

Identifying risk factors for traumatic brain injury (TBI) due to road traffic accidents (RTAs)
and strategies to reduce the burden of secondary brain injury.



Kriste Alberts

(SRNKRI001)

Supervisor: Prof. Anthony Figaji, Prof. Landon Myer

Thesis submitted in fulfilment of a

Masters Degree in Public Health

Division of Epidemiology and Biostatistics

University of Cape Town

January 2024

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Declaration

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Abstract

Background: There is a major knowledge gap in South Africa about detailed risk factors contributing to TBI due to RTAs in children. The objectives of this study were to map the burden of disease and examine circumstantial and clinical information to inform potential intervention strategies.

Methods: This was a descriptive study of patients with TBI admitted to the Red Cross War Memorial Children's Hospital in Cape Town, Western Cape. A retrospective analysis of basic demographic and clinical data were performed from a large database of children admitted with severe TBI. More detailed information about the circumstances of RTAs causing TBI were prospectively collected through interviews with caregivers.

Findings: From a database of 511 paediatric patients with severe TBI (age 13 or less), 403 (78.9%) sustained injuries in RTAs, mostly as pedestrians (71.7%). Males were more often injured (66%) and the median age was 6.8 years. The median time from the accident to tertiary hospital admission was three hours, to obtaining a CT scan was 4.5 hours, and to ICU admission was nine hours. With respect to the circumstances of RTAs, 155 interviews were conducted of which 80.7% involved pedestrian incidents. In 34 incidents (22%), more than one person was injured. Among these, 19 involved parents, with 17 of them (89.5%) dying from their injuries. Among pedestrians, 62% were injured while crossing the road and 57.5% were unaccompanied by an adult. Most commonly, the injured first attended the nearest clinic or day hospital (46%) by travelling with a personal vehicle (53%). Local areas that experienced the most RTAs were Gugulethu (7.7%), Khayelitsha (5.3%) and Mitchells Plain (5.3%).

Interpretation: The study indicates a high incidence of RTAs as a cause of TBI in South African children, particularly among pedestrians. The high rate of unaccompanied children crossing roads, suggests a need for improved road safety education and adult supervision. The clustering of RTAs in specific local communities' points to the need for targeted interventions in high-risk locations. The high mortality rate among parents involved in RTAs with their children underscores the broader impact of these accidents on families and communities.

Funding: This work was supported by the University of Cape Town Postgraduate Funding Office and the Paediatric Neurosurgery Unit.

Acknowledgements

- I would like to express my deepest gratitude to Professor Anthony Figaji and Professor Landon Myer for their unwavering support, invaluable guidance, and insightful feedback throughout the course of my thesis. Their expertise and commitment to academic excellence have been instrumental in shaping this research.
- I extend heartfelt appreciation to my partner, JP Van Rensburg, whose encouragement, understanding, and collaboration significantly enriched this journey. His steadfast support has been a source of strength and inspiration.
- To my family and friends, I am profoundly thankful for your unwavering encouragement, understanding, and patience. Your belief in me has been a driving force behind the completion of this project.
- I would like to acknowledge the University of Cape Town's Postgraduate Funding office for their financial support, which played a crucial role in the realization of this research endeavour. Additionally, I extend my gratitude to the Paediatric Neurosurgery Department for their funding and resources, without which this project would not have been possible.
- This journey has been challenging yet rewarding, and I am deeply appreciative of everyone who has played a part in its success.

Abbreviations

TBI – Traumatic brain injury

RTAs – Road traffic accidents

WHO – World Health Organisation

LMICs - Low - and middle-income countries

MVA – Motor vehicle accident

UCT – University of Cape Town

POPIA – Protection of personal information act

HREC – Human Research Ethics Committee

USA – United States of America

GCS – Glasgow Coma Scale

US – United States

TB – Tuberculosis

HIV – Human Immunodeficiency Virus

HICs – High income countries

SES – Socio-economic status

MOI – Mechanism of Injury

SDG – Sustainable Development Goal

ICU – Intensive care unit

RCWMCH – Red Cross War Memorial Childrens Hospital

sTBI – severe traumatic brain injury

CT – computed tomography

IQR – interquartile range

N – total population

CI – confidence interval

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Part A: Protocol

1. Protocol Synopsis

Title:

Identifying risk factors for traumatic brain injury (TBI) due to road traffic accidents (RTAs) and strategies to reduce the burden of secondary brain injury.

Background:

Road traffic accidents (RTAs) rank among the top reasons for death and disability globally. According to estimates from the World Health Organization (WHO), RTAs lead to approximately 1.35 million fatalities and result in 20-50 million cases of non-fatal injuries and disabilities annually. More than 90% of deaths occur in low- and middle-income countries (LMICs) and the highest RTA death rates occur in Africa.

Environmental risk factors can play a vital role in the risk of RTAs. There is a major knowledge gap in South Africa about detailed risk factors contributing to TBI due to RTAs in children. This includes the circumstances of the injury, which can be important to identify specific initiatives to reduce the occurrence or severity of an RTA-associated head injuries. Furthermore, we know even less about pathways for clinical service delivery for patients. Rehabilitation and care after injury can cause financial hardship especially for those of lower economic status and may lead to loss to follow-up, insufficient post-acute care and poor health outcomes. These key pathways significantly influence secondary brain damage, which in turn, affects the clinical results.

The objective of this study is to improve our understanding of risk factors contributing to RTA-related paediatric TBI in children and identify strategies that might reduce the burden of these injuries in South Africa.

Aims:

Primary Aim: To identify the clinical characteristics of children who sustained severe TBI admitted to Red Cross War Memorial Children's Hospital from 2006 to 2023, with a focus on injuries sustained in an RTA.

Secondary Aim: To identify the risk factors related to severe TBI caused by RTAs in children admitted to Red Cross War Memorial Children's Hospital from 2006 to 2023, that may lead to strategies to reduce risk.

Methodology:

This project was a mixed methods cohort study with a retrospective and prospective component. The retrospective analysis involved interrogation of a large database of children admitted to a major urban paediatric hospital to investigate clinical care pathways of the most vulnerable patients (children with severe TBI). Detailed data on the circumstances of RTAs was prospectively collected through interviews.

The retrospective component included children with severe TBI admitted to Red Cross War Memorial Hospital from 2006 to 2021. The patients were identified by the mechanism of injury variable “MVA – Motor Vehicle Accident” in the Paediatric Neurosurgery Database (HREC166/2009). The prospective component included data from RTAs (all severities from September 2022 to September 2023). Patients were excluded if they had TBI through other mechanisms or had sustained injury from RTAs but without TBI. For the prospective data collection, appropriate patients were recruited at a neurosurgery outpatient clinic where patients were seen for follow-up appointments as well as on presentation to Red Cross War Memorial Children’s Hospital.

Data were collected using an online capturing system, REDCap, and stored directly on the UCT eResearch platform which is a password protected database that is POPIA compliant. Subsequently, data were analysed using the software program R and user interface RStudio. R is a programming language that is used to perform statistical analysis.

Ethics:

Study patients enrolled prospectively were not subjected to any apparent risks by participating in the study and no risk was discernible in the retrospective collection of data. Participation in the study carried no direct benefit to the patients, besides having added to the value of research, by being an integral part in gathering information, which will help to address the gap in literature and statistics of risk factors for TBI because of RTA. This study benefited the Red Cross War Memorial Children’s Hospital in identifying strategies that can be implemented to reduce risk factors of TBI because of RTA.

Ethical approval was obtained by the Department of Surgery Research Committee (Project 2023/021) as well as the Human Research Ethics Committee (HREC REF 196/2023).

2. Introduction

RTAs are among the primary causes of mortality and disability worldwide. The WHO approximates that each year, RTAs are responsible for 1.35 million deaths and between 20 to 50 million cases of non-fatal injuries and disabilities ⁽¹⁾. Over 90% of these fatalities happen in LMICs, with the highest rates of RTA deaths reported in Africa ⁽²⁾.

Public health interventions and social advocacy may play important roles in reducing injuries. For example, a study done in Florida, USA analysed the effectiveness of seatbelts mitigating TBI severity among 803 patients who were in a motor vehicle accident ⁽³⁾. Among these 803 patients, a mere 45% used seatbelts. Independent of their position in the vehicle, individuals who neglected to wear seatbelts demonstrated a higher likelihood of experiencing loss of consciousness ⁽³⁾. Additionally, those who did not wear seatbelts, also presented worse in every outcome with an overall four times increase in the risk of TBI severity ⁽³⁾.

Environmental risk factors can also play a significant role in the risk of RTAs. A 6-year survey was done in Southwest China to assess the characteristics and patterns of injury, specifically due to RTAs as well as understand the public health consequences as a result of this burden ⁽⁴⁾. The study enrolled more than 1000 patients of which 49% took place in urban areas with the highest number of accidents occurring during winter (27.1%) ⁽⁴⁾. Most of the accidents occurred on a dry asphalt road surface (73.5%) with the majority of the RTAs occurring between six and eight in the morning as well as six to nine in the evening ⁽⁴⁾. Additionally, a steep incline in RTAs during weekdays are observed, mostly occurring on sunny days (57.6%) ⁽⁴⁾.

In Soweto, South Africa, a 5-year retrospective review was conducted to address the paucity in available statistics of paediatric patients admitted for TBI ⁽⁵⁾. RTAs were the most frequently reported mechanism of injury (59%) of which 17.5% were in passengers and 2.5% were patients that fell out of moving vehicles ⁽⁵⁾. This study indicated that TBI is the largest contributing mechanism of injury to mortality in children and it should be the primary target for preventative strategies ⁽⁵⁾.

There is a major knowledge gap in South Africa about detailed risk factors contributing to TBI in children, including the circumstances of the injury, which are important to enable identification of specific initiatives to reduce the occurrence or severity of an injury. Furthermore, we know even less about pathways for clinical service delivery for these patients. Recovery and treatment following an injury can lead to financial difficulties, particularly for

individuals with lower economic status. This situation can result in a lack of consistent medical follow-up, inadequate care, and ultimately, suboptimal health results ⁽⁶⁾.

Access to early and effective clinical care can reduce secondary injury and improve outcomes, while delays in care or ineffective care can increase the likelihood of death and long-term disability.

The objectives of this study were to: 1) examine demographic and clinical data of children who sustained an RTA-related TBI, and 2) to examine the social circumstances of RTAs and how patients access clinical care in an urban environment in South Africa.

3. Literature Review

3.1 Chapter 1: Brain Injury

3.1.1 Burden of injury

3.1.1.1 Definition and classification of injury

TBI is characterized by cerebral dysfunction and subsequent damage resulting from an external force or a change in brain function. Symptoms can range from seizures and varying consciousness levels to coma and specific neurological deficits ⁽⁷⁻¹⁰⁾. The severity of TBI is typically assessed using the Glasgow Coma Scale (GCS), which categorizes the injury as mild (GCS 13-15), moderate (GCS 9-12), or severe (GCS 3-8) ^(7, 9, 11, 12). The likelihood of a favourable or unfavourable outcome after a TBI is closely linked to the injury's severity ⁽⁹⁾.

3.1.1.2 Global and local statistics depicting the burden.

Globally, trauma stands as the primary reason for both morbidity and mortality among children, resulting in the loss of one million young lives every year ⁽¹³⁾. In the United States (US), injuries claim the lives of individuals aged one to 34, making it the leading cause of death in this age group, with a significant impact on the five to 19 age category ^(14, 15). This trend extends throughout one's life, as injuries remain the primary contributor to years of potential life lost up to the age of 65 ⁽¹⁶⁾. What is striking is that injuries collectively surpass all other causes of death among children and young adults, emphasising their significance ^(16, 17).

This impact is more pronounced in LMICs, where paediatric trauma outweighs other causes of death, with over 95% of paediatric injury-related mortality occurring in this setting ^(13, 18, 19). In South Africa, for example, injury ranks as the foremost cause of death among young adults and children aged over four years ⁽²⁰⁾. This mirrors patterns observed in the US and Europe, but South Africa bears a higher overall trauma burden. In a troubling comparison with equivalent

data from the US, South Africa exhibits an elevated risk of childhood injury-related mortality, with the likelihood of succumbing to injury during childhood (age five -15 years old) more than sixfold greater ^(15, 20).

Meanwhile, the Global Burden of Disease estimates the profound impact of injuries, attributing 9% of global mortality and 12% of disability across all age groups ^(21, 22). Remarkably, these figures surpass the combined mortality rates of malaria, TB, and HIV ⁽²¹⁾.

Of all the injury types in children, TBI is the most likely cause of death or disability ⁽⁸⁾. Children with TBI's face an elevated risk of mortality or lifelong disabilities, with these injuries accounting for 70-80% of accidental deaths in children post-trauma ⁽²³⁻²⁵⁾. Recognizing the preventability of such injuries underscores the nature of implementing injury prevention programs ⁽²⁶⁾.

The global incidence of TBI is estimated at about 27 million cases annually ⁽⁷⁾. In the United States, the prevalence of TBI is roughly 90.5 per 100,000 people, while in Europe, it exceeds 200 per 100,000 ⁽¹¹⁾. However, research from high-income countries (HICs) may not accurately reflect the TBI burden in LMICs, indicating a need for specific studies and characterizations in these regions ⁽⁸⁾. The prevalence of TBI is notably higher in the developing world, with LMICs experiencing an estimated 3.2 million TBI cases annually, and a 3.5-fold increase in Sub-Saharan African regions ⁽⁷⁾.

Despite limited data on the incidence and prevalence of TBI in South Africa, evidence points to a significant burden, particularly in Sub-Saharan Africa, with rates between 150-170 cases per 100,000 and as high as 316 per 100,000 in LMICs ⁽⁷⁾. Reports indicate that South Africa has an average incidence of 316 TBI cases per 100,000 population each year ⁽¹²⁾. A local study at Groote Schuur Hospital in the Western Cape revealed that around 1,000 patients are admitted annually with TBI, approximately 150 of which are severe cases ⁽⁹⁾. This high disease burden leads to poor patient outcomes, exacerbated by limited resources and an overwhelming demand for care ⁽⁷⁾.

However, these statistics merely scratch the surface of the burden posed by childhood injuries, concealing vital disparities in age, geography, socio-economic status (SES), and injury mechanisms ⁽²¹⁾. These statistics underscore the urgent need for comprehensive strategies to address injury-related mortality, particularly among children and young adults, in both developed and developing nations.

3.1.1.3 Emotional and psychological impact on individuals and families

Parental death is a common association with long-term illness in children ⁽²⁷⁾. Important underlying mechanisms affected by parental death are high-risk behaviour and low SES ⁽²⁷⁾. Research focusing on the academic performance of children who have lost a parent revealed that these bereaved children often have a lower average grade in school and are at an increased risk of not qualifying for secondary education ⁽²⁷⁾. Consequently, providing extra educational support to children who have undergone the death of a parent may help in decreasing their likelihood of facing lower SES in their later life ⁽²⁷⁾.

Each injury statistic represents a child with a tale often filled with pain, loss, and sorrow. However, these narratives also embody hope, as expressed through the voices of those who have survived. By harnessing this emotive energy, there is an opportunity for advocacy to steer research in a direction that ensures every child can anticipate a promising but also secure and safe future. ⁽²¹⁾.

3.1.2 Mechanisms of injury

3.1.2.1 Overview of different mechanisms leading to injury

Most epidemiological studies on TBI's encompass various injury mechanisms beyond RTAs, such as assaults, falls, or gunshot wounds ⁽²⁸⁾. To gain a more comprehensive understanding of the problem's true scope, there is a pressing need for enhanced efforts in collecting accurate epidemiological data.

The definition of the term childhood varies across research studies, significantly impacting demographic characteristics, physiological profiles, and study outcomes ⁽²⁹⁻³¹⁾. Notably, some studies include individuals aged 18-21 within their paediatric categories ⁽²⁹⁻³¹⁾. However, adults and children have different developmental characteristics which influence injury mechanisms and thus, should be studied separately ^(8, 13). Children with TBI are particularly of greater concern given that brain damage so early in their development can have delayed consequences ⁽¹⁰⁾.

Mechanisms of injury (MOI) vary based on factors like injury severity, age groups, and economic contexts ⁽³²⁾. Consequently, fluctuations in the relative proportions of injury mechanisms are observed ⁽²⁶⁾. Mild TBI often results from minor falls, while severe TBI in young children typically stems from significant falls or non-accidental injuries. Conversely, older children face a higher risk of injury in motor vehicle accidents ⁽³²⁾. In studies involving older adolescents, assault emerges as a more common mechanism, although it remains

infrequent in true paediatric series, particularly in developed countries. However, in different economic contexts, instances of blunt and penetrating assaults in children are more frequently reported. The MOI varies among different regions globally and locally. Among children between the ages of ten and 19, RTAs are the leading cause of death ⁽¹³⁾.

The PAPSA Research Study conducted a multicentre study in 2017 identifying RTAs as the most common mechanism of injury in LMICs (41%) with most frequent injuries being head injuries ⁽³³⁾.

3.1.2.2 Risk factors contributing to RTA-induced TBI's.

While various risk factors contribute to RTA-related TBI's, environmental factors stand out. Studies from different regions have highlighted the importance of road conditions, weather, and time of day in RTA occurrence ⁽⁴⁾.

A 6-year survey was done in Southwest China to assess the characteristics and patterns of injury, specifically due to RTAs as well as understand the public health consequences as a result of this burden ⁽⁴⁾. The study enrolled more than 1000 patients of which 49% took place in urban areas with the highest number of accidents occurring during winter (27.1%) ⁽⁴⁾. Most of the accidents occurred on a dry asphalt road surface (73.5%) with the majority of the RTAs occurring between six to eight in the morning and six to nine in the evening ⁽⁴⁾. Additionally, an incline in RTAs during weekdays are observed, mostly on sunny days (57.6%) ⁽⁴⁾. Understanding these environmental elements can help tailor preventative measures.

Behavioural factors such as speeding, drunk driving, and distracted driving (e.g., mobile phone usage) have been identified as major contributors to RTAs ⁽¹⁾.

3.1.2.3 Protective factors mitigating RTA-induced TBI's.

Ganti et al. demonstrated the protective role of seatbelts in reducing TBI severity, emphasizing their importance as a preventative strategy ⁽³⁾. Protective headgear such as a helmet is one of the most effective strategies to reduce TBI when cycling, driving a motorcycle, and skateboarding ⁽⁷⁾.

A retrospective study done in Florida; USA analysed the effectiveness of seatbelts mitigating TBI severity among 803 patients who were in a motor vehicle accident ⁽³⁾. Of these 803 patients, only 45% wore seatbelts and regardless of the position of the patient in the vehicle, those who did not wear seatbelts were more likely to have loss of consciousness ⁽³⁾. Additionally, those

who did not wear seat belts also did worse in every clinical outcome with an overall four-fold increase in the risk of TBI severity ⁽³⁾.

3.2 Chapter 2: Statistics and trends of RTA-related injuries

3.2.1 Prevalence and incidence of RTA-related TBI

TBI stands out as a major contributor to traumatic mortality, carrying the substantial risk of long-term disability ^(21, 28, 34). Approximately half of all TBI's result from RTAs, emphasizing the preventability of these injuries ^(8, 28, 34).

Globally, RTAs contribute significantly to TBI's ⁽¹⁵⁾. These injuries are a substantial public health issue, especially among children and young adults, causing millions of deaths and non-fatal injuries annually ⁽¹⁾. The prevalence of RTA-related TBI, specifically among paediatric populations, underscores the urgency of addressing this issue.

The impact of TBI resulting from RTAs is a major public health issue worldwide, especially in LMICs, with Africa recording some of the highest RTA-related death rates ⁽²⁾. Remarkably, 10% of global RTA-related fatalities occur in Africa, potentially due to inadequate road infrastructure and ineffective safety policy enforcement. The influence of ethnic, geopolitical, and societal factors on the observed patterns of paediatric TBI, however, remains uncertain ⁽¹⁰⁾.

Comparative evidence indicates that India's road traffic fatality rate stands at 22.6 per 100,000, which is significantly higher than the United States' rate of 12.4 per 100,000 ⁽¹³⁾. This data also points to a disproportionately high rate of fatal road traffic injuries among paediatric patients in India ⁽¹³⁾.

In South Africa, a study conducted in Bloemfontein in the Free State province revealed that the most common cause of TBI-related incidents was assault (41.3%), followed by RTAs (30.4%) ⁽¹¹⁾. Another research at the Pietermaritzburg Metropolitan Trauma Service observed that over a two-year period, 384 patients were admitted with TBI due to penetrating injuries ⁽³⁵⁾. This highlights a critical need for better understanding of the incidence and regional variations of RTA-related TBIs within South Africa.

Among paediatric populations, males tend to be more affected than females, with a 1.8 times higher odds of sustaining a severe TBI ^(8, 26). Evidence shows that in cases of paediatric TBI caused by RTA, the largest demographic group affected are pedestrians ⁽⁸⁾. The PAPSA research study identified the mean age of the paediatric population experiencing trauma to be seven years ⁽³³⁾.

