Improving public health surveillance methods to expose the silent epidemic of incident and recurrent traumatic brain injury in the general population

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Abstract

Traumatic brain injury (TBI) remains a public health challenge as it causes considerable long-term disability and mortality, creating an important economic burden for society. Accurate and timely assessments of the TBI burden provide evidence to justify the allocation of healthcare resources and to evaluate injury-mitigating interventions. Unfortunately, current approaches to measuring the burden of incident cases have poor accuracy and are resource-intensive, limiting their applicability. In addition, incident TBI only contributes part of the overall injury burden since recurrent TBI (rTBI) occurs frequently. These repetitive injuries significantly amplify the overall TBI burden by worsening the disability of affected individuals. Despite their important contribution to the overall TBI burden, recurrent injuries are poorly understood and have not been comprehensively described in the general population. Given these important knowledge gaps regarding the measurement and control of the TBI burden, TBI has been called a "silent epidemic". The goal of this thesis, composed of three manuscripts, is to improve the methods used to conduct TBI surveillance for incident and recurrent cases, such that the injury burden can be accurately and comprehensively assessed using readily available data sources, thereby also improving the quality of TBI epidemiological research.

In Manuscript 1, administrative health data from a 25% random sample of Montreal residents from 2000 to 2014 were used to conduct a hierarchical Bayesian latent class analysis. Using these methods, the measurement error-adjusted TBI incidence and the accuracy (sensitivity/specificity) was estimated for widely used TBI case definitions based on the International Classification of Diseases, or on head radiologic examinations, covering the full injury spectrum in children, adults, and the elderly. The latent class approach allowed this analysis to be conducted without the need to define a gold standard definition for TBI, which is not

available. The measurement error-adjusted TBI incidence was 76 (95% CrI = 68 , 85) per 10,000 person-years (underestimated as 54 [95% CrI = 54 , 55] per 10,000 without adjustment). The most sensitive case definitions were radiologic examination claims in adults/elderly (0.48; 95% CrI = 0.43 , 0.55 and 0.66; 95% CrI = 0.54 , 0.79) and emergency department claims in children (0.45; 95% CrI = 0.39 , 0.52). The most specific case definitions were inpatient claims and discharge abstracts (0.99; 95% CrI = 0.99 , 1.00). Strong secular trends in the accuracy of case definitions were noted.

In Manuscript 2, a systematic search was conducted of MEDLINE, EMBASE, and the references of included studies until January 16, 2017, for general population observational studies reporting rTBI risk or risk factors. Estimates were not meta-analyzed due to significant methodologic heterogeneity between studies, which was evaluated using meta-regression. Across all included studies, the 1-year rTBI risk varied from 5-10%. Studies that used administrative data/self-report surveys to ascertain cases tended to report the highest risk estimates. Risk factors measured at time of index TBI that were significantly associated with rTBI in more than one study were male sex, prior TBI before index case, moderate or severe TBI, and alcohol intoxication. Risk factors reported in a single study that were significantly associated with rTBI were a history of epilepsy, not seeking medical care within 24 hours of an injury, and multiple factors indicative of low socioeconomic status. Overall, the rTBI surveillance literature had significant methodological limitations, and the accuracy of case definitions for identifying rTBI for surveillance purposes has not been reported in the literature.

In Manuscript 3, methodological limitations on rTBI surveillance identified in Manuscript 2 were addressed. Bayesian latent class models were developed using the same study population and data source as in Manuscript 1 to estimate the measurement error-adjusted rTBI incidence within 1 year of an index injury, and the accuracy of widely used TBI case definitions. The adjusted 1-year rTBI incidence was 4.48 (95% CrI 3.42 , 6.20) per 100 person-years across all age groups, as opposed to a crude estimate of 8.03 (95% CrI 7.86 , 8.21) per 100 person-years. Patients with higher severity index TBI had a significantly higher risk of rTBI. The most sensitive surveillance case definition to identify rTBI was the radiological examinations of the head case definition across children, adults, and the elderly [0.46 (95% CrI 0.33 , 0.61), 0.79 (95% CrI 0.64 , 0.94), and 0.87 (95% CrI 0.78 , 0.95, respectively)]. The most specific case definition to detect rTBI was the DAD in children [0.9992 (95% CrI 0.9977 , 0.9999)], and emergency room visits claims in adults/elderly [0.9898 (95% CrI 0.9851 , 0.9939) and 0.9957 (95% CrI 0.9928 , 0.9988), respectively]. Median time to rTBI, adjusted for the imperfect diagnosis of index TBI and rTBI, was the shortest in adults (75 days) and the longest in children (120 days).

This thesis demonstrates that accurate TBI surveillance of incident cases is possible with resource-friendly administrative health data, provided that methods are used to account for inherent measurement error. Furthermore, this thesis emphasizes that rTBI, which has previously been largely ignored in the general population, is an important contributor to the overall TBI burden. However, the literature on rTBI epidemiology and surveillance in the general population is scarce and has several methodological limitations. In addition, this thesis addresses these limitations by providing the tools necessary to conduct rTBI surveillance accurately and feasibly with administrative health data. The improvement in incident TBI and rTBI surveillance methods provided in this thesis also allows epidemiological researchers to accurately identify incident TBI and rTBI cases in administrative health data. In doing so, such researchers can provide higher quality evidence with valid inferences on the impact of interventions that mitigate the TBI burden. All of this information together provides a louder voice to the once silent TBI epidemic.

Résumé

Les traumatismes cranio-cérébraux (TCC) demeurent un défi pour la santé publique car elles entraînent une morbidité et une mortalité à long terme considérables, créant un fardeau économique important pour la société. Une évaluation précise du fardeau de blessures des TCC peut fournir des preuves qui permettent de justifier l'allocation des ressources de soins de santé et peut évaluer l'efficacité d'interventions qui ont le potentiel d'atténuer le fardeau de blessures. Malheureusement, les approches actuelles pour mesurer le fardeau des cas incidents ont une précision médiocre et demandent beaucoup de ressources, ce qui limite leur applicabilité. De plus, le TCC incident ne représente qu'une partie du fardeau des blessures, car le TCC récidivant (rTCC) se produit fréquemment. Ces blessures répétitives amplifient considérablement le fardeau de blessure relié au TCC en aggravant la morbidité des personnes affectées. Malgré leur contribution importante au fardeau global des TCC, les blessures récidivantes sont peu étudiées et n'ont pas été décrites de manière exhaustive dans la population générale. Compte tenu de ces importantes lacunes dans les connaissances concernant la mesure et le contrôle du fardeau des TCC, les TCC sont considérés une « épidémie silencieuse ». Le but de cette thèse, composée de trois manuscrits, est d'améliorer les méthodes utilisées pour effectuer la surveillance des TCC pour les cas incidents et récidivants, de sorte que le fardeau des blessures puisse être évalué avec précision et de manière exhaustive à l'aide de sources de données facilement disponibles, ce qui aidera également à améliorer la qualité de recherche épidémiologique sur le TCC.

Dans le premier manuscrit, les données administratives sur la santé d'un échantillon aléatoire de 25% de résidents de Montréal de 2000 à 2014 ont été utilisées pour effectuer une analyse hiérarchique de classes latentes bayésiennes. En utilisant ces méthodes, l'incidence de TCC, ajustée pour les erreurs de mesure, et la précision (sensibilité/spécificité) ont été estimées

pour des définitions de cas de TCC largement utilisées basées sur la Classification Internationale des Maladies, ou sur des examens radiologiques de la tête, couvrant le spectre complet de sévérité des blessures chez les enfants, les adultes et les personnes âgées. L'approche par classe latente a permis de mener cette analyse sans qu'il soit nécessaire d'avoir une définition de l'étalon-or pour le TCC, qui en fait n'existe pas. L'incidence du TCC ajustée en fonction des erreurs de mesure était de 76 (95% CrI = 68 , 85) pour 10 000 années-personnes (sous-estimée à 54 [95% CrI = 54 , 55] pour 10 000 sans ajustement). Les définitions de cas les plus sensibles étaient les demandes d'examen radiologique de la tête chez les adultes/personnes âgées (0.48; 95% CrI = 0.43 , 0.55 et 0.66; 95% CrI = 0.54 , 0.79) et les demandes de facturation de médecin en département d'urgence chez les enfants (0.45; 95% CrI = 0.39 , 0.52). Les définitions de cas les plus spécifiques étaient les demandes de facturation de médecin en milieu hospitalier et les résumés de congé d'hospitalisation (0.99; 95% CrI = 0.99 , 1.00). De fortes tendances séculaires dans la précision des définitions de cas ont été notées.

Dans le deuxième manuscrit, une recherche systématique a été menée sur MEDLINE, EMBASE et dans les références des études incluses jusqu'au 16 janvier 2017, pour des études observationnelles de la population générale rapportant le risque de rTCC ou leurs facteurs de risque. Ces derniers paramètres n'ont pas été méta-analysés en raison d'une importante hétérogénéité méthodologique entre les études, qui a été évaluée par méta-régression. Dans toutes les études incluses, le risque de rTCC à un an variait de 5 à 10%. Les études qui ont utilisé des données administratives/des enquêtes d'auto-évaluation pour déterminer les cas avaient tendance à rapporter des estimations de risque plus élevées. Les facteurs de risque mesurés au moment d'un TCC incident qui étaient significativement associés au rTCC dans plus d'une étude étaient le sexe masculin, avoir subi un TCC avant le cas index, avoir subi un TCC de grade modérée ou sévère et l'intoxication à l’alcool. Les facteurs de risque signalés dans une seule étude qui étaient significativement associés au rTCC étaient un antécédent d'épilepsie, le fait de ne pas se présenter pour des soins médicaux dans les 24 heures suivant une blessure et de multiples facteurs indiquant un statut socioéconomique faible. Dans l'ensemble, la littérature sur la surveillance des rTCC comportait des limites méthodologiques importantes, et l'exactitude des définitions de cas pour identifier les rTCC à des fins de surveillance n'a pas été rapportée dans la littérature.

Dans le troisième manuscrit, les limites méthodologiques de la surveillance des rTCC identifiées dans le deuxième manuscrit ont été adressées. Des modèles de classe latente bayésienne ont été développés en utilisant la même population d'étude et la même source de données que dans le premier manuscrit pour estimer l'incidence de rTCC, corrigée pour les erreurs de mesure, dans l'année qui suit une blessure index, et la précision des définitions de cas du rTCC largement utilisées dans les banques de données administratives de santé. L'incidence ajustée du rTCC à un an était de 4.48 (95% CrI 3.42 , 6.20) pour 100 personnes-années dans tous les groupes d'âge, par opposition à une estimation brute de 8.03 (95% CrI 7.86 , 8.21) pour 100 personnes-années. Les patients avec un indice de gravité de TCC incident plus élevé avaient un risque significativement plus élevé de rTCC. La définition de cas de surveillance la plus sensible pour identifier le rTCC était le cas de définition utilisant les examens radiologiques de la tête pour les trois groupes d’âge qui ont été étudiés (0.46 (95% CrI 0.33 , 0.61) chez les enfants, 0.79 (95% CrI 0.64 , 0.94) chez les adultes et 0.87 (95% CrI 0.78 , 0.95) chez les personnes âgées). La définition de cas la plus spécifique pour détecter le rTCC était les résumés de congé d’hospitalisation chez les enfants [0.9992 (95% CrI 0.9977 , 0.9999)] et les demandes de facturation de médecins pour les visites au département d’urgence chez les adultes/personnes âgées [0.9898 (95% CrI 0.9851 , 0.9939) et 0.9957 (95% CrI 0.9928 , 0.9988), respectivement]. Le délai médian avant le rTCC, ajusté pour le diagnostic imparfait du TCC incident et du rTCC, était le plus court chez l'adulte (75 jours) et le plus long chez l'enfant (120 jours).

Cette thèse démontre qu'une surveillance de TCC précise des cas incidents est possible avec des données de santé administratives, à condition que des méthodes soient utilisées pour tenir compte des erreurs de mesure inhérentes. En outre, cette thèse souligne que le rTCC, qui était auparavant largement ignoré dans la population générale, est un contributeur important au fardeau de TCC dans la population générale. Cependant, la littérature sur l'épidémiologie et la surveillance du rTCC dans la population générale présente plusieurs limites méthodologiques. Cette thèse aborde ces limites en fournissant les outils nécessaires pour effectuer une surveillance de rTCC avec précision et faisabilité avec des données administratives sur la santé. L'amélioration des méthodes de surveillance des cas incidents de TCC et de rTCC fournie dans cette thèse permet également aux chercheurs en épidémiologie d'identifier avec précision les cas incidents de TCC et rTCC dans les données administratives de santé. Ce faisant, ces chercheurs peuvent fournir des preuves de meilleure qualité avec des inférences valables sur l'impact des interventions qui pourraient atténuer le fardeau de blessures. Toutes ces informations ensemble donnent une voix plus forte à l'épidémie des TCC autrefois silencieuse.

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Contribution of authors

This thesis was composed of 3 manuscripts:

Manuscript 1: Lasry O, Dendukuri N, Marcoux J, Buckeridge DL. Accuracy of administrative health data for surveillance of traumatic brain injury: a Bayesian latent class analysis.

Manuscript 2: Lasry O, Liu EY, Powell GA, Ruel-Laliberté J, Marcoux J, Buckeridge DL. Epidemiology of recurrent traumatic brain injury in the general population: a systematic review.

Manuscript 3: Lasry O, Dendukuri N, Marcoux J, Buckeridge DL. Recurrent traumatic brain injury surveillance using administrative health data: a Bayesian latent class analysis.

The objectives of this thesis, addressed through the three manuscripts above, were developed collaboratively with my thesis supervisory committee (Dr. Buckeridge, Dr. Marcoux, and Dr. Dendukuri). I developed the research questions, designed the studies, formulated the statistical plan, and conducted all the analyses for each manuscript. Thereafter, I interpreted the results and provided conclusions for each manuscript. My supervisory committee provided me with feedback and guidance on details related to each of the aforementioned tasks. However, I was provided with independence to complete each study. For each manuscript, each co-author provided feedback and approved its final version.

Dr. Buckeridge is a Professor in the Department of Epidemiology, Biostatistics, and Occupational Health at McGill University, a physician specialist in Public Health and Preventative Medicine, and the Canada Research Chair in Health Informatics and Data Science. As my supervisor, Dr. Buckeridge provided me with access to the PopHR data source needed to complete my analyses and provided me with feedback on each step of my thesis.

Dr. Marcoux is an Assistant Professor is the Department of Neurology and Neurosurgery at McGill University, a Neurosurgeon, specialized in neurotrauma in the Department of Neurology and Neurosurgery at McGill University, and a traumatic brain injury researcher. As one of my supervisors, Dr. Marcoux provided me with feedback as I progressed through my thesis. As a neurotrauma neurosurgeon, she provided specific insights on the substantive topic of my thesis, traumatic brain injury.

Dr. Dendukuri is an Associate Professor in the Department of Medicine at McGill University and is the Director of Technology Assessment Unit of the MUHC Centre for Outcomes Research and Evaluation (CORE). As a committee member, she provided me with feedback and guidance on the Bayesian Latent Class Analysis method I used in Manuscripts 1 and 3.

Statement of originality

This thesis addresses knowledge gaps in TBI surveillance and epidemiologic research. The information provided in this thesis can be used as tools for stakeholders in TBI surveillance such that they conduct accurate and resource friendly TBI surveillance across incident and recurrent cases.

Manuscript 1 provides accuracy measures of case definitions to identify TBI in administrative health data. Given that administrative health data is already widely available and used across jurisdictions, it represents a data source that is inexpensive, compared to cohort studies or trauma registries that are too costly to be a sustainable surveillance tool. This manuscript is the first study to assess the accuracy of TBI case definitions in administrative health data in a population-based fashion, across the full injury spectrum and all age groups. In addition, a perfect reference standard to define TBI, which does not exist, was avoided by using Bayesian latent class models. Previous studies have used clinical TBI diagnostic definitions as reference standards when assessing the accuracy of TBI case definitions in administrative health data, which could lead to bias. Finally, the hierarchical approach I used in this study was also the first study to demonstrate secular trends in the performance of case definitions over time.

Manuscript 2 was the first comprehensive description of the epidemiologic characteristics of rTBI in the general population, whereas most previous research on the topic focused on athlete populations. The systematic review completed in this study provided the first knowledge synthesis on the risk of rTBI in the general population and the risk factors associated with recurrent injuries. In addition, the quality of the literature on the topic was assessed for the first time, allowing for researchers to identify future research directions that are necessary to improve our understanding of the rTBI burden in the general population.

Manuscript 3 is the first study to assess the accuracy of case definitions in administrative health data to conduct rTBI surveillance, and to assess the 1-year measurement error-adjusted rTBI incidence in the general population using administrative health data across the full injury spectrum. This study employed similar methods to Manuscript 1 to validly assess the aforementioned accuracy parameters, without relying on a gold standard rTBI definition. In addition, I provided estimates that retain all uncertainty from the diagnosis of index TBI to the diagnosis of rTBI by using predicted cohorts of index TBI patients from Manuscript 1. As such, TBI surveillance stakeholders and researchers have the information necessary to conduct rTBI surveillance and epidemiologic research, which was largely ignored previously due to a lack of methods to conduct such studies accurately and feasibly.

Chapter 1: Introduction

Traumatic brain injury (TBI) is an important contributor of disability and mortality to populations around the globe, leading to an ongoing public health challenge.[1–6] In Canada, a conservative estimate of the indirect costs related to TBI exceeds $8 billion per year, which stems mainly from mild cases (mTBI or concussions) affecting productive individuals in society.[7] These injuries are the leading cause of disability and mortality among children and young adults in the developed world.[8] As such, accurate and timely assessments of the TBI burden are needed since they provide evidence that justifies the allocation of healthcare resources and allow for disease-mitigating interventions to be validly evaluated.[9] Currently, approaches to conduct TBI surveillance are unable to provide this information for several reasons outlined below. Thus, there is an urgent need to develop improved surveillance methods to control this injury burden.[9,10]

The typical approach to conducting TBI surveillance in developed countries is to rely on administrative health data that use diagnostic codes to identify TBI victims.[11] Using this approach, estimates of TBI incidence vary greatly across most developed countries, ranging from 68-544 per 100,000, mainly because heterogeneous methods are used to estimate the injury burden.[11,12] Moreover, these methods tend to only capture patients that are hospitalized, visit the emergency department or die.[13–15] Thus, most estimates miss up to 90% of cases, namely mild TBI (or concussion) patients who often do not seek care in these healthcare settings.[16–19] Furthermore, while diagnostic codes used in administrative health data can accurately detect moderate or severe TBI cases, their accuracy is poorer for detecting mild cases, even when using data sources such as outpatient physician claims, that capture this type of healthcare utilization.[20–22] Given that mild TBI is highly prevalent and contributes the greatest collective TBI burden for populations, these cases cannot be overlooked.[23–25] Investigators have attempted to address these TBI surveillance limitations by using trauma registries or prospective population-based cohort studies to identify TBI cases that would otherwise be missed.[13,14,26] Trauma-registries, however, are expensive to implement and maintain; they also typically capture only hospitalized patients, while prospective cohort studies are resource-intensive and take time to complete.[27] As such, registries and cohort studies are not feasible TBI surveillance options for stakeholders that want timely surveillance information using limited resources.

Furthermore, incident TBI only explains part of the injury burden since recurrent TBI (rTBI) is also a contributor. These repetitive injuries amplify the overall TBI burden by worsening the disability of affected individuals.[28] However, recurrent injuries are poorly understood and have not been comprehensively described in the general population. Thus, it comes as no surprise that surveillance methodology to accurately assess this supplementary injury burden has not been explored. Consequently, population-based studies focusing on interventions that may mitigate the rTBI burden at the population level have not been possible due to a lack of valid ways to identify such recurrent injuries using administrative health data.

Given these important knowledge gaps regarding the measurement and control of the TBI burden, TBI has been labeled as a “silent epidemic”. [10,11,29,30] This thesis focuses on exposing this epidemic by improving the methods used to assess the TBI burden to enable accurate and feasible measurement of both incident and recurrent cases. With these methodological limitations addressed, stakeholders and researchers in TBI will have the appropriate information to allocate resources to TBI prevention and care, while also having the tools to conduct high-quality etiological research on interventions that can mitigate the risk of incident TBI and rTBI.

Chapter 2: Background

Characteristics of incident TBI epidemiology

TBI has an important impact on the health of populations around the globe.[31] The Global Burden of Disease, Injury and Risk Factors (GBD) study has demonstrated that the incidence of TBI varies significantly between countries, with the main determinants of this variability being age structure, income status, and quality of surveillance data.[31,32] Among all trauma-related injuries, TBI is the most important contributor to deaths and disability.[33] In Canada, the indirect costs of TBI are estimated to exceed $8 billion per year, due mainly to costs arising from injured adults during their productive working years.[4,7] These costs stem from the disability caused by TBI that can last from days to a lifetime, depending on the severity of the injury.[34]

The aforementioned injury burden estimates are contingent on the accuracy of the surveillance methods that are used to produce TBI incidence estimates. Such incidence estimates include the findings from the 2016 GBD study, which estimated that the global TBI incidence was 369 per 100,000. In 2016, a systematic review and meta-analysis on the international incidence of TBI reported a pooled incidence of 295 per 100,000.[35] More specifically, in North America and Europe the incidence of TBI was 227 and 331 per 100,000, respectively, which is in keeping with other reports from Europe.[36]

Across all of these aforementioned studies, there are several findings that are consistent regarding the epidemiological characteristics of TBI and the surveillance methodology employed. First, men tend to have a higher risk of TBI across most age groups, except in the elderly where the risk may be higher in women.[14,31,35] Second, a bimodal peak in incidence in children/young adults and the elderly exists across all of these studies. [14,31,35,36] Third, the mechanism of injury leading to TBI varies by age group with children and the elderly mainly being affected by falls, whereas younger adults are more commonly affected by motor vehicle collisions or assaults. Fourth, the majority of the studies rely on administrative health data to complete their surveillance studies, which have inherent measurement error that is not accounted for. Fifth, these studies identify patients that seek medical care, and more specifically patients that seek care in the emergency department or inpatient setting. As such, many of the milder cases (up to 90%), that are thought to represent an important proportion of injuries, can be overlooked in these surveillance studies.[14,16–19]

These last points regarding the limitations in TBI surveillance methodology were emphasized through a population-based cohort study that was conducted in New Zealand from 2010-2011 in an urban (Hamilton) and rural (Waikato) population.[14] This study actively ascertained TBI cases through clinic and hospital chart review audits every month, encouragement of self-referrals from the community, the review imaging study in the defined population on a weekly basis, the review of coroner reports on a monthly basis, and the review of administrative health data of the population under study. They estimated a TBI incidence of 790 per 100,000, which is significantly higher than estimates that had been previously reported.[14] Approximately 28% of mild TBI and 21% of moderate-severe TBI cases were missed when only ascertaining cases from hospitals and outpatient family practices, which represent the cases that are missed in the aforementioned surveillance studies. In short, traditional approaches that use administrative health data for TBI surveillance underestimate the true incidence due to inherent measurement error in these data.

Clearly, decision-makers and stakeholders in TBI do not have the necessary information to allocate resources to control the injury burden, which is why TBI is labelled as a “silent epidemic”.[9,32] Without accurate surveillance methodology, it is not possible to appropriately assess the impact of TBI-mitigating interventions since cohorts of TBI patients cannot be produced with validity. Thus, improvements in surveillance methodology are an important first step to controlling the TBI burden.

The problematic definition of TBI

A necessary requirement for conducting accurate disease surveillance is to have a valid case definition to identify diseased individuals. For TBI, establishing a valid case definition has been a challenge. Over the last three decades there have been several working groups that have suggested different clinical case definitions of TBI.[11] The most widely accepted definition today is "as an alteration in brain function, or other evidence of brain pathology, caused by an external force".[37] Briefly, the "alteration in brain function" portion of the definition is meant to include patients that have a period of loss of consciousness, loss of memory, neurological deficits or any alteration in mental status. The "other evidence of brain pathology" portion of the definition allows for brain imaging evidence of traumatic brain injury such as hemorrhages or swelling to be used to diagnose TBI. The goal of developing this broad definition was to ensure that patients with all injury severities would be encompassed in a single definition. However, experts have commented on the fact that diagnosing patients with moderate or severe TBI is significantly more reliable than diagnosing patients with mild TBI (mTBI) or concussion. [37] The problem with diagnosing milder injuries is related to many psychological symptoms (related to anxiety, intoxication, and psychiatric comorbidities) that occur at the time of injury that could fit the criterion of "alteration of brain function" and confound the diagnosis.[37] In addition, many mild injuries go unwitnessed and therefore many clinicians face the problem of trying to make a diagnosis without a clinical history. Clearly, this definition complicates how surveillance studies define TBI. As such, there has been a push in the literature to develop new diagnostic tools for TBI such as Magnetic

Resonance Imaging (MRI) and serum biomarkers.[11,37–39] However, the current definitions we have to diagnose TBI patients cannot be considered a gold standard, especially for mTBI patients that contribute the greatest injury burden.[40]

Consequently, TBI definitions based on coding in the International Classification of Disease (ICD) codes are also problematic since they are a natural extension of the clinical definition described above. The most widely accepted ICD definition in the literature is the one proposed by the Centers for Disease Control (CDC), which was described in 2004 and uses the ICD-9 iteration.[41,42] In jurisdictions where ICD-10 is used, new definitions have been proposed through literature reviews and systematic reviews to see how public health professionals are defining TBI through this coding system.[43–45] The difficulties relating to the validity of these coding systems in TBI surveillance will be elaborated on below.

Approaches to conducting TBI surveillance and measuring the injury burden

The practice of public health surveillance involves the "ongoing, systematic collection, analysis, interpretation and dissemination of data on health-related events for use in public health action to reduce morbidity and mortality". [46] Vital records that report mortality data, administrative health data and trauma registries have all been used to achieve these goals.[47] The important concepts that are measured through TBI surveillance are the occurrence (incidence), nature of injury (mechanism of injury), severity of injury and outcomes (morbidity and mortality). [11,47,48] TBI severity is typically evaluated using the Glasgow Coma Score, which classifies patients as having mild, moderate or severe disease.[49] This scale has been validated to predict long-term outcomes of TBI patients and demonstrates the wide spectrum of disease for TBI patients, going from mild concussion to severe TBI that can be lethal. Other methods of assessing severity and outcome have been developed and validated as well, such as the injury severity score and prediction models of long-term disability related to TBI.[50–52] However, identifying incident cases is a prerequisite to using these prediction models.

Administrative health data typically include data on hospitalizations, emergency room visits and outpatient visits. With this surveillance approach, the diagnostic codes from the International Classification of Disease (ICD) are used to identify individuals that have incurred a TBI. The injury spectrum covered by these data varies significantly, depending on how many data sources are used simultaneously. Because of various limitations, the use of these data for TBI surveillance purposes has been widely criticized.[12] These data are not collected for research or surveillance purposes and therefore do not offer all of the variables that may be necessary to produce high-quality surveillance, such as mechanisms of injury, injury severity scoring and outcome measures.[53] Furthermore, the accuracy of the diagnostic codes, as outlined below, to identify TBI patients is problematic.[41] Also, in most instances only hospitalizations and emergency department visits are used to conduct surveillance. As such, most surveillance case definitions (definitions and data sources used to measure incident TBI cases) poorly capture the milder spectrum of disease (mTBI or concussions), which represents 70-90% of the TBI burden that do not seek care in these settings.[16–25] Still, there are many advantages to using these data. First, they are collected routinely for administrative purposes and therefore do not add any costs for data collection. Second, when a single insurer system is in place, they cover the entire population in question and therefore limit selection bias. Third, they are longitudinally collected, which offers a means to assess patient patterns of care. Fourth, by using many different data sources beyond hospitalization and emergency room visit data, it becomes possible to capture the full injury spectrum (from the mildest to most severe cases).

Cohort studies offer a means of conducting surveillance in a longitudinal fashion while offering the possibility to assess all variables that are of interest and relevant to the surveillance goals. Birth cohorts and prospective cohort studies have been conducted and have produced high-quality evidence on the TBI burden. They have also served to highlight the pitfalls of administrative health data by demonstrating how this approach to surveillance underestimates the injury burden by up to 5 fold.[14,15] However, these studies are resource-intensive, expensive and time-consuming. In addition, the definition of TBI still suffers from not having a gold standard, which could bias incidence estimates.[37] Therefore, they are not considered a feasible nor sustainable approach to conducting surveillance for prolonged periods of time.

Trauma registries have been implemented in many jurisdictions in the developed and developing world.[54] Since they are dedicated to collecting trauma-related data, they provide detailed information such as vital signs, injury severity scoring as well as outcomes related to trauma.[47] Nonetheless, they have been criticized because their maintenance, to ensure that high quality data are collected, is costly. In addition, they only cover injuries that would require hospitalization. Consequently, the full disease spectrum cannot be described using this surveillance approach.[47] Lastly, many trauma registries are not population-based and therefore are not appropriate for describing the injury burden of an entire population, which is necessary for public health action.[27]

Performance of ICD coding case definitions to detect TBI cases in administrative health data

Several researchers have evaluated the performance of TBI case definitions that are based on ICD codes used in administrative health data. The ICD-9 case definition developed by the CDC has been shown to have a sensitivity of 45.9% (95% CI 41.3% , 50.2%) and a specificity of 97.8%

(95% CI 97.6% , 97.9%) when compared to a real-time clinical assessment for TBI patients.[20] A study using United States Veterans Affairs administrative data demonstrated a sensitivity of 70% and specificity of 82% for ICD-9 codes in comparison to clinical evaluations as the reference standard.[55] A study done in Rochester, Minnesota, using the Mayo Clinic's linkage of all health services for their catchment area, demonstrated that the CDC ICD-9 case definition only captured 40% of cases identified through their record review.[13] In the United Kingdom, a study comparing the TBI cases detected by ICD-10 codes in administrative health data in comparison to an emergency room register of hospitalization detected poor performance of this coding system as well; only 37% of cases in the register were found in the ICD-10 database and 41% of the cases in the ICD-10 database were found in the register.[21] A systematic review, summarizing the above literature, confirmed these findings.[43] The BIONIC research group in New Zealand conducted the first and only prospective cohort study to assess TBI incidence with active case-finding. They revealed that only 18.6% of cases found actively were coded with an ICD-10 code for TBI.[56] The administrative health data this research group used tended to focus only on hospitalization and emergency room visits, where only a single diagnostic code could be used. Despite these limitations in use of ICD codes, an important point to note is that each of these validation studies have used non-gold standard definitions of TBI as there reference test, and therefore the reported estimates of accuracy measures (sensitivity and specificity) and incidence are not necessarily accurate nor valid.[57] Lastly, all evaluations of the accuracy with which surveillance case definitions identify TBI patients have relied on populations seeking care in the emergency room or those who were hospitalized. Consequently, the accuracy estimates may be biased as obtaining cases from these settings is not representative of the entire injury burden that includes mainly mild TBI patients that do not seek care in these settings.[20]

Critiques of current literature and the need for new approaches to surveillance

Over the last two decades, there has been a rising movement to improve methods to conduct surveillance for TBI, which has been recognized as an important public health problem.[15] The general consensus is that the current quantification of the injury burden is an underestimation and that current surveillance methods fail to adequately describe the TBI disease burden.[1,11,16] For example, Barker-Collo et al. noted that studies in the United States, using similar data sources had widely varying TBI incidence rates, ranging from 68 to 544 per 100,000.[48] Varying case definitions and inclusion of deaths were in part responsible for these varying rates. Due to these discrepancies in measuring and reporting TBI surveillance information, this research group developed guidelines that TBI surveillance stakeholders could follow to conduct comparable and reliable TBI surveillance.[48] The recommendations focused on using standardized case definitions and methods to ascertain TBI cases. They urged researchers to use a prospective study design in a large stable population in addition to using many overlapping data sources to ensure that the disease burden is comprehensively described. Despite these recommendations that were made in 2008, three systematic reviews on TBI epidemiology continue to show that the majority of TBI surveillance studies still use ICD-coded administrative health data.[36,58,59] The lack of adherence to these idealistic recommendations may reflect the infeasibility of conducting resource-intensive TBI surveillance in many jurisdictions. Clearly, the use of passive surveillance methods, mainly administrative health data, remains an important tool to the TBI surveillance community.

Surveillance case definitions based on patterns of care in administrative health data

The use of administrative health data to conduct TBI surveillance is currently limited by the validity of case identification using ICD codes. Even when using clinical definitions, there is no gold standard approach for defining TBI and identifying cases.[11,37] As such, using case definitions based solely on the presence or absence of diagnostic codes cannot provide accurate TBI surveillance information. However, many details of care, which offer diagnostic clues, are included in administrative health data. This rich information is not used in the traditional case definitions described above but can inform the probability of a given patient having incurred a TBI. Administrative health data also offers information from many different sources, such as outpatient claims, emergency department visits and hospitalizations. By understanding the way that patients are referred in the health care system, how their care evolves longitudinally and by referring to clinical guidelines about the management of TBI patients, it is possible to identify trajectories of care that provide clues to the identification of TBI patients, who would otherwise be missed. Such an approach has been used for surveillance of other diseases such as osteoarthritis and rheumatologic diseases.[60,61] By developing TBI case definitions based on patterns of care, administrative health data offers the "story" of patients as they use different health services over time.[60–62] For example, patients that present with other trauma diagnoses but that need a CT scan of the head may in fact be patients with TBI where the diagnosis was miscoded. The use of CT scans of the head to assess TBI patients has been validated with specific clinical guidelines to which clinicians adhere.[63] Lastly, this additional information can be used to estimate injury severity, which is an important parameter needed to properly characterize the TBI burden. Assessing severity-specific incidence through administrative health data and across the full injury spectrum has not been possible, except through prediction models that have been validated only for hospitalized patients or patients seeking care in emergency departments.[50–52] Using the information on the health care utilization patients use, clues to the severity of the injury can also be ascertained.

Overarching goal of valid and precise TBI surveillance case definition performance measures

By evaluating the accuracy of TBI surveillance case definitions based on patterns of care in administrative health data, TBI stakeholders will be able to use administrative health data from their own jurisdiction to conduct accurate surveillance. In doing so, they will be able to estimate the TBI incidence by severity level, correcting the estimates for the case definition they decide to use. More specifically, the widely used ICD codes used to detect TBI patients (such as the ones published by the CDC) can be incorporated into case definitions based on patterns of care, so that the inference from the accuracy assessment of case definitions is generalizable to other jurisdictions.[64,65] Thereafter, the TBI surveillance community will have the resources necessary to conduct accurate and feasible surveillance across the full injury spectrum.

Another important problem arising from the limitations of current surveillance methods is the challenge posed for epidemiological research. Population-based studies that use administrative health data to form TBI cohorts cannot assess the relationship between an intervention intended to mitigate the risk of TBI and the impact of that intervention on TBI patients at a population level. For example, several studies have used administrative health data to assess the association between TBI and the risk of suicide.[66–69] However, these studies identified cohorts of TBI patients using ICD-codes in administrative health data, without addressing the potential problem of measurement error in accurately identifying these patients. The positive association between TBI and a given outcome, such as suicide, can be significantly biased if the cohorts under analysis do not truly represent TBI patients or if many patients are not included in the analysis due to measurement error. In addition, epidemiological research on interventions that are aimed at preventing TBI (e.g., road safety policies, helmet use, falls preventions) or interventions aimed at improving the outcomes of TBI patients (e.g., counselling at the time of injury, type of care and follow up provided, trauma system organization and resources provided to patients) face similar methodological problems, although the problem in this context is measurement error in the outcome as opposed to in the exposure.[70,71] As such, methodology to conduct accurate and feasible surveillance is necessary to assess the impact of public health interventions on TBI occurrence, as well as to validly assess the impact of TBI on other health outcomes.

Recurrent traumatic brain injury (rTBI) epidemiology and its risk factors

Incident TBI represents only a part of the overall TBI burden. An important contribution to this injury burden stems from recurrent TBI (rTBI), where the 1-year risk is thought to be up to 10%.[28] Recurrent TBI has been demonstrated to lead to poorer outcomes for patients. These patients have a higher risk of enduring prolonged post-concussive symptoms, which translate to an increase in productivity losses, even when a repeated injury is considered to be mild and would otherwise not be as significant.[72–74] Studies in both athletes and the general population have demonstrated that patients with rTBI suffer longer duration and severity of disability compared to patients with a single TBI.[28,75] Post-concussive symptoms (such as poor concentration, headaches, and fatigue) and even psychiatric comorbidities are the main factors leading to this increase in disability.[76,77] A growing body of evidence has demonstrated that repetitive TBI, even when mild such as in athletes, can lead to an increased risk of suicide and Chronic Traumatic Encephalopathy (a neurodegenerative disorder consisting of cognitive, personality and motor changes).[66,68,73,78] Furthermore, a dose-response relationship between the number of rTBIs and the risk of Chronic

Traumatic Encephalopathy and dementia-related syndromes has been described.[79] Finally, the shorter the interval between an index TBI and a rTBI, the greater the disability.[77] Patients with previous TBI are therefore an important target for TBI prevention to better control the overall TBI burden.[80]

Most studies on rTBI have been conducted on populations of athletes.[75,81–83] However, the risk of rTBI in the general population is not well studied. Population-based estimates are heterogeneous because of varying follow-up periods, definitions of rTBI, data sources for surveillance, and risk factors studied across populations.[28,84–87] In fact, risk factors for rTBI in the general population have been described only partially, and include age, male sex, falls as an initial mechanism of injury, epilepsy disorders and alcohol use.[28,88,89] Given that rTBI has important consequences for the disability of individuals and that it is common, a comprehensive assessment of the injury burden is needed across different populations such that we can estimate the risk of recurrence and identify risk factors of rTBI.[74,90] Explicitly assessing factors that can explain the heterogeneity in rTBI risk estimates across studies, such as the methodology used to measure rTBI occurrences, is important to properly interpret and compare them. By measuring and describing the rTBI burden across jurisdictions, it would be possible for stakeholders in TBI to be informed about how to allocate resources, raise awareness, and identify patients at risk that can be targeted with prevention strategies. The only review on the topic is narrative and dates back to 1992 when there was little literature on rTBI.[74] Methodology that focuses on conducting accurate rTBI surveillance is lacking and has not been comprehensively assessed in other studies.

Methodological limitations in rTBI surveillance and epidemiological research

As previously mentioned, rTBI is an under-studied entity in the general population. In addition to the few studies assessing rTBI burden in the general population, there has also been a paucity of research on the methodology used to conduct rTBI surveillance across different data sources and injury severities. Similar to the situation for incident TBI surveillance, such information is required for researchers and stakeholders to appropriately understand the injury burden and the risk factors of rTBI. For the same reasons as for incident TBI, there is no gold standard to define or diagnose rTBI. The definition of rTBI is simply another isolated TBI event that is defined the same way as an incident case. Therefore, assessment of the accuracy of administrative health data for rTBI surveillance requires strategies that can circumvent the need to define a perfect reference standard, which does not exist. Furthermore, conducting rTBI surveillance is contingent on identifying incident (first-time) cases accurately. Therefore, conducting research that accurately identifies incident cases, as mentioned above, is a necessary precursor to validly assess the accuracy of rTBI surveillance case definitions and the risk of rTBI in a population. With this information on rTBI surveillance accuracy, stakeholders in rTBI would have a resource-friendly and accurate method to assess the rTBI burden.

In 2004, the World Health Organization's Collaborating Centre Task Force on mTBI conducted a systematic review of non-surgical interventions to prevent adverse outcomes, such as post-concussive symptoms and productivity loses.[91] This review concluded that the only intervention with evidence of a protective effect was providing early and focused educational information to patients. More recent systematic reviews reiterated the idea that early counselling interventions provided through specialized TBI care are associated with a decrease in the risk of subsequent post-concussive symptoms in patients with mTBI.[92–94] Also, these reviews highlighted that there exists an important knowledge gap in the literature regarding evidence-based interventions that mitigate poor outcomes for mTBI patients.[95] As before, mTBI patients contribute the greatest proportion of the overall TBI burden. Therefore evaluating ways to reduce the risk of adverse outcomes, such as rTBI, of these common injuries is critical to controlling the “silent epidemic”.[96]

Unfortunately, studies assessing interventions to mitigate the rTBI burden are not available. In fact, such studies cannot be validly conducted since methods to identify rTBI patients accurately have not been elaborated. As is the case for incident TBI, accurate methods to identify rTBI patients in administrative health data is necessary to accurately assess any injury-mitigating interventions at the population level. Without such knowledge, the outcome of interest (rTBI) would be measured with error, which could lead to biased or imprecise conclusions, depending on whether injury status misclassification is differential or non-differential, which are not helpful to stakeholders or society.[97]

Summary and organization of thesis

In brief, TBI represents a significant public health problem but the burden of TBI is monitored inaccurately and described poorly. With currently used methods, accurate TBI surveillance requires cohort studies that are resource-intensive, which is not a sustainable solution for providing timely surveillance information. Fewer resources are needed to conduct TBI surveillance using administrative health data, which are widely available across jurisdictions, but measurement error inherent to these data leads to inaccurate assessment of the TBI burden. Addressing these limitations requires development of methods for accurate measurement of incident TBI cases in administrative data. The same methods would also allow higher quality epidemiological research on interventions intended to mitigate the TBI burden. Furthermore, rTBI contributes significantly to the overall TBI burden, but has received little attention at the general population level. A comprehensive description of rTBI is needed so that its epidemiological characteristics can be understood. Finally, the development of accurate and feasible approaches for conducting rTBI surveillance is critical to appropriately describe the full injury burden and to conduct higher quality epidemiological research on interventions that may reduce the rTBI burden in populations.

Thus, this manuscript-based thesis aimed to develop methods that can be applied to administrative data to measure the TBI burden accurately across both incident and recurrent cases. In the first manuscript, the accuracy of widely used ICD-coded surveillance case definitions based on patterns of care in administrative health data was estimated. In addition, the measurement error-adjusted TBI incidence was estimated across the full TBI severity spectrum in a population-based sample, without relying on a gold standard definition which does not exist. In the second manuscript, the rTBI burden in the general population was comprehensively assessed and described by systematically reviewing the literature on rTBI risk and associated risk factors, while assessing study-level methodological factors that contribute to the heterogeneity of estimates across different populations. Finally, in the third manuscript, the accuracy of rTBI case definitions used in administrative health data was assessed for conducting rTBI surveillance across the full injury severity spectrum. The 1-year measurement error-adjusted incidence of rTBI in the general population was also estimated, without relying on a gold standard rTBI definition.

