. [1,5] This presumed shift in the epidemiology of TBI in the last decades is most likely the result of two important changes that affect the incidence and epidemiology of TBI: first ageing of the population; increasing age is associated with an absolute increase of TBI. [6,7,8] In the Netherlands the percentage of the population aged 65 years or older was 12.8% in 1990, increased to 17.8% in 2015 and it is estimated to be 26.5% in 2040. [9,10] For other parts of the western world, similar trends are to be expected. Another important development is the decrease in traffic accidents. During the last decades, traffic safety increased and the number of traffic deaths in the Netherlands decreased substantially from 1149 in 1998 to 650 in 2012. [9] Subsequently, falls have surpassed traffic accidents as most important cause of TBI-related deaths. [9] The effects of this presumed shift from mainly young traffic accident victims to elderly fall victims on ED visits and hospitalizations in the Netherlands is unknown.

This study evaluates trends in epidemiology of TBI patients in the Netherlands between 1998 and 2012.

We hypothesize that the ageing population in the Netherlands is associated with an increased incidence of TBI despite a decrease of traffic accidents.

Methods

Data sources

In this observational, longitudinal study all patients with ED visits, hospitalization or mortality because of TBI in the period 1998-2012 were included using the Dutch Injury Surveillance System (Letsel Informatie Systeem; LIS), the National Medical Register (Landelijke Medische Registratie; LMR), and Statistics Netherlands (Centraal Bureau voor de Statistiek; CBS), respectively.

The cause-of-death statistic by CBS is a registration based on all causes of death (ICD-10) from all deceased individuals registered in the Netherlands. The information is based on the compulsory notification of cause of death by the physician treating the deceased at the time of death or by a pathologist. For every deceased a cause-of-death certificate is completed, which is used exclusively for statistical purposes, and is sent to CBS. The reliability of registration of causes of death is generally reasonable to good. [9,11]

The National Medical Register (LMR) has been set up by the hospitals in the Netherlands for the benefit of research and policy. The LMR contains data of admitted patients on demographics (age, sex), hospital, date of admission and injury diagnosis (ICD-9CM).

All general and academic hospitals have statutory obligations to participate in the LMR. Hence, using the LMR data approximates the true number of admissions throughout the Netherlands.[12] The reliability and completeness of LMR data are high.[13,14]

ED visits were extracted from the LIS database; participation in LIS is not compulsory. The LIS database is a continuous monitoring system in which next to demographics, injury diagnoses and injury mechanisms are registered. LIS is based on 13 geographically distributed EDs in The Netherlands, resulting in a representative 12-15% sample of injury-related ED visits that can be extrapolated to national estimates. For extrapolation of the sample, a factor was calculated in which the number of trauma-related ED treatments in LIS hospitals was multiplied by the quotient of all trauma related hospital admissions in the Netherlands divided by trauma related hospital admissions in LIS hospitals. [15,16] In addition, a data set was created to standardize (with 2012 as standard) for differences in distribution of sex and age. This data set was used to perform supplementa analysis. Because of a certain measure of uncertainty, numbers are rounded to thousands in this manuscript.

Inclusion

All patients who attended a Dutch ED for any trauma, were discharged from a Dutch hospital for any trauma or died because of any non-natural cause between 1 January 1998 and 31 December 2012 were included. The study groups comprise all patients who visited the ED for TBI, were admitted for TBI or died from TBI. TBI was defined using the ICD-9CM codes for LMR; the ICD-10 codes for CBS and the LIS codes for ED visits. All patients with intracranial injury and/or a fracture of the skull *(ICD9-CM codes 800-804 and 850–854; ICD10 codes S01.0; S02.0;S02.1; S02.3; S02.7-9; S04.0; S06; S07; S09.7-9; T90.1-2; T90.4-5; T90.8-9)* were included in this group, irrespective of age and sex. The study groups were compared with all ED patients with non-TBI trauma, all admitted patients with non-TBI-trauma or all deaths from non-natural causes other than TBI.

Data and statistical analysis

SPSS for windows (IBM SPSS Statistics, SPSS Inc, Chicago, Illinois, USA) was used for statistical analyses. The data set was subdivided into TBI patients and non-TBI patients, and was deliberately not standardized for age as the effects of ageing of the population on TBI epidemiology are one of the research questions of this study. Cumulative incidence is shown as number of new cases throughout the population of the Netherlands per year. Incidence proportions (per 100,000 per year) were calculated using Statistics Netherlands data [9]. A Poisson regression was used to determine the difference in the increase in incidence over time using a generalized linear model. As the Poisson distribution was used to describe this population, the same method was used to analyze the change in incidence proportions over time. To determine a significant change of cumulative incidence proportions between 1998 and 2012, MedCalc statistical software (version 16.4.3; MedCalc Software, Ostend, Belgium) was used to compare proportion using a c^2-test. Statistical significance was determined by a *P*-value of less than 0.001. The study was approved by the medical ethical review board (METC Zuidwest Holland, number 15-072).

Results

Incidence measures in total population

Between 1998 and 2012 there were ~13,651,000 trauma-related ED visits, of which 500,000 (3.7%) were because of TBI. The total number of hospital admissions for trauma during the study period was 1,958,000, of which 222,000 (11%) were for TBI. The total mortality due to non-natural causes was 86,000, of which 17,000 (20%) were caused by TBI (Table 1).

Between 1998 and 2012, according to the Poisson regression model without correction for age and sex, there was a significant increase in ED visits for TBI, from 153/100,000 in 1998 to 267/100,000 in 2012 (75% increase, $P < 0.001$); in hospital admissions for TBI from 64/100,000 per year to 125/100,000 per year (95% increase, $P < 0.001$); and a nonsignificant change in mortality because of TBI from 6.8/100,000 per year to 7.2/100,000 per year (6% increase, $P = 0.17$).

In comparison with other trauma, the ED visits increased significantly more for TBI ($P < 0.001$). According to the Poisson regression model, ED visits for TBI increased with 4.6% each year versus a decrease of 2.1% for ED visits for other injury types. There was a significant increase ($P < 0.001$) in admissions for TBI (5.5% increase per year) compared with admissions for other injury (3.3% increase per year). The TBI related mortality did not change compared with overall mortality by non-natural causes (TBI related mortality increased 0.8% per year, mortality by other non-natural causes increased 0.9% per year, $P = 0.78$)

Comparing TBI-related admissions with TBI-related ED visits and mortality, the increase in TBI-related hospital admissions (5.5% per year) increased significantly ($P < 0.001$) more than the TBI related ED visits (4.6% per year). Moreover, TBI-related mortality increased significantly less than TBI-related admissions (0.8% vs. 5.5% per year) ($P < 0.001$). The changes in the crude incidence of TBI in the Netherlands between 1998 and. 2012 are shown in Figures 1 and 2.

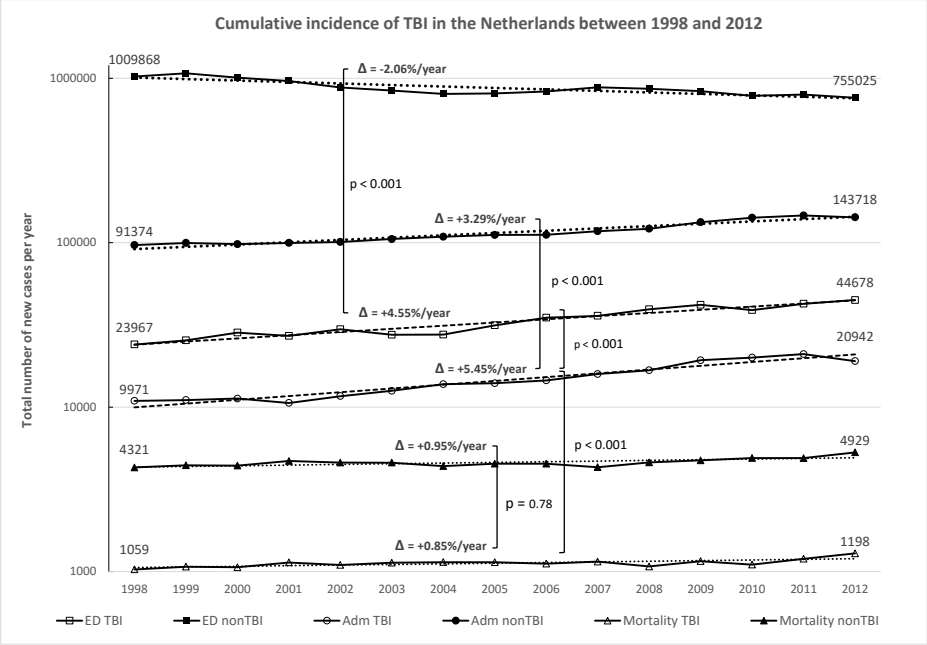

Figure 1

The cumulative incidence of TBI and other injury: ED-visits, admissions and mortality in the Netherlands. A Poisson regression model estimates the best linear fit on logarithmic scale (dotted lines).

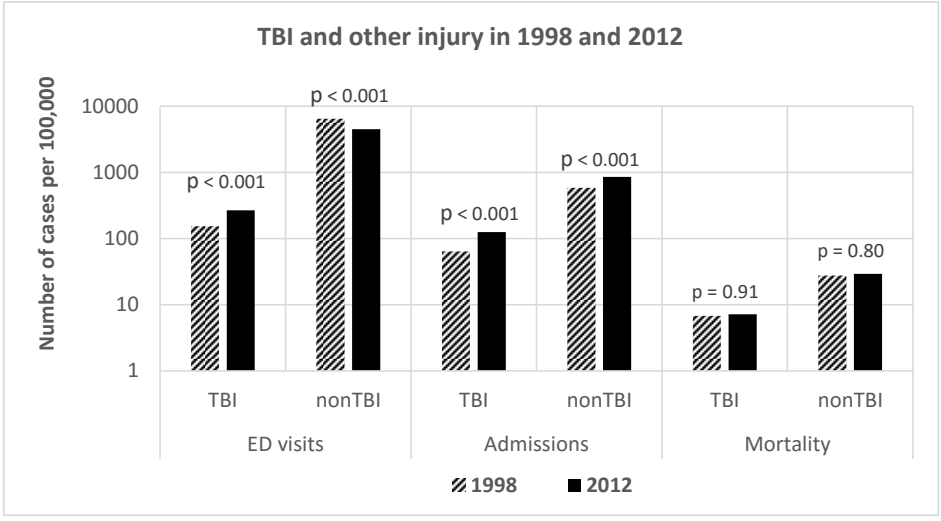

Figure 2

Incidence proportions on a logarithmic scale of TBI and other injury ED-visits, admissions and mortality in the Netherlands, 1998 and 2012 compared.

Table 1. Key figures on traumatic brain injury and other injury between 1998 and 2012 in the Netherlands: emergency department visits, admissions and mortality.

	1998	1999	2000	2001	2002	2003
ED TBI (total)	24,053	25,499	28,415	27,124	29,764	27,555
ED other injury (total)	1,025,522	1,072,796	1,009,383	961,552	878,253	841,291
Admissions TBI (total)	10,928	11,049	11,284	10,608	11,667	12,575
Admissions other injury (total)	96,773	99,688	98,016	99,708	101,038	105,291
Death TBI (total)	1,032	1,071	1,063	1,137	1,097	1,133
Death other non natural causes (total)	4,300	4,434	4,407	4,707	4,600	4,599
ED TBI (65+)	2,270	2,844	3,190	3,196	3,971	4,014
ED other injury (65+)	96,793	103,817	97,048	96,312	93,059	94,644
Admissions TBI (65+)	1,899	1,907	1,932	1,980	2,295	2,606
Admissions other injury (65+)	30,658	31,317	30,739	31,404	31,900	33,942
Death TBI (65+)	349	381	358	399	416	438
Death other non natural causes (65+)	1,837	1,977	1,969	2,237	2,062	2,137
population (total)	15,654,192	15,760,225	15,863,950	15,987,075	16,105,285	16,192,572
population (65+)	2,109,719	2,130,934	2,152,442	2,174,501	2,198,714	2,220,456
% population 65+	13.5%	13.5%	13.6%	13.6%	13.7%	13.7%
% ED TBI 65+/ED TBI total	9.4%	11.2%	11.2%	11.8%	13.3%	14.6%
% Admissions TBI 65+/Admissions TBI total	17.4%	17.3%	17.1%	18.7%	19.7%	20.7%
% Death TBI 65+/Death TBI total	33.8%	35.6%	33.7%	35.1%	37.9%	38.7%

Effects of age

During the study period, the total number of ED visits for TBI by patients aged 65 and older increased from 2270 in 1998 to 10274 in 2012. Besides this absolute increase, there was also a relative increase in ED visits for TBI among those aged 65 and older from 115/100,000 to 388/100,000 per year *(P* < 0.001). For the population younger than 65 years of age, we also observed an increase in TBI-related ED visits; this increase was significantly less (3.1 vs. 9.1% per year*; P* < 0.001) than that in the elderly (from 160/100,000 to 247/100,000 per year; *P* < 0.001). Therefore, the percentage of elderly among patients visiting the ED for TBI increased between 1998 and 2012 (from 9 to 23%).

For TBI-related admissions, the percentage of elderly (≥65) increased from 17 to 28%. Incidence proportions for admissions in the elderly increased from 81/100,000 to 242/100,000 per year *(P* < 0.001). For the population younger than 65 years of age, we also observed an increase in TBI related admissions; this increase was significantly less (3.9 vs. 8.2% per year*; P* < 0.001) than that in the elderly (from 61/100,000 to 104/100,000 per year*; P* < 0.001).

Between 1998 and 2012, the proportion of individuals aged 65 years and older among TBI-related deaths increased from 34% in 1998 to 63% in 2012. In absolute numbers this increase was from 349 in 1998 to 809 in 2012; meanwhile, there was a decrease in TBI-related mortality in the young and middle aged (< 65 years)

2004	2005	2006	2007	2008	2009	2010	2011	2012	Total
27,604	31,439	35,047	35,917	39,391	41,912	38,907	42,516	44,818	499,961
803,445	809,001	831,327	881,374	862,701	834,107	782,246	796,245	761,553	13,150,796
13,799	13,978	14,542	15,897	16,771	19,289	20,022	21,022	19,055	222,486
108,769	111,519	111,667	117,512	121,627	133,218	141,844	146,406	142,693	1,735,769
1,142	1,141	1,117	1,150	1,075	1,157	1,102	1,197	1,292	16,906
4,381	4,531	4,533	4,312	4,612	4,747	4,910	4,900	5,312	69,285
3,834	4,253	5,357	5,659	7,049	7,958	8,351	9,264	10,274	81,484
91,886	94,285	99,633	105,508	105,383	106,745	108,388	115,338	117,514	1,526,353
2,933	3,096	3,416	3,880	4,192	5,374	5,942	6,109	5,395	52,956
34,917	36,150	36,284	38,276	40,360	44,528	49,339	51,202	51,387	572,403
498	520	526	564	535	591	632	708	809	7,724
1,988	2,191	2,351	2,280	2,473	2,535	2,646	2,693	3,000	34,376
16,258,032	16,305,526	16,334,210	16,357,992	16,405,399	16,485,787	16,574,989	16,655,799	16,730,348	
2,251,154	2,288,670	2,330,459	2,368,352	2,414,826	2,471,815	2,538,328	2,594,946	2,716,368	
13.8%	14.0%	14.3%	14.5%	14.7%	15.0%	15.3%	15.6%	16.2%	
13.9%	13.5%	15.3%	15.8%	17.9%	19.0%	21.5%	21.8%	22.9%	
21.3%	22.1%	23.5%	24.4%	25.0%	27.9%	29.7%	29.1%	28.3%	
43.6%	45.6%	47.1%	49.0%	49.8%	51.1%	57.4%	59.1%	62.6%	

from 683 in 1998 to 483 in 2012. When looking at the incidence proportion for TBI mortality, it did not change significantly either for the elderly (from 16/100,000 to 28/100,000 per year; $P = 0.08$) or for the population younger than 65 years of age (from 5/100,000 to 3/100,000 per year; $P = 0.50$). However, the change (3.9% increase per year) in mortality in the population over 65 was significantly more than the change (3.2% decrease per year) in mortality in the population younger than 65 years ($P < 0.001$) (Table 1, Figure 3 and Supplementary Figure 1).

Trauma mechanism

When analyzing different trauma mechanisms in various age groups, it is observed that the increase in TBI-related ED visits is not evenly distributed; road traffic accidents (RTAs) seem to decrease and falls increase as the cause of TBI. Among young and middle aged (< 65 years), Poisson predicted TBI ED visits caused by RTAs decreased from 2682 in 1998 to 2112 in 2012. Translating this into incidence proportion means a decrease from 20 to 15 per 100,000 annually in, respectively, 1998 and 2012. This decrease did not reach statistical significance ($P = 0.39$). The incidence proportion of non-TBI ED visits because of RTAs in the same age group and study period remained more or less stable (from 60 per 100,000 in 1998 to 64 per 100,000 in 2012) ($P = 0.72$). In contrast, Poisson predicted TBI-related ED visits among elderly patients (≥ 65 years) with a fall as the trauma mechanism increased from 853 in 1998 to 4704 in 2012. These figures, translated to incidence proportion, mean an increase from 40 to 173 per 100,000 per year ($P < 0.001$).

The incidence proportion of non-TBI ED visits due to falls in the same age group and study period increased as well but this change was not as impressive; from 1034 to 1436 per 100,000 per year *(P* < 0.001) (Figure 4).

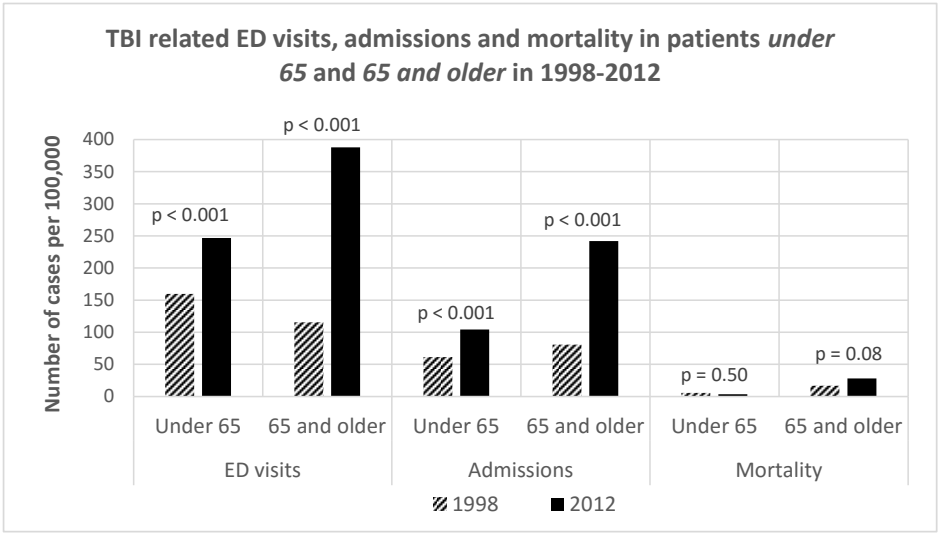

Figure 3

Incidence proportions on a linear scale of TBI ED-visits, admissions and mortality in the Netherlands, population younger than 65 years and 65 years or older compared.

Adjustment for age and gender

When the study population was standardized for age and sex, the TBI-related ED visits and admissions per 100,000 still increased significantly *(P* < 0.001) between 1998 and 2012. The increase was 3.9% for ED visits and 4.6% for admissions annually. With this standardization TBI-related mortality still did not change significantly during the study period *(P* = 0.88) (Supplementary Figure 2).

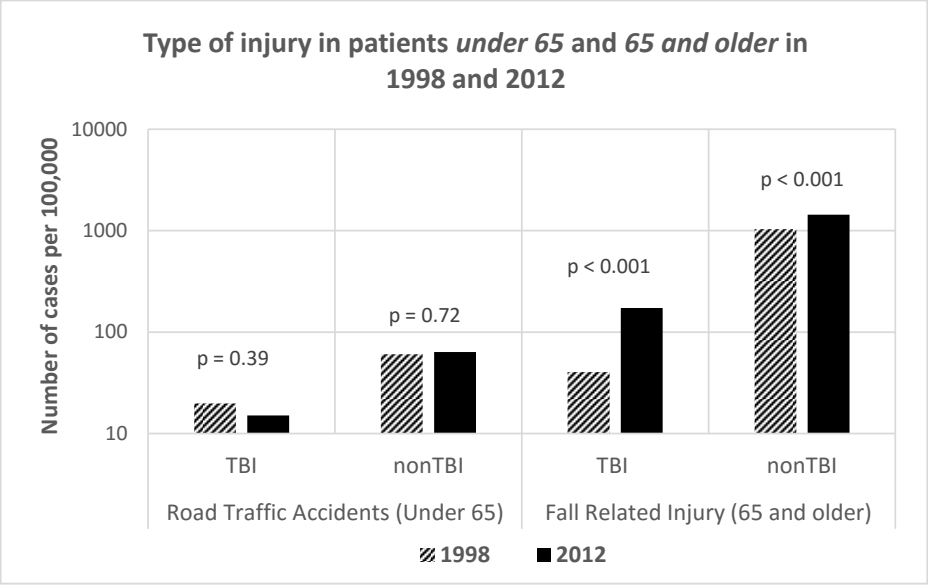

Figure 4

Incidence proportions on a logarithmic scale of ED-visits for TBI and for other injury in the Netherlands. Left: road traffic accidents in population younger than 65 years in 1998 and 2012 compared. Right: falls in population 65 years or older in 1998 and 2012 compared.

Discussion

From 1998 to 2012, there was a significant increase in TBI-related ED visits and hospitalization, whereas TBI-related mortality remained relatively stable. The increase in ED visits and hospital admissions was significantly higher for TBI patients compared with other trauma patients; no such difference was observed for TBI-related deaths compared with other non-natural causes of death. Although the overall TBI-related mortality remained stable there was a change in the demographics of TBI-related mortality. TBI-related deaths in the elderly (≥ 65 years) more than doubled during the study period; TBI related death in the young and middle aged (< 65 years) decreased in contrast.

The observed absolute increase in TBI related ED visits and hospitalizations without a significant increase in mortality rate may be the result of a variety of factors.

First, there is probably an absolute increase of TBI in the population because of ageing of the population and hence more falls and increased use of antiplatelet therapy and anticoagulants. This is also reflected by the observed shift in mortality from mainly young and middle aged to mainly elderly individuals.

Second, a possible explanation for the relative increase in TBI-related ED visits and hospital admissions compared with TBI-related mortality is the increased incidence of less severe TBI. This may be caused by a decrease in traffic accidents and an increase in ground level falls during the study period. This is supported by our finding of a decrease in TBI caused by RTA in the young and middle-aged individuals and a major increase in TBI caused by falls in the elderly. In the late 1990s, traffic accidents caused over 600 TBI-related deaths annually in the Netherlands; by the end of our study period, this number had decreased to about 300.[2] In the same period the number of TBI-related deaths because of falls increased from about 300 to over 650 per year.[2] TBI caused by motorized vehicle accidents result in death approximately four times more often than TBI caused by low-energy falls (6.4 vs. 1.7%).[1] Hence, it makes sense that the number of ED visits and hospitalizations increased much more than the mortality rate during the study period, despite the fact that older patients have a higher TBI mortality than young patients for a given Glasgow Coma Scale score.[17] This is also in line with the result of a recent study from the UK.[18] They studied major trauma patients between 1990 and 2013 and reported a shift in the predominant trauma mechanism from RTAs to falls from less than 2 meter. They also reported a change in the mean age of major trauma patients from 36.1 in 1990 to 53.8 in 2013.

There are several other possible explanations for the increase in TBI-related ED visits and (subsequent) increased admissions that is observed even when correcting for ageing of the population. First, there is probably increased awareness for TBI among the general public, paramedics and general practitioners. Second, the indications for anticoagulant and antiplatelet therapy have expanded in recent years, while these drugs are potential risk factors for traumatic intracranial hemorrhage. This is likely to affect TBI ED visits and admissions even when standardizing for ageing of the population. [6-8, 19-22] Third, fall rates among the elderly may increase and exceed what would be expected merely by ageing of the population. A recent study does support this hypothesis. [23] However, this seems to be in contradiction with the decrease in non-TBI-related ED visits that we observed. Better treatment for osteoporosis could, to some extent, explain this apparent contradiction.[24] Fourth, the change in minor head injury guidelines in the Netherlands in 2010 should be mentioned. Since introduction of the new guidelines an increase in both CT- and hospitalization rate was observed; this could lead to better identification and hence earlier treatment of traumatic intracranial findings.[25,26] Besides better identification and treatment, the threshold for hospitalization might have been lowered during the study period. Our finding that TBI-related admissions increased significantly compared with both TBI-related ED visits and mortality could support this hypothesis. Finally it is possible that the treatment of TBI patients has improved between 1998 and 2012, this could contribute towards a stable TBI-related mortality despite an increasing incidence and is in line with a global trend of decreasing injury-related mortality relative to injury incidence.[27] However, it is not possible to support or refute that conclusion on the basis of our study.

Besides strengths such as size and long duration, this study also has several limitations and the results should be interpreted in the light of these limitations. In contrast to the data on TBI admissions and TBI-related mortality that are (almost) complete, the data regarding TBI-related ED visits are an extrapolation from a limited number (12-15%) of EDs and are indicative only.

The observational nature of this study makes it impossible to draw firm conclusions on the causes of observed changes in TBI-related ED visits, admissions or mortality.

We used existing databases and had to rely on the registered data. Unfortunately, the different databases used did not use the same version of the ICD classification during the study period; the TBI hospitalization and mortality rates were based on ICD9-CM and ICD-10 codes, respectively. This is a limitation when comparing

the different strata of our study. Miscoding cannot be excluded; nonetheless, we do not expect considerable changes in miscoding throughout the years and the changes observed were substantial and consistent and are therefore unlikely to result from miscoding. The TBI hospitalization and mortality rates were based on ICD9-CM and ICD-10 codes; this may result in both false-positive as false-negative cases [5]. An international comparison of absolute numbers mentioned in this article should be done with caution because of the lack of international standardization.

Conclusions

Between 1998 and 2012, the incidence of TBI-related ED visits and hospitalization increased markedly, both in absolute numbers, as compared with other trauma. Despite a 41% reduction in traffic-related deaths in the same period, no reduction in TBI-related deaths was observed. The demographics of TBI-related deaths changed from mainly young and middle-aged individuals (< 65 years) to mainly elderly individuals (≥65 years). These observations are probably caused by a shift in the causative trauma mechanism from mainly traffic accidents (high-energetic trauma) to mainly fall accidents (low-energetic trauma). This hypothesis is supported by our data. However, ageing of the population is not the only cause of the changes observed; the changes observed remained significant when correcting for age and sex. Both policy makers and medical personnel should be aware of these changes in epidemiology. The higher incidence of TBI with a relative stable mortality rate highlights the importance of clinical decision rules to identify patients with a high risk of poor outcome after TBI.

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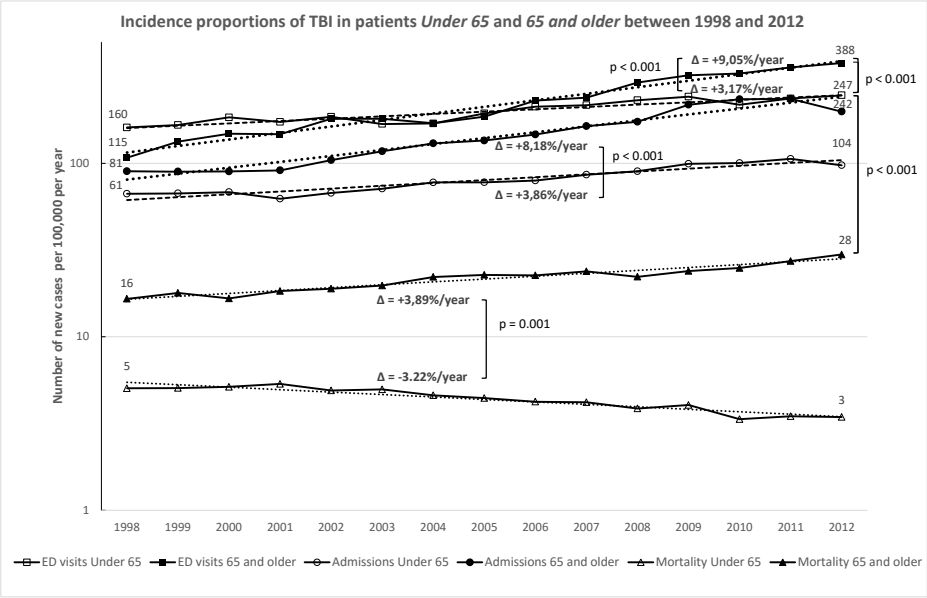
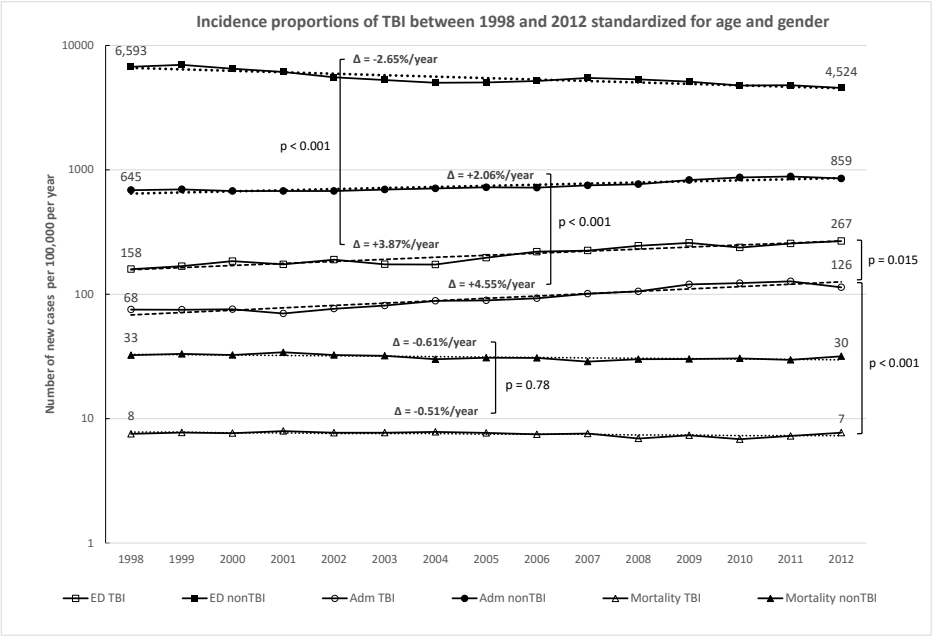
Supplementary Material



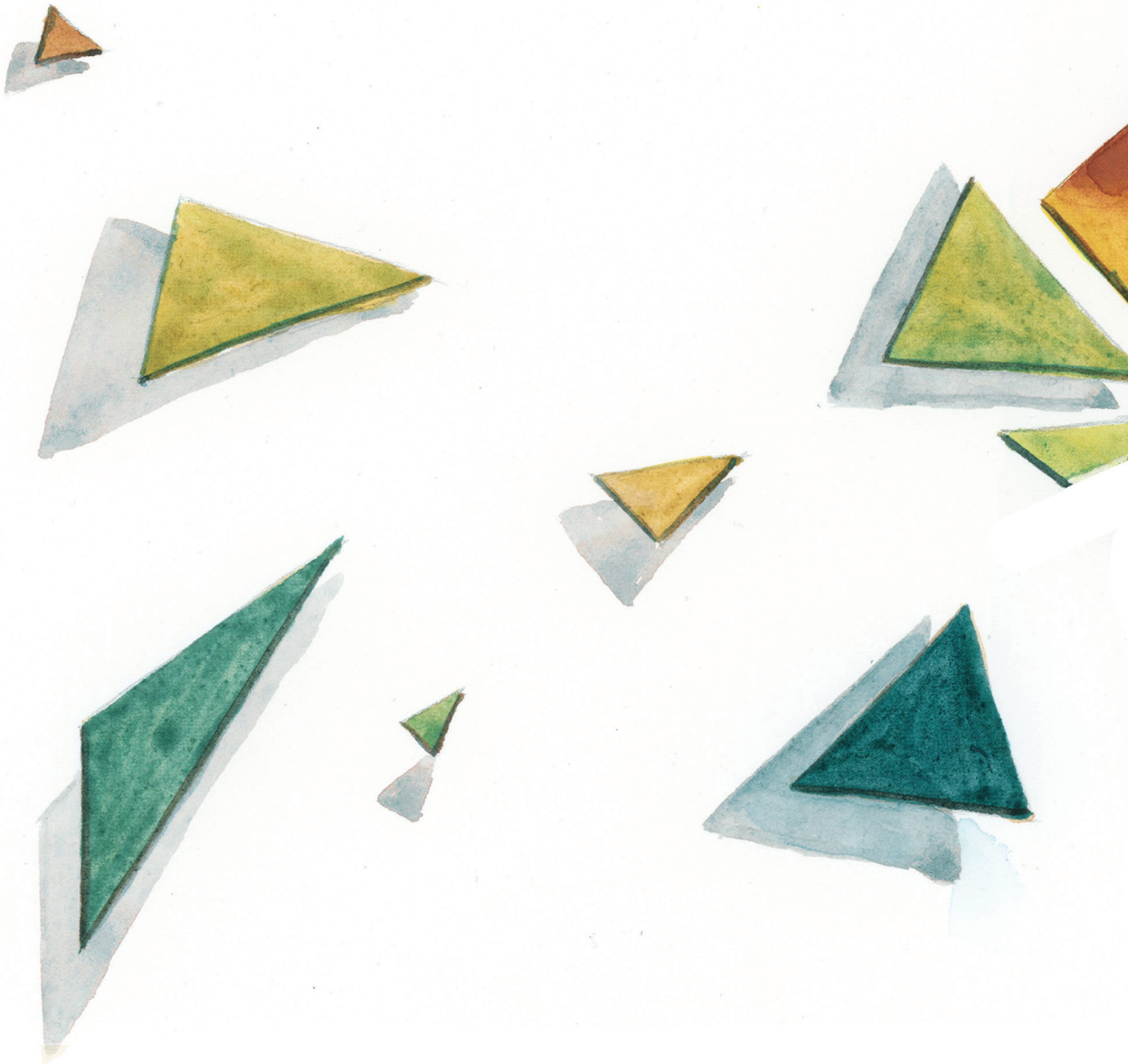
Supplementary Figure 1

Incidence proportions of TBI: ED-visits, admissions and mortality in the Netherlands, population < 65 years and ≥ 65 years compared. A Poisson regression model estimates the best linear fit on logarithmic scale (dotted lines).



Supplementary Figure 2

Incidence proportions standardized for age and gender of TBI and other injury: ED-visits, admissions and mortality in the Netherlands. A Poisson regression model estimates the best linear fit on logarithmic scale (dotted lines).



CHAPTER 3

Effect of the implementation of a new guideline for minor head injury on computed tomography-ratio and hospitalizations in the Netherlands

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ABSTRACT

Objective

A new nationwide guideline for minor head injury was introduced in the Netherlands in 2010. The effect on CT ratio and hospital admission ratio after introduction of the guideline is unknown. The aim was to reduce these numbers as part of cost-effective health care. Therefore, we assessed the effect on these variables after introduction of the guideline.

Methods

We used an interrupted time series study design. Data selection was done three years before (2007-2009) and several years after (2012, 2014, 2015) introduction of the guideline.

Results

Data collection was performed for 3880 patients. Introduction of the new guideline was associated with an increase in CT ratio from 24.6% before to 55% after introduction ($P < 0.001$). This increase is the result of both the new guideline and a secular trend. Besides this, hospital admissions increased from 14.7% to 23.4% ($P < 0.001$) during the study period. This increase was less clearly associated with the new guideline. After introduction of the guideline there was no significant difference in (intra)cranial traumatic findings (2.6% vs. 3.4%; $P = 0.13$) and neurosurgical interventions (0.1% vs. 0.2%; $P = 0.50$).

Conclusions

Between 2007 and 2015, a marked increase in CT ratio and hospital admissions has been observed. The increase in CT ratio seems to be caused both by the new guideline and by a secular trend to perform more CT scans. Adaptations to the guideline should be considered to improve patient care and cost-effectiveness in patients with minor head injury.

Introduction

Minor head injury (MHI) is an everyday problem in emergency departments (EDs). Exact numbers for the Netherlands are lacking, but a distinct increase in ED visits for traumatic brain injury (TBI) has been observed over the past decades.[1] Traumatic intracranial findings occur in 7-10 % of MHI patients and less than 1% will require neurosurgical intervention.[2-4] Computed Tomography (CT) of the head is the most used imaging modality, because it is a fast and reliable method for detecting traumatic findings.[5]

Obtaining a CT-scan for every head trauma is undesirable, because of various reasons such as cost-effectiveness, overdiagnosis, ED crowding and radiation exposure.[6,7] There are various guidelines to determine for which patients a CT-scan is indicated. Many guidelines are derived from the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC).[8,9] These decision rules are externally validated and have a high sensitivity for both clinically important brain injury and neurosurgical intervention.[10-13] Nevertheless, the applicability of these decision rules is limited to patients who experienced loss of consciousness (LOC), post-traumatic amnesia (PTA) or confusion.[8,9] However, intracranial complications occur both in patients with and without LOC and PTA.[14] Therefore, a major disadvantage of these guidelines is the lack of recommendations in case of the absence of LOC and/or PTA.

A decision rule that is applicable to all MHI patients, was established later on by a Dutch research group: the CHIP prediction rule.[3] A recent validation study showed a performance comparable to the CCHR and NOC.[2] The CHIP prediction rule, with some adjustments, led to the development of the current Dutch guideline for MHI in 2010.[15] Although the sensitivity of the guideline is expected to be very high, implications for clinical practice, like the total number of CT-scans performed, are uncertain. The purpose of this study is to determine the impact of the introduction of a new guideline for MHI. We compared CT ratio before and after introduction of the new guideline, and simultaneously the effect on hospital admission rates.