3.2.2 Influence of SES

3.2.2.1 Analysis of how SES affects risks and outcomes of RTA-related TBI's.

TBI in children represents a significant public health issue, imposing a burden across diverse populations and demographics, irrespective of their geographical location or SES ⁽¹⁰⁾. SES plays a crucial role in determining both the risk and outcomes of TBI related to RTAs ⁽⁴⁾. However, the overall impact of SES on the risk factors for paediatric TBI remains unclear, largely due to the paucity of reported data ⁽¹⁰⁾.

In LMICs, road traffic injuries more frequently affect vulnerable road users like pedestrians and cyclists ⁽⁷⁾. Those who are either too young to drive or cannot afford a vehicle are particularly susceptible to fatal injuries. To mitigate this risk, it is essential to develop and implement effective strategies that ensure safe travel for individuals of all SES, from point A to point B.

3.2.2.2 Examination of the role of access to healthcare, education, and other SES factors

The availability of healthcare, educational resources, and other socioeconomic factors critically influence the dynamics of paediatric TBI within a country. One significant aspect affecting patient outcomes is the delay in receiving neurosurgical care. Studies indicate that a mere four-hour delay from the time of injury to surgical intervention can result in a threefold increase in the mortality rate ⁽⁷⁾.

To effectively prevent injury-related disabilities and fatalities, prompt access to high-quality healthcare is essential ⁽³⁶⁾. However, in LMICs, there is growing evidence of substantial barriers to healthcare access. Pre-hospital delays often stem from challenges related to the geographic location of medical facilities, such as long distances, poor road conditions, and lack of adequate transportation ^(7, 36). Post-hospital delays are frequently associated with financial constraints (high direct and indirect healthcare costs), infrastructural limitations (scarcity of healthcare providers equipped with necessary resources and expertise), and the prioritization of resources for treating severe cases ^(7, 36).

Additionally, in developing countries, access to crucial imaging technologies like computed tomography (CT) and magnetic resonance imaging (MRI) remains a significant hurdle, even though these tools are vital for reducing mortality rates in TBI cases ⁽⁷⁾.

3.3 Chapter 3: Prevention strategies for RTA-related injuries

3.3.1 Overview of preventative strategies targeting pedestrians

Preventative strategies targeting pedestrians, such as improved road design, pedestrian education, and the promotion of safe crossing practices, have shown promise in reducing RTA-related TBI's ⁽¹⁾. In 2008, the WHO recognized the severe global impact that injury fostered and subsequently aimed to describe prevention strategies for the five most prevalent causes of child death ⁽³⁷⁾.

According to the WHO's 2013 global status report on road safety, over one-third of road traffic fatalities in LMICs involve pedestrians and cyclists. However, fewer than 35% of LMICs have implemented policies specifically designed to safeguard these vulnerable road users ^(1, 7). Some strategies include campaigns for safety in numbers where road users are safer if they are travelling in larger groups especially for cyclists and pedestrians ⁽¹⁾. Driver awareness behaviour needs to be challenged by active campaigning and increased visibility of road users ⁽¹⁾.

Access to roads is linked to economic development, an evident predictor of poverty ⁽²¹⁾. Typically, road traffic policies are primarily designed with only motorized vehicles in mind, often neglecting the needs and impact on non-motorized vehicles, pedestrians, and settlements ⁽²¹⁾. These policies allow highways to speed through towns, often cutting through established pedestrian routes and thereby posing increased risks and exposure to pedestrians.

Minor injuries sustained by children engaged in non-motorized transport activities, such as bicycling, skateboarding, running, and walking, often have the potential to escalate into more severe incidents ⁽²¹⁾. Addressing and preventing these possible severe outcomes is imperative, without restricting children's utilization of these non-motorized modes of transport. This can be accomplished through the creation of protected playgrounds and providing bright clothing for children ⁽⁸⁾.

The dialogue must widen to encompass the aspects of child health and well-being, considering the immediate risks presented by non-motorized modes of transport against the environmental benefits and essential life skills these activities provide ⁽²¹⁾. Parents often hyperfocus on the immediate perils, not fully considering the future advantages, thereby favouring immediate safety over the acquisition of long-term benefits and skills.

Our challenge, then, is to accurately evaluate and mitigate the immediate risks associated with non-motorized transport while fostering an environment and adopting behaviours that bolster

safety⁽²¹⁾. This initiative requires not only providing safer infrastructure, such as dedicated bike lanes and safe pedestrian crossings but also imparting essential safety education without discouraging the use of these transport modes⁽²¹⁾.

Moreover, advocates in LMICs are grappling with the growing issue of child injuries related to non-motorized transport and are often working with scarce resources and minimal support from international health agencies⁽²¹⁾. Addressing this concern requires immediate attention and action to ensure children's safety and encourage the responsible use of bicycles, skateboards, running and walking as viable, environmentally friendly transport options in these regions.

3.3.2 Exploration of strategies for protecting vehicle passengers

The use of seatbelts, airbags, and child car seats has been recognized as effective protective measures for vehicle passengers⁽³⁾. Ensuring widespread adoption of these safety measures is critical in the context of paediatric TBI prevention.

A study conducted in India demonstrated that focused prevention and management of road traffic injuries could significantly decrease the mortality rate of childhood injuries⁽¹³⁾. In contrast to the United States, where child restraint laws are in place and an 89% usage of child restraints is reported⁽¹³⁾, India lacks national child restraint laws or front seat restrictions, and there is no data on restraint usage⁽¹³⁾. Therefore, introducing potential interventions to increase the use of child safety restraints is crucial⁽¹³⁾.

While RTAs are the leading cause of death in LMICs, most of these countries lack dedicated institutions with the mandate and financial resources to coordinate large-scale interventions⁽³⁸⁾. Argentina serves as an example of how establishing such an institution can help address the injury burden in LMIC contexts⁽³⁸⁾. The country overcame structural barriers to large-scale coordinated interventions by decentralizing to provinces and municipalities, leading to the formation of a national road safety agency equipped with dedicated resources and mandates for coordinating safety programs nationwide⁽³⁸⁾. Although a decrease in RTAs has not been observed yet, this initiative marks a significant step forward, and the agency now needs to set specific goals to combat the burden⁽³⁸⁾.

Enhancing enforced legislation concerning legal driving age and speed limits could also be beneficial, particularly in countries where enforcement policies are weak⁽¹⁰⁾. Moreover, continuous innovation in vehicle safety features, including airbags, seat belts, and other measures, represents an evolving strategy to improve protection for occupants⁽¹⁰⁾.

3.3.3 Strategies for prevention from a policy perspective

Although many recommendations suggest improved law enforcement, active campaigning, and increased education on road safety, many LMICs are financially restricted in their ability to support these interventions.

Korea had decreased the number of children killed in an RTA by more than 95% between 1998 and 2012 ⁽³⁹⁾. This was done through the introduction and implementation of various policies including school zone strategies, school bus improvements, compulsory road safety education and strengthening of the already existing legal framework ⁽³⁹⁾. A key initiative in the success of their policy implementation was the formation of a ‘Transportation safety administration system’ which deliberates on major road traffic safety policies and have authority to review the Transportation Safety Act (Figure 1) ⁽³⁹⁾.

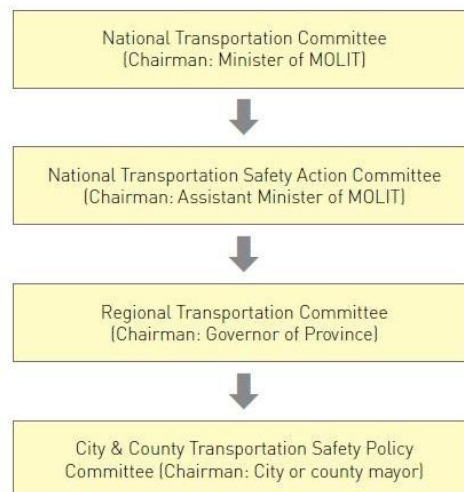


Figure 1: Overview of the Transportation safety administration system in Korea ⁽³⁹⁾.

The school zone system that was implemented through the amendment of the Road Traffic Act included designated safety areas for children within school areas with improved road safety facilities ⁽³⁹⁾. Additional punishment for perpetrators causing accidents within school zones was implemented regardless of auto insurance status ⁽³⁹⁾.

A lesson learnt from Korea to prevent RTAs is to implement policy from the ground up using an inclusive approach (education, engineering, political and social contexts) with the main aim of saving lives.

3.4 Chapter 4: Examination of challenges and barriers to collecting and accessing injury data in South Africa

The scant research on road safety in developing nations, particularly in Africa, does not align with the severity of the issue. With over 85% of global road traffic fatalities occurring in developing countries, the problem is substantial and in response, the WHO unveiled a 5-year plan for preventing RTAs ^(28, 37). A key suggestion of this initiative is to encourage the conduct of research on road safety, mainly in poor countries. In these nations, the lack of sufficient knowledge often hinders the effective distribution of resources needed to tackle the issue, thereby exacerbating the problem ⁽²⁸⁾. Thus, fostering research in these regions is imperative for devising informed strategies and allocating resources efficiently to mitigate road traffic deaths effectively.

The systematic analysis of the Global Burden of Disease Study done in 2017 clearly demonstrates the challenges in research done in LMICs, especially in Sub-Saharan Africa as seen in the Figure below (Figure 2) ⁽⁴⁰⁾.

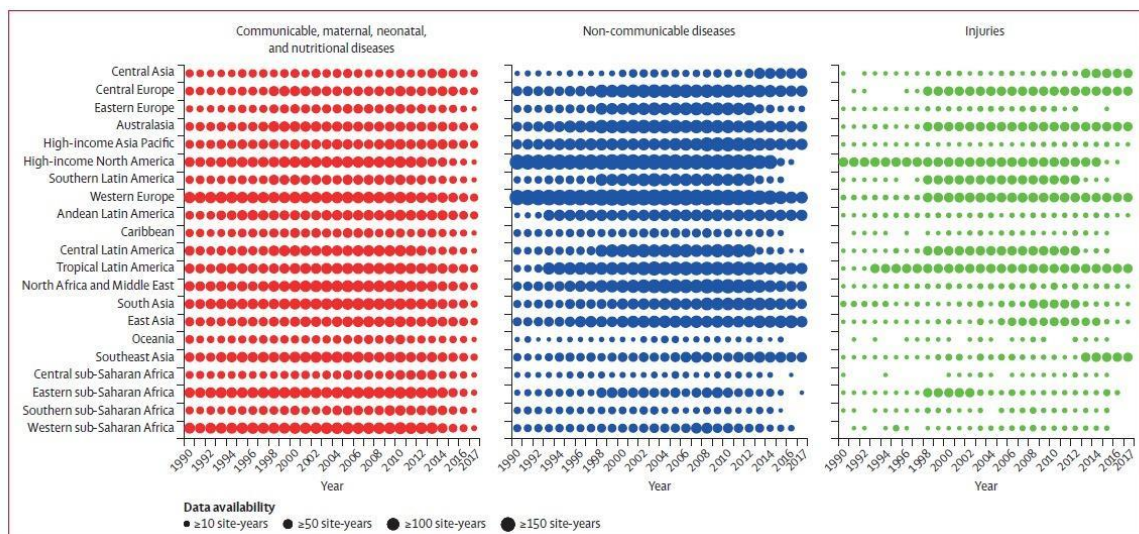


Figure 2: Global Analysis of Data Availability for Disease and Injury Studies from 1990 to 2017 by Region and Disease Category ⁽⁴⁰⁾.

South Africa faces challenges in collecting and accessing injury data, thereby impacting injury prevention efforts ⁽¹⁷⁾. In LMICs, the likelihood of death resulting from TBI is significantly higher compared to HICs. This is particularly evident in Africa, where certain regions report mortality rates as high as 50% for moderate-to-severe cases of TBI ⁽⁷⁾. Despite the clear need for high quality data in LMICs, less than a quarter of all the LMICs have reported data on the burden of TBI in their country ⁽⁸⁾.

Furthermore, one of the primary risk factors leading to severe TBI is RTAs. Considering that only 4% of the world's cars are driven on African roads, yet the continent accounts for 10% of global deaths resulting from RTAs, it is reasonable to anticipate more comprehensive and well-researched localized data on TBI in this context ⁽⁷⁾.

A study done in 2007 showed the trend of research conducted for HIV compared to road traffic injuries in Africa and the world between 1956 and 2006 clearly indicating the lack of research done on RTAs even though RTAs has a higher mortality and morbidity rate (Figure 3) ⁽²⁾.

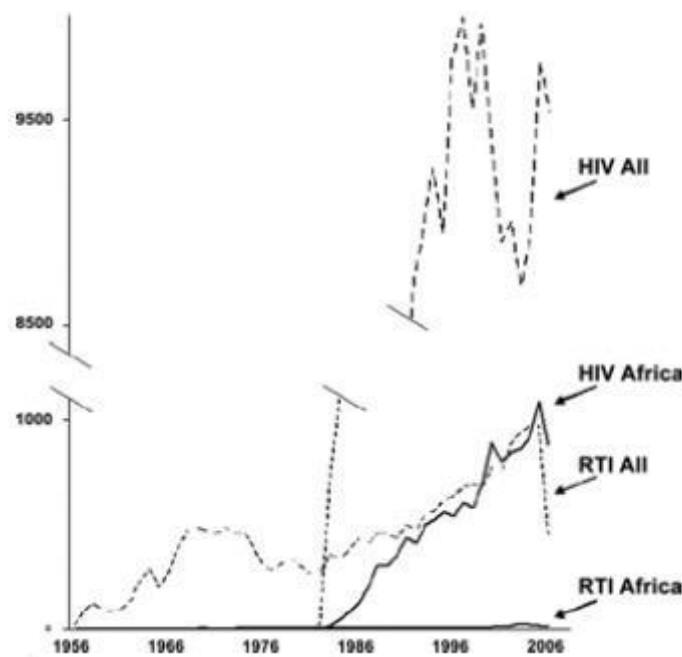


Figure 3: Trends in Scholarly References to Road Traffic Injuries and HIV from 1956 to 2006 Globally and in Africa ⁽²⁾.

Understanding the patterns of injury in paediatric populations may prove vital for changing public policy and implementing the appropriate prevention programs for RTAs ⁽⁸⁾. Achieving the Sustainable Development Goal (SDG) to end preventable deaths by 2030, research for TBI in LMICs is essential ⁽⁸⁾. Recommendations from other countries can guide efforts to enhance data collection, management, and access ⁽¹⁷⁾.

4. Aims and Objectives

4.1 Aims

Primary Aim: To identify the clinical characteristics of children who sustained severe TBI admitted to Red Cross War Memorial Children's Hospital from 2006 to 2023, with a focus on injuries sustained in an RTA.

Secondary Aim: To identify the risk factors related to severe TBI caused by RTAs in children admitted to Red Cross War Memorial Children's Hospital from 2006 to 2023, that may lead to strategies to reduce risk.

4.2 Objectives

1. To retrospectively analyse data from the Paediatric Neurosurgery Database on children who sustained a TBI and who underwent intracranial monitoring to identify potential risk factors for secondary brain injury related to clinical care pathways at a healthcare services level.
2. To prospectively conduct a structured interview of patients' guardians to detail the RTA circumstances to identify strategies to reduce the risk of occurrence at a community level.

5. Methodology

5.1 Study Design

This project was designed as a mixed-methods cohort study with a retrospective and prospective component (Figure 4).

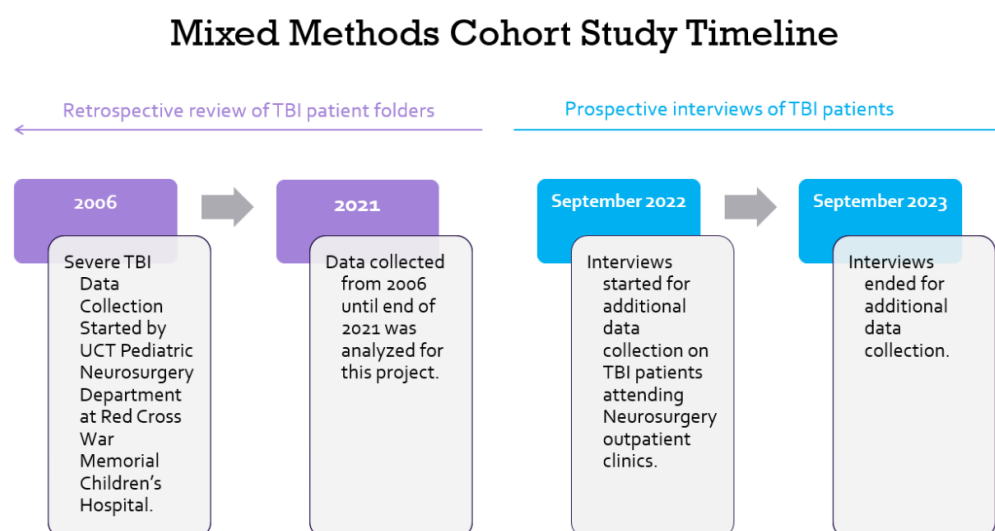


Figure 4: Timeline of a Mixed Methods Cohort Study on Severe Traumatic Brain Injury (TBI) Integrating Retrospective Review and Prospective Interviews from 2006 to 2023.

First, we performed a retrospective analysis of a large database of children (age 13 and under) who were admitted to a major urban hospital with severe TBI (defined as patients presenting in coma [with a Glasgow Coma Score of 8 or less], typically requiring ICU admission and who underwent intracranial monitoring). This enabled interrogation of demographic and clinical data collected from a large number of the most severe cases admitted to RCWMCH in the Western Cape, South Africa from 2006 to 2021. These data were limited to routinely collected information in hospital records.

Second, because data on the circumstances are not usually recorded in the hospital record, we proceeded to collect more detailed information prospectively through interviews with caregivers. This was conducted from September 2022 to September 2023 and involved patients who sustained an RTA-related TBI of any severity. Patients were excluded if they had TBI through other mechanisms or had sustained injury from RTA but without TBI.

5.2 Study Setting and Population

5.2.1 Retrospective study population

The retrospective component included children with severe TBI admitted to Red Cross War Memorial Hospital from 2006 to 2021 and who underwent intracranial monitoring, as detailed data were available in a prospectively maintained database for this group. The RTA patients were identified by the mechanism of injury variable “MVA – Motor Vehicle Accident” in the Paediatric Neurosurgery Database (HREC166/2009). An approximate sample size of 385 patients was needed with a 95% confidence interval and 5% margin of error.

5.2.2 Prospective study population

The prospective study included data from RTAs (all severities from September 2022 to September 2023). Patients were excluded if they had TBI through other mechanisms or had sustained injury from an RTA but without TBI. For the prospective data collection, appropriate patients were recruited at a neurosurgery outpatient clinic where patients were seen for follow-up appointments as well as on presentation to Red Cross War Memorial Children’s Hospital.

For this part of the study, we’ve calculated that we needed approximately 150 patients. This sample size gave us a 95% confidence level, which means if we were to conduct the same study 100 times, we would expect the true value we’re trying to estimate to fall within our calculated range 95 times. Additionally, a 5% margin of error has been set, which is the maximum range in which our sample’s results will differ from the true population value. This balance allows us

to make informed estimates with a reasonable degree of accuracy without needing an impractically large sample.

5.3 Data Collection

5.3.1 Retrospective Data Collection

The variables that were used for the analyses from the data collected retrospectively in the Paediatric Neurosurgery Database can be seen in Appendix A. This data were collected by the Department of Neurosurgery by reading and compiling data from patient records kept at Red Cross War Memorial Children's Hospital.

5.3.2 Prospective Data Collection

In this study, patients were asked questions on the circumstances and environmental factors that were evident during the RTA, through an interview process (Appendix B). Potential patients were screened before the clinic. Subsequently, patients were approached and recruited using informed consent. Interviews took place every Wednesday at a clinically scheduled follow-up appointment at the Neurosurgery outpatient clinic. The interview was conducted face to face in a private consultation room. The questions were asked by the researcher, and the answers given by the patients' guardians were compiled by the researcher. The overall length of participation was ten to 15 minutes and was conducted in English, Afrikaans and isiXhosa with a translator as required. The variables that will be used for analyses from the data collected prospectively during the interview process are shown in Appendix C.

6. Data Management and Analysis Plan

6.1 Variable Definitions

6.1.1 Exposure

Conceptual: TBI because of RTAs.

Operational: TBI identified by sudden damage to the brain from an external force, in this instance, an RTA defined as any injury caused by a motor vehicle.

6.1.2 Outcome

Conceptual: Risk factors such as sex, age, geographic location, and environment as well as strategies to reduce them.

Operational: Risk factors such as sex, age, geographic location, and environment are events that can influence the occurrence and severity of an RTA.

6.2 Data Collection Management

Data were collected using online capturing system REDCap and stored directly on the UCT eResearch platform which is a password protected database that is POPIA compliant. Subsequently, data were analysed using the software program R and user interface RStudio. R is a programming language that is used to perform statistical analysis. Those who were allowed to perform analysis for this study were the student researcher and supervisors involved in this study.