Chapter 3: Complementary information on methodology used in thesis manuscripts

The three manuscripts in this thesis each describe the methodology used to conduct the studies in their respective "Methods" sections and Appendices where supplementary methodological details are explained. For Manuscripts 1 (Chapter 4) and 3 (Chapter 6) I used Bayesian latent class analyses to estimate the accuracy of TBI/rTBI surveillance case definitions and their incidence, without relying on a gold standard TBI definition that does not exist through a cohort study design. In this section, I provide additional details on the methodology used to conduct the studies in Manuscripts 1 and 3. I also provide details on the data source used in these studies and describe how the cohorts to detect incident TBI and rTBI patients were created. Finally, I provide background information on the Bayesian latent class analysis methodology, while demonstrating the rationale for the use of this approach to assess the accuracy of case definitions to detect incident TBI and rTBI in administrative health data. Manuscript 2 used standard systematic review and meta-regression methods, which are described in Chapter 5.

Population Health Record (PopHR)

The data used in Chapters 4 and 6 are multiple, overlapping sources of administrative health data, which are readily available across many jurisdictions.[99–101] All data were retrieved from the Government of Quebec's Régie de l'assurance-maladie du Québec (RAMQ). The RAMQ collects administrative health data on all physician claims and hospitalizations in Quebec. These data contain information on a 25% random sample of all CMA residents in Quebec that are registered with the RAMQ. Over 99% of all Quebec residents are registered with this public insurance provider in the province.[102,103] These administrative health data have previously been used to conduct epidemiological studies on TBI as well as other diseases.[104–106] Given the random sampling of the population, a representative sample of the entire population of the CMA is provided. The cohort used is open and dynamic. Patients exit the cohort as they die or move out of the CMA and newborns and immigrants to Quebec are added to the cohort as they move into the CMA. In addition, it is important to note that multiple Quebec administrative health regions are included in the CMA, such as the Montreal, Laval, Montérégie, Laurentides and Lanaudière regions. This diversity of health regions provides a heterogeneous population that includes both urban and rural areas of the province, allowing inference of our results for both segments of the population. In addition, since most developed jurisdictions in the world have similar TBI epidemiological descriptions and access to similar administrative health data, the findings from this work should be generalizable to other developed jurisdictions.[35,36,58] Patients included in the PopHR database had to be residents of Quebec, registered with the RAMQ, and living in the Montreal CMA, as defined by Statistics Canada.[98] Individuals were excluded from the cohort if they were Quebec residents residing outside the CMA or were visitors from outside the province.

These administrative health data were available through a research grant from the Canadian Foundation for Innovation (CFI) for a project called Population Health Record (PopHR).[102] PopHR is an informatics platform used to develop public health surveillance indicators and monitor population health by using multiple sources of administrative health data. The data used in this project are as described above and follow a 25% random sample of the CMA population for 17 years (1998-2014). All sources of data used in PopHR identify individuals with a unique identifier. Consequently, all sources of data can be linked to provide a portrait of each patient's interaction with the healthcare system. The CFI grant was provided to establish PopHR to conduct research on methods for public health surveillance. For the purpose of this thesis, data from the PopHR platform were used to conduct the incident and recurrent TBI surveillance studies described in Chapters 4 and 6.

Cohort creation for Manuscripts 1 (incident TBI analysis) and 3 (rTBI analysis)

Surveillance information needs to be produced in a timely and systematic manner for it to inform public health action.[47] In practice, this means that surveillance estimates should be completed at regular intervals and that longitudinal information on patients is necessary. For this reason, I used a cohort study design to evaluate the accuracy of widely used TBI surveillance case definitions in administrative health data (described below). The data from PopHR were used to create this cohort. The cohort begins in 1998 and includes a 25% random sample of Quebec residents of the Montreal Census Metropolitan Area (CMA), registered with the Régie de l'assurance-maladie du Québec (RAMQ) and ends at the end of 2014.[98]. For the purpose of this thesis, the analysis was conducted from 2000-2014 to allow for a 2-year "washout" period, where patients that met any TBI surveillance case definition throughout 1998-1999 were removed from the at-risk pool to mitigate the potential bias from including prevalent TBI cases in our analysis. Incident cases of TBI were identified on a yearly basis and were removed from the cohort once they met the definition of one of the surveillance case definitions since they were no longer "at risk" for an incident TBI. More specifically, individuals were considered to be a "suspected" case of incident TBI if they met any of the TBI case definitions, since it is known that the sensitivity and specificity of these case definitions is not 100%.[43,56] These TBI surveillance case definitions are described in further detail below. The person-time contribution to the cohort, measured in person-years, was used as the denominator to calculate TBI incidence. Individuals in the cohort contributed person-time to the denominator used to calculate the incidence from the moment they entered the cohort until the moment they exited the cohort. Individuals exited the cohort as soon as they met a case definition of "suspected TBI", died, or were censored from the dynamic cohort. Figure 1 demonstrates how the cohort was formed and how patients were followed over the 15-year follow-up period.

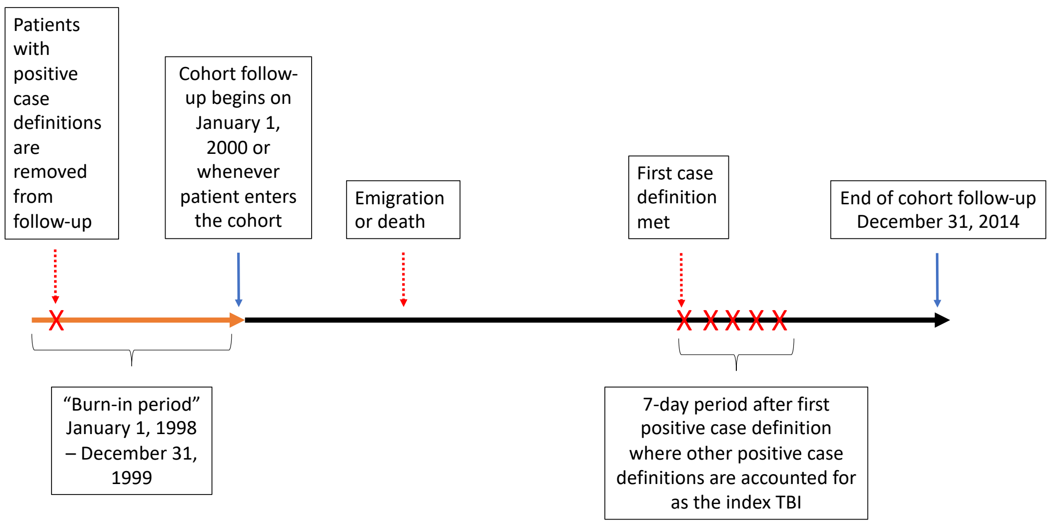

Figure 1: A diagrammatic representation of the cohort used to conduct the analysis in Chapter 4. A 2-year burn-in period from 1998-1999 was used to exclude prevalent cases of TBI, where all patients meeting 1 of 5 case definitions for TBI were removed from the cohort. Patient were then followed-up from their date of cohort entry until emigration from the cohort, death, or when they met one of the 5 case definitions between 2000-2014. From the earliest date a patient met 1 of the 5 TBI case definitions, a 7-day window was permitted for other case definitions to be positive and related to this initial TBI.

In Manuscript 3, the same approach was used to define a cohort to follow-up patients for 1 year after their incident TBI. With this approach, I was able to estimate the 1-year rTBI incidence as well as the accuracy of case definitions to detect rTBI in the first year after incident TBI. The number of patients with incident TBI (the incident TBI cohort) was estimated using simulations of cohorts based on the results of the incident TBI analysis from Manuscript 1. I adopted this approach to ensure that all uncertainty on the diagnosis of incident TBI was carried over to the recurrent TBI analysis. As such, the results were truly representative of all the uncertainty I had around the accuracy estimates of the case definitions and measurement error-adjusted incidence estimates. Chapter 6 provides further details on how these simulations were conducted. As for Manuscript 1, the person-time was calculated for each patient with an incident TBI until they met an rTBI case definition or exited the cohort for another reason (emigration from cohort or death). As above, the latter represented the person-years that people contributed while not being suspected of having a recurrent injury (not meeting any of the case definitions). Figure 2 describes how patients were followed from the time of their index TBI to the moment of their rTBI or cohort exit.

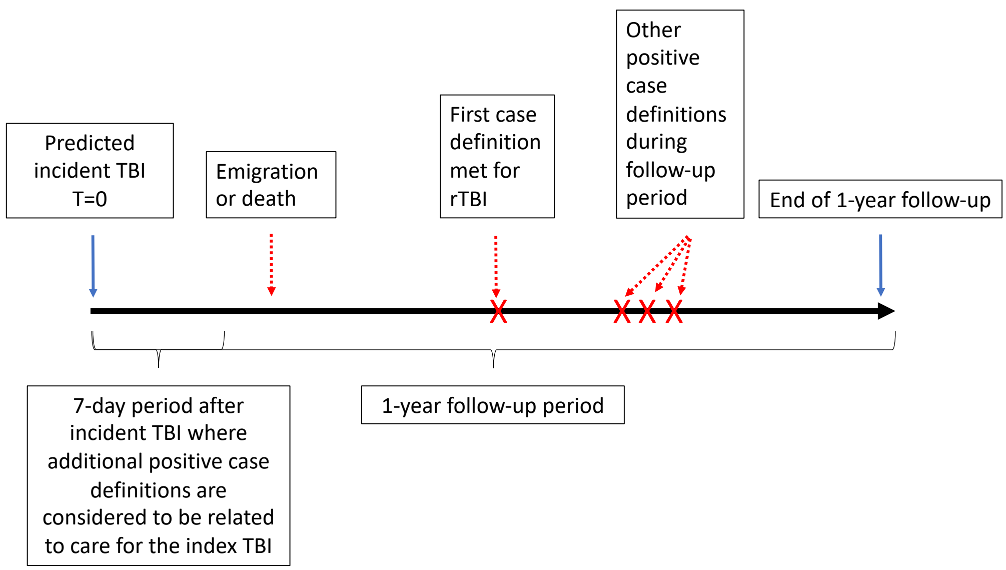

Figure 2: A 1-year cohort follow-up was used to conduct the rTBI analysis. Patients predicted to have an incident TBI entered the cohort for 1 year. All case definitions they were positive for at least 7 days after their incident TBI was considered as a case definition representing a "suspected" rTBI.

Measures used in administrative health data/PopHR

Each data source included in PopHR has a different set of variables that it provides, although there is overlap between sources. The overlap arises from the fact that each data source in PopHR is coded by different individuals that provide independent information. As such, different aspects of the same injury are provided by different individuals/data sources. This overlap of data is important to note as it is one of the justifications for using latent class analysis to evaluate the accuracy of the surveillance case definitions described below.[48]

Hospitalization data includes 1 primary diagnostic field as well as 25 fields for secondary diagnoses. The hospitalization records also include the date of admission/discharge, length of stay, type of care unit where the hospitalization took place, procedures provided during the hospitalization, unique hospital identifier, the date of emergency room admission before the current hospitalization, indicator of in-hospital death, and intervention codes as per the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedure (CCP) (data from 1998-2005) or the Canadian Classification of Health Interventions (data from 2006-2014) (CCI).[107] Physician claims data include a field for a diagnosis (ICD coded), a field for the medical act performed (as coded by the RAMQ billing schedule for the RAMQ), the institution identifier where the medical act was performed, date of service, type of institution, anonymous identifier of the physician providing the medical act, and speciality of the physician.[108] The ICD codes used in the PopHR vary by data source. The physician claims records use the ICD-9 Clinical Modification (ICD-9-CM) .[109,110] The hospitalization data makes use of the ICD-9-CM iteration from 1998-2005 and the ICD-10 Canadian Modification (ICD-10-CM) iteration from 2006-2014.

Widely used TBI surveillance case definitions

TBI surveillance conducted with administrative health data typically uses ICD codes to identify TBI patients. As previously mentioned, these surveillance definitions perform poorly in terms of their sensitivity, which likely underestimates the true TBI incidence.[14,21,43,56] The CDC has developed a TBI definition for surveillance purposes using ICD-9.[64,65] This definition has become popular across the TBI surveillance literature, as evidenced by its repeated use in surveillance and validation studies.[35,36,43] ICD-10 definitions for TBI surveillance have also been elaborated, but there tends to be more variability in the way different investigators make use of these codes. However, a list of ICD-10 codes, identified in a systematic review where optimal codes to define neurotrauma were investigated, provides the most comparable set of codes to the ICD-9 definition.[43] Chapters 4 provides the set of ICD codes that were used to identify TBI cases for each iteration of the coding system.

Use of overlapping administrative health data sources across different care settings

The widely used surveillance case definitions described above provide some clues to the diagnosis of TBI ("suspected" TBI cases). However, when they are used in isolation without considering the different settings where patients can receive care, independent and overlapping information on the potential diagnosis of TBI is overlooked. In doing so, the true injury burden is inaccurately estimated and the injury status of individuals with a potential TBI diagnosis is misclassified. My approach to improving TBI surveillance using administrative health data was to rely on these case definitions but to use them across different care settings, such that overlapping (information from different data sources on the same injury) and independent (information on the same injury from the assessment of different individuals) information on the occurrence of TBI can be used. These independent sources of additional information on the diagnosis of TBI provides information that helps to validate the diagnosis of TBI, especially if there is agreement between data sources. In addition, the care setting where patients are treated, such as the outpatient, emergency room or in-patient setting, provides indirect information of the severity of such injuries. This last point is helpful in classifying patients into injury severity categories, which is a TBI surveillance parameter that cannot be measured directly from administrative health data unless one relies on predictive case definitions that tend to perform poorly for mild TBI patients and are typically limited to providing estimates for hospitalized cases.[51,52,111–113] In short, by using more information about the diagnosis and severity of TBI, the validity and precision of the accuracy measures for the widely used surveillance case definitions improves, as does the measurement error-adjusted incidence estimate for TBI and rTBI.

Bayesian latent class analysis description and justification

I used Bayesian Latent Class Models (BLCMs) to simultaneously evaluate the performance of widely used surveillance case definitions across different care settings in addition to estimating yearly incidence of TBI (Manuscript 1) as well as the 1-year risk of rTBI (Manuscript 3). Latent class analysis is a statistical approach to modelling variables or outcomes that are not directly observable or perfectly measured, such as the diagnosis of TBI/rTBI for which there is no gold standard case definition.[114–116] The latent classes are the categories of a variable that individuals theoretically belong to but that investigators cannot measure perfectly nor directly.[115] With this type of analysis, observations that provide clues (measured imperfectly) as to whether an individual belongs to a certain class are used to model the probability that a given individual belongs to different classes. An application of this statistical approach is when one considers multiple diagnostic tests performed for the same individual to determine whether or not they have a disease when there is no gold standard reference test.[117–119] This application can be extended to the use of surveillance case definitions to determine the disease status of many individuals; each surveillance case definitions can be viewed as a diagnostic test.[60–62,117,120] As such, latent class analysis allows for the estimation of the accuracy of TBI case definitions without the need to define a gold standard definition, which circumvents bias that would otherwise affect such assessments.

Since the administrative health data sources used are overlapping, patients can test positive on one or more surveillance case definitions. The latent class models provide the following relevant parameter estimates: sensitivity, specificity, positive and negative predictive values of each case definition and the incidence of TBI in the population, stratified by severity level. By simultaneously using each case definition with overlapping data sources, each parameter estimate was adjusted for the imperfect performance of the all other surveillance case definitions used in the model.[121]

I decided to use a Bayesian approach to latent class analysis because of the greater flexibility it offers in terms of using prior knowledge, which may be especially valuable if the modelling strategy is non-identifiable or cannot converge due to sparsity of data in the response patterns of latent classes.[122–124] Bayesian approaches allows the use prior knowledge (prior distributions on our parameters of interest) along with our current data (the likelihood function for our data) to model our outcome under study.[125] Since there is a significant amount of literature on the performance of certain TBI surveillance case definitions, the Bayesian approach offers a way to present results where prior knowledge is incorporated if necessary.[117,121] When feasible, non-informative prior distributions were used to allow the observed data to dominate the results. Sensitivity analyses to study the influence of the prior distributions were carried out in all cases. The latter is an additional advantage of a Bayesian approach, since varying prior distributions in sensitivity analyses allows us to confirm the robustness of our main analysis results.[123,124]

A conceptual overview of the BLCM that was used in this thesis for Manuscripts 1 and 3 is provided in Figures 3 and 4, respectively. These heuristic diagrams illustrate the relationship between the observed data and underlying latent variables or classes that are being investigated (patients with the diagnosis of TBI, stratified by severity, and patients without TBI). For

Manuscript 1, it uses the widely used ICD-based case definitions employed in the literature, across four independent data sources that each represent a surveillance case definition (outpatient physician claims, emergency room physician claims, inpatient physician claims, and discharge abstract database).[35,36] In addition, I used a fifth surveillance case definition that captures patients that have any trauma diagnosis (ICD-9 codes 800-999) and that receives a Computed Tomography (CT) scan of the head, Magnetic Resonance Imaging (MRI) of the brain or a skull X-Ray, where these claims occur within 1 days of each other.[126–128] The rationale for this case definition is that clinicians have guidelines to complete these radiological examinations when a TBI is suspected and there is an elevated risk of there being an associated traumatic lesion.[63] The number of response patterns that were possible were 32 (2^5=32) given that 5 case definitions were used. For Manuscript 3, only 4 of the case definitions were used: outpatient physician claims, emergency department physician claims, discharge abstract database, and the aforementioned radiological examination case definition. As such, there were 16 (2^4=16) possible response patterns to the 4 case definitions. The inpatient physician claim was not used in this analysis since patients with prolonged hospitalizations can have delayed inpatient physician claims that would be mistakenly detected as rTBI cases. Also, the discharge abstract database already captures information on hospitalization for TBI, and therefore information on patients hospitalized for rTBI was still available in the model. Finally, model fit was improved when removing the inpatient physician claim case definition. Further details on the decision to exclude the inpatient physician claims are provided in Manuscript 3 (Chapter 6).

The information provided by each surveillance case definition allows the model to identify which patients are in a given class based on their positivity to the case definitions (1 of 32 response patterns for the incident TBI analysis, or 1 of 16 response patterns for the rTBI analysis). Together, the case definitions are thought to provide information on incident TBI cases in addition to the spectrum of injury severity of individuals. For example, the suggested case definitions provide clues on the diagnosis of uncomplicated mild cases that are typically seen as outpatients, complicated mTBI patients that may need to be seen in the emergency department and require additional testing such as brain imaging, and moderate/severe cases that are hospitalized for their injury.[129,130] For Manuscript 1, our a priori model is based on substantive evidence of the TBI disease course and patterns of care in administrative health data that inform its severity. Thus, I hypothesized that the following spectrum of latent variables could be assessed with administrative health data for incident TBI: “mildest” TBI, “more severe” TBI, “most severe” TBI, and “no TBI”.[129] For example, the “mildest” TBI were hypothesized to be cases that mainly presented for outpatient care. The “more severe” cases were more likely to require brain imaging and present to the emergency room. The “most severe” were more likely to represent patients that required hospitalization. Each of these latent classes lies on a spectrum of injury severity that patients may belong to. The case definitions they are positive for informs the model of where on the spectrum they may lie. Lastly, each of these case definitions require that health care utilization events occur within 7 days of each other to be considered as relating to the same injury. This 7-day window allowed for delayed claims in administrative health data for an incident event to be related to the incident event (Figure 1). However, I did not make this window any longer to ensure that recurrent TBI events are not considered as be related to the incident event.

The patterns of case definitions for which patients are positive allow the model to cluster patients into latent classes (Figures 1 and 3). These latent classes (for example, “mildest” TBI, “more severe” TBI, “most severe” TBI, and “no TBI”) are labelled based on the probabilities of an individual being positive for a certain case definition, given that they are in a specific latent class. The probability of a patient being positive to a specific case definition given that they are in a specific latent class is the class-specific sensitivity. Moreover, the probability of a patient being negative to a specific case definition given that they are in the "no TBI" group is the case definition's specificity. The PPV and NPV of each case definition can be calculated using algebraic manipulations of the aforementioned sensitivities/specificities and the estimated TBI incidence.

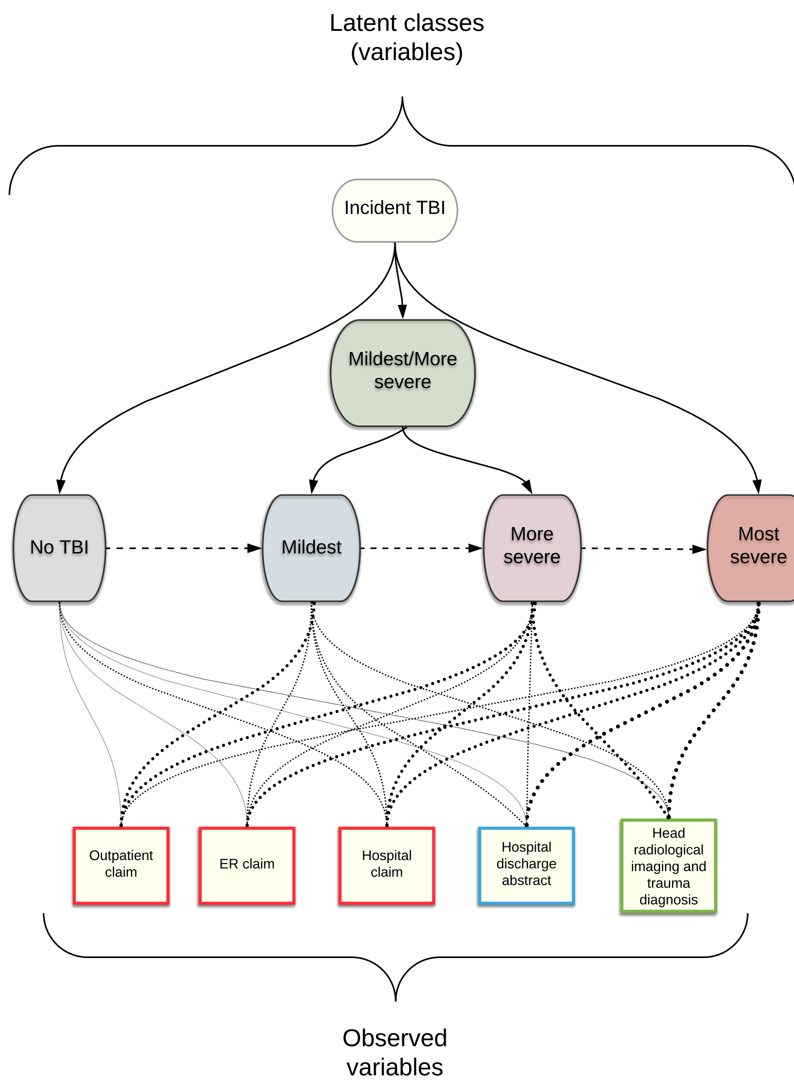

Figure 3: Latent class analysis to model incident TBI in 4 latent classes (TBI severity spectrum) using 5 case definitions. The case definitions in red boxes are from physician claims, the discharge abstract database case definition is shown in blue, and the green box identifies the case definition where a radiological examination of the head physician claim was present simultaneously with any trauma diagnosis claim within 1 day of each other.

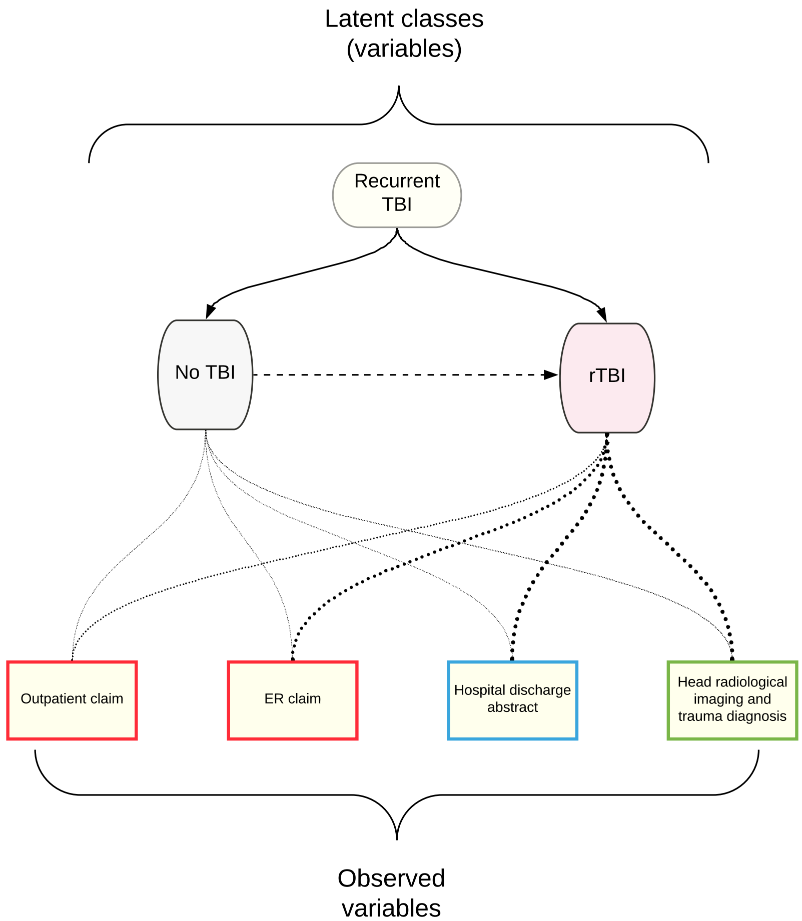

Figure 4: Latent class analysis to model rTBI in 2 latent classes using 4 case definitions. The case definitions in red boxes are from physician claims, the discharge abstract database case definition is shown in blue, and the green box identifies the case definition where a radiological examination of the head claim was present simultaneously with any trauma diagnosis claim within 1 day of each other.

A similar modelling approach was used for the rTBI analysis in Manuscript 3. However, a 2-class model was used given that the data from the predicted cohorts were too sparse to conduct an analysis with more latent classes. The model was unable to converge in 2 and 3-class models without adding significant prior information, which was not available.[131] As such, the rTBI BLCM identified patients that had “rTBI” or “no rTBI”. In addition, the positivity to rTBI case definition had to occur after 7 days of the earliest case definition for index TBI. Patients were allowed to have positive rTBI case definitions from 7 days after the index TBI and up to 365 days after the injury (Figure 2). I did not use a 7-day window to capture a cluster of cases as I did with incident TBI since many patients have follow-ups for their index TBI, such as outpatient visits and repeat radiological imaging of the head, that would take them out of the at-risk pool of the analysis, even though they are still at risk of a true recurrence that can occur thereafter. By omitting the aforementioned 7-day window during which positive case definitions are attributed to the same instance of rTBI, I was able to comprehensively assess the 1-year rTBI incidence and accuracy of rTBI case definitions that incorporate the health care utilization patterns occurring during the 1-year period after incident TBI (Figures 2 and 4). For example, it would be plausible to assume that a patient that solely presents to the outpatient clinic in the 1-year period after incident TBI would be less likely to have a true rTBI compared to a patient that returns to the emergency room, has a CT scan of the head and is readmitted to hospital in the 1-year period after incident TBI.

Chapter 4: Accuracy of administrative health data for surveillance of traumatic brain injury: a Bayesian latent class analysis

Preface to Manuscript 1:

In this first study, the main objective was to evaluate the performance (sensitivity and specificity) of widely used TBI surveillance case definitions in administrative health data to detect incident TBI in a population-based sample of patients. By estimating the performance of each case definition, I was also able to estimate the incidence adjusted for measurement error.

I used ICD codes that have been adopted across many jurisdictions to conduct TBI surveillance with administrative health data. The PopHR cohort was used to detect suspected case of TBI based on 5 different case definitions that span different patterns of care and injury severity on a yearly basis. Bayesian latent class analysis was used to achieve the aforementioned objectives. This analysis used the hints provided by the case definitions as to the diagnosis of TBI without relying on any gold standard TBI definition, which does not exist. Analyses were conducted on a yearly basis from 2000-2014. As such, year-specific analyses were conducted and pooled together through a hierarchical model so that year-specific estimates were available for incidence and accuracy parameters, in addition to pooled estimates that are more precise since they borrow strength from each yearly analysis.

The results of this study are meant to provide the tools necessary for TBI stakeholders to conduct timely and accurate incident TBI surveillance with routinely available administrative health data, an approach that has not been feasible previously. By using the parameter estimates provided in this study, stakeholders will have the information necessary to adjust crude (i.e., based on a single case definition) estimates of the incident TBI burden. Lastly, the evidence from this study also provides epidemiological researchers with the information necessary to construct valid cohorts of TBI patients. Such methodological enhancements to a study allow researchers to perform higher quality etiological research that assesses interventions that may decrease the risk of TBI or adverse consequences these patients can face.

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Manuscript 1

Type of Manuscript: Original Research

Title: Accuracy of administrative health data for surveillance of traumatic brain injury: a Bayesian latent class analysis

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Supplementary data: Available in "Supplementary_data.docx"

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Running head: TBI surveillance accuracy with administrative data

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Keywords: traumatic brain injury, administrative health data, surveillance, latent class analysis

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Abstract

Background: Traumatic brain injury surveillance provides information for allocating resources to prevention efforts. Administrative data are widely available and inexpensive but may underestimate traumatic brain injury burden by misclassifying cases. Moreover, previous studies evaluating the accuracy of administrative data surveillance case definitions were at risk of bias by using imperfect diagnostic definitions as reference standards. We assessed the accuracy (sensitivity/specificity) of traumatic brain injury surveillance case definitions in administrative data, without using a reference standard, to estimate incidence accurately.

Methods: We used administrative data from a 25% random sample of Montreal residents from 2000-2014. We used hierarchical Bayesian latent class models to estimate the accuracy of widely used traumatic brain injury case definitions based on the International Classification of Diseases, or on head radiologic examinations, covering the full injury spectrum in children, adults, and the elderly. We estimated measurement error-adjusted age- and severity-specific incidence.

Results: The adjusted traumatic brain injury incidence was 76 (95% CrI 68 , 85) per 10,000 person–years [underestimated as 54 (95% CrI 54 , 55) per 10,000 without adjustment]. The most sensitive case definitions were radiologic examination claims in adults/elderly (0.48, 95% CrI 0.43 , 0.55 and 0.66, 95% CrI 0.54 , 0.79) and emergency department claims in children (0.45, 95% CrI 0.39 , 0.52). The most specific case definitions were inpatient claims and discharge abstracts (0.99, 95% CrI 0.99 , 1.00). We noted strong secular trends in case definition accuracy.

Conclusions: Administrative data remain a useful tool for conducting traumatic brain injury surveillance and epidemiologic research when measurement error is adjusted for.

Introduction:

Traumatic brain injury is an important public health problem, leading to substantial morbidity in populations around the globe.[1] Accurate and timely assessments of the traumatic brain injury burden are needed to allocate healthcare resources appropriately and to evaluate the return on these investments. Administrative health data are an affordable and widely available data source in many jurisdictions. However, researchers have criticized their utility due to their poor accuracy, which leads to an important underestimation of the injury burden.[2–4]

Underestimation of the traumatic brain injury burden has been demonstrated through cohort studies that accurately assessed incidence by actively seeking new cases. In such cases, the incidence was greater than 80 per 10,000 person–years, in comparison to several studies that estimated lower incidence when using administrative health data.[5,6] Nonetheless, this cohort approach to conducting traumatic brain injury surveillance is not sustainable because of its resource intensiveness.

Traumatic brain injury case definitions based on International Classification of Disease (ICD) codes in administrative health data are thought to have variable accuracy depending on the severity of injury and the specific data source used.[7] These reported accuracy estimates are based on studies of patients treated in higher acuity care settings, such as the emergency department or inpatient wards. As such, these accuracy estimates do not reflect the performance of surveillance case definitions across the full injury spectrum, which leads to an underestimate of traumatic brain injury incidence.[2,8] In addition, these studies used clinical examinations or chart reviews as a gold standard to measure the accuracy of these case definitions. Thus, the estimates from these studies are likely biased since there is no perfect method to diagnose traumatic brain injury.[9]

Administrative health data remain an accessible and resource-friendly tool for conducting traumatic brain injury surveillance and epidemiological research.[6,10] However, a rigorous assessment of their accuracy is necessary to ensure that they can generate valid and accurate information on the traumatic brain injury burden. We aimed to assess the accuracy of widely used traumatic brain injury case definitions in administrative health data across the full injury spectrum in children, adults, and the elderly using a population-based cohort without assuming a perfect reference standard.

Methods:

Study design:

A prospective cohort design was used to evaluate the performance of widely used traumatic brain injury surveillance case definitions from 1 January 2000 to 31 December 2014. For each individual, the first 2 years of person–time contribution after cohort entry was excluded to remove prevalent cases from the analysis. Individuals were followed until they were censored because of death or cohort exit. Suspected cases were removed from the at-risk pool when they met one of the traumatic brain injury case definitions described below. We identified the earliest date when an individual met a case definition. We then assessed whether any other definition was met within 7 days to allow for delayed claims related to the first injury to be ascertained. We used a 7-day window to allow us to ascertain additional case definitions that could be related to the incident case and capture the patterns of care that patients receive when they seek care for traumatic brain injury. However, we did not make this 7-day window larger to minimize the possibility of capturing recurrent cases, which are distinct from incident cases.[11]

Study population and data sources:

We used administrative health data from the Government of Quebec's Régie de l'assurance maladie du Québec (RAMQ). The Régie de l'assurance maladie du Québec collects administrative health data on physician claims and hospitalizations. We used these data for a 25% random sample of all Montreal Census Metropolitan Area residents in Quebec that were registered with the RAMQ from 1998 to 2014.[12] Over 99% of all Quebec residents are registered with this public insurance provider.[13] These data have previously been used to conduct traumatic brain injury epidemiologic research.[14] Physician claims data include an ICD diagnostic code, a medical act, and date of service. The physician claims use the ICD-9 coding system whereas the discharge abstract database uses the ICD-9 from 1998-2005 and the ICD-10 from 2006-2014.

Surveillance case definitions:

Traumatic brain injury surveillance conducted with administrative health data typically uses ICD codes to identify patients that meet a case definition. The Centers for Disease Control have developed a traumatic brain injury surveillance case definition using ICD-9 codes.[15] This definition has become popular across the literature as evidenced by its repeated use.[6,7,10] ICD-10 definitions for traumatic brain injury surveillance that are comparable to the ICD-9 definition codes have also been elaborated (eMethods 1).[7]

Using administrative health data from five sources (outpatient claims, emergency room claims, inpatient claims, hospitalization discharge abstract database, radiologic examination claims), we created a separate case definition for each data source (eFigure 1 and eMethods 1). The first four case definitions were based on ICD-coded traumatic brain injury diagnoses in administrative health data. For these four case definitions, a patient was classified as a suspected case if they were assigned at least one of the ICD-codes in the set during the corresponding type of encounter. The fifth case definition was not based solely on ICD codes; rather, we assessed whether patients had any diagnostic imaging exam of the head (computed tomography [CT] scan of the brain, MRI of the brain or skull X-Ray using RAMQ billing codes 08258, 08259, 08570, 08010, and 08013) within 1 day of having any ICD trauma diagnosis (ICD codes 8XX, 91X, 92X, 93X).[13,16] This last case definition is based on guidelines that recommend brain imaging in traumatic brain injury patients who have a higher risk of complications (hemorrhage, edema), but has not been typically used for surveillance purposes.[16,17] With five different data sources, there were 32 case definition response patterns that patients could have. All but one of the 32 response patterns were positive for at least one case definition and represented the patterns of care that patients may receive. One of the response patterns was negative for all case definitions and was used to identify patients that most likely did not incur an incident traumatic brain injury.

Statistical analysis:

We estimated traumatic brain injury incidence and the accuracy of the five aforementioned case definitions while adjusting for the inherent measurement error of each one using Hierarchical Bayesian Latent Class models.[18] Latent class analysis is a statistical method for probabilistically modeling variables that are not directly observable, such as the diagnosis and severity of traumatic brain injury (eFigure 1).[19,20] This statistical approach has previously been used to ascertain disease surveillance estimates while correcting for measurement error in administrative health data and to assess diagnostic test accuracy when only imperfect reference standards exist.[21] Our five observed case definitions are assumed to be imperfect measures of the underlying traumatic brain injury status. However, by having multiple overlapping sources of information on the diagnosis of traumatic brain injury, the model estimates the accuracy and adjusts for the inherent measurement error of each case definition without having to rely on a gold standard traumatic brain injury definition. A priori, we believed the unknown traumatic brain injury status could be expressed in four unobserved or latent classes representing the spectrum of injury severity: “No traumatic brain injury”, “Mildest traumatic brain injury”, “More severe traumatic brain injury”, or “Most severe traumatic brain injury”. The reasoning for clustering patients into these categories was based on the four types of medical settings where patients seek care for traumatic brain injury: no care, outpatient, emergency department, and inpatient settings. These care settings, or use of healthcare resources, are surrogates for the traumatic brain injury severity spectrum; the most severe cases typically have a high probability of being hospitalized and requiring brain imaging whereas the mildest cases tend to have a lower probability of the latter and a higher probability of seeking outpatient care. Consequently, each individual has a non-zero probability of being classified into one of four classes that depends on which case definitions they are positive for.

Our hierarchical approach allowed us to estimate yearly accuracy parameter and incidence, as well as more precise pooled estimates of these parameters across all years of the analysis.[18] To model sex-specific incidence, we allowed the incidence of each class to vary by sex using logistic regression (eMethods 2). The analysis was stratified by pediatric (<18 years), adult (18-64 years), and elderly (>=65 years) age groups because the incidence and performance of case definitions are expected to vary between these subgroups.[6] Individuals in the cohort contributed person-time as a child, adult, or elderly patient depending on their age group(s) during the follow-up period. We also estimated the sensitivity, specificity, positive predictive value, and negative predictive value for each case definition across all severity classes, such that these estimates could be used to conduct population-wide traumatic brain injury surveillance.[20] Lastly, we provided incidence estimates that would have been calculated if the typical traumatic brain injury ICD-based case definitions were used without adjusting for measurement error. We used normal hyperprior distributions with non-informative means and wide variances over all parameters (eMethods 2). All reported proportions (incidence and accuracy parameters) were calculated using the inverse logit transformation of these normally distributed parameters. We used the Gibbs sampler to estimate the posterior distributions using the likelihood and prior distributions of each parameter that was provided to Just Another Gibbs Sampler (JAGS).[22]

Model fit and convergence:

As above, we hypothesized that our data could model traumatic brain injury incidence in up to four classes. However, we still assessed the fit of two and three-class models using the deviance information criterion.[23] We also estimated the residual correlation between the case definitions to assess whether any conditional dependence exists between the case definitions, which is an assumption that must be met in latent class analysis to ensure inferences are not biased.[20,24] Residual pairwise correlation was verified for the pooled estimates to ensure that this latent class analysis assumption was not violated. When the assumption of conditional independence is met, these correlation residuals are randomly distributed around 0 (eMethods 3).[24] We also assessed model fit by comparing the observed and predicted agreement between pairs of tests across each age group and all years of the analysis (eMethods 4).[25] We used the posterior predictive distribution of our hierarchical Bayesian latent class models by sampling from their posterior distributions for each of the 15 years of the analysis and for each age group.[26] The probability that the observed agreement was greater than the predicted agreement was used to assess whether model fit was appropriate. [26] Finally, we ensured that the labeling of our aforementioned classes was appropriate by assessing whether the class-specific accuracy parameter estimates for each case definition were reasonable for the injury severity (class) they were representing.[20]

To ensure convergence of the model, we placed relatively non-informative constraints in the form of normal priors with constrained means and wide variances on 6 out of 20 accuracy parameters (eMethods 2). We conducted three sensitivity analyses that varied these constraints within a reasonable range, to assess whether our conclusions were robust to our choice of constraints (eMethods 5).

We conducted all analyses in JAGS called from R. Convergence was assessed by verifying the Gelman-Rubin statistic (<=1.1) and traceplots for each parameter. We sampled from the posterior distribution of model parameters by using three parallel Markov chain Monte Carlo simulations with 300,000 iterations after discarding the first 20,000. 95% credible intervals were reported from the highest posterior density intervals and means of the posterior distributions were reported as point estimates. We adhered to the STARD-BLCM guidelines for the reporting of this study.[27]

This study was approved by McGill University's Faculty of Medicine's Institutional Review Board.

Results:

From 2000-2014, 12,682,171 person–years were accrued across all age groups. The majority of radiologic imaging came from CT scans for all age groups (56% in children, 83% in adults, and 95% in the elderly). A higher proportion of adult/elderly individuals visited the emergency department for care in comparison to children who predominantly visited the outpatient setting (Table 1). We demonstrated that class-specific accuracy parameters were consistent with the labelling of each class that represents traumatic brain injury severity (eFigure 2). The four-class model had the lowest deviance information criterion and demonstrated adequate model fit using posterior predictive checks. Also, this model did not demonstrate any conditional dependence between any of the case definitions we used. As such, all of our inferences were drawn from the four-class model (eFigures 3 and 4; eTables 1 and 2).

Traumatic brain injury incidence:

The pooled traumatic brain injury incidence over the 15-year follow-up and across all severities was 76 (95% CrI 68 , 85) per 10,000 person–years after adjusting for measurement error. Incidence increased over the study period in adults and the elderly, whereas it decreased in children (Figure 1). Males had a higher incidence of traumatic brain injury across all classes and age groups except among the elderly where the female incidence was higher. More specifically, elderly females had a higher incidence for the more severe and mildest classes of traumatic brain injury. The incidence of individuals with the mildest traumatic brain injury decreased over time, whereas the incidence of individuals with more severe traumatic brain injury increased (eFigure 5).

For comparison, we also estimated the crude incidence using the ICD-based case definitions without adjusting for measurement error (eTable 3). When ICD-based case definitions are used, incidence is underestimated as 54 (95% CrI 54 , 55) per 10,000 person-years even when all case definitions are simultaneously used.