Methods

Study setting and patients

We used an interrupted time series (ITS) study design. All data were collected from a Dutch non-academic hospital with two separate ED locations. One location concerns a level-1 trauma centre with an annual number of visitors to the ED of 46,500 (2007) – 52,000 (2015); level-1 meaning that all possible traumas can be treated there. The other location is a level-3 trauma centre with an annual number of ED-visitors of 20,000 (2007) – 17,500 (2015). The declining number of visitors to this last ED is due to reallocation of patients to other EDs.

The study periods involved the first three months of six different years: 2007; 2008; 2009; 2012; 2014 and 2015. The 'after period' was intentionally chosen some years after 2010, to guarantee that all hospitals were familiar with the new Dutch guidelines. There is no specific reason for the lack of data concerning the year 2013, other than the data collection being performed in two different time frames.

All patient records concerning MHI were selected manually from the electronic patient records. Data extraction from these records was performed by physicians under supervision of the corresponding author (CvdB). In case no abnormalities or symptoms were specified, these were assumed to be absent. In case of discrepancies or doubt about the information in the patient record the record was reviewed by CvdB.

Patients were included when they met the criteria for MHI as described later in this section. Other inclusion criteria were presentation to the ED within 24 hours of injury, and age of at least 16 years. Exclusion criteria were 'reassessed patients' and 'transferred patients'.

All CT-scans were performed according to standard trauma protocol. Assessment of the CT-scans was carried out by a (neuro)radiologist, and by the treating neurologist. In case of disagreement, a second (neuro)radiologist and neurologist reached consensus.

Data collection

We collected the following data from the electronic patient record: demographic data, Glasgow Coma Scale (GCS) on entry, whether a CT-scan of the head was made, CT findings, hospital admissions and neurosurgical interventions. A neurosurgical intervention is defined as any neurocranial operation for the sustained head trauma carried out by a neurosurgeon within 30 days after the trauma, including the

placement of an intracranial pressure monitoring device. We concurrently verified the presence of major and minor CT-criteria for each patient, according to the 2010 guideline, so that guideline adherence could be measured [15].

The 2010 Dutch MHI guideline

The Dutch guideline for MHI was introduced nationwide in 2010 and was based on the CHIP decision rule [3,15]. It is applicable to all patients with MHI. MHI was defined as: *Head injury is any trauma to the head, other than superficial injuries to the face.*

For minor head injury the following criteria apply:

- *GCS at first examination 13-15*
- *In case of loss of consciousness: no more than 30 minutes*
- *In case of posttraumatic amnesia: no more than 24 hours*

The guideline has major and minor criteria for a head CT. In case of 1 major or 2 minor criteria a CT-scan of the head is indicated.

Major criteria: GCS < 15 on presentation; signs of skull fracture; vomiting; posttraumatic amnesia ≥ 4h; GCS deterioration ≥ 2 points (1 hour after presentation); pedestrian or cyclist versus vehicle; ejected from vehicle; coumarin use, focal neurologic deficit[1]; posttraumatic seizure; suspicion of intracranial injury after focal "high impact" injury[2].

Minor criteria: fall from any elevation; posttraumatic amnesia 2-4 hours; visible injury to the head, (excluding the face); loss of consciousness; GCS deterioration of 1 point (1 hour post presentation); age ≥ 40[3].

Indications for admission according to the guideline are: new clinically significant findings on CT-scan; GCS < 15; focal neurologic deficit; indication for CT-scan, but CT-scan not (yet) performed; alarming signs for the clinician such as intoxication with alcohol and/or drugs; other injuries that require admission[4].

Outcome measures

The primary outcome measure is the change in level and trend in the percentage of head CT-scans for MHI performed: the crude CT ratio and the standardized CT ratio.

1 Focal neurologic deficit was a minor criterium in the original CHIP rule.
2 Suspicion of intracranial injury after focal "high impact" injury was no criterium in the original CHIP rule.
3 Age 40-60 was a minor criterium and age ≥60 was a major criterium in the original CHIP rule.
4 The CHIP rule does not formulate indications for admission.

The crude CT ratio is the percentage of patients with head CT. The standardized CT ratio is the quotient of the number of cases with a head CT and the number of cases with an indication for head CT according to the 2010 guideline.[15]

Secondary outcome measures are the changes in level and trend in the percentage of patients admitted to the hospital and in the number of neurosurgical interventions within 30 days after the trauma. Another secondary outcome measure is guideline adherence. The study was approved by the regional medical research ethics committee and informed consent was waived (IRB Southwest Holland, nr. 13-054).

Statistical analysis

Data were analyzed using descriptive statistics, c^2 tests and Mann-Whitney U tests where appropriate. The impact of the new guideline on CT ratio and admission percentage was analyzed with an interrupted time series approach, hereby controlling for the observed level and trend in the data before the intervention.[16] The following regression model was used:

$U_t = b_0 + b_1T + b_2C_t + b_3TC_t$ where b_0 represents the baseline level before implementation of the new guideline, b_1 represents the change in outcome associated with a time unit increase (representing the underlying trend, slope), b_2 is interpreted as the level change following the intervention and b_3 represents the slope change following the intervention. The time unit used in the model is months.

Significance threshold was set at $P < 0.05$. The statistical package for the social sciences (IBM Corp., IBM SPSS Statistics for Windows, version 22.0. Armonk, New York USA) was used for analyses.

Results

During the study periods a total of 3880 eligible patients were seen at one of the two EDs and were included in our study. Of those patients, 1823 (47.0%) visited the hospital before- and 2057 (53.0%) did so after introduction of the guideline. Patient characteristics are shown in Table 1. Notably, the median age and specifically the proportion of patients over 40 years of age was higher in the group of patients seen after the introduction of de guideline.

Table 1. Basic demographic characteristics and hospital location

	2007-2009 (before group) (n=1823)	2012-2014-2015 (after group) (n=2057)	*P*-value[1]
Demographics			
• Median age y (IQR)	40 (25-60)	46 (28-67)	< 0.001
• Age ≥40y n (%)	917 (50.3)	1211 (58.9)	< 0.001
• Male gender n (%)	1116 (61.2)	1215 (59.1)	0.172
Hospital location			
• Trauma centre	1293 (70.9)	1611 (78.3)	< 0.001

[1]Difference between before-group (2007-2009) and after-group (2012, 2014, 2015).

Traumatic (intra)cranial CT findings were present in 2.6% of patients in the 'before' group and 3.4% of patients in the 'after' group. However, this difference was not significant, as shown in Table 2. Four patients with at the first visit missed (intra) cranial traumatic findings (or possible intracranial findings) were identified, two before introduction of the guideline and two after introduction of the guideline (Supplementary Table 1). Facial fractures were found on CT in merely 0.9% of the 'before' group, and in 4.0% of the 'after' group, this difference was statistically significant. In line with these findings, there was no noteworthy increase in the number of neurosurgical interventions between the 'before' and 'after' group, which was 0.1% in the before group and 0.2% in the after group (Table 2).

Before introduction of the guideline the crude CT ratio was on average 24.6%. After introduction of the guideline, the crude CT ratio increased to 55%. A sensitivity analysis of the period 2012-2015, including only those patients in which the guideline was adhered, showed a similar crude CT ratio of 55.8%. The ITS analysis showed a (non-significant) positive time trend (slope) in crude CT ratio, a significant increase in level after introduction of the new guideline and a slight (non-significant) change of

slope following the introduction of the guideline (Table 3). The standardized CT ratio[5] increased each year and was on average 51.9% before introduction of the guideline and 100.5% after introduction of the guideline (Table 2, Supplementary Table 2). The ITS analysis for standardized CT ratio showed similar results as for the crude CT ratio; a (non-significant) positive time trend (slope) (b_1 = 0.48, p = 0.08), a significant increase in level after introduction of the new guideline (b_2 = 31.85, p = 0.05) and a slight (non-significant) change of slope following the introduction of the guideline (b_3 = -0.21, p = 0.50) (Table 3, Figure 1). Hospital admissions have increased from 14.7% before- to 23.4% after introduction of the guideline. However, there was no significant deviation from the secular trend after introduction of the guideline (Table 2, Table 3).

Table 2. (Standardized) CT ratio, traumatic CT findings, hospital admission and neurosurgical intervention

	2007-2009 (n=1823)	2012-2014-2015 (n=2057)	*P* value[1]
Head CT-scans n (%)	448 (24.6)	1131 (55)	< 0.001
Standardized CT ratio	51.9	100.5	< 0.001
(Intra) cranial traumatic CT findings n (%)	47 (2.6)	70 (3.4)	0.13
• Hemorrhagic intracranial traumatic findings[2]	24 (1.3)	38 (1.8)	
• Isolated skull fracture[3]	9 (0.5)	9 (0.4)	< 0.001
• Intracranial traumatic findings plus fracture	14 (0.8)	23(1.1)	
Isolated facial fracture(s) on CT n (%)	16 (0.9)	83 (4.0)	
Hospital admission n (%)	268 (14.7)	481 (23.4)	< 0.001
Neurosurgical intervention n (%)	2 (0.1)	4 (0.2)	0.50

[1] Difference between before-group (2007-2009) and after-group (2012, 2014, 2015).

[2] hemorrhagic intracranial traumatic findings means all traumatic intracranial findings: subdural hematoma, epidural hematoma, traumatic subarachnoid hemorrhage and parenchymal contusion.

[3] Isolated skull fractures means all fractures to the neurocranium.

Guideline adherence, since the introduction of the guideline, was good; when a CT was indicated according to the guideline, a CT-scan was performed in 85.7% of the patients. In addition, a CT-scan was performed in merely 17.9% of the patients when the guideline dictated not to perform a CT-scan (Supplementary Table 3). That equalizes 84.1% overall guideline adherence.

5 The standardized CT ratio is the quotient of the number of cases with a head CT and the number of cases with an indication for head CT according to the 2010 guidelines.

Table 3. Interrupted time series analysis changes in slope and level of crude and standardized CT ratio and hospital admissions

	Slope 2007-2009 (p value)	Change in level after introduction of new guideline (p value)	Change in slope 2012-2015 (p value)
Crude CT ratio	0.18 (0.27)	19.84 (0.04)	-0.01 (0.94)
Standardized CT ratio	0.48 (0.08)	31.85 (0.05)	-0.21 (0.50)
Hospital admissions	0.29 (0.13)	8.32 (0.43)	-0.23 (0.31)

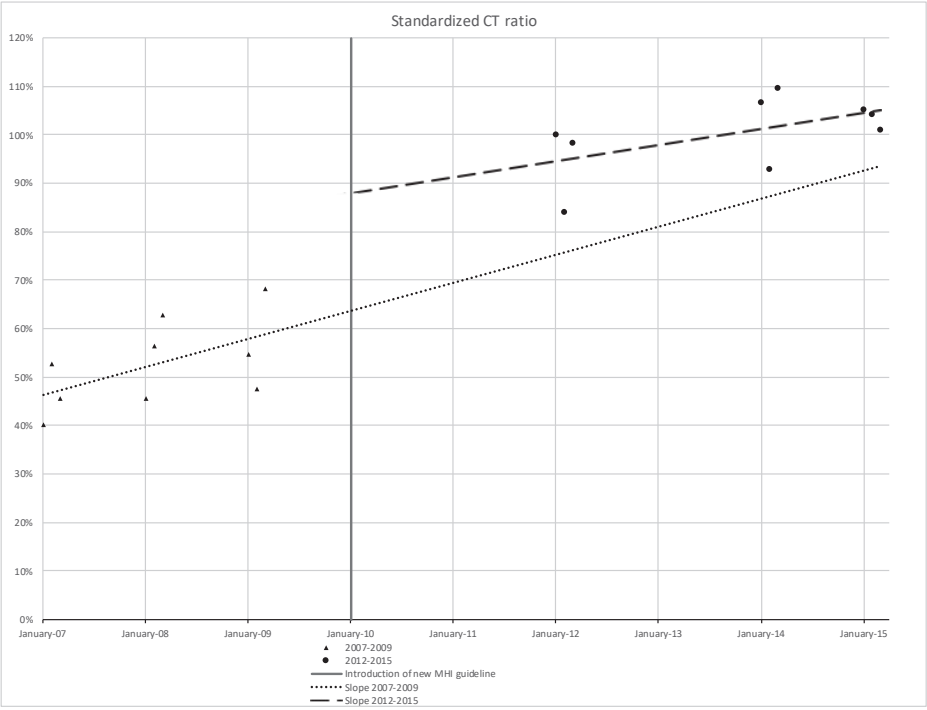

Figure 1.

Interrupted time series analysis changes in slope and level of standardized CT ratio.

This figure shows the standardized CT ratio per month before (triangles) and after (rounds) introduction of the guideline. It also shows the secular trend (slope) in standardized CT ratio before (dotted line) and after (striped line) introduction of the guideline.

Discussion

In this study we found an increase in both the use of CT-scans as well as hospital admissions in patients with MHI, not sufficiently explained by the increase in (intra) cranial traumatic findings.

This is in contrast with the expectation that introduction of the guideline would reduce the number of CT scans as well as the number of hospital admission. A CT reduction of 20-32% was estimated beforehand. Instead of confirming this reduction, we found an increase of 30.4%. A major cause of this increase seems to be the implementation of the new guideline as was demonstrated in the ITS analysis. However, this is probably not the only cause as we also observed a (not statistically significant) secular trend of an increasing standardized CT ratio each year. Easy access to CT scans, more defensive healthcare in general, and emergency department crowding are possible causes of this secular trend. Besides this the CT ratio in the Netherlands is still relatively low in international perspective, where CT ratios for MHI are generally around 65-80%.[7,17,18] Remarkably the implementation trial after introduction of the Canadian CT Head Rule showed similar results, an increase in CT ratio.[17,19] The authors argued this effect was, for the most part, attributable to poor physician adherence to the guideline.[17] However, in our study lack of guideline adherence does not seem to be an important contributing factor with an adherence of 84.1% and an average standardized CT ratio of 100.5% after implementation of the guideline. This is a better guideline adherence than other proposed guidelines for MHI.[17,20]

The increase in CT ratio did not result in less hospitalization, on the contrary. Besides more CT-scans performed, also the proportion of patients admitted to the hospital increased between 2007 and 2015. This was also an unexpected result, since the new guideline dictates that hospitalization is (generally) no longer necessary when the CT-scan shows no traumatic abnormalities. The observed increase in hospital admission ratio may be partially explained by the abandonment of home waking advice in the new guideline. Before introduction of the guideline home waking advice used to be daily routine in certain patients, also when the CT-scan was normal. Home waking advice comprises of regularly waking the patient in the home setting, to make sure he or she is doing well. Because of lack of evidence this advice is no longer part of the new guideline. It is possible that Dutch physicians, instead of discharging the patient, chose for hospitalization for clinical observation.

From the viewpoint of cost-effectiveness there seems to be a lot to gain. The number of CT-scans performed has risen significantly. Moreover, costs are piling up even more with the growth in hospitalizations. Careful evaluation of each admission and CT-scan is therefore needed. A multimodal intervention focusing on physicians could be of importance to reduce CT ratio, as was shown in community hospitals in the USA. [21] Furthermore, adjustment of the guideline should be considered. Examples of such adjustments that could be considered are a higher threshold for performing a CT-scan, more emphasis on clinical judgement or the implementation of other diagnostic modalities such as biomarkers to reduce CT ratio.

The retrospective study design has certain limitations. Missing data were presumed to be absent. For example: if vomiting was not mentioned in the electronic patient record, we presumed absence. This could introduce bias while determining the major and minor criteria for performing a CT-scan. However, this bias would be present in all years studied, and should not be of noteworthy effect for our primary and secondary outcomes. Demonstrating a causal link is also impossible with the retrospective design. Another limiting factor is the possibility of missing traumatic findings in patients who did not undergo a CT. Subsequently it is not possible to draw conclusions about whether too few CT-scans were performed in 2007-2009, or too many were performed in 2012-2015. In line with these limitations, our study was not designed to prove which situation (2007-2009 or 2012-2015) was better in the context of patient safety.

Between 2007 and 2015, a marked increase in CT ratio for MHI as well as hospitalizations has been observed. Several factors seem to contribute to this increase. Most likely, introduction of the MHI guideline is an important contributor at least to the increase in CT ratio. Since health care is getting more expensive and cost-effectiveness more important, an adjustment to the guideline should be considered.

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Supplementary Material

Supplementary Table 1. Patients with (possible) missed traumatic findings

Patient	Year	PTA, LOC, confusion[1]	GCS[1]	CT indication[2]
A	2007	Yes LOC, PTA	15	No[3]
B	2009	No	15	Yes[4]
C	2012	Yes LOC, PTA	14	Yes[5]
D	2014	No	15	Yes[6]

PTA: post traumatic amnesia; LOC: loss of consciousness; GCS: Glasgow Coma Scale score

[2] According to the guideline introduced in 2010.

[3] Age < 40 years, no external injury to the head, LOC, PTA < 2 hours, no other risk factors.

[4] Age ≥ 40 years, external injury to the head, anticoagulants.

[5] Age ≥ 40 years, external injury to the head, LOC, GCS 14, PTA < 2 hours.

[6] Age ≥ 40 years, external injury to the head, anticoagulants. A CT head was not performed for unclear reasons.

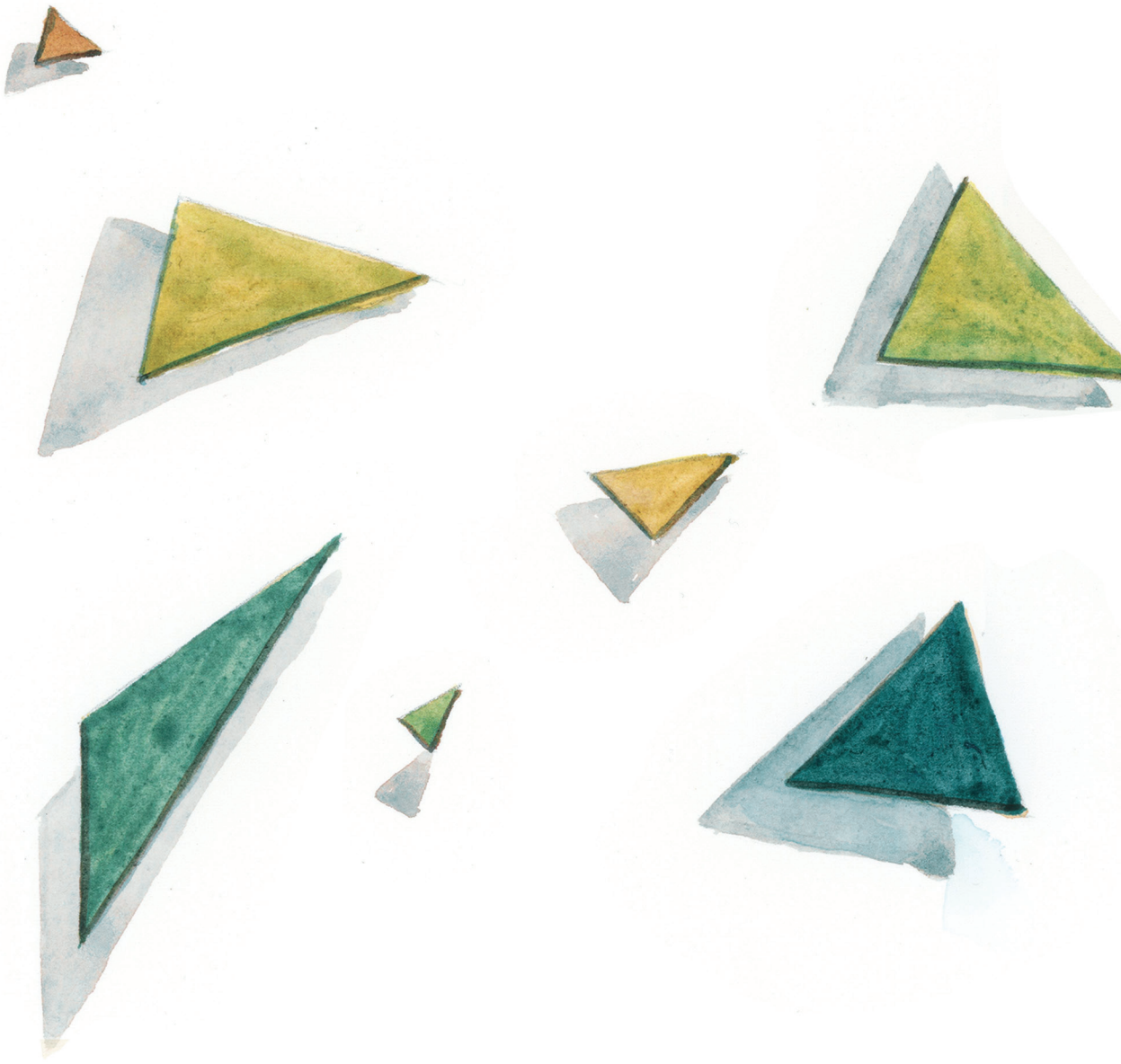
Supplementary Table 2. Crude and standardized CT ratio per year, hospital admission per year

	2007	2008	2009	2012	2014	2015
Crude CT ratio %	24.2	22.2	27.0	51.6	55.6	57.8
CT indication %	52.5	41.0	49.0	54.3	54.1	55.7
Standardized CT ratio %	46.2	54.2	55.1	94.9	102.9	103.8
Hospital admissions %	10.3	16.0	16.9	23.1	19.8	27.4

Supplementary Table 3. Guideline adherence (years 2012, 2014, 2015)

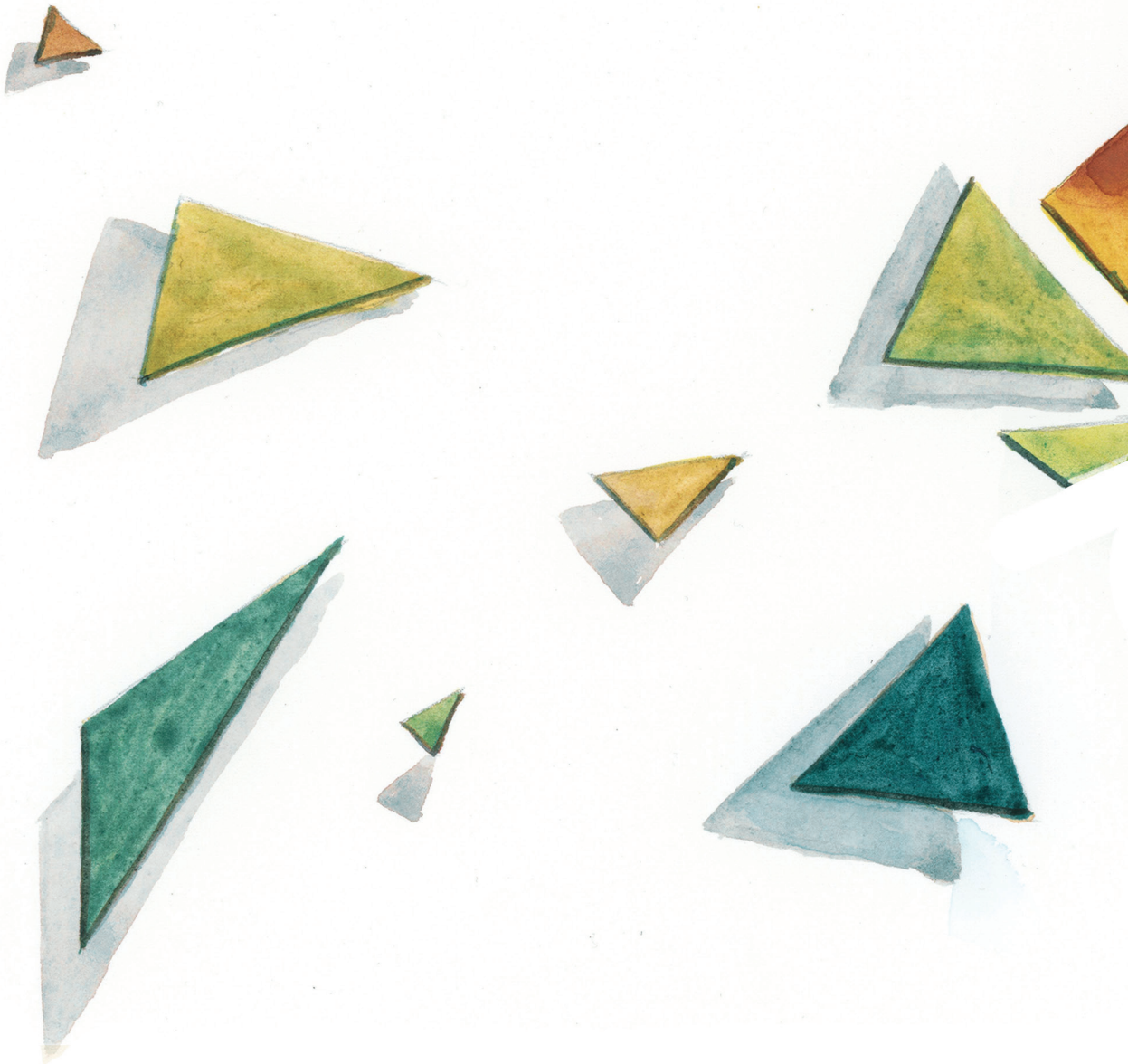
	CT indicated according to guideline	CT not indicated according to guideline
CT performed	964 (85.7%)	167 (17.9%)
CT not performed	161 (14.3%)	765 (82.1%)

	CT on first ED visit	CT on repeat ED visit (within 30 days)	Clinical course
	No CT on first visit	Day 2: epidural hematoma with midline shift, skull fracture	Neurosurgical intervention, full recovery
	No CT on first visit	Day 3: parenchymal contusion, acute subdural hematoma	Conservative treatment, patient died of a non-neurologic cause on day 16
	Yes, no traumatic findings on first CT	Day 10: acute subdural hematoma with midline shift	Several neurosurgical interventions, patient died of a non-neurologic cause on day 27
	No CT on first visit	No repeat ED visit	Patient died of an unknown cause on day 7



PART II

Prevention of- and risk factors for traumatic brain injury



CHAPTER 4

Systematic review and meta-analysis: Is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage?

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ABSTRACT

The objective of this systematic review and meta-analysis is to evaluate whether the pre-injury use of antiplatelet therapy (APT) is associated with increased risk of traumatic intracranial hemorrhage (tICH) on CT scan. Pubmed, Medline, Embase, Cochrane Central, reference lists and national guidelines on traumatic brain injury were used as data sources.

Eligible studies were cohort studies and case-control studies that assessed the relationship between APT and tICH. Studies without control group were not included. The primary outcome of interest was tICH on CT. Two reviewers independently selected studies, assessed methodological quality and extracted outcome data.

This search resulted in ten eligible studies with 20,247 patients with head injury that were included in the meta-analysis. The use of APT in head injury patients was associated with significant increased risk of tICH compared to control (odds ratio 1.87, 95% confidence interval 1.27 to 2.74). There was significant heterogeneity in the studies (I^2 84%), although almost all showed an association between APT use and tICH. This association could not be established for patients on aspirin monotherapy. When considering only patients with mild traumatic brain injury (mTBI) the odds ratio is 2.72 (95% CI 1.92-3.85). The results were robust to sensitivity analysis on study quality.

In conclusion APT in head injury patients is associated with increased risk of tICH, this association is most relevant in patients with mTBI. Whether this association is the result of a causal relationship, and whether this relationship also exists for patients on aspirin monotherapy cannot be established with the current review and meta-analysis.

Introduction

Traumatic brain injury is a major cause for morbidity and mortality worldwide.[1,2] Approximately 5% of emergency department (ED) visits are because of traumatic brain injury (TBI), and in the United States there are approximately 2.5 million TBI related ED visits annually.[1,3] For patients with severe (GCS 3-8) or moderate TBI (GCS 9-12) intracranial complications are frequent and a CT head is indicated in all patients.[4] In contrast, for patients with mild TBI (GCS 13-15) intracranial complications are infrequent (< 10%), and rarely require neurosurgical intervention (< 1%).[5] Nonetheless intracranial complications after head injury do occur and are potentially life threatening. To enhance efficiency without compromising on patient safety various decision rules and guidelines have been developed to identify patients with increased risk of intracranial complications.[4-9]

Whereas many decision rules and guidelines consider the use of vitamin K antagonists (e.g. warfarin) as risk factor for intracranial complications after minor head injury, antiplatelet therapy (APT) is not generally considered to be an independent risk factor for intracranial complications after minor head injury.[4-9] Recent publications however raised the question whether APT increases the risk of brain injury after head trauma.[10-20] Both the American ACEP (American College of Emergency Physicians) clinical policy on this subject as the British NICE (National Institute for Health and Care Excellence) guidelines stressed the need for research on this subject and the Scandinavian guidelines included antiplatelet therapy as a risk factor.[4,9,21] With the ageing population and hence the increasing use of aspirin, ticagrelor, clopidogrel and other antiplatelets the need to establish whether the pre-injury use of APT is associated with traumatic intracranial hemorrhage (tICH) becomes more and more urgent.[1,22]

This meta-analysis aims to quantitatively assess the available data from various studies regarding direct (< 24h) tICH on CT following head injury in relationship to APT use.

Methods

Identification of studies

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) to conduct our review and meta-analysis and also adhered to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[23,24] A search of the databases Pubmed, Medline, Embase, Cochrane Central from inception to 29-09-2015 was made. The following combinations of search terms were used to search all databases: head trauma; brain injury; cerebral injury; brain trauma; cerebral trauma; brain contusion; cerebral contusion; brain concussion; cerebral concussion; anticoagulant; antithrombotic; platelet aggregation inhibitor; vitamin K antagonist; carbasalate calcium; aspirin; acetylsalicylic acid; clopidogrel; ticagrelor; dipyridamole; prasugrel; marcoumar; phenprocoumon; acenocoumarol; noac; doac; apixaban; rivaroxaban; dabigatran; heparin; enoxaparin nadroparin.

We also searched the most important relevant guidelines for references and we searched the reference list of appropriate studies.[4,8,9,21]

Selection criteria, data extraction, quality assessment

We included retrospective as well as prospective observational cohort studies and case-control studies that evaluated the relationship between (any type of) APT use and tICH following head injury on CT in an ED setting. Studies without control group or studies outside the ED were excluded. Studies that only included patients with tICH were also excluded. Severity of the brain injury was no selection criteria for inclusion of the study. The main outcome measure was tICH on head-CT, other outcome measures of interest were neurosurgical intervention and mortality within six months, for studies to be eligible we had to be able to extract data on at least one of these outcomes. No limits were placed on characteristics of participants, date of publication or language of publication.

Three authors (CB, TT, AR) selected articles and extracted data; each step in selection and data extraction was done independently by two of these authors. Any disagreements were resolved by discussion and consensus. We extracted data regarding: study design, study location, sample sizes, characteristics of participants (including age and GCS), intervention (type of APT), control group, outcome measure, measures of effect (including Odds Ratio) and quality of methods. Methodological quality of the studies was assessed independently by two authors (CB, TT, AR) with the Newcastle-Ottawa assessment scale (NOS).[25] Any disagreements were resolved by discussion and consensus. The NOS consists of three components assessing the

studies on selection (four items), comparability (one item) and exposure (three items). Each item is scored with a maximum of one star, except the item comparability, that could be scored two stars; therefore a maximum of nine stars can be scored. We rated studies as low risk of bias if they received nine stars, moderate risk of bias if they received seven or eight stars and high risk of bias if they received less than seven stars.

Several attempts were made to contact all authors of included studies for additional information. The review was registered in the PROSPERO register as number CRD42015025458.

Statistical analysis

The pooled odds ratio and 95% confidence interval were calculated for the relationship between APT use and tICH. Pre-specified subgroup analyses were performed for severity of TBI (GCS > 13 or GCS ≥ 13), type of APT (aspirin; clopidogrel; other) and type of control group (no medication; warfarin). A random effects model was used.

We evaluated heterogeneity with the I^2 test, which represents the proportion of variability not explained by chance alone. The likelihood of publication bias was assessed graphically with a funnel plot.[26]

All analyses were made with RevMan (version 5.3) from The Cochrane Collaboration (2014).

Results

Study selection

The search of Pubmed, Medline, Embase and Cochrane Central returned 831, 1099, 2480, 117 results respectively. After correction for duplicates 3193 articles remained. After selection on title and abstract 3165 articles were excluded, leaving 28 articles. These 28 articles were analyzed in more detail to assess suitability. After this assessment another 17 articles were excluded, leaving eleven articles. Of these eleven articles two were based on the same study results, these results were only used once for this meta-analysis (Figure 1).[15,16]

Study characteristics

Ten studies (eleven publications) with a total of 20,247 participants met the inclusion criteria.[10-20] One study is a retrospective case-control study, the nine other study are cohort studies.[13] Eight cohort studies have a retrospective design and one has a prospective design. All studies are published in English since 2003, and conducted in three different Western countries in level I and II trauma centers (Table 1). Four studies looked specifically at the use of clopidogrel.[13-16, 20] One study assessed specifically the use of aspirin [18]. All other studies included different types and combinations of APT's.[10-12,17,19] The control groups consisted of TBI-patients without (a type of) APT; in the study by Nishijima and in the study by Brewer the control group were TBI-patients on warfarin therapy. The age of included patients and severity of trauma varied between studies as is outlined in Table 1.

Risk of bias within studies

Using the NOS, one study was rated as low risk of bias, while seven studies were rated as moderate risk of bias and two studies were rated as high risk of bias. The NOS ratings are included in Table 1.

In the study by Cull et al selection bias was a major concern. The study included only patients registered in the trauma registry. This trauma registry only includes patients admitted to the hospital.[27] Admitted TBI-patients are not a random selection of all ED TBI patients and both tICH and the use of APT in itself can be reasons for hospital admission. The effect of the possible bias is reflected in the fact that the APT group had relatively less patients with severe TBI compared to the non-APT group (4.7% versus 10.2%) hence the APT-group might not be comparable with the non-APT group.

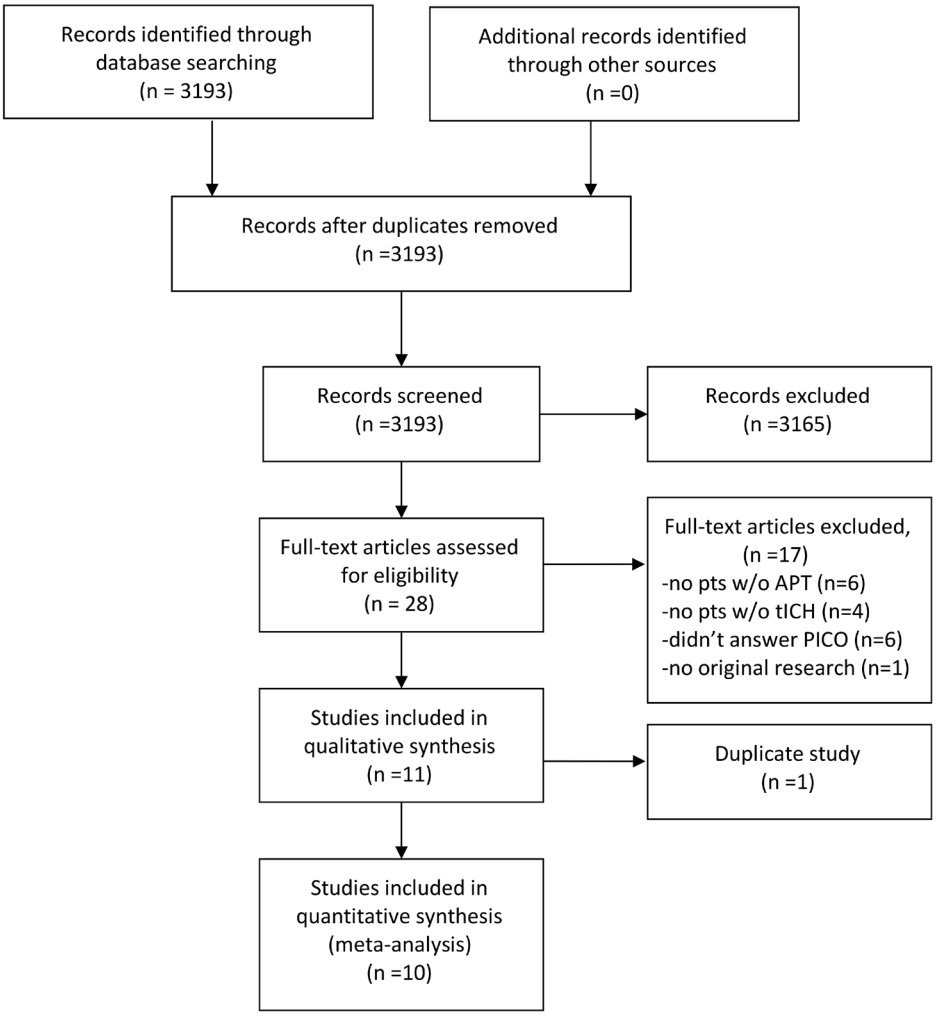

Figure 1

Flow diagram of included studies

Bias in the studies by Ahmed and Dunham encompassed the same selection bias as the study by Cull (admitted patients only) besides this comparability between groups (GCS, age) was not reported in the manuscripts, although we did get this information from the Dunham study group.

Table 1. included studies

Source	Design	Setting	Single/ Multicentre	Country	Age	GCS
Ahmed 2015	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>17	3-15
Brewer 2011	Retrospective cohort	ED, level II	Singlecentre	U.S.A.	>17	15
Cull 2015	Retrospective cohort	ED, level I	Multicentre	U.S.A.	>40	3-15
Dunham 2014	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>59	3-15
Fabbri 2010	Retrospective cohort	ED, level I	Singlecentre	Italy	>9	14.15
Jones 2006	Retrospective case-control	ED, level II	Singlecentre	U.S.A.	>50	3-15
Levine 2013	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>14	15
Nishijima 2012	Prospective cohort	ED, level I/II	Multicentre	U.S.A.	>17	3-15
Riccardi 2013	Retrospective cohort	ED, level II	Singlecentre	Italy	>65	15
Spektor 2003	Retrospective cohort	ED, level I	Multicentre	Israel	>59	9-15

* Patients with concomitant VKA and ASA use were excluded from analysis (Brewer 21 patients, Nishijima 107 patients)

In the study by Brewer selection bias was also a major concern, the study only included trauma registry patients. This trauma registry only included patients admitted to or consulted by the trauma service [20]. These patients likely suffered from greater overall trauma compared to the non-trauma registry patients as stated by the authors. No information regarding comparability between groups was reported.