6.3 Data Analysis

The data were analysed to understand the relationship between multiple variables (risk factors) and how they influenced the occurrence of an RTA using R software and R Studio user interface. Summary statistics were examined for all relevant variables. The dataset was inspected to understand the pattern and extent of missingness.

Multiple imputation, the preferred method for handling data missing at random, was employed to avoid biased estimates ⁽⁴¹⁾. The missing data in the dataset were filled in multiple times to create several complete datasets. The imputation uses a statistical model to predict the missing values based on the relationships observed in the non-missing data ⁽⁴¹⁾. The ‘mice’ package was employed, which makes use of chained equations where each variable with missing data was modelled conditionally upon the others in a round-robin fashion ⁽⁴¹⁾. The ‘mice’ package provides functions that automatically performed the pooling by applying Rubin's rules, which account for both within-imputation variability and between-imputation variability ⁽⁴¹⁾.

6.4 Data Safety and Monitoring

Data for this study was stored in a dedicated folder on the UCT eResearch platform on the UCT Server, to which only authorised members of our research team had access through UCT-assigned access. The eResearch platform provides multiple levels of data security and is POPIA compliant. No data were gathered from a third party, only directly from patients and clinical data sources. No identifiable information was shared. The data collected from this study will be kept indefinitely on the eResearch platform to which authorised members of the research team will have access.

7. Ethical Considerations

7.1 Ethical Approval and Consent

This study was a sub-study for three ongoing research studies in the Paediatric Neurosurgery Unit (HREC 126/2022, HREC 720/2021, HREC 166/2009) as well as the Paediatric Neurosurgery Registry (R018/2022) which are gathering the data to answer these questions (Appendices D - G). Ethical approval was obtained by the Department of Surgery Research Committee (Project 2023/021) as well as the Human Research Ethics Committee (HREC 196/2023) as seen in Appendix H and I, respectively.

7.2 Informed Consent Process

Interview informed consent forms were completed by the patient's guardian while the patients waited for their allocated clinic appointment. Subsequently the interviews took place at the Department of Neurosurgery clinic in a private consultation room. The parents were reassured that the participation in this research interview was completely voluntary, and the primary care of the patient was not affected in any way. The informed consent and assent forms can be seen in Appendix J and K.

7.3 Potential Risks and Benefits

Study patients enrolled prospectively were not subjected to any apparent risks by participating in the study and no risk was discernible in the retrospective collection of data. Participating in the study carried no direct benefit to the patients, besides having added to the value of research, by being an integral part in gathering information which helped to address the gap in literature and statistics of risk factors for TBI because of RTA. This study benefited the Red Cross War Memorial Children's Hospital in identifying strategies that can be implemented to reduce risk factors of TBI because of RTA.

7.4 Privacy and Confidentiality

Participation in the prospective data collection was completely voluntary and patients were not treated any differently based on their decision to participate. Interviews were conducted by the researcher with oversight from the supervisor as required. Consent was obtained by the researcher and not by any of the treating clinicians to avoid therapeutic misconception. All data collected retrospectively and prospectively has a unique identification in the form of a given hospital record number. Personally identifiable information that is not essential to the study was not collected or used in any reports and confidentiality as a patient remained secure. Subsequent uses of data will be subject to standard data use policies which protect anonymity of individuals and institutions.

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Part B Manuscript:

Title page:

Brief title: Identifying risk factors for traumatic brain injury (TBI) due to road traffic accidents (RTAs) and strategies to reduce the burden of secondary brain injury.

Author name(s): Kriste Alberts^{1,2}, Nqobile Thango², Andrew Appiah-Baiden², Themban Hina², Yolandi Ferreira², Nico Enslin², Ursula Rohlwink², Anthony Figaji²

Affiliation(s): 1. School of Public Health, University of Cape Town, Cape Town, South Africa.
2. Division of Neurosurgery, Department of Surgery, Neuroscience Institute, University of Cape Town, Cape Town, South Africa.

Full address(es):

Private Bag X3, Rondebosch, 7701, Cape Town, Western Cape, South Africa

Woolsack Drive, Rondebosch, 7701, Cape Town, Western Cape, South Africa

Abstract:

Background: There is a major knowledge gap in South Africa about detailed risk factors contributing to TBI due to RTAs in children. The objectives of this study were to map the burden of disease and examine circumstantial and clinical information to inform potential intervention strategies.

Methods: This was a descriptive study of patients with TBI admitted to the Red Cross War Memorial Children's Hospital in Cape Town, Western Cape. A retrospective analysis of basic demographic and clinical data were performed from a large database of children admitted with severe TBI. More detailed information about the circumstances of RTAs causing TBI were prospectively collected through interviews with caregivers.

Findings: From a database of 511 paediatric patients with severe TBI (age 13 or less), 403 (78.9%) sustained injuries in RTAs, mostly as pedestrians (71.7%). Males were more often injured (66%) and the median age was 6.8 years. The median time from the accident to tertiary hospital admission was three hours, to obtaining a CT scan was 4.5 hours, and to ICU admission was nine hours. With respect to the circumstances of RTAs, 155 interviews were conducted of which 80.7% involved pedestrian incidents. In 34 incidents (22%), more than one person was injured. Among these, 19 involved parents, with 17 of them (89.5%) dying from their injuries. Among pedestrians, 62% were injured while crossing the road and 57.5% were unaccompanied by an adult. Most commonly, the injured first attended the nearest clinic or day hospital (46%) by travelling with a personal vehicle (53%). Local areas that experienced the most RTAs were Gugulethu (7.7%), Khayelitsha (5.3%) and Mitchells Plain (5.3%).

Interpretation: The study indicates a high incidence of RTAs as a cause of TBI in South African children, particularly among pedestrians. The high rate of unaccompanied children crossing roads, suggests a need for improved road safety education and adult supervision. The clustering of RTAs in specific local communities points to the need for targeted interventions in high-risk locations. The high mortality rate among parents involved in RTAs with their children underscores the broader impact of these accidents on families and communities.

Funding: This work was supported by the University of Cape Town Postgraduate Funding Office and the Paediatric Neurosurgery Unit.

Introduction

RTAs rank as a major global cause of death and disability. The World Health Organization (WHO) estimates that RTAs result in 1.35 million fatalities and between 20 to 50 million non-fatal injuries and disabilities annually. Remarkably, over 90% of these deaths occur in low- and middle-income countries (LMICs), with Africa experiencing the highest RTA mortality rates ⁽¹⁻⁴⁾.

Several environmental risk factors may contribute to varying rates of injuries in different regions. Public health interventions and social advocacy may reduce the burden of injuries but should be informed by what the risk factors in a particular region are, and what aspects of healthcare could be improved ^(5,6).

Traumatic brain injury (TBI) stands as the predominant cause of both mortality and long-term disability in cases of trauma, and RTAs represent a significant contributor to TBI, particularly in children, on a global scale. There is a major knowledge gap in South Africa about more detailed risk factors contributing to RTA-related TBI in children, including the circumstances of the injury, which are important to enable identification of specific initiatives to reduce the occurrence or severity of an injury ⁽⁷⁻¹⁰⁾. Furthermore, we know even less about pathways for clinical service delivery for these patients. This is not only about saving lives – injury-related disability can cause financial hardship especially for those of lower economic status and may lead to loss to follow-up, insufficient care, and poor health outcomes ⁽¹¹⁻¹³⁾.

Access to early and effective clinical care can reduce secondary injury and improve outcomes, while delays in care or ineffective care can increase death and long-term disability. The objectives of this study were to 1) examine demographic and clinical data of children who sustained an RTA-related TBI, and 2) to examine the social circumstances of RTAs and how patients access clinical care in an urban environment in South Africa.

Methods

Study Design

The study consisted of two parts:

First, we performed a retrospective analysis of a large database of children (age 13 and under) who were admitted to a major urban hospital with severe TBI (defined as patients presenting in coma [with a Glasgow Coma Score of 8 or less], typically requiring ICU admission and who underwent intracranial monitoring). This enabled interrogation of demographic and clinical data collected from a large number of the most severe cases admitted to RCWMCH in the Western Cape, South Africa from 2006 to 2021. These data were limited to routinely collected information in hospital records.

Second, because data on the circumstances are not usually recorded in the hospital record, we proceeded to collect more detailed information prospectively through interviews with caregivers. This was conducted from September 2022 to September 2023 and involved patients who sustained an RTA-related TBI of any severity. Patients were excluded if they had TBI through other mechanisms or had sustained injury from RTA but without TBI.

Data Collection

A database of paediatric severe TBI cases is maintained prospectively in the Paediatric Neurosurgery Unit of RCWMCH.

The prospective interviews were conducted with caregivers of children who were attending follow-up clinics at the hospital. Patients were approached and, if willing, were asked questions about the circumstances and environmental factors directed by a formal set of questions. The interview was conducted face to face in a private consultation room. The overall length of participation was ten to 15 minutes and was conducted in English, Afrikaans and isiXhosa with a translator as required.

Statistical Analysis

Data were analysed with R software and R Studio user interface. Summary statistics were examined for all relevant variables. The dataset was inspected to understand the pattern and extent of missingness. Multiple imputation, the preferred method for handling data missing at random, was employed to avoid biased estimates. The imputation uses a statistical model to predict the missing values based on the relationships observed in the non-missing data ⁽¹⁴⁾. The ‘mice’ package was employed, which makes use of chained equations where each variable with

missing data was modelled conditionally upon the others in a round-robin fashion ⁽¹⁴⁾. The ‘mice’ package provides functions that automatically performed the pooling by applying Rubin's rules, which account for both within-imputation variability and between-imputation variability ⁽⁴¹⁾.

Results

Retrospective analysis

During this period, 745 children with TBI who were intubated and ventilated were admitted to the PICU with TBI; 520 patients underwent intracranial monitoring (intracranial pressure monitoring with or without brain tissue oxygen and microdialysis monitoring) and had data recorded in the database. Of these patients, data for nine patients were incomplete and could not be retrieved from existing clinical records; therefore, they were excluded from further analysis, leaving 511 patients who were finally included. The trends of TBI's caused by RTAs over this 16-year period appear to follow a similar pattern to the overall trend of all severe TBIs (Appendix A).

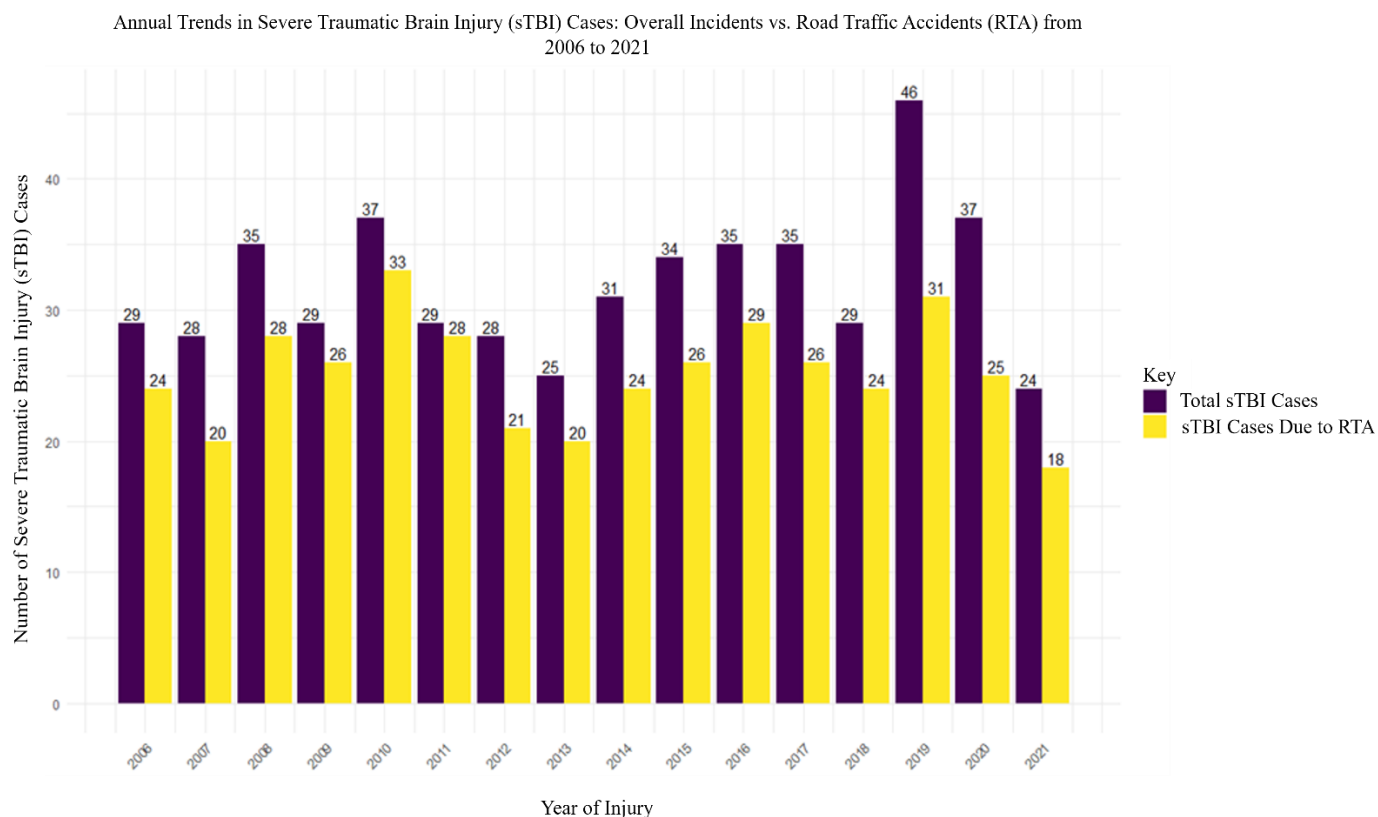


Figure 1: A bar graph showing the Annual Admissions of sTBI Cases Versus RTA-related sTBI Cases at RCWMCH from 2006 to 2021.

A total of 403 (78.9%) patients had a sTBI that was caused by RTAs. Table 1 presents the baseline demographic and clinical characteristics of these cases, stratified by the type of RTA (passenger or pedestrian). Of 403 RTA-injured patients, 114 (28.3%) were passengers in motor vehicles, and 289 (71.7%) were pedestrians.

Age and sex: The median age of the children was 6.8 years, and two thirds (66%) were male.

Other injuries: In addition to the sTBI sustained in the injury, 71% of patients experienced polytrauma and 49% required additional (extracranial) surgical procedures.

Secondary insults: Secondary insults are events that occur that may worsen outcomes in patients with acute brain injury. Common physiological insults include hypoxia (defined by pulse oximetry less than 90%) and arterial hypotension (based on age-related norms); both of which have been associated with worse outcomes previously. Around half of the cases had episodes of hypoxia or hypotension before or on arrival at hospital (Table 1).

Transfer to clinical care: Over 70% of patients were intubated pre-arrival and were mostly transferred indirectly to another treatment location (68%) before transfer to the definitive hospital. The median time from the time of the injury to admission at RCWMCH was three hours. Obtaining a head CT scan is a standard diagnostic procedure in the workup of these patients to identify possible intracranial lesions that may require emergency surgery: from time of injury to the time that the CT scan was done was 4.5 hours. The time from injury to ICU admission was nine hours and to intracranial monitor placement was 11 hours.

Length of stay: The median duration that the patients remained in ICU was nine days and for intracranial monitoring was five days.

Table 1: A table showing the baseline demographic summary statistics of patients with severe TBI, stratified by type of RTA.

Characteristic (n = Total population included for calculation)		Overall, Total Population (N) = 403	Passenger, N = 114	Pedestrian, N = 289
Age at Injury (years) Median (IQR)		6.8 (4.3, 9.4)	6.8 (3.5, 9.9)	6.8 (4.6, 9.0)
Sex (n = 403) Frequency (%)	Male	265 (66%)	76 (67%)	189 (65%)
	Female	138 (34%)	38 (33%)	100 (35%)
Initial Haemoglobin Score (grams per decilitre) Median (IQR)		10 (8.80, 11.20)	9.50 (8.10, 11.00)	10.10 (9.10, 11.20)
Other Injuries (n = 403) Frequency (%)	Yes	286 (71%)	81 (71%)	205 (71%)
	No	117 (29%)	33 (29%)	84 (29%)
Intubated Pre-arrival. *(n = 384) Frequency (%)	Yes	297 (77%)	79 (73%)	218 (79%)
	No	87 (23%)	29 (27%)	58 (21%)
Transfer to Hospital *(n = 383) Frequency (%)	Direct	124 (32%)	30 (28%)	94 (34%)
	Indirect	259 (68%)	76 (72%)	183 (66%)
Secondary Insults *(n = 203) Frequency (%)	None	106 (52%)	32 (52%)	74 (52%)
	Hypoxia	36 (18%)	9 (15%)	27 (19%)
	Hypotension	43 (21%)	11 (18%)	32 (23%)
	Hypoxia and Hypotension	18 (8.9%)	9 (15%)	9 (6.3%)
Time to Admission (hours) Median (IQR)		3.0 (1.3, 13)	4.0 (1.5, 8.0)	3.0 (1.0, 5.4)
Time to ICU (hours) Median (IQR)		9 (7, 13)	10 (8, 16)	9(6, 13)
Time to CT (hours) Median (IQR)		4.5 (2.4, 7.0)	5.0 (2.9, 9.4)	4.0 (2.0, 6.6)
Time to Intracranial Monitoring (hours) Median (IQR)		11 (8, 19)	11 (8, 19)	11 (7, 18)
Duration of Intracranial Monitoring (days) Median (IQR)		5.0 (4.0, 8.1)	5.0 (4.0, 9.0)	5.0 (4.0, 8.0)
Duration in ICU (days) Median (IQR)		9 (6, 13)	9 (5, 14)	9 (6, 13)
Other Surgery *(n = 357) Frequency (%)	Yes	176 (49%)	59 (56%)	117 (47%)
	No	181 (51%)	47 (44%)	134 (53%)
<i>*Calculations were made based on data available for that category.</i>				

The time to treatment from injury was analysed. As seen in Figure 2, the time from the injury to admission has the narrowest spread of times; the median time was three hours. The outliers likely reflect patients who were transferred from outside the Cape Metro. The time to obtaining a head CT scan was 4.5 hours, which reflects the resuscitation times, availability of the CT scanner, and organization of transport from the trauma unit to the CT scanner. The time to ICU admission shows greater variability (median of nine hours); this may be influenced by resuscitation times, time in the operating room before ICU admission, and ICU bed availability.

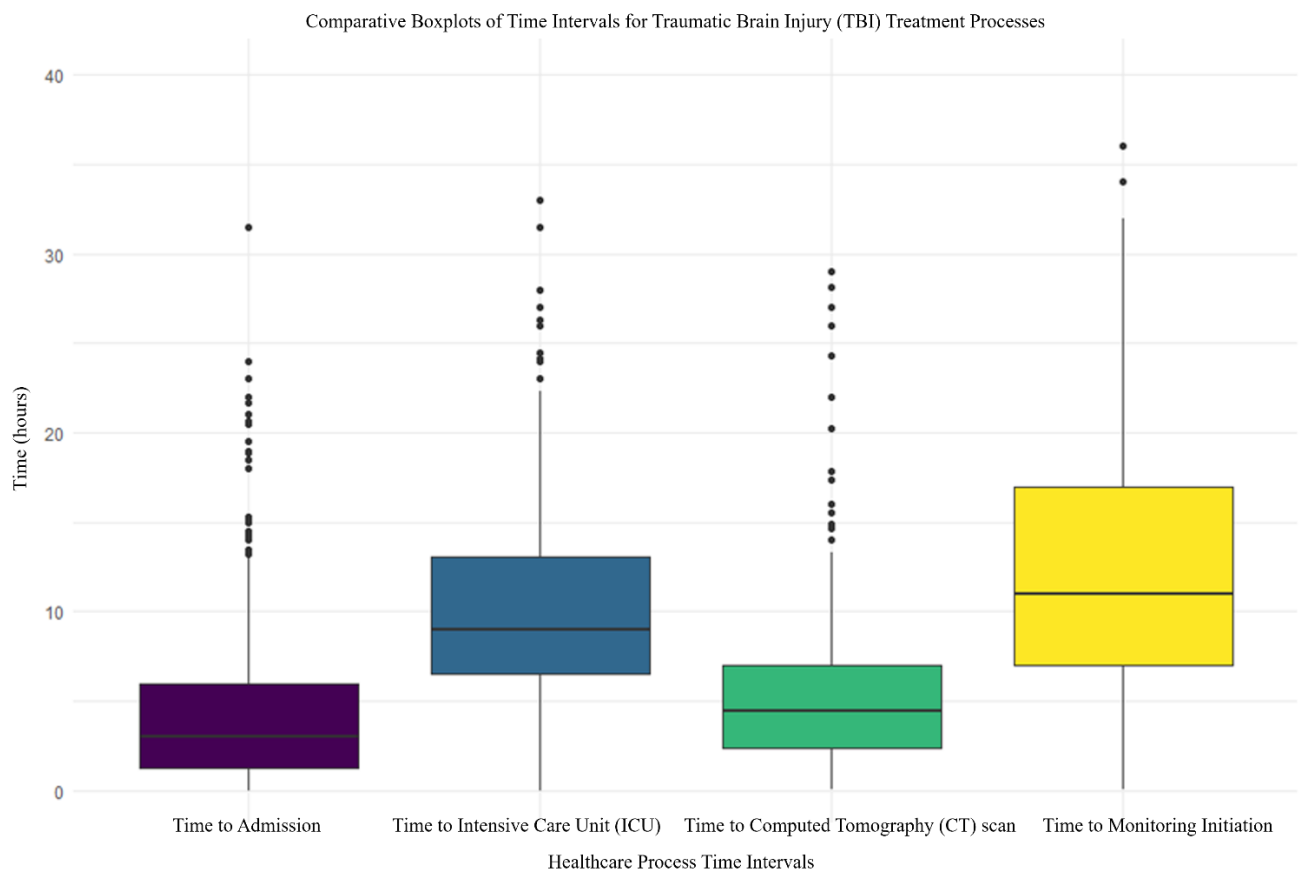


Figure 2: Boxplots showing the Distribution of Time Intervals from Injury to Critical Care Interventions for TBI Patients.