Surveillance case definition accuracy:

The accuracy of the five case definitions varied between children and adults (Table 2). In adults and the elderly, the radiologic imaging case definition had the highest sensitivity (0.48, 95% CrI 0.43 , 0.55 and 0.66, 95% CrI 0.54 , 0.79) to detect traumatic brain injury across the entire injury spectrum. In contrast, this case definition had a much lower sensitivity when used for children. For children, the emergency department claims case definition was the most sensitive (0.45, 95% CrI 0.39 , 0.52). Across the three age groups, the inpatient physician claim case definition tended to have the highest specificity (0.99, 95% CrI 0.99 , 1.00). The case definition with the highest positive predictive value was the radiologic examination for all age groups followed by the discharge abstract database and inpatient physician claims.

Secular trends in case definitions' performance over the 15-year study period were identified (Figures 2 and 3). For children, the sensitivity of radiologic examinations and outpatient physician claims progressively became less sensitive. For adults and the elderly, the sensitivity of the radiologic imaging case definition increased over the study period, whereas the sensitivity of the outpatient physician claim case definition decreased over time. The sensitivity of the emergency department claim case definition improved over time. The inpatient physician claim case definition did not follow any specific trend except in the elderly where from 2006-2008 there was a temporary drop in its specificity. For children, the specificity of emergency department physician claims started to decrease sharply as of 2009, but these estimates were imprecise. In adults and the elderly, the specificity of the discharge abstract database case definition started to decrease as of 2006.

Sensitivity analyses:

We allowed the priors on the accuracy parameters of the "mildest" class, which we used as constraints, to vary within reasonable ranges and we also forced the radiologic examination case definition to have the lowest specificity of the five case definitions we used. In these sensitivity analyses, traumatic brain injury incidence and the accuracy of case definitions were similar to the main analysis (eFigure 6).

Discussion:

We have provided an assessment of the performance of traumatic brain injury case definitions in administrative health data for surveillance across the full spectrum of severity, without relying on a gold standard case definition. The accuracy of these case definitions varies between age groups and over time. Adjusting for the imperfect accuracy of these case definitions allows stakeholders to accurately estimate traumatic brain injury incidence, which would otherwise be underestimated. These findings also have implications for validly identifying traumatic brain injury cases in administrative health data for epidemiologic research purposes.

Surveillance case definition performance in administrative health data

Previous studies have typically estimated the accuracy of traumatic brain injury surveillance case definition based on individuals seeking care in a single-care setting.[7] As such, these studies did not provide information on how surveillance case definitions perform across the entire injury spectrum. A systematic review on this topic demonstrated that similar ICD-9 surveillance case definitions to the one we assessed for emergency department visits had a sensitivity of 46% and a specificity of 98% when investigating patients solely seeking care in the emergency department.[7] However, when we evaluated the performance of the emergency department case definition to detect the full severity spectrum of cases, its sensitivity was lower since many patients are treated outside the emergency department. In contrast, the discharge abstract database and inpatient physician claim case definitions had the lowest sensitivity to detect traumatic brain injury across the full injury spectrum, since most cases are mild and seek outpatient or emergency department care.[28] Furthermore, our study demonstrates that the radiologic examination case definition, which is typically not used for surveillance purposes, is highly sensitive in the adult and elderly populations. In short, since most traumatic brain injury cases are treated in the emergency department, surveillance case definitions using emergency department physicians claims and radiologic examinations are the most sensitive, whereas case definitions covering the inpatient setting, representing more severe cases that are easier to diagnose, are the most specific.[9]

The traumatic brain injury literature has reiterated that standardized methods to conduct surveillance are required to have comparable injury burden estimates over time and across jurisdictions.[2,4] The accuracy estimates we provide can potentially be used to standardize estimates across jurisdictions and provides flexibility to stakeholders to use the data source(s) available to them and thereafter adjust for the measurement error inherent in those data. We also estimated that the positive predictive value of case definitions vary from 45% to 99%. This finding has important implications for epidemiologic research that uses administrative health data. Given that most studies use ICD-based case definitions to identify cases in administrative health data, many false positive cases are included, which limits the validity of inferences from such studies.

Measuring traumatic brain injury incidence in administrative health data

When administrative health data are used to conduct traumatic brain injury surveillance, there are substantial differences in estimates based on the type of data that are used. In jurisdictions where only hospitalizations are accounted for, incidence can vary from being less than 10 to greater than 60 per 10,000.[15,29] The estimates are higher when emergency department and outpatient visits are also included.[5] Even then, many investigators have emphasized that administrative health data may not be appropriate for conducting traumatic brain injury surveillance since they tend to produce underestimates of the true injury burden.[1,2] For example, a study that used a cohort design to estimate traumatic brain injury incidence in New Zealand demonstrated that the incidence is over 80 per 10,000 person–years, which is higher than the estimates typically reported using administrative health data.[5] This same research group also demonstrated that only 20% of incident cases were detected using administrative heath data in their jurisdiction.[3] We have demonstrated that this underestimation can be overcome by adjusting for measurement error in administrative health data.

Despite this measurement error, the epidemiologic characteristics of traumatic brain injury in the general population that we demonstrated in our study are consistent with other reports. Adults and the elderly tended to have a slight increase in incidence over time, related to more care sought in the emergency department, which is similar to other populations.[30] In children, incidence decreased over time. This trend has not been thoroughly investigated in children but is supported by studies that comprehensively assessed incidence across the full spectrum of care.[31] Our study once again demonstrates the bimodal age distribution of traumatic brain injury, where children and the elderly having the highest incidence.[15] We also demonstrate that males are at an overall higher risk of traumatic brain injury.[6] However, our study highlights that among the elderly females have a higher occurrence of traumatic brain injury. Although this finding is not consistent across all populations, other studies have shown similar trends.[30,32]

Recurrent traumatic brain injury is also an important contributor to the injury burden in the general population. Our study focused on incident traumatic brain injury because the determinants of and disability from recurrent traumatic brain injury are distinct from those of incident events.[11] Consequently, recurrent traumatic brain injury surveillance should be conducted and modeled separately from incident events in order to appropriately assess how much of the burden stems from recurrent events, which tends to be more disabling than first-time injuries. Furthermore, the accuracy of administrative health data to detect recurrent traumatic brain injury is likely to be different from incident cases; patients with incident traumatic brain injury oftentimes have follow-up care with physicians, which may be confused with cases of recurrence.[11] As such, further studies that use a similar approach to what we present in this study should be used for conducting surveillance of recurrent cases.

Secular trends and heterogeneity by age groups

The performance of case definitions changed over time in our study. For example, the sensitivity of radiologic examinations increased in adults and the elderly over time, whereas this case definition became less sensitive in children. These findings are likely related to changes in the use of CT scans of the head for traumatic brain injury, which were used more frequently in adults after clinical guidelines that supported their use were published in the early 2000s.[16] In contrast, the sensitivity of this case definition decreased for children after clinical decision rules were published that advocated for less imaging use in children to investigate traumatic brain injury.[17] The specificity of the claims related to hospitalization case definitions in adults and the elderly decreased as of 2005/2006, which is the same year the Government of Quebec developed a new policy that outlined indications for hospitalizing traumatic brain injury patients and when the discharge abstract database switched from the ICD-9 to the ICD-10 coding iterations.[33] These changes may have temporarily led to more false positive cases of traumatic brain injury in data sources that detect hospitalized cases, which could explain its lower specificity. Briefly, case definition accuracy changes over time, due to changes in clinical practice and health care policy, which should be considered when conducting surveillance.

Traumatic brain injury surveillance case definitions in administrative health data differ in performance across age groups. This heterogeneity probably reflects the distribution of traumatic brain injury severity and the type of care that is sought in different age groups. As previously mentioned, the most sensitive case definition was radiological imaging in adults and the elderly whereas emergency department physician claims were the most sensitive in children.[16,17] Moreover, outpatient physician visits were more sensitive in children and adults when compared to the elderly, likely because elderly patients have more severe injuries that require more involved care in the emergency department or inpatient setting.[34]

Limitations

Our study has several limitations. First, we used a cohort of Montreal residents to assess the accuracy of surveillance case definitions, which may not be generalizable to all populations and which may have different distributions of traumatic brain injury determinants and risk factors. However, several systematic reviews have demonstrated that the epidemiology of traumatic brain injury in developed countries is similar in terms of the distribution of severity.[6,10,31] Still, the approach we used to estimate incidence is applicable in other jurisdictions and can be used to accurately estimate incidence using administrative health data that are available to stakeholders. Second, we needed to rely on non-informative prior information and assumptions to complete the

Bayesian analysis. Nonetheless, the many sensitivity analyses we conducted based on varying assumptions demonstrated that the overall conclusions were robust. Third, the diversity of administrative health data we used to conduct this study may not be available in all jurisdictions where traumatic brain injury surveillance is conducted, limiting the use of certain case definition performance measures we provided. Still, we provided parameter estimates for all points of care that traumatic brain injury patients may use.

Conclusion:

Administrative health data remain an important resource for conducting traumatic brain injury surveillance given their low cost and ability to provide timely information. However, incidence estimates from these data should be adjusted for measurement error to avoid underestimating the injury burden. With such an approach, standardizing the assessment of this burden over time and across jurisdictions may be feasible. Finally, epidemiologic research using administrative health data to identify traumatic brain injury cases should account for the imperfect accuracy of case definitions to ensure valid inferences are provided.

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Tables and Figures for Manuscript 1

	Children (<18 years)	Adults (18-64 years)	Elderly (≥65 years)
Person–years of follow-up (2000-2014)			
Total	2,558,910	8,315,379	1,807,882
Male	1,290,218	4,110,863	760,891
Female	1,268,692	4,204,516	1,046,991
Case definitions (n)			
Outpatient claims	7,992	8,710	1,873
Emergency department claims	20,119	16,825	7,427
Inpatient claims	877	1,911	1,725
Discharge abstract database	1,657	2,697	2,934
Radiological imaging of the brain with a diagnosis of trauma	5,029	19,243	18,635
Adjusted pooled incidence (95% CrI) per 10,000 person-years from 2000-2014			
Class 2 ("Mildest traumatic brain injury")	33 (23 , 42) M:F 1.93 (1.77 , 2.13)	6.1 (3.5 , 8.7) M:F 0.92 (0.80 , 1.04)	2.8 (0.00 , 5.7) M:F 0.42 (0.01 , 1.15)
Class 3 ("More severe traumatic brain injury")	96 (62, 131) M:F 1.63 (1.47 , 1.86)	32 (27 , 37) M:F 1.45 (1.35 , 1.56)	141 (123 , 162) M:F 0.76 (0.72 , 0.79)
Class 4 ("Most severe traumatic brain injury")	5.7 (5.3 , 6.1) M:F 1.73 (1.46 , 1.98)	3.0 (2.7 , 3.2) M:F 2.71 (2.40 , 3.04)	10 (8.5 , 11) M:F 1.79 (1.56 , 2.05)
Incidence by age group	135 (102 , 171) M:F 1.71 (1.27 , 2.16)	41 (35 , 46) M:F 1.41 (1.32 , 1.51)	154 (134 , 175) M:F 0.79 (0.73 , 0.86)
Population incidence across all age groups		76 (68 , 85) M:F 1.22 (1.18 , 1.27)	

Table 1: Descriptive statistics of the study cohort used, stratified by three age groups. The pooled (across all years of analysis) traumatic brain injury incidence for each severity (class) is provided as well as a weighted overall incidence. All the incidence estimates reported are adjusted for

measurement error through the latent class modelling approach that was used. The male:female (M:F) incidence ratios are provided for each incidence measure reported. CrI indicates credible interval.

	Sensitivity (pooled) (95% CrI)	Specificity (pooled) (95% CrI)	Positive predictive value (pooled) (95% CrI)	Negative predictive value (pooled) (95% CrI)
Children				
Outpatient claim	0.14 (0.10 , 0.19)	0.9988 (0.9986 , 0.9990)	0.62 (0.54 , 0.70)	0.9884 (0.9850 , 0.9916)
ED claim	0.45 (0.39 , 0.52)	0.9982 (0.9969 , 0.9995)	0.78 (0.63 , 0.95)	0.9925 (0.9901 , 0.9949)
Inpatient claim	0.02 (0.02 , 0.03)	0.9999 (0.9999 , 0.9999)	0.92 (0.89 , 0.94)	0.9869 (0.9833 , 0.9901)
Discharge abstract database	0.04 (0.03 , 0.05)	0.9999 (0.9999 , 0.9999)	0.90 (0.85 , 0.94)	0.9871 (0.9835 , 0.9903)
Radiological examination of head	0.14 (0.11 , 0.17)	0.9999 (0.9999 , 0.9999)	0.94 (0.89 , 1.00)	0.9884 (0.9849 , 0.9915)
Adults				
Outpatient claim	0.13 (0.10 , 0.17)	0.9995 (0.9994 , 0.9996)	0.53 (0.42 , 0.64)	0.9964 (0.9959 , 0.9970)
ED claim	0.34 (0.30 , 0.39)	0.9993 (0.9992 , 0.9995)	0.69 (0.63 , 0.74)	0.9973 (0.9968 , 0.9978)
Inpatient claim	0.05 (0.04 , 0.05)	0.9999 (0.9999 , 0.9999)	0.81 (0.78 , 0.83)	0.9961 (0.9956 , 0.9967)
Discharge abstract database	0.05 (0.05 , 0.06)	0.9999 (0.9999 , 0.9999)	0.70 (0.63 , 0.76)	0.9961 (0.9956 , 0.9967)
Radiological examination of head	0.48 (0.43 , 0.55)	0.9997 (0.9995 , 0.9999)	0.86 (0.77 , 0.95)	0.9979 (0.9974 , 0.9983)
Elderly				
Outpatient claim	0.03 (0.02 , 0.04)	0.9994 (0.9992 , 0.9996)	0.45 (0.26 , 0.62)	0.9850 (0.9831 , 0.9870)
ED claim	0.21 (0.19 , 0.23)	0.9992 (0.9990 , 0.9994)	0.80 (0.75 , 0.86)	0.9878 (0.9861 , 0.9895)
Inpatient claim	0.05 (0.05 , 0.06)	0.9998 (0.9997 , 0.9999)	0.84 (0.77 , 0.91)	0.9854 (0.9833 , 0.9873)
Discharge abstract database	0.06 (0.05 , 0.08)	0.9995 (0.9993 , 0.9997)	0.68 (0.59 , 0.77)	0.9856 (0.9835 , 0.9875)
Radiological examination of head	0.66 (0.54 , 0.79)	0.9999 (0.9996 , 0.9999)	0.99 (0.96 , 0.99)	0.9947 (0.9921 , 0.9974)

Table 2: Pooled (across all years of analysis) performance measures of each case definition under investigation for each age group collapsed across the full injury spectrum. CrI = credible interval, ED = emergency department, PPV = positive predictive value, NPV = negative predictive values.

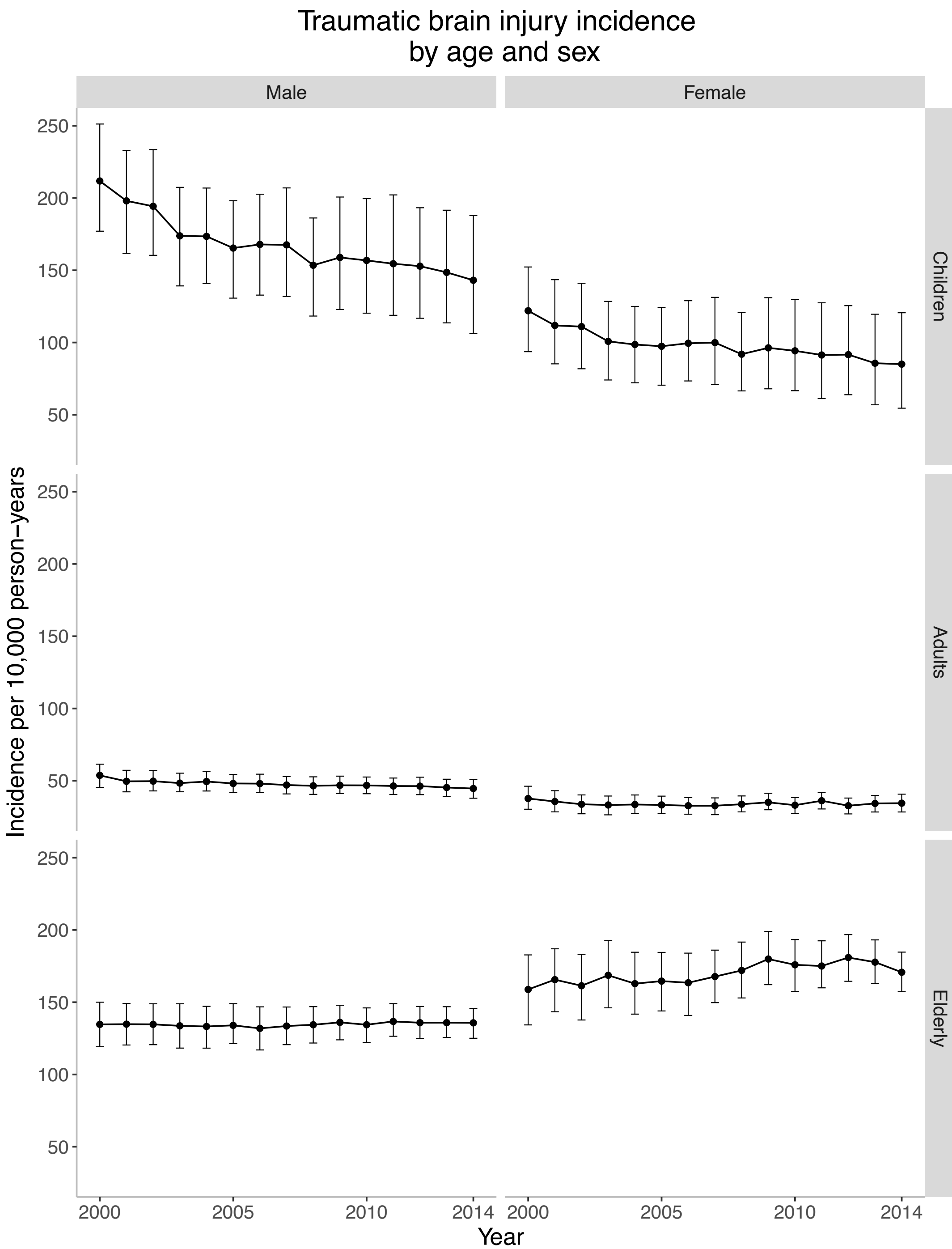


Figure 1: Trends over time in traumatic brain injury incidence across age groups and stratified by sex.

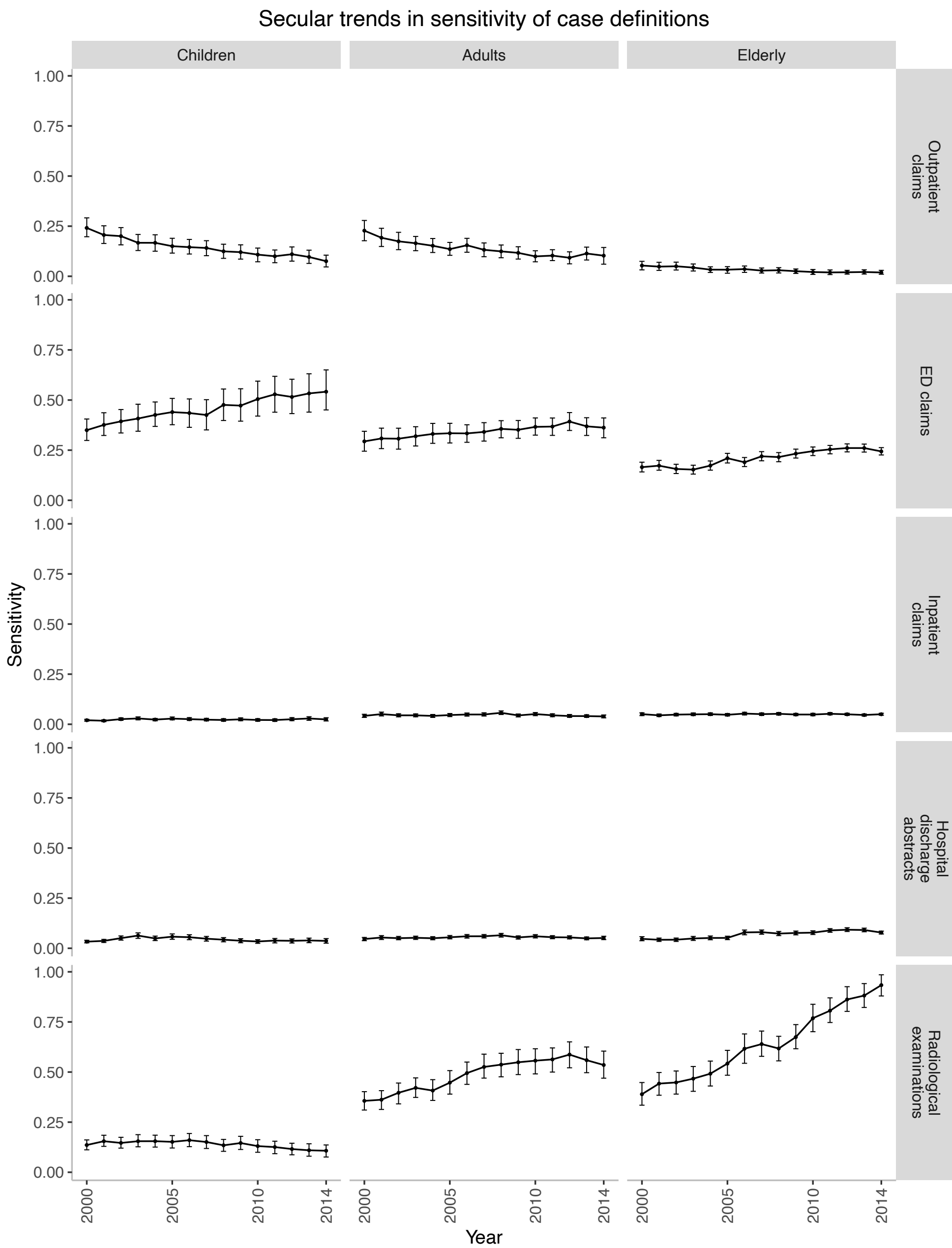


Figure 2: Secular trends in the sensitivity of each case definition from 2000 to 2014 for each age group. ED = emergency department.

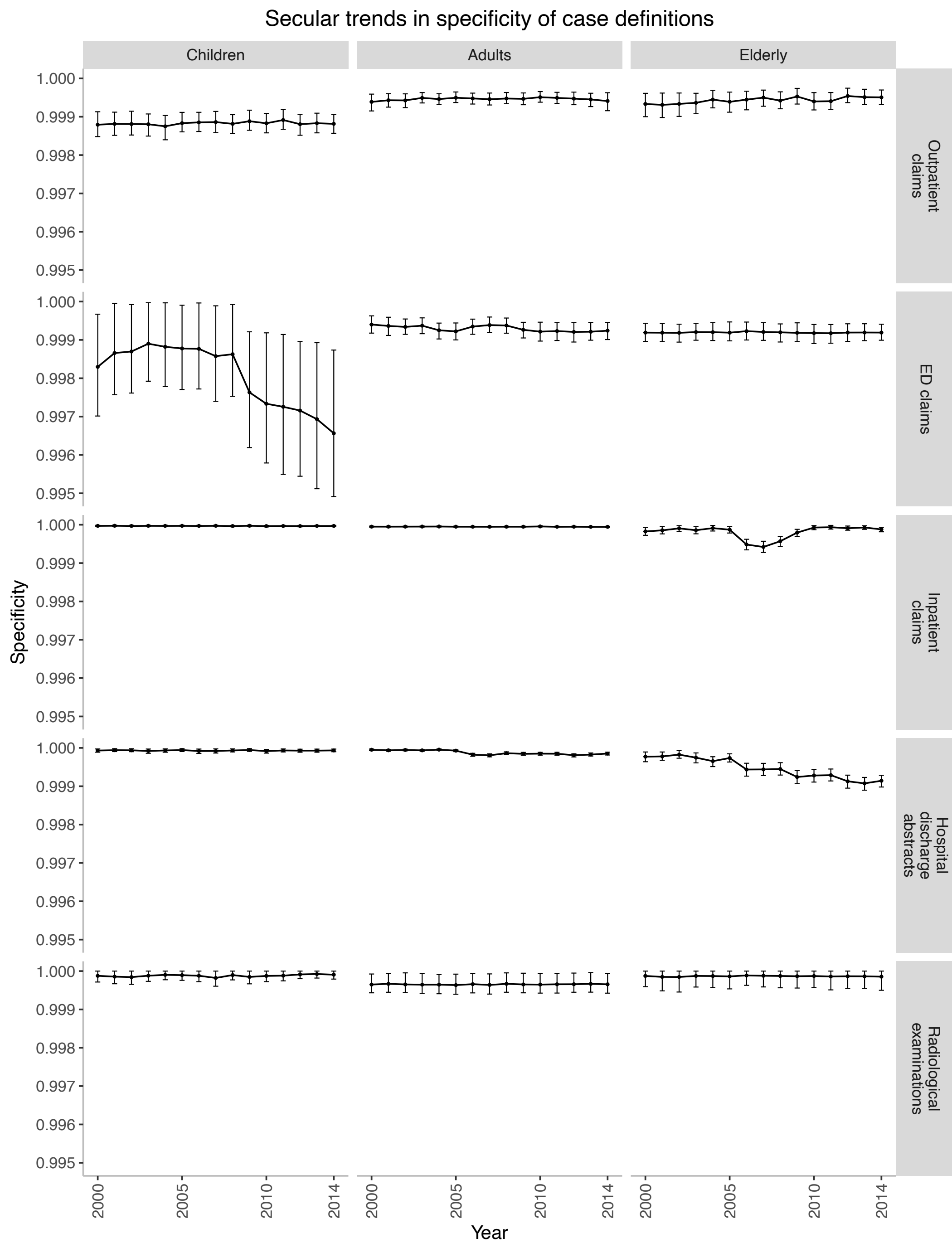


Figure 3: Secular trends in the specificity of each case definition from 2000 to 2014 for each age group. ED = emergency department

Supplementary digital content for Manuscript 1

eMethods 1: International Classification of Disease Codes and RAMQ procedure codes used to define the surveillance case definitions

Case definition	ICD-9	ICD-10*	RAMQ procedure code
Outpatient physician claim	800.X 801.X 803.X 804.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Emergency department claim	800.X 801.X 803.X 804.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Inpatient physician claim	800.X 801.X 803.X 804.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Hospitalization discharge abstract database	800.X 801.X 803.X 804.X 850.X-854.X 950.1 950.2 950.3 959.0	S01.X S02.1 S02.3 S02.7 S02.8 S02.9 S04.X S06.X S07.X S09.7 S09.8 S09.9 T02.0 T02.10 T04.0 T06.0 T90.X	N/A
Radiological exam of the head within 1 day of a claim for any trauma diagnosis	8XX 91X 92X 93X 94X 95X	N/A	08258 08259 08570 08010 08013

ICD codes used in the main analysis to identify traumatic brain injury. The ICD-9 codes are taken from the surveillance definition developed by the Centers for Disease Control, while the ICD-10 codes are taken from a systematic review identifying the commonly used ICD-10 case definitions for traumatic brain injury.[1,2] *The hospitalization discharge abstract case definition made use of the ICD-9 iteration from 2000-2005 and the ICD-10 iteration from 2006-2014. The radiological exam of the head case definition was defined as patients that had a head imaging claim by a radiologist within 1 day of having a traumatic brain injury diagnosis claim by another physician.[3] ICD = International classification of disease, RAMQ = Régie de l'assurance maladie du Québec.

eMethods 2: Model specification for 4-class latent class analysis

The hierarchical Bayesian latent class model we used in the analysis is described below. The lower level of the hierarchy was used to model the year-specific parameters, while the higher level of the hierarchy was used to pool together the year-specific estimates to obtain more accurate estimates through a borrowing-of-strength approach. By using a hierarchical model, we were able to obtain year-specific incidence and accuracy parameters without having to assume a specific functional form on how the parameters would change over time, such that we could identify secular trends in traumatic brain injury incidence and the accuracy of case definitions. We adapted our work to models that were previously developed in similar contexts.[4,5]

Regarding the lower level of the hierarchy, there were 32 possible case definition response patterns to the p=5 case definitions ($2^p = 2^5 = 32$). Since our analysis allows traumatic brain injury incidence to vary by sex, the number of responses is actually 64 since there are 32 possible responses for each sex. The latent class analysis models the probability of having a response vector $T_i = 1 \ldots 64$ to the $p = 1 \ldots 5$ case definitions used in the model for each year $j = 1 \ldots 15$ of analysis. The count (n_{ij}) of individuals in each combination of responses in each year is modelled with a multinomial distribution where N_j is the total count of person-years contributed in the j^{th} year of the analysis. For latent classes, k (as defined below), were used in this analysis. T_{ipj} represents the case definition response (binary – 1 or 0) of the p^{th} case definition for the i^{th} case definition response pattern in the j^{th} year. L_{ikj} represents each latent class k of the i^{th} case definition response pattern in the j^{th} year. The year and class-specific accuracy parameters (which are the class-specific probability of being positive or negative for the p^{th} case definition and i^{th} case definition response pattern in the j^{th} year – $P\left(T_{ipj} \middle| L_{ikj}\right)$) are represented in the lower level of the hierarchical model and provide year-specific accuracy estimates of each case definition for each latent class. In other words, $P\left(T_{ipj} = 1 \middle| L_{ikj}\right)$ is the class-specific sensitivity (for the k^{th} class) of the p^{th} case definition in the j^{th} year. $P\left(T_{ipj} = 0 \middle| L_{ikj}\right)$ is the specificity of the p^{th} case definition in the j^{th} year when k = 1 (the "no traumatic brain injury" or non-injured class).

The year and class-specific incidence of traumatic brain injury, $P(L_{ikj} = k)$, is allowed to vary by sex through a logistic regression model shown below. The α_male_{kj} and β_female_{kj} parameters are year and class-specific parameters in the logistic regression model that allow the year-specific and class-specific incidence, $P(L_{ikj} = k)$, to vary by sex. $female_i$ is an indicator variable identifying whether a pattern of case definitions is for females (1) or males (0). As such, α_male_{kj} is the intercept of the regression model and represents the year and class-specific incidence for males, and β_female_{kj} allows this male-specific incidence to vary for females ($\alpha\_male_{kj} + \beta\_female_{kj}$ would represent the incidence for females in the k^{th} class for the j^{th} year).

For each year of the analysis there were a total of 26 parameters estimated in the lower level of the hierarchy (20 accuracy parameters, 3 incidence parameters for males, and 3 incidence parameters that allow incidence to vary for females). These parameters were all sampled from normal distributions of their hyperparameters at the higher level of the hierarchy.

Observed data:

p=1 = outpatient physician claims
p=2 = emergency department claims
p=3 = inpatient claims
p=4 = traumatic brain injury diagnosis in discharge abstract database
p=5 = radiological examination of the head in the context of any other traumatic injury

k=1 = class 1 (No traumatic brain injury)
k=2 = class 2 (Mildest traumatic brain injury)
k=3 = class 3 (More severe traumatic brain injury)
k=4 = class 4 (Most severe traumatic brain injury)

n_{ij}, where *i* represents 1…64 possible case definition response patterns (represented by vector T_i as above) in a contingency table for each sex (total of 32 case definition response patterns for each sex = 32*2 = 64 possible case definition response patterns). N_j represents the total number of individuals across all case definition response patterns for a given year *j*.

Lower level of the hierarchy (year-specific estimates):

Parameters in the lower level of the hierarchy:

Year-specific accuracy parameters for each case definition p in each latent class k (logit transformed):

$$logit\left(P\left(T_{ipj}=1\middle|L_{ikj},\mu_{pk},\sigma_{pk}\right)\right) \sim N(\mu_{pk},\sigma_{pk})$$

$$\left(T_{ipj}=0\middle|L_{ikj},\mu_{pk},\sigma_{pk}\right)=1-\left(T_{ipj}=1\middle|L_{ikj},\mu_{pk},\sigma_{pk}\right)$$

Class and year-specific sensitivity = $P\left(T_{ipj}=1\middle|L_{ikj},\mu_{pk},\sigma_{pk}\right)$

Year-specific specificity = $P\left(T_{ipj}=0\middle|L_{i1j},\mu_{p1},\sigma_{p1}\right)$

Year-specific probability of being in a specific latent class (K_j) given a specific case definition response pattern:

$$P\left(L_{ikj}=K_j \mid T_{ij}\right)=\frac{P\left(L_{ikj}\right)\prod_{p=1}^{P}P\left(T_{ipj}\middle|L_{ikj}\right)}{\sum_{k=1}^{K}P\left(L_{ikj}\right)\prod_{p=1}^{P}P\left(T_{ipj}\middle|L_{ikj}\right)}$$

Class-specific (severity-specific) and year-specific incidence collapsed across males and females:

$$Incidence\ of\ Class\ K_j = \frac{\sum_{i=1}^{64} P\left(L_{ikj} = K_j \middle| T_{ij}\right) * n_{ij}}{N_j}$$

Logistic regression to model variability in year-specific incidence by sex:

$$logit(P\left(L_{ikj}\right)) = \ \alpha\_male_{kj} +\ \beta\_female_{kj} * female_i\ (for\ k\ 2,3,4)$$
$$P\left(L_{i1j}\right) = 1 - P\left(L_{i2j}\right) - P\left(L_{i3j}\right) - P\left(L_{i4j}\right)$$

$$\alpha\_male_{kj}|l_k, \sigma_{mk} \sim normal(l_k, \sigma_{mk})$$
$$\beta\_female_{kj}|f_k, \sigma_{fk}\ \sim normal(f_k, \sigma_{fk})$$

<u>Likelihood for the latent class model:</u>

$$P\left(T_{ij}\right) = \sum_{k=1}^{K} P(L_{ikj}) \prod_{p=1}^{P} P\left(T_{ipj} \middle| L_{ikj}\right)$$

$$Likelihood\ \propto \prod_{j=1}^{15} \prod_{i=1}^{64} P\left(T_{ij}\right)$$

$$n_{ij}|T_{ij}, N_j \sim multinomial\ (P(T_{ij}), N_j)$$

As mentioned above, a second (higher) level of the hierarchy pools the class-specific accuracy and incidence parameters across the 15 (*j*) years of analysis, which allows for a borrowing of strength to achieve more precise estimates. The higher-level hyperparameters of the hierarchical model are presented below where pooling of year-specific (j^{th}) estimates for the class-specific $P\left(T_{ipj} \middle| L_{ikj}\right)$ accuracy parameters, the class-specific α_male_{kj} parameters, and the class-specific β_female_{kj} parameters occurs. In other words, these lower-level parameters were drawn from a normal distribution of their respective hyperparameters, where the means of these normal distributions (u_{pk}, l_k, and f_k) are the logit transformation of their hyperparameter and their standard deviation is a heterogeneity parameter as defined below (σ_{pk}, σ_{mk}, and σ_k). Since the hyperparameters are all proportions, it was necessary to take their logit transformation in order to transform them to parameters on a continuous scale that are bounded from [-∞,∞]. Thereafter, the inverse logit transformation was used to convert them back to proportions (u'_{pk}, l'_k, and f'_k). μ'_{pk} represents the mean of the pooled accuracy parameter (across all years of the analysis) for each case definition in each of the 4 latent classes. l'_k represents the mean of the pooled incidence parameter (across all years of the analysis) for each of the 4 latent classes. f'_k represents the mean of the pooled incidence variation parameter (across all years of the analysis) for females for each of the 4 latent classes (in other words, f'_k represents the difference in incidence between males and females).

The prior distributions (or hyperpriors) for this Bayesian analysis were on the higher-level parameters (or hyperparameters). The hyperprior distributions for the heterogeneity parameters (σ_{pk}, σ_{mk}, and σ_k) were selected as $uniform(0,2)$ since this represents non-informative prior distributions for heterogeneity parameters of incidence and accuracy. These heterogeneity hyperprior distributions are non-informative since a variation of 0 to 2 on the logit scale allows the proportions to vary widely from year to year, which is unlikely for the accuracy and incidence parameters (proportions) that we are estimating. A total of 26 heterogeneity parameters were used, one for each parameter described in the lower level of the hierarchy. For each yearly incidence we used non-informative priors based on incidence estimates in the literature.[6–8] For the class-specific accuracy parameters (u'_{pk}) we used non-informative hyperprior distributions except for 6 out of the 20 accuracy hyperparameters ($P\left(T_{ip}\middle|L_{ik}\right)$), where relatively non-informative constraints were placed to ensure model convergence and avoid label switching of the latent class model (see "Constraints/assumptions" section below). By specifying the priors and likelihood of our model in JAGS, the posterior distribution of each parameter was estimated using the Gibbs sampler.[9]

Higher level of the hierarchy (pooled estimates across all years of the analysis):

Hyperparameters in the higher level of the hierarchy:

Class-specific accuracy parameters (20 hyperparameters) – $\mu'_{pk} = P\left(T_{ip}\middle|L_{ik}\right)$

Class-specific incidence parameter for males (3 hyperparameters) - l'_k

Class-specific incidence variation parameter for females (3 hyperparameters) - f'_k

Heterogeneity parameters for male incidence, incidence variation parameter for females, and accuracy parameters that allow these parameters to vary by year of analysis (26 hyperparameters) - $\sigma_{mk}, \sigma_{fk},$ *and* σ_{pk}*, respectively.*

Hyperprior distributions on hyperparameters:

Hyperprior distributions on heterogeneity hyperparameters used for pooling of year-specific estimates:

$$\sigma_{fk} \sim uniform(0,2)$$
$$\sigma_{mk} \sim uniform(0,2)$$
$$\sigma_{pk} \sim uniform(0,2)$$

Hyperprior distributions on class-specific incidence hyperparameters for males:

$$P(l'_2) \sim uniform\ (0,0.02)$$
$$P(l'_3) \sim uniform\ (0,0.02)$$
$$P(l'_4) \sim uniform\ (0,0.005)$$

$$P(l'_1) = 1 - P(l'_2) - P(l'_3) - P(l'_4)$$
$$l_k = logit(l'_k)$$

$$incidence\ in\ males_k = l'_k$$

Hyperprior distribution for hyperparameter that allows class-specific incidence to vary in females in comparison to males:

$$f'_k \sim uniform(0,1)$$
$$f_k = logit(f'_k)$$

$$incidence\ in\ females_k = inverse\ logit(l_k + f_k)$$

Hyperprior distribution on accuracy hyperparameters (specific constraints outlined below):

$$\mu'_{pk} \sim uniform(0,1)$$
$$\mu_{pk} = logit(\mu'_{pk})$$

Constraints/assumptions:

Since label switching can lead to non-convergence of latent class models, we imposed constraints in the form of relatively non-informative prior distributions.[10] Briefly, in the 4-class model we forced the hospitalization case definition to have an accuracy of at least 0.5 ($u'_{44} \sim uniform(0.5, 1)$ within the "most severe" class (Class 4). For the "mildest" class (Class 2) we forced the outpatient claim case definition to have an accuracy of at least 0.5 ($u'_{12} \sim uniform(0.5, 1)$ and the four other case definitions to have a maximum accuracy of 0.25 ($u'_{p=2\ldots5,k=2} \sim uniform(0, 0.25)$. These constraints were used to "label" the classes appropriately to avoid non-convergence. These constraints indicate that the sensitivity of the discharge abstract database case definition to identify the "most severe" traumatic brain injury patients and the outpatient physician claims case definition to identify the "mildest" traumatic brain injury patients is at least 50%, whereas the four other case definitions have a maximum sensitivity of 25% to identify the "mildest" traumatic brain injury patients. This prior information is supported by previous literature investigating the accuracy of these parameters.[11,12]

The constraints we used on 6 of the lower and higher hierarchical accuracy parameters to avoid label switching and improve the efficiency of convergence are as follows:

$$\mu'_{44} \sim uniform(0.5,1)$$
$$\mu'_{12} \sim uniform(0.5,1)$$
$$\mu'_{22} \sim uniform(0,0.25)$$
$$\mu'_{32} \sim uniform(0,0.25)$$

$$\mu'_{42} \sim uniform(0,0.25)$$
$$\mu'_{52} \sim uniform(0,0.25)$$

$$P\left(T_{i4j} \middle| L_{4j}\right) \sim N(logit(\mu'_{44}), \sigma_{44}) \text{ Truncated } (0,)$$
$$P\left(T_{i1j} \middle| L_{2j}\right) \sim N(logit(\mu'_{12}), \sigma_{12}) \text{Truncated } (0,)$$
$$P\left(T_{i2j} \middle| L_{2j}\right) \sim N(logit(\mu'_{22}), \sigma_{22}) \text{ Truncated } (,-1)$$
$$P\left(T_{i3j} \middle| L_{2j}\right) \sim N(logit(\mu'_{32}), \sigma_{32}) \text{ Truncated } (,-1)$$
$$P\left(T_{i4j} \middle| L_{2j}\right) \sim N(logit(\mu'_{42}), \sigma_{42}) \text{ Truncated } (,-1)$$
$$P\left(T_{i5j} \middle| L_{2j}\right) \sim N(logit(\mu'_{52}), \sigma_{52}) \text{ Truncated } (,-1)$$

Derived parameters:

Using simple algebraic manipulations, it is possible to assess the sensitivities, specificities, positive predictive values and negative predictive values for each case definition *p* across all latent classes and years of analysis. N_{iT} and N_t represent the total number of person-years for each response pattern and the total amount of person-years for entire population under study across the entire follow-up period (not year-specific as we had in the lower level of the hierarchy), respectively.