The most important bias in the study by Fabbri was detection bias, as only in 63.3% of patients a CT scan was made.

The case-control study by Jones had very limited information in the manuscript and we were not able to get in contact with the authors. The study included both patients with head injury as patients without head injury and patients were matched for age, sex, mechanism of injury and Injury Severity Score. Because patients were

No of pts	APT	Control	Selection	Compari-bility	Outcome	Risk of bias
163	clopidogrel, ASA	No APT	**	**	***	Moderate risk
141*	clopidogrel	VKA	**	*	***	High risk
1547	clopidogrel, ASA	No APT/VKA	**	**	***	Moderate risk
148	clopidogrel, ASA	No APT/VKA	**	**	***	Moderate risk
14228	ASA, ticlopidine, indobufen	No APT	****	**	**	Moderate risk
86†	clopidogrel	No clopidogrel	-	*	**	High risk
658	clopidogrel	No clopidogrel/ VKA	***	**	***	Moderate risk
1064*	clopidogrel	VKA	****	**	***	Low risk
2149	clopidogrel, ASA, ticlopidine	No APT/VKA	****	*	***	Moderate risk
231	ASA	No APT/VKA	**	**	***	Moderate risk

† Not all patients sustained a head trauma, patients without head trauma were excluded from analysis (40 patients)

not matched for GCS and no information is provided regarding GCS we do not know if the groups are comparable in this regard, GCS is known to be the most important predictor of tICH.[5,6]

In the retrospective study by Levine only patients that underwent a CT-head were included, this may have caused selection bias.

The study by Nishijima is the only prospective trial in this review, it was generally well set up, unfortunately patients on clopidogrel were only compared to warfarin and not to a control group without antithrombotic medication. This may underestimate the risk of clopidogrel as warfarin is generally regarded as a risk factor for tICH.[4,8,9]

The study by Riccardi did not report comparability of baseline characteristics between the APT group and the non-APT group.

Finally in the study by Spektor it was not clear from the manuscript in which way the selection of patients was done and if consecutive patients were included.

Outcomes

Combining all data for a summary OR we found an increased risk for tICH in patients with APT versus patients without APT. The overall OR was 1.87 (95% CI 1.27-2.74) (Table 2, Figure 2)

Risk of bias across studies

Strong evidence of heterogeneity (I^2 84%) was observed. To explore this heterogeneity a funnel plot was drawn, which showed only minor asymmetry with no indication for publication bias. (Supplementary Figure 1)

Additional analysis

Based on the risk of bias a sensitivity analysis was performed, excluding all studies with a high risk of bias. The odds ratio for APT as a risk factor for the development of intracranial traumatic complications was 2.02 (95% CI 1.33-3.08; I^2 87%) for the low-intermediate risk of bias studies. We also performed a sensitivity analysis excluding the study by Spektor, which only included patients with aspirin use. The result of that analysis was an OR of 2.02 (95% CI 1.35-3.03; I^2 85%). Finally we did a sensitivity analysis that only included studies with patients with mild TBI (GCS 13-15), which resulted in an OR of 2.72 (95% CI 1.92-3.85; I^2 53%).

Table 2. study outcomes

Source	tICH APT-group	tICH non-APT-group
Ahmed (2015)	35/52 (67.3%)	56/111 (50.5%)
Brewer (2011)	15/36 (41.7%)	23/84 (27.4%)
Cull (2015)	198/422 (46.9%)	504/1125 (44.8%)
Dunham (2014)	35/76 (46.1%)	23/72 (31.9%)
Fabbri (2010)	180/1366 (13.2%)	700/12862 (5.4%)
Jones (2006)	9/25 (36.0%)	10/21 (47.6%)
Levine (2013)	3/10 (30%)	14/648 (2.2%)
Nishijima (2012)	29/252 (11.5%)	36/705 (5.1%)
Riccardi (2013)	22/617 (3.6%)	25/1532 (1.6%)
Spektor (2003)	27/110 (24.5%)	31/121 (25.6%)

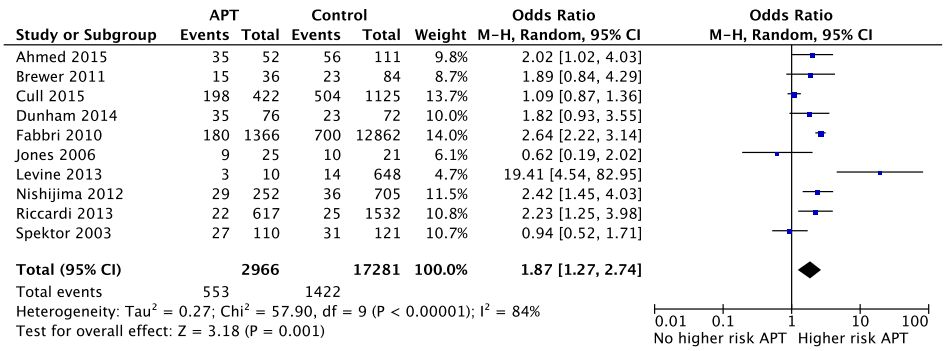

Figure 2

Forrest plot of included studies.

Discussion

We conducted a systematic review and meta-analysis of the literature to assess the association between the use of APT and tICH.

Evidence from the nine available studies suggests that pre-injury APT use is associated with an increased incidence of tICH. However, this conclusion should be interpreted with caution given the high heterogeneity and methodological flaws of several included studies in this review. To our knowledge the current meta-analysis is the only quantitative analysis of pooled data on this topic.

The use of APT seems to be most relevant in patients with mild TBI, it is in these patients that APT use may direct the clinical decision whether to scan or admit the patient or not.

Important to mention, but outside the scope of this review, there are indications that patients on APT not only have a higher risk of tICH, but those with tICH also do have a higher risk of unfavorable outcome.[13,28-32]

Studies comparing APT and VKA therapy are limited, the limited studies available mainly included patients with clopidogrel and patients with warfarin therapy.[15,16,20] These studies do not show that the tICH risk associated with clopidogrel use is lower than that associated with warfarin use. Hence it could be advisable to use the same guidelines for scanning and disposition for clopidogrel therapy as apply for VKA therapy in (mild) TBI patients. Whether this is also advisable for other antiplatelet therapy cannot be answered based on the current review.

Another consideration, which is also outside the scope of this review, is whether routine administration of platelets in patients with tICH and APT is useful. There is only low quality evidence from observational studies, and the results of these studies are contradictory.[31-36] Both a systematic review and a recent guideline by the AABB (formerly American Association of Blood Banks) conclude that there is insufficient evidence to recommend for or against platelet transfusion in patients with tICH while receiving APT.[37,38] Routine administration of platelets in TBI patients receiving APT without evidence of hemorrhage on CT does not seem to be indicated.[38]

Limitations

This review and meta-analysis has a number of limitations and the results of this review should be interpreted in the light of these limitations. First, the patient population, APT use, control group and outcome definitions are not the same across studies. This resulted in significant heterogeneity across studies. Second, the overall quality of the included studies was low. All the original studies were observational studies and almost all studies had a retrospective design with consequently a higher risk of bias. Especially selection bias was a concern in many of the included studies. Because of the design of the studies it is impossible to establish a causal relationship of APT use and the risk of tICH. Confounding, as in any meta-analysis of observational studies, may introduce considerable bias. Another limitation is that in this review APT is considered as a group, it is unlikely however that all different antiplatelet medications will have the same risk of tICH, there were insufficient studies on different antiplatelet medications to specify the risk of different APT's. Especially for patients on low-dose aspirin monotherapy it is uncertain if the risk for tICH is increased, the only included study that assessed aspirin as risk factor for tICH did not find an increased risk. Finally although tICH is generally regarded as important in the disposition and treatment of TBI patients, this is in fact a surrogate outcome for mortality and morbidity following TBI.

Clinical implications

Considering the observed association between APT use and tICH, APT use should be considered as a potential risk factor for tICH in future guidelines regarding (mild) TBI. Whether patients on low-dose aspirin monotherapy do have an increased risk of tICH as well cannot be concluded based on the current review and meta-analysis because of limited literature.

Conclusions

Although the estimates of the association between APT and tICH are clinically relevant, they are still somewhat preliminary and do not prove that APT use increases the risk of tICH. Additional prospective studies are needed to confirm and quantify findings further. These studies could also give an indication whether a causal relationship between APT and tICH is probable, and explore the risks of different types of APT's.

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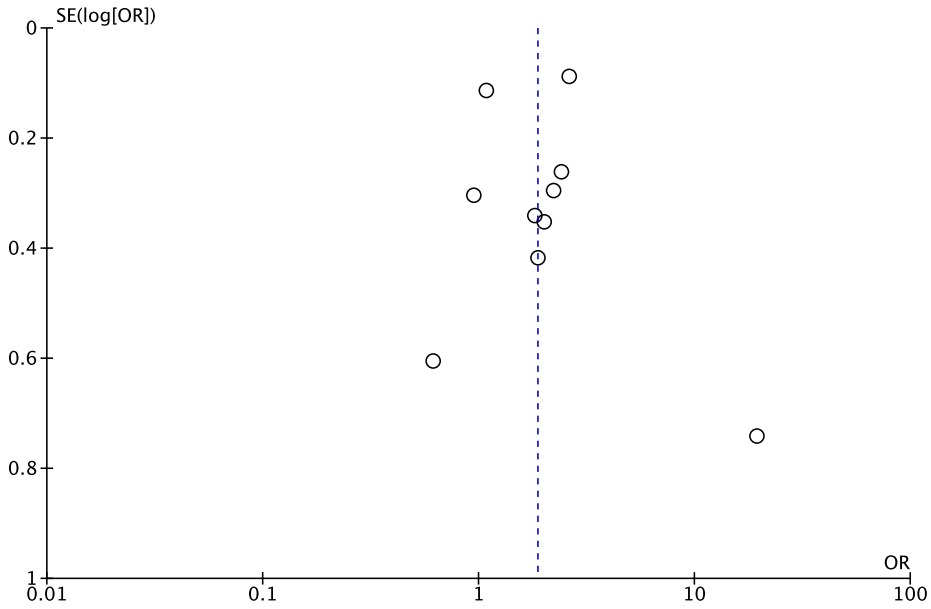
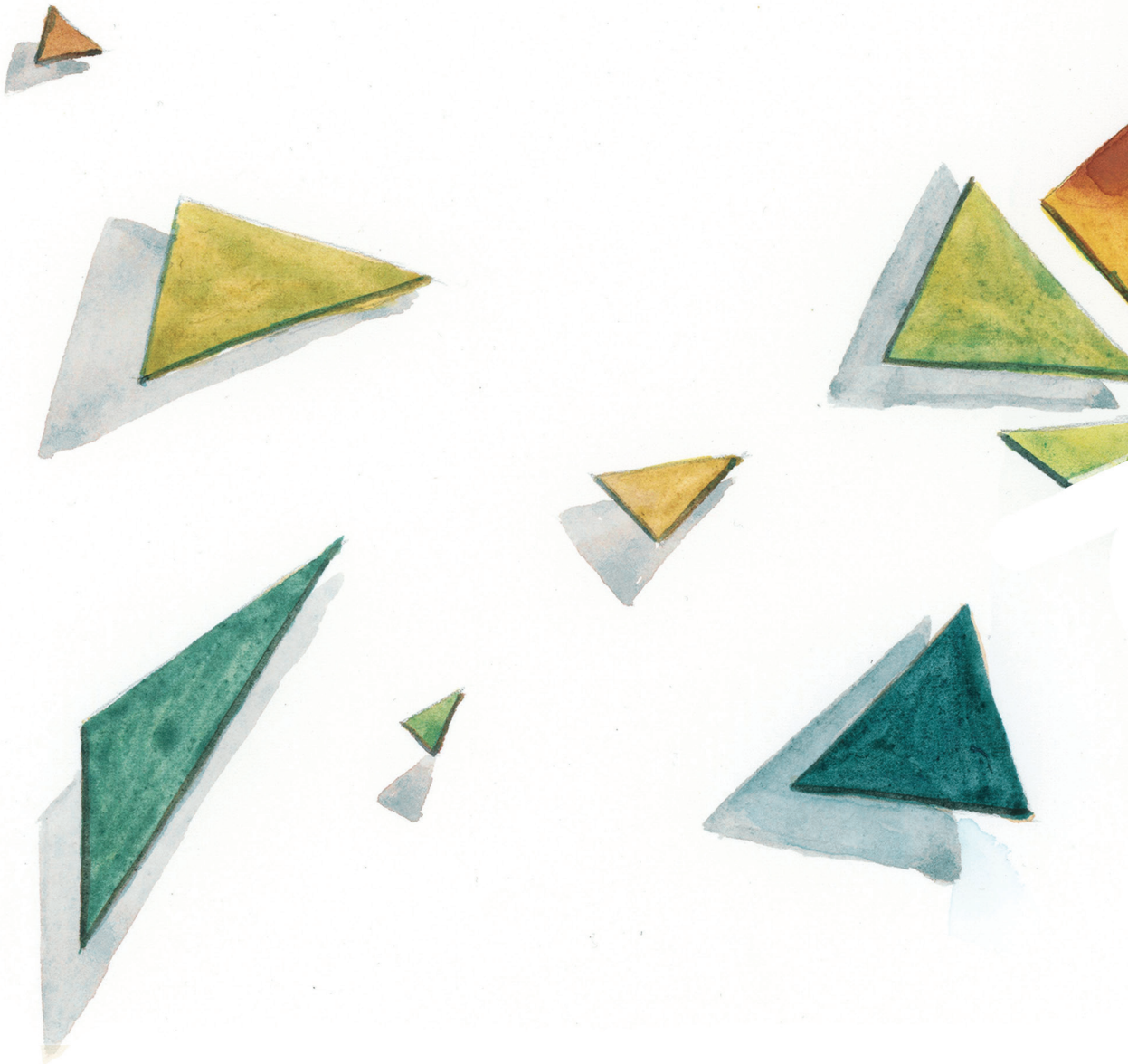
Supplementary Material



Supplementary Figure 1.

Funnel plot of included studies.



CHAPTER 5

Bicycle helmets and bicycle-related traumatic brain injury in the Netherlands

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ABSTRACT

The aim of this study was to determine the association between bicycle helmet use in adults (16 years and older) and traumatic brain injury (TBI) in emergency departments (EDs) in the Netherlands

The conducted research was a retrospective case-control study in patients aged 16 years and older that sustained a bicycle accident and therefore visited the EDs of participating hospitals throughout 2016. Cases were patients with TBI; controls were patients without TBI but with other trauma. Exposure was defined as helmet wearing during the accident.

In total 2133 patients were included in the study, 361 case patients and 1772 controls. Within the TBI group (cases) 3.9% of the patients wore a helmet compared to 7.7% of patients in the control (non-head injury) group (odds ratio [OR] 0.49, 95% confidence interval [CI] 0.28-0.86). No difference in helmet wearing was observed in patients that sustained accidents which involved motorized vehicles (OR 0.91; 95% CI 0.29-2.83).

In conclusion adult patients (≥ 16 years of age) with TBI had a significantly lower odds of wearing a bicycle helmet than adult patients with other trauma, adding more evidence that wearing a bicycle helmet effectively protects against TBI.

Introduction

Worldwide cycling is a popular form of recreation and a cheap and environmentally friendly mode of transportation. In the Netherlands, a small and densely populated country, cycling is very popular. In fact, the Netherlands could be called the number one cycling country in the world. An average of approximately 900 kilometers per inhabitant is cycled each year, this is by far the most in the world and about 20 times as much as in the United States{Stichting BOVAG-RAI mobiliteit, #4}.[1-3] This translates to 27% of all trips in the Netherlands being done by bicycle, again more than in any other country in the world.[4]

{Stichting BOVAG-RAI mobiliteit, #4}Cycling is also a relative safe mode of transportation compared to other modes of transportation and the health benefits of cycling are substantially higher than the risks associated with cycling. [5,6] Moreover, there is a correlation between bicycle use in a country and the fatality rate among cyclists. Higher bicycle use in a country is associated with lower fatalities with the Netherlands having the lowest fatality rate per kilometer cycled. [3] However, despite investments in road safety and overall decreasing incidence of traffic fatalities, injuries and fatalities among cyclists did not significantly decrease in the last 20 years in the Netherlands. Currently, bicycle accidents are responsible for over 70% of all severely injured traffic participants in the Netherlands.[7] Severe injury as a result of bicycle accidents has increased by 35% in the last 10 years and. Especially in elderly traffic participants this increase is significant even when correcting for ageing of the population, one possible explanation is that the elderly do cycle a lot more nowadays than they used to in the past, for example because of the introduction of e-bikes.[7,8] The rise of traumatic brain injury (TBI) is not only responsible for the growing incidence of persons with bicycle related injury presenting at the emergency department (ED), but TBI is also the most important cause of death and long-term disability from bicycle injury.[9-13] Hence, it is crucial to reduce TBI incidence among cyclists.

An obvious way to realize less TBI in cyclists could be by promoting bicycle helmets. However, both public opinion and the scientific literature are divided about bicycle helmets. Some claim that bicycle use decreases after helmets became obligatory in different countries and as a result the health benefits of helmets were negated. For example, bicycle use in New Zealand declined by 51% after it became obligatory to wear a bicycle helmet. [14] Other authors question whether there is any causality between the decline in cycling and the bicycle helmet law.[15,16] Regarding the protective value of bicycle helmets two meta-analysis that included mostly case-

control studies both concluded that bicycle helmets reduce serious and fatal head injury by approximately 60-70%.[17,18] However, some other studies question (the magnitude of) this protective effect of bicycle helmets.[19-22]

Although many studies have been done to examine the effectiveness of bicycle helmets, remarkably no such study has been performed in the Netherlands. In contrast to other countries, in the Netherlands bicycle helmets are not mandatory or common and bicycle helmet use is fiercely debated.[23-25]

In the current study we examine the association between bicycle helmet use in adults (16 years of age and older) and TBI cases in EDs in the Netherlands.

Methods

Data sources and inclusion

In this retrospective case-control study patients aged 16 years and older who sustained a bicycle accident and therefore visited the EDs of participating hospitals throughout 2016 were included using the Dutch Injury Surveillance System (Letsel Informatie Systeem; LIS). Cases were defined as patients with TBI who visited the ED of one of the participating hospitals; controls were defined as patients without TBI but with other trauma who visited these EDs. Exposure was defined as (self-reported) helmet-wearing during the accident.

The LIS database is a continuous monitoring system in which in addition to demographics, injury diagnoses and injury mechanisms are registered. LIS is based on 13 geographically distributed EDs in the Netherlands, resulting in a representative 12%-15% sample of injury-related ED visits that can be extrapolated to national estimates. For extrapolation of the sample a factor was calculated in which the number of trauma-related ED treatments in LIS hospitals was multiplied by the quotient of all trauma-related hospital admissions in the Netherlands divided by trauma-related hospital admissions in LIS hospitals.[26-29]

To study bicycle-related accidents, extra information was gathered in all LIS hospitals in 2016. Patients who sustained a bicycle accident received a questionnaire within two months after their visit to the ED. Patients were asked to complete the questionnaire online or to fill out a paper questionnaire. Ultimately, a sensitivity analysis was conducted in which the study population was corrected for selective (non-)response by a weighing factor, using the age and gender distribution from the total patient population for bicycle accident-related ED treatments from the LIS database.

The study was submitted to the medical ethics review committee (reference number W16_151#16.175) which concluded that the Medical Research Involving Human Subjects Act (WMO) was not applicable. Therefore, official approval of this study by the medical ethics review committee and was not required.

Exclusion

All participants who were not driving on public roads (i.e. parcourse, dirt track, private property) were excluded. Because we focused on the risk on TBI in normal traffic, we also excluded cyclists who were travelling at a self-reported speed of 25 km/h or more.

Patients with *isolated* injury to the eyeball and/or to the scalp were excluded from the control group because helmet wear possibly protects against these injuries. Patients with a combination of injuries that included scalp or eyeball injury were not excluded from the study.

Data and statistical analysis

Data were analyzed using descriptive statistics, χ^2 tests and Mann-Whitney U tests where appropriate. Significance threshold was set at $P < 0.05$. The Statistical Package for the Social Sciences (IBM Corp., IBM SPSS Statistics for Windows, version 22.0. Armonk, New York, USA) was used for statistical analysis.

Results

Between January 1, 2016 and December 31, 2016, 9013 patients were treated for a bicycle accident in the ED of participating LIS hospitals. Of these 9013 patients 3146 returned a usable questionnaire. After exclusion of patients under 16 years of age, or with other exclusion criteria, 2133 patients were included in the analysis (Figure 1). These 2133 patients were 361 cases (patients with TBI) and 1772 controls (patients without TBI). Of the entire group 60.4% were female. The mean age was 58.5 years. To assess comparability of cases (patients with TBI) and controls (patients without TBI), patients *without* helmet wear were compared between cases and controls. It appeared that patients with TBI were more often male than controls; no other significant differences were observed between cases and controls (Table 1).

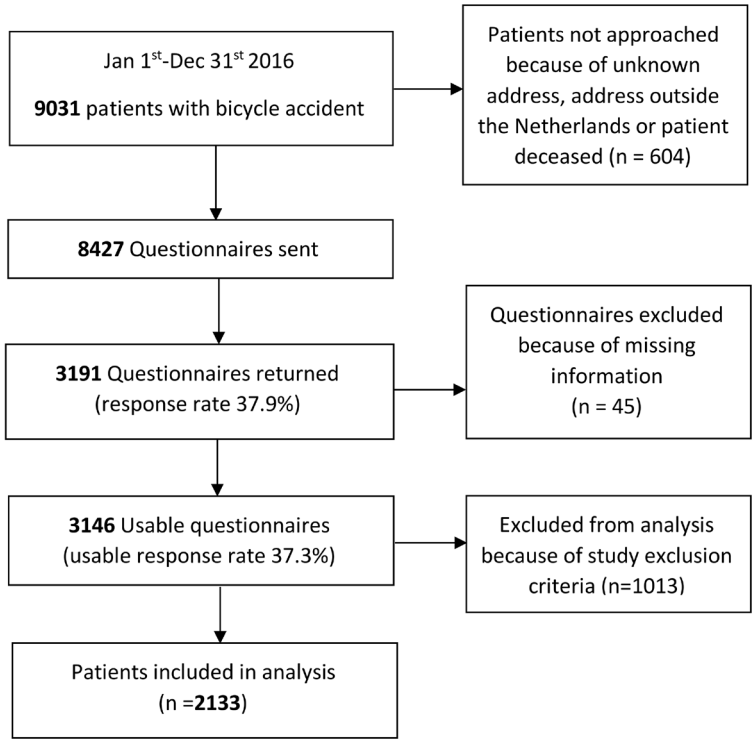

Figure 1.

Overview of cases included in analysis

Table 1a. Baseline characteristics of cases and controls all patients.

	Cases (TBI) n=361	**Controls (non-TBI) n=1772**	**Missing**	***P*-value**
Age, years (mean)	58.7	58.5	0	0.63
Male sex (n, %)	161 (44.6%)	684 (38.6%)	0	0.03
Helmet wear (n, %)	14 (3.9%)[1]	135 (7.7%)[1]	16 (0.8%)	0.03
Motorized vehicle collision (n, %)	70 (40.9%)[2]	242 (32.4%)[2]	1214 (56.9%)[#]	0.03
Bicycle type (n, %)			26 (1.2%)	
Commuter bicycle	205 (57.7%)[3]	951 (54.3%)[3]		0.23
Mountain bike	8 (2.3%)[3]	46 (2.6%)[3]		0.69
Racing bike	18 (5.1%)[3]	125 (7.1%)[3]		0.16
Bike with pedal support	117 (33.0%)[3]	602 (34.4%)[3]		0.61
Other	7 (2.0%)[3]	28 (1.6%)[3]		0.62

[1] Unknows and missings (for helmet wear) are excluded: cases (TBI) n=359, controls (non-TBI) n=1758

[2] Unknows and missings (for cause of accident) are excluded: cases (TBI) n=171, controls (non-TBI) n=748

[3] Unknowns and missings (for bike types) are excluded: cases (TBI) n=355, controls (non-TBI) n=1752

Table 1b, Baseline characteristics of cases and controls *only patients without helmet wear*

	Cases (TBI) n=345	**Controls (non-TBI) n=1623**	**Missing**	***P*-value**
Age, years (mean)	59.0	58.7	0	0.71
Male sex (n, %)	149 (43.2%)	566 (34.9%)	0	< 0.01
Motorized vehicle collision (n, %)	66 (40.5%)[1]	225 (33.4%)[1]	1131 (57.5%)[#]	0.09
Bicycle type (n, %)			26 (1.2%)	
Commuter bicycle	202 (59.6%)[2]	935 (58.3%)[2]		0.67
Mountain bike	7 (2.1%)[2]	23 (1.4%)[2]		0.39
Racing bike	6 (1.8%)[2]	31 (1.9%)[2]		0.84
Bike with pedal support	117 (34.5%)[2]	589 (36.7%)[2]		0.44
Other	7 (2.1%)[2]	25 (1.6%)		0.51

[1] Unknows and missings (for cause of accident) are excluded: cases (TBI) n=163, controls (non-TBI) n=674

[2] Unknowns and missings (for bicycle types) are excluded: cases (TBI) n=339, controls (non-TBI) n=1603

[#] The high number of missings is probably caused by the nature of the question “what did you collide with?” in many cases this was unknown or not applicable.

Within the TBI group (cases) 3.9% of patients wore a helmet compared to 7.7% of patients in the control (non-TBI) group (odds ratio [OR] 0.49, 95% confidence interval [CI] 0.28-0.86). These differences were clearly visible in patients with accidents that did not involve motorized vehicles (OR 0.27; 95% CI: 0.08-0.87). In contrast, in patients with accidents that involved motorized vehicles no difference was found between the groups (OR 0.91; 95% CI: 0.29-2.83; Table 2).

Table 2. Odds for traumatic brain injury in cyclists

	Odds ratio	95% confidence interval		*p*-value
Odds for TBI wearing a helmet	0.49	0.28	0.86	0.01
Odds for TBI in a motorized vehicle collision wearing a helmet	0.91	0.29	2.83	0.87
Odds for TBI in an accident without motorized vehicle wearing a helmet	0.27	0.08	0.87	0.03
Odds for mild traumatic brain injury wearing a helmet	0.47	0.25	0.88	0.02
Odds for severe traumatic brain injury wearing a helmet	0.54	0.17	1.74	0.30

For all different types of bicycles patients were less likely to have worn a helmet in the TBI group compared to the control (other injury) group. However, this difference did not reach statistical significance in any of the bicycle types (Table 3).

Table 3. Odds for traumatic brain injury per bicycle type (helmet wearing vs not helmet wearing)

	Odds ratio	95% confidence interval		*p*-value
Commuter bicycle	0.58	0.07	4.65	0.61
Mountain bike	0.15	0.02	1.32	0.09
Racing bike	0.67	0.23	1.93	0.45
Bike with pedal support	0.26	0.02	4.57	0.36

A sensitivity analysis was performed to correct for selective (non)-response to the questionnaire. This additional analysis did not essentially change the results of the study. The odds of wearing a bicycle helmet in TBI compared with other trauma was 0.52 (95% CI: 0.29-0.94) in the sensitivity analysis.

Discussion

Adult patients (≥ 16 years of age) who presented to the ED with TBI wore a bicycle helmet significantly less often than adult patients that presented with other trauma. Therefore, wearing a bicycle helmet appears to effectively protect against TBI. However, when focusing on adult cyclists who experienced a motorized vehicle collision (MVC) we found no indication for a reduced risk of TBI because of bicycle helmet use.

In recent years there has been a fierce discussion about the use, active promotion, or even obligation of bicycle helmets. On one side of the spectrum are the promotors of bicycle helmets who claim that it is a good way to halt the growing incidence of bicycle related TBI especially in vulnerable groups such as children and elderly.[22,25,30-32] On the other end of the spectrum there is fierce opposition to active promotion or obligatory use of bicycle helmets. Opponents of (obligatory) helmet use doubt the protection offered by helmets and fear that obligatory helmet use will lead to decline in cycling.[13,24,33,34]

In our control group 7.7% of patients wore a helmet, which is comparable to results of a survey conducted in 2008, in which 7.5% of all cyclists with a self-reported speed of less than 25km/h without head injury wore a helmet (unpublished data, obtained from VeiligheidNL).[35] In our control group helmet use is still very infrequent on commuter bicycles (0.8%), but high on racing bikes (75%) and mountain bikes (49%). These results are all comparable to those in the 2008 survey.

The results of this study appear to show that helmet use in cyclists reduces the risk of TBI. However, the case-control design of the study makes it impossible to draw firm conclusions regarding a causal relationship or magnitude of this relationship. Opponents of this theory point out that another explanation for the observed OR is that cyclists with helmet-use are more often sports cyclists (mountain bikers and racing cyclists) who according to some might have relatively more non-TBI trauma than other cyclists.[36] Our results do not support this explanation, as the ratio between TBI and non-TBI was not different for (non-helmet wearing) sports cyclists compared to those on normal bicycles.

We found no significant relationship between bicycle helmet use and (reduced) risk of TBI when bicyclists were involved in MVCs. This could be explained by the fact that bicycle helmets are designed to protect against an impact of approximately 20km/h, in most MVCs the impact is likely to be (much) higher.[37] The assumed

larger protective effect in one-sided bicycle crashes compared with bicycle-MVCs is in line with an earlier study.[38] However, this does not have to discredit the bicycle helmet use because motorized vehicles were involved in a minority of TBIs in our study. This is in line with other research on this subject that also shows that in the majority of the patients with TBI no motorized vehicles were involved.[25]

Strengths and limitations

The current study is the first study of its kind in the Netherlands. Strengths of the study are the large number of participants and the detailed information obtained. Limitations of our study include the lack of exact information about the bicycle helmet use in the Netherlands in non-injured cyclists. Therefore, we used patients who presented to the ED without head injury as a control group as we had exact information about helmet use in that group. In addition, bicycle helmet use in our study (7.7% in the control group) was comparable to a survey in 2008 that showed a bicycle helmet use of 7.5% in patients without head injury.[35] Another related limitation is the case-control design of the study; therefore only association and no causal relationship between helmet use and TBI can be proven. Also, the response rate of 37% is an additional limitation of this study. The primary analysis was conducted using the unweighted results, hence not corrected for selective non-response. Therefore, these results may not be representative for the entire LIS population. To take this into account a sensitivity analysis, corrected for selective non-response in certain demographic groups, was also performed.

Possible selective non-response based on injury severity is not known and could not be corrected for. However, we have no indication that this affected patients with or without helmets unevenly.

Conclusions

In this study we found that patients with TBI due to bicycle accidents did not wear helmets as often as a comparable control group. This association could not be established for patients with TBI as a result of a collision between a bicycle and a motorized vehicle. This study has some limitations, but the results strongly suggest that TBI in adult cyclists could be reduced if cyclists in the Netherlands would wear a helmet more often. Future research should focus on establishing the exact frequency of bicycle helmet use in the Netherlands and ways to promote this without discouraging cycling.

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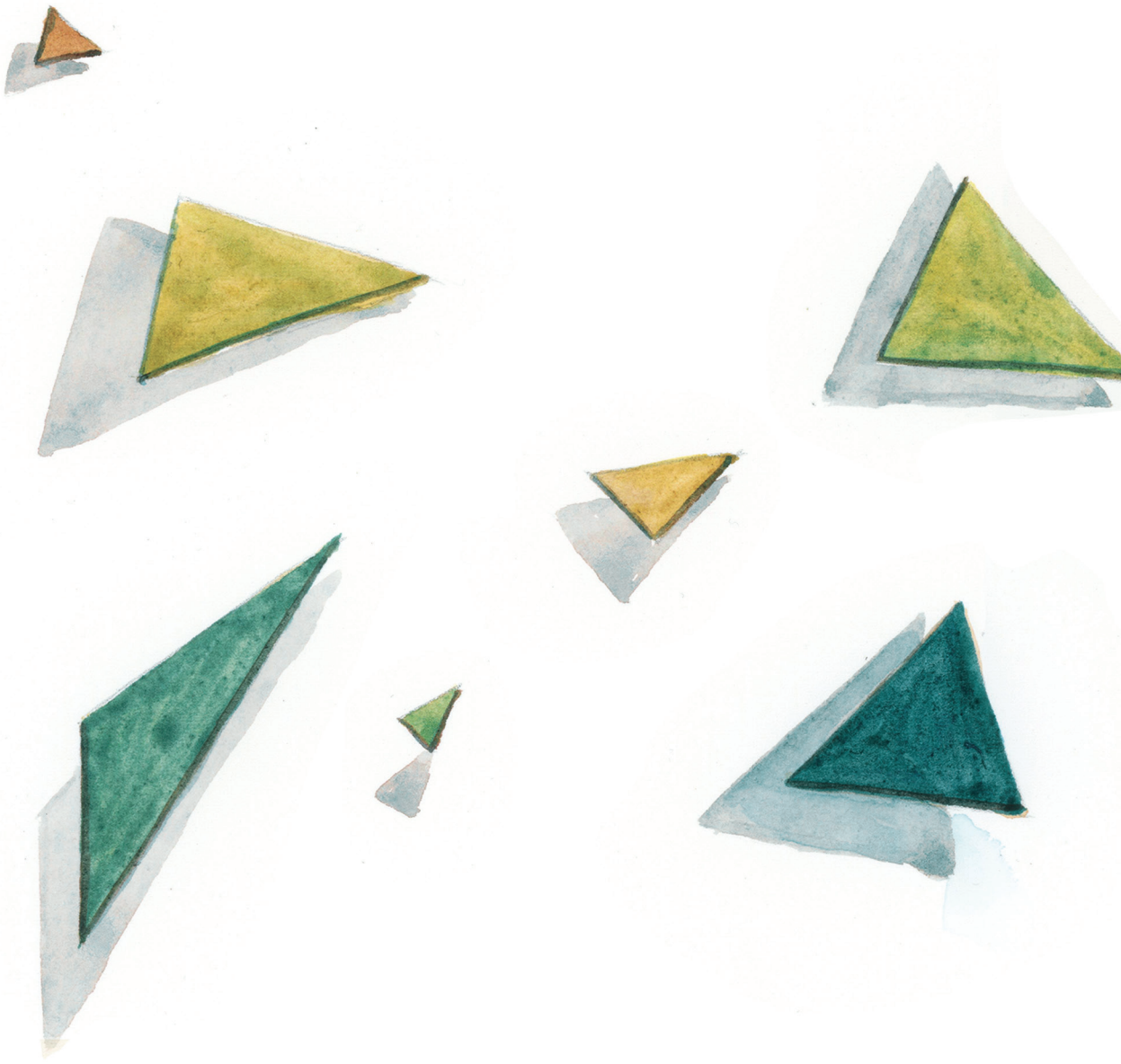
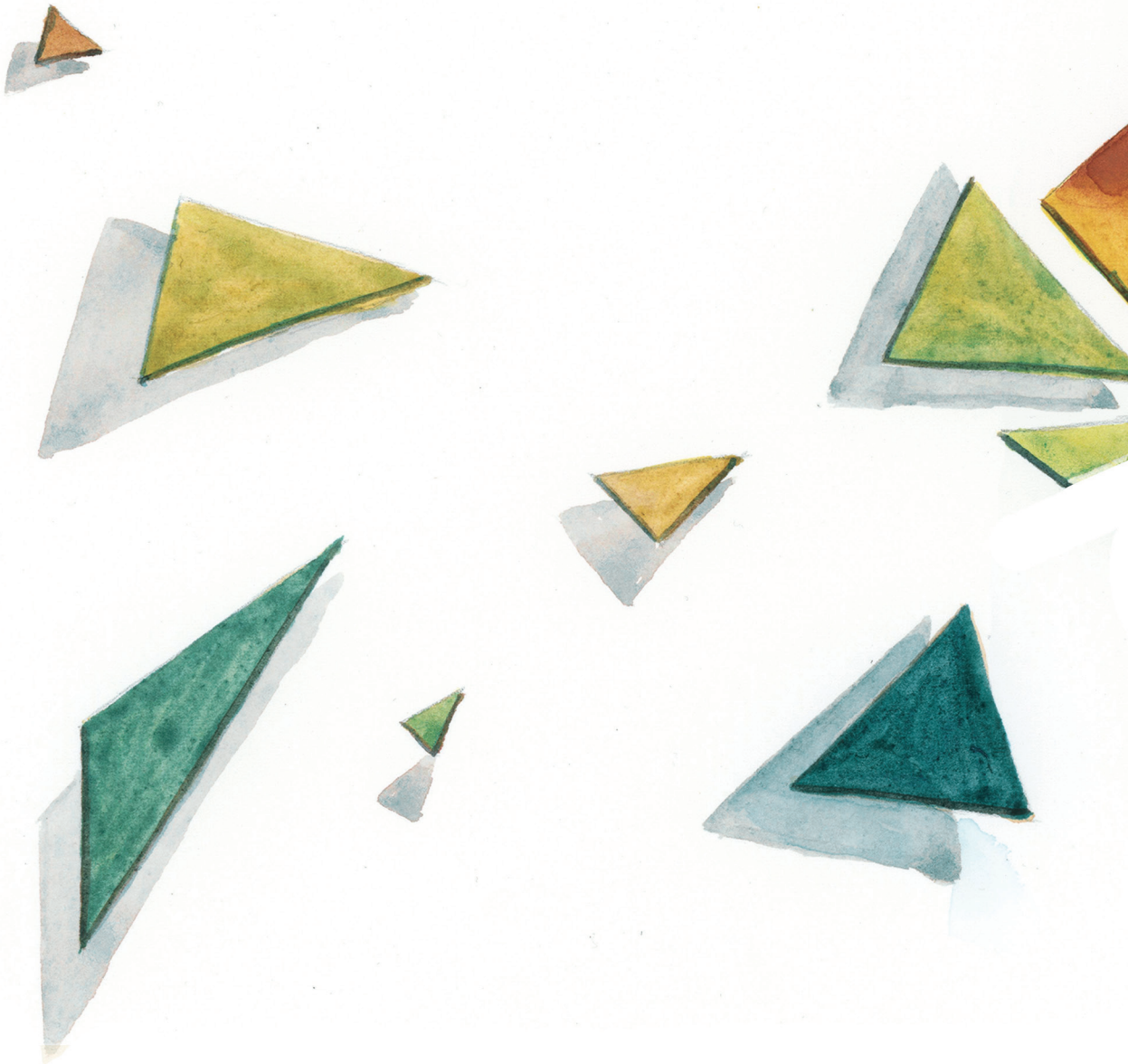


PART III

Decision rules for patients with minor head injury and mild traumatic brain injury



CHAPTER 6

External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands

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ABSTRACT

Objective

To externally validate four commonly used computed tomography (CT) decision rules for minor head injury (MHI).