Multiple imputation was performed to deal with the missing data and limit potential biases (Appendix B and C show the percentage of missingness before and after multiple imputation, respectively). Table 3 in Appendix D presents model statistics of the different models.

In this study, multiple imputation effectively addressed missing data, revealing pivotal insights into trauma patient outcomes. The most striking finding comes from Model Three, which shows that direct hospital transfers significantly reduce admission times by an average of 3.9 hours compared to indirect transfers, a result underscored by a p-value less than 0.001 and narrow confidence intervals. This highlights the critical impact of streamlined hospital transfers

on patient care efficiency. In contrast, other models, such as the analysis of injury mechanisms and time-sensitive interventions like ICU admission and monitor placement, did not demonstrate statistically significant effects. Particularly, the time to ICU admission and monitor placement, although shorter with direct transfers, lacked statistical significance. The comprehensive analysis underscores the nuanced nature of trauma care, where certain logistical aspects, notably direct hospital transfer, markedly influence patient flow and treatment timelines, while others, like the specifics of injury mechanism, do not significantly alter additional injury risks or critical care timelines.

Prospective analysis

A total of 155 interviews were conducted with caregivers of patients who experienced a TBI of any severity due to an RTA. These were conducted at the Neurosurgery outpatient clinic of RCWMCH. Of the 155 patients that were recruited, 30 (19.4%) were passengers and 125 (80.7%) were pedestrians; median ages were 7.7 and 6.8, respectively (Table 2). In 34 (22%) of the cases, the RTA had resulted in more than one person being injured or hospitalised. Of those who were injured in addition to the child, 19 of them were parents of which 17 (89.5%) died. Among the parents who died, four cases involved the father, nine cases involved the mother, and three cases involved both the mother and father (one case was only noted as the parent).

Road accidents occurred more often on urban roads (46%) and most often the injured was taken to the nearest clinic or local day hospital (46%) and was transported by a personal vehicle (53%).

In 71% of the cases, the RTA occurred within 5km of where the patient lived. When subgrouped by the mechanism of injury, passengers (55%) more likely experience an RTA further away from home compared to pedestrians (22%).

Of the 155 patients included, 48 had made a RAF application.

Table 2: A table showing the baseline demographic summary statistics of patients interviewed, stratified by type of RTA.

Characteristic (n = Total population included for calculation)		Overall, Total Population (N) = 155	Passenger, N = 30	Pedestrian, N = 125
Age at injury (years) Median (IQR)		7.0 (4.0, 9.2)	7.7 (3.1, 10.9)	6.8 (4.2, 9.0)
Term of year *(n = 154) Frequency (%)	Holiday	38 (25%)	11 (37%)	27 (22%)
	School term	116 (75%)	19 (63%)	97 (78%)
Other people injured. Frequency (%)		34 (22%)	22 (73%)	12 (9.6%)
Time of week (n = 155) Frequency (%)	Weekday	92 (59%)	12 (40%)	80 (64%)
	Weekend	63 (41%)	18 (60%)	45 (36%)
Time of day *(n = 153) Frequency (%)	Morning	27 (18%)	14 (50%)	73 (58%)
	Afternoon	87 (57%)	10 (36%)	29 (23%)
	Evening	39 (25%)	4 (14%)	23 (18%)
Type of road (n = 155) Frequency (%)	National	25 (16%)	15 (50%)	10 (8%)
	Rural	59 (38%)	4 (13%)	55 (44%)
	Urban	71 (46%)	11 (37%)	60 (48%)
First treatment location (n = 155) Frequency (%)	Local clinic/day hospital	71 (46%)	9 (30%)	62 (50%)
	Local hospital	39 (25.3%)	11 (37%)	28 (22.6%)
	RCWMCH	45 (29%)	10 (33%)	35 (28%)
Transport used *(n = 153) Frequency (%)	Air transport	1 (0.7%)	1 (3.3%)	0 (0%)
	Ambulance	68 (44%)	21 (70%)	47 (38%)
	Personal Vehicle	81 (53%)	7 (23%)	74 (60%)
	**Other	3 (2.1%)	1 (3.3%)	2 (1.6%)

Distance from home *(n = 150) Frequency (%)	Within 5km	107 (71%)	13 (45%)	94 (78%)
	More than 5km	43 (29%)	16 (55%)	27 (22%)
Applied for Road Accident Fund *(n = 154) Frequency (%)	No	106 (69%)	16 (55%)	90 (72%)
	Yes	48 (31%)	13 (45%)	35 (28%)
*Calculations were made based on data available for that category.				
**Other transport used includes walking, rescue vehicles or police vans.				

There is no clear indication that there is a significant difference in the age distribution across the different mechanisms of injury (pedestrians or passengers) as seen in Appendix E. Most RTAs occur in the afternoon. Additional figures to view the distribution of data can be seen in Appendix F and G.

Pedestrian injuries: Of these, 62% of patients were struck while crossing the road, and 36% were struck while walking or playing on the pavement or verge. Of those who were crossing the road 57.5% were doing so unaccompanied by an adult. The pedestrians were most likely to experience a RTA because of being hit by a privately-owned car (56.8%) followed by Taxi's (16%), and 'bakkies' (11.2%). Other vehicles involved included trucks, busses, and motorbikes. Of all the pedestrian RTAs, there were 27 cases where the perpetrator was not identified and drove away (hit and run), 63% of these were Taxis.

Passenger injuries: Among passengers, the most common vehicle that was involved in the crash was a car (56.6%) followed by a 'bakkie' (33.3%, being transported in the back). Nine patients were ejected from the vehicle they were in and all of them were unrestrained. Some form of restraint such as a seatbelt or child car seat was only used in 16.6% of patients.

One child had been cycling and was not wearing any protective headgear.

Time of injury: Through the week, 92 occurred on weekdays, and 63 on the weekend. With a year consisting of 261 weekdays and 104 weekend days, analysis showed that the incidence was 35.2% (0.352 rate) on weekdays and higher on weekends (60.6%, 0.606 rate).

The same was done for the term of year, in relation to school days and holidays. The data encompasses a total of 154 known days of sustaining a TBI, of which 116 occurred during school days and 38 during holidays. The annual calendar includes approximately 202 school

days and 62 holiday days. Thereby concluding that there is a higher risk of obtaining a head injury during the holiday periods 61% (0.61 rate) compared to during the school term 57% (0.57 rate).

Accessing care: To understand access to care through distance from the treating facility (RCWMCH), the location of RTAs was analysed. Figure 3 shows the general distribution of RTA locations in red, relative to the treatment location of RCWMCH in blue. Some cases are transferred to RCWMCH from further afield (Appendix H).

The regions that accounted for most of the cases were Gugulethu (7.7%), Philippi (7.1%), Khayelitsha and Mitchells Plain (5.3%, respectively), Delft and Nyanga (4.5%, respectively) (Appendix I).

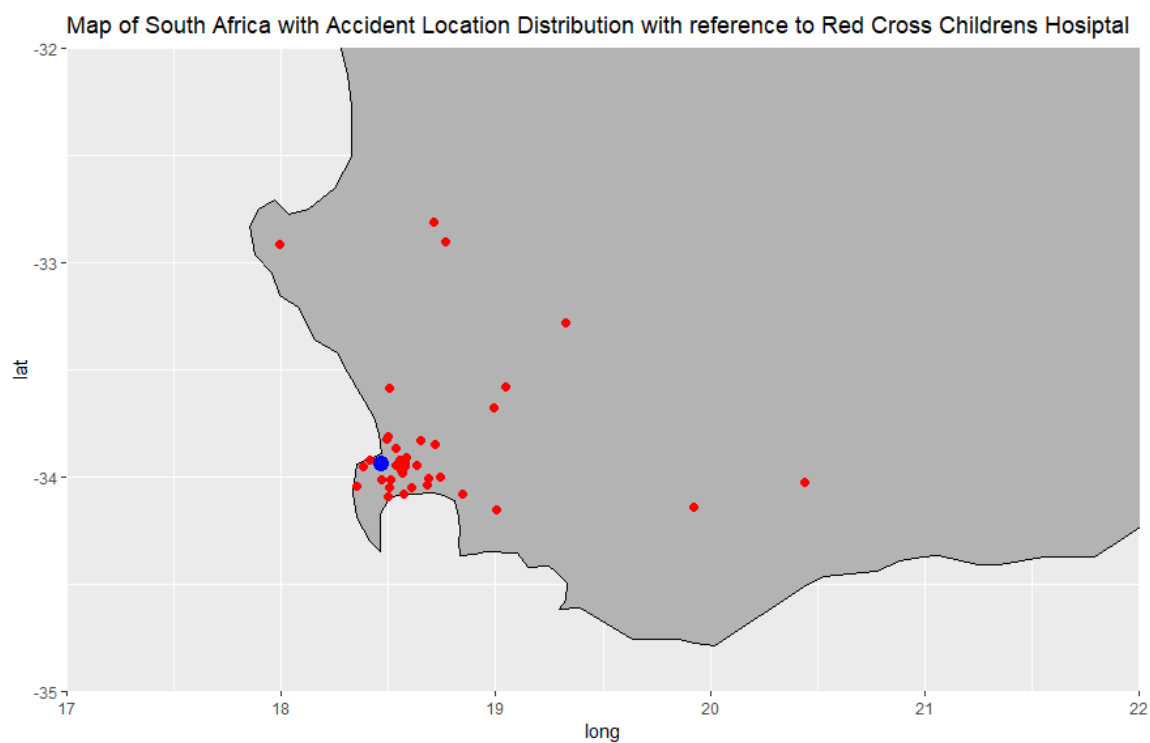


Figure 3: A map of RTA occurrence in South Africa with reference to admission at RCWMCH.

Discussion

In the 2018 World Health Report on road accidents, it was recognized that in the five years since the prior report, the scale of the problem had continued to grow, with deaths due to RTA increasing to 1.35 million a year, nearly 3700 deaths occur on the road every day ^(15, 16). This remains the number one cause of death in older children ^(2, 15-18). This report also indicates that the risk of death due to RTA is three times higher in LMICs compared to HICs with no decrease in death due to RTA in any low-income country since 2013 ^(15, 16, 19).

The death rate is highest in Africa, and more than half of the RTAs occur among vulnerable road users i.e. pedestrians ^(12, 15, 16). With over 85% of global road traffic fatalities occurring in developing countries, the problem is substantial and in response, the WHO unveiled a 5-year plan for preventing RTAs ^(8, 9). A key suggestion of this initiative is to encourage the conduct of research on road safety. In these nations, the lack of sufficient knowledge often hinders the effective distribution of resources needed to tackle the issue, thereby exacerbating the problem ^(8, 20). Despite the clear implications for the burden of disease for children from RTAs in South Africa, there remains much that we do not know about the risk factors and how well our public health systems manage the burden. To add to our knowledge in this area, this study provides data about the circumstances of the RTAs as well as patients' access to emergency health care. This is important because delays in accessing optimized care are associated with increased secondary insults and worse outcomes.

The retrospective analysis highlights the significant role of RTAs as the primary cause of severe TBI in children. This is a critical observation since brain injuries constitute the leading cause of trauma-related fatalities and disabilities in the paediatric population. The demographic characteristics observed in this study align with findings from other research ^(21, 22). The median age of affected children was 6.8 years, with a predominance of males (66%), and a majority being pedestrians (71.7%). It's important to note that the median age of children in studies may vary depending on the definition of "children" (some include individuals up to age 19 or 21). Bandyopadhyay et al. reported a mean age range for children with TBI in included studies of 22.4 months to 7.7 years ⁽²³⁾. Given the mean age of 6.8 years, aligning road safety education with the start of mandatory schooling could be a crucial intervention. Programs focusing on safe road-crossing practices and the necessity of adult accompaniment could be integrated into the school curriculum, reducing the risk of unaccompanied minors being involved in RTAs.

In another population-based study, it was observed that 69% of children with severe TBI were male ⁽⁸⁾.

Male children were 1.8 times more likely than female children to experience TBI ⁽²³⁾. These findings may be influenced by differences in risk-taking behaviours between male and female children and the possibility that parents may be less likely to restrict the exploratory behaviour of male children compared to female children ⁽²³⁾. Therefore, the consistent pattern of these observations suggests a potential need for targeted injury prevention campaigns that consider these gender-based differences.

We know even less about pathways for clinical service delivery for patients with severe TBI due to RTAs. Delays in time to access definitive care increase adverse outcomes because of the higher risk of secondary insults (such as hypoxia and hypotension) as well as delayed evacuation of intracranial haematomas or management of brain swelling. Evidence suggests that a delay of just four hours from injury to surgical care is associated with a 3-fold increase in death rate ⁽¹²⁾. To prevent injury related disabilities and deaths, fast access to superior quality healthcare is needed ^(13, 24). Despite the goal of a golden hour for trauma resuscitation, the median time for arrival at the hospital for definitive care was three hours. Furthermore, likely because the CT scanner is not in the trauma unit, the median time to obtain the scan was 4.5 hours after the incident. Delayed imaging results in delayed surgery to evacuate space-occupying mass lesions such as extradural and subdural haematomas.

Delays in prehospital care are mostly a result of challenges linked to the long distance to facilities and lack of sufficient transport with rapid response times ^(12, 13). Furthermore, it is worth noting that access to imaging remains a significant challenge in developing countries, even though a CT scan is a crucial requirement for reducing mortality in cases of TBI ^(12, 25, 26).

By comparison, a German study demonstrated a time to CT scan after injury of 1.46 hours ⁽²⁷⁾. Public health interventions and social advocacy may play important roles in reducing injuries. For example, a study from the US analysed the effectiveness of seatbelts mitigating TBI severity among 803 patients who were in a motor vehicle accident ⁽⁵⁾. Of these 803 patients, only 45% wore seatbelts and regardless of the position of the patient in the vehicle, those who did not wear seatbelts were more likely to have loss of consciousness ⁽⁵⁾. Additionally, those who did not wear seatbelts also did worse in every outcome with an overall four times increase in the risk of TBI severity ⁽⁵⁾.

Environmental risk factors can also play a significant role in the risk of RTA. A 6-year survey was done in Southwest China to assess the characteristics and patterns of injury,

specifically due to RTA as well as understand the public health consequences because of this burden ⁽⁶⁾. The study enrolled more than 1000 patients of which 49% took place in urban areas with the highest number of accidents occurring during winter (27.1%) ⁽⁶⁾. Most of the accidents occurred on a dry asphalt road surface (73.5%) with most of the RTA occurring between six and eight in the morning and six to nine in the evening ⁽⁶⁾.

Prospectively, a high proportion of parents who were involved in the accident died. This is important because not only does the child have to manage possible injury-related disability, but parental death is also a common association with long-term illness in children and worsening school outcomes, there is a greater chance for high-risk behaviour and low SES later in life ^(28, 29).

It is a societal concern that of the children injured while crossing the road, 57.5% were doing so unaccompanied by an adult. The high incidence of unaccompanied minors being injured suggests a need for increased adult supervision. Community-led initiatives where children are escorted to school by volunteers or parents, could significantly reduce these incidents ⁽³¹⁾. It is also concerning that a large number of children were struck while seemingly safe on the pavement or verge of the road.

Furthermore, the issue of "hit-and-run" incidents, particularly those involving public transport vehicles, presents a critical challenge in reducing RTAs involving children. To address this, stricter enforcement of traffic regulations specifically targeting public transport vehicles is crucial. Implementing mandatory driver education programs focusing on pedestrian safety, along with regular audits of public transport operators, could help mitigate these incidents ⁽³¹⁾. Public awareness campaigns highlighting the legal and moral consequences of hit-and-run accidents, combined with increased penalties for offenders, could serve as strong deterrents ⁽³¹⁾. Additionally, establishing designated pedestrian zones and improving infrastructure around schools and residential areas—such as the installation of speed cameras and pedestrian crossing signals—can reduce the risk of such accidents ⁽³¹⁾.

Children are at higher risk on the weekends and during the school holidays. Given the elevated risk of RTAs during holidays and weekends, targeted traffic calming measures in high-risk areas, including the implementation of speed bumps, enhanced pedestrian crossings, and increased traffic patrols, could be effective in mitigating these risks. In the Cape metro, the largest number of cases occurred in Gugulethu (7.7%), Philippi (7.1%), Khayelitsha and Mitchells Plain (5.3%, respectively), Delft and Nyanga (4.5%, respectively). Targeted intervention in these regions may reduce the burden of TBI ⁽³⁰⁾. These interventions are possible - for example, Korea had decreased the number of

children killed in an RTA by more than 95% between 1998 to 2012 ⁽³¹⁾, through the introduction and implementation of various policies including school zone strategies, school bus improvements, compulsory road safety education and strengthening of the already existing legal framework ⁽³¹⁾.

A major strength of this work lies in its comprehensive approach to understanding TBI in children due to RTAs in South Africa, a topic previously underexplored. The use of a large database from the Red Cross War Memorial Children's Hospital provides a robust data set, ensuring that findings are grounded in a substantial sample size, enhancing the study's reliability. Additionally, the combination of retrospective data analysis with prospective interviews adds depth to the research, enabling a more nuanced understanding of the circumstances leading to TBI. This multifaceted approach not only maps the burden of disease but also provides valuable circumstantial and clinical insights, making the study novel and meaningful.

However, the study faces limitations that open avenues for further research. The focus on a single hospital may limit the generalizability of the findings to the wider South African context or to other regions. In addition, future research should consider expanding the scope of patient cohorts to include adults, as this can provide valuable comparative insights into the factors influencing TBI in different age groups and lead to more comprehensive strategies for injury prevention and intervention. Furthermore, the reliance on interviews for circumstantial data introduces potential biases, as the data quality is contingent on the accuracy and completeness of the caregivers' recollections. This aspect points to the need for more systematic and comprehensive data collection methods in future studies.

In summary, while the study makes significant contributions to understanding the complex dynamics of TBI in children due to RTAs in South Africa, its findings should be considered within the context of its methodological scope and the need for broader, more diverse research to build upon these foundational insights.

Conclusion

RTAs are the leading cause of severe TBI in children in the Western Cape region of South Africa, which likely reflects similar patterns in the rest of the country. Several areas for concern are highlighted in this report, identifying key areas in which social engagement by government and local communities can reduce the risk to vulnerable children. Moreover, key delays to definitive medical and surgical care are identified that may worsen clinical outcomes and can be improved by better prehospital and intra-hospital protocols.

Manuscript Appendices:

Appendix A: Trends of TBI over 16-year period

As seen in Figure 4, the trends of TBI's caused by RTAs over this 16-year period appear to follow a similar pattern to the overall trend of all severe TBIs. Notably, there is a sharp peak around 2018, indicating a particularly high incidence of severe TBI's that year. This peak, along with other fluctuations, is mirrored in both datasets, emphasizing the influence of RTAs on the overall severe TBI statistics.



Figure 4: A line graph showing the Comparative Analysis of Yearly sTBI Incident Trends and RTA-Related sTBI at RCWMCH from 2006 to 2021.

Appendix B: Missing data plot before multiple imputation

This plot is used to understand how much of the data is missing and identify if the data is missing at random to help decide on which multiple imputation model to use.