Probability of being in a specific class given a case definition response pattern:

$$P(l'_{ik} = K|\, T_i) = \frac{P(l'_{ik}) \prod_{p=1}^{P} P\left(T_{ip} \middle| l'_{ik}\right)}{\sum_{k=1}^{K} (l'_{ik}) \prod_{p=1}^{P} P\left(T_{ip} \middle| l'_{ik}\right)}$$

Class-specific incidence pooled across all years of the analysis and for both sexes:

$$Incidence\ of\ Class\ K = Inc_k = l'_k = \frac{\sum_{i=1}^{64} P(l'_{ik} = K|T_i) * N_{iT}}{N_T}$$

$$Total\ incidence = Inc_T = \sum_{k=1}^{K} l'_k$$

Pooled accuracy parameters across all years of the analysis for each of the p case definitions:

$$Sensitivity_p = \frac{Inc_2 * \mu'_{p2} + Inc_3 * \mu'_{p3} + Inc_4 * \mu'_{p4}}{Inc_2 + Inc_3 + Inc_4}$$

$$Specificity_p = 1 - \mu'_{p1}$$

$$PPV_p = \frac{Sensitivity_p * Inc_T}{Sensitivity_p * Inc_T + (1 - Specificity_p)(1 - Inc_T)}$$

$$NPV_p = \frac{Specificity_p * (1 - Inc_T)}{(1 - Sensitivity_p) * Inc_T + (Specificity_p)(1 - Inc_T)}$$

eMethods 3: Residual correlation analysis

Pairwise residual correlation between two case definitions (p and q) as described in Qu et al. [13]:

$$Residual\ pairwise\ correlation_{pq} = Observed\ correlation_{pq} - Expected\ correlation_{pq}$$

$$Correlation_{pq} = \frac{P(Y_p = 1, Y_q = 1) - \mu_p\mu_q}{\sqrt{\mu_p(1-\mu_p)\mu_q(1-\mu_q)}}$$

<u>Observed correlation:</u>

$$\mu_p = \frac{1}{N}\sum_{j=1}^{15} y_{pn}$$
$$\mu_q = \frac{1}{N}\sum_{j=1}^{15} y_{qn}$$
$$P(Y_p = 1, Y_q = 1) = \frac{1}{N}\sum_{j=1}^{15} y_{pn}\, y_{qn}$$

$where\ j\ is\ each\ year\ of\ the\ analysis, N\ is\ the\ total\ size\ of\ the\ population\ for\ the\ 15\ years\ of\ the\ study\ period, and\ y_{pn}, y_{qn}\ are\ the\ total\ counts\ of\ individuals\ positive\ for\ a\ given\ case\ definition\ in\ a\ given\ year.$

<u>Expected correlation:</u>

$$\mu_p = \sum_{k=1}^{4} l'_k \mu'_{pk}$$
$$\mu_q = \sum_{k=1}^{4} l'_k \mu'_{qk}$$
$$P(Y_p = 1, Y_q = 1) = \sum_{k=1}^{4} l'_k \mu'_{pk} \mu'_{qk}$$

$where\ l'_k, \mu'_{pk}, and\ \mu'_{qk}\ are\ as\ described\ in\ eMethods\ 2, and\ K\ represents\ each\ of\ the\ 4\ latent\ classes.$

N.B.: The residual correlation was estimated only for the pooled parameters (upper level of the hierarchy) from the main analysis.

eMethods 4: Model fit using the posterior predictive distribution

Discrepancy measures to assess model fit such as the χ^2 statistic and the likelihood ratio have been previously shown to be inappropriate to assess model fit of latent class models.[14] As such, we conducted posterior predictive checks that compared the observed and predicted agreement between pairs of tests, pq as has been demonstrated previously.[5,15] We drew 3000 samples from the posterior predictive distribution of the higher-level of the hierarchy to simulate predictions of the counts, $n.new$, of each of the 32 case definition response patterns for each sex (a total of T_i = 64 response patterns).[14] We also used the observed counts for each of case definition response patterns, n, to estimate the observed agreement between each of the case definition pairs. The observed and expected agreement between pairs of tests, (pq), was estimated as detailed below. We then estimated the probability that the observed agreement would be greater than the predicted agreement within the 3000 samples that were drawn for each pair of tests $(P(Observed\ agreement_{pq})\ > P(Predicted\ agreement_{pq}))$, which is also known as a Bayesian p-value.[15] When these probabilities are close to 0 or 1 there is evidence to suggest that model fit may be inappropriate. We conducted this analysis for each age group as shown in eTable 2.

A similar analysis was conducted on year-specific estimates from the lower level of the hierarchical model. 150 different comparisons (10 comparisons per year of analysis, for j = 15 years of analysis) need to be made for each age group (children, adults and elderly). For brevity, we only provided the probabilities of the observed versus predicted agreement between tests (Bayesian p-value) across all years and age groups of analysis (eFigure 1). When these probabilities are very close to 0 or 1, there may be evidence that model fit is inappropriate.

$$Predicted\ agreement_{pq} = \frac{\sum_{i=1}^{64} n.new_i * (T_{ip}T_{iq} + \left(1 - T_{ip}\right)\left(1 - T_{iq}\right))}{\sum_{i=1}^{64} n.new_i}$$

$$Observed\ agreement_{pq} = \frac{\sum_{i=1}^{64} n_i * (T_{ip}T_{iq} + \left(1 - T_{ip}\right)\left(1 - T_{iq}\right))}{\sum_{i=1}^{64} n_i}$$

eMethods 5: Prior information used in the three sensitivity analyses

We conducted 2 sensitivity analyses by varying the values of the priors used as constraints within a reasonable range to ensure that our selection of prior information did not change the overall conclusions of the main analysis. Since little information is known on the accuracy of the radiological examination case definition, we conducted a third sensitivity analysis where we forced this case definition to be the least specific by ordering the prior values of the uninjured class (Class 1 – "No traumatic brain injury") in such a way that the radiological examination case definition had the lowest specificity. In doing so, we assessed the robustness of our results based on the a priori assumption that this case definition would be sensitive but less specific than the others.[16]

Sensitivity analysis 1: The sensitivity of discharge abstract database to identify hospitalized traumatic brain injury and sensitivity of outpatient physician claims to identify "mildest traumatic brain injury" are at least 25%.

$$\mu'_{44} \sim uniform(0.25,1)$$
$$\mu'_{12} \sim uniform(0.25,1)$$
$$\mu'_{22} \sim uniform(0,0.25)$$
$$\mu'_{32} \sim uniform(0,0.25)$$
$$\mu'_{42} \sim uniform(0,0.25)$$
$$\mu'_{52} \sim uniform(0,0.25)$$

$$P\left(T_{i4j}\middle|L_{4j}\right) \sim N(logit(\mu'_{44}), \sigma_{44}) \text{ Truncated (-1,)}$$
$$P\left(T_{i1j}\middle|L_{2j}\right) \sim N(logit(\mu'_{12}), \sigma_{12}) \text{Truncated (-1,)}$$
$$P\left(T_{i2j}\middle|L_{2j}\right) \sim N(logit(\mu'_{22}), \sigma_{22}) \text{ Truncated (,-1)}$$
$$P\left(T_{i3j}\middle|L_{2j}\right) \sim N(logit(\mu'_{32}), \sigma_{32}) \text{ Truncated (,-1)}$$
$$P\left(T_{i4j}\middle|L_{2j}\right) \sim N(logit(\mu'_{42}), \sigma_{42}) \text{ Truncated (,-1)}$$
$$P\left(T_{i5j}\middle|L_{2j}\right) \sim N(logit(\mu'_{52}), \sigma_{52}) \text{ Truncated (,-1)}$$

Sensitivity analysis 2: The sensitivity of the emergency department physician claims, inpatient physician claims, discharge abstract database and radiological examination are up to 50% to detect "mildest traumatic brain injury".

$$\mu'_{44} \sim uniform(0.5,1)$$
$$\mu'_{12} \sim uniform(0.5,1)$$
$$\mu'_{22} \sim uniform(0,0.5)$$
$$\mu'_{32} \sim uniform(0,0.5)$$
$$\mu'_{42} \sim uniform(0,0.5)$$
$$\mu'_{52} \sim uniform(0,0.5)$$

$$P\left(T_{i4j}\middle|L_{4j}\right) \sim N(logit(\mu'_{44}), \sigma_{44}) \text{ Truncated } (0,)$$
$$P\left(T_{i1j}\middle|L_{2j}\right) \sim N(logit(\mu'_{12}), \sigma_{12}) \text{Truncated } (0,)$$
$$P\left(T_{i2j}\middle|L_{2j}\right) \sim N(logit(\mu'_{22}), \sigma_{22}) \text{ Truncated } (,0)$$
$$P\left(T_{i3j}\middle|L_{2j}\right) \sim N(logit(\mu'_{32}), \sigma_{32}) \text{ Truncated } (,0)$$
$$P\left(T_{i4j}\middle|L_{2j}\right) \sim N(logit(\mu'_{42}), \sigma_{42}) \text{ Truncated } (,0)$$
$$P\left(T_{i5j}\middle|L_{2j}\right) \sim N(logit(\mu'_{52}), \sigma_{52}) \text{ Truncated } (,0)$$

Sensitivity analysis 3: The specificity of the case definitions in the physician claims database are ordered in such a way that the radiological examination case definition has the lowest specificity. We assumed that the inpatient physician claims had the highest specificity, followed by the emergency department and outpatient physician claims based on the fact that higher-severity traumatic brain injury is easier to diagnose than lower severity traumatic brain injury.[17]

$$P\left(T_{ip}\middle|L_1\right) = \mu'_{p1} \text{ such that,}$$

$$(1 - \mu'_{31}) > (1 - \mu'_{21}) > (1 - \mu'_{11}) > (1 - \mu'_{51})$$

eTable 1: Observed and expected counts by case definition response pattern

Case definition response pattern					Children		Adults		Elderly	
Outpatient claim	Emergency department claim	Inpatient claim	Discharge abstract database	Radiological examination of the head	Observed	Expected	Observed	Expected	Observed	Expected
-	-	-	-	-	2,528,467	2,529,023	8,276,839	8,277,425	1,783,001	1,783,142
-	-	-	-	+	1,885	1896	10,682	10,671	12,815	13,247
-	-	-	+	-	362	332	940	868	1,142	1,012
-	-	-	+	+	156	146	523	473	588	485
-	-	+	-	-	105	101	450	444	457	384
-	-	+	-	+	61	36	369	290	324	334
-	-	+	+	-	81	80	35	39	53	24
-	-	+	+	+	144	164	418	519	295	306
-	+	-	-	-	17,519	17,277	10,347	10,307	2,994	3,054
-	+	-	-	+	1,220	1,234	5,095	5,069	3,344	3,167
-	+	-	+	-	243	229	47	46	39	52
-	+	-	+	+	224	218	250	301	373	284
-	+	+	-	-	32	35	49	48	23	35
-	+	+	-	+	31	53	111	185	132	202
-	+	+	+	-	124	120	27	25	11	24
-	+	+	+	+	264	248	433	330	418	330
+	-	-	-	-	6,620	6,326	7,175	6,834	1,496	1402
+	-	-	-	+	884	922	1,048	1,021	272	284
+	-	-	+	-	4	6	3	4	3	4
+	-	-	+	+	8	7	7	6	2	6
+	-	+	-	-	3	3	5	5	1	3
+	-	+	-	+	1	2	4	5	4	4
+	-	+	+	-	2	4	0	0	0	0
+	-	+	+	+	8	8	2	5	2	2
+	+	-	-	-	306	320	164	227	27	32
+	+	-	-	+	116	83	288	216	58	54

+	+	-	+	-	8	5	0	1	0	1
+	+	-	+	+	11	10	6	4	3	2
+	+	+	-	-	1	1	0	2	0	0
+	+	+	-	+	2	3	2	3	0	2
+	+	+	+	-	4	6	1	0	0	0
+	+	+	+	+	14	12	5	3	5	2
Deviance information criterion (4 classes)					3929		5180		49967	
Deviance information criterion (3 classes)					4870		5305		49964	
Deviance information criterion (2 classes)					7252		8738		52053	

Observed and expected counts of individuals in all 32 different combinations of case definition responses collapsed across males and females for the 4-class model. The Deviance Information Criterion for each 2, 3 and 4-class analyses is provided for the models used for each analysis in each age group.

eTable 2: Model fit of higher level of the hierarchical model (pooled across all years) using posterior predictive checks to compare observed and predicted agreement between pairs of case definitions

	Children			Adults			Elderly		
Case definition pair (*pp'*)	**Observed agreement**	**Predicted agreement**	**Pr (O > P)**	**Observed agreement**	**Predicted agreement**	**Pr (O > P)**	**Observed agreement**	**Predicted agreement**	**Pr (O > P)**
1,2	0.9894	0.9895	0.55	0.9970	0.9971	0.60	0.9950	0.9951	0.72
1,3	0.9966	0.9967	0.71	0.9987	0.9988	0.66	0.9980	0.9981	0.70
1,4	0.9963	0.9964	0.72	0.9986	0.9987	0.68	0.9974	0.9976	0.89
1,5	0.9957	0.9958	0.65	0.9970	0.9970	0.57	0.9890	0.9891	0.50
2,3	0.9922	0.9922	0.53	0.9979	0.9979	0.53	0.9956	0.9957	0.76
2,4	0.9922	0.9922	0.51	0.9978	0.9978	0.52	0.9952	0.9954	0.76
2,5	0.9916	0.9916	0.52	0.9971	0.9972	0.52	0.9904	0.9901	0.36
3,4	0.9995	0.9995	0.73	0.9996	0.9996	0.69	0.9983	0.9984	0.89
3,5	0.9981	0.9981	0.49	0.9978	0.9978	0.52	0.9900	0.9901	0.48
4,5	0.9980	0.9980	0.52	0.9978	0.9978	0.54	0.9899	0.9898	0.47

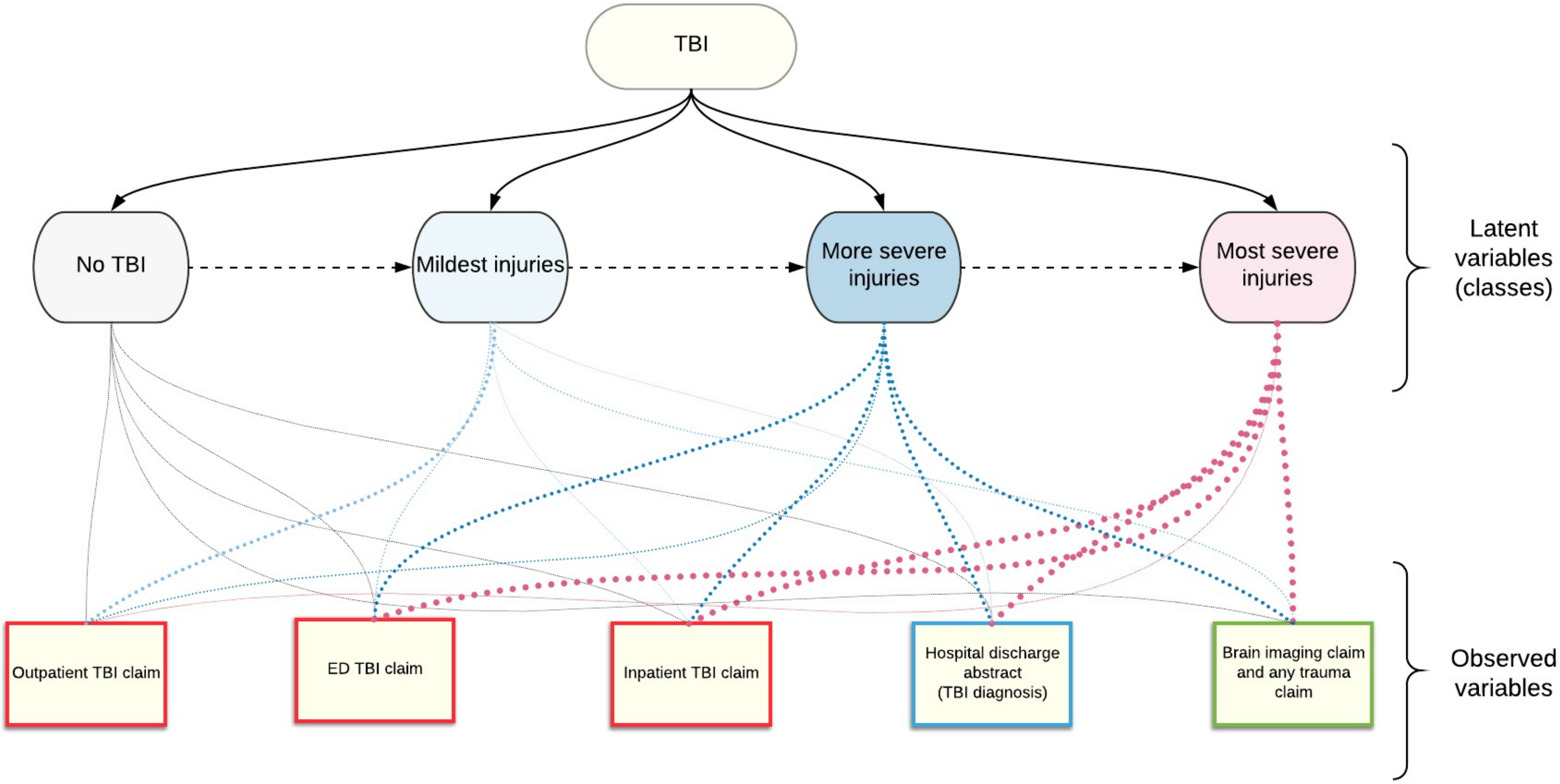
Model fit assessing the observed and predicted agreement between pairs of case of definitions pooled across all years of the analysis. The probability that the observed agreement is greater than the predicted agreement between pairs of case definitions is used to assess whether or not model fit is appropriate.[14] When probabilities are close to 0 or 1, then model fit may be inappropriate (eMethods 4). The pairs of case definitions are as defined in eMethods 2: 1 = outpatient physician claim, 2 = emergency department physician claim, 3 = inpatient physician claim, 4 = discharge abstract database, 5 = radiological examination of the head with a diagnosis of trauma. Pr = probability, P = predicted agreement, O = observed agreement.

eTable 3: Unadjusted traumatic brain injury incidence estimates based on widely used ICD-based case definitions.

	Crude incidence per 10,000 person-years (95% CrI)		
	Children	Adults	Elderly
Outpatient claims	31 (31 , 32)	11 (10 , 11)	10 (9.9 , 11)
Emergency department claims	79 (78 , 80)	20 (20 , 21)	41 (40, 42)
Inpatient claims	3.4 (3.2 , 3.6)	2.3 (2.2 , 2.4)	9.5 (9.1 , 100)
Discharge abstract database	6.5 (6.2 , 6.8)	3.2 (3.1 , 3.4)	16 (16 , 17)
All ICD-based case definitions combined	112 (110 , 113)	33 (33 , 34)	67 (66 , 68)
Weighted overall incidence using all ICD-based case definitions		54 (54 , 55)	

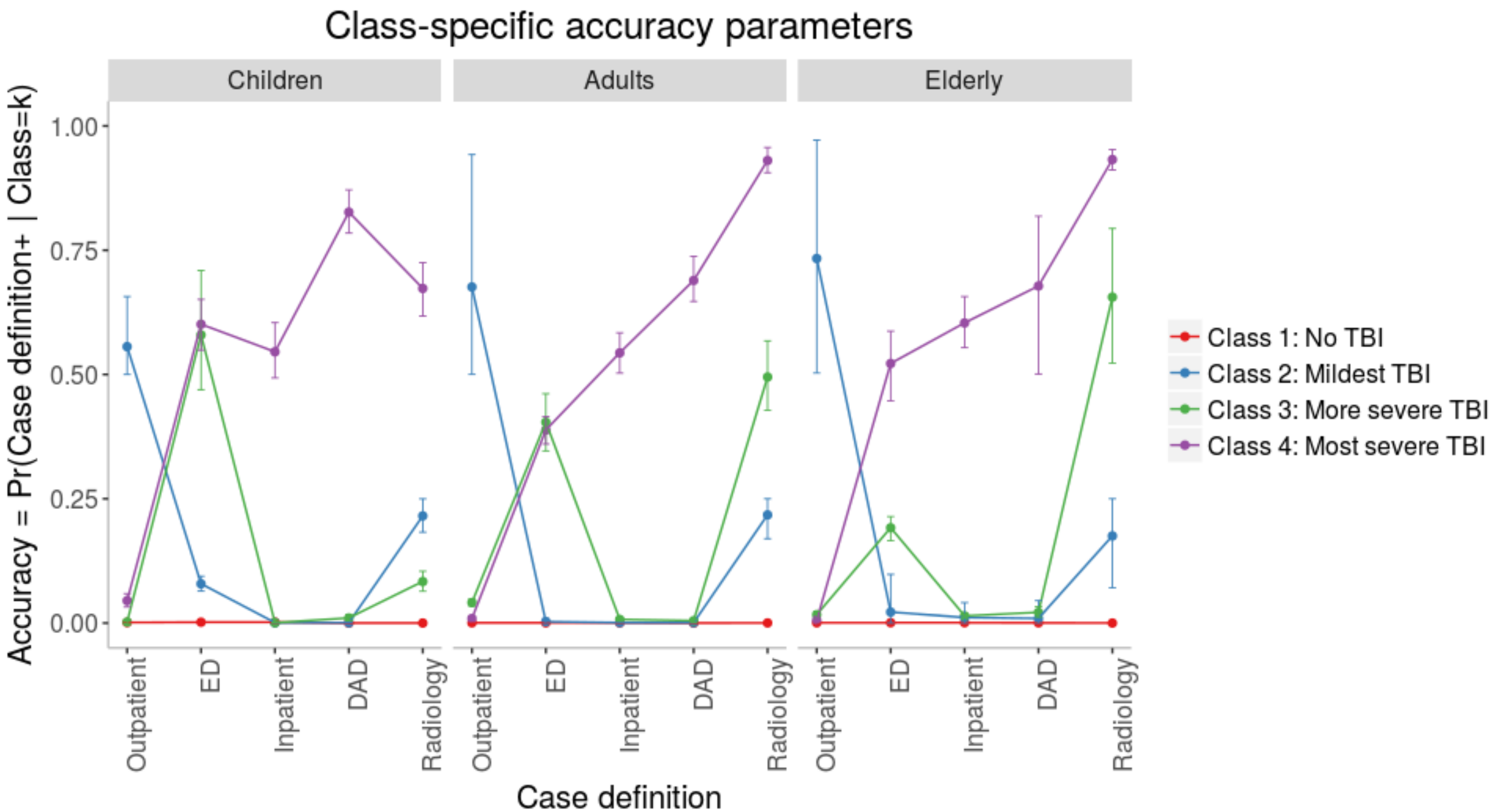
Crude traumatic brain injury incidence estimates based on ICD case definitions (outpatient claims, emergency department claims, inpatient claims and discharge abstract database diagnoses) that are widely used in the literature without adjusting for measurement error.[1,2] The radiological examination case definition is not used in this demonstration as it is not a typical ICD-based case definition that has been used to conduct traumatic brain injury surveillance in other jurisdictions. CrI = Credible interval, ICD = international classification of disease.

eFigure 1: Heuristic diagram outlining the data sources and latent variables used in the latent class analysis



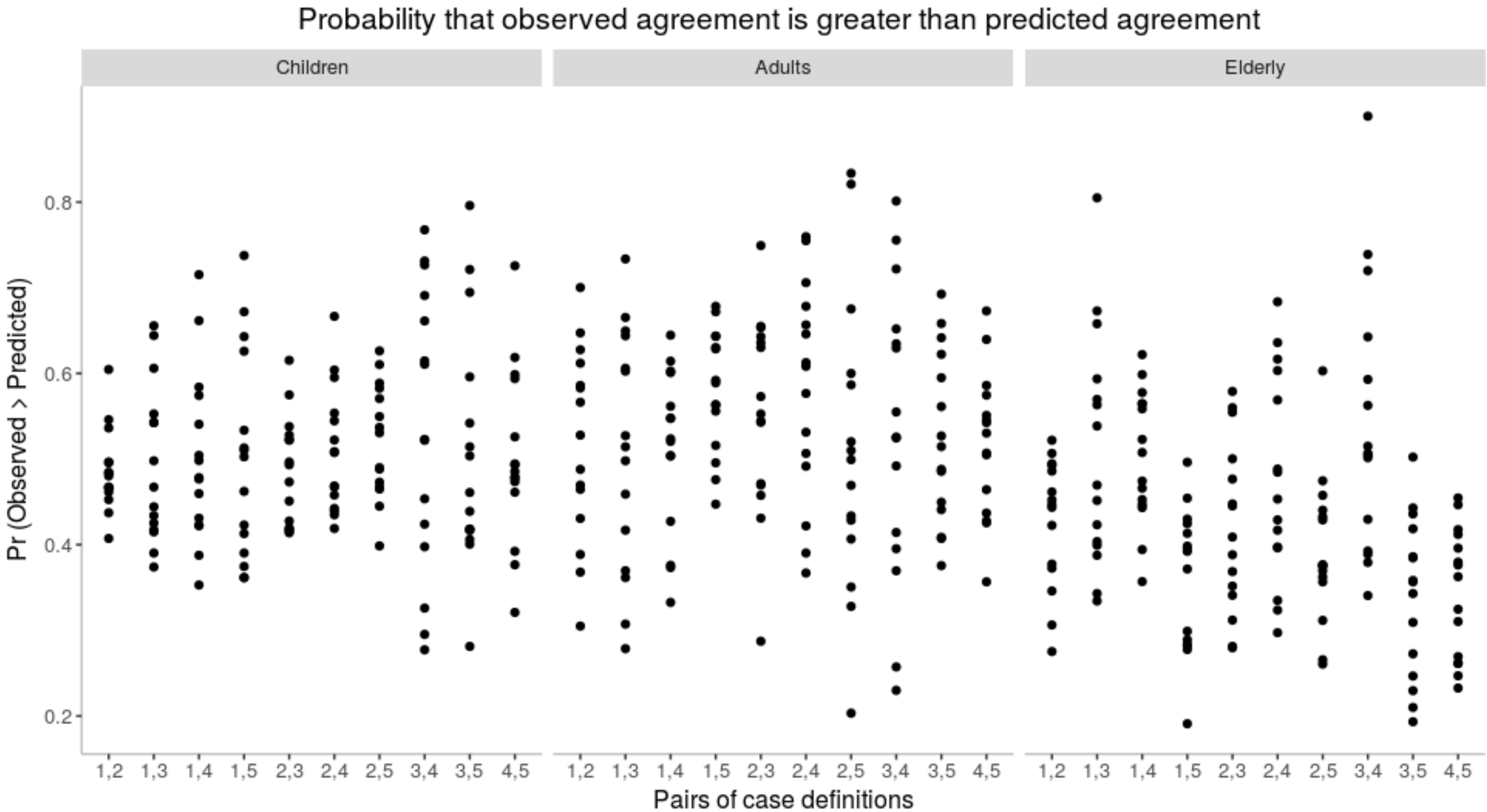
Heuristic diagram demonstrating the data sources and latent variables modelled in the latent class analysis. The 5 case definitions (directly observable data) are used to identify patients with suspected traumatic brain injury. These observed data provide information on where a traumatic brain injury case lies on the spectrum of injury severity, from cases with the mildest to most severe injuries. The dotted lines connecting the observed variables to the latent variables are weighted based on the a priori probability of the observed variable informing a specific latent class. Observed variables in the red boxes indicate data sources for physician claims in different care settings where ICD-based traumatic brain injury case definitions were used. The blue box indicates that ICD-based case definitions were used to ascertain suspected traumatic brain injury cases in hospitalization data from discharge abstracts. Finally, the green box indicates the radiological examination case definition that was used where any patient having any trauma diagnosis within 1 day of having a radiological examination of the head was a suspected traumatic brain injury case. ED = emergency department, TBI = traumatic brain injury.

eFigure 2: Class-specific accuracy parameters by age group



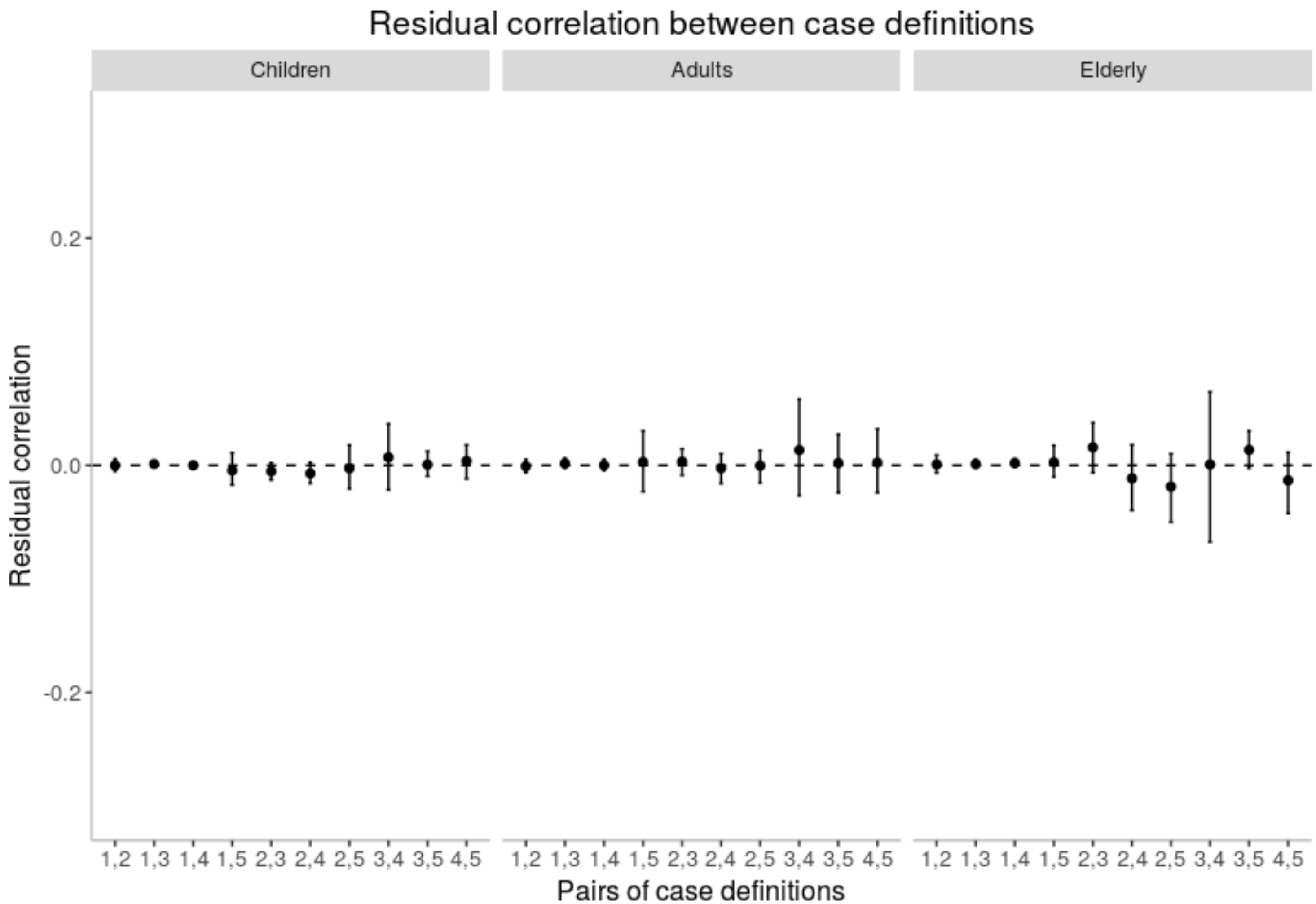
Pooled accuracy parameters by latent class across the 3 age groups studied in the main analysis. These estimates are representative of the sensitivity of each case definition in each age group for each severity (latent class) as opposed to their performance collapsed across the full injury spectrum as shown in Table 3. ED = emergency department claims, DAD = discharge abstract database, TBI = traumatic brain injury.

eFigure 3: Model fit assessment of the lower level of the hierarchy (year-specific) using posterior predictive checks across all age groups



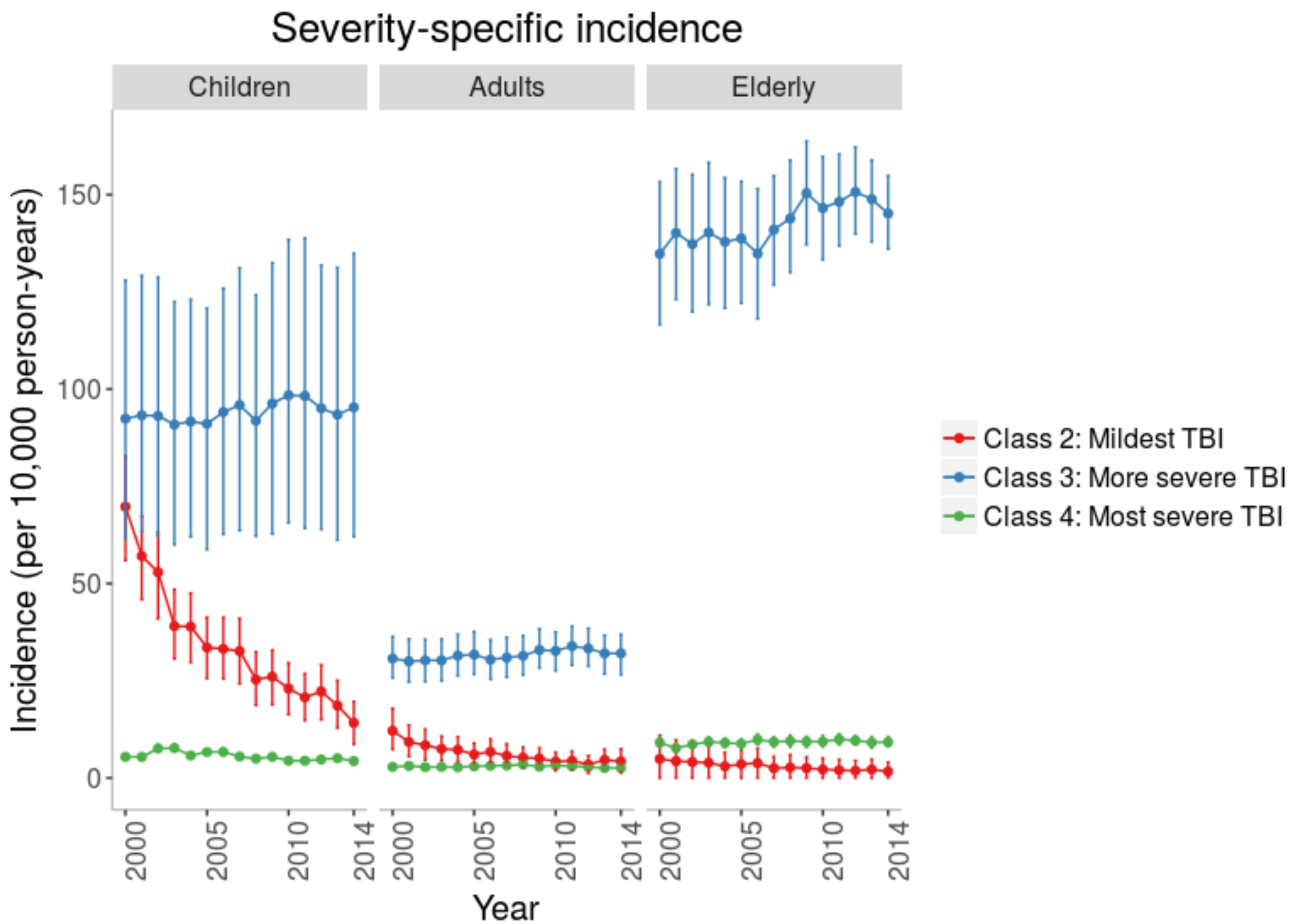
Model fit assessment comparing the probability that the observed agreement between pairs of case of definitions is greater than the predicted agreement (also known as Bayesian *p*-values*)*, as described in eMethods 4. The analysis was conducted for every year of follow-up and across the 3 age groups. None of the probabilities were close to 0 or 1. As such, there was no strong evidence to support that model fit was inappropriate across all years of the analysis for each age group. The pairs of case definitions are as defined in eMethods 2: 1 = outpatient physician claim, 2 = emergency department physician claim, 3 = inpatient physician claim, 4 = discharge abstract database, 5 = radiological examination of the head with a diagnosis of trauma.

eFigure 4: Assessment for conditional dependence between case definition



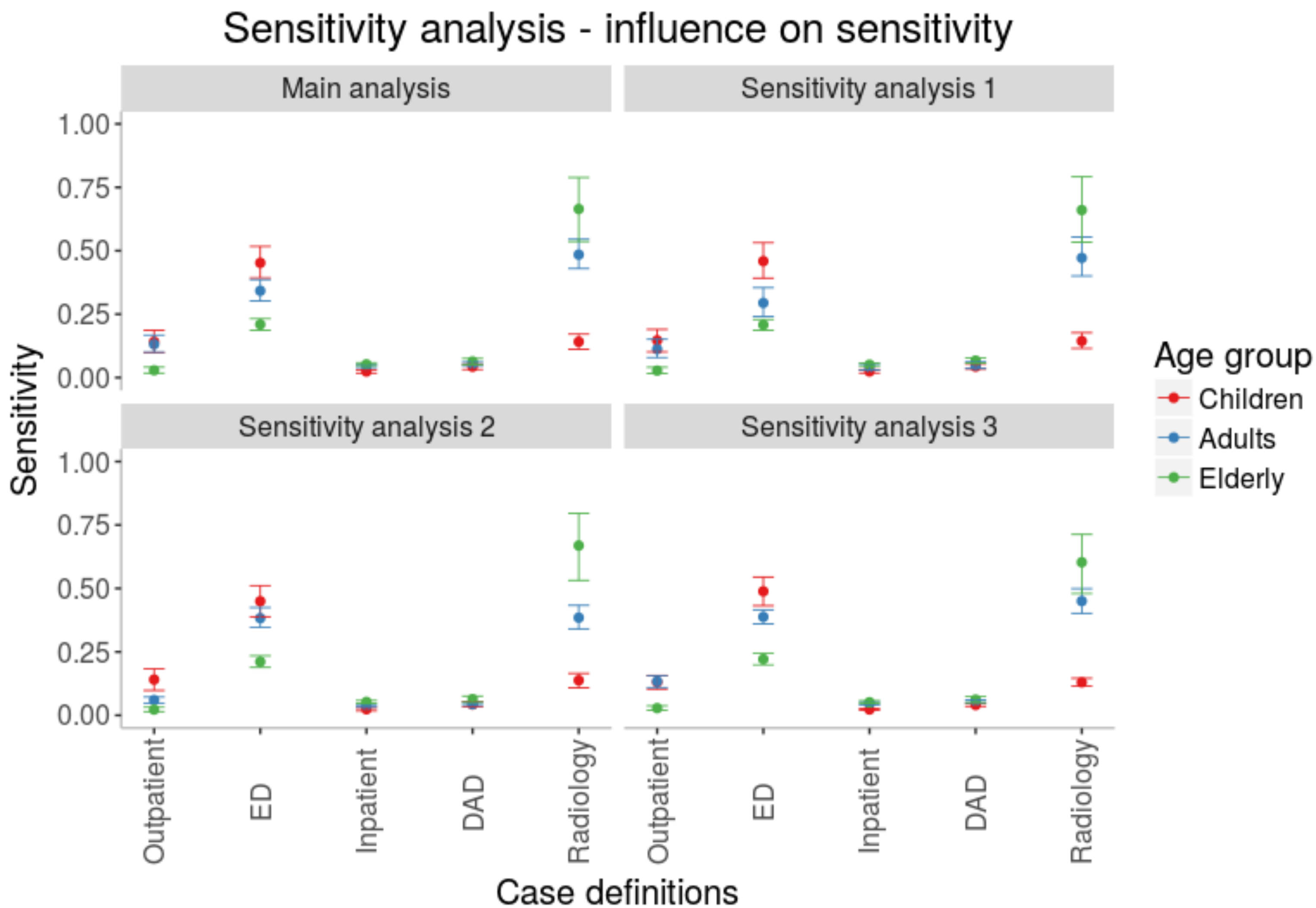
Residual correlation plot, as explain in eMethods 3, demonstrating that there is no significant residual correlation between pairs of case definitions for all 3 age groups. The pairs of case definitions are as defined in eMethods 2: 1 = outpatient physician claim, 2 = emergency department physician claim, 3 = inpatient physician claim, 4 = discharge abstract database, 5 = radiological examination of the head with a diagnosis of trauma.

eFigure 5: Severity-specific incidence

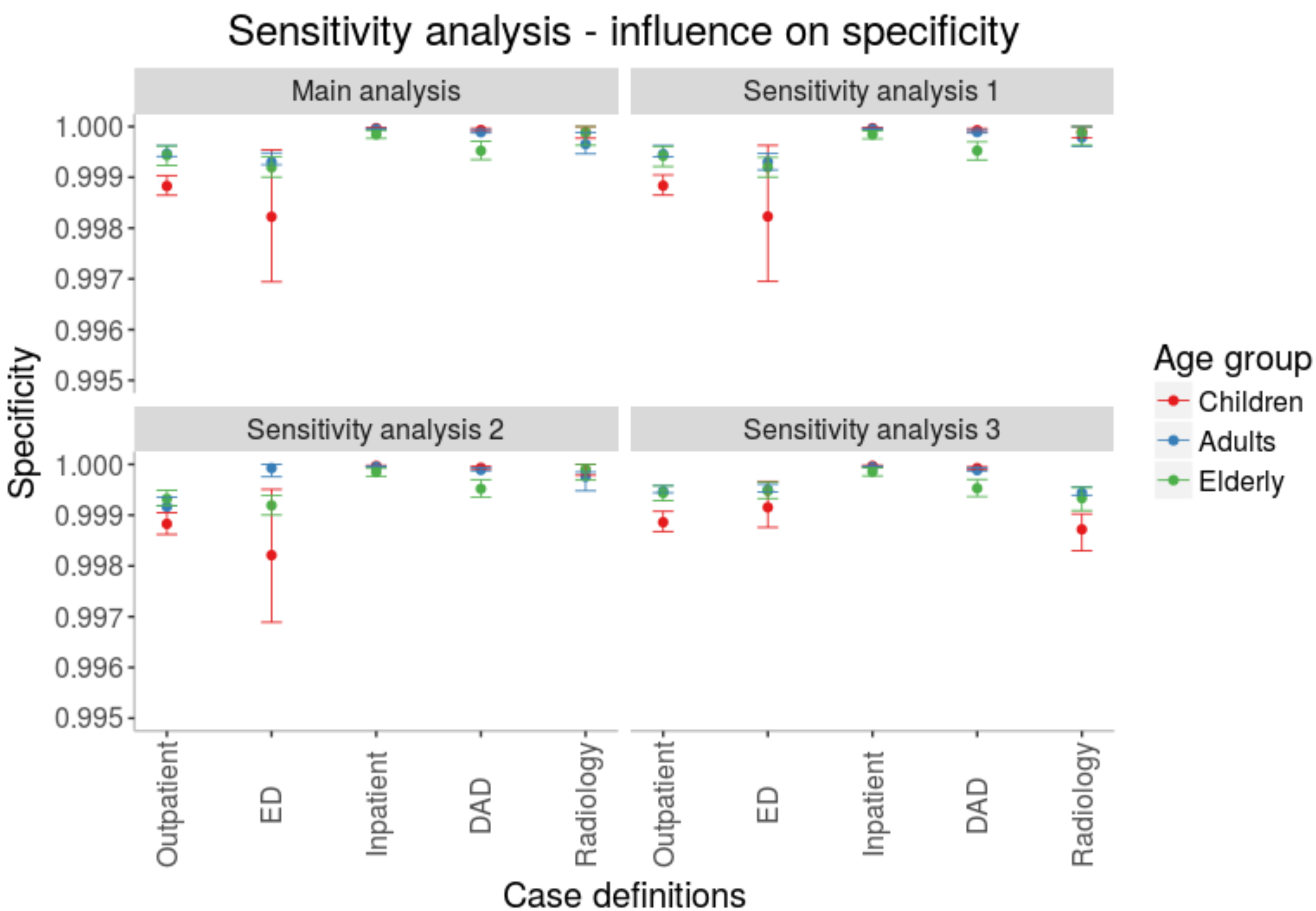


Trends in the incidence by latent class (severity) across the 3 age groups. Class 1(No traumatic brain injury) is not shown. TBI = traumatic brain injury.