Design and Setting

Prospective multicenter cohort study in three university and six non-university hospitals in the Netherlands.

Participants

Consecutive adult patients aged 16 years and over who presented with MHI at the emergency department with a Glasgow Coma Scale score of 13-15 between March 2015 and December 2016.

Main outcome measures

The primary outcome was any intracranial traumatic finding on CT; the secondary outcome was a potential neurosurgical lesion on CT. We compared the sensitivity, specificity and clinical usefulness, (defined as net benefit, a weighted sum of true positive classifications) of four CT decision rules: CT in Head Injury Patients (CHIP) rule; New Orleans Criteria (NOC); Canadian CT Head Rule (CCHR); and National Institute for Health and Care Excellence (NICE) guideline for head injury.

Results

For the primary analysis, only six centers that included patients with and without CT were selected. Of 4557 eligible patients who presented with minor head injury, 3742 (82%) received a CT scan; 384 (8%) had a intracranial traumatic finding on CT, and 74 (2%) had a potential neurosurgical lesion. The sensitivity for any intracranial traumatic finding on CT ranged from 73% (NICE) to 99% (NOC); specificity ranged from 4% (NOC) to 61% (NICE). Sensitivity for a potential neurosurgical lesion ranged between 85% (NICE) and 100% (NOC); specificity from 4% (NOC) to 59% (NICE). Clinical usefulness depended on thresholds for performing CT scanning: the NOC rule was preferable at a low threshold, the NICE rule was preferable at a higher threshold, whereas the CHIP rule was preferable for an intermediate threshold.

Conclusions

Application of the CHIP, NOC, CCHR, or NICE decision rules can lead to a wide variation in CT scanning among patients with minor head injury, resulting in many unnecessary CT scans and some missed intracranial traumatic findings. Until an existing decision rule has been updated, any of the four rules can be used for patients presenting minor head injuries at the emergency department. Use of the CHIP rule is recommended because it leads to a substantial reduction in CT scans while missing few potential neurosurgical lesions.

Introduction

Minor head injury (MHI) or mild traumatic brain injury is a common injury increasingly seen in emergency departments.[1,2] Possible causes for this increase are ageing of the population and increased awareness of the potential intracranial complications of MHI among general practitioners and paramedics.[3,4] Although the risk of intracranial complications after MHI is low, the consequences are important as these patients require close observation and sometimes even neurosurgical intervention.[5] Several clinical decision rules exist that aim to identify those patients with MHI who are at high risk for intracranial complications and need computed tomography (CT) of the head. Examples of frequently used decision rules are: the New Orleans Criteria (NOC); Canadian CT Head Rule (CCHR); and the National Institute for Clinical Excellence (NICE) guideline for Head injury (Supplementary Table 1).[6-8]

The purpose of these rules is to detect all relevant intracranial traumatic lesions while minimizing the number of unnecessary CT scans. Relevant lesions are those that need neurosurgical intervention or prolonged clinical observation because of a risk of neurological deterioration. Although the number of patients that present at the emergency departments with MHI has increased substantially, the overall incidence of disease specific mortality after head injury has remained fairly stable.[9] An increased number of patients leads to more CT scans, longer waiting times at the emergency department, burden for the patients, radiation risks, and higher costs.[10] The need for reliable CT decision rules for MHI to reduce unnecessary CT scans is therefore even more apparent.

Two of the decision rules have been developed for patients who had had blunt trauma to the head, have a Glasgow Coma Scale (GCS) of 13-15 at presentation, and have experienced loss of consciousness (LOC) and/or posttraumatic amnesia (PTA).[6,7] However, these rules cannot be applied to patients without LOC or PTA.[11,12] Therefore a new decision rule was developed, the CT in Head Injury Patients (CHIP) rule, which includes patients with and without LOC or PTA.[13] The potential reduction of CT scans by use of the CHIP rule was estimated at 23% compared to scanning of all patients.[13]

The NOC, CCHR and NICE guideline were externally validated in previous studies, but there has been no external validation of the CHIP rule, even though this is necessary to determine whether the rule is generally applicable.[14-21] Our aim was to perform an external validation of frequently used CT decision rules for MHI (CHIP, NOC, CCHR, NICE) and compare their performance in a multicenter study in the Netherlands in university and non-university hospitals.

Methods

Study design

We conducted a prospective, multicenter cohort study between March 2015 and December 2016 in the Netherlands. Three university emergency departments (all level 1 trauma centers) and six non-university emergency departments (trauma level 1 (two centers), trauma level 2 (two centers) and trauma level 3 (two centers)) participated in this study. The emergency departments were all situated at an urban location. Institutional ethics and research board approval was obtained and informed consent was waived.

Inclusion criteria were age 16 years and over, presentation within 24 hours after blunt trauma to the head and a GCS score of 13-15 at presentation at the emergency department. Patients with and without LOC or PTA were included. We excluded all patients with a GCS score less than 13, patients younger than 16 years, transferred from other hospitals or with any contra-indication for CT.

Definition of risk factors

Clinical data concerning risk factors for intracranial complications used in the CCHR, NOC, NICE and CHIP decision rules were collected.[6-8,13] These clinical risk factors were: age, history of coagulopathy, use of anticoagulants, dangerous trauma mechanism (pedestrian/cyclist versus vehicle, ejected from vehicle, fall from elevation (more than 1 meter or 5 stairs) or an equivalent mechanism), fall from any elevation, loss of consciousness reported by patient or witness (presence and duration), retrograde amnesia (presence and duration), posttraumatic amnesia (presence and duration), headache, vomiting (frequency), intoxication with drugs or alcohol (history or suggestive findings on examination), posttraumatic seizure, GCS score on presentation, significant injury above clavicles, suspected open or depressed skull fracture, contusion of skull, clinical signs of skull base fracture (for example: raccoon eyes, battle sign, hemotympanum, CSF otorrhea, CSF rhinorrhea, palpable discontinuity, bleeding from ear), neurological deficit (paresis, dysphasia or other such as cranial nerve damage including diplopia, changes in sensibility, asymmetrical reflexes or pathological reflexes, coordination problems and ataxia), GCS deterioration 1 hour after presentation.

Main outcome measures

The primary outcome was any intracranial traumatic finding on CT, defined as a subdural hematoma, epidural hematoma, subarachnoid hemorrhage, cerebral lesions (hemorrhagic contusion, non-hemorrhagic contusion, diffuse axonal injury), intraventricular hemorrhage, and skull fracture. The secondary outcome was any

potential neurosurgical lesion, which was defined as an intracranial traumatic finding on CT which could lead to a neurosurgical intervention or death. Examples of potential neurosurgical lesions are an epidural hematoma, large acute subdural hematoma (mass), large contusion(s) (mass), depressed skull fracture, and any lesion with a midline shift or herniation. To compare our findings with previous studies we also assessed the performance of decision rules for detecting neurosurgical interventions. All outcome measures were chosen a priori.

Study procedures

During patient inclusion in the study, neurologists (in training) and emergency physicians (in training) followed their local guideline for CT scanning in patients with MHI. Most participating centers used the same national guideline based on the CHIP rule, two centers followed a slightly adapted guideline (Supplementary Table 2).

Eligible patients were consecutively included by trained researcher physicians, who did not personally interview the patients. Clinical data were collected before diagnostic tests as far as possible by using forms the clinicians could fill in for each patient. The head CT scans were performed according to a routine trauma protocol at each hospital. The CT scans were interpreted by (neuro)radiologists who were aware of the patient's history and clinical findings, but they were not aware of the actual score of the CT decision rules.

The clinical risk factors were collected by taking the patient's history or information from a witness or family member. Characteristics such as injury severity score were also collected. All patients' details about hospital admission, neurosurgical intervention, and moment of discharge were collected. If the patient was scanned, details about CT findings were recorded. The electronic health records were reviewed 30 days after the injury to assess follow-up information about a neurosurgical intervention. All data were entered by researcher physicians in the case report forms of the web based data management system OpenClinica (LCC, version 3.12.2).

Data management

After patient inclusion and data entering, two authors (KAF and CLvdB) checked the database for correct patient inclusion and completeness of data using IBM statistical package for social sciences (SPSS) version 21. Missing data were assumed to be missing at random; so to avoid bias, missing data were imputed on the basis of all the risk factors mentioned above, using multiple imputation (n=5) with the "multivariate imputation by chained equations" function in R, version 3.3.2 (R foundation for statistical computing).

Data analysis

The study population was described in terms of demographic characteristics, risk factors, admission to the hospital, and neurosurgical intervention. In patients with a CT scan, we also evaluated any intracranial traumatic findings and potential neurosurgical lesions on CT. Continuous variables were described as mean and interquartile range, categorical variables as frequencies and percentages.

The diagnostic performance of the CHIP, NOC, CCHR, and NICE decision rules for detecting intracranial traumatic findings and potential neurosurgical lesions were compared. Because the NOC and CCHR rules were developed in a specific patient population, we performed the analysis in our entire study population, as well as in a subset of the study population (based on the inclusion/exclusion criteria of the development studies of the NOC and CCHR; referred to as original NOC and original CCHR), and in our entire study population with adjustment of the rules. In the adjusted rules, the exclusion criteria of the NOC and CCHR rules were added as additional risk factors (referred to as adjusted NOC and adjusted CCHR). For the NOC rule, a Glasgow coma scale score of 13 or 14 and presence of neurological deficit were added. Finally, for the CCHR rule, use of anticoagulation, post-traumatic seizure, and presence of neurological deficit were added. All patients who had a risk factor according to the NOC or CCHR rules scored positive on these rules, indicating that they needed a CT scan.

The sensitivity, specificity, and proportion of patients needing a CT scan (with 95% confidence intervals) were assessed for each of the four decision rules. Sensitivity was calculated by dividing the number of patients in whom the outcome measure was present and the decision rule was positive, by the total number of patients in whom the outcome measure was present. Specificity was calculated by dividing the number of patients in whom the outcome measure was absent and the decision rule was negative, by the total number of patients in whom the outcome measure was absent. The Cochran's Q test was used to directly compare the sensitivities and specificities between the four decision rules, but it should be noted that results of this test do not automatically imply that any one rule is better than the other.[22] The proportion of patients needing a CT scan was calculated by dividing the number of patients in whom the decision rule was positive by the total number of patients. Confidence intervals were calculated by a bootstrapping method in R, which analyses the performance for each rule 500 times and derived the confidence intervals from the results.

In patients without a CT scan the outcomes could not be observed. In these patients the expected outcomes (any intracranial traumatic finding and potential neurosurgical lesion) were imputed based on their risk factors with multiple

imputation, in order to avoid selection bias and thus yield unbiased estimates of sensitivity and specificity.[23] This imputation was possible for patients from six of the nine centers, because the other three centers had not included patients without a CT scan. The patients with and without CT scans (with imputed outcomes) from these six centers were used for the primary analysis. In addition, we analyzed all patients with a CT scan from all the centers in a secondary (sensitivity) analysis, which in theory would lead to an overestimation of sensitivity and underestimation of specificity of all the rules.

In this decision problem, avoiding false negatives was more important than avoiding false positives: a false negative result leads to not performing a CT scan and thus potentially misses a lesion, whereas a false positive result leads to performing an unnecessary CT scan. The decision rule should identify all patients with potential neurosurgical lesions and most with intracranial traumatic findings, because of the severe clinical consequences (intracranial surgery, neurological sequelae, death).

Net proportional benefit has been proposed to incorporate such weighting in calculation of clinical usefulness of decision rules.[24,25] For each rule, we expressed the net proportional benefit using the formula: (true positives/total number) - weight×(false positives/total number). Over a range of different weights, the net proportional benefit was calculated and compared with the scanning of all patients. The weight in this formula expresses the ratio of harmful consequences due to a false positive divided by the harmful consequences of a false negative, and it is equivalent to the odds of a lesion above which one would perform a CT scan. At a low threshold for performing CT, we would avoid false negatives of the decision rule (that is, maximize true positives) at the cost of performing many CT scans: if the threshold is 1%, this level implies performing 100 CT scans to avoid one missed lesion. At a higher threshold for performing CT, we would avoid false positives of the decision rule: if the threshold is 10%, this level implies performing 10 CT scans to avoid one missed lesion. We considered an intermediate range of thresholds (4-6% for any traumatic finding and 0.5%-1% for potential neurosurgical lesion) acceptable from a clinical point of view.[24,26] Net proportional benefit expresses the true positives and the decision rule with the highest net benefit at the intermediate thresholds has the highest clinical value.[24] All statistical analyses were performed using R software, version 3.3.2 (R foundation for statistical computing, Vienna, Austria).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are plans to disseminate the results of the research to the relevant patient community.

Results

Between March 2015 and December 2016, 5839 consecutive patients with MHI were entered in the database in the participating centers (Figure 1). After checking the in- and exclusion criteria 322 patients were excluded from the study (GCS score < 13, age < 16 years or no blunt head injury). In three out of nine centers only patients with a CT were included (n=960). The remaining six centers included patients with and without a CT (n=4557).

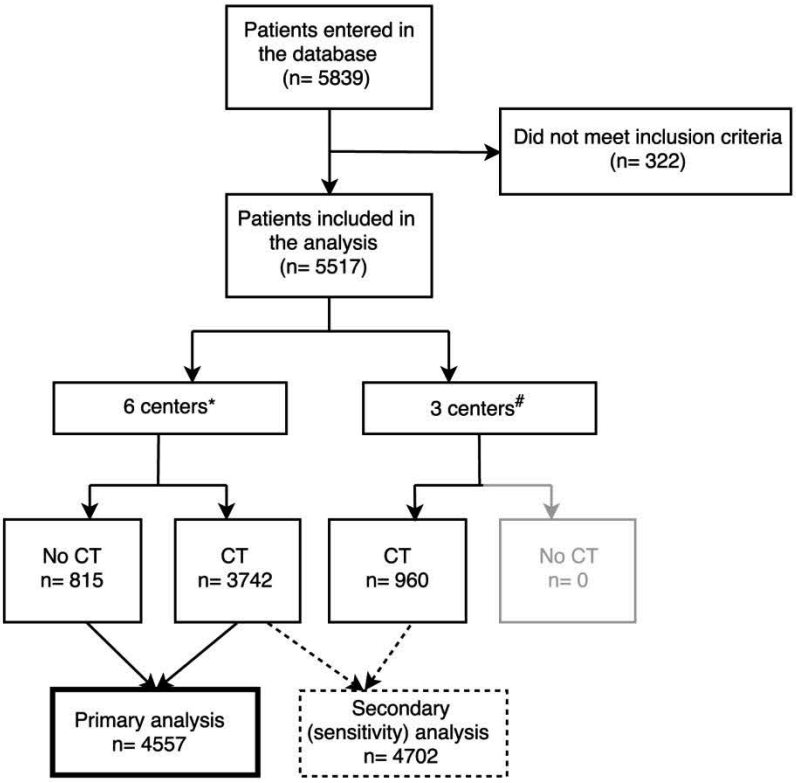

Figure 1. Study flow diagram.

*Six centers=one university center (trauma level 1) and five non-university centers (trauma levels 1 (two centers), 2 (one), 3 (two)), including patients with and without CT scans; three centers=two university centers (both trauma level 1) and one non-university center (trauma level 2), including only patients with a CT scan. CT=computed tomography

For the primary analysis 4557 patients from six centers were included; 3742 patients (82.1%) received a CT scan and 815 (17.9%) did not. Compared with patients who received a CT scan, more patients without a scan had a Glasgow coma scale score of 15 (n=3109 (83.1%) v n=805 (98.8%)), and fewer patients experienced loss of consciousness (n=1136 (30.3%) v n=56 (6.8%)) or post-traumatic amnesia (n=1075 (28.7%) v n=29 (3.5%); Table 1). Some data were unknown to the including physician, which was most frequently the case for retrograde amnesia (n=675, 14.8%), loss of consciousness (n=651, 14.3%), post-traumatic amnesia (n=502, 11%), and headache (n=630, 13.8%; Table 1).

Table 1. Baseline characteristics of 4557 study patients from six centers*.

	All patients (n=4557)	**Missing**	**Patients with CT (n=3742)**	**Patients without CT (n=815)**
Age mean in years (range)	53.1 (16-101)	-	56.9 (16-101)	35.7 (16-96)
Sex, n male (%)	2656 (58.3%)	-	2145 (57.3%)	511 (62.7%)
GCS score at presentation		-		
• GCS 13	143 (3.1%)		141 (3.8%)	2 (0.2%)
• GCS 14	500 (11.0%)		492 (13.1%)	8 (1.0%)
• GCS 15	3914 (85.9%)		3109 (83.1%)	805 (98.8%)
Use of anticoagulation		29 (0.6%)		
• None	4045 (88.8%)		3233 (86.4%)	812 (99.6%)
• Coumarin	418 (9.2%)		418 (11.2%)	-
• Direct oral anticoagulants	54 (1.2%)		53 (1.4%)	1 (0.1%)
Use of thrombocyte aggregation inhibitors	615 (13.5%)	33 (0.7%)	577 (15.4%)	38 (4.7%)
Bleeding disorder	44 (1%)	33 (0.7%)	41 (1.1%)	3 (0.4%)
Mechanism of injury		47(1.0%)		
• Road traffic accident pedestrian	64 (1.4%)		57 (1.5%)	7 (0.9%)
• Road traffic accident cyclist	162 (3.6%)		152 (4.1%)	10 (1.2%)
• Fall from height	574 (12.6%)		532 (14.2%)	42 (5.2%)
• Other†	3710 (81.4%)		2955 (79.0%)	755 (92.6%)
Ejected from vehicle	150 (3.3%)	56 (1.2%)	135 (3.6%)	15 (1.8%)
Loss of consciousness		651 (14.3%)		
• None	2714 (59.6%)		1968 (52.6%)	746 (91.5%)
• 15 minutes or less	1160 (25.5%)		1105 (29.5%)	55 (6.7%)
• More than 15 minutes	32 (0.7%)		31 (0.8%)	1 (0.1%)

Table 1. Continued

	All patients (n=4557)	**Missing**	**Patients with CT (n=3742)**	**Patients without CT (n=815)**
Retrograde amnesia		675 (14.8%)		
• None	3425 (75.2%)		2637 (70.5%)	788 (96.7%)
• 30 minutes or less	312 (6.8%)		303 (8.1%)	9 (1.1%)
• More than 30 minutes	145 (3.2%)		144 (3.8%)	1 (0.1%)
Posttraumatic amnesia		502 (11%)		
• None	2951 (64.8%)		2185 (58.4%)	766 (94.0%)
• Up to 2 hours	976 (21.4%)		948 (25.3%)	28 (3.4%)
• 2-4 hours	69 (1.5%)		68 (1.8%)	1 (0.1%)
• More than 4 hours	59 (1.3%)		59 (1.6%)	-
Intoxication with drugs or alcohol	1031 (22.6%)	85 (1.9%)	922 (24.6%)	109 (13.4%)
Posttraumatic seizure	36 (0.8%)	68 (1.5%)	33 (0.9%)	3 (0.4%)
Headache	1410 (30.9%)	630 (13.8%)	1208 (32.3%)	202 (24.8%)
Vomiting		50 (1.1%)		
• Once	158 (3.5%)		148 (4.0%)	10 (1.2%)
• Twice or more	144 (3.2%)		142 (3.8%)	2 (0.2%)
GCS deterioration (after 1 hr)		23 (0.5%)		
• 1 point	38 (0.8%)		38 (1.0%)	-
• 2 or more points	12 (0.3%)		12 (0.3%)	-
Neurological deficit‡	130 (2.9%)	141 (3.1%)	128 (3.4%)	2 (0.2%)
Signs of skull base fracture	144 (3.2%)	25 (0.5%)	139 (3.7%)	5 (0.6%)
Visible injury of the head	2564 (56.3%)	19 (0.4%)	2208 (59%)	356 (43.7%)
Visible injury of the face	1631 (35.8%)	22 (0.5%)	1315 (35.1%)	316 (38.8%)
Suspicion of open fracture	11 (0.2%)	40 (0.9%)	11 (0.3%)	-
Injury Severity Score, mean (range)	6.5 (0-75)	-	7.1 (0-75)	3.5 (0-29)

Data are number (%) of patients unless stated otherwise. CT=computed tomography.
*These centers refer to those on the left-hand side of figure 1, for the primary analysis.
†Includes patients with mild head injury such as a bumped head against an object.
‡History or suggestive findings on examination (eg, nystagmus, abnormal walking).

In 384 patients (8.4%), CT showed an intracranial traumatic finding, mostly consisting of traumatic subarachnoid hemorrhages (n=182; 4.0%) and skull fractures (n=150; 3.3%; Table 2). Of 74 (1.6%) patients with a potential neurosurgical lesion, 18 (0.4%) underwent a neurosurgical intervention for head injury within 30 days after the injury.

In 116 of 3742 patients without LOC and in 117 of 3742 patients without PTA an intracranial traumatic finding was found (Table 3). In total 20 patients without LOC had a potential neurosurgical lesion and four patients underwent a neurosurgical intervention. In patients without PTA, 14 had a potential neurosurgical lesion and three patients underwent a neurosurgical intervention.

Table 2. Traumatic CT findings in 3742 patients with a CT scan from six centers*

CT finding	**N (%)**
CT finding†	384 (8.4%)
Skull fracture	150 (3.3%)
• Depressed fracture	19 (0.5%)
• Linear fracture	66 1.4%)
• Skull base fracture	68 (1.5%)
Subarachnoid hemorrhage	182 (4.0%)
Contusion	
• Small	115 (2.5%)
• Large (mass)	10 (0.2%)
Subdural hematoma	
• Small	126 (2.8%)
• Large (mass)	22 (0.5%)
Epidural hematoma	
• Small	30 (0.7%)
• Large (mass)	5 (0.1%)
Suspicion of DAI on CT	13 (0.3%)
Basal cisterns compressed or obliterated	11 (0.2%)
CT shift	
• 0-4mm	16 (0.4%)
• 5mm or more	9 (0.2%)

CT = computed tomography, DAI = diffuse axonal injury

*These centers refer to those on the left-hand side of figure 1, for the primary analysis.

†some patients had more than 1 CT finding

In a subgroup analysis of the 3914 patients with a Glasgow coma scale score of 15, more than half the patients (n=2465, 63%) had no loss of consciousness and no post-traumatic amnesia. Ninety-three (3.8%) patients had any intracranial traumatic finding, seven (0.3%) had a potential neurosurgical lesion, and one underwent a neurosurgical intervention.

Table 3. Baseline characteristics of 3742 patients with a CT scan from six centers*, according to status of CT findings

	Normal CT (n=3358)	**Abnormal CT (n=384)**	**All patients with CT (n=3742)**
Age mean in years (range)	56.6 (16-101)	59.1 (17-98)	56.9 (16-101)
Sex, n male (%)	1901 (56.6)	244 (63.5%)	2145 (57.3%)
GCS score at presentation			
• GCS 13	94 (2.8%)	47 (12.2%)	141 (3.8%)
• GCS 14	401 (11.9%)	91 (23.7%)	492 (13.1%)
• GCS 15	2863 (85.3%)	246 (64.1%)	3109 (83.1%)
Use of anticoagulation			
• None	2886 (85.9%)	347 (90.4%)	3233 (86.4%)
• Coumarin	387 (11.5%)	31 (8.1%)	418 (11.2%)
• Direct oral anticoagulants	50 (1.5%)	3 (0.8%)	53 (1.4%)
Use of thrombocyte aggregation inhibitors	502 (15.0%)	75 (19.5%)	577 (15.4%)
Bleeding disorder	39 (1.2%)	2 (0.5%)	41 (1.1%)
Mechanism of injury			
• Road traffic accident	48 (1.4%)	9 (2.3%)	57 (1.5%)
Pedestrian			
• Road traffic accident cyclist	127 (3.8%)	25 (6.5%)	152 (4.1%)
• Fall from height	451 (13.4%)	81 (21.1%)	532 (14.2%)
• Other†	2691 (80.1%)	264 (68.8%)	2955 (79%)
Ejected from vehicle	120 (3.6%)	15 (3.9%)	135 (3.6%)
Loss of consciousness			
• None	1852 (55.2%)	116 (30.2%)	1968 (52.6%)
• 15 minutes or less	943 (28.1%)	162 (42.2%)	1105 (29.5%)
• More than 15 minutes	21 (0.6%)	10 (2.6%)	31 (0.8%)
Retrograde amnesia			
• None	2443 (72.8%)	194 (50.5%)	2637 (70.5%)
• 30 minutes or less	251 (7.5%)	52 (13.5%)	303 (8.1%)
• More than 30 minutes	102 (3.0%)	42 (10.9%)	144 (3.8%)
Posttraumatic amnesia			
• None	2068 (61.6%)	117 (30.5%)	2185 (58.4%)
• Up to 2 hours	776 (23.1%)	172 (44.8%)	948 (25.3%)
• 2-4 hours	54 (1.6%)	14 (3.6%)	68 (1.8%)
• More than 4 hours	38 (1.1%)	21 (5.5%)	59 (1.6%)
Intoxication *	836 (24.9%)	86 (22.4%)	922 (24.6%)
Posttraumatic seizure	26 (0.8%)	7 (1.8%)	33 (0.9%)
Headache	1086 (32.3%)	122 (31.8%)	1208 (32.3%)

Table 3. Continued

	Normal CT (n=3358)	Abnormal CT (n=384)	All patients with CT (n=3742)
Vomiting			
• Once	131 (3.9%)	17 (4.4%)	148 (4.0%)
• Twice or more	119 (3.5%)	23 (6.0%)	142 (3.8%)
GCS deterioration (after 1 hr)			
• 1 point	33 (1.0%)	5 (1.3%)	38 (1.0%)
• 2 or more points	6 (0.2%)	6 (1.6%)	12 (0.3%)
Neurological deficit ‡	100 (3.0%)	28 (7.3%)	128 (3.4%)
Signs of skull base fracture	89 (2.7%)	50 (13.0%)	139 (3.7%)
Visible injury of the head	1945 (57.9%)	263 (68.5%)	2208 (59%)
Visible injury of the face	1181 (35.2%)	134 (34.9%)	1315 (35.1%)
Suspicion of open fracture	6 (0.2%)	5 (1.3%)	11 (0.3%)
Injury Severity Score, mean (range)	6.2 (0-54)	15.2 (1-75)	7.1 (0-75)

Data are number (%) of patients unless stated otherwise. CT=computed tomography.
*These centers refer to those on the left-hand side of figure 1, for the primary analysis.
†Includes patients with mild head injury such as a bumped head against an object.
‡History or suggestive findings on examination (eg, nystagmus, abnormal walking).

Of all 4557 patients, 1511 (33.2%) were admitted to the hospital for head injury and other reasons. Of the admitted patients, 226 (5.0%) were admitted for two nights or longer because of head injury; 52 (1.1%) had neurological deterioration during admission, and six (0.1%) were intubated for longer than 24 h. Eleven (0.2%) patients died as a result of head injury, and 21 (0.5%) died as a result of a different illness or trauma.

Performance of the decision rules

After imputation of outcomes in patients without a CT scan, 23 of 815 patients had any intracranial traumatic finding and no patient had a potential neurosurgical lesion. None of these 815 patients without a CT scan had undergone a neurosurgical intervention in 30 days after injury. The sensitivity for identifying patients with any intracranial traumatic finding on CT ranged from 72.5% for the NICE criteria to 98.8% for the NOC (Table 4; Supplementary Figure 1).

Table 4. Performance of the four decision rules* used for CT in 4557 patients with minor head injury presenting at six centers†

	Positive	**Negative**
	n	**n**
CHIP n=4557		
Any traumatic finding on CT		
CHIP - Positive	383	3253
CHIP - Negative	24	897
Potential neurosurgical lesion		
CHIP - Positive	72	3564
CHIP - Negative	2	919
NICE n=4557		
Any traumatic finding on CT		
NICE - Positive	295	1624
NICE - Negative	112	2526
Potential neurosurgical lesion		
NICE - Positive	63	1856
NICE - Negative	11	2627
NOC n=4557		
Any traumatic finding on CT		
NOC - Positive	402	3966
NOC - Negative	5	184
Potential neurosurgical lesion		
NOC - Positive	74	4294
NOC - Negative	0	189
CCHR n=4557		
Any traumatic finding on CT		
CCHR - Positive	327	2314
CCHR - Negative	80	1836
Potential neurosurgical lesion		
CCHR - Positive	65	2576
CCHR - Negative	9	1907

*CHIP=CT in head injury patient rule; NICE=National Institute for Health and Care Excellence guideline for head injury; NOC=New Orleans criteria; CCHR=Canadian CT head rule. †These centers refer to those on the left-hand side of figure 1, for the primary analysis.

	Sensitivity % (CI)	Specificity % (CI)	Positive likelihood ratio (CI)	Negative likelihood ratio (CI)
	94.1 (91.5 to 96.3)	21.6 (20.4 to 22.9)	1.20 (1.16 to 1.23)	0.27 (0.17 to 0.40)
	97.3 (93.1 to 100)	20.5 (19.4 to 21.7)	1.22 (1.17 to 1.26)	0.13 (0 to 0.34)
	72.5 (67.8 to 77.2)	60.9 (59.3 to 62.5)	1.85 (1.72 to 2.0)	0.45 (0.37 to 0.53)
	85.1 (76.4 to 92.9)	58.6 (57.1 to 60.1)	2.06 (1.84 to 2.27)	0.25 (0.12 to 0.40)
	98.8 (97.6 to 99.8)	4.4 (3.8 to 5.1)	1.03 (1.02 to 1.05)	0.28 (0.06 to 0.53)
	100 (100 to 100)	4.2 (3.6 to 4.8)	1.04 (1.04 to 1.05)	0 (0 to 0)
	80.3 (76.1 to 84.2)	44.2 (42.7 to 45.9)	1.44 (1.35 to 1.52)	0.44 (0.36 to 0.55)
	87.8 (79.7 to 94.9)	42.5 (41.0 to 44.1)	1.53 (1.40 to 1.66)	0.29 (0.12 to 0.47)

The sensitivity for identifying patients with potential neurosurgical lesions was 100% for NOC, the NICE criteria had the lowest sensitivity (85.1%) for identifying potential neurosurgical lesions (Table 4). The NICE criteria would have missed 11/74 patients with potential neurosurgical lesions (Supplementary Table 3). The CHIP criteria would have missed two patients with potential neurosurgical lesions, these patients both had a small epidural hematoma, which did not need neurosurgical treatment and one of them had surgery to repair a depressed skull fracture (Supplementary Table 3).

The specificity for identifying any intracranial traumatic finding was lowest for the NOC (4.4%) and highest for the NICE criteria (60.9%). The specificity for potential neurosurgical lesions ranged from 4.2% (NOC) to 58.6% (NICE criteria). The sensitivity and specificity differed significantly between all the rules (Cochran's Q, $P < 0.001$). Sensitivity and specificity for the original CCHR and NOC were slightly different from the adjusted versions (see the methods section for definition of the original and adjusted groups; (Supplementary Table 4A, 4B). For the outcome of neurosurgical intervention, the NOC rule had the highest sensitivity (100%) and the NICE criteria the highest specificity (58.1%; (Supplementary Table 5).

Clinical usefulness

The decision curve of the NOC rule was almost identical to CT scanning all patients in both study outcomes (Figure 2). When using a low threshold for performing CT (to avoid false negatives of the decision rule), we found that the NOC rule and the scanning of all patients had the highest net proportional benefit. When using a high threshold for performing CT (to avoid false positives), we found that the NICE criteria had the highest net proportional benefit (Figure 2). Over a narrow range of intermediate thresholds, the CHIP criteria had the highest net proportional benefit (0.038-0.054 for intracranial traumatic findings and 0.008-0.012 for potential neurosurgical lesions). For the neurosurgical intervention outcome, the differences in net proportional benefit were small (Supplementary Figure 2).

Proportion of patients needing CT

According to the different decision rules the proportion of the study population needing CT was 95.9% (95% confidence interval 95.3% to 96.5%) with the NOC; 79.8% (78.6% to 80.9%) with the CHIP criteria; 58.0% (56.4% to 59.4%) with the CCHR and 42.1% (40.6% to 43.6%) with the NICE criteria. To increase the sensitivity of the CHIP criteria to the level of the NOC, 733 more CTs would have been needed to identify 19 more patients with intracranial traumatic findings and two more patients with a potential neurosurgical lesion.

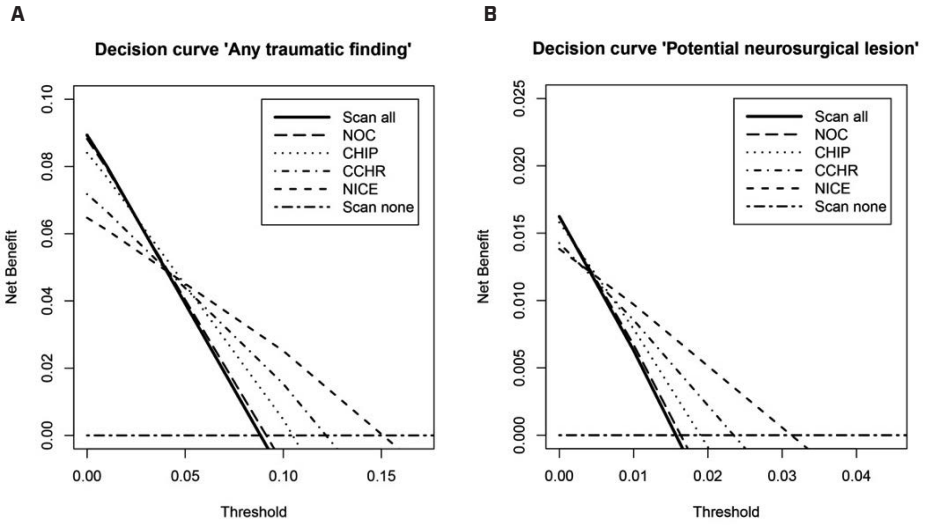

Figure 2.

Decision curves for study outcomes showing net proportional benefit per CT decision rule

CT=computed tomography; CHIP=CT in head injury patient rule; NICE=National Institute for Health and Care Excellence guideline for head injury; NOC=New Orleans criteria; CCHR=Canadian CT head rule; scan all=scanning of all patients; scan none=scanning no patients. For each rule, the net proportional benefit was calculated with the formula: (true positives/total number) - weight×(false positives/total number)

Secondary (sensitivity) analysis in all patients receiving CT scans

In all included centers, 4702 patients received a CT scan (Figure 1). Most of these patients had a Glasgow coma scale score of 15 at presentation (n=3798; 80.8%), 1511 (32.1%) experienced loss of consciousness, and 1480 (31.5%) had post-traumatic amnesia (Supplementary Table 6A). We found that 528 (11.2%) patients had an intracranial traumatic finding on CT (Supplementary Table 6B). Although the sensitivity of all rules was higher and the specificity lower, their ordering was the same. The NOC rule had the highest sensitivity (99.1%) and lowest specificity (3.1%) for any intracranial traumatic finding, whereas the NICE guideline had the highest specificity (50.3%) and lowest sensitivity (77.5%; Supplementary Figure 3). Net proportional benefit analysis showed the same pattern as in the primary analysis (Supplementary Figure 3).

Discussion

Principal findings

In this large, multicenter, external validation study of CT decision rules for MHI patients, the NOC had the highest sensitivity and was the only rule with a 100% sensitivity for potential neurosurgical lesions. Nevertheless, the high sensitivity of the NOC comes at the cost of an extremely low specificity with as consequence that practically all patients require a CT scan. The NICE guideline had the highest specificity and the lowest proportion that required a CT but at the cost of a low sensitivity. The sensitivity of the CHIP criteria was high (97% for potential neurosurgical lesions) with an acceptable specificity and a substantial reduction in the proportion requiring CT. Of note, the sensitivity for identifying patients with any intracranial traumatic finding on CT was less than 100% for all decision rules.

Which decision rule is the best for the situation depends on several factors. It depends not only on its characteristics but also on how many CT scans the physician is willing to perform to identify one patient with an intracranial traumatic finding or potential neurosurgical lesion. Because a potential neurosurgical lesion could have serious consequences, such as a neurosurgical intervention or even death, most professionals would agree that the sensitivity of the decision rule should be 100%.[27] However, it is less easy to agree on the desired sensitivity for finding any intracranial traumatic lesion, because not all small intracranial traumatic findings have clinical consequences. If a CT decision rule gives a false positive result, the patient receives an unnecessary CT and will be discharged after spending a few hours in the emergency department. If the rule gives a false negative result, the patient will be discharged without a CT and an intracranial traumatic finding will be missed. If this intracranial traumatic finding was a potential neurosurgical lesion and adequate therapy was omitted or was given too late, this could have serious consequences.[27]

The net proportional benefit analysis may help in finding the best decision rule for different thresholds, but the interpretation of the curves may be challenging.[24] If a low threshold is chosen, the best rule to use in order to identify all patients with any lesion is the NOC, but this would imply that practically all patients undergo CT. At a high threshold, using the NICE criteria avoids unnecessary scans and has the highest net proportional benefit, but important lesions may be missed. For the outcome potential neurosurgical lesion a very low net proportional benefit threshold and 100% sensitivity is desired. For intermediate thresholds, using the CHIP criteria makes a trade-off between avoiding missed lesions while achieving a substantial reduction in CTs of 21%. For the outcome intracranial traumatic finding the threshold can be higher, because it

is not necessary that all findings are identified. From a societal perspective, not only clinical usefulness but also cost-effectiveness is important. A cost-effectiveness study showed that a prediction rule needs a sensitivity of at least 97% for identifying potential neurosurgical lesions in order to be cost-effective, otherwise performing CT in all patients with MHI is more cost-effective.[26] In our study, only the NOC and the CHIP criteria fulfilled this criterion.