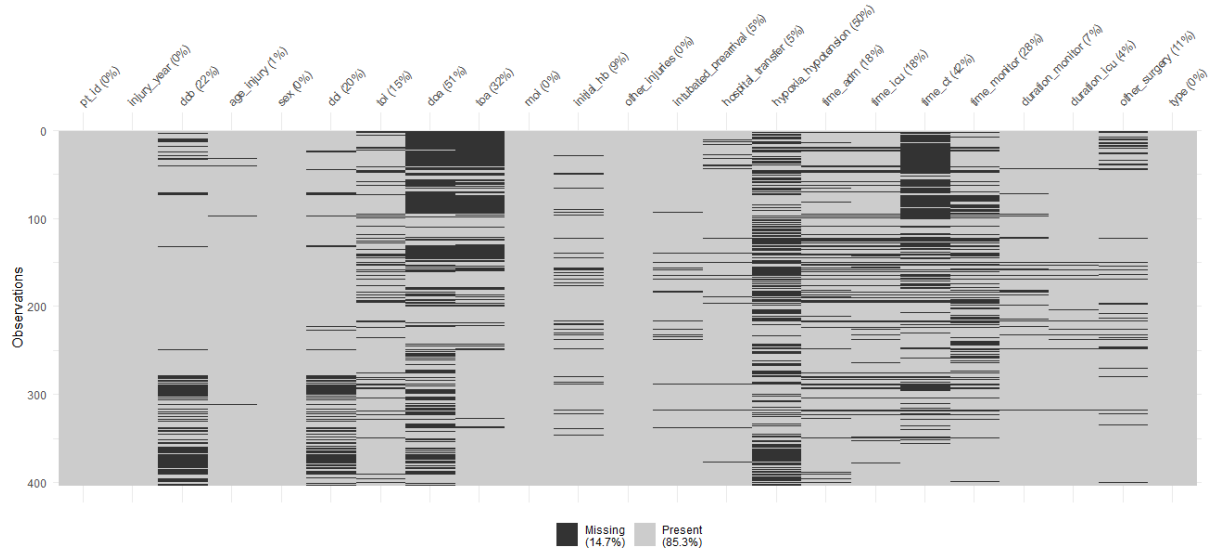


Figure 5: A plot showing missingness across all variables in the severe TBI database before multiple imputation was performed.

Appendix C: Missing data plot after multiple imputation

This is the same plot generated as in Appendix A that shows how much of the data is missing after the multiple imputation was performed. Variables that were not included in the analysis were not imputed (date of admission, time of admission and other surgery), hence the data is still missing.

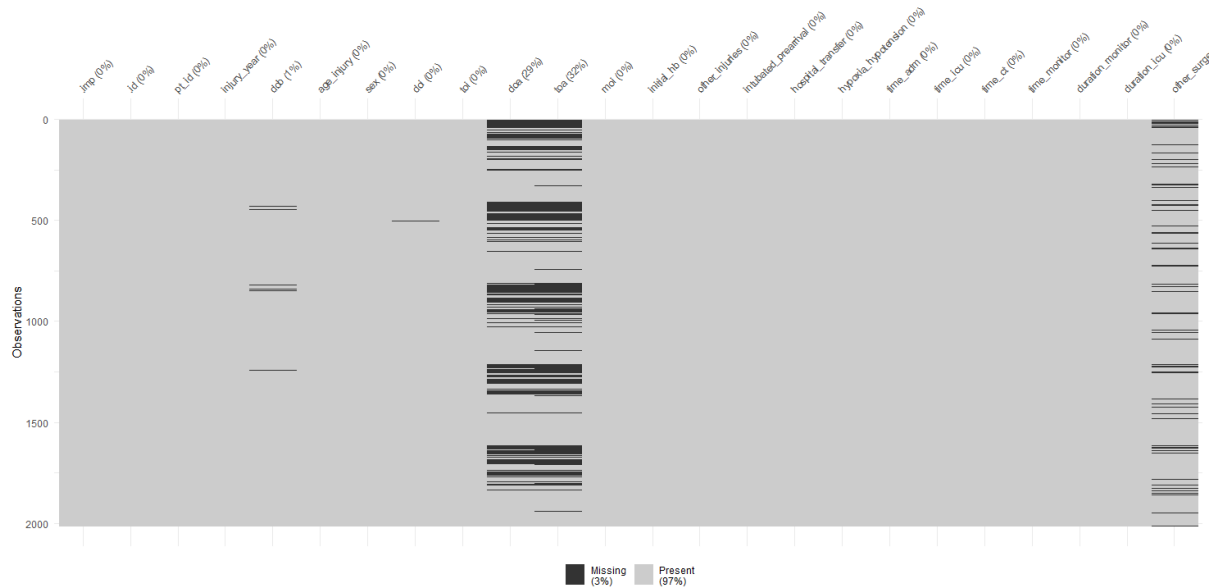


Figure 6: A plot showing missingness across all variables in the severe TBI database after multiple imputation was performed.

Appendix D: Table of model statistics for multivariate regression models

Multiple imputation was performed to deal with the missing data and limit potential biases (Appendix B and C show the percentage of missingness before and after multiple imputation, respectively). Table 3 presents model statistics of the different models.

Table 3: A table showing the model statistics of multivariate regression models.

Covariates	Log-Odds	95% CI (lower limit; upper limit)	Z-statistic	P-value
Model One: Logistic Regression Model for Mechanism of Injury with reference to Additional Injuries				
Intercept	0.898	(1.635; 3.684)	4.348	< 0.001
Pedestrian	-0.006	(0.616; 1.606)	-0.024	0.981
<i>Reference Category for Model One is Passengers</i>				
Model Two: Multinomial Logistic Regression Model for Secondary Brain Injury				

Hypoxia	Intercept	-1.724	(0.068; 0.468)	-3.606	< 0.001
	Time to Admission	-0.125	(0.712; 1.093)	-1.396	0.208
	Time to ICU	0.055	(0.993; 1.125)	1.784	0.083
	Time to CT	-0.006	(0.671; 1.472)	-0.045	0.966
	Time to Monitor	0.039	(0.971; 1.114)	1.415	0.211
	Intubation Pre-arrival	0.099	(0.458; 2.662)	0.229	0.820
Hypotension	Intercept	-0.530	(0.230; 1.505)	-1.168	0.255
	Time to Admission	-0.076	(0.799; 1.074)	-1.142	0.279
	Time to ICU	0.052	(0.987; 1.124)	1.647	0.111
	Time to CT	-0.056	(0.743; 1.204)	-0.590	0.580
	Time to Monitor	-0.007	(0.946; 1.042)	-0.310	0.761
	Intubation Pre-arrival	-0.213	(0.306; 2.138)	-0.472	0.644
Hypoxia and Hypotension	Intercept	-2.714	(0.013; 0.340)	-3.383	0.002
	Time to Admission	0.049	(0.907; 1.217)	0.721	0.484
	Time to ICU	-0.058	(0.863; 1.032)	-1.293	0.201
	Time to CT	0.043	(0.899; 1.212)	0.693	0.513
	Time to Monitor	0.023	(0.965; 1.085)	0.899	0.395
	Intubation Pre-arrival	0.846	(0.250; 21.739)	0.846	0.418
<i>Reference for Model Two is baseline value of 0</i>					
Model Three: Linear Regression Model for Time to Admission					
Intercept		6.083	(210.011;915.238)	16.848	< 0.001
Direct Hospital Transfer		-3.887	(0.007; 0.063)	-6.855	< 0.001
Model Four: Linear Regression Model for Time to ICU					
Intercept		10.809	(1767.804;13850.890)	21.060	< 0.001
Direct Hospital Transfer		-1.186	(0.0584; 1.596)	-1.420	0.158
Model Five: Linear Regression Model for Time to CT scan					
Intercept		6.987	(17678.040; 13850.890)	12.422	< 0.001
Direct Hospital Transfer		6.988	(0.0584; 1.596)	-3.416	0.002
Model Six: Linear Regression Model for Time to Monitor Placement					
Intercept		16.106	(1127259; 8657471)	15.165	< 0.001
Direct Hospital Transfer		-3.054	(0.007; 3.055)	-1.533	0.142
<i>Reference Category for Model Three-Six is indirect hospital transfer</i>					

In model one we looked at the type of mechanism (whether a patient was a pedestrian or passenger) and the outcome of having other injuries in addition to TBI. The intercept represents the log odds of other injuries when all predictors are zero. The intercept is statistically significant (p-value<0.001) with 95% Confidence Interval (CI) of (1.635; 3.684).

Looking at the pedestrian mechanism with reference category as passenger, the p-value is remarkably high (p-value = 0.981) which indicates that being a pedestrian is not a significant predictor of other injuries in addition to TBI in this model. However, the intercept being significant suggests that the baseline likelihood of other injuries (when mechanism is at its reference level or is zero) is significantly different from zero.

In model two, none of the predictors (time to admission, time to ICU, time to CT scan, time to monitor placement and intubation pre-arrival) are significant for predicting the occurrence of hypotension. All the p-values are greater than 0.05 and 95% confidence intervals are very wide. For the occurrence of hypoxia, the time to ICU is marginally significant ($p = 0.083$) with a narrow 95% confidence interval of (0.993; 1.125), however, none of these predictors are statistically significant for predicting hypoxia. The results are similar in the prediction of hypoxia and hypotension.

Model three suggests that on average, the time of admission is 3.887 hours less when there is a direct hospital transfer compared to an indirect hospital transfer. This result is statistically significant (p-value < 0.001) with 95% confidence intervals (0.007; 0.063).

Model four suggests that time to ICU admission is 1.196 hours less when there is a direct hospital transfer compared to an indirect hospital transfer. However, this result is not statistically significant (p-value = 0.158) with 95% confidence intervals (0.0584; 1.596). In summary, the model suggests that while the average time to ICU admission is significantly high when there is an indirect hospital transfer, the effect of direct hospital transfer on reducing the time to ICU admission is not statistically significant.

Model five suggests on average, the time to CT scan decreases by about 2.93 hours when there is a direct hospital transfer compared to an indirect hospital transfer. This result is statistically significant (p-value = 0.002) with 95% confidence intervals (0.0584; 1.596). This suggests a significant relationship between direct hospital transfer and the time to CT scan.

Model six suggests that time to monitor placement is three hours less when there is a direct hospital transfer compared to an indirect hospital transfer. However, this result is not statistically significant (p-value = 0.142) with 95% confidence intervals (0.007; 3.055). The model suggests that while the average time to monitor placement is significantly high when there is an indirect hospital transfer, the effect of direct hospital transfer on reducing the time to monitor placement is not statistically significant.

Appendix E: Interaction plot

There is no clear indication that there is a significant difference in the age distribution across the different mechanisms of injury (pedestrians or passengers) as seen in Figure 7. Most RTAs occur in the afternoon. Additional figures to view the distribution of data can be seen in Appendix F and G.

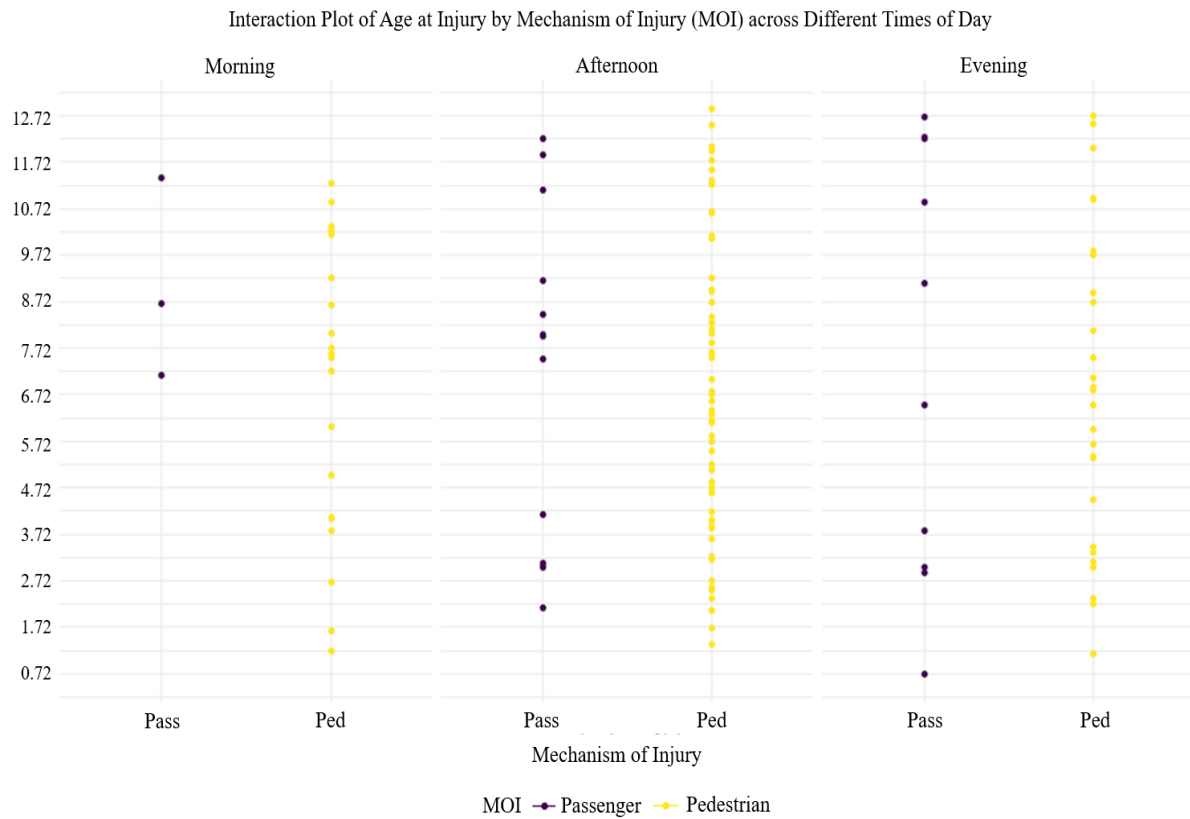


Figure 7: An interaction plot showing Age Distribution by Mechanism of RTA Injury (Passenger vs. Pedestrian) at Different Times of Day.

Appendix F: Heat map

Figure 8 shows a heat map with increasing colour intensity with an increase in the number of RTAs that occur during various times of the day and across the different school term and holidays of the year.

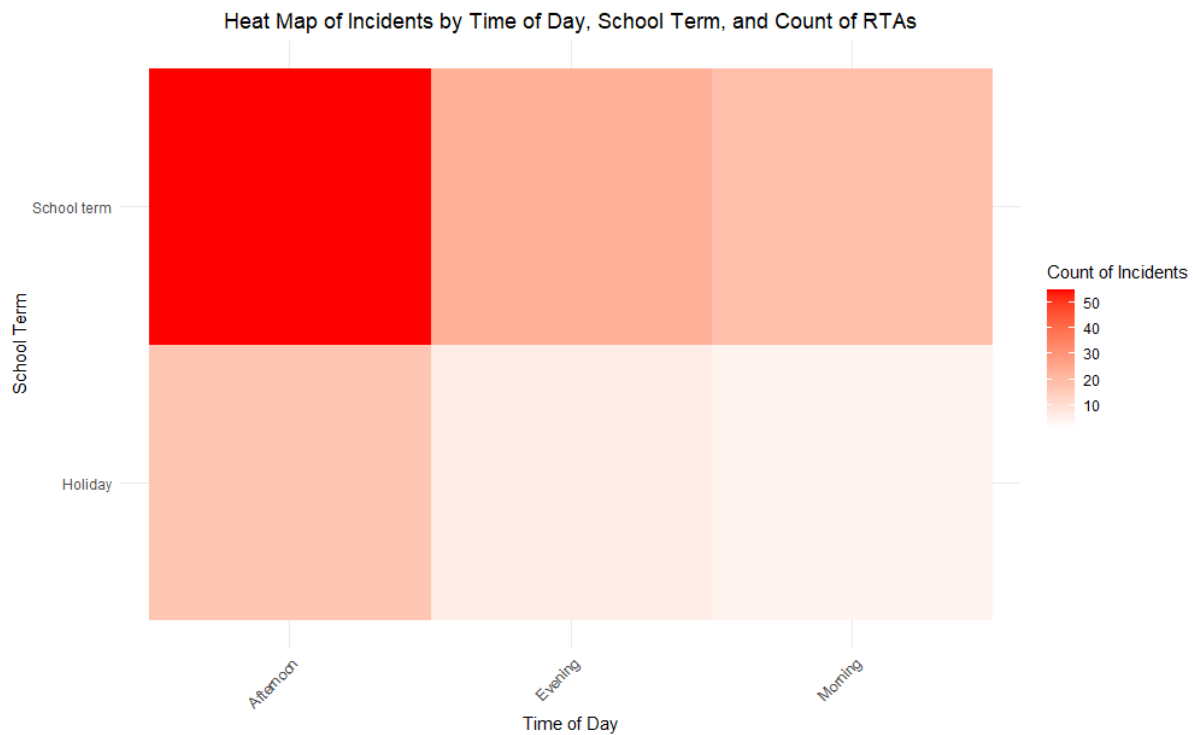


Figure 8: A heat map showing the distribution of RTAs at different times of the day, across terms of the year.

Appendix G: Bubble chart

Figure 9 shows a bubble with increasing circle size with an increase in the number of RTAs that occur during various times of the day and across the different school term and holidays of the year.

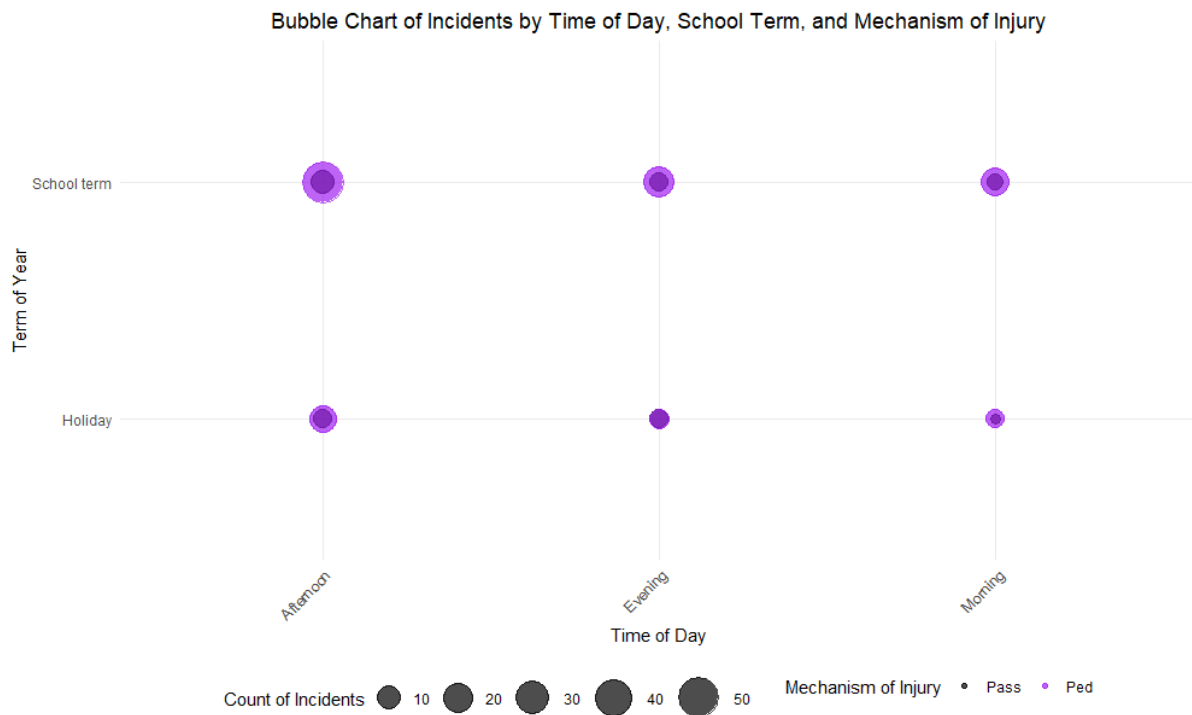


Figure 9: A bubble chart showing the number of RTA by time of day across terms of year and of RTA.

Appendix H: Map of RTA in South Africa

In the figure below, the general distribution of RTA locations can be seen in red, relative to the treatment location of RCWMCH in blue, across South Africa (Figure 10).

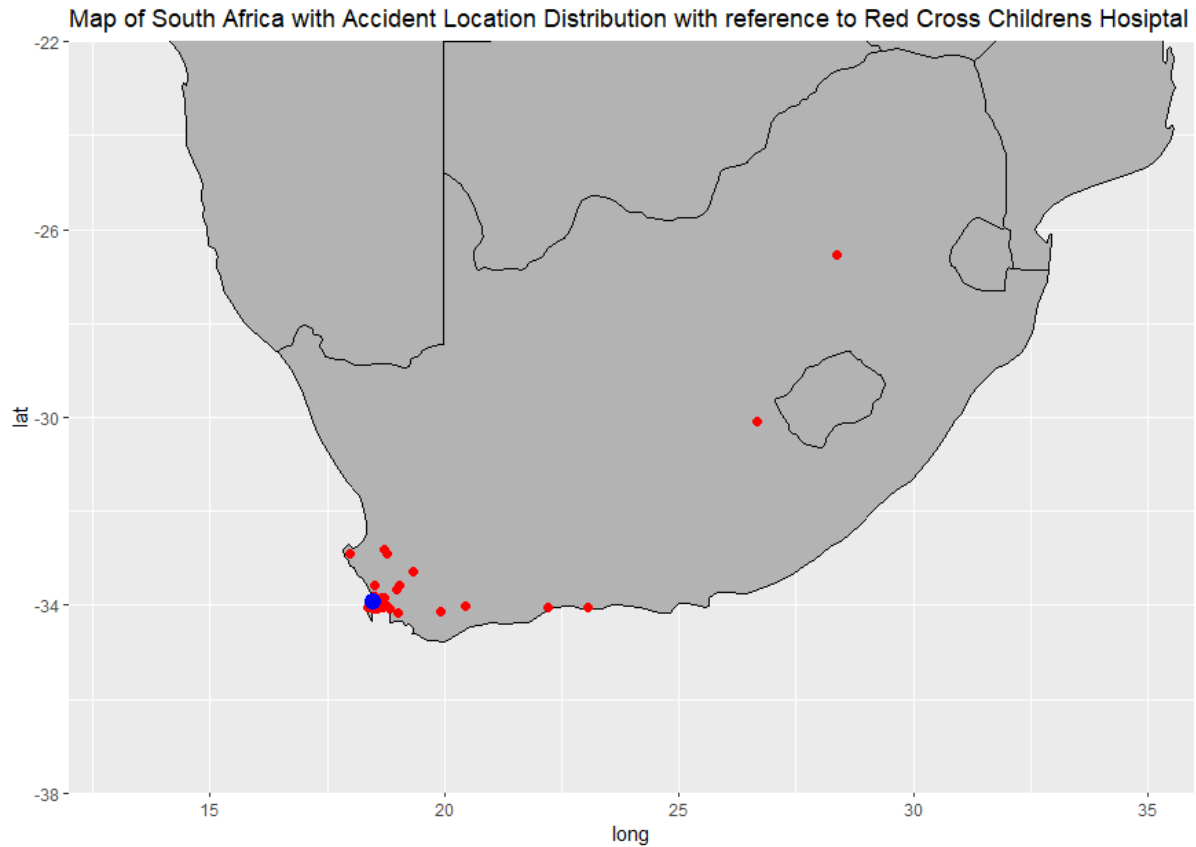


Figure 10: A map of RTA locations across South Africa relative to treatment location, RCWMCH.