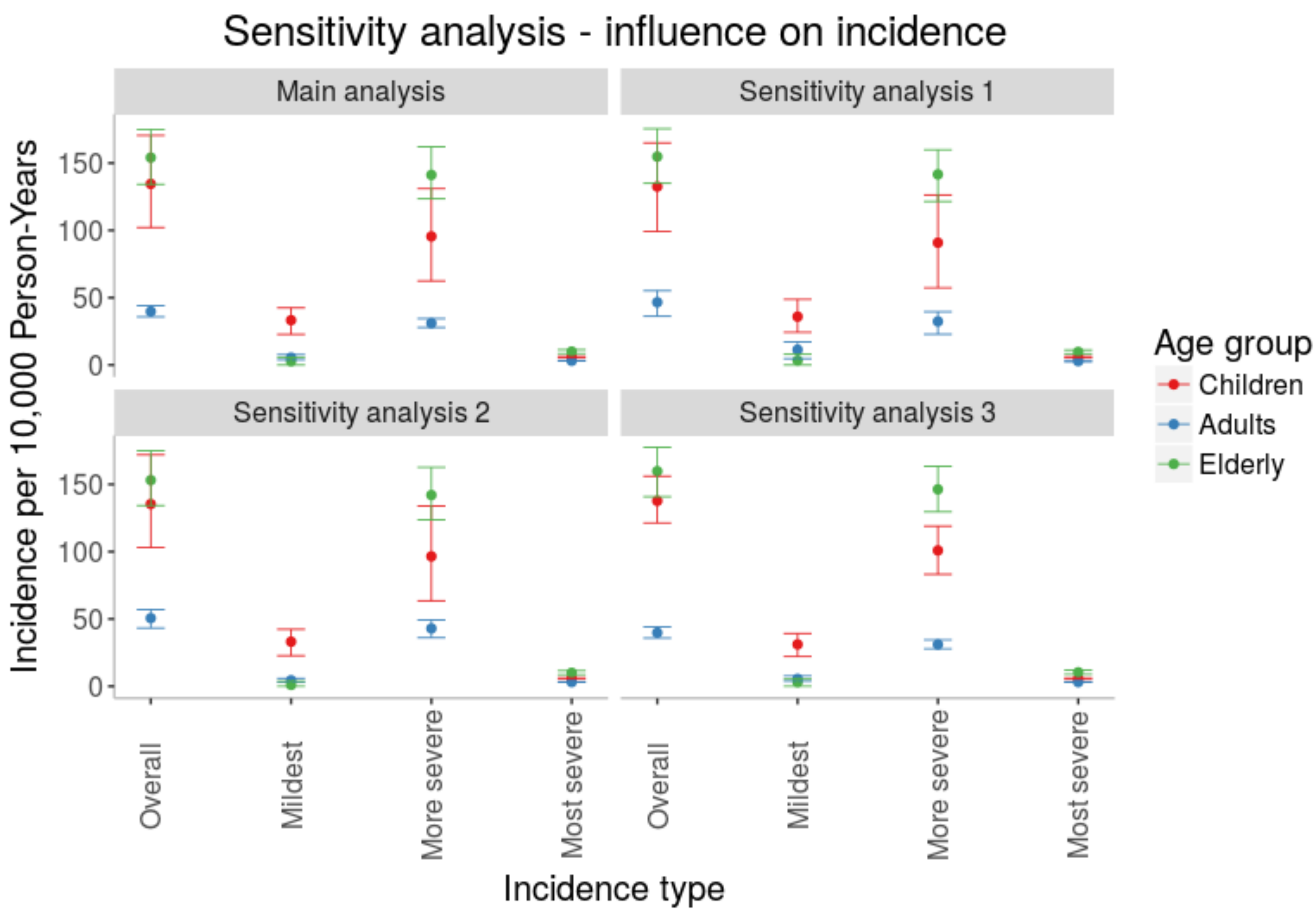
eFigure 6A: **Sensitivity analysis – influence on sensitivity**



eFigure 6B: Sensitivity analysis – influence on specificity



eFigure 6C: Sensitivity analysis – influence on incidence



Sensitivity analyses to verify robustness of main analysis results. For each sensitivity analysis, the pooled (across all years of analysis) sensitivity and specificity of each case definition for each age group is provided and compared to the main analysis results (eFigure 6A and 6B). In addition, the overall incidence and incidence across different classes is provided for each sensitivity analysis (eFigure 6C). The different prior distributions and assumptions used in each analysis are provided in eMethods 5. ED = emergency department, DAD = discharge abstract database, radiology = radiological examination case definition.

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Chapter 5: Epidemiology of recurrent traumatic brain injury in the general population: a systematic review

Preface to Manuscript 2

In Chapter 4, I provided the tools to TBI stakeholders to conduct accurate surveillance and epidemiological research of incident TBI cases using routinely available administrative data. However, this type of analysis only addresses a segment of the overall TBI burden, since recurrent cases are not accounted for. Research on rTBI has been mainly conducted in athletes, demonstrating that repetitive TBI are an important contributor to disability and mortality in that population. In the general population, there has been a paucity of research on the topic.

In this manuscript, I aimed to assess the rTBI risk and risk factors associated with rTBI in the general population through a systematic review. The review also focused on identifying study-level methodological factors that influence the reported rTBI risks. Finally, the quality of the literature was reviewed by assessing the internal and external validity of the estimates provided by each study included in the review. The evidence generated by this study advances the current understanding of the contribution of recurrent injuries to the overall TBI burden, in addition to revealing information that identifies which TBI patients at higher risk of rTBI. The latter is necessary when allocating resources for interventions that may mitigate the risk of recurrences. Finally, this review provides a critical assessment of the methodological limitations that influence the quality of rTBI surveillance studies.

This study was published in *Neurology* in 2017:

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Manuscript 2

Epidemiology of recurrent traumatic brain injury in the general population:
a systematic review

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Abstract:

Objective: We aimed to comprehensively assess recurrent traumatic brain injury (rTBI) risk and risk factors in the general population.

Methods: We systematically searched MEDLINE, EMBASE and the references of included studies until January 16, 2017 for general population observational studies reporting rTBI risk and/or risk factors. Estimates were not meta-analyzed due to significant methodological heterogeneity between studies, which was evaluated using meta-regression.

Results: Twenty-two studies reported recurrence risk and 11 reported on 27 potential risk factors. rTBI risk was heterogeneous and varied from 0.43% (95% CI 0.19 , 0.67%) to 41.92% (95% CI 34.43 , 49.40%), with varying follow-up periods (3 days to 55 years). Median time to recurrence ranged from 0.5-3.8 years. In studies where cases were ascertained from multiple points-of-care, at least 5.50% (95% CI 4.80 , 6.30%) of patients experienced a recurrence after a 1-year follow-up. Studies that used administrative data/self-report surveys to ascertain cases tended to report higher risk. Risk factors measured at time of index TBI that were significantly associated with rTBI in more than one study were: male sex, prior TBI before index case, moderate or severe TBI, and alcohol intoxication. Risk factors reported in a single study that were significantly associated with rTBI were epilepsy, not seeking medical care, and multiple factors indicative of low socio-economic status.

Conclusions: rTBI is an important contributor to the general population TBI burden. Certain risk factors can help identify individuals at higher risk of these repeated injuries. However, higher quality research that improves on rTBI surveillance methodology is needed.

Introduction:

Traumatic brain injury (TBI) causes considerable long-term disability and mortality, creating an important economic burden for society.[1-3] Epidemiological investigations have demonstrated that TBI is a heterogeneous public health problem because of varying injury determinants and differing ways to define TBI since there is no gold standard to diagnose the condition.[4] Another level of heterogeneity arises from the injury burden being composed of both incident and recurrent TBI (rTBI) cases, which are distinct entities.[5] However, the epidemiological characteristics of rTBI in the general population have not been comprehensively investigated, as most studies on the topic have focused on athletes.[566–9]

Patients with rTBI are known to have poorer outcomes even when a repeated injury is mild.[10–12] In the acute phase, individuals with rTBI have greater disability for a longer duration when compared to individuals with a single TBI.[9] This disability is mainly manifested as more severe post-concussive symptoms and psychiatric comorbidities.[9,13] In the long-term, there is growing evidence that repetitive head trauma leads to an increased risk of suicide and Chronic Traumatic Encephalopathy.[10,14–16]

As such, preventing rTBI is important for controlling the overall general population TBI burden.[17] To achieve the latter, a comprehensive assessment of its epidemiological characteristics in the general population is required. One aim of this systematic review was to estimate rTBI risk in the general population across all disease severities and age groups. A second aim was to identify rTBI risk factors (RFs) and assess their strength of association with rTBI. We also planned to assess factors that explain heterogeneity in estimates reported across studies.

Methods:

This systematic review was conducted following a pre-specified protocol, which is available on PROSPERO (CRD42017055597), and adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Search strategy and selection criteria:

We performed a systematic search of MEDLINE and EMBASE between database inception (1946 and 1947, respectively) and October 15, 2016 (updated on January 16, 2017) for studies that reported rTBI risk and/or RFs. In consultation with a librarian experienced in conducting systematic review searches, we developed a broad search strategy consisting of 2 concepts using keywords and MeSH/EMTREE indexing terms (Methods e-1). Briefly, concept 1 was for TBI (keywords: “brain injur*”, “concussion”, “head injur*”) and concept 2 was for recurrence (keywords: “recur*”, “recidivis*”, “repeat*”, “repetit*”, “multiple”). The “AND” Boolean operator was used to combine these two concepts. We restricted our search to studies published in English or French and excluded conference abstracts. OL reviewed all titles/abstract and full-texts and one of three other authors independently reviewed a subset of the same studies (EL, GP, JRL). All selected titles/abstracts went on to full-text review. Adjudication was used to resolve any disagreement between reviewers during full-text review.

The inclusion criteria for this systematic review were studies that reported on the proportion of rTBI cases (individuals experiencing a repeated TBI after an initial injury) among a cohort of index TBI cases with a defined follow-up period and/or studies that reported on RFs and their association measure for a cohort of index TBI cases. We assessed all baseline characteristics of the index TBI cohort that were potential RFs. Since our objective was to estimate rTBI risk, we excluded studies that reported rTBI prevalence. As this review focused on rTBI in the general population, we excluded studies that reported estimates on specific population subgroups (e.g., athletes, veterans). We also excluded case reports and reviews. The bibliographies of all included studies were hand searched to identify additional studies that met the review's inclusion criteria. If two publications used the same study population, we included the study with the larger sample size.

Two reviewers (OL reviewed all studies) independently completed data extraction and quality assessment using a pilot-tested data extraction and quality assessment form. The following variables were extracted: total number of recurrent events, size of index TBI cohort, follow-up period (total time followed since index TBI or average follow-up period for studies recruiting index cases over many years), crude and adjusted association measures of all RFs (or individual counts of rTBI cases/non-cases that are exposed/unexposed to the RFs), covariates used to adjust RF association measures, age groups included in the study, mean age, sex proportions, TBI severity distribution, data source (administrative health data/survey vs. registry/medical charts), inclusion criteria for TBI patients, and TBI/rTBI case definitions. Authors of included studies were contacted if data on the counts of rTBI or index TBI cases were missing.

Quality assessment was completed using the Methodological Evaluation of Observational Research (MORE), which evaluates the quality of incidence and RF studies based on internal and external validity domains.[19] With this quality assessment tool each domain is scored as "OK", "minor flaw", "major flaw" or "poor reporting". This quality assessment checklist has been used in systematic reviews that adapt the tool to their research question.[20,21] The quality assessment was conducted while assessing the studies' ability to validly estimate rTBI risk and the association between RFs and rTBI. For the quality assessment of RFs, only the internal validity was assessed since the external validity criteria were identical to those evaluated for the rTBI risk quality assessment. The quality of studies was summarized by the proportion of items that were scored as "OK", "minor flaw", "major flaw" or "poorly reported".

Statistical analysis:

We reported the rTBI risk (incidence of repeat TBI among a cohort of patients with an initial TBI over a defined follow-up period) and the association measures for rTBI RFs. Crude estimates were reported as risk ratios or odds ratios and adjusted estimates as hazard ratios or odds ratios (depending on how studies reported them). It was decided a priori that if study methods and characteristics were too heterogeneous, a meta-analysis would not be completed.

We planned to use meta-regression analysis for both rTBI risk and association measures of the RFs if at least 10 studies reported on a given RF. This constraint was to ensure that the meta-regression analysis was sufficiently powered.[22] The following factors were assessed as heterogeneity factors: age groups included (children versus adults or entire population), follow-up period (half of study period for studies recruiting TBI cases longitudinally), study quality (number of "OK" criteria), data source to ascertain rTBI cases (administrative/survey data versus registry/clinical assessment) and comprehensiveness of cases ascertained (at one versus multiple points-of-care – ER, hospitalization or outpatient). Data sources were categorized as such because administrative data and self-report surveys have been shown to be less accurate than clinical assessment or registries to ascertain TBI cases.[23] The amount of between-study heterogeneity explained by these covariates was estimated with the R^2 statistic.[22]

All analyses were conducted in STATA 14 and forest plots were produced using R (Metafor package).

Results:

Our search identified 8319 potentially relevant citations and 357 publications were retained for full-text review. A total of 29 publications met the inclusion criteria for rTBI risk assessment. Seven of these publications were studies completed on the same population as another publication that met the inclusion criteria but that had a smaller sample size. As such, 22 studies[24-45] were retained for rTBI risk analysis and 11 studies[26,30-32,35-37,40,43,46,47] were retained for the analysis of rTBI RFs (Figure 1). A meta-analysis was not completed because of significant methodological heterogeneity between included studies.

rTBI Risk:

The included studies contained 406,982 TBI cases, 38,981 of which went on to have an rTBI. The risk of rTBI varied from 0.43% (95% CI 0.19 , 0.67%) to 41.92% (95% CI 34.43 , 49.40%) (Figure 2). After at least 1-year follow-up, 5.50% (95% CI 4.80 , 6.30%) of individuals had a recurrent event when rTBI cases were ascertained at multiple points-of-care. Follow-up time ranged from 3 days to 55 years. Study methods and characteristics were heterogeneous (Table 1 and further details in Table e-1) and only 50% of the studies had a primary aim related to rTBI. Cases were mainly ascertained from administrative data (41%)[25-30,34,39,44], but some studies used surveys (18.1%)[24,32,35,37], medical charts (31.8%)[31,36,38,40,42,43,45] and trauma registries (9%)[33,41]. Index and rTBI case definitions varied significantly across studies. In four studies[25,31,33,40], all age groups were included, whereas all other studies limited the population to specific age groups. One study restricted TBI and rTBI cases to sports-related injuries in the general population.[34] Five studies reported the risk of rTBI at different follow-up time after index TBI.[28,33,34,40,41] Many recurrent events occurred early after the index case; the median time to rTBI was under 6 months in 1-year long studies that used a comprehensive rTBI case ascertainment definition.[40,41] In contrast, the median time to recurrence was 3.8 years for a study with a 15-year follow-up period that only included rTBI cases hospitalized for less than 2 days (Figure e-1).[28]

MORE-defined study quality revealed that internal validity had more flaws and poor reporting than external validity. Regarding internal validity criteria, all studies poorly reported on at least 1 item and 21 studies had at least 1 minor flaw. In contrast, 6 studies did not have any flaws or poor reporting for external validity criteria (Figure 3 and Table e-2). For internal validity, the most common major flaw, minor flaw and poorly reported criteria were: not using a validated method to measure rTBI occurrence, using a data source intended for health care purposes to measure incidence, and not reporting the precision of rTBI estimates, respectively. For external validity, the most common major flaw, minor flaw and poorly reported criteria were: using a non-general population sampling frame, not adjusting for sampling bias, and not providing a flow diagram of participants included/excluded from the study, respectively.

We explained the heterogeneity of estimates between studies through meta-regression analysis. The data source used to ascertain cases explained 25-29% of the between-study variance, with studies using administrative data or surveys reporting higher risks. Studies ascertaining cases at more than 1 point-of-care (ER, hospital, clinic) tended to report higher risks, but this only explained 9% of the between-study variance. Other study-level factors, including study follow-up time, did not explain significant heterogeneity (Table e-3).

Risk factors for rTBI:

Eleven studies reported on 27 different potential RFs. The RFs at the time of initial injury that were significantly associated with a higher risk of rTBI in more than a single study were male sex (3/8 studies), prior TBI (3/5 studies), moderate/severe TBI (2/4 studies), and alcohol intoxication (3/4 studies). Other studies measuring these RFs generally reported estimates in the same qualitative direction but with less precision. RFs significantly associated with a higher risk of rTBI but where estimates were only reported in a single study were epilepsy disorder[46], and not seeking medical care[40]. Moreover, several factors related to low socio-economic status (lowest decile income level[26], uninsured status[46], low education level[47], parental criminal history[26]) were associated with higher rTBI risk. In contrast, rural residence and non-white race was associated with a decrease in rTBI risk, although these estimates were imprecise. Multiple studies reported other RFs (age, education level of parents, and mechanism of injury) but their association with rTBI occurrence were less conclusive because of conflicting results or imprecise estimates (Figure 4). When reported, adjusted RF association measures generally showed the same qualitative association as the crude association measures but were often imprecise. Meta-regression analysis was not completed for RF association measures since no RF was reported by at least 10 studies (lack of power to conduct the analysis).

RF quality assessment was variable across different RFs and the 10 studies that reported on them (Figure e-3). Poor reporting and minor flaws were identified across all RFs. Major flaws were common and affected all risk factors, except for not seeking medical care within 24 hours. Many of the same quality assessment criteria were affected across different risk factors for a given study. The most common major flaw was not validating the method used to measure rTBI occurrence, and the most common minor flaw was that many studies' data sources were primarily inended for medical purposes. Poor reporting was most frequently the result of not providing any justification for the sample size used (Table e-4).

Discussion:

The epidemiological characteristics of rTBI in the general population were previously uncharacterized. This systematic review has comprehensively described the important contribution that rTBI has to the overall TBI burden. After 1 year of follow-up from the time of an index TBI, at least 5.5% of individuals will have a recurrence that requires medical attention. As such, these recurrent events play an important role in amplifying the TBI burden since they are known to be associated with increased disability. [14–16] Furthermore, we have shown that many recurrent events occur in the first six months after index TBI. Previous evidence demonstrates that shorter intervals between index TBI and rTBI are associated with greater disability since the injured brain is still recovering from the initial injury.[48,49] Thus, these early recurrences, which are common, are particularly burdensome to the general population.

Our study demonstrates that many RFs for rTBI are similar to those for incident TBI. Males have a higher incidence of TBI across all populations and age groups, which is similar to the association we found for rTBI.[21,50] In addition, we described an increasing risk of rTBI among younger children in one study[26], which resembles the pattern seen for first-time injuries.[51] Older age has also been shown to be a risk factor for incident TBI, although this characteristic was inconclusive for rTBI in our study.[52] Given this evidence, rTBI may also have a bimodal distribution where younger children and older adults are at higher risk, but further investigation is warranted. Also, alcohol intoxication is known to increase the risk of TBI and appears to be an important factor in predicting rTBI.[53] In fact, one study demonstrated that brief alcohol interventions at the time of index trauma reduce the risk of trauma recurrence.[54] Moreover, patients with an epilepsy disorder seem to be at higher risk of rTBI, which supports the idea that patients with epilepsy have a higher risk of injuries.[55] Finally, our study demonstrates that lower socio-economic status is associated with an increased risk of rTBI, which is substantiated by other studies that have provided similar findings.[56,57]

We also identified RFs for rTBI that differ from those for index injuries or are unique for rTBI. Patients with a moderate or severe index TBI are more likely to endure an rTBI than cases with a mild index TBI, suggesting that more disabling injuries are associated with a greater risk of recurrence.[58] Similarly, prior TBI before the initial injury under study also predicted a higher risk of recurrence, which indicates that rTBI risk in the general population increases as more injuries occur. Similar evidence in athlete populations supports this association.[8] Furthermore, non-white race and rural residence tended to demonstrate a protective, yet imprecise, association for rTBI. Similarly, some RFs related to lower socio-economic status (unemployed parents, low parental education) are also associated with a decreased rTBI risk. These RFs are typically associated with an increased risk for incident TBI.[59] Such discrepancies may be explained by the fact that individuals in these social settings may have poorer access to health care, which would lead to an underestimation of their rTBI risk. Clearly, further investigations on these RF associations are required. In short, knowledge of these RFs provides stakeholders in TBI prevention with a means to identify patients at higher risk of recurrence, such that prevention efforts geared towards these individuals may be prioritized.

As this review confirms, there has only been limited research on rTBI epidemiology in the general population. In contrast, there has been significant research dedicated to this topic in athletes.[8] For example, interventions to reduce the risk of rTBI in athletes, such as delaying return-to-play, have been shown to be effective.[8] Analogous interventions that mitigate the risk of rTBI in the general population have not been investigated, perhaps because there had never been a comprehensive description of its frequent occurrence. Despite the extensive review we completed, we must highlight that many studies we included have important validity flaws since half of them did not have a primary aim related to rTBI. Therefore, research that primarily focuses on rTBI is required to produce higher-quality evidence on the topic. In such studies, it would be important to develop and use uniform methods to measure rTBI and baseline RFs, which is similar to what has been suggested to improve the quality of incident TBI surveillance.[23] In addition, the timing of injuries after the index case should be reported so that the high-risk period of recurrence can be thoroughly assessed. By following such recommendations there would be less methodological heterogeneity between studies, which would allow for better comparisons of rTBI epidemiological characteristics across jurisdictions and time.

An important contributor to the aforementioned heterogeneity of rTBI risk and RF associations is the variability of case-definitions for rTBI across different data sources. This heterogeneity similarly affects surveillance studies for incident TBI where comparing estimates across jurisdictions is challenging.[21,23] However, when studying rTBI, varying follow-up times used to assess the outcome as well as the unknown validity of case definitions further complicate this problem. Regarding incident TBI, administrative data have been shown to be inaccurate at identifying cases (sensitivity of 45-70% and specificity of >97%), but such information is not available for rTBI.[60] We demonstrated that studies using administrative health data or surveys report higher rTBI risk, which suggests that these data sources may lack specificity for detecting rTBI cases. For example, participants in studies using surveys to assess rTBI may over-report the occurrence of events. In studies using administrative data, this lack of specificity may result from ICD-coded claims being identified as rTBI when they are in fact follow-up visits for the index TBI. This problem is particularly apparent in Chu (2016)[39] where a high rTBI risk of 36% over a follow-up period of up to 3 years was reported. These authors did not exclude medical claims with a TBI diagnosis for a certain period after the index TBI, as was done in other studies to ensure that follow-up visits for the index case were not counted as rTBI cases.[26-27,29,34] Since administrative health data provide a feasible and timely approach to conduct surveillance and epidemiological research, studies evaluating the accuracy of case-detection algorithms for rTBI in these data sources are required.

Our systematic review has several limitations. First, publication bias may have occurred since we only included the peer-reviewed literature and public health reports on rTBI may be available in the grey literature. We decided to omit these studies since an important component of this review was to focus on the quality assessment of included studies and the MORE checklist was not designed to evaluate the grey literature. Second, there was significant heterogeneity in the methods and populations used to assess rTBI risk and RFs across studies. This limited our ability to meta-analyze the risk and RF association measure estimates even when studies had similar follow-up periods. Although we were unable to estimate the risk of rTBI over time, we still demonstrated that there is a tendency for the risk to be the highest in the first months to years after the index case. Finally, many RFs only had crude association measures reported. Confounding of the association between the RFs and the rTBI outcome is thus possible. Conclusions on association measures did not change when comparing crude and adjusted estimates, but we must still cautiously interpret them.

Conclusion:

rTBI affects a significant proportion of individuals with TBI, oftentimes early after a first injury, amplifying the overall TBI burden in the general population. Several factors can help identify patients at a higher risk of recurrence. However, there is significant heterogeneity of estimates between studies and methodological flaws compromise the quality of the literature on the topic. As such, further high-quality research is needed to validate approaches for measuring rTBI occurrence so that it is possible to accurately conduct surveillance, assess risk factors and evaluate potential rTBI-mitigating interventions in the general population.

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Tables and Figures for Manuscript 2

Author (Year)	Country	Study period	Study Design (rTBI as primary aim)	Follow -up (years)	Inclusion criteria for index TBI	Data source	rTBI definition	Age grou p	Time to rTBI	rTBI / Index TBI (n)	rTBI risk
Chen, H[24] (2007)	US	1993-1996	Case-control (No)	30-80	Self-report of any TBI from controls in New England matched to ALS cases on age, sex and area code from 1993-1996	Survey	Patient self-report of TBI requiring medical care during lifetime	30-80	NA	10 / 42	0.24
Annegers, JF[25] (1998)	USA	1935-1984	Cohort (No)	0-50	Inpatient, ED or outpatient visits for TBI	Administrative: Medical Record Linkage System of the Rochester Epidemiology Project	Clinical definition	All	NA	397 / 5984	0.07
Sariaslan, A[26] (2016)	Sweden	1973-2013	Cohort (No)	3-40	Inpatient, ED and outpatient visits for TBI of individuals born from 1973-1985 occurring before the age of 25	Administrative: National Patient Register	ICD 8/9/10 TBI code15 days after index TBI	0-25	NA	12680 / 104290	0.12
Richard, YF[27] (2015)	Canada	1987-2008	Cohort (No)	0-22	Inpatient, ED and outpatient visits for TBI	Administrative: Régie de l'assurance maladie du Québec medical services database	ICD-9 TBI code 90 days after index	0-17	NA	3595 / 21047	[a]0.17

Teasdale, TW[28] (2014)	Denmark	1979-2009	Cohort (Yes)	0-30	Inpatient visits for men with concussion for less than 2 days and who were assessed by the Draft Board after age 18 between 2006-2010	Administrative: Ministry of Health database (Landspatientregister)	ICD 9/10 TBI code 3 days after index TBI	0-35	Median: 3.8 years	450 / 6614	0.068
McMillan, TM[29] (2014)	UK	1995-2011	Case-control (No)	15	Inpatient visits in Glasgow with mild head injury (GCS>=13)	Administrative: Information Services Division of the National Health Survey of Scotland	ICD 9/10 code	>14	NA	428 / 2428	0.176
Winqvist, S[30] (2008)	Finland	1978-2000	Cohort (Yes)	0-23	Inpatient or ED visits lasting >24 hours for TBI	Administrative: Finnish Hospital Discharge Register	ICD 8/9/10 codes for TBI	12-34	NA	21 / 236	0.09
Vaaramo, K[31] (2014)	Finland	1999-2009	Cohort (Yes)	11	ED visits for TBI at a single hospital	Discharge register and ED checklist (index TBI)/ Administrative data of hospitalizations and hospital charts (rTBI)	ICD-10 TBI code from National Hospital Discharge Register and hospital charts from Oulu hospital	All	NA	29 / 431	0.067

Bijur, PE[32] (1996)	UK	1970-1980	Case-control (Yes)	10	Parent self-report of any TBI for community children in the UK	National survey	Parent self-report	0-10	NA	329 / 1915	0.17
Wilson, DA[33] (2014)	USA	1998-2011	Case-control (Yes)	0-14	Inpatient/ED visits for TBI	South Carolina TBI Surveillance System	ICD-9 TBI code 1 week after index	All	[b]11.6% at 1 month and 23.1% at 6 months	15522 / 236164	0.066
Harris, A[34] (2012)	Canada	1997-2008	Cohort (Yes)	0-12	ED visits for sports injuries within 5 hospitals' catchment areas of Edmonton's Metropolitan Area	Administrative: Ambulatory Care Classification System	ICD 9/10 TBI code 14 days after index TBI	1-35 years	Median: 613 days	213 / 959	0.222
Edna, TH[35] (1987)	Norway	1979-1984	Cohort (No)	5	Inpatient visits at 4 surgical departments	Survey	Patient self-report	15-64	NA	76 / 470	0.16
Partington, MW[36] (1960)	UK	1952-1958	Cohort (No)	0-7 years	Inpatient visits for head injury at a single children's hospital 1952-1958	Medical chart	Clinical diagnosis	0-13	NA	19 / 1155	0.016

Liu, J[37] (2013)	China	2004-2005	Cohort (Yes)	0-6	Community sample of 6-year-old school children in Jintan	Parent self-report Survey	Parent self-report	0-6	NA	70 / 167	0.42
Lee, MA[38] (2010)	US	2004-2008	Cohort (No)	0 to 4.5	All concussion patients referred to an outpatient practice	Medical chart	Clinical	11-19	NA	128 / 674	0.19
Chu, SF[39] (2016)	Taiwan	2004-2006	Cohort (No)	0-3	All medical claims for TBI in 2004/2005	Administrative: Longitudinal Health Insurance Database of Taiwan	ICD-9 TBI code	>18	NA	4651 / 12931	0.359
Theadom, A[40] (2015)	New Zealand	2010-2011	Cohort - case-control for risk factor analyses (Yes)	1	Inpatient/outpatient visits and self-reported cases in Hamilton, New Zealand	Clinical interview, medical chart, self-report, administrative health data	Clinical: diagnostic committee established diagnosis	All	61.1% at 6 months	72 / 725	0.1
Swaine, B[41] (2007)	Canada	2000-2003	Cohort (Yes)	1	ED visits for TBI to 2 pediatric provincial neurotrauma centres	ED trauma registry (index TBI) and parent self-report (rTBI)	Parent self-report of TBI requiring medical attention	1-18	58.2% 6 months	198 / 3599	0.055
Klonoff, H[42] (1971)	Canada	1968-1970	Case-control (No)	1	Inpatient and ED visits for TBI presenting to a single pediatric hospital	Medical chart and parent self-report survey	Parent self-report	0-16	NA	30 / 298	0.10

Taubman, B[43] (2016)	USA	2011-2013	Case-control (Yes)	0-1.5	Outpatient primary care visits for concussion without intracranial lesions on imaging, occurring within 7 days of TBI and for patients not hospitalized greater than 24 hours	Medical chart	Clinical definition	11-19	NA	5 / 95	0.053
Collins, CL[44] (2014)	US	2010-2011	Cohort (No)	0-1	Inpatient, ED and outpatient visits at a single pediatric hospital	Administrative: local hospital database	ICD-9 TBI code 90 days after index	0-20	NA	46 / 3971	0.01
Ganti, L[45] (2015)	US	2008-2011	Cohort (Yes)	72 hours	ED visits at single level 1 trauma centre (GCS >=13)	Administrative: local hospital database and medical chart for severity and rTBI assessment	Patients presentin g back to the same ED with a new TBI	>18	NA	12 / 2787	0.004

Table 1: Description of 22 included studies that assess rTBI risk/incidence. TBI = traumatic brain injury, rTBI = recurrent traumatic brain injury, GCS = Glasgow Coma Score, ED = Emergency department, ALS = Amyotrophic Lateral Sclerosis, NA = Not available/reported. Further details on the characteristics of the studies are available in Table e-1. [a]Authors were contacted to obtain the number of rTBI events and the average follow-up period (15.4 years) of the index TBI cases. [b]Median time to injury was taken from Saunders (2009)[47], which was conducted on the same population as Wilson (2014)[33].

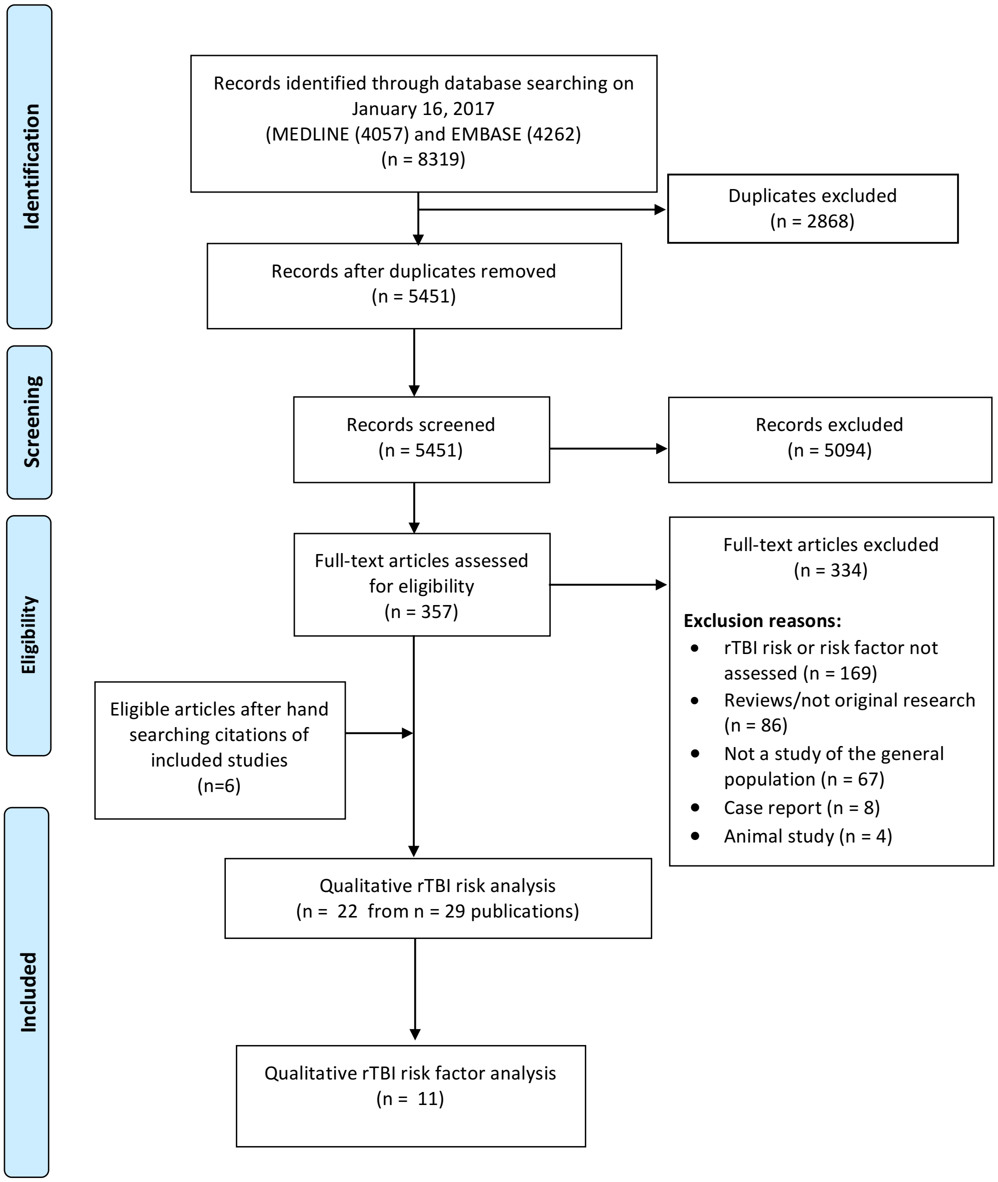


Figure 1: PRISMA flow-chart of included and excluded studies
Flow-diagram of search results for the systematic review. The detailed search strategy is available in Methods e-1. Results e-1 provides a list of all included studies for the rTBI risk and RF analysis. Results e-1 also provides a list of the 7 publications that were excluded from the analysis because they had the same population as one of the 22 included studies.

Author (Year)	Average follow-up (years)	rTBI (n)	Index TBI (n)	Risk [95% CI]
Chen, H (2007)[24]	55	10	42	0.238 [0.109, 0.367]
Annegers, JF (1998)[25]	25	397	5984	0.066 [0.060, 0.073]
Sariaslan, A (2016)[26]	21.5	12680	104290	0.122 [0.120, 0.124]
Richard, YF (2015)[27]	15.44	3595	21047	0.171 [0.166, 0.176]
Teasdale, TW (2014)[28]	15	450	6614	0.068 [0.062, 0.074]
McMillan, TM (2014)[29]	15	428	2428	0.176 [0.161, 0.191]
Winqvist, S (2008)[30]	11.5	21	236	0.089 [0.053, 0.125]
Vaaramo, K (2014)[31]	11	29	431	0.067 [0.044, 0.091]
Bijur, PE (1996)[32]	10	329	1915	0.172 [0.155, 0.189]
Wilson, DA (2014)[33]	7	15522	236164	0.066 [0.065, 0.067]
Harris, A (2012)[34]	6	213	959	0.222 [0.196, 0.248]
Edna, TH (1987)[35]	5	76	470	0.162 [0.128, 0.195]
Partington, MW (1960)[36]	3.5	19	1155	0.016 [0.009, 0.024]
Liu, J (2013)[37]	3	70	167	0.419 [0.344, 0.494]
Lee, MA (2010)[38]	2.25	128	674	0.190 [0.160, 0.220]
Chu, SF (2016)[39]	1.5	4651	12931	0.360 [0.351, 0.368]
Theadom, A (2015)[40]	1	72	725	0.099 [0.078, 0.121]
Swaine, B (2007)[41]	1	198	3599	0.055 [0.048, 0.062]
Klonoff, H (1971)[42]	1	30	298	0.101 [0.067, 0.135]
Taubman, B (2016)[43]	0.75	5	95	0.053 [0.008, 0.098]
Collins, CL (2014)[44]	0.5	46	3971	0.012 [0.008, 0.015]
Ganti, L (2015)[45]	0.01	12	2787	0.004 [0.002, 0.007]

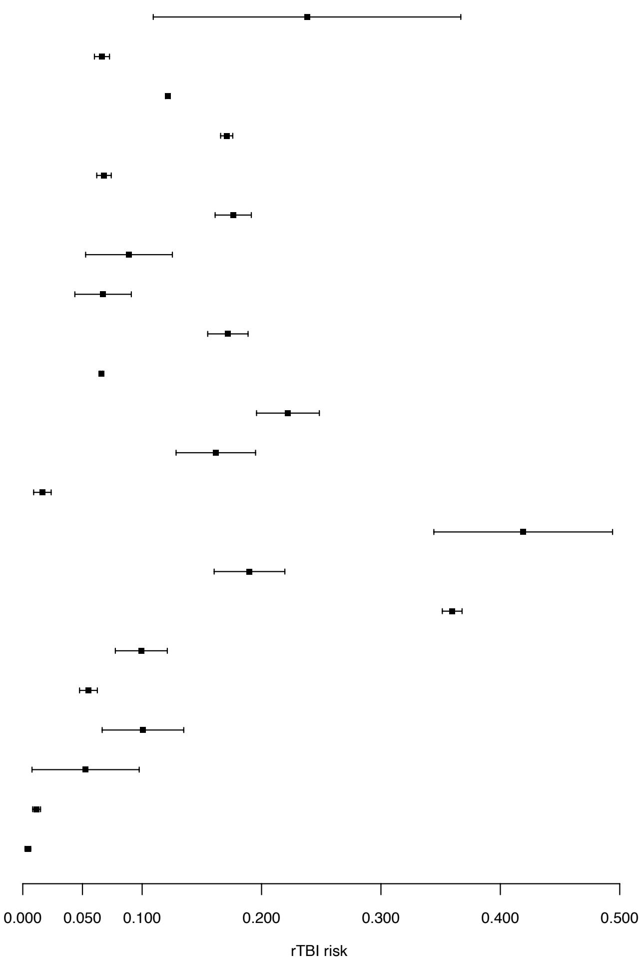


Figure 2: rTBI risk estimates
rTBI risks reported in the 22 included studies. The forest plot is ordered from studies with the longest to shortest average follow-up period. TBI = traumatic brain injury, rTBI = recurrent traumatic brain injury.