Comparison with other studies

Several other studies have validated and compared the sensitivity and specificity of CT decision rules for adult MHI patients, but only the NOC, CCHR and NICE decision rules have been externally validated.[13-17,28] Our study adds the CHIP rule to externally validated decision rules and compares it head-to-head with the other rules. Validation studies vary in design and in outcome measures (eg, clinically significant findings on CT are not uniformly defined), and are therefore difficult to compare. In addition, the case mix of our study is different from previous validation studies because we included all patients with blunt traumatic minor head injury, including those without risk factors. Our study is in line with earlier findings that the NOC rule has a high sensitivity but leads to a high scan rate, whereas the CCHR rule and NICE guideline can reduce the number of CT scans substantially, but at the cost of a lower sensitivity. However, the potential reduction in CT scans has not been proved in clinical practice yet. In terms of sensitivity and specificity, the CHIP rule lies between the NOC and CCHR rules.

All the decision rules in this study have been designed for an emergency department population. Although only the NICE and CHIP criteria have been designed to apply to all patients with minor head injury, in daily practice the NOC and CCHR rules probably apply to these patients as well. Therefore, we also investigated adjusted versions of the NOC and CCHR rules, which are applicable to all patients with minor head injury. The sensitivity and specificity of these two adjusted rules were comparable to the sensitivity and specificity of their original versions.

Our study population had a mean age of 53.1 years; by comparison, patients in the development studies for the NOC, CCHR, and CHIP rules had a mean age of 36-41 years. This difference is probably indicative of ageing of the population, but other factors such as changed referral patterns or increasing incidence fall accidents might contribute as well.[9] The percentage of patients with any intracranial traumatic finding (8.4%) was comparable with most other studies (6.9%-12.1%).[6,7,13] The percentage of patients who underwent a neurosurgical intervention within 30 days after injury in our study (0.4%) was low compared to most other studies (0.4%-1.5%). This difference

might be because the indication for neurosurgery not only depends on clinical factors, but also differs from country to country and from neurosurgeon to neurosurgeon and could have changed over time.[29] We therefore believe that instead of actual neurosurgical interventions, it is better to use 'potential neurosurgical lesions' as outcome measure. The confidence intervals for neurosurgical intervention were wide (sensitivity 71%-100%) because of the low prevalence of this outcome.

Patients with MHI presenting at the emergency department not only reflect the ageing of the population but also the result of the decision rules themselves. In the Netherlands, use of anticoagulants (coumarines or direct oral anticoagulants) is considered a risk factor for intracranial complications and a reason for referral to the emergency department in both the ambulance and general practitioner protocols.[30] The percentage of patients using anticoagulants in our study was higher than in the CHIP rule development study (9.2% vs 12.7%).[15]

Limitations

A limitation of our study was that not all consecutive patients with minor head injury were scanned. Following the guidelines for CT scanning at the participating centers resulted in patients with 0-1 minor criteria who did not undergo a CT scan. Therefore, patients who did not receive a CT scan but had intracranial traumatic findings (that is, those with false negative results) could have been missed. To detect this patient subgroup and precisely estimate their relative frequency among unscreened patients would need many thousands of individuals, which was not feasible. Missing patients without a CT scan could have led to a slight overestimation of the sensitivity and an underestimation of the specificity. We therefore performed the primary analysis on data from six centers which also collected data for patients without a CT scan. For all the rules, the new calculated sensitivities were a little lower and the specificities higher, as expected. The fact that most centers in our study used CT guidelines based on the CHIP rule could have introduced a bias in favor of the CHIP rule, owing to possible missed lesions (because the patient was not scanned according to the local guideline) that would have been detected by the other rules. However, by imputing the outcomes of the patients without a CT scan, we were able to keep this bias to a minimum.

Because most physicians used the CHIP rule on a regular basis, they were more likely to apply it correctly. However, many risk factors are the same for all rules and the validation was performed based on the scored risk factors, not on the physicians' judgment of a rule being positive or negative. In addition, in our centers, it is clinical practice to assess not only risk factors from the CHIP rule, but also other risk factors

such as headache and retrograde amnesia. In our study, it was unclear how quickly patients proceeded to CT and whether lesions appeared after this time. However, af Geijerstam et al. concluded in a literature review that the risk for developing an intracranial lesion after an early normal CT is very low.[31]

Another limitation was the possibility that we missed patients undergoing a neurosurgical intervention in a different hospital. However, because the participating centers were all the primary neurosurgery centers of the area, this potential bias is highly unlikely. Furthermore, because we used potential neurosurgical lesions as a secondary outcome instead of neurosurgical intervention, our main findings would not have been affected. In the development studies of the four decision rules, potential neurosurgical lesions were not used as an outcome measure.

Conclusions and policy implications

Application of the CHIP, NOC, CCHR, or NICE decision rules leads to a wide variation in CT scanning among patients with minor head injury, resulting in unnecessary CT scans and missed intracranial traumatic findings. Only the NOC rule did not miss potential neurosurgical lesions, but this was at the cost of having to scan nearly all patients. Although the NICE guideline had the highest reduction of CT scans (58%), missing 15% of patients with potential neurosurgical lesions would be unacceptable to most physicians in the emergency department, because it would mean that for every 200 patients not be scanned according to the NICE criteria, one patient would turn out to have a potential neurosurgical lesion.

Of the four investigated rules, the CHIP rule performed the best with an acceptable sensitivity of 97% for potential neurosurgical lesions according to previous cost effectiveness analysis, the highest net proportional benefit at intermediate thresholds, and a substantial reduction of CT scans of 21% compared with the scanning of all patients. Updating an existing decision rule might increase the sensitivity and specificity for detecting potential neurosurgical lesions. Until this update is conducted, it is justified to use any of the four rules for patients with minor head injury presenting at the emergency department. We recommend use of the CHIP rule because it leads to a substantial reduction of CT scans and misses very few potential neurosurgical lesions.

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Supplementary Material

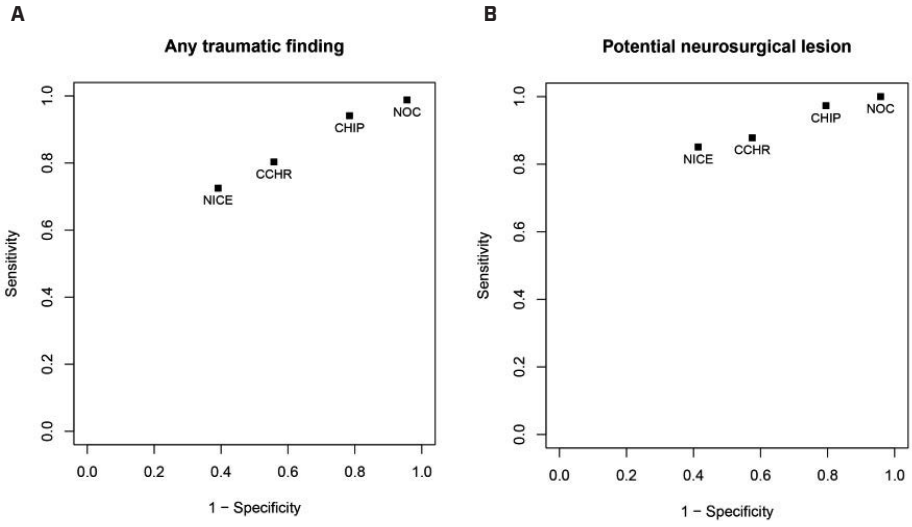
Supplementary Table 1. Overview of decision rules CCHR, NOC, CHIP and NICE

Study	Patient population	Indications for CT
NOC: New Orleans Criteria Haydel et al, 2000	GCS score of 15, loss of consciousness, normal findings on brief neurological examination, >3y	Clinical findings: • Headache (diffuse or local) • Vomiting • Age > 60 years • Drug or alcohol intoxication • Deficits in short-term memory (persistent anterograde amnesia in patient with otherwise normal GCS) • Physical evidence of trauma above clavicles • Seizure
CCHR: Canadian CT Head Rule Stiell et al, 2001	GCS score 13-15, witnessed LOC, definite amnesia or witnessed disorientation, age > 16y Exclusion: use of anticoagulation or obvious open skull fracture	High risk for intervention: • GCS < 15 at 2 hours after injury • Suspected open or depressed skull fracture • Any sign of basal skull fracture • Vomiting 2 or more episodes • Age 65 years or older Medium risk for brain injury on CT: • Amnesia before impact 30 min or more • Dangerous mechanism (pedestrian vs vehicle, ejected from vehicle, fall from elevation ≥ 3 feet, or 5 stairs)
CHIP: CT in Head Injury Patients Smits et al, 2007	GCS 13-14 or GCS of 15 and 1 risk factor, age ≥16	CT indicated if ≥ 1 major criterion: • Pedestrian or cyclist vs vehicle • Ejected from vehicle • Vomiting • PTA of 4 hours or more • Clinical sign of skull fracture • GCS < 15 • GCS deterioration ≥ 2 points (1 hour after presentation) • Use of anticoagulant therapy • Posttraumatic seizure • Age 60 years or older CT indicated if ≥ 2 minor criteria: • Fall from any elevation • Persistent anterograde amnesia • PTA of 2-4 hours • Contusion of skull • Neurologic deficit • LOC • GCS deterioration of 1 point (1 hour after presentation) • Age 40-60 years

Supplementary Table 1. Continued

Study	Patient population	Indications for CT
NICE: National Institute for Health and Care Excellence guideline: Head injury	Adults with head injury	<u>Perform CT within 1 hour:</u> • GCS < 13 • GCS < 15 at 2 hours after injury • Suspected open or depressed skull fracture • Any sign of basal skull fracture • Posttraumatic seizure • Focal neurologic deficit • More than one episode of vomiting since head injury <u>Perform CT within 8 hours:</u> • Current warfarin treatment <u>LOC and/or PTA and:</u> • Age > 65 years • History bleeding or clotting disorder • Dangerous mechanism of injury • More than 30minutes retrograde amnesia of events before head injury

CT = computed tomography, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia, LOC = loss of consciousness



Supplementary Figure 1. Performance of the CT decision rules (6 centers, n=4557).

CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule

Supplementary Table 2. Overview CT guidelines used in participating centers

	National guideline
Number of centers	7
1 or more major criteria	• GCS < 15 (including persisting PTA) • 2 or more points deterioration in GCS (1 hour after presentation) • Vomiting • Posttraumatic seizure • Signs of skull fracture • Pedestrian or cyclist versus vehicle • Ejected from motor vehicle • PTA ≥ 4 hours • Use of anticoagulants • Focal neurologic deficit • Suspicion of intracranial injury after focal “high impact” injury
2 or more minor criteria	• Fall from any elevation • LOC • Posttraumatic amnesia 2-4 hours • Visible injury to the head, excluding the face (without signs of fracture) • 1 point deterioration in GCS (1 hour post presentation) • Age > 40 years

CT = computed tomography, GCS = Glasgow Coma Scale, PTA = posttraumatic amnesia, LOC =loss of consciousness, INR = international normalized ratio, NOACS = novel oral anticoagulants

	Local guideline 1	Local guideline 2
1		
	• GCS < 15 • 2 or more points deterioration in GCS (1 hour after presentation) • Vomiting • Posttraumatic seizure • Age ≥60 years • Signs of skull fracture • Dangerous mechanism (Pedestrian or cyclist versus vehicle; Ejected from motor vehicle; Fall from more than 1m or 5 stairs; Or equivalent mechanism) • Post traumatic amnesia ≥ 4 hours • Coagulopathy, e.g. use of coumarin derivate (INR >1.7), NOACs, or chronic alcohol abuse • Focal neurologic deficit • Intoxication that impairs neurological examination	• GCS < 15 (including persisting PTA) • Deterioration in GCS • Vomiting > 1 time • Posttraumatic seizure • Signs of skull fracture • Dangerous mechanism (Pedestrian or cyclist versus vehicle; Ejected from motor vehicle; Fall from high elevation) • Post traumatic amnesia > 1 hour • Use of anticoagulants/coagulopathy • Focal neurologic deficit
	• Fall from < 1 m • LOC • PTA 2-4 hours • Persisting PTA (recall deficit) • Traumatic injury above the clavicles • 1 point deterioration in GCS (1 hour post presentation) • Age 40-60 years	• Fall from any elevation • LOC • Unclear trauma mechanism • Visible injury to the head, excluding the face (without signs of fracture) • Violence • Age > 65 years

Supplementary Table 3. Overview of missed neurosurgical lesions

	Patient characteristics	CT result	Missed by rule
1	32y, assault blunt instrument, intoxication, significant injury to the head, focal high impact injury	Small EDH, skull fracture	CHIP, NICE, CCHR
2	21y, scooter vs motor vehicle, high energy trauma, significant injury to face and head	Small EDH, small ASDH, skull fracture	CHIP, NICE, CCHR
3	69y, fall from scooter, headache, significant injury to the head	Small EDH	NICE
4	52y, fall from standing height, LOC, PTA, significant injury to the head	Small EDH, tSAH	NICE, CCHR
5	37y, fall from scooter, intoxication, LOC, retrograde amnesia < 30 min, PTA 2-4hrs	Small EDH, tSAH, small ASDH	NICE, CCHR
6	26y, forklift against head, LOC, PTA, headache, significant injury to the head, focal high impact injury	Small EDH, tSAH, small ASDH, contusion (small), skull fracture	NICE, CCHR
7	22y, fall from standing height, LOC, retrograde amnesia <30min	Small EDH	NICE, CCHR
8	36y, assault blunt instrument, LOC, PTA, significant injury to the head, focal high impact injury	Small EDH, skull fracture (depressed)	NICE, CCHR
9	88y, scooter vs truck, high energy trauma, significant injury to the head	Small EDH, skull fracture	NICE
10	24y, bicycle vs motor vehicle, high energy trauma, significant injury to the face, LOC, PTA, headache	Small EDH, contusion (small), skull fracture	CCHR
11	40y, bicycle vs bicycle, significant injury to the head, PTA, headache	Small EDH, contusion (small), skull fracture	NICE, CCHR
12	89y, fall from standing height, significant injury to the face	Large ASDH	NICE

CT = computed tomography, EDH = epidural hematoma, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, CCHR = Canadian CT Head Rule ASDH = acute subdural hematoma, LOC = loss of consciousness, PTA = posttraumatic amnesia, tSAH = traumatic subarachnoid hemorrhage

Supplementary Table 4A. NOC and CCHR validation in population with in- and exclusion criteria as in development cohort (6 centers)

	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
Original NOC n=1147 (subset of population with in- and exclusion criteria of original NOC study)				
Any traumatic finding on CT			98.6 (96.4 to 100)	3.5 (2.4 to 4.5)
NOC - Positive	137	973		
NOC - Negative	2	35		
Potential neurosurgical lesion			100 (100 to 100)	3.3 (2.3 to 4.2)
NOC - Positive	20	1090		
NOC - Negative	0	37		
Original CCHR n= 1683 (subset of population with in- and exclusion criteria of original CCHR study)				
Any traumatic finding on CT			81.6 (76.8 to 86.2)	42.5 (39.9 to 45.1)
CCHR - Positive	209	821		
CCHR - Negative	47	606		
Potential neurosurgical lesion			85.1 (74.0 to 94.2)	39.5 (37.2 to 41.9)
CCHR - Positive	40	990		
CCHR - Negative	7	646		

CI = 95% confidence interval, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule, CT= computed tomography

Supplementary Table 4B. Adjusted NOC and adjusted CCHR validation in entire study population (6 centers)

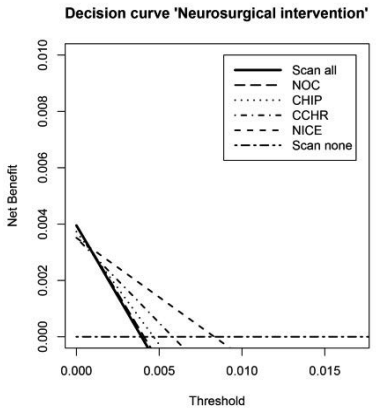
	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
Adjusted NOC n=4557 (including in- and exclusion criteria of original study as risk factors)				
Any traumatic finding on CT			98.8 (97.6 to 99.8)	4.0 (3.4 to 4.5)
NOC - Positive	402	3984		
NOC - Negative	5	166		
Potential neurosurgical lesion			100 (100 to 100)	3.8 (3.2 to 4.3)
NOC - Positive	74	4312		
NOC - Negative	0	171		
Adjusted CCHR n=4557 (including in- and exclusion criteria of original study as risk factors)				
Any traumatic finding on CT			81.8 (77.6 to 85.7)	42.0 (40.4 to 43.6)
CCHR - Positive	333	2409		
CCHR - Negative	74	1741		
Potential neurosurgical lesion			87.8 (79.7 to 94.9)	40.3 (38.9 to 41.7)
CCHR - Positive	65	2677		
CCHR - Negative	9	1806		

CI = 95% confidence interval, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule, CT= computed tomography

Supplementary Table 5. Performance of rules with outcome neurosurgical intervention (6 centers)

	Positive n	Negative n	Sensitivity % (CI)	Specificity % (CI)
CHIP n=4557				
Neurosurgical intervention			94.4 (81.8 to 100)	20.3 (19.2 to 21.4)
CHIP – Positive	17	3619		
CHIP – Negative	1	920		
NICE n=4557				
Neurosurgical intervention			88.9 (71.4 to 100)	58.1 (56.6 to 59.6)
NICE – Positive	16	1903		
NICE – Negative	2	2636		
NOC n=4557				
Neurosurgical intervention			100 (100 to 100)	4.2 (3.6 to 4.7)
NOC – Positive	18	4350		
NOC – Negative	0	189		
CCHR n=4557				
Neurosurgical intervention			88.9 (71.4 to 100)	42.2 (40.7 to 43.8)
CCHR – Positive	16	2625		
CCHR – Negative	2	1914		

CI = 95% confidence interval, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule



Supplementary Figure 2. Decision curves showing net benefit for the outcome neurosurgical intervention.

CT = computed tomography, CHIP = CT in head Injury Patient rule, NICE = National Institute for Health and Care Excellence, NOC = New Orleans Criteria, CCHR = Canadian CT Head Rule. Per rule net benefit was calculated using the formula: (true positives/n) – weight*(false positives/n).

Supplementary Table 6A. Baseline characteristics all patients with a CT scan (9 centers, n =4702)

	Normal CT (n=4174)	Abnormal CT (n=528)	All patients with CT (n=4702)
Age mean in years (range)	55.5 (16-101)	58.6 (16-98)	55.9 (16-101)
Sex, n male (%)	2372 (56.8%)	337 (63.8%)	2709 (57.6%)
GCS score at presentation			
• 13	138 (3.3%)	69 (13.1%)	207 (4.4%)
• 14	557 (13.3%)	140 (26.5%)	697 (14.8%)
• 15	3479 (83.3%)	319 (60.4%)	3798 (80.8%)
Use of anticoagulation			
• None	3581 (85.8%)	474 (89.8%)	4055 (86.2%)
• Coumarin	490 (11.7%)	45 (8.5%)	535 (11.4%)
• NOACS	56 (1.3%)	3 (0.6%)	59 (1.3%)
Bleeding disorder	47 (1.1%)	3 (0.6%)	50 (1.1%)
Mechanism of injury			
• RTA pedestrian	60 (1.4%)	12 (2.3%)	72 (1.5%)
• RTA cyclist	164 (3.9%)	36 (6.8%)	200 (4.3%)
• Fall from height	574 (13.8%)	124 (23.5%)	698 (14.8%)
• Other	3325 (79.7%)	348 (65.9%)	3673 (78.1%)
Ejected from vehicle	183 (4.4%)	32 (6.1%)	215 (4.6%)
LOC			
• None	2192 (52.5%)	153 (29.0%)	2345 (49.9%)
• 15 minutes or less	1238 (29.7%)	225 (42.6%)	1463 (31.1%)
• More than 15 minutes	30 (0.7%)	18 (3.4%)	48 (1.0%)
Retrograde amnesia			
• None	2819 (67.5%)	227 (43.0%)	3046 (64.8%)
• 30 minutes or less	445 (10.7%)	96 (18.2%)	541 (11.5%)
• More than 30 minutes	142 (3.4%)	58 (11.0%)	200 (4.3%)
PTA			
• None	2456 (58.8%)	154 (29.2%)	2610 (55.5%)
• Up to 2 hours	970 (23.2%)	200 (37.9%)	1170 (24.9%)
• 2-4 hours	80 (1.9%)	22 (4.2%)	102 (2.2%)
• More than 4 hours	144 (3.4%)	64 (12.1%)	208 (4.4%)
Intoxication *	1075 (25.8%)	117 (22.2%)	1192 (25.4%)
Post-traumatic seizure	31 (0.7%)	11 (2.1%)	42 (0.9%)
Headache	1358 (32.5%)	184 (34.8%)	1542 (32.8%)
Vomiting			
• Once	173 (4.1%)	27 (5.1%)	200 (4.3%)
• Twice or more	161 (3.9%)	35 (6.6%)	196 (4.2%)

Supplementary Table 6A. Continued

	Normal CT (n=4174)	Abnormal CT (n=528)	All patients with CT (n=4702)
GCS deterioration			
• 1 point	35 (0.8%)	6 (1.1%)	41 (0.9%)
• 2 or more points	9 (0.2%)	9 (1.7%)	18 (0.4%)
Neurological deficit	104 (2.5%)	29 (5.5%)	133 (2.8%)
Signs of skull base fracture	109 (2.6%)	77 (14.6%)	186 (4.0%)
Visible injury of the head	2237 (53.6%)	338 (64.0%)	2575 (54.8%)
Visible injury of the face	1420 (34.0%)	178 (33.7%)	1598 (34.0%)
Suspicion of open fracture	8 (0.2%)	17 (3.2%)	25 (0.5%)
ISS, mean (range)	6.5 (0-54)	15.3 (1-75)	7.5 (0-75)

CT = computed tomography, GCS = Glasgow Coma Scale, NOACS = novel oral anticoagulants, RTA= road traffic accident, LOC = loss of consciousness, PTA = posttraumatic amnesia, ISS = Injury Severity Score

*history or suggestive findings on examination (for example nystagmus, abnormal walking, etc.)

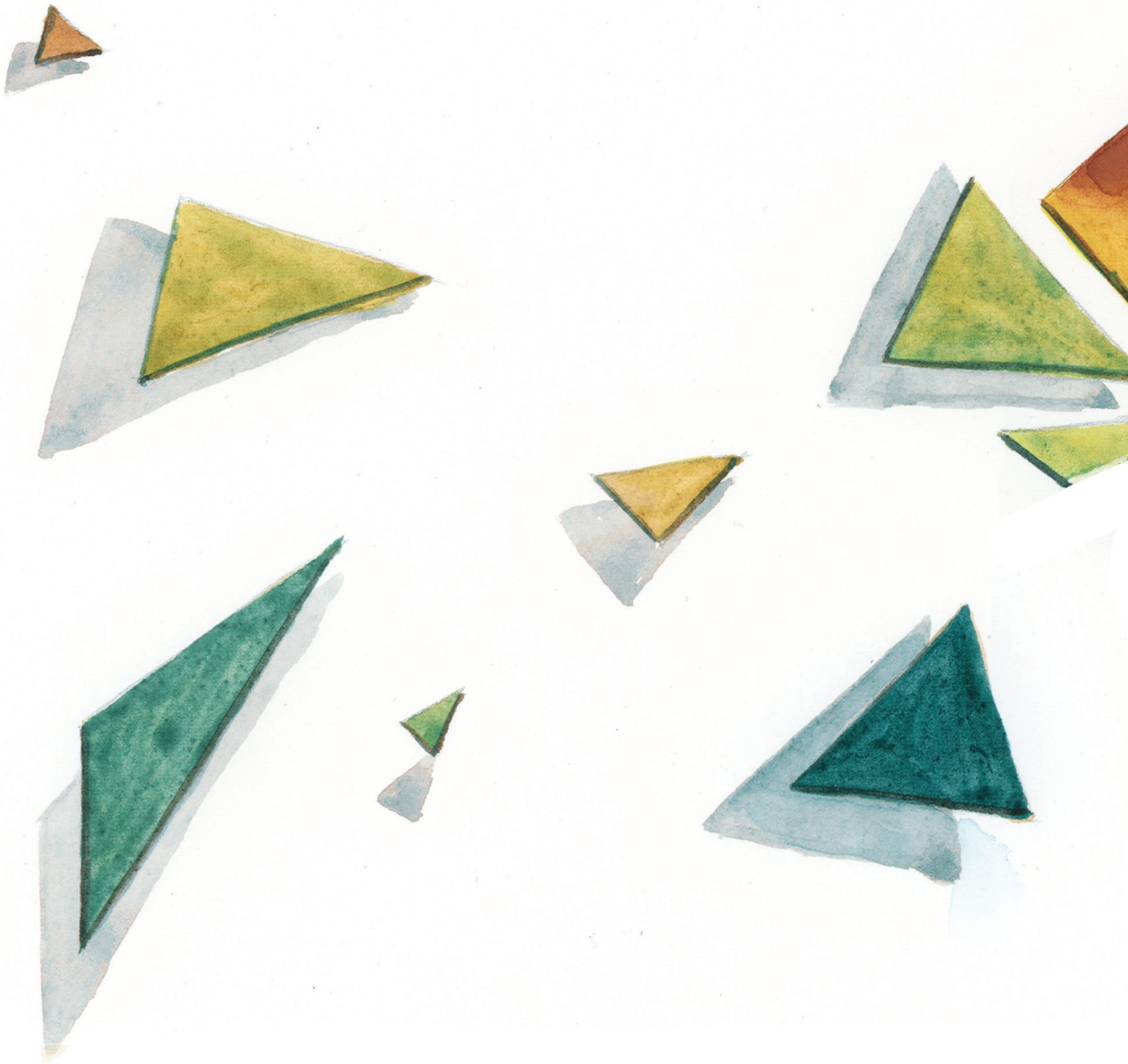
**GCS deterioration 2 hrs after presentation

Supplementary Table 6B. Traumatic CT findings all patients with a CT scan (9 centers, n=4702)

CT finding	N (%)
CT finding	528 (11.2%)
Skull fracture	213 (4.5%)
• Depressed fracture	25 (0.5%)
• Linear fracture	103 (2.2%)
• Skull base fracture	89 (1.8%)
Subarachnoid hemorrhage	266 (5.7%)
Contusion	
• Small	154 (3.3%)
• Large (mass)	14 (0.3%)
Subdural hematoma	
• Small	173 (3.7%)
• Large (mass)	27 (0.6%)
Epidural hematoma	
• Small	47 (1.0%)
• Large (mass)	5 (0.1%)
Suspicion of DAI on CT	14 (0.3%)
Basal cisterns compressed or obliterated	13 (0.3%)
CT shift	
• 0-4mm	22 (0.5%)
• 5mm or more	13 (0.3%)

CT = computed tomography, DAI = diffuse axonal injury

*some patients had more than 1 CT finding



CHAPTER 7

Update of the CHIP (CT in Head Injury Patients) decision rule for patients with minor head injury based on a multicenter consecutive case series

Submitted

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ABSTRACT

Objective

To update the existing CHIP (CT in Head Injury Patients) decision rule for detection of (intra)cranial findings in adult patients following minor head injury (MHI).

Methods

The study is a prospective multicenter cohort study in the Netherlands. Consecutive MHI patients of 16 years and older were included. Primary outcome was any (intra) cranial traumatic finding on computed tomography (CT). Secondary outcomes were any potential neurosurgical lesion and neurosurgical intervention. The CHIP model was validated and subsequently updated and revised. Diagnostic performance was assessed by calculating the c-statistic.

Results

Among 4557 included patients 3742 received a CT (82%). In 383 patients (8.4%) a traumatic finding was present on CT. A potential neurosurgical lesion was found in 73 patients (1.6%) with 18 (0.4%) actually undergoing neurosurgery. The original CHIP underestimated the risk of traumatic (intra)cranial findings in low-predicted-risk groups, while in high-predicted-risk groups the risk was overestimated. The c-statistic of the original CHIP model was 0.72 (95% CI 0.69-0.74) and it would have missed two potential neurosurgical lesions and one patient that underwent neurosurgery. The updated model performed better over a wide range of predicted risks (c-statistic 0.77 95% CI 0.74-0.79). At the same CT rate as the original CHIP (75%), the updated CHIP would not have missed any (potential) neurosurgical lesions.

Conclusions

Use of the updated CHIP decision rule is a good alternative to current decision rules for patients with MHI. In contrast to the original CHIP the update identified all patients with (potential) neurosurgical lesions without increasing CT rate.

Introduction

Minor head injury (MHI) is a common and increasing cause of emergency department (ED) visits worldwide.[1-3] With ageing of the population it is expected that the burden caused by MHI will continue to rise in the next decades. The vast majority (>90%) of patients with MHI will have no (intra)cranial traumatic lesions.[4,5] Nonetheless, (intra)cranial traumatic lesions can result in severe disability or death and therefore require clinical observation and a small percentage needs neurosurgical intervention. This study aims to provide a method to improve selection of patients that require a head computed tomography (CT) to identify traumatic lesions.

Currently the most used technique to rule out traumatic findings after MHI is CT. CT is widely available and the fraction of patients receiving a CT for MHI has increased significantly in the last decades.[6,7] The use of CT has many advantages because it is fast and reliable. However, its increasing use in MHI also has several important disadvantages. First, a CT exposes the patient to radiation risks.[8] Second, a CT is costly and should, in the light of ever-expanding healthcare costs, only be used when necessary. Last but not least, performing more diagnostic procedures such as CT may lead to prolonged ED throughput times and thus result in ED-crowding.[9] With increasing ED visits for MHI it is more important than ever to identify those patients that will benefit from a CT.

To enhance selective use of head-CT several decision rules for MHI have been developed. Worldwide the most used decision rules are probably the Canadian CT Head Rule (CCHR) and the New Orleans Criteria (NOC).[10,11] Both CCHR as NOC are only applicable to patients with loss of consciousness, post traumatic amnesia or confusion. However, most patients with MHI do not experience any of these and (intra)cranial findings can be present even in the absence of these risk factors.[12,13] Therefore, another decision rule was developed in four level one trauma centers in the Netherlands in the beginning of this century. This rule is applicable to *all* ED patients with MHI, the CT in Head Injury Patients (CHIP) rule.[4] The ACEP (American College of Emergency Physicians) clinical policy for neuroimaging in MHI includes recommendations from the CHIP study for patients without loss of consciousness or posttraumatic amnesia.[14]

We recently validated the CHIP-rule and compared it to the NOC and the CCHR. [15] In line with an ageing population, the patient population in this validation-study differed substantially from the original CHIP, NOC and CCHR studies.[1,4,10,11,15] The population was older and trauma was more often caused by ground level falls. In

this validation-study sensitivity and specificity for any traumatic finding were 94% and 22% for the CHIP rule; 99% and 4% for the NOC and 80% and 44% for the CCHR. Based on these results we concluded that the CHIP rule performed well compared to several other prediction rules in terms of a proper balance between specificity and sensitivity. Nonetheless, we also conclude that there is room for improvement of the CHIP because the sensitivity for detecting (potential) neurosurgical lesions was less than 100%.[15]

Given the potential for improvement of the CHIP, the changing demographic characteristics of MHI patients and the fact that the CHIP was developed in level one trauma centers only, there seems to be need for an update of the CHIP. Therefore, the aim of the current study is to update and improve the CHIP decision rule for detection of (intra)cranial findings following MHI.

Methods

Study design and setting

This prospective, multicenter cohort study was conducted in the Netherlands, data were collected between March 1st 2015 and January 1st 2017. Three level 1, one level 2 and two level three EDs participated in the study.[16]

Selection of participants

Consecutive patients of 16 years and older with MHI who arrived at one of the participating EDs within 24 hours after blunt trauma to the head were included. MHI was defined as:

Any trauma to the head, other than superficial injuries to the face and:

- *Glasgow Coma Scale (GCS) score 13-15 at first examination*
- *Loss of consciousness (not required): no more than 30 minutes*
- *Posttraumatic amnesia (not required): no more than 24 hours*

Patients who were transferred from another hospital were excluded. Clinical data concerning risk factors as used in the CHIP-rule and additional risk factors were collected (Supplementary Table 1).[17]

Outcomes

Similar to the original CHIP, the primary outcome was any (intra)cranial traumatic finding on CT, defined as: subdural hematoma, epidural hematoma, subarachnoid hemorrhage, hemorrhagic contusion, non-hemorrhagic contusion, diffuse axonal injury, intraventricular hemorrhage, and skull fracture. The secondary outcome was any potential neurosurgical lesion, which was defined as an (intra)cranial traumatic finding on CT which could lead to a neurosurgical intervention or death.[15] The following traumatic findings were labelled as potential neurosurgical lesions: epidural hematoma, large acute subdural hematoma (mass), large contusion(s) (mass), depressed skull fracture, and any lesion with midline shift or herniation. Another secondary outcome was neurosurgical intervention for traumatic skull or brain injury within 30 days. A prerequisite of the (updated) model was not to miss any potential neurosurgical findings.

Study procedures and analysis

We described study procedures and data management in detail elsewhere.[15] Sample size was based on 20 eligible variables in multivariable logistic regression. Per variable at least 10 events of the primary outcome measure were required. Based on earlier research the estimated incidence of traumatic findings on CT was 7.4%, hence at least 2703 scanned patients had to be included.[7]

In accordance to the original CHIP-study, we imputed loss of consciousness and posttraumatic amnesia as present if data was missing or unknown. Other missing data were assumed to be missing at random. We imputed missing data based on all risk factors mentioned above using "Multivariate Imputation by Chained Equations" (MICE) in R. Outcomes could not be observed in patients without CT. Therefore, we imputed the expected outcomes based on their risk factors with multiple imputation, acknowledging the uncertainty of imputations by performing the imputation multiple times (n=5).[18] Baseline and outcome are first reported without imputation mentioning any missing data. We used data with imputed outcomes for the primary analysis, similar to our previous study.[15] We performed a sensitivity analysis by including scanned patients only (without outcome imputation). Analyses were performed using IBM Statistical Package for Social Sciences version 24 and R foundation for statistical computing software, version 3.3.2.

Institutional ethics and research board approval was obtained, and informed consent was waived.

Validation and updating

Model validation, updating and revision were based on the methodology as described by Steyerberg.[19] First, we validated the original CHIP-rule. The predicted risk of any (intra)cranial traumatic finding was calculated for each patient using the original risk factors, regression coefficients and intercept. We calculated the observed frequency of any (intra)cranial traumatic finding in our dataset and present this in a calibration plot. A locally weighted regression curve (LOESS) was used in the calibration plot.

Updating of the CHIP decision model was performed based on the difference in fit of the CHIP-model and a newly fitted model in the current data.[19]

To update the CHIP we performed re-calibration as a first step. The intercept was updated to correct a potential deviation in 'calibration-in-the-large'. Calibration-in-the-large refers to whether the mean observed outcome is equal to the mean predicted outcome. The second step was to update both the intercept and the overall calibration slope. The third step was to re-estimate the intercept and the regression coefficients of the original CHIP predictors in the study data.

Model revision

In the next steps the model was extended with new predictors and existing predictors with limited predictive value were eliminated. We assessed performance by calculating the area under the receiver operating characteristic curve (c-statistic). Calibration was assessed by plotting the observed proportions versus predicted chances of the primary outcome (calibration plot). A locally weighted regression curve (LOESS) was used in the calibration plot.

To improve the performance of the model in future populations, we multiplied the regression coefficients by a shrinkage factor obtained using bootstrapping. The updated model (without shrinkage factor) was cross-validated six times by re-estimating the intercept and regression coefficients in five centers and testing it in the sixth center. We present the validated c-statistics in a forest plot.

Results

We included 4557 consecutive eligible MHI patients during the study period. Patient characteristics are summarized in Table 1 and Supplementary Table 2. Compared to the original CHIP-study the current study population was older (53 versus 41 years) and more often female (42% versus 28%). Regarding trauma mechanism more injuries were the result of ground level falls (37% versus 22%) and less injuries were the result of assaults (15% versus 24%).[20]

Table 1. Baseline characteristics update study versus original CHIP study

	Update study (n=4557)	**Missing**	**Original CHIP (n=3181)**
Inclusion period	2015-2016		2002-2004
Age mean in years (range)	53.1 (16-101)	0	41.4 (16-102)
Sex, n male (%)	2656 (58.3%)	0	2246 (70.5%)
GCS score at presentation		0	
• GCS 13	143 (3.1%)		151 (4.7%)
• GCS 14	500 (11.0%)		568 (17.9%)
• GCS 15	3914 (85.8%)		2462 (77.4%)
Use of anticoagulation		29 (0.6%)	
• None	4045 (88.8%)		2963 (93.1%)
• Coumarin	418 (9.2%)		218 (6.9%)
• Direct oral anticoagulants	54 (1.2%)		NA
• Other	11 (0.2%)		0
Use of thrombocyte aggregation inhibitors (TAI)	615 (13.5%)	33 (0.7%)	
• None	3909 (85.9%)		unknown
• ASA monotherapy	405 (8.9%)		unknown
• Other TAI or combination	210 (4.6%)		unknown
Bleeding disorder	44 (1%)	33 (0.7%)	unknown
High Energy Trauma[a]	583 (12.7%)	3 (0.1%)	1457 (45.8%)
Mechanism of injury		0	
• Pedestrian or cyclist versus vehicle	226 (5.0%)		100 (3.1%)
• Road traffic accident other	1019 (22.4%)		unknown
• Ground level fall	1699 (37.3%)		691 (21.7%)
• Fall from height (>1 meter)	574 (12.6%)		513 (16.1%)
• Assaults or other violence	659 (14.5%)		771 (24.2%)
• Sports or recreational activitiy	158 (3.5%)		unknown
• Other[b]	222 (4.9%)		unknown

Table 1. Continued

	Update study (n=4557)	Missing	Original CHIP (n=3181)
Ejected from vehicle	150 (3.3%)	56 (1.2%)	65 (2.0%)
Focal high impact trauma	74 (1.6%)	5 (0.1%)	unknown
Loss of consciousness	1192 (26.2%)	651 (14.3%)	1951 (61.3)
Posttraumatic amnesia		502 (11%)	
• None	2951 (64.8%)		2181 (68.6%)
• Up to 2 hours	976 (21.4%)		916 (28.8%)
• 2-4 hours	69 (1.5%)		69 (2.2%)
• More than 4 hours	59 (1.3%)		15 (0.5%)
Intoxication with drugs or alcohol[c]	1031 (22.6%)	85 (1.9%)	1367 (43%)
Posttraumatic seizure	36 (0.8%)	68 (1.5%)	23 (0.7%)
Vomiting		50 (1.1%)	342 (10.8%)
• Once	158 (3.5%)		
• Twice or more	144 (3.2%)		
GCS deterioration[d]		23 (0.5%)	
• 1 point	38 (0.8%)		51 (1.6%)
• 2 or more points	12 (0.3%)		17 (0.5%)
Neurological deficit	130 (2.9%)	141 (3.1%)	304 (9.6%)
Signs of skull base fracture	144 (3.2%)	25 (0.5%)	66 (2.1%)
Visible injury of the head	2564 (56.3%)	19 (0.4%)	2861 (90%)

CT = computed tomography, GCS = Glasgow Coma Scale, NA = not applicable, ASA= Acetylsalicylic acid or carbasalate calcium

[a]In the update study this was defined as: High risk auto crash (intrusion >30cm to occupant site or >45cm to any other site, ejection from automobile, death in same passenger compartment, vehicle telemetry data consistent with high risk of injury); Auto versus pedestrian/bicyclist; motorcycle crash >32km/h (20 miles/h); fall from >6 meters (20 feet). The exact definition in the original CHIP is not known and may differ.