Appendix I: Map of local regions with most RTAs

The regions that accounted for most of the cases were Gugulethu (7.7%), Philippi (7.1%), Khayelitsha and Mitchells Plain (5.3%, respectively), Delft and Nyanga (4.5%, respectively) (Figure 11).

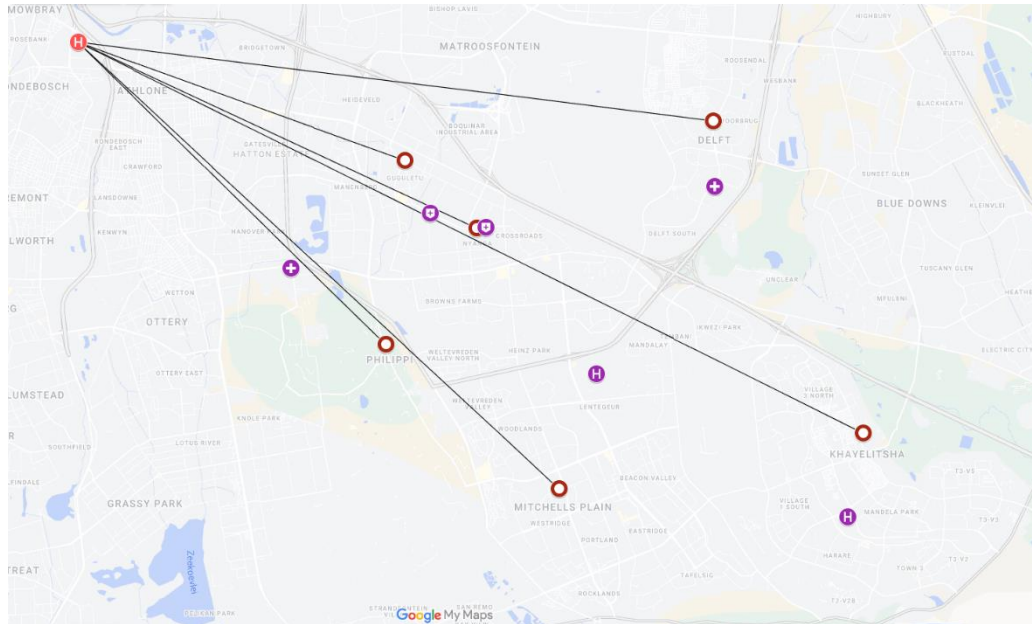


Figure 11: A map showing local areas that experienced the largest number of cases.

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Part C Appendices:

Appendix A: Variables for retrospective analysis

This table shows the variables recorded in the Paediatric Neurosurgery Database. Variables highlighted in yellow were used for data analyses in this project.

Variable name	Variable description	Variable type
Hospital Number	Unique patient identifier	Numerical Discrete
DOB	Date of birth	Numerical Ordinal
Age at Injury	Age at which patient was injured	Numerical Continuous
Gender	Male or Female	Categorical Binary
Date of injury	Date at which patient was injured	Numerical Ordinal
Time of injury	Time at which patient was injured	Numerical Continuous
Date of Admission	Date on which patient was admitted to RXH	Numerical Ordinal
Time of Admission	Time at which patient was admitted to RXH	Numerical Continuous
Mechanism of Injury	Type of injury	Categorical Nominal
GCS at scene	Glasgow Coma Score	Numerical Discrete
GCS post-resuscitation	Glasgow Coma Score	Numerical Discrete
Initial BP	First recorded blood pressure	Numerical Continuous
Initial Hb	Haemoglobin (grams per decilitre)	Numerical Continuous
Other injuries	Any additional injuries	Categorical Nominal
Intubated pre-arrival?	Was the patient intubated before arrival at Red Cross War Memorial Children's Hospital?	Categorical Binary
Transfer to hospital	Was the transfer direct or indirect	Categorical Binary
Time to adm	Time from injury to admission (hours)	Numerical Continuous
Time to ICU	From time of injury (hours)	Numerical Continuous
Time to CT	From time of injury (hours)	Numerical Continuous
Time to monitor	From insertion of monitors (30 minutes after surgical start time) (hours)	Numerical Continuous
Monitors	What type of monitors are placed	Categorical Nominal
Duration of monitoring	The time of monitoring (days)	Numerical Continuous
Duration in ICU	The time patient was in ICU (days)	Numerical Continuous
Other surgery	Any additional surgery	Categorical nominal
Clinical outcome	The outcome of the patient is at discharge	Categorical
Secondary Insults	Before admission or during trauma resus time	Categorical Binary
Most recent evaluation	Date of the most recent evaluation	Numerical Ordinal
Duration of follow-up	Total time patient has been followed up (months)	Numerical Continuous
NDC	Are the patients referred to the neuro developmental clinic	Categorical Binary
Contact details	Cell phone numbers of family members	Numerical Discrete

Height	Height of the patient (cm)	Numerical Continuous
Weight	Weight of the patient (kg)	Numerical Continuous
Head circumference	Circumference of the patient's head (cm)	Numerical Continuous
Risk of mortality score (PICU)	Mortality score identified by ICU	Numerical Continuous
Language	The native language that the patient and the parents can understand and speak	Categorical Nominal

Appendix B: Interview Questions

Patient name **Patient folder number** **Patient age (at time of injury):**

1. What was the nature of the road traffic accident?

a. Pedestrians

- struck while on pavement/verge
- struck while crossing the road
 - With an adult
 - Unaccompanied
- Was the driver of the vehicle identified? Or/
- Was it a hit and run?
- What kind of vehicle were they struck by - car, bus, taxi, train?

b. Passenger in a vehicle

- restrained—
 - seatbelt or
 - child car seat
- unrestrained
- Sitting in the front
- Sitting in the back
- Did the vehicle roll?
- Ejected from the vehicle
- Was the vehicle a car, bus, taxi, motorbike (Helmet Y/N)?
- What kind of vehicle were they in - car, bus, taxi, train?

c. Passenger transported in the back of a bakkie

d. Cyclist. Helmet Y/N

e. Additional information –

2. When did the accident happen?

- During school term
- During holidays
- What time?

- | | | | |
|---------------------------------|-------------------------------|-----------------------------------|--|
| ☐ Morning | ☐ Weekday | ☐ Exact time: | ☐ On the way to school |
| ☐ Afternoon | ☐ Weekend | | ☐ On the way from school |
| ☐ Evening | | | |

3. Were there other people injured in the accident?

- Yes, but no other hospitalisations or deaths
- Yes, others were hospitalised but no deaths were reported
 - Parent Y/N – if so, both Y/N?
- Yes, and there were some deaths
 - Parent Y/N – if so, both Y/N?
- No other people were injured

4. Where did the accident happen?

- On a rural road
- On an urban road
- On a national road
- Within 5 km of home
- More than 5 km from home.
- Travelling from
 - one town to another town within a province OR
 - interprovincial.

5. How was the child first taken to hospital/clinic from the scene?

- Via ambulance
- Via personal vehicle
- Via air transport
- Other _____

6. Where was the child taken first?

- Local clinic/ day hospital
- Local hospital
- Red Cross Children's Hospital

7. How long did it take from the time of the accident to arrival (to nearest half hour)?

- at first hospital/ clinic _____
- at RCWMCH _____

8. Where did the accident happen (nearest town/ suburb if in Cape Town)?

- nearest town (if not CT): _____
- suburb (if CT): _____

9. How far away from RCWMCH did the accident happen? (km)

10. Is there a Road Accident Fund claim in process?

- Yes
 - When was this initiated? _____
 - Has it been settled? _____
 - Who are the acting attorneys? _____
- No
 - If not, why? _____

Appendix C: Variables for prospective analysis

Variable name	Variable description	Variable type
Hospital Number	Unique patient identifier	Numerical Discrete
Age at Injury	Age at which patient was injured	Numerical Continuous
Nature of the road accident	Pedestrian or Passenger	Categorical Binary
Pedestrian		
Position of patient	Was the patient struck on pavement or while crossing the road?	Categorical Binary
Accompanied	Was the child accompanied?	Categorical Binary
Driver of the vehicle identified	Was this accident a case of hit and run?	Categorical Binary
Vehicle	Type of vehicle that caused the RTA	Categorical Nominal
Passenger		
Restrained	Was the patient restrained?	Categorical Binary
Type of restraint	What type of restraint was used?	Categorical Nominal
Position in vehicle	Was the patient in the front or back of the vehicle?	Categorical Binary
Vehicle rolled	Did the vehicle roll?	Categorical Binary
Ejected from vehicle	Was the patient ejected from the vehicle?	Categorical Binary
Type of vehicle	Type of vehicle patient was in during RTA	Categorical Nominal
Other vehicle involved	Type of vehicle involved in the RTA	Categorical Nominal
General Variables		
Holiday	RTA during holiday or school term	Categorical Binary
Time of day	Morning, Afternoon, Evening	Categorical Ordinal
Time of RTA	Exact time	Numerical Continuous
Time of week	Weekday or Weekend	Categorical Binary
Destination	On way to or from school	Categorical Binary
Other people injured	Hospitalisation or death of family member	Categorical Nominal
Type of road	Rural, Urban, National	Categorical Nominal
Distance from home	Within 5km	Categorical Binary
Mode of transport	How was patient taken to hospital?	Categorical Nominal
First hospital taken to	Where was patient taken first?	Categorical Nominal
Time to first hospital	Time it took to get to the first hospital from time of accident (hours)	Numerical Continuous
Time to Red Cross Hospital	Time it took to get to Red Cross Hospital from time of accident (hours)	Numerical Continuous
Suburb	The nearest suburb the RTA happened	Categorical
Distance to hospital	Distance from the nearest suburb to Red Cross Hospital (km)	Numerical Continuous
Road Accident Fund		
RAF	Is the RAF claim in process?	Categorical Binary
Initiated	When was the claim initiated?	Categorical Binary
Settled	Has the claim been settled?	Categorical Binary
Attorney	Who are acting attorneys?	Categorical

Appendix D: HREC 126/2022



**UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee**



**Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms**

08 April 2022

HREC REF: 126/2022

Prof A Figaji
Division of Neurosurgery
Neuroscience Institute-
Room 617, 5th Floor- Red Cross Children's Hospital
Email: Anthony.Figaji@uct.ac.za

Dear Prof Figaji

PROJECT TITLE : SMALL NON-CODING RNA AS BIOMARKERS IN CHILDREN WITH BRAIN INJURY

Thank you for your response letter, addressing the issues raised by the Faculty of Health Sciences Human Research Ethics Committee (HREC)

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:

<http://www.health.uct.ac.za/fhs/research/humanethics/forms>

Approval is granted for one year until the 30 April 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF 126/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix E: HREC 720/2021



FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	28/02/24
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee			Date Signed 2/3/23

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

Please use the latest form found on our website:

<http://www.health.uct.ac.za/fhs/research/humanethics/forms>

Comments to PI from the HREC

--

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	28 February 2023		
HREC REF Number	720/2021	Current Ethics Approval was granted until	28 Feb 2023
Protocol title	Identifying Genomics Factors Related to Outcomes After Traumatic Brain Injury		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☒ No	
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Anthony Figaji		

28 February 2022

Page 1 of 7

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period).

**HUMAN RESEARCH
ETHICS COMMITTEE**

01 MAR 2023

**HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN**



Department / Office Internal Mail Address	Anthony.figaji@uct.ac.za
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1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval? Note: Any annual approvals for Full Committee review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)	☐ Yes	☐ No

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please (tick ✓) appropriate box for billing purposes:

<u>Submission Type</u>	<u>Description</u>	<u>New fee (Vat Incl.)</u>	<u>tick ✓</u>
Research funded solely from UCT departmental/divisional/group budget	Annual evaluation of research progress report for re-certification	R0,00	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	R0,00	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R7000,00	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	R3 710.00	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R6000.00	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	R1 500,00	☒

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for Invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	
Vat Number:	



Contact person	
Telephone number	
Email Address	
2. Internal Journal Billing:	
Fund Number:	471344
Cost Centre Number:	NRS503
Account Holder Name:	Prof Anthony Figaji
Division of Account Holder:	Neurosurgery

2. List of documentation for approval

Protocol v 2.0 28 February 2023
 Consent – prospective cases v 2.0 28 February 2023
 Consent – retrospective cases v 2.0 28 February 2023
 Consent – prospective cases, telephonic v 1.0 28 February 2023
 Consent – retrospective cases, telephonic v 1.0 28 February 2023
 Consent – controls v 2.0 28 February 2023
 Consent – controls, telephonic v 1.0 28 February 2023
 Assent – prospective cases v 2.0 28 February 2023
 Assent – prospective cases telephonic v 1.0 28 February 2023
 Assent – retrospective cases v 2.0 28 February 2023
 Assent – retrospective cases telephonic v 1.0 28 February 2023
 Assent – controls v 2.0 28 February 2023
 Assent – controls telephonic v 2.0 28 February 2023

3. Protocol status (tick ✓)

☒	Open Enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	100
Number of participants enrolled, since last HREC Progress report (continuing review)	100
Additional number of participants still required	60

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	4
---	---

6. Cumulative summary of participants

Total number of participants who provided consent	100
Number of participants determined to be ineligible (i.e. after screening)	12
Number of participants currently active on the study	100
Number of participants completed study (without events leading to withdrawal)	100
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
One hundred patients that have had a traumatic brain injury have been enrolled to date. Of that hundred, 34 have been prospective patients and the rest are retrospective patients enrolled during our outpatient clinic.

8. Protocol violations and exceptions (tick ✓ all that apply)

☒	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review



9. Amendments (tick ✓ all that apply)

☒	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☒	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).

Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

None.

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

☐ Yes ☐ No ☒ Not applicable

If yes, please describe:

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?

☐ Yes ☒ No ☐ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?

☐ Yes ☒ No ☐ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name		Report attached	☐ Yes	☐ No	☒ Not applicable
		DSMB report attached	☐ Yes	☐ No	☒ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☒ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐ Increased	
☐ Decreased	
☒ Shown no change	
If there has been a change, please explain:	
N/A	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
N/A

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ✓)		
☐ Yes	☐ No	☒ Not Applicable – N/A
If yes, please complete the following:		
Insurer's name:		
Policy no.		*Coverage Period:
<i>For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.</i>		

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☒ No



If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):

15. Signature

My signature certifies that the above is complete and correct.

Signature of PI		Date	2023-02-28
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Appendix F: HREC 166/2009



FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	30.4.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee			Date Signed 22/4/2022

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	22/04/2022		
HREC REF Number	166/2009	Current Ethics Approval was granted until	30/11/2021
Protocol title	Registry for paediatric neurocritical care		
Principal Investigator	Professor Anthony Figaji		
Department / Office Internal Mail Address	6th Floor ICH Building, Room 616, Red Cross War Memorial Children's Hospital, Klipfontein Road, Rondebosch, 7700		
1.1 Does this protocol receive US Federal funding?		☐ Yes	☒ No

2. Protocol status (tick ✓)

☒	Research-related activities are ongoing
☐	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval	350
Total number of records or specimens collected, reviewed or stored since last progress report	20
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes ☒ No

4. Signature

Signature of PI		Date	22/04/2022
-----------------	--	------	------------

Appendix G: R018/2022



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-Room 46 Old Main Building
Groote Schuur Hospital
Observatory 7925

Email: hrec-enquiries@uct.ac.za

Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 July 2022

HREC REF: R018/2022

Prof A Figaji

Department of Paediatrics Neurosurgery Unit
Red Cross War Memorial
Children's Hospital
Email PI: Anthony.figaji@uct.ac.za

Dear Prof Figaji

PROJECT TITLE: Paediatric Neurosurgery Registry and Repository

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee for review and approval.

The HREC has **approved** the registration of your database/registry/repository.

The registration of this database/repository/registry is valid until 30 July 2025.

Please provide the HREC with an update if the database continues beyond this period.

Please Note: All research, including that undertaken for a master's or doctoral degree, using registered databases, registries, and repositories, requires submission as a new study. It requires an application form (FHS013) and a protocol which has undergone departmental review. The study will receive its own HREC REF number which will be linked to the main database or repository.

Please note that any studies using the collected data require separate ethics approval.

Please quote the above HREC Reference Number R018/2022 in all your correspondence.

Yours sincerely

A handwritten signature in black ink, appearing to read 'A. Blockman', written over a horizontal line.

PP PROFESSOR MARC BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Appendix H: Departmental Ethics Approval



UNIVERSITY OF CAPE TOWN



Department of Surgery
Departmental Research Committee
A/Prof Maritz Laubscher
Groote Schuur Hospital
Observatory 7925
South Africa
Tel (021) 404 5108
Email: maritz.laubscher@uct.ac.za

9 Jun 2023

Miss K Alberts

Department of Surgery
University of Cape Town

Dear Miss Alberts

RE: Project 2023/021

PROJECT TITLE: Identifying Risk Factors For Traumatic Brain Injury (Tbi) With A Focus On Road Traffic Accident (Rta)-Related Injuries And Strategies To Reduce The Burden Of Secondary Brain Injury.

The above protocol has been reviewed by the Department of Surgery Research Committee. I am pleased to inform you that the committee approved the scientific merit of the study, and endorse the protocol for submission to the relevant ethics committee.

Although this letter serves as confirmation that the above protocol has successfully passed through the surgical DRC, respective ethics committees still require DRC chair signature before submission.

Please use the above project number in all future correspondence,

A/PROF MARITZ LAUBSCHER
CHAIR SURGICAL DRC

Appendix I: HREC Ethics Approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za

Website: <https://health.uct.ac.za/home/human-research-ethics>

12 April 2023

HREC REF: 196/2023

Prof A Figaji

Division of Neurosurgery
Room 617, Institute of Child Health
Red Cross Children's Hospital
Email: Anthony.figaji@uct.ac.za
Student: SRNKRI001@myuct.ac.za

Dear Prof Figaji

PROJECT TITLE: IDENTIFYING RISK FACTORS FOR TRAUMATIC BRAIN INJURY (TBI) WITH A FOCUS ON ROAD TRAFFIC ACCIDENT (RTA)-RELATED INJURIES AND STRATEGIES TO REDUCE THE BURDEN OF SECONDARY BRAIN INJURY (SUB-STUDIES: 126/2022, 720/2021, 166/2009 & R018/2022)
(MASTERS CANDIDAE-KRISTE ALBERTS)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2024.

Please submit a progress form, using the standardised Annual Report Form (FHS016) if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Kriste Alberts will also be involved in this study.

Please quote the HREC REF 196/2023 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix J: Informed Consent Form

CONSENT FOR A CHILD TO ACT AS A PARTICIPANT IN A RESEARCH STUDY: RETROSPECTIVE STUDY

TITLE: Identifying genomic factors related to outcomes after traumatic brain injury

**PRINCIPAL
INVESTIGATOR:** Professor Anthony Figaji

Paediatric Neurosurgery Unit, Ward D1
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch
7700
Tel: +27 21 658 5049

What are my child and I being asked to do?

DESCRIPTION: _____ (name and relationship) is being invited to participate in this clinical research project that forms part of a study on the genetic and environmental influences on recovery of paediatric brain injury.

What is this study about?

In this research study we want to learn more about how genes and the environment may affect how children recover from a Traumatic Brain Injury (TBI), which your child had. Genes are the building blocks of our body; they are found inside of our cells and decide how our bodies respond to things like injuries. The environment that we live in, including how we are brought up and the people we have around us, can also affect how our bodies respond to injury. By understanding how genes and the environment affect recovery from a TBI we may be able to improve the way we treat patients with a TBI in the future.