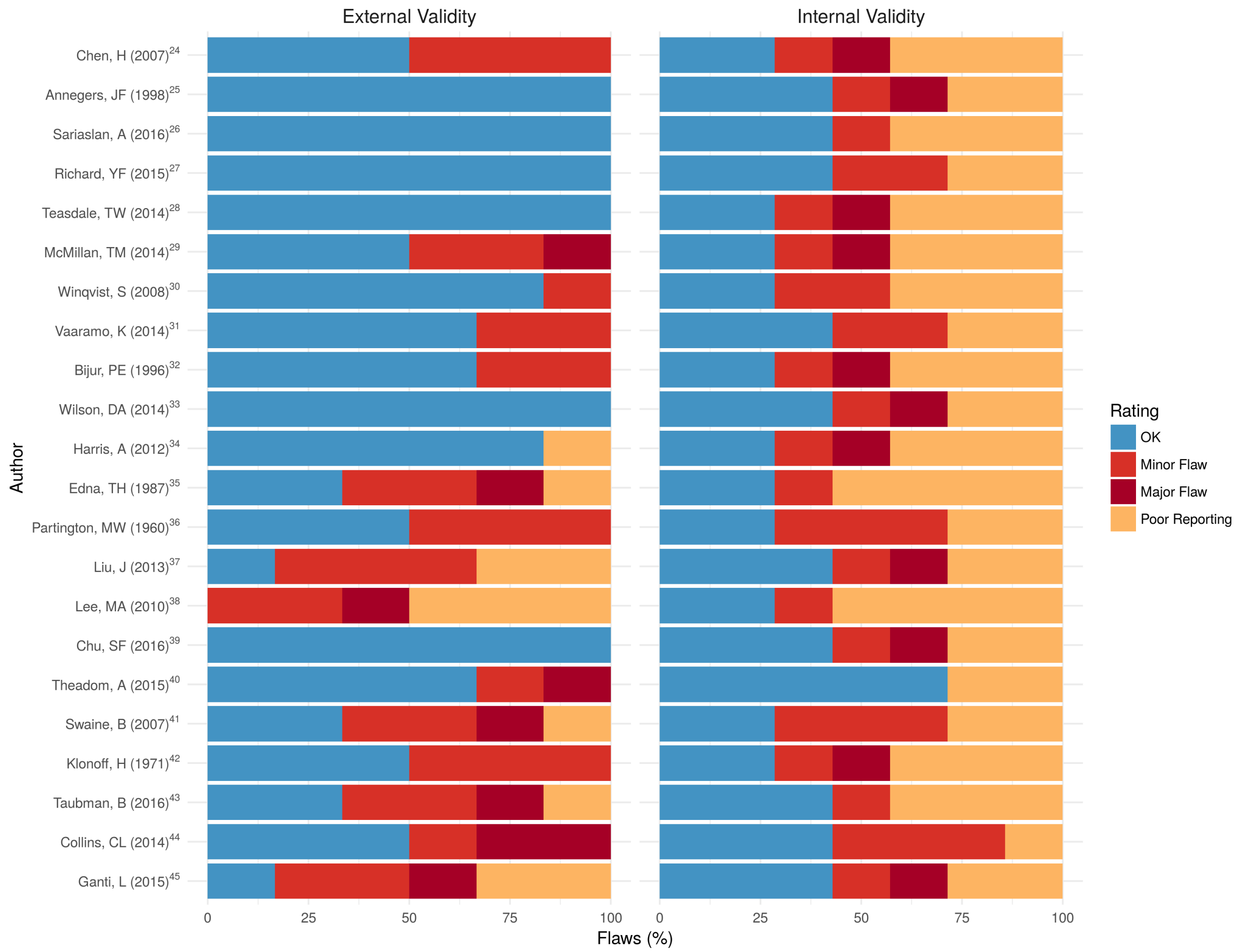


Figure 3: Quality assessment for rTBI risk

Quality assessment of rTBI risk stratified by internal and external validity. The proportion of each type of response to the 6 external validity criteria and 7 internal validity criteria is shown. Table e-2 provides a summary of the criteria used in the quality assessment

Risk factor	Study	RF+/ rTBI+	RF+/ rTBI−	RF−/ rTBI+	RF−/ rTBI−	Crude RR	Adjusted HR/OR
Sex (Male)	Sariaslan, A[26]	9154	58027	3526	33583	1.43 (1.38–1.49)	
	Winqvist, S[30]	14	154	7	61	0.85 (0.34–1.92)	0.86 (0.33–2.28)
	Vaaramo, K[31]	36	528	16	247	1.05 (0.59–1.86)	0.88 (0.47–1.64)
	Bijur, PE[32]	232	904	97	682	1.64 (1.32–2.04)	
	Edna, TH[35]	60	283	16	111	1.39 (0.83–2.32)	
	Partington, MW[36]	15	810	4	351	1.61 (0.54–4.83)[a]	
	Liu, J[37]	39	57	31	40	0.93 (0.65–1.33)	
	Saunders, L[46]	214	2607	89	1447	1.31 (1.03–1.66)	1.28 (1.00–1.65)
Prior TBI	Vaaramo, K[31]	6	28	46	747	3.04 (1.40–6.63)	3.39 (1.32–8.72)
	Edna, TH[35]	14	49	62	345	1.46 (0.87–2.44)	
	Theadom, A[40]	43	31	28	38		1.88 (0.96–3.69)[b]
	Taubman, B[43]	24	10	66	80	2.91 (1.30–6.52)[c]	
	Saunders, L[46]	24	158	279	3896	1.97 (1.34–2.91)	1.62 (1.08–2.42)
Severity (moderate/severe vs. mild)	Sariaslan, A[26]	2427	21187	7346	73330	1.13 (1.08–1.18)	
	Winqvist, S[30]	2	28	19	187	0.72 (0.18–2.95)	1.43 (0.28–7.22)
	Vaaramo, K[31]	10	101	19	301	1.52 (0.73–3.16)	
	Saunders, L[46]	160	1800	142	2254	1.37 (1.11–1.71)[d]	1.24 (1.00–1.54)[d]
Alcohol intoxication	Winqvist, S[30]	9	27	12	188	4.17 (1.89–9.16)	4.41 (1.53–12.70)
	Vaaramo, K[31]	28	268	24	507	2.09 (1.24–3.54)	2.51 (1.38–4.56)
	Theadom, A[40]	13	13	57	56		0.98 (0.42–2.30)[b]
	Saunders, L[47]	46	435	101	1517	1.53 (1.10–2.14)	
Rural	Winqvist, S[30]	7	150	14	65	0.25 (0.11–0.60)	0.23 (0.09–0.59)
	Liu, J[37]	10	19	60	78	0.79 (0.46–1.36)	
	Theadom, A[40]	17	19	55	53		0.86 (0.41–1.83)[b]
	Saunders, L[46]	70	1042	233	3012	0.88 (0.68–1.14)	
Mechanism (fall vs. other)	Winqvist, S[30]	2	36	19	179	0.55 (0.13–2.26)	
	Theadom, A[40]	29	24	43	48		1.35 (0.68–2.66)[b]
	Saunders, L[46]	109	1212	194	2842	1.29 (1.03–1.62)	
Single parent	Sariaslan, A[26]	4807	30765	7873	60845	1.18 (1.14–1.22)	
	Winqvist, S[30]	3	15	18	200	2.02 (0.66–6.21)	1.64 (0.45–6.02)
	Liu, J[37]	1	5	67	89	0.39 (0.06–2.34)	
Age (10−year increase)[e]	Vaaramo, K[31]					1.22 (1.00–1.34)	1.11 (1.00–1.34)
	Saunders, L[46]					1.03 (0.98–1.07)	0.96 (0.82–1.05)
Drug use	Theadom, A[40]	7	3	62	65		2.45 (0.61–9.89)[b]
	Saunders, L[47]	13	111	134	1941	1.62 (0.95–2.79)	
Race (non−white)	Theadom, A[40]	56	55	16	17		1.08 (0.50–2.35)[b]
	Saunders, L[46]	77	1196	226	2858	0.83 (0.64–1.06)	0.65 (0.50–0.84)
Polytrauma	Theadom, A[40]	42	42	24	28		1.17 (0.58–2.33)[b]
	Saunders, L[46]	203	2931	100	1123	0.79 (0.63–1.00)	
Lifetime psychiatric comorbidity in parent	Sariaslan, A[26]	4187	26461	8493	65149	1.18 (1.14–1.23)	
	Liu, J[37]	6	4	64	93	1.47 (0.86–2.53)	
Parent's education (<High school)	Sariaslan, A[26]	2563	16696	10117	74914	1.12 (1.07–1.17)	
	Liu, J[37]	18	45	52	52	0.57 (0.37–0.88)[f]	
Education (<College)	Saunders, L[47]	111	1294	36	658	1.52 (1.06–2.19)	
Medical comorbidities	Saunders, L[46]	146	1914	157	2140	1.04 (0.84–1.29)	
Insurance (uninsured)	Saunders, L[46]	108	1026	195	3028	1.57 (1.26–1.97)	
Epilepsy	Saunders, L[46]	40	316	263	3738	1.71 (1.25–2.34)	
Father's occupation (unemployed)	Liu, J[37]	1	7	69	90	0.29 (0.05–1.82)	
Mother's occupation (unemployed)	Liu, J[37]	2	9	68	88	0.42 (0.12–1.48)	
Father's smoking status (non−smoker)	Liu, J[37]	15	16	52	78	1.21 (0.80–1.84)	
Mother's age at child's birth (<25 years)	Liu, J[37]	14	24	56	73	0.85 (0.54–1.35)	
Lead (>=10ug/dL in blood)	Liu, J[37]	5	7	65	90	0.99 (0.50–1.99)	
Parent with a criminal history	Sariaslan, A[26]	6722	42365	5958	49245	1.27 (1.23–1.31)	
Income (lowest decile)	Sariaslan, A[26]	1531	9797	11149	81813	1.13 (1.07–1.18)	
Comorbid psychiatric condition	Vaaramo, K[31]	4	26	48	749	2.21 (0.85–5.74)	
Not seeking medical care within 24 hours	Theadom, A[40]	19	8	53	64		2.87 (1.16–7.09)[b]
Skull fracture	Edna, TH[35]	14	60	62	334	1.21 (0.72–2.04)	

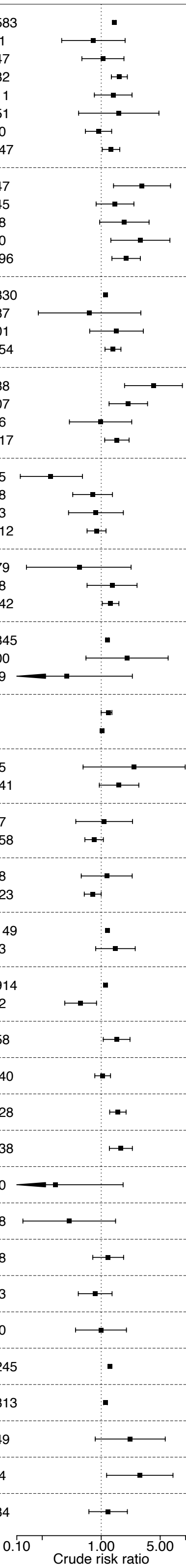


Figure 4: Summary of association measures for all identified risk factors.
Forest plot of association measures for the 27 risk factors identified in the systematic search and measured at baseline (incident TBI). Covariates used for adjustment and matching are provided in Table e-5. [a]Risk ratio was calculated using all occurrences of rTBI and not for individual patients (data were not available, there were 44 repeat injuries in 25 patients). [b]All studies reported by Theadom (2015)[40] are adjusted odds ratios because cases and controls were matched. [c]Crude estimate is an odds ratio. [d]Comparison is severe versus moderate/mild. [e]Crude estimate is a hazard ratio and standardized mean differences are not shown but reported in Figure e-2. [f]Data are shown for father's education only, but similar estimates were also reported for mother's education (not shown). RR = risk ratio, HR = hazard ratio, OR = odds ratio. Saunders (2009)[46] and Saunders (2009)[47] were used to assess RFs instead of Wilson (2014)[33], which did not report RFs but had a larger sample size for the same study population.

Supplementary Online Content for Manuscript 2

Methods e-1: Search strategy used in MEDLINE and EMBASE

MEDLINE

1 craniocerebral trauma/ or brain injuries/ or exp brain concussion/ or exp brain hemorrhage, traumatic/ or exp head injuries, closed/ or exp head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/
2 ((brain or head) adj (trauma or injur*)).mp.
3 tbi*.mp.
4 concussion*.mp.
5 Recurrence/
6 (recur* adj30 (concussion* or injur* or tbi)).mp.
7 ((repeat* or repetitive or recidivis*) adj30 (concussion* or injur* or tbi)).mp.
8 ((multiple adj1 concussion*) or (multiple adj3 injur*) or (multiple adj1 tbi).mp.
9 1 or 2 or 3 or 4
10 5 or 6 or 7 or 8
11 9 and 10
12 limit 11 to (english or french)

EMBASE

1 brain injury/ or exp acquired brain injury/ or exp brain concussion/ or exp traumatic brain injury/
2 head injury/
3 ((brain or head) adj (trauma or injur*)).mp.
4 tbi*.mp.
5 concussion*.mp.
6 1 or 2 or 3 or 5
7 recurrent disease/
8 (recur* adj30 (concussion* or injur* or tbi)).mp.
9 (((repeat* or repetitive or recidivis*) adj30 (concussion* or injur* or tbi))).mp.
10 ((multiple adj1 concussion*) or (multiple adj3 injur*) or (multiple adj1 tbi)).mp.
11 7 or 8 or 9 or 10
12 6 and 11
13 limit 12 to (conference abstract or conference paper or conference proceeding or "conference review")
14 12 not 13
15 limit 14 to (english or french)

Table e-1: Detailed study characteristics

Author (Year)	Index TBI definition	rTBI definition	Data source	Inclusion criteria	Age	Gender	Severity distribution of index
Chen, H (2007)[24]	Patient self-report on head injury requiring medical attention during their lifetime	Same as index	Survey	Controls from New England matched to ALS cases on age, sex and area code from 1993-1996	30-55: 33% 56-65: 29% 66-80: 38%	Male: 61%	N/A
Annegers, JF (1998)[25]	Clinical definition (not specified)	Same as index	Medical Record Linkage System of the Rochester Epidemiology Project	Inpatient, outpatient or ED visits for TBI from 1935-1984	N/A	N/A	N/A

Sariasian, A (2016)[26]	ICD-8: 800-804, 850–854, ICD-9: 800-804, 850–854, ICD-10: S01.0–S01.9, S02.0-S02.3, S02.7–S02.9, S04.0, ICD-10: S01.0–S01.9, S02.0-S02.3, S02.7–S02.9, S04.0, S06.0–S06.9, S07.0-S07.1, S07.8-S07.9, S09.7–S09.9, T01.0, T02.0, T04.0, T06.0, T90.1-T90.2, T90.4-T90.5, T90.8-T90.9	Sane as index TBI occurring at least 15 days after the first injury	National Patient Register	Inpatient, ER and outpatient visits for TBI of individuals born from 1973-1985	Mean 13.8 (SD = 0.02) for single, 12.0 (SD = 0.06) for recurrent	Male: 64.4%	22.6% moderate/severe and 77.4% mild
Richard, YF (2015)[27]	ICD-9: 800-804, 851-854	ICD-9 occurring 90 days after index TBI	Régie de l'assurance maladie du Québec medical services database	Inpatient, ER and outpatient visits for TBI during 1987	N/A	Male: 67.3%	N/A
Teasdale, TW (2014)[28]	ICD-9: 850 ICD-10: S06.0	Same as index but only >3	Ministry of Health database,	Men hospitalized with concussion for less than 2 days	For single concussions only:	Male: 100%	N/A (meant to only include concussions)

		days after index TBI	Landspatient-register	and who were assessed by the Draft Board (~82%) between 2006-2010	0-6 41% 7-12: 27.1% 13-testing: 27.1% post-testing: 4.8%		
McMillan, TM (2014)[29]	Clinical diagnosis as identified by research team (compared to administrative data)	Same as index but only after February 1996	Information Services Division of the National Health Survey of Scotland	Hospital admissions in Glasgow with mild head injury (GCS 13-15) February 1995 to February 1996	Median: 39 (range 14-98)	Male: 76.9%	100% mild
Winqvist, S (2008)[30]	ICD 8/9: 800, 801, 803, 850, 851–854 ICD 10: S02.0–S02.11, S06.0–S06.9, S07.1	Same as index TBI	Finnish Hospital Discharge Register	Inpatient or ER visits >24 for TBI	Mean 20.2 (SD = 5.5) for single TBI, mean 21.0 (SD = 5.8) for rTBI	Male: 71.2%	87.2% mild, 12.8% moderate/ severe
Vaaramo, K (2014)[31]	Clinical from Oulu hospital charts (not specified)	ICD-10 from National Hospital Discharge Register S06.0-S06.9 (inpatient	Discharge register and ER checklist (index TBI)/ Administrative data and hospital chart (rTBI)	Visits at Oulu Hospital ER for TBI during 1999 (index TBI)	Mean 38.6 (22.8)	Male: 68.2%	86.6% mild, 13.4% moderate/severe

		only) and hospital charts from Oulu hospital					
Bijur, PE (1996)[32]	Parent self-report interpreted by trained coders	Same as index	National survey	Community children born in April 1970	N/A	Male: 59.3%	N/A
Wilson, DA (2014)[33]	ICD-9: 800.x, 801.x, 804.x, 850.x, 854.x, 959.01	Same as index occurring 1 week after index TBI	South Carolina TBI surveillance system	Inpatient/ED visits for TBI from 1998-2011	Mean 34.1 (25.1) for group without ESD	Male: 56.9%	14.4% severe
Harris, A (2012)[34]	ICD-9: 800, 801, 803, 804, 850-854, 925 ICD-10: S02-S02.1, S02.7-S02.9, S06, S07, T02-T02.01	Same as index TBI but >14 days after	Ambulatory Care Classification System	ED visits for sports injuries within 5 hospitals' of residents of Edmonton's Census Metropolitan Area	N/A	Male: 76.9%	N/A
Edna, TH (1987)[35]	Clinical (loss of consciousness or skull fracture or development of an intracranial hematoma)	Patient self-report	Survey	Hospital admissions at 4 surgical departments	N/A	Male: 72.9%	88.5% mild
Partington, MW (1960)[36]	Clinical diagnosis: coma, stupor, drowsiness, confusion, vomiting,	Same as index	Medical charts	Inpatient visits for head injury at Sheffield Children's	0-4: 36% 5-9: 47% 10-13: 17%	Male: 70%	98.5% mild/moderate

	convulsions, lacerations of the head or bleeding from nose/ear with a plausible history of an accident that could cause a TBI			Hospital 1952-1958			
Liu, J (2013)[37]	Parent self-report	Parent self-report	Survey	Community sample of 6-year-old school children in Jintan	N/A	Male: 57.4%	N/A
Lee, MA (2010)[38]	Clinical (not defined)	Same as index	Medical chart	All concussion patients referred to an outpatient practice from July 2004 to December 2008	Mean 14.99 (1.84)	Male: 62.6%	N/A
Chu, SF (2016)[39]	ICD-9: 800.XX-804.XX, 850.XX-854.XX	Same as index	Longitudinal Health Insurance Database of Taiwan	All medical claims for TBI in 2004/2005 >18 years of age	18-45: 55.2%, 46-65: 27.4%, >65: 17.5%	Male: 50.2%	N/A
Theadom, A (2015)[40]	Clinical: diagnostic committee established diagnosis	Same as index TBI	Clinical interview, medical charts, self-report, administrative health data	Inpatient/outpatient visits and self-reported cases in Hamilton New Zealand in 2010-2011	Mean rTBi cases 23,99 (SD = 17.95)	Male: 54% (for rTBI cases)	1.4% moderate, 0% severe, 98.6% mild

Swaine, B (2007)[41]	Trauma registry: minor HI, skull fracture, intracranial injury, concussion, facial injuries if struck forcefully	Parent self-report of TBI requiring medical attention	ED trauma registry (index TBI)	ED visits for TBI to 1 of 2 pediatric provincial neurotrauma centres and agree to participate in follow-up survey from 2000-2003	Mean 6.5 (SD = 4.5)	Male: 65%	N/A
Klonoff, H (1971)[42]	Clinical diagnosis: Possible head injury-contusion, abrasion	Parent self-report of subsequent head injury	Medical chart and survey	ED and hospital visits for TBI presenting to Health Centre for Children (Vancouver General Hospital) from April 1968 to March 1969	Mean 6.5 years (emergency group) and 6.94 years (hospitalized group)	Male: 63.5%	N/A
Taubman, B (2016)[43]	Clinical: head trauma or acceleration-deceleration injury to the head with neurological symptoms	Same as index	Physician chart	Primary care visits for concussion without intracranial lesions on imaging, occurring within 7 days of TBI and for patients not hospitalized greater than 24 hours over an 18-month period	Mean 14.33	Male: 59%	100% mild

Collins, CL (2014)[44]	ICD-9: 310.2, 800.0, 800.5, 801.0, 801.5, 803.0, 803.5, 804.0, 804.5, 850.0, 850.1, 850.5, 850.9, 854.0, 959.0, 800-801.9, 803-804.9	Same as index TBI occurring 90 days after index TBI and medical records reviewed	Local hospital database	All TBI visits at Midwest Children's Hospital (inpatient, ER, outpatient)	Mean 7.77 (SD = 5.88)	Male: 61.9%	92% mild, 8% moderate/severe
Ganti, L (2015)[45]	ICD-9: 800.0-804.9, 850.0-854.1, 959.01, 995.55	Chart review of patients presenting to ED with rTBI within 72 hours of index TBI	Administrative data from local hospital database and medical chart for severity assessment	Patients presenting to a single hospital's Level 1 ED with mTBI (GCS >+13)	Mean 43 (SD = 21.5) for patients with no return to ED	Male 57.5%	100% mild

Additional study characteristics. TBI = traumatic brain injury, rTBI = recurrent traumatic brain injury, ICD = international classification of disease, GCS = Glasgow Coma Score, ED = emergency department, SD= standard deviation, N/A= Not available/reported. [a]Median time to injury was taken from Saunders (2009)[47], which was conducted on the same population as Wilson (2014)[33].

Table e-2: Summary of criteria used to conduct quality assessment for rTBI risk

	OK	Major flaw	Minor Flaw	Poor reporting	N/A
General characteristics					
Funding of study	18 (81.9%)			4 (18.1%)	
Role of funding organization in data analysis and interpretations of the results	15 (68.2%)			7 (31.8%)	
Conflict of interest	16 (72.7%)			6 (27.3%)	
Ethical approval of the study	14 (63.6%)			8 (36.4%)	
Aim of study (not related to rTBI)[a]	11 (50%)			11 (50%)	
External validity					
General population based sampling frame	11 (50%)			4 (18.1%)	7 (31.8%)
Non-general population based sampling frame		7 (31.8%)			15 (68.2%)
Assessment of sampling bias	9 (40.9%)		13 (59.1%)		
Estimate bias: Response rate in total sample	20 (90.9%)			2 (9.1%)	
Exclusion rate from the analysis	18 (81.9%)		1 (4.5%)	3 (13.6%)	
Sampling bias is addressed in the analysis	7 (31.8%)		15 (68.2%)		
Subject flow	16 (72.7%)			6 (27.3%)	
Internal validity					
Source to measure incidence	1 (4.5%)		21 (95.5%)		
Reference period defined	22 (100%)				
Validation of outcomes measurements	2 (9.1%)	8 (36.4%)	10 (45.5%)	2 (9.1%)	
Reliability of the estimates		3 (13.6%)		19 (86.4%)	
Reporting of Incidence	10 (45.5%)			12 (54.5%)	
Precision of estimation				22 (100%)	
Reporting of incidence type	22 (100%)				

Summary of quality assessment for rTBI risk across internal and external validity domains using the Methodological Evaluation of Observation Research (MORE) checklist. A total of 6 external validity and 7 internal validity criteria were assessed for each study. [a]Primary aim of study was focused on rTBI in 11/22 studies. N/A = Not applicable, rTBI = recurrent traumatic brain injury.

Table e-3: Heterogeneity assessment of rTBI risk through meta-regression

Study-level characteristic	Beta	95% CI	Adjusted R^2 (%)
Average follow-up (years)	0.001	-0.003 , 0.005	-3.57
Average follow-up (years) – log transformed	0.01	-0.01 , 0.04	2.14
Age (studies only including children/young adults vs. all age groups/adults)	0.02	-0.08 , 0.11	-4.72
Primary aim of study to assess rTBI	-0.03	-0.12 , 0.06	-3.17
Study quality (number of "Ok" criteria)	-0.002	-0.025 , 0.020	-5.42
Comprehensiveness of rTBI cases ascertained (>1 point-of-care versus 1 point-of-care)	0.08	-0.014 , 0.17	8.75
Data source (administrative/survey versus trauma registry/clinical)	0.12	0.04 , 0.20	29.41
Data source (administrative/survey versus trauma registry/clinical) adjusted for log follow-up time	0.12	0.02 , 0.22	25.71

Meta-regression of study-level factors against rTBI risk estimate (outcome) with the adjusted R^2 representing the proportion of between-study variance explained. Follow-up time was transformed on the log scale as the risk of rTBI tended to rise slower with longer follow-up time.

Table e-4: Summary of criteria used to conduct quality assessment for rTBI risk factors

	OK	Major flaw	Minor flaw	Poor reporting	N/A
Source of measure incidence of chronic diseases	9 (15%)		51 (85%)		
Reference period if applicable	60 (100%)				
Severity	56 (93.3%)	4 (6.7%)			
Validation of outcomes measurements	10 (16.6%)	34 (56.7%)	13 (21.7%)	3 (5%)	
Source to measure exposure	9 (15%)		51 (85%)		
Reference period for exposure	34 (56.6%)		1 (1.7%)		25 (41.6%)
Intensity	8 (13.3%)		20 (33.3%)		32 (53.3%)
Measurements of the exposure	40 (66.6%)	1 (1.7%)	18 (30%)	1 (1.7%)	
Reliability of exposure estimates	18 (30%)		3 (5%)	39 (65%)	
Differential non-response between cases and controls (case-control studies only)	14 (23.3%)				46 (76.7%)
Confounding factors assessed	29 (48.3%)	18 (30 %)	13 (21.7%)		
Measurement of confound-ding factors	12 (20%)		37 (61.7%)	11 (18.3%)	
Loss of follow-up	30 (50%)			30 (50%)	
Exposure measurement for cases and controls (case-control studies only)	14 (23.3%)				46 (76.7%)
Masking of exposure status for investigators who measured dependent variables	2 (3.3%)		10 (16.7%)	48 (80%)	
Statistical analysis	35 (58.3%)	22 (36.7%)	3 (5%)		
Assessment of temporality	58 (96.7%)		2 (3.3%)		
Appropriateness of statistical model to reduce research specific bias	25 (41.7%)		24 (40%)	11 (18.3%)	
Dose-response with exposure	12 (20%)		19 (31.7%)		29 (48.3%)
Reporting of tested hypothesis	24 (40%)	26 (43.3%)		10 (16.7%)	
Precision of estimates	33 (55%)		23 (38.3%)	4 (6.7%)	
Sample size justification				60 (100%)	

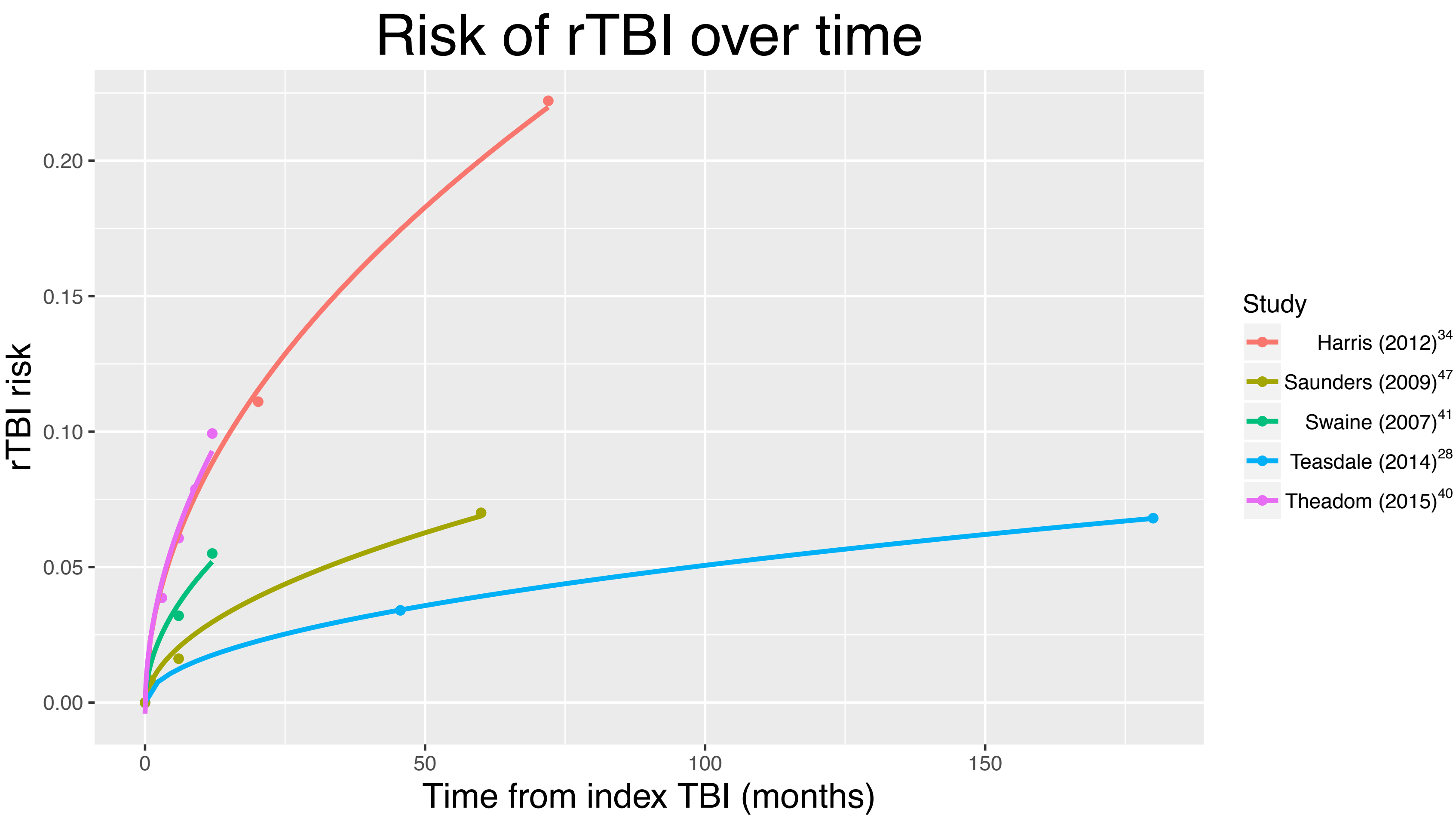
Summary of quality assessment using the Methodological Evaluation of Observation Research (MORE) checklist. Since the external validity assessment for RFs is the same as for the risk QA (eTable 2), only the internal validity assessment is shown. A total of 22 criteria were assessed for each risk factor in each study. N/A = Not applicable.

Table e-5: Covariates used in adjusted risk factor association measures

Study	Covariates in adjustment set	Reported effect measure
Saunders (2009)[46]	Age Sex Mechanism of injury Medical insurance type Seizures Prior TBI	HR
Winqvist (2008)[30]	Sex Alcohol intoxication at index TBI Rural/urban residence Mechanism of injury TBI severity Marital status of parents	HR
Vaaramo (2014)[31]	Age Sex TBI severity Prior TBI Prior harmful drinking Alcohol intoxication at index TBI	HR
Theadom (2015)[40]	Matched on Age, Sex and TBI severity	OR

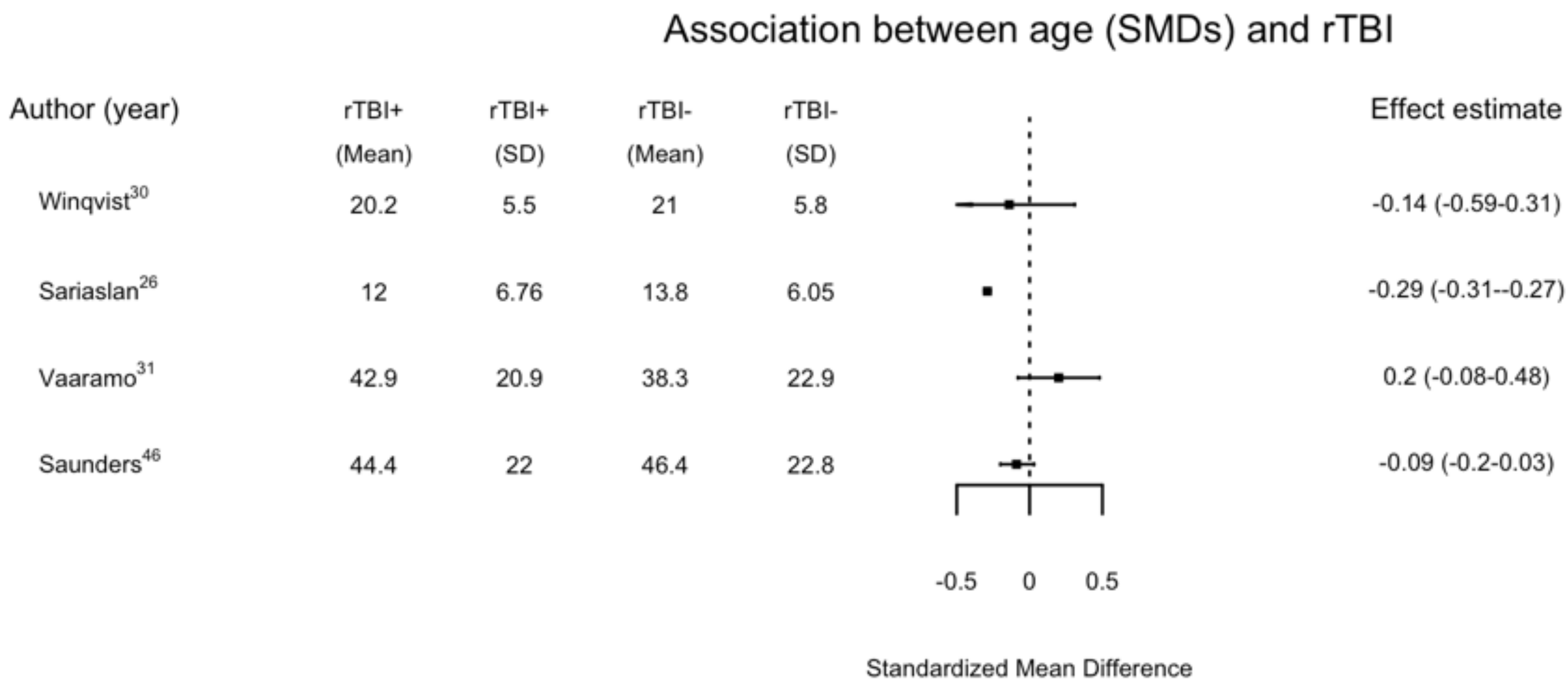
Studies reporting adjusted measures and the covariates used in the adjustment set. N.B. Theadom (2015)[40] matched cases and controls on the listed factors, and all adjusted measures are reported as ORs. OR = Odds ratio, HR = Hazard ratio, TBI = traumatic brain injury.

Figure e-1: Relationship between time after index TBI and rTBI risk



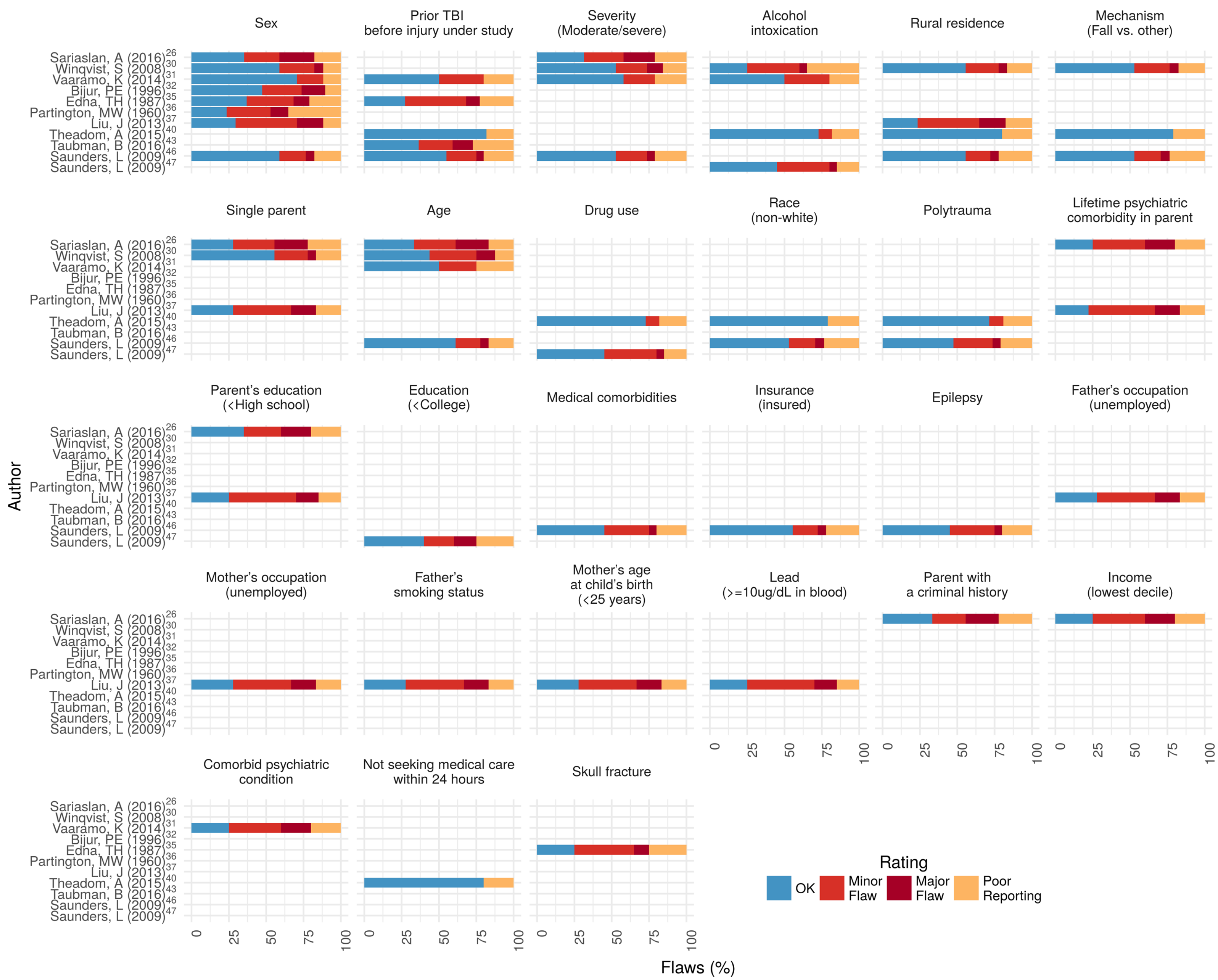
Relationship between time after index TBI and rTBI risk. The 5 studies that reported the risk of rTBI at different times of follow-up are included in this plot. The curves were produced using a square-root function to smooth over the points.

Figure e-2: Forest plot of the association between age and rTBI (standardized mean differences)



Studies reporting the association between age and rTBI. No pooling of estimates was completed because of significant heterogeneity. Sariaslan (2009)[26] and Winqvist (2009)[30] were studies conducted in children/young adult populations whereas Saunders (2009)[46] and Vaaramo (2014)[31] were conducted in all age groups. SMD = standardized mean difference, SD = standard deviation.

Figure e-3: Study-specific quality assessment for rTBI risk factors



Quality assessment for the 27 risk factors identified in the systematic search. Only the internal validity domain was assessed as the external validity assessment is the same as for the rTBI risk quality assessment shown in eTable 2. The proportion of each type of response to the 22 criteria is shown. eTable 4 provides a summary of each criteria used in the quality assessment.

Results e-1: Breakdown of references used in the rTBI risk and rTBI risk factor analyses

References of included studies in the rTBI risk analysis (n=22):

1. Chen H, Richard M, Dandler DP, Umbach DM, Kamel F. Head Injury and Amyotrophic Lateral Sclerosis. Am J Epidemiol 2007;166:810-816.
2. Annegers J, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20-24.
3. Sariaslan A, Sharp DJ, D'Onofrio BM, Larsson H, Fazel S. Long-Term Outcomes Associated with Traumatic Brain Injury in Childhood and Adolescence: A Nationwide Swedish Cohort Study of a Wide Range of Medical and Social Outcomes. PLoS Med 2016;13:e1002103.
4. Richard YF, Swaine BR, Sylvestre M-P, Lesage A, Zhang X, Feldman DE. The association between traumatic brain injury and suicide: are kids at risk? Am J Epidemiol 2015;182:177-184.
5. Teasdale TW, Frosig AJ, Engberg A. Adult cognitive ability and educational level in relation to concussions in childhood and adolescence: A population study of young men. Brain Inj 2014;28:1721-1725.
6. McMillan TM, Weir CJ, Wainman-Lefley J. Mortality and morbidity 15 years after hospital admission with mild head injury: a prospective case-controlled population study. J Neurol Neurosurg Psychiatry 2014;85:1214-1220.
7. Winqvist S, Luukinen H, Jokelainen J, Lehtilahti M, Nayha S, Hillbom M. Recurrent traumatic brain injury is predicted by the index injury occurring under the influence of alcohol. Brain Inj 2008;22:780-785.
8. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: A long-term follow-up study. Eur J Neurol 2014;21:293-298.
9. Bijur PE, Haslum M, Golding J. Cognitive outcomes of multiple mild head injuries in children. J Dev Behav Pediatr 1996;17:143-148.
10. Wilson DA, Selassie AW. Risk of severe and repetitive traumatic brain injury in persons with epilepsy: a population-based case-control study. Epilepsy Behav 2014;32:42-48.
11. Harris AW, Voaklander DC, Jones CA, Rowe BH. Time-to-subsequent head injury from sports and recreation activities. Clin J Sport Med 2012;22:91-97.
12. Edna TH, Cappelen J. Late post-concussional symptoms in traumatic head injury. An analysis of frequency and risk factors. Acta Neurochir (Wien) 1987;86:12-17.
13. Partington MW. The Importance of Accident-Proneness in the Aetiology of Head Injuries in Childhood. Arch Dis Child 1960;35:215-223.
14. Liu J, Li L. Parent-reported mild head injury history and behavioural performance in children at 6 years. Brain Inj 2013;27:1263-1270.
15. Lee MA, Fine B. Adolescent concussions. Conn Med 2010;74:149-156.
16. Chu S, Chiu W, Lin H, Chiang Y, Liou T. Hazard Ratio and Repeat Injury for Dementia in Patients With and Without a History of Traumatic Brain Injury: A Population-Based Secondary Data Analysis in Taiwan. Asia Pacific J Public Heal 2016;28:519-527.
17. Theadom A, Parmar P, Jones K, et al. Frequency and impact of recurrent traumatic brain injury in a population-based sample. J Neurotrauma 2015;32:674-681.
18. Swaine BR, Tremblay C, Platt RW, Grimard G, Zhang X, Pless IB. Previous head injury is a risk factor for subsequent head injury in children: a longitudinal cohort study. Pediatrics 2007;119:749-758.
19. Klonoff H. Head injuries in children: predisposing factors accident conditions, accident proneness and sequelae. Am J Public Health 1971;61:2405-2417.
20. Taubman B, McHugh J, Rosen F, Elci OU. Repeat Concussion and Recovery Time in a Primary Care Pediatric Office. J Child Neurol 2016;31:1607-1610.
21. Collins CL, Yeates KO, Pommering TL, et al. Direct medical charges of pediatric traumatic brain injury

in multiple clinical settings. Inj Epidemiol 2014;1.
22. Ganti L, Conroy LM, Bodhit A, et al. Understanding why patients return to the emergency

References of studies included in the risk factor analysis (n=11):

1. Taubman B, McHugh J, Rosen F, Elci OU. Repeat Concussion and Recovery Time in a Primary Care Pediatric Office. J Child Neurol 2016;31:1607-1610.
2. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: A long-term follow-up study. Eur J Neurol 2014;21:293-298.
3. Theadom A, Parmar P, Jones K, et al. Frequency and impact of recurrent traumatic brain injury in a population-based sample. J Neurotrauma 2015;32:674-681.
4. Winqvist S, Luukinen H, Jokelainen J, Lehtilahti M, Nayha S, Hillbom M. Recurrent traumatic brain injury is predicted by the index injury occurring under the influence of alcohol. Brain Inj 2008;22:780-785.
5. Sariaslan A, Sharp DJ, D'Onofrio BM, Larsson H, Fazel S. Long-Term Outcomes Associated with Traumatic Brain Injury in Childhood and Adolescence: A Nationwide Swedish Cohort Study of a Wide Range of Medical and Social Outcomes. PLoS Med 2016;13:e1002103.
6. Edna TH, Cappelen J. Late post-concussional symptoms in traumatic head injury. An analysis of frequency and risk factors. Acta Neurochir (Wien) 1987;86:12-17.
7. Bijur PE, Haslum M, Golding J. Cognitive outcomes of multiple mild head injuries in children. J Dev Behav Pediatr 1996;17:143-148.
8. Liu J, Li L. Parent-reported mild head injury history and behavioural performance in children at 6 years. Brain Inj 2013;27:1263-1270.
9. Partington MW. The Importance of Accident-Proneness in the Aetiology of Head Injuries in Childhood. Arch Dis Child 1960;35:215-223.
10. Saunders LL, Selassie AW, Hill EG, et al. A population-based study of repetitive traumatic brain injury among persons with traumatic brain injury. Brain Inj 2009;23:866-872.
11. Saunders LL, Selassie AW, Hill EG, et al. Pre-existing health conditions and repeat traumatic brain injury. Arch Phys Med Rehabil 2009;90:1853-1859.