[b]Includes patients with mild head injury such as bump head against object.

[c]History or suggestive findings on examination (for example nystagmus, abnormal walking, etc.).

[d]GCS deterioration 2 hrs after presentation

Of the 4557 included patients 3742 received a CT (82%). Compared to patients with CT, those without CT were on average younger (36 versus 57 years) and almost all of them had a GCS of 15 (99%). According to the CHIP-rule 3412 (75%) patients should have received a CT because of a predicted risk of ≥3% for traumatic (intra)cranial findings (Table 2).[4]

Table 2. CT rate in patients above and below the CHIP CT threshold (predicted risk ≥3%) (n=4557)

	CT performed, traumatic findings present (n=383)	**CT performed, traumatic findings absent (n=3359)**	**CT *not* performed, imputed as traumatic findings present (n=23)**	**CT *not* performed, imputed as traumatic findings absent (n=792)**
CHIP predicted risk ≥3% (n=3412)	367 (8.1%)	2841 (62.3%)	9 (0.2%)	195 (4.3%)
CHIP predicted risk <3% (n=1145)	16 (0.4%)	518 (11.4%)	14 (0.3%)	597 (13.1%)

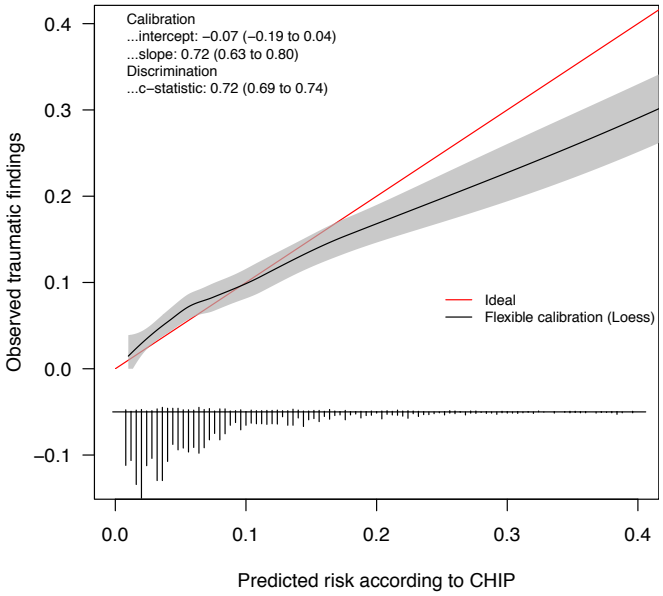

Figure 1. Calibration plot original CHIP

Calibration plot original CHIP, range 0 to 40% predicted and observed risk. A 95% confidence interval is given for intercept, slope and c-statistic.

In 383 of 4557 patients (8.4%) a traumatic (intra)cranial finding was present on CT (Supplementary Table 3). A potential neurosurgical lesion was found in 73 patients (1.6%) with 18 (0.4%) undergoing neurosurgery. In total 1511 patients (33%) were hospitalized for any cause. The vast majority of patients (n=340, 89%) with traumatic findings on head-CT were hospitalized. In total 32 patients (0.7%) died during their hospital admission, in 11 patients (0.2%) this was a result of their traumatic brain injury.

Validation

Figure 1 shows observed frequency of traumatic (intra)cranial findings in our population compared with the predictions according to the CHIP-model. In the low-predicted-risk patients, the original CHIP slightly underestimated the risk, while in the high-predicted-risk patients the model overestimated the risk. By applying the original CHIP-rule 30 traumatic findings would have been missed, including two potential neurosurgical lesions and one neurosurgical intervention. In total 1145 patients (25%) had no indication for CT according to the original CHIP (at a cut-off value of 3% predicted-risk). The sensitivity of the original CHIP for any traumatic lesion was 93% (95% CI 90-95%) and the specificity was 27% (95% CI 26-28%). Sensitivity and specificity for potential neurosurgical lesions were 97% (95% CI 90-100%) and 25% (95% CI 24-27%) respectively. Sensitivity and specificity for neurosurgical intervention were 94% (95% CI 73-100%) and 25% (95% CI 24-26%).

The c-statistic for any traumatic finding was 0.72 (95% CI 0.69-0.74). For potential neurosurgical lesions and for actual neurosurgical interventions the c-statistic was 0.82 (95% CI 0.77-0.87) and 0.84 (95% CI 0.73-0.94) respectively.

Updating

The overall observed frequency of traumatic (intra)cranial findings was slightly lower in our population (8.9%[1]) compared to the CHIP predicted frequency (9.4%) ($P < 0.001$). To correct for this “calibration in the large” the intercept was adjusted.

After that, we refitted the regression slope, the new calibration slope ($b_{overall}$) was significantly steeper in the updated model compared to the original model ($P < 0.001$). This adjustment would increase sensitivity to 97%, but at the cost of a decline in specificity to 11% (at a cut-off value of 3% predicted-risk).

Next, we re-estimated regression coefficients of original risk factors in the current dataset. Some regression coefficients were similar in the validation data and the CHIP-model, others differed and two (use of anticoagulants and ejection from vehicle) had a negative regression coefficient in our dataset. Because we consider a protective effect of risk factors clinically implausible we omit these predictors from the updated model. (Supplementary Table 4)

1 The observed frequency of traumatic findings of 8.9% includes imputed data, hence the discrepancy with the earlier mentioned 8.4%.

Model revision

Several updated models have been considered of which the model in Table 3 showed the best performance in terms of c-statistic and calibration (Table 3 and Figure 2). All selected variables showed significant effects ($P < 0.05$). The c-statistic for any traumatic finding was 0.77 (95% CI 0.74-0.79). For potential neurosurgical lesions and for neurosurgical intervention lesions the c-statistic was 0.87 (95% CI 0.84-0.91) and 0.92 (95% CI 0.86-0.98) respectively.

Table 3. Variables included in updated CHIP with regression coefficients

Risk factor	Odds ratio	Beta-coefficient	*P* value	Penalized beta-coefficient
Signs of skullbase fracture	4.6	1.53	<0.01	1.48
GCS 13	2.5	0.90	<0.01	0.88
GCS 14	1.6	0.48	<0.01	0.46
Contusion skull	1.8	0.59	<0.01	0.57
Vomiting more than once	1.7	0.52	0.05	0.50
Age (per year over 16)	1.0	0.01	<0.01	0.01
Post traumatic amnesia 0 to 2h (or unknown)	2.0	0.70	<0.01	0.67
Post traumatic amnesia 2 to 4h	2.6	0.96	<0.01	0.93
Post traumatic amnesia >4h	5.7	1.73	<0.01	1.68
Loss of consciousness (or unknown)	1.9	0.62	<0.01	0.61
Neurologic deficit	2.5	0.90	<0.01	0.87
Fall from any elevation	1.6	0.49	<0.01	0.47
Use of antiplatelet therapy[a]	1.7	0.51	<0.01	0.49
Dangerous trauma mechanism[b]	1.9	0.64	<0.01	0.62
Focal high impact trauma	2.4	0.87	<0.01	0.84

To determine the need for a CT scan the beta-coefficients of present risk factors have to be added (for age multiplied by age in years over 16). The intercept is -4.34 and the intercept for the penalized estimation is -4.27. The predicted probability of a traumatic intracranial finding equals: $1/(1+e^{-(-4.27+\text{penalized beta score})})$. A penalized beta score of 0.79 equals a predicted probability of a traumatic intracranial finding of 3.0%

[a]Acetylsalicylic acid monotherapy or carbasalate calcium monotherapy should not be regarded as risk factor.

[b]Definition: High risk auto crash (intrusion >30cm to occupant site or >45cm to any other site, ejection from automobile, death in same passenger compartment, vehicle telemetry data consistent with high risk of injury); Auto versus pedestrian/bicyclist; motorcycle crash >32km/h (20 miles/h); fall from >6 meters (20 feet)

At a cut-off value for CT of *3% predicted-risk of any traumatic finding*, similar to original CHIP, the sensitivity of the updated CHIP was 92% (95% CI 89-94%) and the specificity was 27% (95% CI 26-28%). Sensitivity and specificity over a range of cut-off

values are shown in supplementary Table 5. Sensitivity and specificity for potential neurosurgical lesions at a cut-off value for CT of *3% predicted-risk of any traumatic finding* were 100% (95% CI 95-100%) and 26% (95% CI 25-27%) respectively. At this cut-off value sensitivity and specificity for neurosurgical intervention were 100% (95% CI 82-100%) and 26% (95% CI 24-27%).

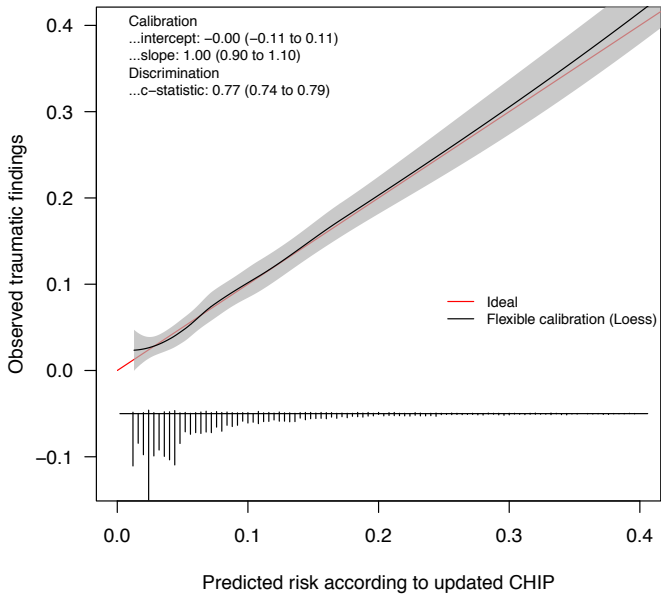

Figure 2. Calibration plot updated CHIP

Calibration plot updated CHIP, range 0 to 40% predicted and observed risk. A 95% confidence interval is given for intercept, slope and c-statistic.

Internal validation of the updated model using bootstrapping indicated optimism for the c-statistic, which we expected to decrease from 0.77 to 0.76 for any traumatic (intra)cranial finding. Internal validation using crossvalidation per center would decrease the c-statistic from 0.77 to 0.73 (Supplementary Figures 1 and 2). To correct for optimism penalized beta-coefficients were calculated (Table 3).

A sensitivity analysis only including scanned patients showed similar results for the updated CHIP. The c-statistic for any traumatic finding was 0.76 (95% CI 0.73-0.78). The c-statistic for potential neurosurgical lesions and neurosurgical intervention was 0.85 (0.81-0.89) and 0.90 (0.84-0.97) respectively. At a cut-off of *3% predicted-risk* 16 traumatic (intra)cranial findings were missed of which none was a potential neurosurgical lesion or needed neurosurgical intervention (sensitivity 96%; specificity 34%).

Discussion

The aim of this study was to update the CHIP decision rule, this was done in a large multicenter study in a contemporary Dutch cohort. The original CHIP-model underestimated the risk of traumatic (intra)cranial findings in low-predicted-risk patients, while in high-predicted-risk patients the risk was overestimated. The updated model performed better over a wide range of predicted risks.

The updated model uses three variables less than the original CHIP-model (12 versus 15) which makes it easier to use. The c-statistic for any traumatic finding would improve from 0.72 to 0.77. From the calibration plot it can be concluded that especially in the low-predicted-risk groups the updated model performs better than the original. Performance in these low-predicted-risk groups is most important because the high-predicted-risk groups will be scanned regardless of the exact predicted risk. Probably even more important, in contrast to the original CHIP, the updated CHIP would not miss any potential neurosurgical lesions or patients that actually underwent neurosurgery. Compared to the original CHIP-study potential neurosurgical lesions have been added as secondary outcome measure besides actual neurosurgical intervention. Neurosurgical intervention is rare in MHI patients and the decision to operate a patient is surgeon and country dependent.[21] Nonetheless nobody wants to miss a traumatic epidural hematoma or a large acute subdural hematoma, therefore the term potential neurosurgical lesion was introduced to more objectively identify the traumatic findings that definitely should not be missed. Hence, the largest gain of the updated model compared to the original CHIP is better identification of patients with (potential) neurosurgical lesions.

In the original CHIP-study a cut-off value of *3% predicted-risk for any traumatic finding* for performing a CT is used. This rather arbitrary threshold is used in this update study as well. Nevertheless, one could argue that a different cut-off value can be more suitable depending on setting and preferences. For cut-off levels up to *3.5%* and 6.0% *predicted risk for any traumatic finding* sensitivity for respectively potential neurosurgical lesions and actual neurosurgical intervention remained 100% in our study sample.

A striking difference between the original CHIP and this update is that the use of anticoagulants is no longer found to be a predictor of traumatic (intra)cranial findings, neither in univariable nor in multivariable analysis. Although it is impossible to establish the exact cause of this surprising change there are some possible explanations. First anticoagulants may be a smaller risk factor than previously thought. There are only

few studies that have established the risk of anticoagulant therapy for traumatic intracranial hemorrhage in MHI.[22,23] A recent systematic review found a pooled incidence of traumatic findings in MHI patients that used anticoagulants of 8.9%.[22] However, there was a large variation and in the two largest studies in the review this incidence was only 4%. A second reason for the difference could be that referral patterns have changed. Possibly patients on anticoagulant therapy are referred to the ED for less severe trauma than patients without anticoagulant therapy. This potential difference was nonetheless not reflected in the multivariable analysis. Finally we do not know how well anticoagulants were used, it is known that patients on anticoagulants frequently have a sub-therapeutic INR.[24] However, although anticoagulant use was not a risk factor for traumatic findings in the current study, a low threshold for scanning these patients should be considered in our opinion because traumatic findings may have a worse outcome in the presence of anticoagulant use.[25-27] Scanning all patients on anticoagulant therapy would (at a 3% *predicted-risk* scanning-threshold) lead to 81 extra CTs and a reduction of two patients with missed traumatic findings (sensitivity 92%; specificity 25%).

In contrast to the original CHIP-rule we choose to present the detailed results only, the updated decision rule will be integrated into an easy to use app. A simplified decision rule is less reliable and not necessary anymore because everybody uses smart phones and electronic patient records are widespread.

Future research is needed to externally validate this updated CHIP decision rule. Until now the CHIP-model has only been validated in The Netherlands. To increase generalizability validation data should preferably also be collected in other countries.

A limitation of this study is that not all consecutive MHI patients received a CT. This is a result of the current Dutch guidelines for patients with MHI[28]. Patients that were not scanned could possibly have had traumatic findings that would have been missed. To anticipate these possible false negatives, the outcomes of these patients were imputed. Because of different scanning rates in hospitals all different risk profiles of patients were present in the non imputed dataset. Nonetheless, differential patterns of missing data may introduce unknown biases despite multiple imputation.

The CHIP-rule predicts the presence or absence of traumatic findings on CT. Nonetheless, the real outcome of interest is the long-term clinical outcome which was not assessed in the current study.

Because there was no follow-up for discharged patients with a negative CT (or without CT) it is possible that some of these patients would have developed traumatic findings on consecutive scans. However development of an intracranial lesion after a normal CT is rare.[29]

In summary use of the updated CHIP decision rule should be considered in patients with MHI. Compared to the original CHIP the updated rule seems to be better able to identify patients with (potential) neurosurgical lesions without increasing the CT rate. In the current study anticoagulant use was not identified as independent risk factor for traumatic findings. Nonetheless a low threshold for scanning these patients is advised because of potentially worse outcome of traumatic intracranial hemorrhage in the presence of anticoagulant use. Future research is needed to externally validate the updated CHIP decision rule.

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Supplementary Material

Supplementary Table 1. Definition of potential risk factors

Risk factor	Explanation (if necessary)
Age	Age in years
GCS score on presentation	GCS score on presentation to the ED
Change in GCS	One hour after presentation to the ED
Clinical signs of skull fracture	Raccoon eyes, battle sign, hemotympanum, CSF otorrhea, CSF rhinorrhea, palpable discontinuity, bleeding from ear
Contusion of skull	Any injury above the eyebrows other than an abrasion or superficial cut
Vomiting	As reported or observed, presence and frequency
Posttraumatic amnesia (PTA)	As reported or observed, presence and duration (PTA unknown is considered to be PTA in the 'up to two hours' category)
Loss of consciousness (LOC)	As reported or observed, presence and duration (LOC unknown is considered to be present)
Neurologic deficit	Any deficit not known to be pre-existent such as: paresis, dysphasia or other such as cranial nerve damage including diplopia, changes in sensibility, asymmetrical reflexes or pathological reflexes, coordination problems and ataxia
Headache	At presentation to the ED, generalized or local
Use of anticoagulant therapy	Known or reported use of: vitamin K antagonists, NOACs, therapeutic (low molecular weight) heparin
Use of antiplatelet therapy	Known or reported use of antiplatelet medication including type. In the final decision model acetylsalicylic acid monotherapy or carbasalate calcium monotherapy is not regarded as risk factor[a]
Fall from any elevation	As reported or observed (standing height is not considered any elevation)
Pedestrian or cyclist versus motorized vehicle	As reported or observed
Ejected from vehicle	As reported or observed
Posttraumatic seizure	As reported or observed
Dangerous trauma mechanism	As reported or observed. Definition according to CDC guidelines for field triage[1]: High risk auto crash (intrusion >30cm to occupant site or >45cm to any other site, ejection from automobile, death in same passenger compartment, vehicle telemetry data consistent with high risk of injury); Auto versus pedestrian/bicyclist; motorcycle crash >32km/h (20 miles/h); fall from >6 meter (20 feet)

Supplementary Table 1. Continued

Risk factor	Explanation (if necessary)
Fall from elevation	As reported or observed. Fall from more than 1 meter or 5 stairs
Intoxication with alcohol or drugs	History or suggestive findings on examination
Focal high impact injury	As reported or observed. Suspicion of intracranial injury after focal high impact injury (e.g. struck with a baton, golf or hockey ball)

[a] The decision not to consider acetylsalicylic acid or carbasalate calcium monotherapy was based on our data and a recent systematic review[2].

Supplementary Table 2. Univariable analysis of potential risk factors

Variable	Total n=4557	Patients tICH[a] (n=406)	Odds Ratio	95% CI lower	95% CI upper	*P* value
age (years)	53.1	57.5	1.09	1.04	1.14	0.00
trauma mechanism, n (%)						
pedestrian or cyclist vs vehicle	230 (5.0)	37 (9.1)	2.06	1.42	2.97	0.00
fall from any elevation	940 (20.6)	138 (34.0)	2.15	1.73	2.68	0.00
ejected from vehicle	154 (3.4)	16 (3.9)	1.19	0.70	2.02	0.51
high energy trauma	588 (12.9)	92 (22.7)	2.16	1.68	2.77	0.00
symptoms						
(any) vomiting, n (%)	311 (6.8)	40 (9.9)	1.57	1.10	2.22	0.01
vomiting > once, n (%)	147 (3.2)	23 (5.7)	1.95	1.24	3.08	0.00
PTA[b]						
PTA 0-2h, n (%)	976 (21.4)	173 (42.8)	4.43	3.49	5.61	0.00
PTA 2-4h, n (%)	69 (1.5)	14 (3.5)	5.23	2.84	9.64	0.00
PTA > 4h, n (%)	59 (1.3)	21 (5.2)	11.35	6.49	19.87	0.00
PTA unknown	498 (10.9)	59 (14.6)	2.76	2.00	3.81	0.00
LOC[c]						
LOC 0-15min, n (%)	1160 (25.5)	166 (41.0)	3.24	2.55	4.12	0.00
LOC 15-30min, n (%)	32 (0.7)	10 (2.5)	8.82	4.09	19.00	0.00
LOC unknown, n (%)	648 (14.2)	96 (23.7)	3.38	2.56	4.46	0.00
headache, n(%)	1650 (36.2)	165 (40.6%)	1.23	1.00	1.51	0.05
posttraumatic seizure	38 (0.8)	8 (2.0)	2.76	1.26	6.06	0.01

Supplementary Table 2. Continued

Variable	Total n=4557	Patients tICH[a] (n=406)	Odds Ratio	95% CI lower	95% CI upper	*P* value
external evidence of injury						
signs of skull base fracture, n (%)	148 (3.2)	52 (12.8)	6.21	4.35	8.85	0.00
contusion of the skull, n (%)	2574 (56.5)	276 (68.0)	1.71	1.38	2.13	0.00
injury to the face, n (%)	1631 (36.0)	142 (34.5)	0.93	0.75	1.15	0.51
neurologic examination						
GCS[d] (15=reference)						
GCS 15, n (%)	3914 (85.9)	267 (65.8)				
GCS 14, n (%)	500 (11.0)	91 (22.4)	3.04	2.35	3.94	0.00
GCS 13, n (%)	143 (3.1)	48 (11.8)	6.90	4.77	9.98	0.00
GCS deterioration (after 1h), n (%)						
1 point deterioration	38 (0.8)	5 (1.2)	1.58	0.61	4.06	0.35
2 points deterioration	12 (0.3)	6 (1.5)	10.41	3.34	32.43	0.00
neurologic deficit, n (%)	134 (2.9)	28 (6.9)	2.83	1.84	4.34	0.00
use of anticoagulant therapy, n (%)	486 (10.7)	34 (8.4)	0.75	0.52	1.08	0.12
use of antiplatelet therapy[e], n (%)	211 (4.6)	33 (8.1)	1.98	1.34	2.91	0.00
intoxication, n (%)	1057 (23.2)	90 (22.2)	0.94	0.73	1.20	0.61

[a]tICH: traumatic intracranial hemorrhage/any traumatic finding
[b]PTA: posttraumatic amnesia
[c]LOC: Loss of consciousness
[d]GCS: Glasgow Coma Scale score
[e]Excluding acetylsalicylic acid or carbasalate calcium monotherapy

Supplementary Table 3. Traumatic CT findings in 3742 patients with a head computed tomography (CT)

CT finding	**N (%)[a,b]**
Any traumatic CT finding	383 (8.4%)
Skull fracture	150 (3.3%)
Depressed fracture	19 (0.5%)
Linear fracture	66 (1.4%)
Skull base fracture	68 (1.5%)
Subarachnoid hemorrhage	182 (4.0%)
Contusion	
Small	115 (2.5%)
Large (mass)	10 (0.2%)
Subdural hematoma	
Small	126 (2.8%)
Large (mass)	22 (0.5%)
Epidural hematoma	
Small	30 (0.7%)
Large (mass)	5 (0.1%)
Suspicion of diffuse axonal injury on CT	13 (0.3%)
Basal cisterns compressed or obliterated	10 (0.2%)
CT shift	
• 0-4mm	16 (0.4%)
• 5mm or more	9 (0.2%)

[a] Some patients had more than 1 CT finding

[b] Percentage of the total number of patients (n=4557)

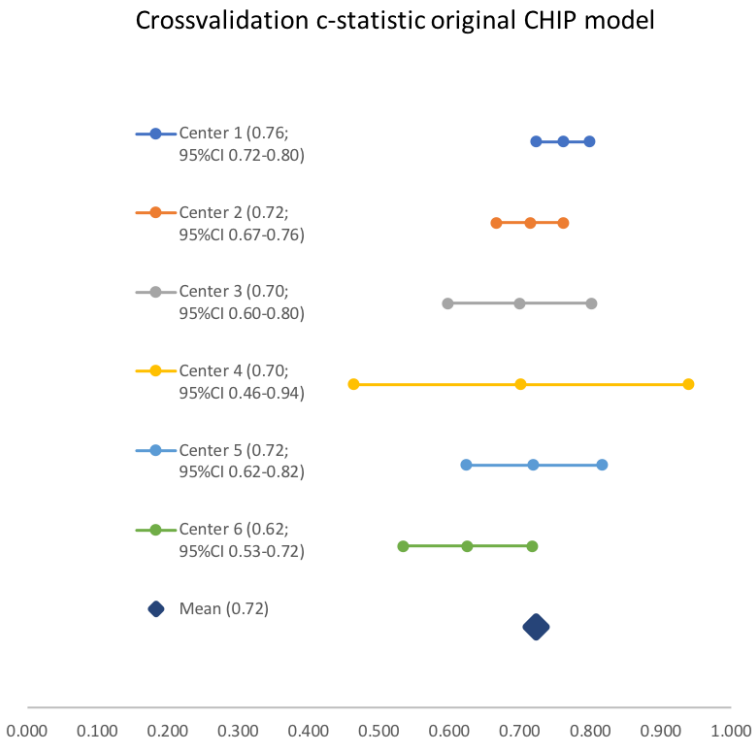
Supplementary Table 4. Re-estimation of regression coefficients CHIP

Risk factor	Odds ratio	Beta-coefficient	*P* value
Signs of skullbase fracture	4.7	1.55	<0.01
GCS 13	3.2	1.20	<0.01
GCS 14	2.0	0.68	<0.01
Contusion skull	1.8	0.59	<0.01
Vomiting	1.2	0.19	0.33
Age (per year over 16)	1.0	0.01	<0.01
Post traumatic amnesia 2 to 4h	1.5	0.42	0.21
Post traumatic amnesia > 4h	3.7	1.52	<0.01
Loss of consciousness (or unknown)	2.5	0.91	<0.01
Neurologic deficit	2.6	0.95	<0.01
Fall from any elevation	1.8	0.59	<0.01
Use of anticoagulant therapy	0.7	-0.42	0.04
GCS deterioration	1.1	0.08	0.78
Pedestrian or cyclist versus vehicle	1.9	0.62	<0.01
Ejected from vehicle	0.9	-0.11	0.72
Posttraumatic seizure	1.6	0.48	0.29
Intercept -4.12			

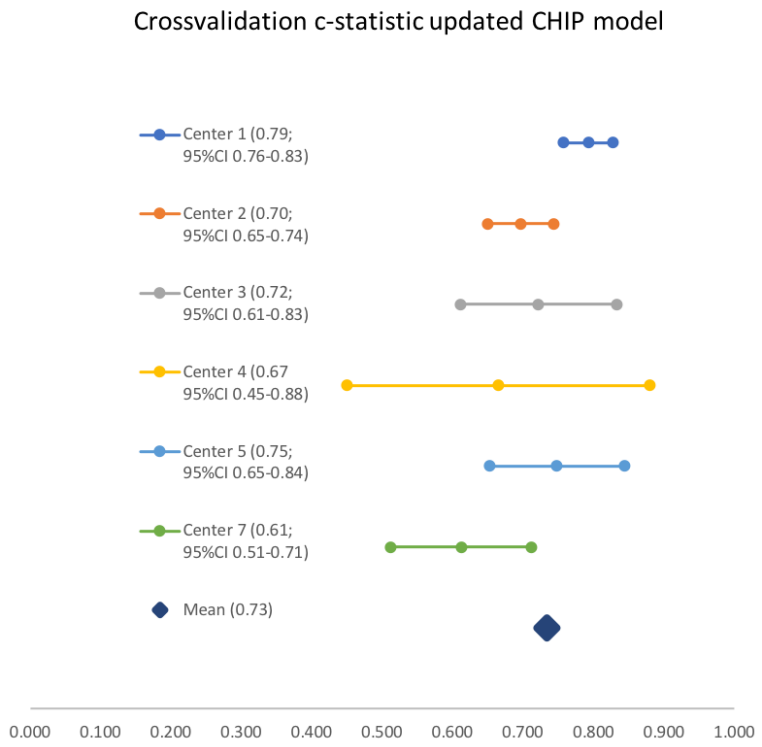
To determine the need for a CT scan the beta-coefficients of present risk factors have to be added (for age multiplied by age in years over 16). The predicted probability of a traumatic intracranial finding equals: $1/(1+e^{-(-4.12+\text{beta score})})$.

Supplementary Table 5. Performance of updated CHIP at different cut-off levels (n=4557)

Cut-off (predicted risk)	CT scans prevented (%)	Traumatic findings missed (total n=406)	Potential neuro-surgical findings missed (total n=73)	Neuro-surgical inter-ventions missed (total n=18)	Sensitivity (any traumatic finding)	Specificity (any traumatic finding)
1.5%	211 (4.6%)	6	0	0	99%	4.9%
2.0%	409 (9.0%)	8	0	0	98%	9.7%
2.5%	764 (17%)	18	0	0	96%	18%
3.0%	1155 (25%)	33	0	0	92%	27%
3.5%	1397 (31%)	36	0	0	91%	33%
4.0%	1663 (37%)	45	2	0	89%	39%
4.5%	1965 (43%)	59	4	0	86%	46%
5.0%	2249 (49%)	72	4	0	82%	52%
5.5%	2388 (52%)	77	4	0	81%	56%
6.0%	2512 (55%)	81	4	0	80%	58%
6.5%	2640 (58%)	88	5	1	78%	62%



Supplementary Figure 1. Crossvalidation c-statistic original CHIP model per center



Supplementary Figure 2. Crossvalidation c-statistic updated CHIP model per center

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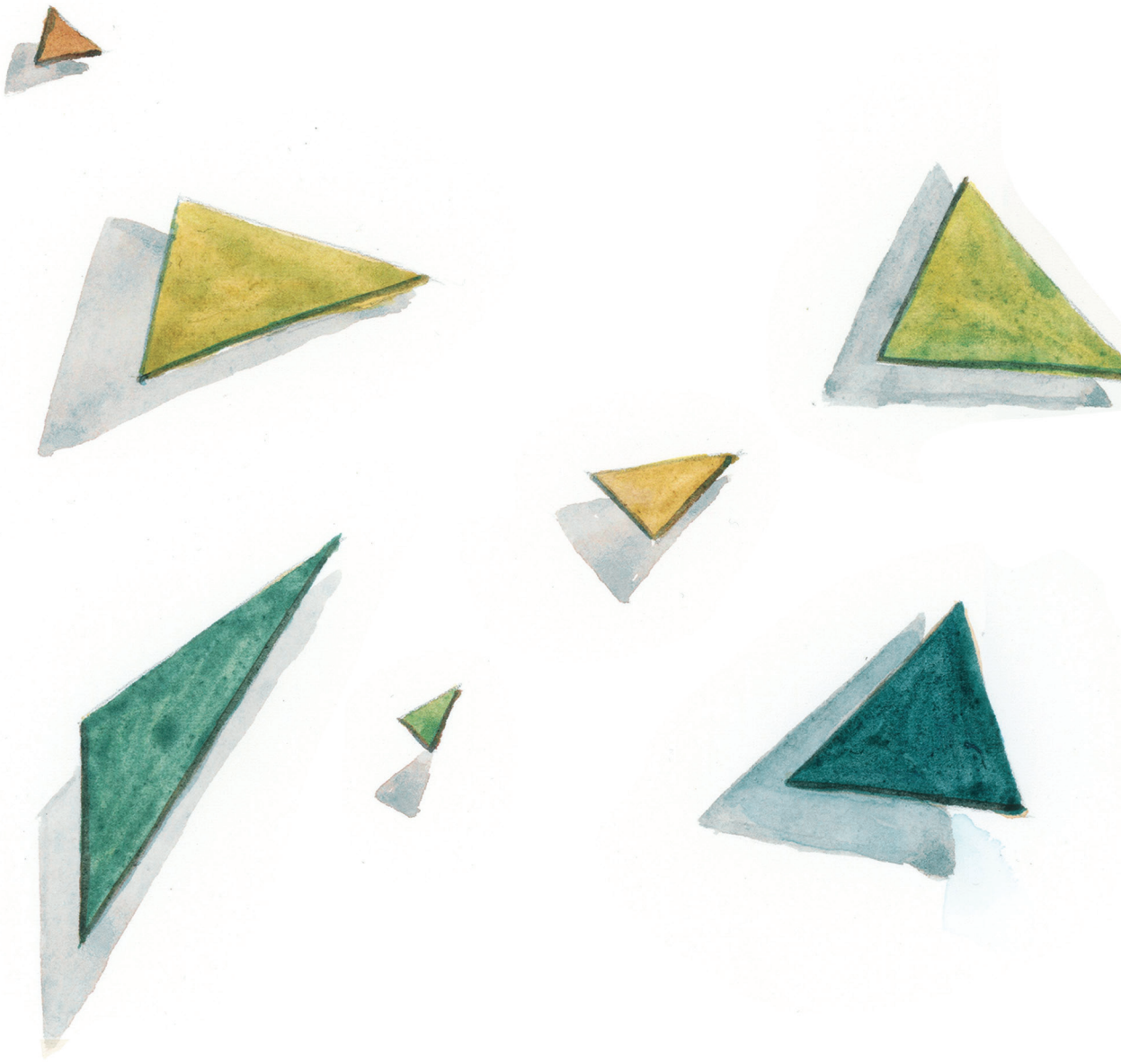
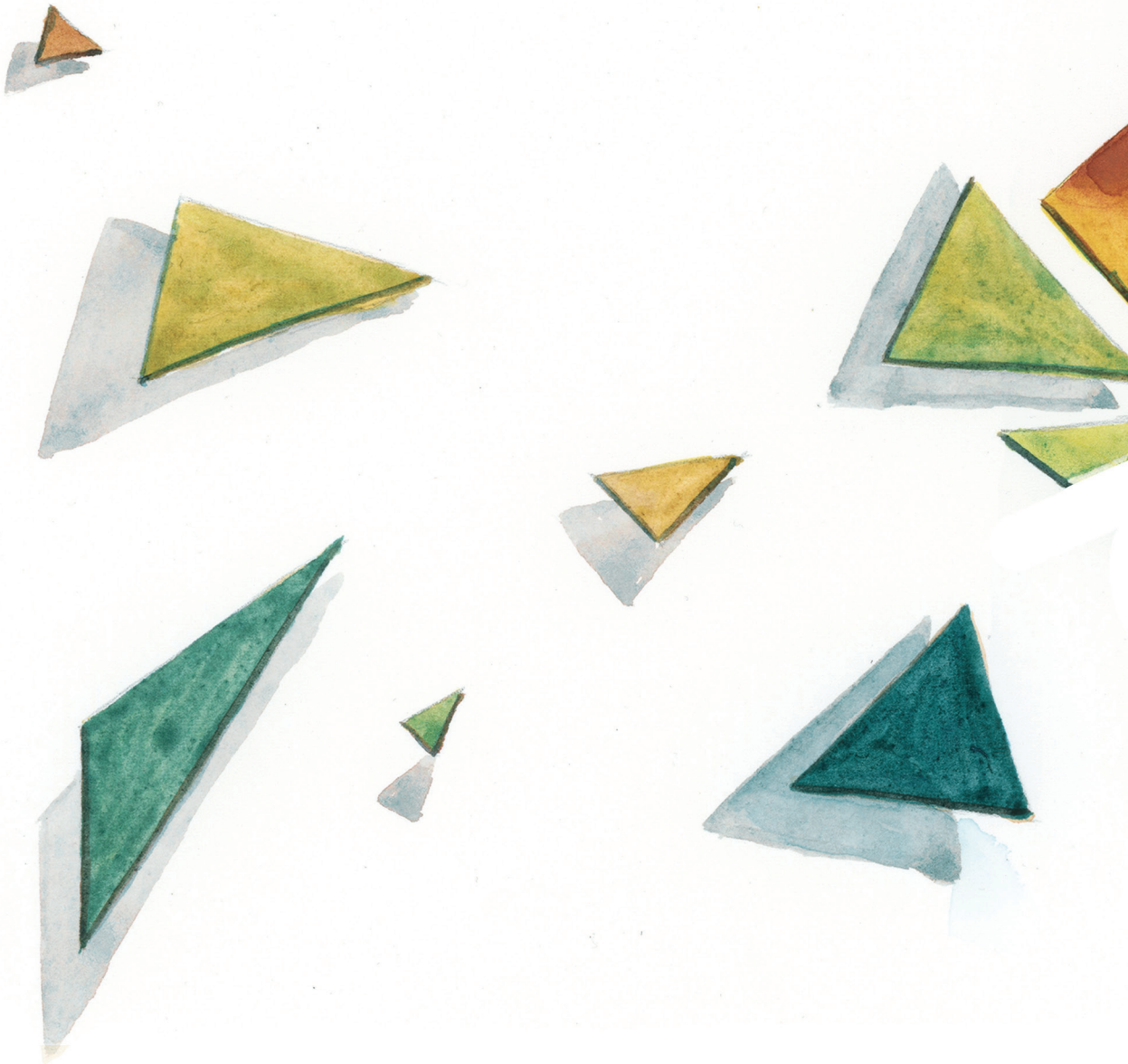


PART IV

Conclusions



CHAPTER 8

General discussion

General discussion

This thesis describes the epidemiology, risk factors, preventive measures and decision rules for diagnostics in patients with head trauma and traumatic brain injury (TBI) in emergency departments (EDs) in the Netherlands.