Who is being asked to participate in this study?

We are asking to include your child in this study as they have had a moderate or severe TBI.

What will my child's participation in this study involve?

Your child will be asked to spit into a tube/cup or a sponge may be used to collect the spit. When your child comes back to our clinic as part of their normal follow-up appointments, we will conduct assessments called neuropsychological tests to see how your child is recovering from their brain injury. These tests will involve your child answering some questions or doing some simple tasks, for example building blocks, counting, remembering, jumping and other activities like these. In addition to clinical data we will also collect data about your child's

environment, this includes their rehabilitation (for example physio) and schooling, and some information about your schooling.

We will test the blood and spit samples to see if there are genes that may decide how the body recovers from the brain injury, and we will use the information about their environment to understand what other factors may affected your child's recovery. We are not sure which genes may be important as we do not have enough information about this yet. The results will focus only on the genes that may be involved in recovery from brain injury and we will not look for genes that are involved in other diseases. We will not report the results of the gene studies we do to the patients or their parents because it will take more research for us to properly understand the meaning of our gene results. That is why we also ask your permission to keep left over samples for future studies about traumatic brain injury.

The information from this study will be looked at together with information collected as part of clinical routine data collection.

For how long will my child's medical record information be kept and used for research purposes?

The investigators ask permission to use your child's de-identified health information and spit samples until your child is 18 years old. When they turn 18, we will ask their permission to continue to use their information and samples. We may use the samples for future studies on genetics in brain injury as we learn more about the importance of genes in the brain. We do not know what those future studies will look like, but the studies will first be approved by science and human research ethics review boards and none of those studies will ever know your child's name or identifiable information.

What are the possible risks of my child's participation in the study?

There are no risks of injury or hurt to your child during collection of the samples. We will not look for genes involved in any other illness or paternity testing. If answering questions and sharing information about yourself makes you uncomfortable you do not have to answer any question that makes you nervous.

Your child's name and any identifying information will be removed from the samples and data. This means there will be no way of anyone knowing what your child's results are. Being part of this study will not cost you any money. There may be other risks which we do not know about yet.

Benefits

This study will not benefit your child now, but we hope that the information we learn may help us to give better care to children who have traumatic brain injuries in the future.

May I refuse to participate in this genetics study?

It is your choice whether you want your child to be part of this genetics study. If you choose not to participate this will not affect your child's care in any way.

How will my child's privacy be protected?

When we collect samples or data we will add a code and not your child's name. Nobody will know that your child participated in this study other than you and the researchers. The data will also be entered into a secure database. No information that can be linked to your child will be sent outside of Red Cross Children's Hospital. De-identifiable information (information that cannot be linked to your child) will be shared with our study collaborators at other research facilities that are assisting us with the data analysis. If we need help with analysing the samples we may share de-identified samples with our collaborators at other labs.

Is my child's participation in the study voluntary?

Your child's participation in this study is voluntary. Whether or not you provide your permission for participation in this study will have no effect on your child's current or future medical care at this hospital or other local hospitals.

May I take back, at a future date, my consent for participation in this study?

You may take back, at any time, your consent for your child's participation in the study. To do this please ask for Professor Figaji in Ward D1 and he will help you.

What happens if I get hurt taking part in this study?

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006, which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.

The insurer will not pay for harm if, during the study, your child:

- Uses medicines or other substances that are not allowed
- Does not follow the study doctor's instructions

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court. It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

*

Voluntary Consent and Authorization

The above information has been explained to me and all of my questions have been answered. Any future questions I have about this research project will be answered by one of the investigators listed on the first page of this consent document at the telephone number(s) given.

The UCT FHS Human Research Ethics Committee can be contacted on [021 406 6338](tel:0214066338) in case patients have any questions regarding their rights and welfare as research subjects on the study

Participant's (Child's) Name (print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research project without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research project, and for the storage of their samples for use in potential future research on brain injury that have been approved by the necessary scientific and human research ethics boards. A copy of this consent form will be given to me.

Parent or Guardian's Name (Print)

Relationship to Participant (Child)

Parent's or Guardian's Signature

Date

Certification of Informed Consent

I have explained the nature and the purpose of this research and the disclosure of the child's medical information to the parent(s) or legally authorized guardian(s). They have had the opportunity to ask questions. Based on this conversation, I believe that they understand what this research project involves. The physicians and research staff will be available to address future questions as they arise.

Printed Name of Person Obtaining Consent

Role in Study

Signature of Person Obtaining Consent

Date

Explanation of Lack of Assent: (For children who are not capable of understanding the study procedures and their potential discomforts and benefits).

I do not believe my child is capable of giving assent for participation.

Signature of Parent(s) or Guardian(s)

Appendix K: Informed Assent Form

ASSENT FOR A CHILD TO ACT AS A PARTICIPANT IN A RESEARCH STUDY: RETROSPECTIVE COHORT

TITLE: Identifying genomic factors related to outcomes after traumatic brain injury

PRINCIPAL INVESTIGATOR: Professor Anthony Figaji

Paediatric Neurosurgery Unit, Ward D1
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch
7700
Tel: +27 21 658 5049

SOURCE OF SUPPORT: Medical Research Council of South Africa

What am I being asked to do?

You, _____ (name) are being invited to join our research project.

What is this study about?

In this study we want to learn more about how children get better after a brain injury. To do that we need to compare children who had a brain injury to children who did not have a brain injury but injured another part of their body, like you have. Many things affect how we heal from injury, these can be things that are part of our bodies (for example how strong our bodies are) and things that are outside our bodies (for example physiotherapy and medicine). One thing inside our bodies that helps us to heal, is our genes. Genes are the building blocks of our body, they decide things like whether we will be short or tall, good at sport, or good at school and also how quickly we get better after a brain injury. By understanding these things, such as genes, and how they help us heal we may be able to find better ways to treat children with a head injury in the future.

Why am I being asked to be a part of this study?

We are asking all children like you who are 0 – 13 years old and who have had an injury to the head.

What will happen to me as part of this study?

You will be asked to spit in a tube/cup or we will rub a cotton bud on the inside of your mouth. Also, when you come to see us at the outpatients clinic, we will do some fun activities together (like building blocks, reading, counting) to see how you are recovering. We will test

the spit to see if can find any genes which decide how you will get better from your injury. We are not sure which genes may be important as we do not know enough about them yet. . That is why we also ask your permission to keep your left over blood for more studies we may need to do in the future. When you turn 18 years old you can decide if we can still keep your left-over spit or if we should throw it away.

Will I be hurt if I take part in this study?

Nothing in this study will hurt you. No-one else will know you are in this study and your spit will get a special number so that no one knows it is yours.

Do I have to be in the study?

It is your choice to be in the study. Your parents have said that you can take part if you want to but it's still up to you to decide. If you say 'no' it won't affect how you are treated in hospital.

Can I leave the study if I decide I don't want to take part anymore?

You can tell us at any time if you want to leave the study. If you decide you don't want to be in the study any more, you can tell Professor Figaji in ward D1.

*

Assent for Participation in the Study:

This research has been explained to me, and I agree to join in this study.

Signature of Child-Subject

Date

Printed Name of Child-Subject

Verification of Explanation: (For children who are capable of understanding the registry procedures and their potential discomforts and benefits but physically unable to sign)

I certify that I have carefully explained the purpose and nature of this research study to the child-subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e., assent) to participate in this study.

Investigator's Signature

Date

I believe my child understands what this research involves and that he/she has given his/her assent for participation.

Signature(s) of Parent(s) or Guardian(s)

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Manuscripts must be solely the work of the author(s) stated, must not have been previously published elsewhere, and must not be under consideration by another journal. *The Lancet* journals are signatories of the [Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals](https://www.icmje.org), issued by the International Committee of Medical Journal Editors (ICMJE Recommendations), and to the Committee on Publication Ethics (COPE) code of conduct for editors. We follow COPE's guidelines.

[Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals](https://www.icmje.org)
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<https://publicationethics.org/core-practices>

How to submit your paper

Manuscript submission

Manuscript submission to all *Lancet* journals is free. Payment of article processing fees is made after acceptance (see later). Manuscripts should be submitted online via the *The Lancet Public Health's* online submission and peer review website (known as EM) at www.editorialmanager.com/thelancetpublichealth

- Simply log on to EM and follow the on-screen instructions for all submissions
- If you have not used EM before, you will need to register first. In EM, the corresponding author is the person who enters the manuscript details and uploads the submission files
- Inclusion of illustrations (eg, photographs, graphs, diagrams) is a prerequisite for many publication types. Submission of original and editable artwork files is encouraged. Digital photography files should have a resolution of at least 300 dpi and be at least 107 mm wide. Before and after images should be taken with the same intensity, direction, and colour of light
- In almost all cases, if you have a finished manuscript, you should submit it, rather than contacting *The Lancet Public Health* to enquire whether an unseen manuscript is likely to be accepted. Unless you have been asked by the Editor to submit by email, you should use the online system for all types of submission, including Correspondence
- If you have any technical problems or questions, please contact our dedicated journal office inbox at editorial@lancet.com, the editor at publichealth@lancet.com, or visit our [Support Center](#) for further assistance

Covering letter

- You should upload your covering letter at the "Enter Comments" stage of the online submission process
- Use the covering letter to explain why your paper should be published in *The Lancet Public Health* rather than elsewhere

Statements, permissions, and signatures

Authors and contributors

- Designated authors should meet all four criteria for authorship in the ICMJE Recommendations
- All authors, and all contributors (including medical writers and editors), should specify their individual contributions at the end of the text
- We require that more than one author has directly accessed and verified the underlying data reported in the manuscript. For research articles that are the result of an academic and commercial

First submissions to *The Lancet Public Health* should include:

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- 2 Manuscript including tables and panels
- 3 Figures
- 4 Author statement form (see next section)
- 5 Declaration of interests and source of funding statements (see next section)
- 6 In-press papers—one copy of each with acceptance letters
- 7 Protocols and CONSORT details for randomised controlled trials (see Articles)
- 8 We encourage disclosure of correspondence from other journals and reviewers, if previously submitted, and we might contact relevant editors of such journals
- 9 Research in context panel, for all primary research Articles

partnership, at least one of the authors named as having accessed and verified data must be from the academic team. The contributors statement should state who those authors are.

- All authors should confirm that they had full access to all the data in the study and accept responsibility to submit for publication
- We encourage collaboration and coauthorship with colleagues in the locations where the research is conducted
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- Please include written consent of any cited individual(s) noted in acknowledgments or personal communications
- For author groups of more than 30 members, we encourage use of a collaborator or study group for any additional authors. For this collaborator or study group, if they wish to be indexed to the paper, please provide a separate document with a table of first names and surnames of all members of the group (this is to ensure that PubMed and similar databases encode the names correctly).

[Author statement form](https://www.thelancet.com/for-authors/forms?section=tlph-author-sig)
<https://www.thelancet.com/for-authors/forms?section=tlph-author-sig>

[ICMJE Recommendations](https://www.icmje.org)
<https://www.icmje.org>

Reporting sex-based and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals, model

Sex and Gender Equity Research
(SAGER) Guidelines
[https://
researchintegrityjournal.
biomedcentral.com/
articles/10.1186/s41073-016-
0007-6](https://researchintegrityjournal.biomedcentral.com/articles/10.1186/s41073-016-0007-6)
SAGER guidelines checklist
[https://ese.aphub.com/
article/86910/](https://ese.aphub.com/article/86910/)

ICMJE COI form
[https://www.thelancet.
com/for-authors/
forms?section=icmje-coi](https://www.thelancet.com/for-authors/forms?section=icmje-coi)
Joint ICMJE statement
[https://www.thelancet.com/
for-authors/forms?section=icmje-
statement](https://www.thelancet.com/for-authors/forms?section=icmje-statement)

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author/dei?trial=true](https://beta.elsevier.com/about/policies-and-standards/author/dei?trial=true)

organisms, or eukaryotic cells, investigators should integrate sex-based and gender-based analyses into their research design according to evolving funder/sponsor requirements and best practices within a field. Authors should address their research's sex and/or gender dimensions in their manuscript. In cases where they cannot, they should discuss this as a limitation to their research's generalisability. With research involving cells and model organisms, researchers should use the term "sex". With research involving humans, researchers should consider which terms best describe their data (see Definitions section below). Authors can refer to the *Sex and Gender Equity in Research (SAGER) Guidelines* and the *SAGER guidelines checklist*. They offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting, and research interpretation. However, there is no single, universally agreed-upon set of guidelines for defining sex and gender or reporting sex-based and gender-based analyses.

Definitions

In human research, the term "sex" carries multiple definitions. It often refers to an umbrella term for a set of biological attributes associated with physical and physiological features (eg, chromosomal genotype, hormonal levels, internal and external anatomy). It can also signify a sex categorisation, most often designated at birth ("sex assigned at birth") based on a newborn's visible external anatomy. The term "gender" generally refers to socially constructed roles, behaviours, and identities of women, men, and gender-diverse people that occur in a historical and cultural context, and might vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact, and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man), concordant, and static. However, these constructs exist along a spectrum that includes additional sex categorisations and gender identities, such as people who are intersex/have differences of sex development (DSD), or identify as non-binary. In any given person, sex and gender might not align, and both can change. Sex and gender are not entirely discrete concepts and their definitions continue to evolve. Biology and society influence both, and many languages do not distinguish between them. Since the terms "sex" and "gender" can be ambiguous, authors should describe the methods they use to gather and report sex-related and/or gender-related data (eg, self-report or physician-report, specific biological attributes, current sex/gender, sex assigned at birth, etc) and discuss the potential limitations of those methods. This will enhance the research's precision, rigor, and reproducibility, and avoid ambiguity or conflation of terms and the constructs to which they refer. Authors should use the term "sex assigned at birth" rather than "biological sex", "birth sex" or "natal sex" as it is more accurate and inclusive. When ascertaining gender and sex, researchers should use a two-step process: (1) ask for gender identity allowing for multiple options and (2) if relevant to the research question, ask for sex assigned at birth. In addition to this defining guidance and the *SAGER guidelines*, you can find further information about reporting sex and gender in research studies on Elsevier's diversity, equity, and inclusion in the publishing author guide available [here](#).

The use of AI and AI-assisted technologies in scientific writing

Where authors use AI and AI-assisted technologies in the writing process, these technologies should only be used to improve readability and language of the work and not used to replace researcher tasks such as producing scientific insights, analysing and interpreting data, or drawing scientific conclusions. Applying these technologies should only be done with human oversight and control, and authors should carefully review and edit the result because AI can generate authoritative-sounding output that can be incorrect, incomplete, or biased. Authors should not list AI and AI-assisted technologies as an author or co-author, nor cite AI as an author. Authors are ultimately responsible and accountable for the originality, accuracy, and integrity of the work; and should disclose the use of AI and AI-assisted technologies in a statement at the end of the article.

Forms and signatures

For Comments and Correspondence, we require you to upload your forms at submission. For original research (Articles), we will request these forms after peer review. The following signed statements are required:

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- [Conflicts of interest statements](#) (ICMJE forms)
- Statements of role, if any, of medical writer or editor
- Acknowledgments—written consent of cited individual
- Personal communications—written consent of cited individual
- Use of copyright-protected material—signed permission statements from author and publisher

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Declaration of interests

A conflict of interest exists when professional judgement concerning a primary interest (such as patients' welfare or validity of research) may be influenced by a secondary interest (such as financial gain). Financial relationships are easily identifiable, but conflicts can also occur because of personal relationships or rivalries, academic competition, or intellectual beliefs. A conflict can be actual or potential, and full disclosure to the Editor of all relationships is a requisite. Purposeful failure to disclose conflicts is a form of misconduct and might lead to publication of a correction or even to retraction. All submissions to *The Lancet Public Health* must include disclosure of all relationships in which there is a potential or actual conflict of interest, even if it not directly relevant to the submitted work. The Editor may use such information as a basis for editorial decisions and will publish all disclosures that authors declare on their conflict of interests form. It is the corresponding author's responsibility to check that all declarations made by authors on their conflicts of interest form are included at the end of the manuscript. Agreements between authors and study sponsors that interfere with authors' access to all of a study's data, or that interfere with their ability to analyse and interpret the data and to prepare and publish manuscripts independently, may represent conflicts of interest, and should be avoided. Authors may be required to provide the journal with any such agreements in confidence.

- At the end of the text, under a subheading "Declaration of interests", all authors must disclose any financial and personal

relationships with other people or organisations, even if it does not directly relate to the submitted work. Examples of financial conflicts include employment, consultancies, stock ownership, honoraria, paid expert testimony, patents or patent applications, and travel grants, all within 3 years of beginning the work submitted. If there are no conflicts of interest, authors should state that none exist.

- All authors are required to provide a Conflict of Interest Statement and should complete a standard form, which is available at <https://www.thelancet.com/for-authors/forms?section=icmje-coi>. The form has been modified by the ICMJE following consultation with authors and editors. Further information is available in a joint ICMJE statement published on July 1, 2010. For more information see *Lancet* 2009; 374: 1395–96.
- For Comments, *The Lancet Public Health* will not publish if an author, within the past 3 years, and with a relevant company or competitor, has any stocks or shares, equity, a contract of employment, or a named position on a company board; or has been asked by any organisation other than *The Lancet Public Health* to write, be named on, or to submit the paper (see *Lancet* 2004; 363: 2–3).

Role of the funding source

- All sources of funding should be declared as an acknowledgment at the end of the text.
- At the end of the Methods section, under a subheading "Role of the funding source", authors must describe the role of the study sponsor(s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
- If there is no Methods section, the role of the funding source should be stated as an acknowledgment. If the funding source had no such involvement, the authors should state this.

Role of medical writer or editor

- If a medical writer or editor was involved in the creation of your manuscript, we need a signed statement from the corresponding author to include their name and information about funding of this person.
- This information should be added to the Acknowledgments or Contributors section.
- We require signed statements from any medical writers or editors declaring that they have given permission to be named as an author, as a contributor, or in the Acknowledgments section.

Patient and other consents

- Appropriate written consents, permissions, and releases must be obtained where you wish to include any case details, personal information, and/or images of patients or other individuals in *The Lancet* journals in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. Studies on patients or volunteers need approval from an ethics committee and informed consent from participants. These should be documented in your paper.
- Do not use "blackout" bars or similar devices to anonymise patients in clinical images: if you have taken consent appropriately masking is not needed.
- Since the consent form needs to comply with the relevant legal requirements of your particular jurisdiction, we do not provide

sample forms; this is your responsibility. Your affiliated institution should be able to provide an appropriate form.

- For the purposes of publishing in *The Lancet* journals, a consent, permission, or release should include, without limitation, publication in all formats (including print, electronic, and websites), in sublicensed and reprinted versions (including translations), and in other works and products.
- To respect your patient's and any other individual's privacy, please do not send signed forms to *The Lancet Public Health*. Please instead complete the patient consent section of the *Author statements* while retaining copies of the signed forms in the event they should be needed.
- If consent, permission, or release is made subject to any conditions, *The Lancet Public Health* must be made aware in writing of all such conditions before publication.
- For more information about our policy, please visit <https://www.elsevier.com/about/our-business/policies/patient-consent>.

Patient Consent form
<http://www.thelancet.com/ph/assets/raw/Lancet/authors/lancet-consent-form.pdf>

Types of article and manuscript requirements

Please ensure that anything you submit to *The Lancet Public Health* follows the guidelines provided for each article type. For instruction on how to format the text of your paper, including tables, figures, panels, and references, please see our [Formatting guidelines](#).

Red section (Articles)

Articles

- *The Lancet Public Health* prioritises reports of original research that are likely to change practice or thinking.
- We invite submission of all trials, whether phase 1, 2, 3, or 4. For phase 1 trials, we consider those of a novel substance for a novel indication, if there is a strong or unexpected beneficial or adverse response, or a novel mechanism of action.
- We require the registration of all interventional trials, whether early or late phase, in a primary register that participates in WHO's International Clinical Trial Registry Platform (see *Lancet* 2007; 369: 1909–11) or in ClinicalTrials.gov, in accord with ICMJE recommendations. We also require full public disclosure of the minimum 24-item trial registration dataset at the time of registration and before recruitment of the first participant (see *Lancet* 2006; 367: 1631–35). The registry must be independent of for-profit interest.
- Reports of trials must conform to [CONSORT 2010 guidelines](#) and should be submitted with their protocols.
- All reports of randomised trials should include a section entitled Randomisation and masking, within the Methods section. Please refer to *The Lancet's* [formatting guidelines for randomised trials](#).
- Cluster-randomised trials must be reported according to [CONSORT extended guidelines](#).
- Randomised trials that report harms must be described according to [extended CONSORT guidelines](#).
- Studies of diagnostic accuracy must be reported according to [STARD guidelines](#).
- Observational studies (cohort, case-control, or cross-sectional designs) must be reported according to the [STROBE statement](#), and should be submitted with their protocols.
- We encourage the registration of all observational studies on a WHO-compliant registry (see *Lancet* 2010; 375: 348).