References of studies meeting inclusion criteria for rTBI risk but excluded because another included study used the same study population with a larger sample size (n=7):

1. Theadom A, Starkey NJ, Dowell T, et al. Sports-related brain injury in the general population: an epidemiological study. J Sci Med Sport 2014;17:591-596.
2. Annegers JF, Grabow JD, Groover R V, Laws ERJ, Elveback LR, Kurland LT. Seizures after head trauma: a population study. Neurology 1980;30:683-689.
3. Saunders LL, Selassie AW, Hill EG, et al. A population-based study of repetitive traumatic brain injury among persons with traumatic brain injury. Brain Inj 2009;23:866-872.
4. Saunders LL, Selassie AW, Hill EG, et al. Pre-existing health conditions and repeat traumatic brain injury. Arch Phys Med Rehabil 2009;90:1853-1859.
5. Selassie AW, Wilson DA, Pickelsimer EE, et al. Incidence of sport-related traumatic brain injury and risk factors of severity: A population-based epidemiologic study. Ann Epidemiol 2013;23:750-756.
6. Peters TL, Fang F, Weibull CE, Sandler DP, Kamel F, Ye W. Severe head injury and amyotrophic lateral sclerosis. Amyotroph Lateral Scler Frontotemporal Degener 2013;14:267-272.
7. Annegers JF, Grabow JD, Kurland LT, Laws ERJ. The incidence, causes, and secular trends of head trauma in Olmsted County, Minnesota, 1935-1974. Neurology 1980;30:912-919.

*The two Saunders (2009)[46,47] publications were excluded from the rTBI risk assessment because Wilson

(2014)[33] used a larger sample size for the same population in their study. However, the two Saunders (2009)[46,47] publications were used in the risk factor analysis as they reported risk factors not included in the Wilson (2014)[33] publication.

References (numbered as in the main manuscript)

24. Chen H, Richard M, Dandler DP, Umbach DM, Kamel F. Head Injury and Amyotrophic Lateral Sclerosis. Am J Epidemiol 2007;166:810-816.
25. Annegers J, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20-24.
26. Sariaslan A, Sharp DJ, D'Onofrio BM, Larsson H, Fazel S. Long-Term Outcomes Associated with Traumatic Brain Injury in Childhood and Adolescence: A Nationwide Swedish Cohort Study of a Wide Range of Medical and Social Outcomes. PLoS Med 2016;13:e1002103.
27. Richard YF, Swaine BR, Sylvestre M-P, Lesage A, Zhang X, Feldman DE. The association between traumatic brain injury and suicide: are kids at risk? Am J Epidemiol 2015;182:177-184.
28. Teasdale TW, Frosig AJ, Engberg A. Adult cognitive ability and educational level in relation to concussions in childhood and adolescence: A population study of young men. Brain Inj 2014;28:1721-1725.
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30. Winqvist S, Luukinen H, Jokelainen J, Lehtilahti M, Nayha S, Hillbom M. Recurrent traumatic brain injury is predicted by the index injury occurring under the influence of alcohol. Brain Inj 2008;22:780-785.
31. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Head trauma sustained under the influence of alcohol is a predictor for future traumatic brain injury: A long-term follow-up study. Eur J Neurol 2014;21:293-298.
32. Bijur PE, Haslum M, Golding J. Cognitive outcomes of multiple mild head injuries in children. J Dev Behav Pediatr 1996;17:143-148.
33. Wilson DA, Selassie AW. Risk of severe and repetitive traumatic brain injury in persons with epilepsy: a population-based case-control study. Epilepsy Behav 2014;32:42-48.
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35. Edna TH, Cappelen J. Late post-concussional symptoms in traumatic head injury. An analysis of frequency and risk factors. Acta Neurochir (Wien) 1987;86:12-17.
36. Partington MW. The Importance of Accident-Proneness in the Aetiology of Head Injuries in Childhood. Arch Dis Child 1960;35:215-223.
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38. Lee MA, Fine B. Adolescent concussions. Conn Med 2010;74:149-156.
39. Chu S, Chiu W, Lin H, Chiang Y, Liou T. Hazard Ratio and Repeat Injury for Dementia in Patients With and Without a History of Traumatic Brain Injury: A Population-Based Secondary Data Analysis in Taiwan. Asia Pacific J Public Heal 2016;28:519-527.
40. Theadom A, Parmar P, Jones K, et al. Frequency and impact of recurrent traumatic brain injury in a population-based sample. J Neurotrauma 2015;32:674-681.
41. Swaine BR, Tremblay C, Platt RW, Grimard G, Zhang X, Pless IB. Previous head injury is a risk factor for subsequent head injury in children: a longitudinal cohort study. Pediatrics 2007;119:749-758.

42. Klonoff H. Head injuries in children: predisposing factors accident conditions, accident proneness and sequelae. Am J Public Health 1971;61:2405-2417.
43. Taubman B, McHugh J, Rosen F, Elci OU. Repeat Concussion and Recovery Time in a Primary Care Pediatric Office. J Child Neurol 2016;31:1607-1610.
44. Collins CL, Yeates KO, Pommering TL, et al. Direct medical charges of pediatric traumatic brain injury in multiple clinical settings. Inj Epidemiol 2014;1.
45. Ganti L, Conroy LM, Bodhit A, et al. Understanding why patients return to the emergency department after mild traumatic brain injury within 72 hours. West J Emerg Med 2015;16:481-485.
46. Saunders LL, Selassie AW, Hill EG, et al. A population-based study of repetitive traumatic brain injury among persons with traumatic brain injury. Brain Inj 2009;23:866-872.
47. Saunders LL, Selassie AW, Hill EG, et al. Pre-existing health conditions and repeat traumatic brain injury. Arch Phys Med Rehabil 2009;90:1853-1859.

Chapter 6: Recurrent traumatic brain injury surveillance using administrative health data: a Bayesian latent class analysis

Preface to Manuscript 3

Chapter 5 provided new evidence about the epidemiology of rTBI in the general population. The risk of rTBI at 1 year was estimated to be between 5-10% and risk factors for the development of rTBI included male sex, increasing age, increased severity of index TBI, prior history of TBI, not seeking medical care for index TBI within 24 hours of an injury, and lower socio-economic status. The meta-regression analysis I completed demonstrated that study-level factors such as the use of administrative health data tended to yield higher rTBI risk estimates. The time to recurrence also suggested that up to 50% of patients have a rTBI in first 6 months after their injury, meaning that the window of opportunity to intervene to prevent a recurrence is shortly after the incident TBI. However, these estimates of timing are based on detecting rTBI using case definitions that have not been validated. The systematic review also highlighted that there are significant limitations in the quality of the literature regarding rTBI surveillance. Most studies had important flaws in the internal and external validity of the estimates they reported. Two important problems that were highlighted was that the definition of rTBI in administrative health data is not validated, and, that many studies are not population-based which limits the generalizability of findings. Clearly, methods used to conduct rTBI surveillance have limitations, and further research on the topic is necessary.

The study presented in this chapter was completed to address methodological limitations in rTBI surveillance identified in the last chapter. I adopted the same approach as in Chapter 4 by using Bayesian latent class analysis to evaluate the performance of widely used ICD-based case definitions in administrative health data, while estimating the measurement error-adjusted rTBI incidence, in a population-based sample of Montreal residents. Cohorts of incident TBI patients, stratified by index TBI severity, were predicted from the posterior predictive distribution of the index TBI analysis from Chapter 4. The 1-year TBI incidence and the performance of each case definition was assessed across all predicted cohorts, with the final parameter estimates pooled together. This strategy allowed me to propagate the uncertainty through both analyses, which provides a true portrait of the precision of the estimates in this study. I also assessed the median time to rTBI after adjusting for the probability that an individual truly had an incident TBI and rTBI. With this information, stakeholders focused on mitigating the overall TBI burden, composed of incident and recurrent cases, will have the information to perform accurate rTBI surveillance and valid epidemiological research of potential interventions that may mitigate the rTBI risk.

This study will be submitted for publication shortly.

Manuscript 3

Recurrent traumatic brain injury surveillance using administrative health data: a Bayesian latent class analysis

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Abstract

Background: Traumatic brain injury (TBI) causes significant disability and mortality in populations across the globe. Incident TBI accounts for only part of the overall injury burden since recurrent TBI (rTBI) occurs frequently. These repeated injuries amplify the overall TBI burden by worsening the disability of affected individuals. Accurate and timely surveillance information on recurring injuries is necessary to justify the allocation of resources to prevention efforts and to conduct high quality epidemiological research. However, the validity of methods used to conduct rTBI surveillance has not been established, and therefore the accuracy of conducting rTBI surveillance is not known. This study aims to evaluate the performance of administrative health data surveillance case definitions for rTBI and to estimate the 1-year rTBI incidence, across the entire severity spectrum of index and recurrent injuries.

Methods: A 25% random sample of administrative health data for Montreal residents from 2000-2014 was used. The probability of a patient having an index TBI during the study period, ascertained from a previous analysis, was used to construct 1000 cohorts of index TBI patients. Four widely used TBI surveillance case definitions, based on the International Classification of Disease and/or the use of radiological examinations of the head, were then applied to data for each cohort to ascertain suspected cases of rTBI within 1 year of an index TBI. Bayesian latent class models, stratified by age group (children, adults, and elderly), were used to estimate the performance of each case definition and the 1-year rTBI incidence adjusted for measurement error. The results of the 1000 analyses were pooled to propagate the uncertainty from the diagnosis of index TBI through to the diagnosis of rTBI in the present analysis.

Results: The adjusted 1-year rTBI risk was 4.48 (95% CrI 3.42 , 6.20) per 100 person-years across all age groups, compared to a crude estimate of 8.03 (95% CrI 7.86 , 8.21) per 100 person-years. Patients with a severe index TBI had a significantly higher risk of rTBI. The radiological examination of the head surveillance case definition was the most sensitive to detect rTBI for children, adults, and the elderly [0.46 (95% CrI 0.33 , 0.61), 0.79 (95% CrI 0.64 , 0.94), and 0.87 (95% CrI 0.78 , 0.95, respectively)]. The most specific case definition to detect rTBI was the discharge abstract database case definition in children [0.9992 (95% CrI 0.9977 , 0.9999)]. In contrast, the most specific case definition in adults and the elderly was based on the emergency room physician claims case definition [0.9898 (95% CrI 0.9851 , 0.9939) and 0.9957 (95% CrI 0.9928 , 0.9988), respectively]. Median time to rTBI, adjusted for the imperfect diagnosis of index TBI and rTBI was the shortest in adults (75 days) and the longest in children (120 days).

Conclusions: Conducting rTBI surveillance using administrative health data is efficient and accurate, provided that measurement error is accounted for. The methods and results reported provide critical tools for to stakeholders in TBI that must monitor the occurrence of the overall injury burden accurately, and for investigators who conduct epidemiological research.

Background:

Traumatic brain injury (TBI) continues to cause significant disability in populations across the globe.[1] These injuries are responsible for an important economic burden and represent the most important cause of mortality and morbidity among young adults.[2] A broad body of research has been conducted describing the epidemiology of these injuries and assessing ways to mitigate their associated disability.[3,4] However, the overall injury burden reflects not only incident (first-time) injuries, but also recurrent injuries.[5–8]

Within a 1-year period after an index TBI, recurrent TBI (rTBI) affects 5-10% of individuals.[9] These recurrent injuries are associated with poorer outcomes, such as an increase in post-concussive symptoms leading to additional productivity losses.[10–12] Moreover, recent evidence has demonstrated that rTBI is associated with long-term complications, such as suicide and Chronic Traumatic Encephalopathy.[11,13–15] Despite the important morbidity related to these injuries, there is a paucity of research on how to monitor these recurrences.[9,16] Public health surveillance of these recurrent injuries is primordial to understanding the TBI burden and assessing whether interventions destined to mitigate them are effective. Feasible approaches to conducting such surveillance are needed to ensure that rTBI can be monitored across populations in a timely and comparable fashion.[2,17]

Administrative health data are a widely available and affordable resource for conducting surveillance.[4,18,19] Although these data are commonly used to conduct TBI surveillance of index injuries, their accuracy for conducting rTBI surveillance has not been assessed.[9] In addition, no perfect reference standard to diagnosis TBI, and by extension rTBI, has been elaborated. As such, assessing the accuracy of case definitions that detect these injuries requires methods that circumvent the need to define a perfect reference standard.[18] The aim of this study was to assess the accuracy of surveillance case definitions used in administrative health data to identify rTBI up to 1 year after an index TBI in children, adults, and elderly across the full spectrum of injury severity in a population-based cohort, without relying on a gold-standard definition of rTBI.

Methods:

Study design, population and data sources:

We used a prospective cohort design to ascertain cases of rTBI in cohorts of index TBI patients, stratified by index injury severity and age group (children [<18 years], adults [18-64 years], and elderly [>=65 years]). Index TBI patients were identified using a previous latent class analysis that predicted the probability of individuals having an index TBI based on case definitions they met.[18] We only considered case definitions to identify rTBI at least 7 days after the earliest index TBI claim, since we assumed that claims that occurred within 7 days of each other after an index TBI may represent delayed health care claims related to that index TBI.[18,20]

We used a cohort of residents of the Census Metropolitan Area (CMA) of Montreal from 2000-2014. The cohort is dynamic with membership maintained to represent a 25% random sample of the CMA of Montreal population. Administrative health data from the Régie de l'Assurance-Maladie du Quebec (RAMQ) were used for the analysis.[21,22] These data have been used previously to conduct population-based studies in TBI.[23–25] They include all physician claims and the discharge abstract database (DAD) of hospitalizations for members of the cohort. The physician claims data were coded using the ICD-9 CA standard, whereas the DAD was coded using the ICD-9 from 2000-2006 and the ICD-10 from 2007-2014. Suspected recurrence was defined using 4 case definitions described below. We estimated the risk of rTBI over a 1-year period, using the person-time contribution of the index TBI cohort until 1-year follow-up, censoring from the cohort, or meeting the case definition of an rTBI surveillance case definition.

rTBI surveillance case definitions:

We used 4 ICD-based surveillance case definitions for administrative health data that have been or could be applied widely across different jurisdictions (Appendix 1).[4,19,26] The first two case definitions were based on physician claims with a TBI diagnostic code in the outpatient and emergency department, respectively. We defined a third case definition as any TBI diagnostic code contained in the DAD for hospitalizations (primary or secondary diagnosis). We defined the 4th case definition as any patient that had a radiological examination of the head (computed tomography [CT] scan of the brain, magnetic resonance imaging of the brain or skull x-ray using RAMQ billing codes 08258, 08259, 08570, 08010, and 08013) while simultaneously having a physician claim for any traumatic event (defined as ICD-9 codes 8XX, 91X, 92X, 93X) within 1 day of each other.[22,27] These 4 case definitions span the entire severity spectrum of rTBI patients, from patients only seeking outpatient care to patients requiring hospitalization. In addition, these case definitions for TBI/rTBI are overlapping, since patients can be positive for one or all four. This overlap is a prerequisite for latent class analysis, since the model validates the accuracy of each case definition by the patterns of agreement between case definitions.[23,25] We excluded inpatient physician claims with a diagnosis of TBI as a case definition because of poor model fit, due to a strong correlation with the DAD case definition, and the potential for conditional dependence or correlation (described below) between these two case definitions to bias the results. Table 1 demonstrates that the "suspected" rTBI cases were comparable in number when excluding the inpatient physician claims.

Patients had a response pattern of positive case definitions based on whether they met these case definitions at least 7 days after their index TBI and up to 365 days after it. We included these temporal constraints for 2 reasons. First, in our previous analysis on incident cases, we had placed a constraint that all claims had to occur within 7 days of the earliest claim for the combination of case definitions to be attributed to the incident TBI. Therefore, all claims that occurred within the first 7 days after an incident TBI were assumed to be related to the incident event. Second, we wanted to ensure that the estimates we provided for surveillance case definitions reflected the entire spectrum of care patients received for rTBI up to 1 year after their index injury. If we were to limit rTBI case definitions to occur within 7 days of the earliest rTBI claim, patients with follow-up appointments (not true recurrences) would be detected and taken out of the rTBI at-risk pool. Thus, potential rTBI patients would be excluded if they were to have a true recurrence after such a follow-up appointment.

Statistical analysis:

The methods we used to conduct the analysis are similar to the Bayesian latent class analysis we used to assess the accuracy of the same case definitions for index TBI.[18] Briefly, we used Bayesian Latent Class Models (BLCMs) to simultaneously assess the accuracy of the 4 overlapping surveillance case definitions defined above. Latent class models are used to probabilistically measure unobservable or indirectly observable variables such as the diagnosis of TBI or rTBI. [23,28,29] By simultaneously assessing whether patients are positive for 1 or more of the 4 overlapping case definitions, these models can estimate the accuracy of the cases definitions to identify rTBI. This statistical approach circumvents the need to define a gold standard for the TBI diagnosis, which does not exist.[24] Consequently, this approach is a powerful tool for assessing the accuracy of surveillance case definitions since there is no perfect reference standard to define TBI or rTBI either clinically or from administrative health data. These models provide parameter estimates for the rTBI incidence, as well as the sensitivity and specificity of the case definitions under study. By using multiple overlapping sources of administrative health data that provide clues to the diagnosis of rTBI, the model adjusts each of these parameters for the inherent measurement error of each case definition.[30] Using algebraic manipulations of these parameters we can also derive the positive and negative predictive values (PPV and NPV) of each case definition. We used a 2-class model in the present rTBI analysis ("no rTBI" and "rTBI") to prevent sparsity of data when analyzing recurrent cases, which would lead to non-convergence of our latent class model.[18] A Bayesian approach was preferred since prior distributions can be used to help with model convergence when response patterns to the case definitions are sparse, as well as to perform sensitivity analyses that confirm the robustness of our results.[31–33] The full model specification is described in Appendix 2 and heuristic diagrams of the models are provided in Appendix 7.

To carry over the uncertainty from our original analysis on index TBI to the present analysis, we predicted cohorts of index TBI from the original model. We simulated cohorts of TBI patients based on the case definitions for which patients were positive during their index TBI (Appendix 2 and 7). The cohorts of index TBI patients were predicted in 2 severity groupings ("mildest/more severe TBI" and "most severe TBI"). More specifically, the "mildest" and "more severe" index TBI cases from our original analysis on incident TBI were grouped together as the "mildest/more severe" group, which represent patients that were likely to be treated in the outpatient/emergency room setting. The other cohort of patients consisted of the "most severe" TBI cases that were more likely to require hospitalization for their injury.[18] An attempt was made to predict three cohorts of incident TBI patients, but the distribution of case definition response patterns were too sparse in the "mildest" incident TBI group, leading to non-convergence of the

BLCM without including significant amounts of informative prior information, which was not available.[9] We conducted three separate analyses for children, adults, and the elderly, since each of these age groups have unique TBI epidemiological characteristics across populations worldwide.[1,4,17] We used logistic regression to model the association between sex and rTBI incidence using a sex covariate for each severity class in the latent class model.

We performed 1000 predictions from our index TBI model for each severity class and for each age group to carry over the uncertainty of an individual actually having an index TBI. With the resulting two "simulated" cohorts for each age group (each age group had a "mildest/more severe" and "most severe" TBI cohort), we used the 4 case definitions described above to assess their accuracy to identify rTBI cases within 1 year after the index injury. The posterior distribution for the 1000 analyses for each age group and injury severity were pooled. We also estimated the overall rTBI incidence and accuracy measures for the 4 case definitions across the 3 age groups by pooling the results, weighted by the size of the index TBI cohort, for each age group. Prior information was required to conduct the analysis because of the sparsity of data that occurs during different iterations of the analysis for each predicted cohort.[31,34,35] Thus, we used relatively non-informative prior information to circumvent this problem based on the results of our previous analysis on index TBI.[9,18] The description of the prior distributions we used are available in Appendix 2.

Model fit, selection and convergence:

When using latent class analysis, a fundamental assumption is that the multiple case definitions used in the model are conditionally independent given disease status. If this assumption is violated, the rTBI incidence estimates and accuracy parameters may be biased. We verified model fit, and that this assumption was not violated, by conducting posterior predictive checks that assessed the probability that the observed agreement between pairs of case definitions were greater than their predicted agreement (Appendix 3).[23,36] The 2-class model did not demonstrate significant correlation between pairs of case definitions.

We assessed the crude median time to rTBI using the date of the first positive case definition as the time of recurrent injury. To assess the validity of this measure, we also estimated an adjusted median time to rTBI which adjusted for the probability that an individual was a true incident TBI and rTBI case (Appendix 4).

Sensitivity analyses:

We allowed the prior information to vary within plausible ranges to assess whether the prior information had an impact on the conclusions of the primary analysis (Appendix 2 and 5).

All analyses were conducted in Just Another Gibbs Sampler (JAGS) called from R. Convergence diagnostics were performed by assessing traceplots and the Gelman-Rubin statistic (<1.1). The parameters were sampled from their posterior distribution using 3 parallel chains of Markov chain Monte Carlo simulations with 20,000 iterations and a burn-in of 5,000 iterations by specifying the likelihood and prior distributions of each one for the Gibbs sampler. 95% credible intervals and medians were reported from the highest posterior densities for estimated parameters. The reporting of this study adhered to the recommended STARD-BLCM guidelines.[37] This study was approved by the Institutional Review Board of McGill University's Faculty of Medicine.

Results:

From 2000 to 2014, there were 7,532 suspected rTBI cases within 1 year of their incident event. The crude 1-year rTBI risk was 8.03 (95% CrI 7.86 , 8.21) per 100 person-years. The measurement error-adjusted rTBI risk from the Bayesian latent class analysis was lower (4.48 (95% CrI 3.42 , 6.20) per 100 person-years). The crude median time to recurrence was 98 days in children, 25 days in adults and 39 days in the elderly. The adjusted median time to recurrence was more delayed across all age groups than the crude estimate (Table 1).

The rTBI risk was most elevated for the elderly population (9.03 per 100 person-years, 95% CrI 7.68 , 10.24) and the lowest in children (1.69 per 100 person-years, 95% CrI 1.11 , 2.73). When comparing male and female incidence across the entire population of incident TBI patients, female sex was associated with a higher risk of rTBI. However, male sex was associated with a higher risk of rTBI compared to female sex when individually assessing the incidence of rTBI in children and adults. Patients with a “most severe” index TBI had a significantly higher risk of rTBI in comparison to patients with a “mildest/more severe” index TBI, across all age groups (overall “most severe” to “mildest/more severe” incidence ratio = 1.824, 95% CrI 1.146 , 2.478) (Table 2).

The most sensitive rTBI case definition was based on a radiological examination with a diagnosis of trauma and the least sensitive was based on the DAD, except for the elderly where the outpatient claims were the least sensitive. In children, the case definition based on the DAD was the most specific, whereas in adults and the elderly it was the emergency room physician claim. The least specific case definition in children was the ER claim. The DAD and radiological examination case definition had the highest PPV in children. In contrast, in adults the radiological examination and in the elderly the ER claim had the highest PPV, respectively (Table 3).

As shown in Figure 1, there was heterogeneity in the performance of case definitions across age groups and index TBI severity. In terms of sensitivity, the emergency room claim, DAD case definition and radiological examination case definition were higher in the "most severe" cohort compared to the "mildest/more severe" cohort. Regarding specificity, the DAD and the radiological examination claim was lower in the "most severe" index TBI cohort across the 3 age groups. Similarly, the PPV and NPV showed differences between the two index TBI severity groups.

Model fit across the three age groups was deemed appropriate based on posterior predictive checks as shown in Appendix 5. Five sensitivity analyses where the prior information used in the main model was varied within plausible ranges were conducted. In each of these sensitivity analyses, the overall conclusions of the main analysis were unchanged (Appendix 6).

Discussion:

The impact of rTBI on the overall TBI burden has largely been overlooked in the general population.[9,16] This study provides the first assessment of the accuracy of administrative health data to conduct rTBI surveillance across the full severity spectrum of injuries, without relying on a gold standard TBI or rTBI definition.[9] The performance of surveillance case definitions and incidence estimates vary significantly by age groups and index TBI severities. Measurement error in administrative health data leads to overestimation of the rTBI burden when using these data. We have demonstrated that accurate rTBI surveillance is feasible using widely applicable surveillance case definitions in administrative health data, provided that measurement error is accounted for.

Accuracy of surveillance case definitions to conduct rTBI surveillance and epidemiological research:

There has been a considerable amount of research on the methodology used to conduct incident TBI surveillance.[2,3,18,26,38] However, a systematic review of the epidemiology of rTBI in the general population demonstrated the lack of similar research for rTBI.[9] The present study demonstrates that the accuracy of case definitions to detect rTBI is different from the accuracy of cases definitions to detect incident TBI. This finding may be explained by the different patterns of care patients follow for an rTBI compared to an index TBI. For example, our previous study demonstrated that the case definition using radiological examination claims with a concomitant diagnosis of any trauma had the highest sensitivity for TBI in adults and the elderly.[18] This case definition had a lower sensitivity for TBI in children, probably due to the concern of radiation exposure and its consequences.[39,40] In contrast, the present study on rTBI demonstrates that the radiological examination case definition is more sensitive than for incident TBI, with a sensitivity of 46-87% across the three age groups, to detect rTBI. Radiological examinations may be more sensitive for rTBI as compared to incident TBI, including for children, because clinicians may be using imaging studies more liberally for patients with rTBI; these patients may have a more severe clinical presentation and be at risk of more severe complications related to repeated head trauma.[16,41] In addition, guidelines to conduct imaging in the context of TBI have only been validated for incident TBI, which may lead to more widespread use of imaging in rTBI since there are no firm guidelines to limit its use.[27,42]

We showed that the DAD case definition has the lowest sensitivity since most recurrent cases do not require hospitalization, which is similar for incident TBI.[18] However, the DAD case definition had the highest specificity to detect incident TBI, which was not true for assessing rTBI.[18] This difference may be explained by the fact that repeat admission to hospitals for other causes can have traumatic brain injury as a secondary diagnosis in the DAD. Moreover, the PPV of the outpatient physician claims case definition in the rTBI analysis was lower than in the incident TBI study, emphasizing that it detects many false positives. This finding suggests that this case definition identifies patients with follow-up appointments for their incident TBI, as has been recommended by the Quebec Ministry of Health and Social Services.[43] In short, the causes of measurement error in case definitions that identify rTBI appear to be distinct from those for case definitions for incident TBI.

rTBI incidence:

A wide variation in the estimates of rTBI incidence in the general population has been reported, due to heterogenous surveillance methods used across studies.[9] Comparing the 1-year risk of rTBI occurrence, studies published in the literature reported a range of estimates from 5.5-10%.[9] Two of these studies focused on pediatric populations.[44,45] Our estimate of rTBI incidence in children was lower (1.69 per 100 person-years, 95% CrI 1.11 , 2.73). This result is likely explained by differences in methodology. First, in these two studies, parent self-report was used as the outcome for rTBI, which may overestimate the true incidence. In contrast, our crude risk of rTBI in children was 5.2% in children, which is similar to the estimates published by Swaine et al., which used the Quebec pediatric population as we did.[44] In their study, parents provided a self-report of children requiring medical care for a rTBI. As such, without measurement error adjustment, the incidence of rTBI is overestimated using administrative health data.

The rTBI incidence we reported in adults and the elderly was higher than in children, which is in keeping with previous studies demonstrating that increasing age is a risk factor for rTBI.[46,47]

Theadom et al. completed an assessment on the rTBI incidence in the general population in New Zealand.[16] They reported a rTBI incidence of 9.9% at 1-year follow-up, in comparison to 4.48 (95% CrI 3.42 , 6.20) per 100 person-years in our present study. The difference in estimates can be explained by many factors that surveillance researchers should consider. First, Theadom et al.'s study used a cohort study design to ascertain all cases of incident TBI in two defined regions of New Zealand, and then assessed rTBI up to 1 year after the index injury. However, only 52% of eligible incident TBI cases were included in the follow-up for their assessment of rTBI risk, which may have biased the results. Many baseline covariates compared between participants in the study and non-participants were similar. Nonetheless, injury severity was not compared between these two groups, which may have an impact on the results. For example, if many milder cases, compared to more severe cases, were to preferentially not participate, there may be an overestimate of rTBI risk, since more severe index injuries have a higher risk of recurrence. Also, Theadom et al. were able to identify rTBI who did not present to medical care, which we were unable to assess using administrative health data. Furthermore, measurement error may have contributed to an overestimate of their reported 1-year risk, since we noted that our crude rTBI incidence estimate was almost twice as large as our measurement error-adjusted estimate.

Assessing the time-to-recurrence of rTBI is important as it defines a window of opportunity during which interventions may help mitigate the risk of recurrent injuries. We adjusted the median time to recurrence for measurement error in identifying rTBI. In doing so, we identified that the median time to recurrence varied from 75 days to 120 days (approximately 2-4 months), depending on the age group in question, with adults having the shortest time to recurrence and children having the longest. Previous studies have identified that 58.2-61.1% of recurrent injuries occur within the first 6 months.[16,44] Theadom et al. demonstrated that up to 38.9% of rTBI cases occurred within the first 3 months, which is in keeping with our findings. Therefore, interventions to mitigate the occurrence of rTBI must occur soon after an index case. Unfortunately, there is no published evidence describing interventions that may reduce the risk of rTBI in the general population.[9]

Clearly, more research is necessary to identify strategies to reduce the risk of rTBI, which tends to occur within the first few months post-index injury. The accuracy of case definitions to identify rTBI is important to consider when conducting epidemiological research. By using the methods and results from this study, investigators have the tools to construct valid cohorts of index TBI patients, assess their outcome of rTBI accurately, and thereafter make valid inferences regarding the association between interventions and rTBI.

Variation of rTBI risk and case definition accuracy across age, sex, and index TBI severity:

As for index TBI, the risk of rTBI varies by age and sex. As mentioned above, the risk of recurrence increases with increasing age.[46,47] In comparison to the index TBI, rTBI does not seem to have a bimodal peak among children and the elderly.[48] Male patients tend to have a higher risk of rTBI compared to females in both children and adults. However, the risk of rTBI in elderly females was higher than in males, which is in keeping with the literature on incident TBI.[3,18,49] In fact, since the risk of rTBI was the highest in the elderly age group and females had a higher risk in this age group, the overall risk of rTBI is higher in females than in males in our study population. A systematic review assessing the association between sex and rTBI found no conclusive evidence supporting this association, with many studies reporting unprecise association measures crossing the null.[9] Further investigation of the association between sex and risk of rTBI is necessary, as these associations may be different than for incident TBI.

Our study emphasized that index TBI severity is an important determinant of rTBI. Across all age groups, patients with a “most severe” index TBI had a significantly higher risk of a recurrent injury compared to patients with milder injuries. However, the precision of estimates varied widely across the 3 age groups. Previous studies have reported similar findings, although the magnitude of association was smaller than in the present study.[46,47,50,51] This discrepancy can be explained by the fact that our study included patients across the entire spectrum of injury severity, whereas other studies have tended to include only hospitalized patients or only patients presenting to the emergency department.[9] We also compared the rTBI risk of the “most severe” index TBI cases (patients likely to be hospitalized) to those with a “mildest/more severe” index TBI (patients unlikely to be hospitalized). As such, we contrasted groups with a greater difference in severity in comparison to previous studies. Interestingly, this observation raises the possibility that there exists a dose-response relationship between index TBI severity and rTBI risk; as the severity of the index TBI increases, the risk of rTBI appears to increase. Although this phenomenon has not been extensively investigated, patients with more severe TBI are known to have a higher rate of cognitive and physical disability, which may lead to a vulnerability to sustain a second injury.[52]

The performance of the surveillance case definitions also varied by index TBI severity. We demonstrated that among the cohort of patients with a “mildest/more severe” index TBI, sensitivity was highest for case definitions based on emergency department physician claims and radiological examinations. In contrast, for patients with a “most severe” index TBI, the DAD and radiological examinations case definitions tended to have the highest sensitivity. Moreover, the specificity and PPV of the DAD and radiological examinations case definitions were higher in patients with a “mildest/more severe” index TBI compared to a “most severe” index TBI. A possible explanation for these findings is that patients with a higher severity index TBI are more likely to obtain follow-up imaging for their index injury and may be readmitted to a rehabilitation centre where a new DAD entry with a TBI diagnosis is entered, which leads to more false positives. Nonetheless, since these two case definitions still had a higher sensitivity in patients with a higher severity index TBI, there is the possibility that patients with a higher severity index TBI not only have a higher risk of rTBI but also a greater risk of a higher severity recurrent injury (and therefore a higher risk of hospitalization for their rTBI). Further research to explore this finding is necessary since our analysis had only 2 latent classes ("rTBI" and "no rTBI") and could not assess the severity of rTBI. Clearly, the clinical pathways patients follow after their index TBI is highly dictated by their index TBI severity.[53,54] In short, the variability in how the case definitions perform by age group and index TBI severity is important for stakeholders in surveillance and epidemiological research who may be investigating the risk of rTBI in specific TBI subpopulations.

Limitations:

Our study has limitations that should be considered when interpreting its results. First, we used administrative health data from a single jurisdiction, which may limit the generalizability of the results across other health regions. Nonetheless, administrative data tend to be similar across jurisdictions and extensive research on TBI epidemiology demonstrates that TBI epidemiological characteristics are consistent across the developed word.[1] Second, we used prior information, which assisted with model convergence, but may have influenced our results. However, we used plausible prior distributions and completed several sensitivity analyses to demonstrate the robustness of our main analysis' results. Third, our study only includes patients that sought medical care for their index TBI and rTBI. As such, our results likely represent an underestimate of the true injury burden. Fourth, when using administrative health data claims, follow-up visits, rehospitalizations for other causes, and follow-up radiological examinations for an incident TBI may be falsely classified as rTBI events. Our latent class analysis circumvented this problem by using overlapping administrative health data with information provided by different providers. Our model fit was appropriate, which confirms there was no significant conditional dependence between the case definitions we used, the main assumption that must be met for the method to produce valid results. In addition, we performed multiple sensitivity analyses to force the prior distributions of the specificities of our case definitions to be larger or unconstrained, which did not alter the overall conclusions of our main analysis. Fifth, since we retained uncertainty from the first incident TBI analysis through to the rTBI analysis in this study, we had a sparsity of data that did not allow us to assess the severity of rTBI events through more latent classes. In addition, we were not able to assess secular trends in the incidence of rTBI and in the performance of case definitions. Future studies with stronger power and less sparse data should investigate the latter.

Conclusion:

rTBI is an important contributor to the overall population burden of TBI. Administrative health data are a useful tool to conduct accurate and efficient rTBI surveillance while adjusting for measurement error. The methods and results from this study provide stakeholders in rTBI with the tools and information necessary to justify the allocation of resources for the care of these patients. They also provide a means to conduct valid epidemiological research that investigates strategies to reduce the rTBI burden and thereby help address the overall TBI burden.

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Tables and figures for Manuscript 3

Table 1: Summary of suspected incident TBI cases and rTBI cases identified from administrative health data surveillance case definitions from 2000-2014

	"Suspected" incident cases (n)	**Mean predicted cohort size of "true" incident TBI (n, across 1000 simulations)**	**"Suspected" recurrent cases (n)**	**rTBI crude risk (95% CrI)**	**Crude median time to recurrence (days)**	**Adjusted median time to recurrence (days) (95% CrI)**
Children (0-17)	30,433	35,161 Male : 60.3% "Most severe": 7.82%	1567 (1607)*	0.052 (0.049 , 0.054)	98	120 (116 , 125)
Outpatient claim	7,992		600			
Emergency room claim	20,119		847			
Hospital physician claim	877		(92)*			
Discharge abstract database	1,657		62			
Radiological exam	5,029		234			
Adults (18-64)	38,486	38,454 Male: 56.7% "Most severe": 11.1%	3205 (3,414)*	0.083 (0.081 , 0.086)	25	75 (73 , 77)
Outpatient claim	8,710		1,489			
Emergency room claim	16,825		646			
Hospital physician claim	1,911		(637)*			
Discharge abstract database	2,697		338			
Radiological exam	19,243		1,013			
Elderly (65+)	24,881	23,655 Male: 37.9% "Most severe": 10.0%	2760 (3,193)*	0.111 (0.107 , 0.115)	39	109 (108 , 110)
Outpatient claim	1,873		274			
Emergency room claim	7,427		539			
Hospital physician claim	1,725		(934)*			
Discharge abstract database	2,934		544			
Radiological exam	18,635		1,884			

Distribution of patients that were positive for at least 1 of the case definitions for rTBI in administrative health data across the three age groups in the study. The estimates of mean predicted cohort size and adjusted median time to recurrence were calculated as described in Appendices 2 and 4, respectively. The proportion of males in the cohort and the proportion of patients that were in the “most severe” stratification of the predicted cohorts is also provided. *The hospital (inpatient) physician claims were not used in the rTBI analysis but were used in the incident TBI analysis. In brackets, the total suspected rTBI cases are shown when the hospital physician claims are included to identify rTBI cases.

Table 2: Measurement error-adjusted rTBI incidence by age group

	rTBI incidence per 100 person-years (95% CrI)
Children (0-17 years)	1.69 (1.11 , 2.73) M:F = 1.142 (0.918 , 1.453) S:M = 1.685 (0.432 , 3.807)
Adults (18-64 years)	3.57 (2.39 , 5.16) M:F = 1.409 (1.130, 1.673) S:M = 3.219 (1.853 , 4.626)
Elderly (65+ years)	9.03 (7.68 , 10.24) M:F = 0.999 (0.920 , 1.100) S:M = 1.051 (0.852 , 1.313)
Across all age groups	4.48 (3.42 , 6.20) M:F = 0.857 (0.737 , 1.024) S:M = 1.824 (1.146 , 2.478)

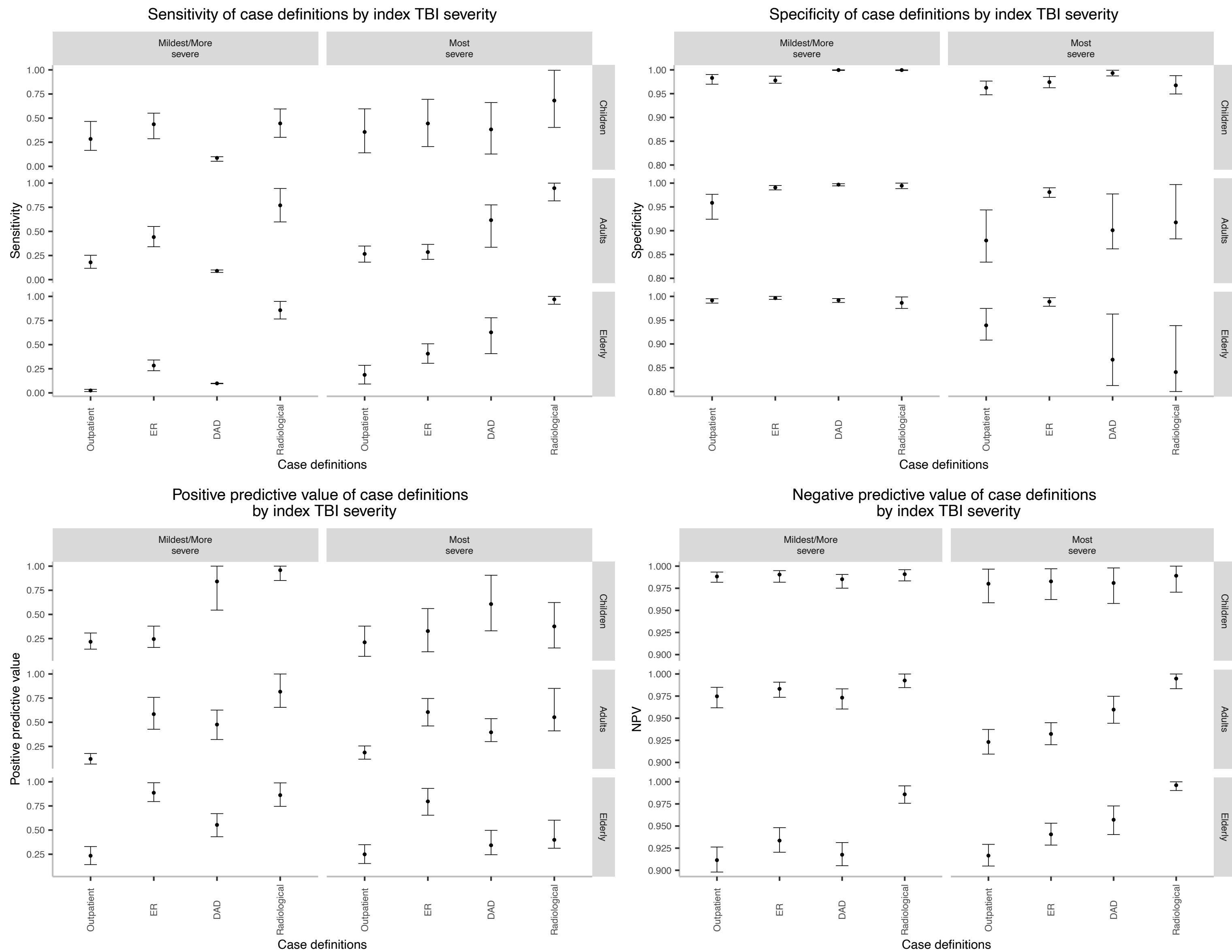
The measurement error-adjusted incidence of rTBI across age groups and index TBI severities are as shown above. The male:female (M:F) and "Most severe":"mild/more severe" (S:M) index TBI severity incidence ratios are also shown.