Interpretation and clinical implications of main findings

Current situation and trends in traumatic brain injury

Chapter 2 of this thesis demonstrated a 75% increase in ED visits and a 95% increase in hospitalizations for TBI in the Netherlands between 1998 and 2012. In contrast, TBI-related mortality remained stable. Similar trends in TBI-related ED visits and mortality are observed in other high-income countries.[1,2]

In most high-income countries the epidemiology of patients with TBI is changing.[3] Nowadays the average patient with TBI is older and more often female than one or two decades ago. This trend was confirmed in our own studies (chapter 6). Moreover, the relative and absolute increase in ED visits by elderly TBI patients is higher than expected based on ageing of the population alone. Several explanations for these changes are: increased awareness of TBI especially in the elderly, changed guidelines and increased use of antiplatelet and anticoagulant drugs. Finally, the elderly participate in society until a higher age and live longer independently than in the past. These developments could lead to more fall accidents. [4-6]

The major changes in epidemiology and causative trauma mechanism we observed in our studies have significant clinical implications. Almost all decision rules for minor head injury that are being used globally have been based on studies from the beginning of this century [7-9]. The results of these studies have been adopted in (inter)national guidelines and are still being used in daily practice today. It is highly questionable whether the results and decision aids from those studies are still as valid today in a totally different population, in comparison with the population two decades ago. For example head injury caused by ground level falls leads less often to death or severe TBI compared to other (high energetic) trauma mechanisms.[10] Nonetheless, given a certain Glasgow Coma Scale (GCS) score the mortality is higher in older patients than in young patients with TBI.[11] This implies that identification of head injury patients with (intra)cranial lesions is potentially unreliable in guidelines that are based on old decision rules. Therefore, guidelines should be validated in the current population, as we did for the Dutch population (Chapter 6).

In chapter 3 of this thesis we demonstrated that the current Dutch guideline did not have the desired effect of less CT-scans and/or less hospitalizations. In contrast both CT ratio and hospitalizations increased. These effects are not solely the consequence of the new guideline. Nonetheless a critical appraisal of the guideline is needed as the effects of the introduction of the guideline are the opposite to what was expected. Examples of possible adjustments to the guideline that could be considered to limit the number of CT-scans are adjustment of the guideline to the current population, a higher threshold for performing a CT-scan and more emphasis on clinical judgement or the implementation of other diagnostic modalities such as biomarkers. Furthermore, a multimodal intervention focusing on physicians could be of importance to reduce the number of CT scans and or the number of hospitalizations.[12]

Prevention of traumatic brain injury

Not only the demographics of patients changed, also causative trauma mechanisms changed in our studies. In the ageing population more injuries resulted from ground level falls compared to the past when violence and motorized vehicle accidents were predominant causative mechanisms (chapters 2,6,7). These changes are in line with changes observed in other high-income countries.[1,13] In light of the rapidly increasing number of ED visits for TBI in combination with limited treatment options, much effort should be made to prevent head injury and TBI.

As mentioned above, ground level falls, especially in the elderly, are the most important and increasing cause of TBI in the Netherlands. Not only are falls the most important cause, falls in elderly individuals also lead relatively more often to head/brain injury than in the past.[14] Besides a major cause of (head)injury, falls are also a major cause of death in the Netherlands.[6] The number of deaths caused by falls is increasing rapidly. In 2018 the mortality caused by ground level falls was almost three times higher than at the beginning of this century.[15] An important cause for the increase in fall-related injury is ageing of the population. However, fall rates in the elderly exceed the expected number of falls which would be expected by ageing of the population alone.[4,16,17] In the Netherlands increased fall rates in the elderly, amongst other explanations such as increased awareness, might be caused by the fact that elderly live independently until a higher age than in the past.[18]

Falls in elderly individuals can be reduced by exercise and fall prevention programs.[19-25] The increase in the number of fall-related TBIs in older adults suggests an urgent need to enhance fall-prevention efforts in that population.[14,26]

Besides ground level falls another increasingly important, typically Dutch cause of TBI are bicycle accidents. Compared to other countries the use of bicycle helmets is low by commuter and recreational cyclists in the Netherlands. While the mortality risk (number of traffic deaths per kilometer) of other modes of transportation decreased in the past 20 years in the Netherlands, bicycle-related mortality did not decrease. [27] International studies have shown that bicycle helmet use may decrease TBI.[28] In chapter 5 of this thesis we demonstrated that more frequent use of bicycle helmets would probably lead to a decrease in TBI in the Netherlands. After a recent appeal from a group of physicians, helmets will become obligatory for light mopeds (up to 25km/h) in the Netherlands.[29], Introduction of helmet laws for bicyclists could lead to a reduction of bicycle use and therefore turn out to be counter-productive for public health.[30] Hence, provision of good information and stimulation of voluntary bicycle helmet use seems to be the best option.

Risk factors for traumatic brain injury, antiplatelet therapy

Controversy exists whether antiplatelet therapy should be considered as a risk factor for intracranial complications in patients with head injury. Several mostly low to moderate quality studies have been conducted that studied the effect of antiplatelet therapy on the risk of intracranial complications in head injury. In this thesis we conducted a systematic review and meta-analysis of these studies (chapter 4). This review suggests that pre-injury antiplatelet therapy, other than acetylsalicylic acid (ASA) monotherapy, is associated with an increased incidence of traumatic intracranial hemorrhage. However, this should be interpreted with caution given the high heterogeneity and methodological flaws of several studies included in the systematic review. For patients on ASA monotherapy the available evidence was insufficient to establish whether this should be considered as a risk factor as well. Besides the fact that patients with antiplatelet therapy seem to have a higher risk of intracranial complications, there are indications that these patients also have higher risk of an unfavorable outcome. [31-33] Hence, a low scanning threshold is warranted for patients on antiplatelet therapy.

Decision rules for patients with minor head injury and mild traumatic brain injury

Several decision rules have been developed to efficiently identify patients with head injury that have intracranial complications. As mentioned before, most of these decision rules have been developed at the beginning of this century, when the demographics of patients with head injury were quite different from nowadays. Four frequently used decision rules were validated and compared in chapter 6 of this thesis. The New Orleans Criteria (NOC), the Canadian CT Head Rule (CCHR), the National Institute for Health and Care Excellence (NICE) and the CT in Head Injury

Patients (CHIP) rule.[7-9,34] We concluded that all four decision rules (NICE, CCHR, NOC, CHIP) that were validated could be used. However, all of them have important limitations, either scanning almost all patients or missing significant lesions. On the one hand the NOC had the highest sensitivity, but at the cost of a low specificity; on the other hand the NICE had the highest specificity but at the cost of a low sensitivity. Which decision rule is preferred depends on how many unnecessary CT scans you are willing to make to prevent one missed traumatic lesion. The clinical implication from chapter 6 is clear, the decision rules should be updated.

Consequently we performed an update of the CHIP rule which is described in chapter 7. The updated CHIP rule consists of 12 variables, compared to 15 in the original CHIP rule. Compared to the original CHIP the updated rule could better identify patients with (potential) neurosurgical lesions without increasing, or potentially decreasing, the CT rate. In accordance with our findings from chapter 4 of this thesis, the use of antiplatelet therapy was associated with traumatic findings on CT and was included in the decision rule. Surprisingly anticoagulant (e.g. coumarins) use was not identified as independent risk factor for traumatic findings. Nonetheless a low threshold for scanning these patients is advised both because of potentially worse outcome of traumatic intracranial hemorrhage in the presence of anticoagulant use, and because these results have not yet been confirmed in a validation study.[31-33]

Instead of a fixed scan threshold we gave insight to an increase or decrease in scanning threshold, with subsequently a shift in balance between specificity and sensitivity. In this way clinicians or guidelines can tailor their advice depending on how many unnecessary CT scans they are willing to make to prevent one missed traumatic lesion.

Limitations

The limitations of each individual study included in this thesis have been discussed in the relevant chapters. Some general limitations will be mentioned here.

Different data sources have been used for different studies included in this thesis. Chapters 3, 6 and 7 contain data collected by our own study group, for chapters 2 and 5 we used data from external sources and chapter 4 is a systematic review. This may lead to a difference in interpretation or definition of TBI. As a consequence the presented incidence figures have to be interpreted with caution.

An important limitation of the CREST (CT Refinement Study), presented in chapters 6 and 7, is that not all consecutive MHI patients received a CT-scan. Participating centers followed the applicable guidelines for CT scanning, patients without risk factors or with one minor criteria did not have a CT-scan. Therefore, patients who did not receive a CT but had intracranial traumatic findings (false negative patients) could have been missed. Possible solutions for this problem could have been either scanning all participating patients or a follow-up study. Scanning all patients did not seem completely ethical and would have led to longer throughput times in the participating busy EDs and would therefore probably have jeopardized the completeness of our study. Both more CT-scans and a follow-up study would have increased costs of the study substantially, this was not feasible considering the available budget. In the studies presented in chapters 6 and 7 we solved this problem by using imputation of the outcome based on present risk factors.

All studies included in this thesis have been conducted in a limited number of EDs in the Netherlands (except for the systematic review). Circumstances in other countries, or other EDs may differ. Therefore, extrapolating results from this thesis should be done with caution in other countries or other hospitals. Even more important, all studies have been conducted in EDs and results may not be valid for other settings such as general practitioners' practices or emergency medical services.

Future perspectives

Future studies will have to externally validate the updated CHIP rule, not only in the Netherlands, but preferably also in other countries. Besides that an increasing body of evidence exists that blood-based biomarkers for TBI can improve the diagnostic accuracy and clinical decision making.[35] In the past decades several potential **biomarkers** have been identified for this purpose. Some promising examples of these are: S100B, Glial fibrillary acidic protein (GFAP), Ubiquitin carboxy terminal hydrolase L1 (UCH-L1) and NSE (neuron-specific enolase). However, apart from S100B which is included in the Scandinavian Neurotrauma Guidelines, the use of biomarkers in clinical practice is still very limited at the moment.[36] Future studies should aim to study the effectiveness of incorporation of these biomarkers into clinical decision rules. For biomarkers to be of added value to current practice they should naturally be valid and reliable. Besides, they should be readily available and affordable. Finally, biomarkers should offer added value by either increasing precision or reducing costs and throughput times.

We demonstrated that CT rates increased after implementation of new minor head injury guidelines. We aimed to increase diagnostic accuracy to improve the existing CHIP rule on which the Dutch guideline was based. Nonetheless, it has not been proven that clinical decision rules for minor head injury do outperform **clinical judgement** (clinical gestalt). Therefore, future research should also compare clinical judgement with existing decision rules for minor head injury. Off course the experience of the physician has to be considered in this kind of research as clinical judgement is likely to improve with more experience. It is important to mention that guidelines are tools to facilitate clinical decision making and are not carved in stone. Whenever possible, the patient should be involved in decision making to come to a shared decision.

In the Netherlands, as well as in other countries, there are different guidelines for head injury for general practitioners, emergency medical services (EMS) and emergency departments (EDs).[37-39] As long as these guidelines are well aligned there does not have to be a problem. However, for each of these guidelines a different interpretation of available literature is being made. As we discussed in an opinion article, this leads to different, not well aligned guidelines and different treatment under similar circumstances.[40] Future guidelines for general practitioners, EDs and EMS should ideally be made jointly, or at least be **harmonized** and offer similar treatment under similar circumstances.

In this thesis we used fairly large patient series, nonetheless there are many more patients with TBI in the Netherlands than we could possibly include in our study. A **population-based registry** for patients with (mild) TBI could potentially include tens of thousands of patients annually in the Netherlands alone. Clinical information from such a database could be used to enhance decision making regarding diagnostics and the (acute) treatment of TBI. This could be done either by machine learning algorithms or by traditional regression models.

As discussed before we should focus on ways to prevent TBI, especially in the elderly. Fall prevention programs should be evaluated and effective **fall prevention programs** should be implemented. Implementation of such programs can be challenging and ways to better implement these programs should be studied.

Finally, the studies presented in this thesis as well as other TBI decision rules focus on CT results and short-term outcomes. Naturally, these are not the real outcomes of primary interest. It would be very valuable to relate clinical and CT findings in the acute setting to **long-term outcomes**.

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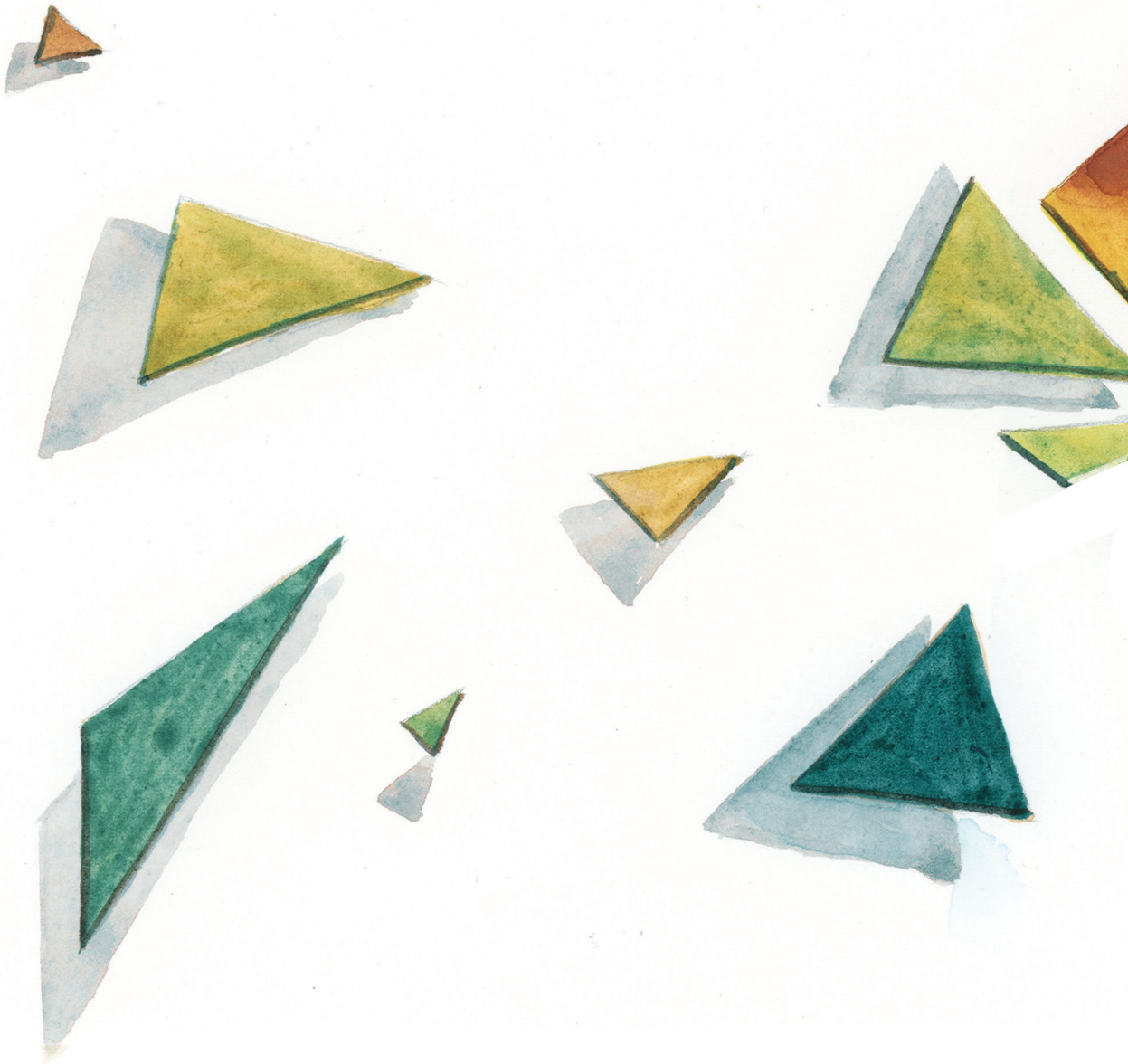


CHAPTER 9

Summary

Summary

Chapter 1 describes the background and aims of this thesis. Each year millions of people die and even more become disabled as a result of traumatic brain injury (TBI). The incidence of TBI is increasing worldwide. In high income countries TBI falls are the most important cause of TBI in an ageing population.

Computed Tomography (CT) is the most used imaging technique to rule out intracranial complications of head injury. To enhance selective use of CT for patients with head injury several decision rules have been developed. Most of these rules are applicable only for patients who have loss of consciousness, amnesia or confusion. However, many patients with head injury do not have any of these and are still at risk for (intra) cranial lesions. Therefore, the CT in Head Injury Patients (CHIP) decision rule was developed in the Netherlands. The CHIP decision rule is applicable to almost all patients with head injury and a Glasgow Coma Scale score (GCS) between 13 and 15. The Dutch guideline for minor head injury is, regarding CT indications, based on the CHIP decision rule with some minor modifications.

There are many uncertainties and controversies regarding the epidemiology, diagnostics and acute treatment for (mild)TBI. Therefore, the aim of this thesis was to study changes in epidemiology, preventive measures and decision rules for diagnostics for patients with head injury and TBI in emergency departments in the Netherlands.

Part I
Changing trends in traumatic brain injury

In **Chapter 2** a longitudinal study that evaluated trends in TBI related emergency department (ED)-visits, hospitalization and mortality in the Netherlands between 1998 and 2012 is presented. Data from the Dutch Injury Surveillance System (Letsel Informatie Systeem; LIS), the National Medical Register (Landelijke Medische Registratie; LMR), and Statistics Netherlands (Centraal Bureau voor de Statistiek; CBS) were used for ED-visits, hospitalization and mortality respectively.

Between 1998 and 2012 there was a 75% increase in ED visits for TBI, a 95% increase for TBI related hospitalization; overall mortality due to TBI did not change significantly. Despite the overall increase in TBI related ED visits this increase was not evenly distributed among age groups or trauma mechanisms. In patients younger than 65 years, a declining trend in ED visits for TBI caused by road traffic accidents was seen. Among patients 65 years or older, ED visits for TBI caused by a fall increased markedly.

TBI related mortality shifted from mainly young and middle aged (67%) individuals and (< 65 years) to mainly elderly (63%) individuals (≥ 65 years) between 1998 and 2012.

Chapter 3 describes the effect on CT ratio and hospital admission ratio after introduction of a new guideline for minor head injury in the Netherlands in 2010. The study had an interrupted time series study design. Data selection was performed manually, and was done three years before (2007-2009) and several years after (2012, 2014, 2015) introduction of the guideline.

Data collection was performed for 3880 patients. Introduction of the new guideline was associated with an increase in CT ratio from 24.6% before to 55% after introduction ($p<0.001$). This increase is both the result of a secular trend and a result of the introduction of the new guideline itself. Besides this, hospital admissions increased from 14.7% to 23.4% ($p<0.001$) during the study period, this increase was less clearly associated with the introduction of the new guideline. After introduction of the guideline there was no significant increase in intra(cranial) traumatic findings with 2.6% vs. 3.4% ($P = 0.13$). Neither did it lead to more neurosurgical interventions with 0.1% vs. 0.2% ($P = 0.50$).

Part II
Prevention of- and risk factors for traumatic brain injury

In **Chapter 4** we describe a systematic review and meta-analysis, with the objective to evaluate whether the pre-injury use of antiplatelet therapy (APT) is associated with increased risk of traumatic intracranial hemorrhage (tICH) on CT scan. Pubmed, Medline, Embase, Cochrane Central, reference lists and national guidelines on traumatic brain injury were used as data sources.

Eligible studies were cohort studies and case-control studies that assessed the relationship between APT and tICH. Studies without control group were not included. The primary outcome of interest was tICH on CT. Two reviewers independently selected studies, assessed methodological quality and extracted outcome data.

The search resulted in ten eligible studies with 20,247 patients with head injury that were included in the meta-analysis. The use of APT in head injury patients was associated with significant increased risk of tICH compared to control (odds ratio 1.87, 95% confidence interval 1.27 to 2.74). There was significant heterogeneity in the studies (I^2 84%), although almost all showed an association between APT use and tICH. This association could not be established for patients on acetylsalicylic acid monotherapy. When considering only patients with mild traumatic brain injury (mTBI) the odds ratio is 2.72 (95% CI 1.92-3.85). The results were robust to sensitivity analysis on study quality.

In conclusion APT in head injury patients is associated with increased risk of tICH, this association is most relevant in patients with mTBI. Whether this association is the result of a causal relationship, and whether this relationship also exists for patients on acetylsalicylic acid monotherapy could not be established with the review and meta-analysis.

Chapter 5 describes a case-control study with the aim to determine the association between bicycle helmet use in adults (16 years and older) and traumatic brain injury in EDs in the Netherlands.

The conducted study was a retrospective case-control study in patients aged 16 years and older that sustained a bicycle accident and therefore visited the EDs of participating hospitals throughout 2016. Cases were patients with traumatic brain injury (TBI), controls were patients without TBI but with other trauma. Exposure was defined as helmet wearing during the accident.

In total 2133 patients were included in the study, 361 cases (patients with TBI) and 1772 controls (patients without TBI). Within the TBI group (cases) 3.9% of the patients wore a helmet compared to 7.7% of patients in the control (non-head injury) group (OR 0.49, 95% CI 0.28-0.86). No difference in helmet wearing was observed in patients that sustained accidents which involved motorized vehicles (OR 0.91; 95% CI 0.29-2.83).

In conclusion adult patients (≥ 16 years) with TBI had a significantly lower odds for wearing a bicycle helmet than adult patients with other trauma (without TBI), adding more evidence that wearing a bicycle helmet effectively protects against TBI.

Part III
Decision rules for patients with minor head injury and mild traumatic brain injury

Both for chapter 6 and for chapter 7 results from the CREST study were used. The CREST study is a prospective cohort study in nine EDs in the Netherlands. The participants were consecutive adult (≥ 16 years) patients who presented with minor head injury (MHI) at the ED with a GCS score of 13-15 between March 2015 and December 2016.

Primary outcome was any (intra)cranial traumatic finding on CT. Secondary outcomes were any potential neurosurgical lesion and neurosurgical intervention within 30 days. Among 4557 included patients 3742 received a head CT (82%). In 383 patients (8.4%) a traumatic finding was present on CT. A potential neurosurgical lesion was found in 73 patients (1.6%) with 18 (0.4%) actually undergoing neurosurgery.

Chapter 6 describes the external validation of four commonly used computed tomography (CT) decision rules for MHI in a prospective cohort study in nine EDs in the Netherlands. We compared the sensitivity, specificity and clinical usefulness (defined as net benefit, a weighted sum of true and false positive classifications) of four CT decision rules: CT in Head Injury Patients (CHIP) rule; New Orleans Criteria (NOC); Canadian CT Head Rule (CCHR); and National Institute for Clinical Excellence (NICE) guideline for head injury.

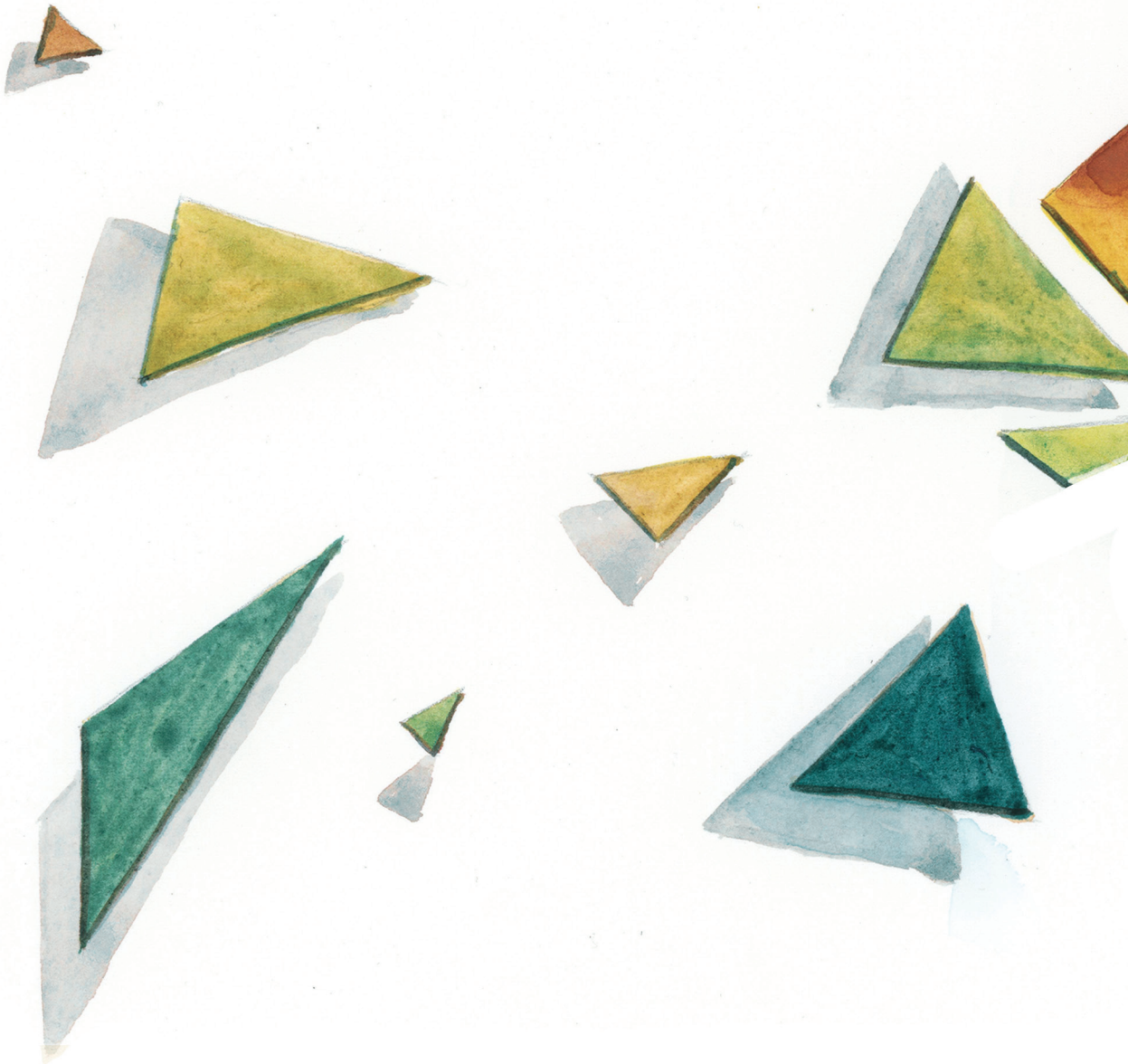
The sensitivity for any intracranial traumatic finding on CT ranged between 73% (NICE) and 99% (NOC); specificity ranged from 4% (NOC) to 61% (NICE). Sensitivity for a potential neurosurgical lesion ranged between 85% (NICE) and 100% (NOC); specificity from 4% (NOC) to 59% (NICE). Clinical usefulness depended on thresholds for CT scanning: at a low threshold the NOC was preferable and at a higher threshold the NICE was preferable; whereas for an intermediate threshold the CHIP rule was preferable.

Application of CHIP, NOC, CCHR, or NICE decision rules leads to a wide variation in CT scanning among MHI patients, resulting in many unnecessary CTs and some missed intracranial traumatic findings. Use of the CHIP rule was recommended because it leads to a reduction of CTs while missing very few potential neurosurgical lesions. Besides this an update of the CHIP rule (or another decision rule) was recommended.

In **Chapter 7** we present this update of the CHIP rule. Similar to chapter 6 we used data from the CREST study for this chapter. The CHIP model was validated and subsequently updated and revised. Diagnostic performance was assessed by calculating the c-statistic.

The original CHIP underestimated the risk of traumatic findings in the low-predicted-risk groups, while in the high-predicted-risk groups the risk was overestimated. The c-statistic of the original CHIP model was 0.72 (95%CI 0.69-0.74). The original CHIP model would have missed two potential neurosurgical lesions and one patient that underwent neurosurgery. The updated model performed better over a wide range of predicted risks. The c-statistic of the updated model was 0.77 (95%CI 0.74-0.79). At a similar CT rate as the original CHIP, the updated CHIP would not have missed any (potential) neurosurgical lesions.

Chapter 8 constitutes the general discussion and clinical implications of the main findings, general limitations and future perspectives.



CHAPTER 10

Dutch Summary (Nederlandse Samenvatting)

Dutch Summary (Nederlandse Samenvatting)

Hoofdstuk 1 beschrijft de achtergrond en doelen van dit proefschrift. Jaarlijks overlijden er miljoenen mensen ten gevolge van traumatisch hersenletsel of lopen blijvend letsel op. De incidentie van traumatisch hersenletsel neemt wereldwijd toe. In 'westerse' landen, met een vergrijzende populatie, zijn valongevallen de belangrijkste oorzaak van traumatisch hersenletsel.

Een CT-scan is de meest gebruikte modaliteit om intracraniële bloedingen uit te sluiten bij patiënten met hoofd letsel. Om gepast gebruik van CT-scans voor patiënten met hoofdletsel te bevorderen zijn verschillende beslisregels ontwikkeld. De meeste van deze beslisregels zijn uitsluitend te gebruiken bij patiënten met (doorgemaakt) bewustzijnsverlies, posttraumatische amnesie of verwardheid. Veel patiënten met hoofdletsel hebben dit echter niet en kunnen desondanks mogelijk wel een intracraniële bloeding hebben. Daarom is aan het begin van deze eeuw de CHIP (CT in Head Injury Patients) beslisregel ontwikkeld in Nederland. De CHIP beslisregel is toepasbaar bij vrijwel alle patiënten met hoofdletsel en een Glasgow Coma Score (GCS) tussen 13 en 15. De Nederlandse richtlijn voor licht traumatisch hoofd-hersenletsel is voor een belangrijk deel gebaseerd op de CHIP beslisregel.

Er bestaat nog veel onzekerheid en verschil van inzicht rondom de epidemiologie, diagnostiek en acute behandeling van (licht) traumatisch hoofd-hersenletsel (LTH). Het doel van dit proefschrift is daarom het evalueren van (veranderingen in) epidemiologie van traumatisch hoofd-hersenletsel (deel I); het evalueren van risicofactoren en preventieve maatregelen voor traumatisch hoofd-hersenletsel en tot slot (deel III) het vergelijken, valideren en verbeteren van beslisregels voor licht traumatisch hoofd-hersenletsel (LTH).

Deel I
Veranderende trends in traumatisch hersenletsel

In **Hoofdstuk 2** beschrijf ik een longitudinale studie naar trends in spoedeisende hulp (SEH) bezoeken, opnames en overlijdens ten gevolge van traumatisch hersenletsel in Nederland tussen 1998 en 2012 gepresenteerd. Voor deze studie is data afkomstig van het Letsel Informatie Systeem (LIS), de Landelijke Medische Registratie (LMR) en het Centraal Bureau voor de Statistiek (CBS) gebruikt.

Tussen 1998 en 2012 was er een toename van 75% voor spoedeisende hulp (SEH) bezoeken voor traumatisch hersenletsel en een toename van 95% voor ziekenhuis opnames ten gevolge van traumatisch hersenletsel. Voor het aantal overlijdensgevallen ten gevolge van traumatisch hersenletsel werd geen significante verandering gezien in de studieperiode. Alhoewel er over de gehele linie dus een toename in het aantal SEH bezoeken voor traumatisch hersenletsel werd gezien, was deze toename niet gelijkmatig verdeeld over leeftijdsgroepen of traumamechanismen. Bij patiënten jonger dan 65 jaar werd bijvoorbeeld een afname gezien in traumatisch hersenletsel ten gevolge van verkeersongevallen. Bij patiënten van 65 jaar en ouder werd daarentegen juist een forse toename van het aantal SEH bezoeken ten gevolge van valongevallen waargenomen.

Waar het in 1998 nog overwegend (67%) jongeren en mensen van middelbare leeftijd (< 65 jaar) waren die overleden ten gevolge van traumatisch hersenletsel, waren het in 2012 juist overwegend (63%) ouderen (≥ 65 jaar) die overleden waren aan traumatisch hersenletsel.

Hoofdstuk 3 beschrijft de ontwikkeling in het aantal CT-scans en het aantal opnames voor LTH na de introductie van een nieuwe richtlijn in 2010. In deze studie wordt een '*interrupted time series*' analyse gebruikt. Van drie jaar voor (2007-2009) en verschillende jaren na (2012, 2014, 2015) introductie van de richtlijn werd data verzameld.

In totaal werden 3880 patiënten geïncludeerd. De introductie van de nieuwe richtlijn was geassocieerd met een toename van het percentage patiënten met LTH waarin een CT-scan wordt gemaakt van 24,6% voor introductie naar 55% na introductie (P < 0,001). Deze toename is echter niet uitsluitend toe te schrijven aan de introductie van de nieuwe richtlijn, er is ook sprake van een onderliggende trend van steeds meer CT-scans. Naast het percentage CT-scans nam ook het percentage opnames toe, van 14,7% naar 23,4% in de studieperiode (P < 0,001).

Deze toename was minder duidelijk geassocieerd met de introductie van de nieuwe richtlijn. Na introductie van de nieuwe richtlijn was er geen significante toename in het percentage traumatische afwijkingen dat werd gevonden (2,6% versus 3,4%; *P* = 0,13). Ook was er geen significant verschil in het aantal neurochirurgische ingrijpen (0,1% versus 0,2%; *P* = 0,50).

Deel II
Preventie van- en risicofactoren voor traumatisch hersenletsel

In **Hoofdstuk 4** wordt een systematische review en meta-analyse beschreven. We onderzochten of patiënten die voorafgaand aan een hoofdletsel trombocytenaggregatieremmers gebruikten een hoger risico hadden op een traumatische intracraniële bloeding. Voor deze review werden verschillende databases (Pubmed, Medline, Embase, Cochrane Central) en nationale richtlijnen geraadpleegd. Alleen studies waarbij er ook een controlegroep was werden geïncludeerd. De primaire uitkomstmaat was een traumatische intracraniële bloeding op CT-scan. Twee reviewers hebben onafhankelijk van elkaar de studies geselecteerd, geanalyseerd en de relevante data geëxtraheerd.

Tien relevante studies met in totaal 20.247 patiënten werden geïncludeerd in de meta-analyse. Het gebruik van trombocytenaggregatieremmers bij patiënten met hoofdletsel was geassocieerd met een significant verhoogd risico op een traumatische intracraniële bloeding (odds ratio 1,87; 95% betrouwbaarheidsinterval 1,27-2,74). Er was forse heterogeniteit tussen de studies (I^2 84%), maar vrijwel alle studies lieten een associatie zien tussen het gebruik van trombocytenaggregatieremmers en de aanwezigheid van een traumatische intracraniële bloeding op CT-scan. Deze associatie kon niet aangetoond worden voor patiënten die acetylsalicylzuur monotherapie hadden. Wanneer uitsluitend naar patiënten met LTH werd gekeken werd een soortgelijke associatie gevonden (odds ratio 2,72; 95% betrouwbaarheidsinterval 1,92-3,85).

Het gebruik van trombocytenaggregatieremmers voorafgaand aan een hoofdletsel is geassocieerd met een verhoogd risico op een traumatisch bloeding. Of dit een causaal verband betreft en of deze associatie ook bestaat voor patiënten die uitsluitend acetylsalicylzuur gebruikten kon niet worden aangetoond.

Hoofdstuk 5 beschrijft een case-control studie waarin de associatie tussen het dragen van een fietshelm bij volwassenen (16 jaar en ouder) en het optreden van traumatisch hersenletsel wordt onderzocht.

Het onderzoek is verricht in 2016 in deelnemende Nederlandse SEH afdelingen. Patiënten van 16 jaar en ouder die de SEH bezochten in verband met een fietsongeval werden geïncludeerd. Cases waren patiënten die de SEH bezochten wegens

traumatisch hersenletsel. Controles waren patiënten zonder traumatisch hoofd-hersenletsel die de SEH bezochten in verband met ander letsel. De 'exposure' die onderzocht werd betrof het al dan niet dragen van een fietshelm gedurende het fietsongeval.

In totaal werden 2133 patiënten geïncludeerd in de studie. Er waren 361 patiënten met traumatisch hersenletsel en 1772 patiënten zonder traumatisch hersenletsel. In de groep patiënten met traumatisch hersenletsel (cases) had 3,9% een helm gedragen tijden het ongeval, in de groep zonder traumatisch hersenletsel (controles) droeg 7,7% een helm tijdens het ongeval. Dit resulteert in een odds ratio van 0,49 voor het dragen van een fietshelm tussen cases en controles, met een 95% betrouwbaarheidsinterval van 0,28-0,86. Bij patiënten die een ongeval hadden gehad waarbij een gemotoriseerd voertuig betrokken was werd geen verschil gezien tussen het gebruik van fietshelmen tussen cases en controles (odds ratio 0,91; 95% betrouwbaarheidsinterval 0,29-2,83).

Patiënten met traumatisch hersenletsel droegen minder vaak een fietshelm dan patiënten met ander letsel (zonder hersenletsel). Dit versterkt het bewijs dat een fietshelm effectief beschermt tegen traumatisch hersenletsel.

Deel III
Beslisregels voor patiënten met licht traumatisch hoofd-hersenletsel

Voor zowel hoofdstuk 6 als voor hoofdstuk 7 is gebruik gemaakt van resultaten van de CREST studie. Het betreft hier een prospectieve cohort studie op negen SEH afdelingen in Nederland. Deelnemers aan de studie waren patiënten van 16 jaar en ouder die een van de deelnemende SEH's bezochten in verband met LTH tussen maart 2015 en december 2016.

De primaire uitkomstmaat was de aanwezigheid van een traumatische (intra)craniële afwijking op CT. Secundaire uitkomstmaten waren de aanwezigheid van een afwijking die potentieel neurochirurgisch behandeld moest worden en neurochirurgische interventie binnen 30 dagen. Van de 4557 patiënten die zijn geïncludeerd in de studie kregen 3742 (82%) een CT-scan van het hoofd; 383 (8,3%) hadden traumatische (intra)craniële afwijkingen op CT. Bij 73 patiënten (1,6%) was er sprake van een potentieel neurochirurgische afwijking en bij 18 patiënten (0,4%) is daadwerkelijk neurochirurgisch ingegrepen.