WHO's International Clinical Trial Registry Platform
<http://www.who.int/ictrp/network/trds/en/index.html>
[Clinical trials](http://clinicaltrials.gov)
<http://clinicaltrials.gov>
ICMJE recommendations
<http://icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html>
[CONSORT 2010 guidelines](http://www.consort-statement.org/consort-2010)
<http://www.consort-statement.org/consort-2010>
[Formatting guidelines for randomised trials](https://www.thelancet.com/for-authors/forms?section=rct)
<https://www.thelancet.com/for-authors/forms?section=rct>
[CONSORT extended guidelines](http://www.consort-statement.org/extensions/extensions/)
<http://www.consort-statement.org/extensions/extensions/>
[STARD guidelines](http://www.equator-network.org/reporting-guidelines/stard/)
<http://www.equator-network.org/reporting-guidelines/stard/>
[STROBE statement](http://www.strobe-statement.org/)
<http://www.strobe-statement.org/>

STREGA guidelines
<http://www.equator-network.org/reporting-guidelines/strobe-strega/>

PRISMA guidelines
<http://www.prisma-statement.org/>

Formatting guidelines for meta-analyses
<https://www.thelancet.com/for-authors/foms?section=meta-analysis>

GATHER statement
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(16\)30388-9/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(16)30388-9/fulltext)

CONSORT-AI Extension guidelines
[https://doi.org/10.1016/S2589-7500\(20\)30218-1](https://doi.org/10.1016/S2589-7500(20)30218-1)

SPRIT-AI Extension guidelines
[https://doi.org/10.1016/S2589-7500\(20\)30219-3](https://doi.org/10.1016/S2589-7500(20)30219-3)

To find reporting guidelines, see
<http://www.equator-network.org>

Human Gene Organisation
<http://www.genenames.org/>

MIAME guidelines
<http://fged.org/projects/miame/>

Array and GEO
<http://www.ebi.ac.uk/microarray-as/ae/>
<http://www.ncbi.nlm.nih.gov/geo>

- Genetic association studies must be reported according to **STREGA guidelines**
- Systematic reviews and meta-analyses must be reported according to **PRISMA guidelines**. Please refer to *The Lancet's* **formatting guidelines for systematic reviews and meta-analyses**.
- Reports of studies of global health estimates should be reported according to the **GATHER statement** (see *Lancet* 2016; 388: e19–23)
- Clinical trials that report interventions using artificial intelligence must be described according to the **CONSORT-AI Extension guidelines** and their protocols must be described according to the **SPRIT-AI Extension guidelines**
- To find reporting guidelines see: <http://www.equator-network.org>
- When using a study group, collaborator group, or Consortia instead of authors' names, please be aware that individuals' names will not explicitly appear when your published Article is uploaded to MEDLINE/PubMed. Your Article will still be discoverable via a search for a specific named author, but only the collective name given to the study will appear on that platform. If you need more information, please contact us.

All Articles should, as relevant:

- Be up to 3500 words (4500 for randomised controlled trials) with 30 references (the word count is for the manuscript text only)
- Include an abstract (semistructured summary), with five paragraphs (Background, Methods, Findings, Interpretation, and Funding), not exceeding 250 words. Our electronic submission system will ask you to copy and paste this section at the "Submit Abstract" stage
- For randomised trials, the abstract should adhere to CONSORT extensions: abstracts (see *Lancet* 2008; 371: 281–83)
- When reporting Kaplan-Meier survival data, at each timepoint, authors must include numbers at risk, and are encouraged to include the number of censored patients.
- For intervention studies, the abstract should include the primary outcome expressed as the difference between groups with a confidence interval on that difference (absolute differences are more useful than relative ones). Secondary outcomes can be included as long as they are clearly marked as secondary and all such outcomes are reported
- Use the recommended international non-proprietary name (rINN) for drug names. Ensure that the dose, route, and frequency of administration of any drug you mention are correct
- Use gene names approved by the **Human Gene Organisation**. Novel gene sequences should be deposited in a public database (GenBank, EMBL, or DDBJ), and the accession number provided. Authors of microarray papers should include in their submission the information recommended by the **MIAME guidelines**. Authors should also submit their experimental details to one of the publicly available databases: **ArrayExpress** or **GEO**
- Include any necessary additional data as part of your EM submission
- All accepted Articles should include a link to the full study protocol published on the authors' institutional website (see *Lancet* 2009; 373: 992 and *Lancet* 2010; 375: 348)
- We encourage researchers to enrol women and ethnic groups

into clinical trials of all phases, and to plan to analyse data by sex and by race

Putting research into context

- All research papers (including systematic reviews/meta-analyses) submitted to any journal in *The Lancet* family must include a panel putting their research into context with previous work in the format outlined below (see *Lancet* 2014; 384: 2176–77, for the original rationale). This panel should not contain references. Editors will use this information at the first assessment stage and peer reviewers will be specifically asked to check the content and accuracy
- The Discussion section should contain a full description and discussion of the context. Authors are also invited to either report their own, up-to-date systematic review or cite a recent systematic review of other trials, putting their trial into context of the review

Research in context

Evidence before this study

This section should include a description of all the evidence that the authors considered before undertaking this study. Authors should briefly state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate.

Added value of this study

Authors should describe here how their findings add value to the existing evidence.

Implications of all the available evidence

Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Research in context panels should not contain references; key studies mentioned here should be referenced in the main text.

Data sharing

From September 21, 2020, all submitted research Articles must contain a data sharing statement, to be included at the end of the manuscript. Data sharing statements must include:

- Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others ("undecided" is not an acceptable answer);
- What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set);
- Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form);
- When these data will be available (beginning and end date, or "with publication", as applicable);
- Where the data will be made available (including complete URLs or email addresses if relevant);
- By what access criteria data will be shared (including with whom,

for what types of analyses, by what mechanism – eg, with or without investigator support, after approval of a proposal, with a signed data access agreement – or any additional restrictions).

See [table](#) for examples. Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. [Mendeley Data](#) is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.

Blue section (Comment, Correspondence, etc)

Editorial

- Editorials are the voice of *The Lancet Public Health*, and are written in-house by the journal's editorial-writing team and signed "The Lancet Public Health"

Comment

- This section contains Commentaries that accompany papers published in *The Lancet Public Health* or on issues of wide-reaching concern in Public Health. Comments linked to policy decisions are welcomed. Most Comments are commissioned, but unsolicited Comments (no more than 750 words, ten references, and one figure, panel, or small table) are also welcome. Comments may be peer reviewed
- The place to respond to something we have published is in our **Correspondence** section
- See **Conflicts of Interest** guidelines for comments

Correspondence

- Letters should be written in response to previous content published in *The Lancet Public Health*
- Letters for publication must reach us within 4 weeks of publication of the original item and should be no longer than 250 words and 5 references
- Letters of general interest, unlinked to items published in the journal, can be up to 400 words long
- Correspondence letters are not usually peer reviewed, but we might invite replies from the authors of the original publication, or pass on letters to these authors
- Only one table or figure is permitted, and there should be no more than five references and five authors
- All accepted letters are edited. Proofs will be sent out to authors before publication

Corrections

- Any substantial error in any article published in *The Lancet Public Health* should be corrected as soon as possible. Blame is not apportioned; the important thing is to set the record straight.
- The *Lancet* journals have a [policy](#) for types of errors that we do and do not correct. We will always correct any error affecting a non-proprietary drug name, dose, or unit, any numerical error in the results, or any factual error in the interpretation of results. Authorship format changes after publication to

facilitate a different visualisation in MEDLINE/PubMed will not be done.

Green section (Reviews, Viewpoints, Health Policy, Commission)

Reviews

Most reviews are commissioned, but unsolicited short outlines (300–400 words) can be directed to the Editor. If you have already written the paper, please submit it for consideration via our [online system](#).

- Reviews should be either a definitive overview of a major topic connected with public health
- Manuscripts will be assessed in-house and those judged suitable will be peer reviewed before an editorial decision is made
- Reviews should be no more than 4500 words, with a maximum of 75 references
- References selected for publication should be chosen for their importance, ease of access, and for the "further reading" opportunities they provide; citations to papers published in non-peer-reviewed supplements are discouraged. In addition to references, authors should consider supplying a short list of useful websites where readers can find further information on the subject
- A 150 word unstructured summary should be included. Use of up to 5–6 illustrations is encouraged to aid the reader
- Complete transparency about the choice of material included is important to any Review paper. Therefore, all Reviews should include a brief section entitled "Search strategy and selection criteria" stating the sources (including databases, MeSH and free text search terms and filters, and reference lists from journals or books) of the material covered, and the criteria used to include or exclude studies. Citations to papers published in non-peer-reviewed supplements are discouraged. Since these papers should be comprehensive, we encourage citation of publications in non-English languages.

Systematic reviews should be prepared according to the PRISMA guidelines

Viewpoint

Viewpoints are opinion pieces that use the best evidence to develop a robust argument on a topic of immediate relevance to public health. They should have a novel and clear point to make, with the aim of provoking transformational thinking at a high level. Length guidelines are up to 2500 words and with a maximum of 30 references.

Health Policy

Manuscripts considered for this section are narrative reviews (not original research) and should follow the same guidelines as a Review. These papers should cover developments in public health related to policy, health systems, or economics. Other related topics will be considered. Please contact the Editor before submitting to ensure the proposed topic is suitable.

Commissions

Topics for *The Lancet Public Health* Commissions are selected by our editors, who work with academic partners to identify the most pressing issues in public health with the aim of producing

MENDELEY data
<https://data.mendeley.com>

For online system see
www.editorialmanager.com/thelancetpublichealth

For *The Lancet* journals' policy on corrections of errors see
<https://www.thelancet.com/for-authors/forms/section=correction>

recommendations to change policy or practice. All Commissions are academic publications and are subject to the same rigorous peer review process as all other research papers published in our journals. The *Lancet Public Health* does not provide direct financial support to Commissioners for the research or writing of the reports. Funding is sought directly by authors, with oversight from our editors.

Series

Series are collections of papers (usually between three and five) on a broad topic within the public health field. They are generally commissioned by the editors, but suggestions are welcome by email. We would not consider a large collection of papers on a narrow topic—eg, a single public health programme. This type of collection is better suited to a journal supplement (*The Lancet Public Health* does not publish supplements).

Formatting guidelines

Language

- Manuscripts should be submitted in English. Authors writing in Chinese, Portuguese, or Spanish may wish to use the Webshop (<http://webshop.elsevier.com/languageservices>) to provide an English translation of their manuscript for submission.

Title page

- A brief title, author name(s), preferred degree (one only), affiliation(s), and full address(es) of the authors must be included. The name and address of the corresponding author should be separately and clearly indicated with email and telephone details.

Formatting of text

- Type a single space at the end of each sentence
- Do not use bold face for emphasis within text
- We use a comma before the final “and” or “or” in a list of items
- Type decimal points midline (ie, 23.4, not 23.4). To create a midline decimal on a PC: hold down ALT key and type 0183 on the number pad, or on a Mac: ALT shift 9
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use single hard-returns to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use the automated features of your software, such as hyphenation, endnotes, headers, or footers (especially for references). Please use page numbering
- Guidelines on formatting tables are available in the [artwork guidelines](#)

References

- Cite references in the text sequentially in the Vancouver numbering style, as a superscripted number after any punctuation mark. For example:
“...as reported by Saito and colleagues.¹⁵”
- Two references are cited separated by a comma, with no space. Three or more consecutive references are given as a range with an en rule. To create an en rule on a PC: hold down CTRL key and minus sign on the number pad, or on a Mac: ALT hyphen

- References in tables, figures, and panels should be in numerical order according to where the item is cited in the text
- Here is an example for a journal reference (note the use of tab, bold, italic, and the en rule or “long” hyphen):
“15[tab]Saito N, Ebara S, Ohotsuka K, Kumeta J, Takaoka K. Natural history of scoliosis in spastic cerebral palsy. *Lancet* 1998; **351**: 1687–[en rule]92.”
- Give any subpart to the title of the article
- If there are six authors or fewer, give all six in the form: surname space initials comma
- If there are seven or more give the first three in the same way, followed by et al
- For a book, give any editors and the publisher, the city of publication, and year of publication
- For a chapter or section of a book, also give the authors and title of the section, and the page numbers
- For online material, please cite the URL, together with the date you accessed the website
- Online journal articles can be cited using the DOI number
- References that are in press can be cited in the reference list with “(in press)” added after the journal name
- For personal communications and unpublished work, please cite in-text rather than in the reference list in the format “(unpublished)” or “(Smith R, unpublished)” if it is your own observation, or “(Jones E, institution, personal communication)” if it is someone else’s observation
- Do not put references in the Summary or Research in context and Search strategy and selection criteria panels
- If preprints are central to your work or cover crucial developments in the topic(s) covered in your paper, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including [preprint] before the reference, and specifically referred to as a preprint in the main text. Where a preprint has subsequently become available as a peer-reviewed article, the formal publication should be used as the reference.

Figures

Our in-house illustrators redraw most figures into *Lancet* style. The quality of the files we receive from authors has a direct effect on the accuracy and time taken to prepare figures that are suitable for publication.

We have different criteria for photographic and illustrative files, the following notes are a summary of our ideal requirements, but a detailed description is in the [artwork guidelines](#)

- For images (photographs or photographic images) that are used as part of illustration or image composite figures we require a file that is no less than 300 dpi when set at its final printed size. Ideal file formats are TIF or JPG
- For trial profiles, study profiles, and CONSORT diagrams, please supply as an editable flow diagram in Word (.doc) or PowerPoint (.ppt) file
- For illustrations (all non-photographic line-work and general drawing) we require editable vector files that contain selectable geometry and fonts (editable text). The editability of files depends on the package they were created in, but as a rule we would prefer to receive any of the following: Adobe Illustrator

Formatting guidelines for text, tables, and figures
Guidelines on formatting of text, tables, and figures can be found at <https://www.thelancet.com/pb/assets/raw/lancet/authors/artwork-guidelines.pdf>

(.ai) file; Adobe Illustrator or generic .eps files exported from a graphics program; vector-based PDF, PowerPoint, or Word file; or SVG file. If authors are unable to supply files in any of these formats, our in-house illustrators can offer guidance on whether it is more economical to export or convert the file into another format, or to redraw from scratch. When files are exported to eps files, we would prefer text to be exported "as text" rather than "as objects", which is especially crucial for files such as forest plots in which there is a lot of text

- If your figures are annotated, please supply two copies of each of these figures as separate files (one annotated copy and one non-annotated and editable copy). Our in-house illustrators will annotate according to journal style using the annotated figures as a guide. For multi-part figures, please supply the individual parts as well as a combined version to be used as a guide for our illustrators to recreate the files
- Images that have been published previously should be accompanied by a statement indicating permission to reproduce the image. If required, further assistance can be obtained from the editorial team. If you have used previously published images, you must obtain permission from the copyright holder of the paper, which might be the authors or the publisher. If all the figures are your own and have not been published before, then this requirement does not apply

Guidelines for supplementary material

All material should be submitted as one PDF (with a table of contents and numbered pages) with the paper and will be peer reviewed. Material will be published at the discretion of *The Lancet* journals' editors. For clinical trials, we encourage authors to include a copy of the study protocol. All material should be provided in English.

Text

- Main heading for the web extra material should be in 12 point Times New Roman font **BOLD**
- Text should be in 10 point Times New Roman font, single spaced
- Headings should be in 10 point **BOLD**

Tables

- Main table heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced
- Tables should be in 8 point Times New Roman font, single spaced
- Headings within tables should be in 8 point **BOLD**

Data

- Numbers in text and tables should always be provided if % is shown
- Means should be accompanied by SDs, and medians by IQR
- p values should be given to two significant figures, unless $p < 0.0001$

Drug names

- Recommended international non-proprietary name (rINN) is required

- We encourage use of neuroscience-based nomenclature for psychotropic drugs

References

- Vancouver style—eg,
Smith A, Jones B, Clements S. Clinical transplantation of tissue-engineered airway. *Lancet* 2008; **372**: 1201–09.
Hourigan P. Ankle injuries. In: Chan D, ed. Sports medicine. London: Elsevier, 2008: 230–47.
- Numbered in order of mention in appendix and numbered separately from references in the full paper

Figures

- All images must have a minimum resolution of 300 dpi, width 107 mm
- Main figure heading should be in 10 point Times New Roman font **BOLD**
- Legends should be in 10 point, single spaced

Audio/video material

- The paper to which the audio or video clip relates should be mentioned in the recording
- Audio clip and video files should be accompanied with brief text explaining the content of the audio, names of interviewers/ interviewees, date of recording, and place of recording if relevant
- Written consent from all parties must be obtained (see also the above section on **Patient and other consents**)

Audio

- Audio material submitted as an mp3 file, no larger than 50 Mb
- Your paper may be selected for a podcast. If so, the Web Editor will contact you to arrange a pre-recorded interview to discuss your paper. For more information, see **Audio**

Audio
<http://www.thelancet.com/audio>

Video

- Video material should be submitted in .mp4 format with aspect ratio of 16:9, and be no larger than 50 Mb
- We welcome your videos and invite you to submit any video material (reports, interviews, scans, imaging) for consideration in the online journal. Please ensure that all those featured in the video have given permission for publication (see also the previous section on **Patient and other consents**)
- All video files can be submitted alongside your article in EM

Disclosure of results before publication

- Presentation of data at a scientific meeting, as a poster, abstract, orally, on a CD, or as an abstract on the web, or on a preprint server does not conflict with submission to the *Lancet* journals. As a member journal of the International Committee for Medical Journal Editors, *The Lancet Public Health* does not regard results that are posted in the same clinical trials registry in which primary registration resides as a previous publication, if the results are presented in the form of a brief structured abstract or table
- The *Lancet* journals operate an embargo system, whereby

Drug names
For more on neuroscience-based nomenclature see [http://www.thelancet.com/pdfs/journals/lancet/PIIS2215-0366\(17\)30098-6.pdf](http://www.thelancet.com/pdfs/journals/lancet/PIIS2215-0366(17)30098-6.pdf)

journalists are given access to papers and press releases ahead of publication, allowing them a protected window to develop their stories. We believe that this window can help encourage balanced and accurate coverage of peer-reviewed scientific and medical research to inform public debate. As such, we ask that authors and their institutions refrain from actively seeking media attention for articles that have been submitted to *The Lancet Public Health* or that are available as a preprint. The important steps of thorough peer review and experienced editorial scrutiny and guidance, together with putting research findings into a wider context and highlighting implications for clinical practice, will make the final published paper in *The Lancet Public Health* very different to the submitted or preprint version. Coverage that results from pre-publication communication can impact media interest at the time of publication and our ability to support responsible journalism

- For more information on Preprints with *The Lancet*, please see www.thelancet.com/preprints. For additional questions regarding media, please contact pressrelease@lancet.com

Online publication

- *The Lancet Public Health* publishes papers online as they become ready. You will be informed at least a week in advance of the Online publication date

How *The Lancet Public Health* handles your paper

Acknowledgment

- Receipt of your paper will be acknowledged by an email containing a reference number, which should be used in all future communications

Checking for plagiarism, duplicate publication, and text recycling

- At our discretion, material that we are interested in publishing will be checked by editors using CrossCheck (see *Lancet* 2011; 377: 281–82). We expect that such papers are written in a way that offers new thinking without recycling previously published text.

Peer review

- *The Lancet Public Health* operates a single-anonymised peer-review process
- Every Article and Meta-analysis published in *The Lancet Public Health* has been peer reviewed. Occasional contributions (eg, Commentaries) are accepted without peer review
- On submission to *The Lancet Public Health*, your report will first be read by one or more of the journal's staff of physicians and scientists. This is an important feature of our selection process and many papers are turned away on the basis of in-house assessment alone. That decision will be communicated quickly
- Research papers are followed by peer review by at least three reviewers. You will receive notification of which editor is handling the peer review of your paper.

Decision

- Submissions that survive in-house and peer review might be

referred back to authors for revision. This is an invitation to present the best possible paper for further scrutiny by the journal; it is not an acceptance

- Authors should give priority to such revisions; the journal will reciprocate by making a final decision quickly
- Two copies of the revised version should be sent back, one of which should be highlighted to show where changes have been made. Detailed responses to reviewers' comments, in a covering letter, are also necessary

The *Lancet* journals and other Elsevier journals

- If your paper is rejected by *The Lancet Public Health*, we might judge it suitable to pass to other editors in the *Lancet*-group for consideration or to editors of other relevant journals within Elsevier's portfolio

Appeals

- Sometimes editors make mistakes. When we do, we like to hear about them. If an author believes that an editor has made an error in declining a paper, we welcome an appeal. In your appeal letter, which should be sent to publichealth@lancet.com, please state why you think the decision is mistaken, and set out your specific responses to any peer reviewers' comments if those seem to have been the main cause of rejection
- At least two editors will decide whether to invite a revised manuscript and whether re-review, or otherwise, is indicated

Proofs

- *The Lancet* journals employ highly skilled Assistant Editors, and it is likely that your paper will be substantially edited after acceptance to ensure that it is accurate, clear, and understandable to a wide readership
- All figures will be redrawn into *The Lancet Public Health* style by our in-house illustrators
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Editorial research

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