In **Hoofdstuk 6** wordt de externe validatie van vier veel gebruikt CT beslisregels voor patiënten met LTH beschreven. De primaire uitkomstmaat was de aanwezigheid van een traumatische (intra)craniële afwijking op CT. De secundaire uitkomstmaat was de aanwezigheid van een afwijking die potentieel neurochirurgisch behandeld moest worden.

Specificiteit, sensitiviteit en klinisch nut (gedefinieerd als 'net benefit', een gewogen som van echt en vals positieve classificaties) van vier beslisregels werden geëvalueerd: CT in Head Injury Patients (CHIP); New Orleans Criteria (NOC); Canadian CT Head Rule (CCHR); en de National Institute for Health and Care Excellence (NICE) richtlijn voor hoofdletsel.

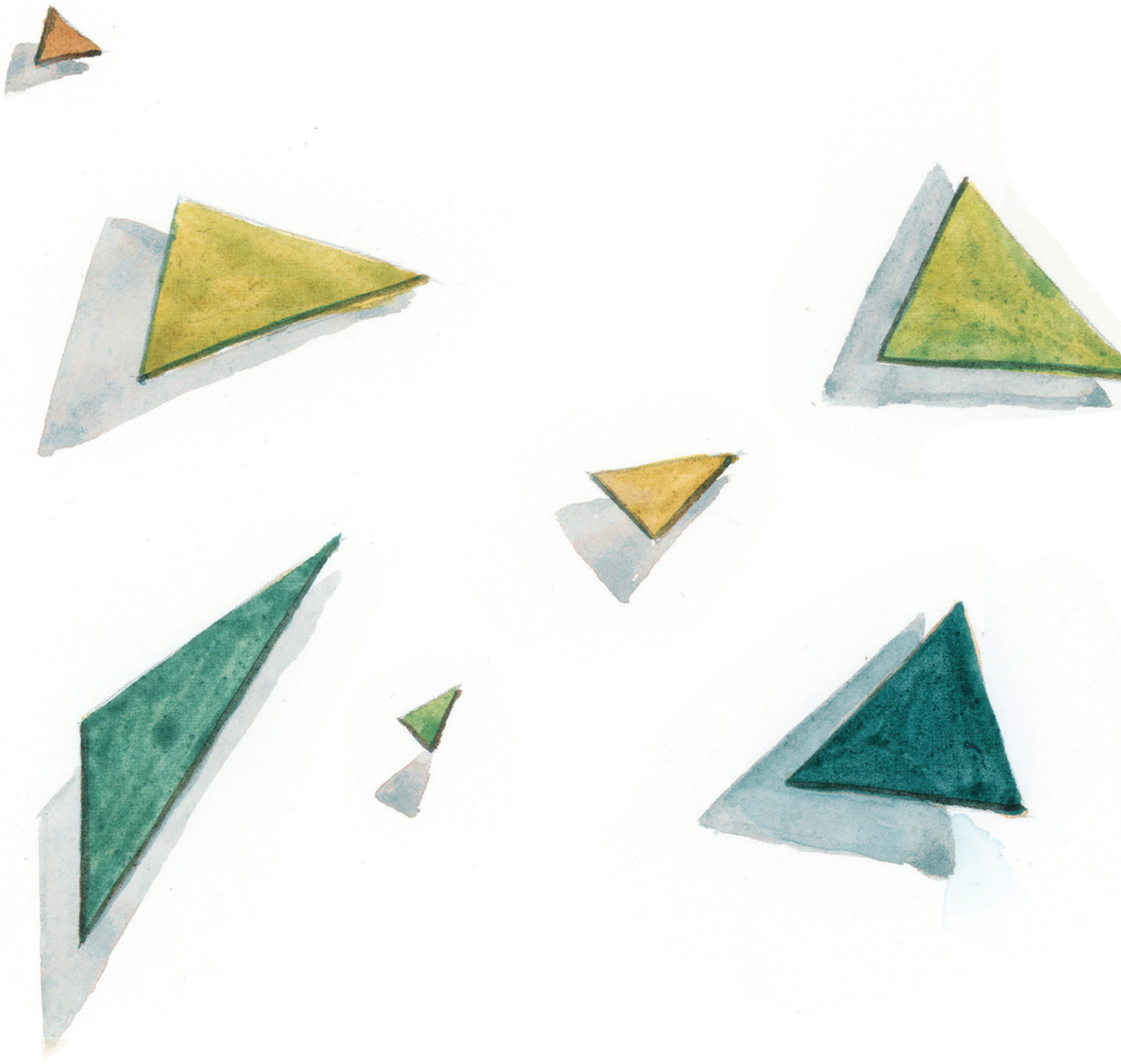
De sensitiviteit voor een traumatische afwijking op CT-scan varieerde van 73% (NICE) tot 99% (NOC). De specificiteit varieerde van 4% (NOC) tot 61% (NICE). De sensitiviteit voor potentieel neurochirurgische afwijkingen varieerde van 85% (NICE) tot 100% (NOC); en de specificiteit van 4% (NOC) tot 59% (NICE). Het klinisch nut hangt af van de (zelf bepaalde) drempel voor een CT-scan. Bij een lage drempel voor het maken van een CT-scan is de NOC te verkiezen, bij een hoge drempel de NICE. Voor het tussengelegen spectrum (een intermediaire drempel) is de CHIP te verkiezen.

Concluderend kan gesteld worden dat de toepassing van verschillende beslisregels leidt tot een grote variatie in het aantal CT-scans dat gemaakt wordt bij patiënten met LTH. Dit resulteert in veel onnodige CT-scans en enkele gemiste traumatische afwijkingen. Omdat de CHIP slechts enkele potentieel neurochirurgische afwijkingen miste en leidde tot een aanzienlijke reductie in CT-scans werd het gebruik van de CHIP geadviseerd. Daarnaast werd geadviseerd om een update van de CHIP uit te voeren.

In **Hoofdstuk 7** wordt deze update van de CHIP gepresenteerd. Ook voor deze update is gebruik gemaakt van data van de CREST studie. Het CHIP model werd gevalideerd en vervolgens geupdate en gereviseerd. De diagnostische prestatie werd beoordeeld door de 'c-statistic' te berekenen.

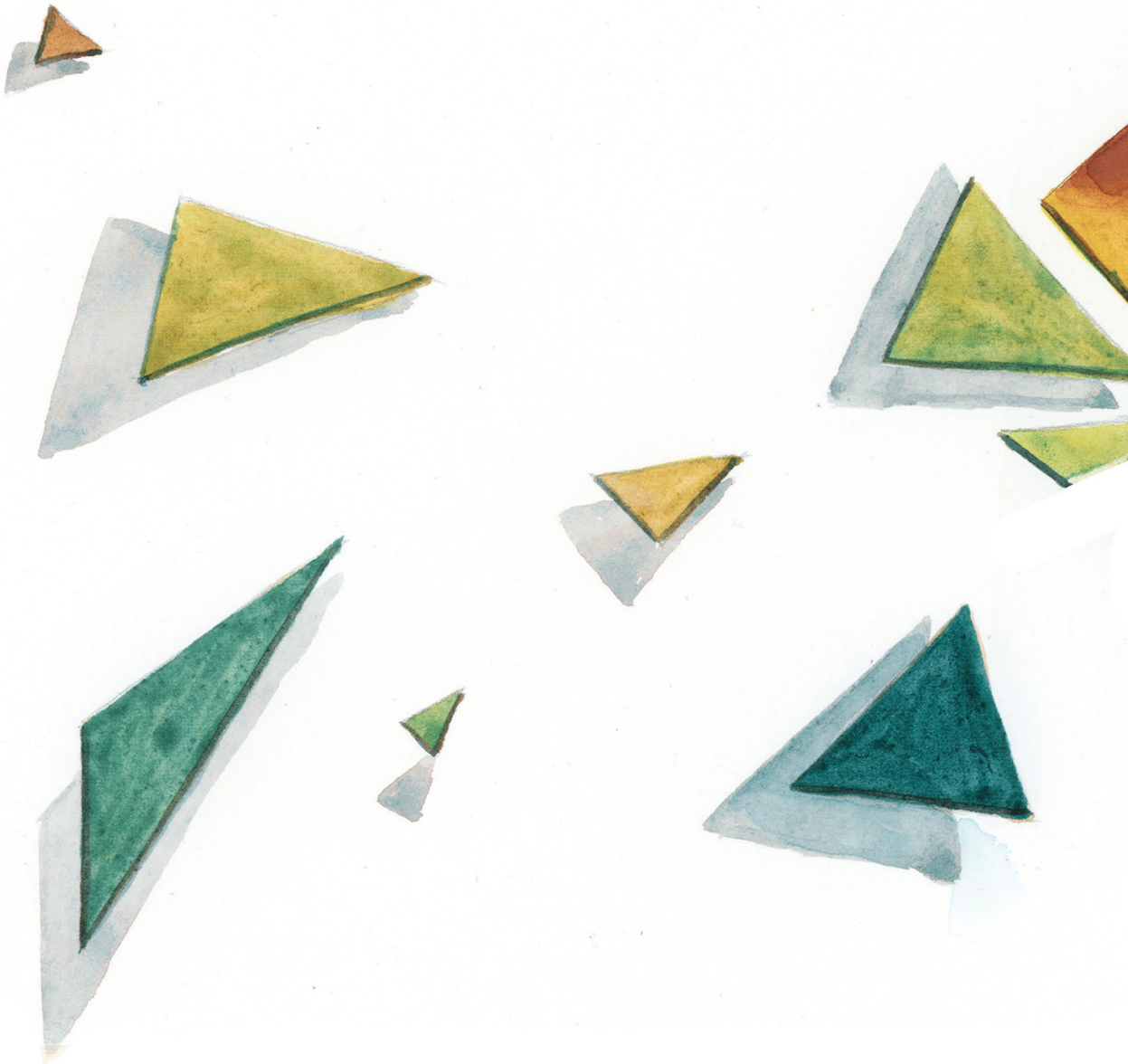
De oorspronkelijk CHIP onderschatte het risico op traumatische afwijkingen in de groep patiënten met een laag voorspeld risico, voor de groep patiënten met een hoog voorspeld risico werd het risico juist overschat. De c-statistic van de oorspronkelijke CHIP was 0,72 (95% betrouwbaarheidsinterval 0,69-0,74). Het oorspronkelijke CHIP model zou twee potentieel neurochirurgische afwijkingen gemist hebben, waarvan één patiënt daadwerkelijk neurochirurgisch ingrijpen onderging. Het geupdate model presteerde beter over een grote range van voorspelde risico's. De c-statistic van het geupdate model was 0,77 (95% betrouwbaarheidsinterval 0,74-0,79). Bij een vergelijkbaar aantal CT-scans als de oorspronkelijke CHIP zou het geupdate model geen patiënten met (potentieel) neurochirurgische afwijkingen gemist hebben.

Hoofdstuk 8 bevat de algemene discussie, klinische implicaties van de belangrijkste bevindingen, algemene beperkingen en een perspectief voor toekomstig onderzoek.



APPENDICES

Abbreviations
List of publications
Curriculum vitae
PhD portfolio
Dankwoord



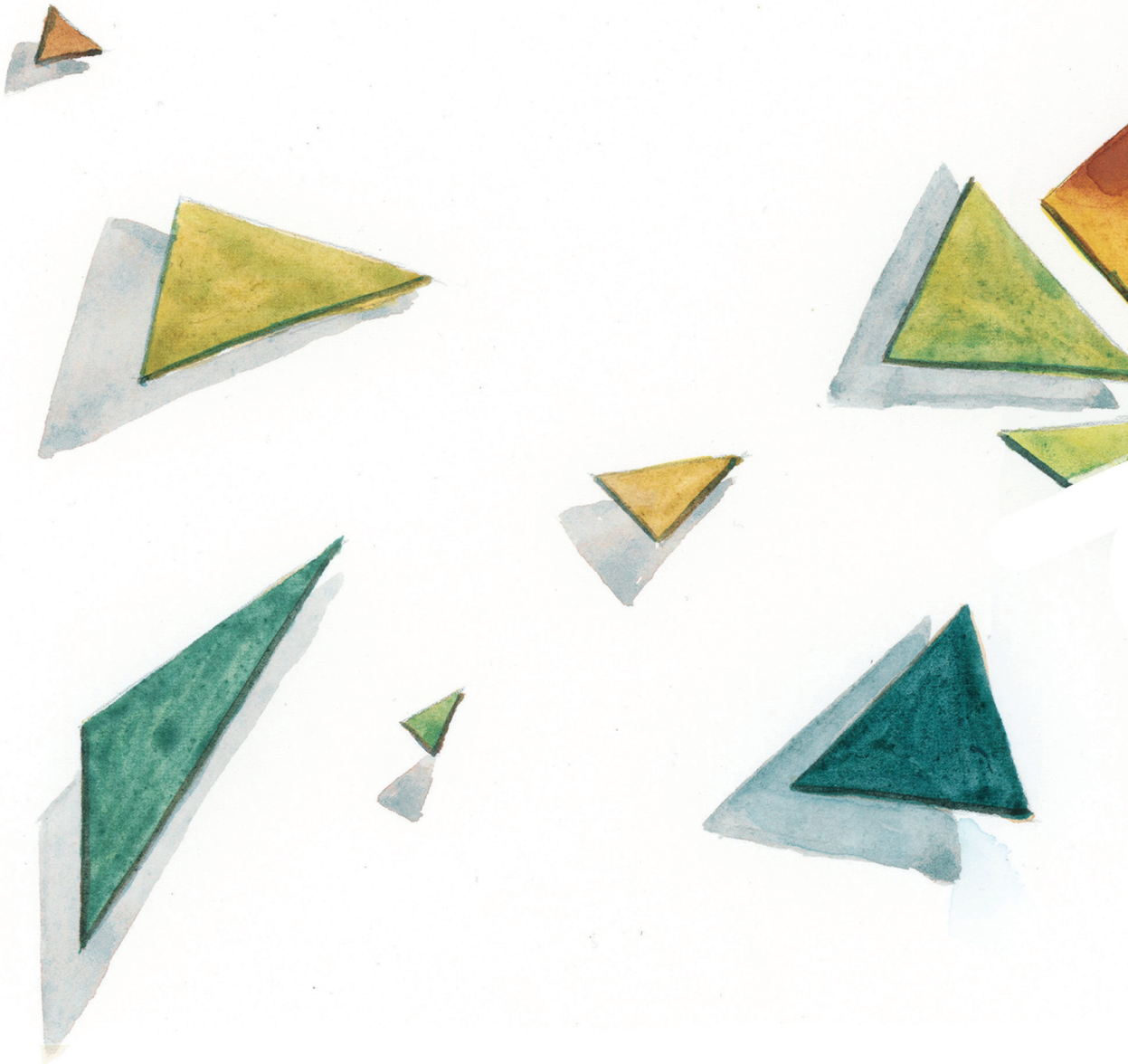
APPENDIX

Abbreviations

Abbreviations

AABB	formerly American Association of Blood Banks
ACEP	American College of Emergency Physicians
APT	Antiplatelet Therapy
ASA	Acetylsalicylic acid
CBS	Statistics Netherlands (Centraal Bureau voor de Statistiek)
CCHR	Canadian CT Head Rule
CHIP	CT in Head Injury Patients
CI	Convidence Interval
CREST	CT Refinement Study
CRF	Case Report Form
CSF	Cerebro Spinal Fluid
CT	Computed Tomography
DAI	Diffuse Axonal Injury
DOACs	Directly acting Oral Anticoagulants (synonym NOAC)
ED	Emergency Department
EMS	Emergency Medical Services
GCS	Glasgow Coma Scale
GFAP	Glial Fibrillary Acidic Protein
ICD	International Classification of Disease
INR	International Normalized Ratio
ITS	Interrupted Time Series
LIS	Dutch Injury Surveillance System (Letsel Informatie Systeem)
LMR	National Medical Register (Landelijke Medische Registratie)
LOC	Loss Of Consciousness
LOESS	Locally Estimated Scatterplot Smoothing (or locally weighted regression curve)
LTH	Licht Traumatisch Hoofd-hersenletsel
MHI	Minor Head Injury
MICE	Multivariate Imputation by Chained Equations
MOOSE	Meta-analysis Of Observational Studies in Epidemiology
mTBI	Mild Traumatic Brain Injury
MVC	Motorized Vehicle Collision
NICE	National Institute for Health and Care Excellence (formerly National Institute for Clinical Excellence)
NOACs	Non vitamin K (or Novel) Oral Anticoagulants (synonym DOAC)
NOC	New Orleans Criteria
NOS	Newcastle-Ottawa assessment Scale

NSE	Neuron-Specific Enolase
OR	Odds Ratio
PTA	Post Traumatic Amnesia
RTA	Road Traffic Accidents
SEH	Spoedeisende Hulp
SPSS	Statistical Package for Social Sciences
TBI	Traumatic Brain Injury
tICH	Traumatic Intracranial Hemorrhage
UCH-L1	Ubiquitin Carboxy Terminal Hydrolase L1
VKA	Vitamin K Antagonsist
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met mensen)



APPENDIX

List of Publications

Included in this thesis

van den Brand CL, Karger LB, Nijman STM, Valkenberg H, Jellema K. Bicycle helmets and bicycle related Traumatic Brain Injury in the Netherlands. *Neurotrauma Reports.* 2020;1(1):201-206 (no impact factor yet)

van den Brand CL*, Perotti JR*, van der Linden MC, Tolido T, Jellema K. Effect of the implementation of a new guideline for minor head injury on computed tomography-ratio and hospitalizations in the Netherlands. *Eur J Emerg Med.* 2020;27(6):441-446 (impact factor 2.170; Q1 in Emergency Medicine)

Foks KA*, **van den Brand CL***, Lingsma HF, van der Naalt J, Jacobs B, de Jong E, den Boogert HF, Sir Ö, Patka P, Polinder S, Gaakeer MI, Schutte CE, Jie KE, Visee HF, Hunink MGM, Reijners E, Braaksma M, Schoonman GG, Steyerberg EW, Jellema K, Dippel DWJ. External validation of computed tomography decision rules for minor head injury: prospective, multicentre cohort study in the Netherlands. *BMJ.* 2018;362:k3527 (impact factor 30.223; Q1 in Medicine)

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* both authors contributed equally

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Santing JAL, **van den Brand CL**, Jellema K. Traumatic Brain Injury in Patients Receiving Direct Oral Anticoagulants. *J Emerg Med*. 2020 Oct 14 [Epub ahead of print]

Santing JAL, **van den Brand CL**, Jellema K. Traumatic Brain Injury during the SARS-CoV-2 Pandemic. *Neurotrauma Reports.* 2020;1(1):5-7

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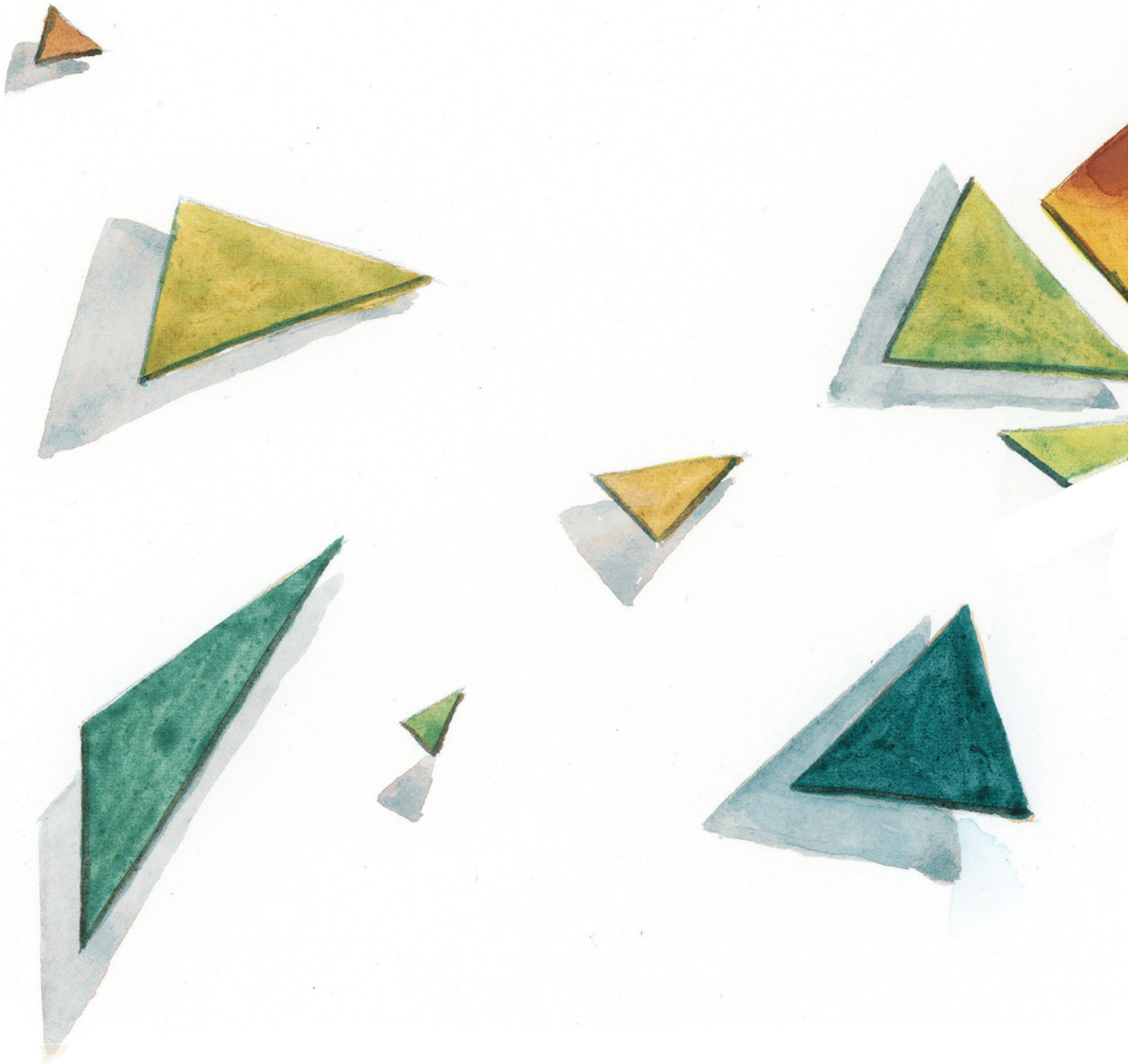


APPENDIX

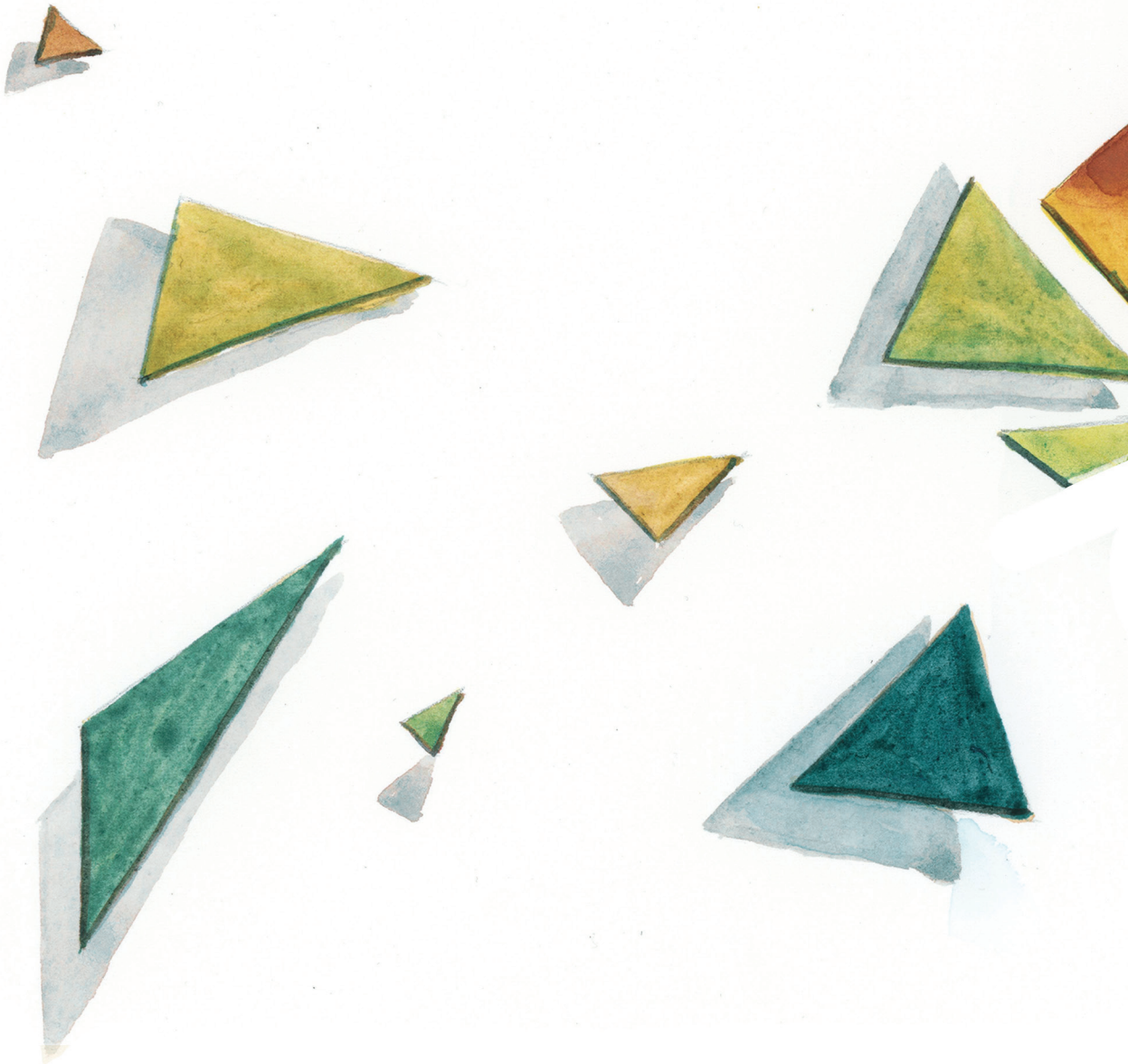
Curriculum vitae

Curriculum vitae

Crispijn Lennart van den Brand was born on March 24th 1975 in Rotterdam. After graduating from secondary school at the Rotterdams Montessori Lyceum he studied Medicine at the Leiden University. During his study he worked at Bio Implant Services in Leiden. In 2005 he graduated from Medical School and started working as a resident at the Department of Surgery in the Medical Center Haaglanden, The Hague and Leidschendam. Hereafter he worked as a resident at the Amphia hospital in Breda before returning to the Medical Centre Haaglanden in 2009 to become a resident in Emergency Medicine. Formal training in Emergency Medicine started in 2010 under supervision of Floris Idenburg. During his residency Crispijn started doing research in the field of Emergency Medicine together with, among others Christien van der Linden and Menno Gaakeer. At the end of 2011 he became an Emergency Physician and continued to work in the Medical Center Haaglanden (since 2016 Haaglanden Medical Center). In 2019 he completed a Master in Health Economics, Policy and Law at the Erasmus University, Rotterdam. Since 2019 he is working as head of the registry and research department at the Dutch Institute for Clinical Auditing (DICA), Leiden.

Crispijn was a member of the board of the Dutch Society of Emergency Physicians from 2009 until 2017 and was president of this society from 2013 until 2016. He has been a board member of the Netherlands Emergency Medicine Research Fund (SGOfonds) since 2013 and he cofounded the Netherlands Emergency department Evaluation Database (NEED) in 2016. Since 2017 he has chaired the medical expert committee of the board of the Orange Cross Foundation (Oranje Kruis).

Around 2012 he developed the ideas for this present thesis, together with Korné Jellema. The thesis was made possible thanks to a grant of the St. Jacobus Foundation. He started this thesis under supervision of Prof. M.G.M. Hunink and Prof. P. Patka in 2014. Together with Kelly Foks he designed and coordinated the CHIP Refinement Study (CREST) a multicenter study in patients with minor head injury. His research focuses on Neurotrauma Care and on the organization of Emergency Care.



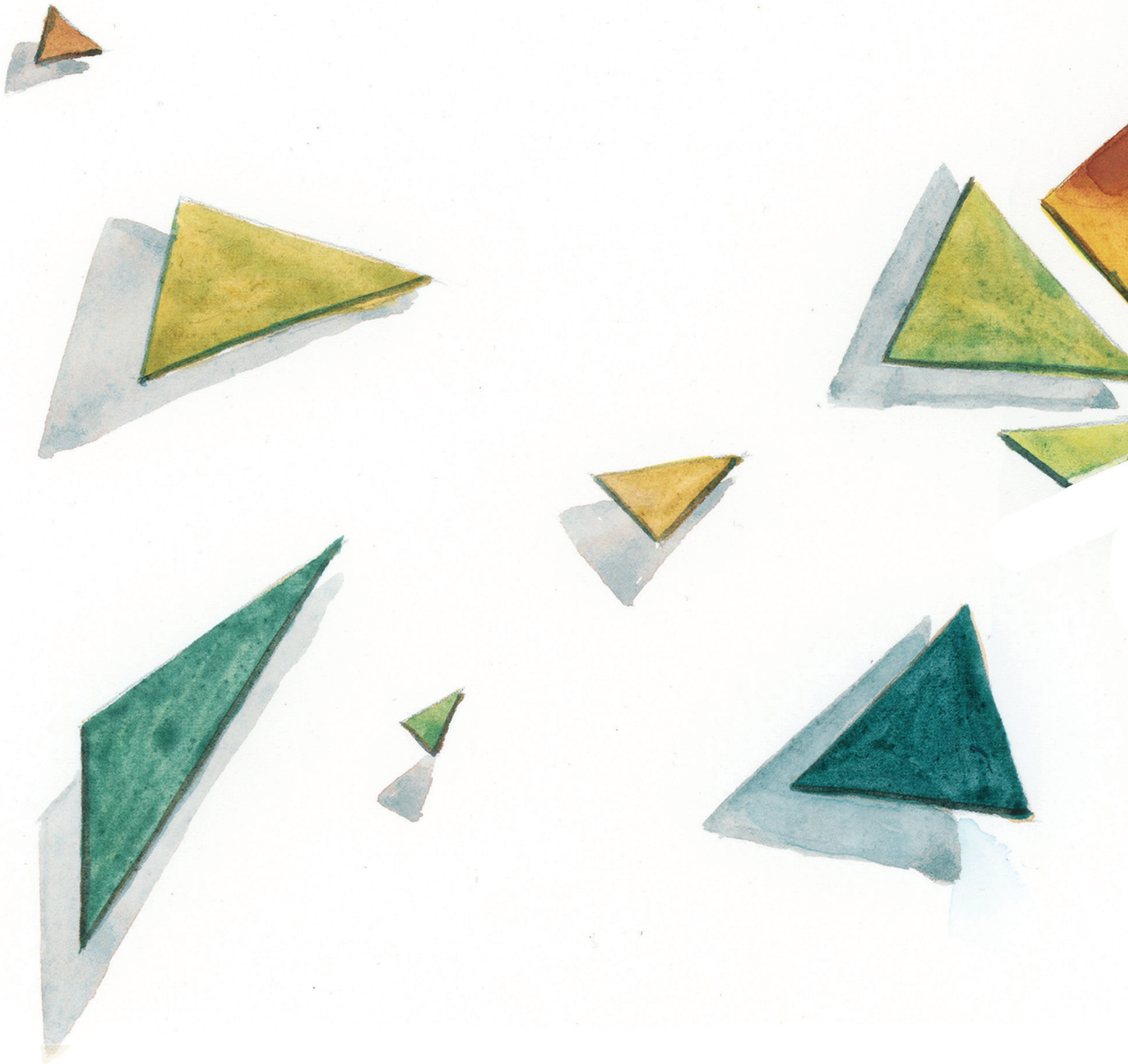
APPENDIX

PhD Portfolio

PhD Portfolio

	Institute	Year	Workload (ECTS)
Courses			
Epidemiological research: design and interpretation	EpidM	2013	4
Principles of epidemiological data analysis	EpidM	2013	3
Systematic review and meta-analysis	EpidM	2014	2
Good Clinical Practice	HMC	2014	0.9
Scientific Integrity	EUR	2016	0.3
DTA review and meta-analysis	Cochrane	2016	0.4
Generic Instructor Course	ALSG	2017	0.4
Basiscursus Regelgeving en Organisatie voor Klinisch Onderzoekers (BROK)	EMWO	2017	0.5
Academic writing PhD students	EUR	2018	0.6
Master Health Economics Policy and Law (ESHPM)	EUR	2018-2019	60
Regression analysis (ESP09)	EUR	2018	1.9
Oral presentations			
The startup of Emergency Medicine in the Netherlands International Conference on Emergency Medicine (Hong Kong)	IFEM	2014	1
Minor head injury, a minor problem? Regionaal onderwijs (Dordrecht)	NVSHA	2015	1
CT Indicatiestelling bij licht traumatisch hoofd-hersenletsel Regionaal neurotrauma overleg (The Hague)	HMC	2016	1
CT ratio doubled after introduction of new minor head injury guidelines World Congress on Brain Injury (The Hague)	IBIA	2016	1
Minor head injury, a minor problem? The European Emergency Medicine Congress (Vienna)	EuSEM	2016	1
Minor head injury, a minor problem? Werkgroep Educatieve Symposia (Rotterdam)	WES	2016	1
Mild Traumatic Brain Injury Regionaal onderwijs (Den Haag)	NVSHA	2016	1

	Institute	Year	Workload (ECTS)
CHIP update Regionale refereeravond neurologen (Dordrecht)	NVN	2019	1
Remember that patient with minor head injury Dutch North Sea Emergency Medicine Conference (Egmond)	NVSHA	2019	1
Inter(national) scientific meetings			
Dutch North Sea Emergency Medicine Conference	NVSHA	2015-2019	2
The European Emergency Medicine Congress	EuSEM	2014-2016	2.1
International Conference on Emergency Medicine	IFEM	2014	1.1
ACEP Scientific Assembly	ACEP	2014-2016	3
World Congress on Brain Injury	IBIA	2016	0.9
International journal peer review activity			
European Journal of Emergency Medicine 12x		2014-2020	1.2
Guideline participation			
Addendum Richtlijn Licht Traumatisch Hoofd-hersenletsel	NVN	2017	0.7
Student and resident teaching and supervision			
Supervision of residents in the emergency department	HMC	2014-2018	5
Supervision of residents with collecting and analyzing data	HMC and DICA	2014-2020	5
Supervision of research project by master student	HMC	2015	2
Total ECTS			**107.4**



APPENDIX

Dankwoord

Dankwoord

Dit proefschrift had niet tot stand kunnen komen zonder de hulp van velen zowel professioneel als privé. Ik wil iedereen hiervoor hartelijk danken. Dit geldt zeker ook de patiënten die deel hebben genomen aan de verschillende onderzoeken in dit proefschrift. Ik hoop dat dit proefschrift bijdraagt aan preventie van hersenletsel en het verbeteren van zorg voor patiënten met hersenletsel. Daarnaast wil ik graag de St. Jacobus Stichting bedanken voor de subsidie die de totstandkoming van dit proefschrift mogelijk heeft gemaakt. Een aantal mensen wil ik met name bedanken.

Prof. dr. M.G.M. Hunink, beste Myriam, wij hebben elkaar leren kennen bij aanvang van dit promotietraject. Zeer waardevol en inspirerend was jouw bijdrage aan de verschillende onderzoeken. Jouw grote kennis op het gebied van medische besliskunde en jouw ervaring als PI van de CHIP studie hebben mij erg geholpen bij de totstandkoming van dit proefschrift. Veel dank hiervoor, heel mooi om op ons beider verjaardag dit traject af te sluiten!

Prof. dr. P. Patka, beste Peter, alhoewel je niet meer officieel mijn promotor bent ben je dat gevoelsmatig zeker nog wel. Jij was betrokken bij de start van dit promotietraject en bracht me in contact met Myriam. Ik wil je zeer bedanken voor de mogelijkheid die je me hebt geboden om te promoveren op dit onderwerp en de manier waarop je me hiermee op weg hebt geholpen.

Dr K. Jellema, beste Korné, jij stond aan de wieg van dit proefschrift. Toen ik je jaren geleden benaderde met de observatie dat we steeds meer diagnostiek bij patiënten met hoofdletsel leken te doen en dat ik dat graag zou willen onderzoeken was jij gelijk enthousiast. Na onze eerste publicatie in het NTvG kwam de bal aan het rollen en opperde jij of ik niet zou willen promoveren op dit onderwerp. Gedurende mijn hele promotie ben jij zeer nauw betrokken geweest, stond me bij met raad en daad en kwam je steeds met mooie nieuwe plannen. Als ik je een manuscript stuurde ter revisie had ik vaak dezelfde dag nog een zeer gedetailleerd antwoord. Heel mooi om samen ook na afronding van dit proefschrift verder te bouwen aan de kennis op dit zeer interessante onderwerp. Beste Korné, dankjewel voor deze mooie samenwerking.

Prof. dr. J. van der Naalt, Prof. dr. M. Smits, Prof. dr. E.W. Steyerberg, Prof. dr. D. Dippel, Prof. dr. V.A. de Ridder, dr. K.E. Jie, veel dank dat jullie dit proefschrift hebben willen beoordelen en plaats hebben willen nemen in de oppositiecommissie. Prof. dr. J.S. Huff, thank you very much for your willingness to evaluate this thesis and to participate in the opposition committee.

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Mijn mede-onderzoekers en co-auteurs met wie ik de afgelopen jaren samen heb mogen werken aan de verschillende andere onderzoeken die in dit proefschrift zijn opgenomen: Lennard Karger, Susanne Nijman, Joeri Perotti, Christien van der Linden, Tanya Tolido, Roelie Postma, Victoria van de Craats, Frank Lengers, Christa Bénit, Femke Verbree, Annelijn Rambach, Huib Valkenberg. Jullie hebben een belangrijke bijdrage geleverd aan dit proefschrift, veel dank voor wat ik van jullie heb mogen leren. Christien, jouw aanstekelijke enthousiasme voor het doen van onderzoek heeft ook mij geholpen in het doen van onderzoek en de lol ervan in te zien.

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