Table 3: Performance of surveillance case definitions to detect rTBI cases in administrative health data stratified by age group

	Sensitivity (95% CrI)	Specificity (x10^{-2}) (95% CrI)	Positive predictive value (95% CrI)	Negative predictive value (95% CrI)
Children				
Outpatient claim	0.29 (0.18 , 0.45)	9.817 (9.688 , 9.888)	0.21 (0.15 , 0.29)	0.988 (0.981 , 0.992)
ER claim	0.44 (0.31 , 0.55)	9.774 (9.720 , 9.853)	0.25 (0.17 , 0.37)	0.990 (0.982 , 0.994)
Discharge abstract database	0.11 (0.07 , 0.15)	9.992 (9.977 , 9.999)	0.74 (0.51 , 0.93)	0.985 (0.976 , 0.990)
Radiological examination of head with a diagnosis of trauma	0.46 (0.33 , 0.61)	9.973 (9.920 , 9.999)	0.77 (0.58 , 0.89)	0.991 (0.984 , 0.996)
Adults				
Outpatient claim	0.19 (0.13 , 0.25)	9.516 (9.164 , 9.694)	0.13 (0.08, 0.18)	0.969 (0.955 , 0.980)
ER claim	0.42 (0.33 , 0.52)	9.898 (9.851 , 9.939)	0.60 (0.48 , 0.74)	0.979 (0.967 , 0.987)
Discharge abstract database	0.14 (0.11 , 0.21)	9.876 (9.726 , 9.948)	0.31 (0.21 , 0.44)	0.969 (0.956 , 0.979)
Radiological examination of head with a diagnosis of trauma	0.79 (0.64 , 0.94)	9.874 (9.762 , 9.963)	0.70 (0.55 , 0.85)	0.992 (0.983 , 0.999)
Elderly				
Outpatient claim	0.04 (0.03 , 0.05)	9.872 (9.814 , 9.910)	0.24 (0.17 , 0.31)	0.912 (0.900 , 0.925)
ER claim	0.29 (0.25 , 0.35)	9.957 (9.928 , 9.988)	0.87 (0.79 , 0.96)	0.934 (0.922 , 0.947)
Discharge abstract database	0.15 (0.12 , 0.18)	9.809 (9.746 , 9.874)	0.44 (0.35 , 0.53)	0.921 (0.910 , 0.933)
Radiological examination of head with a diagnosis of trauma	0.87 (0.78 , 0.95)	9.732 (9.602 , 9.866)	0.76 (0.66 , 0.87)	0.987 (0.977 , 0.996)

Overall performance of each of the five case definitions for each age group across both index TBI severities.

Figure 1: Performance of surveillance case definitions by index TBI severity.



Performance of each data source to perform rTBI surveillance stratified by each age group and incident TBI severity. “Outpatient” = outpatient claims, “DAD” = discharge abstract database, “Radiology” = radiological examination claim in the context of any trauma diagnosis.

Manuscript 3 Appendix

Appendix 1: International classification of disease codes used to ascertain traumatic brain injury cases from 2000 to 2014

Case definition	ICD-9	ICD-10*	RAMQ procedure code
Outpatient physician claim	800.X 801.X 803.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Emergency department claim	800.X 801.X 803.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Inpatient physician claim	800.X 801.X 803.X 850.X-854.X 950.1 950.2 950.3 959.0	N/A	N/A
Hospitalization discharge abstract database	800.X 801.X 803.X 850.X-854.X 950.1 950.2 950.3 959.0	S01.X S02.1 S02.3 S02.7 S02.8 S02.9 S04.X S06.X S07.X S09.7 S09.8 S09.9 T02.0 T02.10 T04.0 T06.0 T90.X	N/A

Radiological exam of the head within 1 day of a claim for any trauma diagnosis	8XX 91X 92X 93X 94X 95X	N/A	08258 08259 08570 08010 08013

ICD codes used in the main analysis to identify recurrent traumatic brain injury. The ICD-9 codes are taken from the surveillance definition developed by the Centers for Disease Control, while the ICD-10 codes are taken from a systematic review identifying the commonly used ICD-10 case definitions for traumatic brain injury.[1,2] *The hospitalization discharge abstract case definition made use of the ICD-9 iteration from 2000-2005 and the ICD-10 iteration from 2006-2015. The radiological exam of the head case definition was defined as patients that had a head imaging claim by a radiologist within 1 day of having a traumatic brain injury diagnosis claim by another physician.[3] ICD = International classification of disease, RAMQ = Régie de l'assurance maladie du Québec

Appendix 2: Model specification of the latent class model

Simulated cohorts of incident TBI cases by age group and index TBI severity:

The analysis used *j*=1000 predicted cohorts of incident TBI cases across all three age groups. The probability of an individual having an incident TBI of specific severity Sev given a response pattern of positive case definitions T_i=1…32 was used to predict cohorts of incident TBI. 32 response patterns were available given that *p*=5 case definitions were used in the incident TBI analysis (2^5=32 patterns). These probabilities $P(Sev = s|T_i)$ were ascertained from our analysis that investigated incident TBI in the same population with the same case definitions.[4] The posterior predictive distribution from this previous analysis was sampled 1000 times to ascertain the 1000 predictions. Patients not positive for any case definition in the index TBI analysis also had a small non-zero probability to have a diagnosis of TBI. By definition, these individuals could not be positive for any suspected rTBI since they were not positive for any case definition. Thus, a follow-up time after incident TBI could not be defined for these individuals. We assumed they were followed for 365 days since the average follow-up time in the cohort we used is greater than 365 days.

The predicted cohorts were stratified by incident injury severity into two groups: "mildest/more severe" and "most severe" TBI, as was described in the previous analysis on incident TBI. We were unable to stratify across the 3 injury severities we had identified in our previous latent class analysis due to a lack of power, which led to non-convergence of the latent class model. We therefore decided to group the "mildest" and "more severe" groups together, since they represent a group of incident TBI patients that are primarily managed in the outpatient setting, whereas the "most severe" group represents patients that are hospitalized and receive more advanced care. We stratified the analysis to allow all accuracy parameters and incidence parameters to vary by index TBI severity. As such, two cohorts for each age group were predicted for a total of 6 predicted cohorts that were subsequently each analyzed using the latent class model described below. Using the aforementioned probabilities, a categorical distribution with the probability distributions were used to classify individuals into one of three categories of incident TBI: "no TBI", "mildest/more severe TBI", or "most severe TBI". The latter was repeated *j*=1000 times and the category that an individual was placed in, Sev_{ij}, was based on their pattern of positivity for the 5 case definitions. As such, a "mildest/more severe" ($Sev = s = 2$) and a "most severe" ($Sev = s = 3$) cohort was formed 1000 times for each age group. The latent class analysis described below was repeated 1000 times for each of these two severity groups of incident TBI and for the three age groups. The parameter estimates from each of the 1000 simulations were pooled together to get final overall summary estimates across all simulated cohorts from the posterior distribution of each analysis. By simulating these 1000 cohorts for each incident TBI severity and age group, we ensured that all the uncertainty of the incident TBI diagnosis from the initial analysis was carried over to the present analysis on rTBI. Appendix 7A and 7B provide heuristic diagrams that describe the latent class models that were used to predict the cohorts and to complete the rTBI analysis, respectively.

For the incident TBI cohort predictions for the "mild/more severe TBI group" - *s*=2:

$$Sev_{ij} \sim categorical(P(Sev = s|T_i)) \text{ for } j\text{=1:1000}$$
$$Sev_{ij} = 1 \; if \; Sev_{ij} = 2$$

$$Sev_{ij} = 0 \; if \; Sev_{ij} = 1$$

For the incident TBI cohort predictions cohort for the “most severe incident TBI group” - *s*=3:

$$Sev_{ij} \sim categorical(P(Sev = s|T_i)) \text{ for } j\text{=1:1000}$$
$$Sev_{ij} = 1 \; if \; Sev_{ij} = 3$$
$$Sev_{ij} = 0 \; if \; Sev_{ij} = 1$$

N.B.: The incident TBI cohort predictions were completed independently for *s*=2 and *s*=3 in each age group as shown directly above.

$$n_{ij,Sev=s} = Sev_{ij} * n_i \text{ for } s\text{=2,3}$$

Where n_i are the counts of individuals with an i^{th} case definition response pattern in the incident TBI cohort.

$N_{j,Sev=s} = \sum_{i=1}^{32} n_{ij,Sev=s}$ for *s*=2,3 where $N_{j,Sev=s}$ is the total size of the incident TBI cohort for the j^{th} simulation and *Sev*=*s* severity (for *s*=2,3).

By forming these cohorts of individuals with “true” incident TBI, we were able to follow individuals for rTBI case definitions after their incident TBI for each of the j^{th} simulations. As shown above, $n_{ij,Sev=s}$ can be a positive integer or 0, depending on whether a given simulation categorized an i^{th} case definition response pattern to be a “true” incident TBI or not. In the case where $n_{ij,Sev=s}$ was 0, individuals with this incident TBI case definition response pattern were not considered to have TBI and therefore were not followed for the rTBI case definition response patterns described below. In addition, their person-time contribution to the analysis was not considered since they were not considered as part of the cohort for that particular j^{th} prediction. More specifically, six groups of incident TBI cohorts were predicted for each severity *s*=2 and *s*=3 within each age group (children, adults, and elderly).

p=1 = outpatient physician claims
p=2 = emergency room claims
p=3 = inpatient claims
p=4 = TBI diagnosis in discharge abstract database
p=5 = radiological examination of the head in the context of any other traumatic injury

s=1 = Incident class 1 (“No TBI”)
s=2 = Incident class 2 (“Mildest/more severe TBI”)
s=3 = Incident class 3 (“Most severe TBI”)

Bayesian latent class model

The basic latent class model we used in the analysis is shown below. In short, there are 16 possible responses to the *pr*=4 case definitions ($2^{pr} = 2^4 = 16$). We excluded inpatient physician claims with a diagnosis of TBI since many of these claims represent daily claims that physicians submit during prolonged hospitalizations for an index TBI. The other case definitions we used circumvent this problem since the patient must leave the hospitalization setting to be positive for another case definition. In addition, the DAD provides the same information regarding inpatient hospitalizations for TBI. Also, strong correlation between these two case definitions was identified when we attempted an analysis where inpatient physician claims were used. As such, these claims were excluded to maintain model parsimony and avoid bias through correlation with the DAD case definition (see explanation below on conditional independence of case definitions).

Since our analysis allows rTBI incidence to vary by sex, the number of responses is actually 32 since there are 16 possible responses for each sex. The latent class analysis models the probability of having a response vector $T_{irj,Sev=s}$= 1…16 of the *pr* = 1…4 case definitions used in the model for 1 year after occurrence of an incident TBI for each j^{th} simulated cohort (a total of 32 response vectors) with *Sev*=*s* (where *s*=2 or *s*=3). The person-years ($n_{irj,Sev=s}$) contributed over a one-year period after an incident TBI to each combination of responses is modelled with a multinomial distribution where $N_{rj,Sev=s}$ (for *j*=1000) is the total count of person-years contributed after incident TBI in the j^{th} simulated incident TBI cohort. The accuracy parameters are the sensitivity of the pr^{th} case definition – $P\left(T_{iprj}\middle|\, L_{ikrj}\right)$. The incidence of rTBI, $P(L_{ikrj})$, is allowed to vary by sex through a logistic regression model shown below. The α_male_{kr} and β_female_{kr} parameters are heterogeneity variables that allow the incidence to vary by sex ($sex_{ij,Sev=s}$). The "*r*" subscript indicates that the parameter in the model represents the rTBI analysis, in contrast to the incident TBI analysis from our previously completed investigation on the topic. The "*Sev*" subscript indicates the severity cohort under analysis. Six latent class models were conducted; one for each age group and index TBI severity (3 age groups with 2 index TBI severity cohorts per age group provides a total of 6 analyses). The posterior distribution of each parameter for each simulation was estimated using Gibbs sampling of the full conditional distributions defined below.[5] These posterior distributions for each parameter/age group/severity were pooled together to ascertain our final estimates that retain all uncertainty from our analyses.

pr=1 = outpatient physician claims
pr=2 = emergency room claims
pr=3 = TBI diagnosis in discharge abstract database
pr=4 = radiological examination of the head in the context of any other traumatic injury

kr=1 = Recurrent class 1 (No rTBI)
kr=2 = Recurrent class 2 (rTBI)

General latent class model and likelihood:

$$P\left(T_{irj,Sev=s}\right) = \sum_{kr=1}^{Kr} P(L_{ikrj,Sev=s}) \prod_{pr=1}^{Pr} P\left(T_{iprj,Sev=s}\middle|L_{ikrj,Sev=s}\right)$$

$$Likelihood \propto \prod_{i=1}^{32} P\left(T_{irj,Sev=s}\right)$$

$$n_{irj,Sev=s}|T_{irj,Sev=s}, N_{rj,Sev=s} \sim multinomial\ (P(T_{irj,Sev=s}), N_{rj,Sev=s})$$

Where n_{irj} and N_{rj} is predicted for each severity (s=2 and s=3) and age group from the j=1000 simulated cohorts described above.

Logistic regression to model variability in incidence by sex:

$$logit(P(L_{ikrj,Sev=s}) = \alpha_{male_{krj,Sev=s}} + \beta_{female_{krj,Sev=s}} * sex_{ij,Sev=s} \ (for\ k = 2)$$
$$P(L_{i1rj,Sev=s}) = 1 - P(L_{i2rj,Sev=s})$$

Constraints and assumptions using prior information:

Since label switching can lead to non-convergence of latent class models, we imposed constraints in the form of relatively non-informative prior distributions, which were informed by previous literature.[6] In our 2-class model for the "mild/more severe" index TBI cohort analysis, we forced discharge abstract database to have a maximum sensitivity of 10% and for the emergency room physician claim to have a sensitivity of at least 10%. In addition, we constrained the specificity of all 4 case definitions to be at least 80%, which is quite uninformative based on previous literature on index TBI surveillance.[4] For the "most severe" index TBI cohort, we only required constraints on the specificities. These constraints were used to allow the model to converge. They are considered relatively uninformative priors given that the literature has shown that less than 5% of mild TBI patients that have rTBI are admitted to hospital.[7] Our previous analysis on incident TBI also found that the sensitivity of case definitions for index TBI are well within the range of these constraints.[4] We also constrained the incidence in males to 10% since the highest 1-year risk of rTBI was reported to be 9.9% in a previously published systematic review on the topic.[8] The prior information for the parameter $\beta_{female_{kj,Sev=s}}$, which allows the incidence to vary by sex was in the form of a non-informative prior (N(0,0.01)). We constrained this last prior distribution (T(-0.5,0.1)) to limit how much higher the female incidence can be than the male incidence. The latter is supported by the fact that most TBI and rTBI epidemiological studies demonstrates a higher risk of TBI in males.[4,8–10] We conducted numerous sensitivity analyses that vary these priors within a reasonable range to ensure that our results were robust.

These constraints we used on the accuracy parameters are shown below:

General accuracy parameter:

$$P(T_{iprj,Sev=s} = 1 | L_{ikrj,Sev=s}) \sim uniform(0,1)$$

Specific accuracy parameters with constraints are:

$$P(T_{i2rj,Sev=2} = 1 | L_{i2rj,Sev=2}) \sim uniform(0.1,1)$$
$$P(T_{i3rj,Sev=2} = 1 | L_{i2rj,Sev=2}) \sim uniform(0,0.1)$$
$$P(T_{iprj,Sev=2,3} = 1 | L_{i1rj,Sev=2,3}) \sim uniform(0,0.2)$$

Incidence parameters with constraints are:

$$inv.logit\left(\alpha_{male_{krj,Sev=s}}\right) \sim uniform(0,0.1)$$
$$\beta_{female_{krj,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

<u>Other parameters derived from the aforementioned parameters:</u>

Probability of being in a specific class given a case definition response pattern:

$$P\left(L_{ikrj,Sev=s} = K_{rj,Sev=s} \mid T_{irj,Sev=s}\right) = \frac{P\left(L_{ikrj,Sev=s}\right)\prod_{pr=1}^{Pr} P\left(T_{iprj,Sev=s} \middle| L_{ikrj,Sev=s}\right)}{\sum_{kr=1}^{Kr} P\left(L_{ikrj,Sev=s}\right)\prod_{pr=1}^{Pr} P\left(T_{iprj,Sev=s} \middle| L_{ikjr,Sev=s}\right)}$$

Class-specific incidence across both sexes:

$$Incidence\ of\ Class\ k_{rj,Sev=s} = \frac{\sum_{i=1}^{32} P\left(L_{ikrj,Sev=s} = K_{rj,Sev=s} \middle| T_{irj,Sev=s}\right) * n_{irj,Sev=s}}{\sum_{i=1}^{32} n_{irj,Sev=s}}$$

$$Sensitivity_{prj,Sev=s} = P\left(T_{iprj,Sev=s} = 1 \middle| L_{i2rj,Sev=s}\right)$$
$$Specificity_{prj,Sev=s} = P\left(T_{iprj,Sev=s} = 0 \middle| L_{i1rj,Sev=s}\right)$$

$$PPV_{prj,Sev=s} = \frac{Sensitivity_{prj,Sev=s} * Inc_{2rj,Sev=s}}{Sensitivity_{prj,Sev=s} * Inc_{2rj,Sev=s} + (1 - Specificity_{prj,Sev=s})(1 - Inc_{2rj,Sev=s})}$$

$$NPV_{prj,Sev=s} = \frac{Specificity_{prj,Sev=s} * (1 - Inc_{2rj,Sev=s})}{(1 - Sensitivity_{prj,Sev=s}) * Inc_{2rj,Sev=s} + (Specificity_{prj,Sev=s})(1 - Inc_{2rj,Sev=s})}$$

All parameters above had their *j*=1000 posterior distributions pooled together to ascertain final estimates that are reported.

As mentioned above, the 1000 predicted cohort sizes for each of the 6 cohorts across the 2 incident TBI severity groups and 3 age groups was ascertained in our model. Using these distributions of cohort sizes, we provided summary estimates of the aforementioned parameters by weighting the parameters based on the cohort size of each stratified group. As such, we were able to provide summary estimates across both severity groups of the sensitivity, specificity, PPV, NPV, and rTBI incidence for each age group. We also estimated the overall rTBI risk across the entire population through the same weighting strategy based on predicted cohort sizes.

$$Parameter\ across\ both\ incident\ severity\ groups = \frac{N_{rT,Sev=2} * parameter \quad + \; N_{rT,Sev=3} * parameter}{N_{rT,Sev=2} + N_{rT,Sev=3}}$$

$$N_{rT,Sev=s} = \sum_{j=1}^{1000} N_{rj,Sev=s}$$

<u>Prior information used in sensitivity analyses:</u>

The five following sensitivity analyses were conducted by varying the prior information used on the accuracy parameters that did not use non-informative prior distributions in the main analysis. All other prior distributions defined above were kept the same in the sensitivity analyses, unless otherwise noted below.

Sensitivity analysis 1: The prior information on the sensitivity of the discharge abstract database case definition is loosened to a maximum of 25%.

$$P\big(T_{i2rj,Sev=2} = 1\big|L_{i2rj,Sev=2}\big) \sim uniform(0.1,1)$$
$$P\big(T_{i3rj,Sev=2} = 1\big|L_{i2rj,Sev=2}\big) \sim uniform(0,0.25)$$
$$P\big(T_{i3rj,Sev=3} = 1\big|L_{i2rj,Sev=3}\big) \sim uniform(0,0.25)$$

With the other constraints maintained as previously described:

$$P\big(T_{iprj,Sev=s} = 1\big|L_{i2rj,Sev=s}\big) \sim uniform(0,1)$$
$$P\big(T_{iprj,Sev=2,3} = 1\big|L_{i1rj,Sev=2,3}\big) \sim uniform(0,0.2)$$
$$inv.logit\left(\alpha_{male_{2j,Sev=s}}\right) \sim uniform(0,0.1)$$
$$\beta_{female_{2j,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

Sensitivity analysis 2: The specificity of the radiological examination case definition is forced to be less than 95%.

$$P\big(T_{i5rj,Sev=2,3} = 1\big|L_{i1rj,Sev=2,3}\big) \sim uniform(0.05,0.2)$$

With the other constraints maintained as previously described:

$$P\big(T_{iprj,Sev=s} = 1\big|L_{i2rj,Sev=s}\big) \sim uniform(0,1)$$
$$P\big(T_{i2rj,Sev=2} = 1\big|L_{i2rj,Sev=2}\big) \sim uniform(0.1,1)$$
$$P\big(T_{i3rj,Sev=2} = 1\big|L_{i2rj,Sev=2}\big) \sim uniform(0,0.1)$$
$$P\big(T_{iprj,Sev=2,3} = 1\big|L_{i1rj,Sev=2,3}\big) \sim uniform(0,0.2)$$
$$inv.logit\left(\alpha_{male_{2j,Sev=s}}\right) \sim uniform(0,0.1)$$

$$\beta_{female_{2j,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

Sensitivity analysis 3: The specificity of the outpatient physician claim case definition is forced to be less than 95%.

$$P\left(T_{i1rj,Sev=2,3} = 1 \middle| L_{i1rj,Sev=2,3}\right) \sim uniform(0.05,0.2)$$

With the other constraints maintained as previously described:

$$P\left(T_{iprj,Sev=s} = 1 \middle| L_{i2rj,Sev=s}\right) \sim uniform(0,1)$$
$$P\left(T_{i2rj,Sev=2} = 1 \middle| L_{i2rj,Sev=2}\right) \sim uniform(0.1,1)$$
$$P\left(T_{i3rj,Sev=2} = 1 \middle| L_{i2rj,Sev=2}\right) \sim uniform(0,0.1)$$
$$P\left(T_{iprj,Sev=2,3} = 1 \middle| L_{i1rj,Sev=2,3}\right) \sim uniform(0,0.2)$$
$$inv.logit\left(\alpha_{male_{2j,Sev=s}}\right) \sim uniform(0,0.1)$$
$$\beta_{female_{2j,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

Sensitivity analysis 4: The specificity of the emergency physician claims and the discharge abstract database case definitions are not constrained.

$$P\left(T_{i2rj,Sev=2,3} = 1 \middle| L_{i1rj,Sev=2}\right) \sim uniform(0,1)$$
$$P\left(T_{i3rj,Sev=2,3} = 1 \middle| L_{i1rj,Sev=2}\right) \sim uniform(0,1)$$

With the other constraints maintained as previously described:

$$P\left(T_{iprj,Sev=2,3} = 1 \middle| L_{i2rj,Sev=2,3}\right) \sim uniform(0,1)$$
$$P\left(T_{i2rj,Sev=2} = 1 \middle| L_{i2rj,Sev=2}\right) \sim uniform(0.1,1)$$
$$P\left(T_{i3rj,Sev=2} = 1 \middle| L_{i2rj,Sev=2}\right) \sim uniform(0,0.1)$$
$$P\left(T_{iprj,Sev=2,3} = 1 \middle| L_{i1rj,Sev=2,3}\right) \sim uniform(0,0.2)$$
$$inv.logit\left(\alpha_{male_{2j,Sev=s}}\right) \sim uniform(0,0.1)$$
$$\beta_{female_{2j,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

Sensitivity analysis 5: The incidence for males is constrained to being less than 15% instead of 10%.

$$inv.logit\left(\alpha_{male_{2j,Sev=2,3}}\right) \sim uniform(0,0.15)$$

With the other constraints maintained as previously described:

$$P\left(T_{iprj,Sev=s} = 1 \middle| L_{ikrj,Sev=s}\right) \sim uniform(0,1)$$

$$P\left(T_{i2rj,Sev=2} = 1\middle|L_{i2rj,Sev=2}\right) \sim uniform(0.1,1)$$
$$P\left(T_{i3rj,Sev=2} = 1\middle|L_{i2rj,Sev=2}\right) \sim uniform(0,0.1)$$
$$P\left(T_{iprj,Sev=2,3} = 1\middle|L_{i1rj,Sev=2,3}\right) \sim uniform(0,0.2)$$
$$\beta_{female_{2j,Sev=s}} \sim Normal(0,0.01)T(-0.5,0.1)$$

Appendix 3: Posterior predictive distribution (Bayesian p-values) to assess model fit by age group

Typical approaches to assessing model fit in other statistical models, such as Discrepancy (χ^2 statistic and the likelihood ratio), are not appropriate to assess model fit in latent class models.[11] For latent class analysis, conducting posterior predictive checks that compare the observed and predicted agreement between pairs of tests (or case definitions), pq, has been shown to be an adequate way of assessing model fit and ensuring there is no residual correlation between pairs of tests.[12,13] We drew 3000 samples from the posterior predictive distribution for each of j=1000 simulated cohorts to establish the "*expected*" counts, $n.new_{irj}$, of each of the 16 case definition response patterns for each sex (a total of T_{irj} = 32 response patterns).[11] We also used the j=1000 simulated cohorts for each of the case definition response patterns,$n_{irj,Sev=s}$, which was established using predictions of each response patterns from our previous analysis on incident TBI, as the *"observed"* counts. The observed and expected agreement between pairs of tests, (pq), was estimated as detailed below. We then estimated the probability that the observed agreement would be greater than the predicted agreement within the 3000 samples that were drawn for each pair of tests $(P(Observed\ agreement_{pqrj,Sev=s}) > P(Predicted\ agreement_{pqrj,Sev=s}))$, which is also known as a Bayesian p-value, and across the j=1000 simulated cohorts.[13] When these probabilities are close to 0 or 1 there is evidence to suggest that model fit may be inappropriate. We conducted this analysis for each age group across the "mildest/more severe" and "most severe" incident TBI cohorts across the j=1000 simulated cohorts. The "r" subscript indicates that the parameter in the model represents the rTBI analysis, in contrast to the incident TBI analysis from our previously completed investigation on the topic.

When these probabilities are very close to 0 or 1, there may be evidence that model fit is inappropriate.

$$Predicted\ agreement_{pqrj,Sev=s} = \frac{\sum_{i=1}^{64} n.new_{irj} * (T_{iprj,Sev=s}T_{iqrj,Sev=s} + \left(1 - T_{iprj,Sev=s}\right)\left(1 - T_{iqrj,Sev=s}\right))}{\sum_{i=1}^{64} n.new_{irj,Sev=s}}$$

$$Observed\ agreement_{pqrj,Sev=s} = \frac{\sum_{i=1}^{64} n_{irj,Sev=s} * (T_{iprj,Sev=s}T_{iqrj,Sev=s} + \left(1 - T_{iprj,Sev=s}\right)\left(1 - T_{iqrj,Sev=s}\right))}{\sum_{i=1}^{64} n_{irj,Sev=s}}$$

The j=1000 simulations were combined together to obtain the Bayesian p-value of each pair of case definitions for each age group and index TBI severity cohort.

Appendix 4: Crude and adjusted median time to rTBI recurrence by age group

The crude median time to rTBI was estimated for each age group using the earliest case definition that an individual was positive for after their incident TBI. However, an adjusted median time to recurrence was also assessed to assess the validity of this crude measure. To do the latter, we estimated the probability that an individual had an incident TBI based on their case definition response pattern for incident TBI. We also estimated the same probability for rTBI using the case definition response pattern for rTBI. The product of these probabilities was the overall probability that the individual was a true rTBI case. The crude recurrence time was defined as the earliest time when a patient met a case definition for rTBI during the 1-year follow-up period. These probabilities were used as weights for the crude time to recurrence estimate mentioned above. j=1000 simulations of the accuracy parameters from the incident TBI and rTBI analyses were taken to conduct 1000 analyses, such that the uncertainty in the accuracy parameters was maintained in this analysis. 1000 estimates for median time to rTBI were established for each age group. The median of these 1000 analyses represented the overall median time to recurrence, as shown below. The "*r*" subscript indicates that the parameter in the model represents the rTBI analysis, in contrast to the incident TBI analysis from our previously completed investigation on the topic.

<u>The probability of incident TBI and rTBI is as follows:</u>

For incident TBI:

$$P\left(L_{ikj} = K_j \mid T_{ij}\right) \quad = P\left(L_{ikj}\right) \prod_{p=1}^{P} P\left(T_{ipj} \middle| L_{ikj}\right)$$

For rTBI:

$$P\left(L_{ikr} = K_{rj} \mid T_{irj}\right) \quad = P\left(L_{ikrj}\right) \prod_{pr=1}^{Pr} P\left(T_{iprj} \middle| L_{ikrj}\right)$$

Where K is an incident case, Kr is recurrent case, L_{ik}/L_{ikr} is the incidence across all classes for incident TBI/rTBI, p is 1 of 5 case definitions, pr is1 of 4 case definitions, T_i is 1 of 32, and T_{ir} is 1/16 case definition response patterns for the i^{th} individual with suspected rTBI.

The accuracy parameters (as distributions), across all severities of incident TBI, $P\left(T_{ip} \middle| L_{ik}\right)$ and $P\left(T_{ipr} \middle| L_{ikr}\right)$ were established from the previously completed study on incident TBI and the main analysis of the current study on rTBI, respectively.

$$Weight_{ij,Sev=s} = P\left(L_{ikj} = K_j \mid T_i\right) \quad * P\left(L_{ikrj} = K_{rj} \mid T_{irj}\right)$$

$$Adjusted\ time\ to\ recurrence_j = \frac{rec_{time_i} * Weight_{ij}}{\sum_{i=1}^{n} Weight_{ij}}$$

$Median\ time\ to\ recurrence \quad = Median\ (adjusted\ time\ to\ recurrence_{j)}$ for j=1:1000

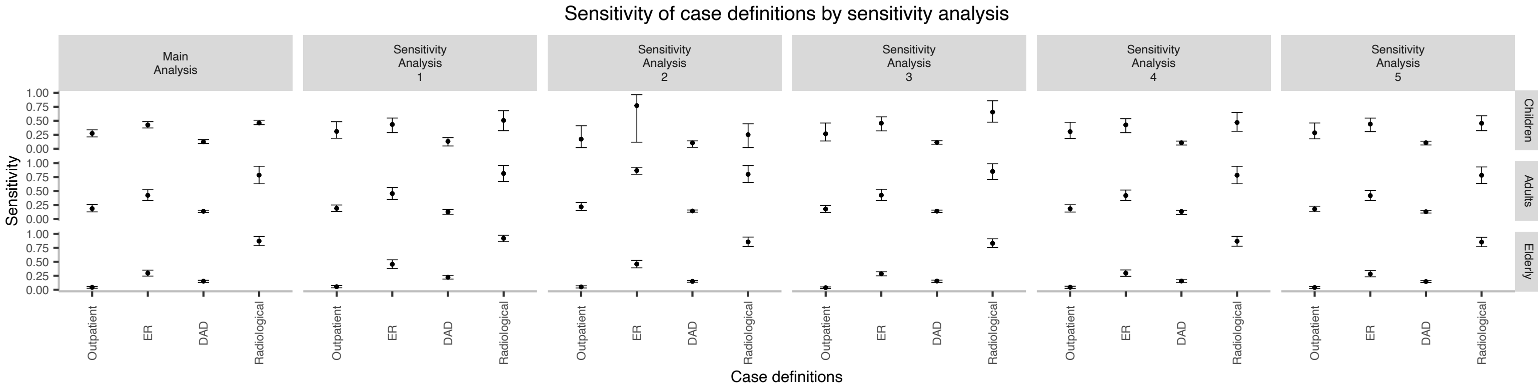
Where *n* is the total number of patients with *suspected* rTBI in each age group cohort.

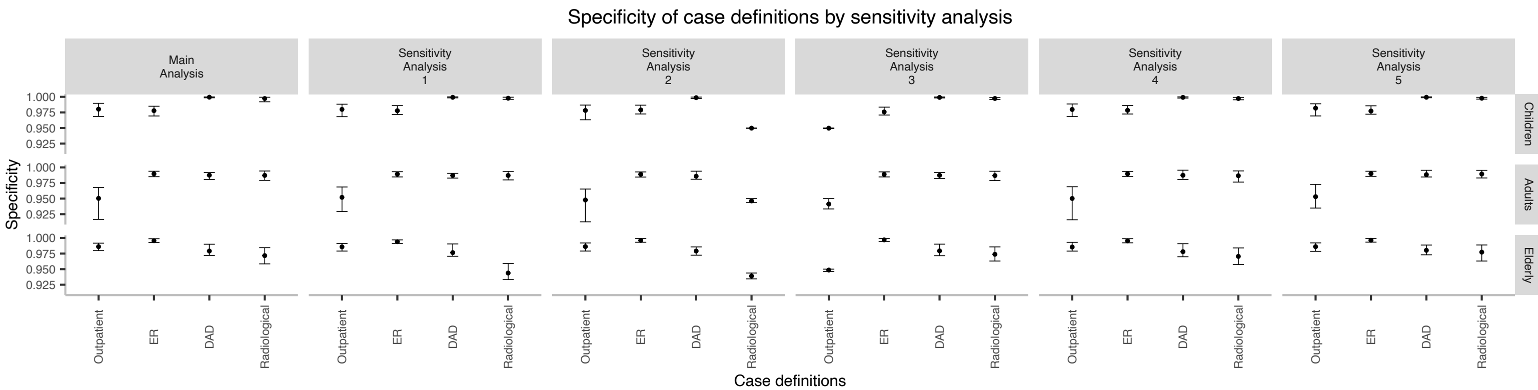
Appendix 5: Model fit assessment using Bayesian *p*-values across each age group in the main analysis

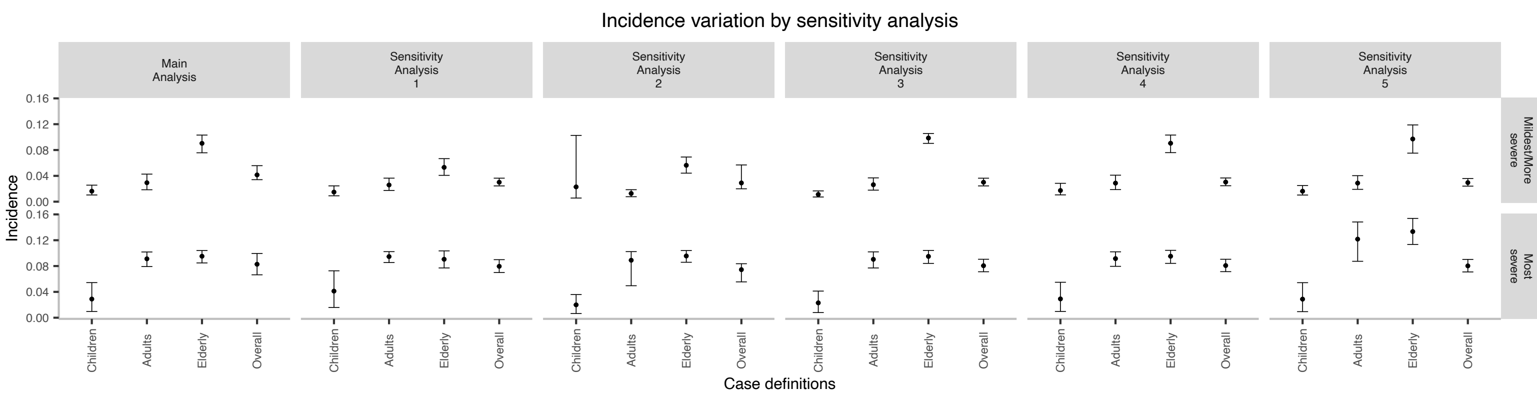
	Children		Adults		Elderly	
	Pr (Observed > Predicted)					
Case definition pair (*pq*)	Mildest/ more severe	Most severe	Mildest/ more severe	Most severe	Mildest/ more severe	Most severe
1,2	0.30	0.55	0.60	0.55	0.57	0.29
1,3	0.27	0.65	0.44	0.6	0.11	0.40
1,4	0.61	0.53	0.44	0.35	0.46	0.28
2,3	0.68	0.53	0.50	0.18	0.84	0.14
2,4	0.44	0.60	0.50	0.38	0.47	0.35
3,4	0.69	0.63	0.63	0.56	0.83	0.78

Model fit assessing the observed and predicted agreement between pairs of case of definitions pooled across both severities of index TBI. The probability that the observed agreement is greater than the predicted agreement between pairs of case definitions is used to assess whether or not model fit is appropriate.[11] When probabilities (also known as Bayesian *p*-values) are close to 0 or 1, then model fit may be inappropriate (Appendix 3). The pairs of case definitions are as defined in Appendix 2: 1 = outpatient physician claim, 2 = emergency department physician claim, 3 = discharge abstract database, 4 = radiological examination of the head in the context of any trauma diagnosis.

Appendix 6: Sensitivity analyses



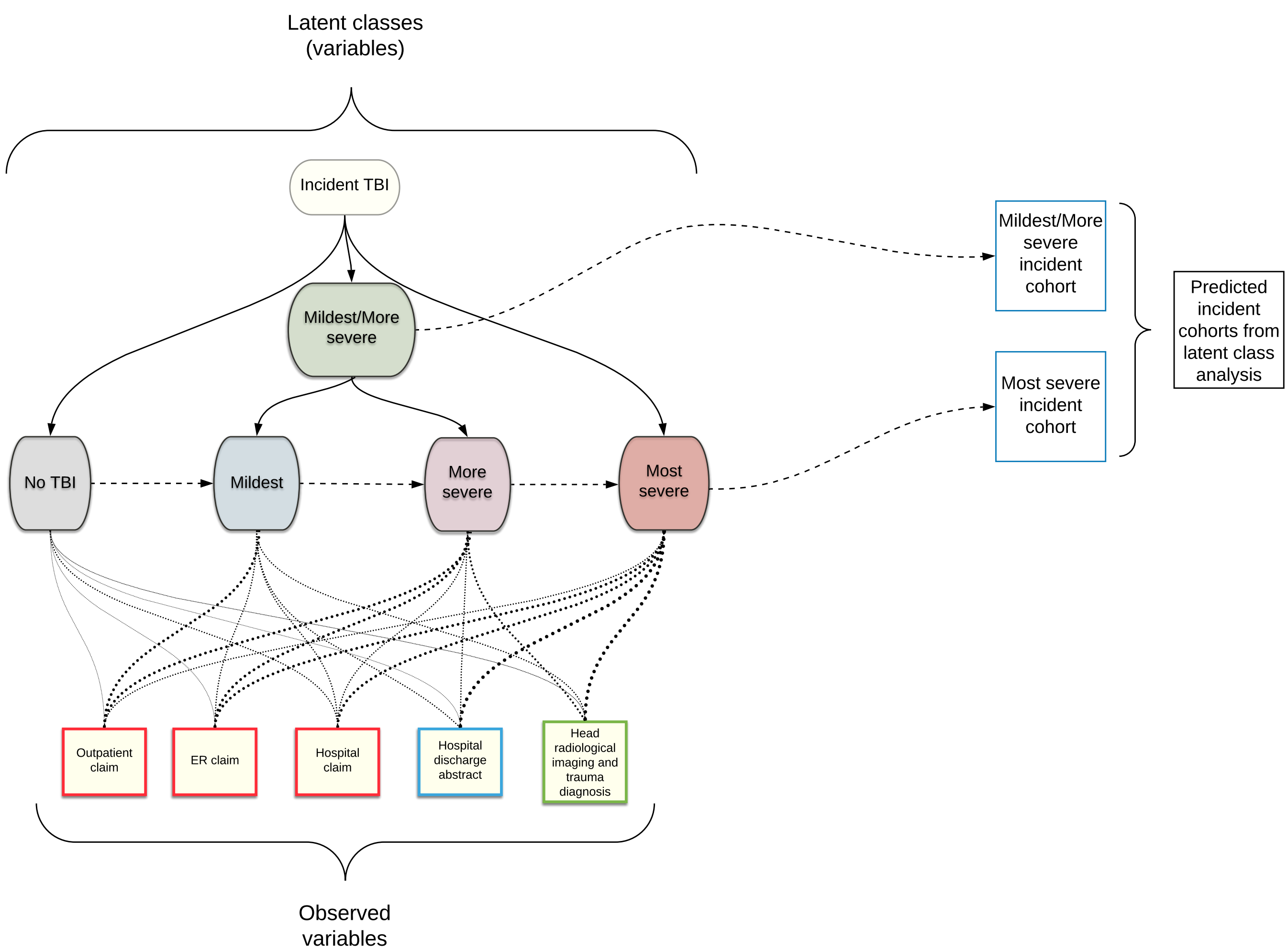




Three sensitivity analyses were completed that varied the prior information we used the main analysis within plausible ranges. The estimates from these three analyses were compared to the estimates from the main analysis above. The prior information varied in these three sensitivity analyses is as described at the end of Appendix 2. “Outpatient” = outpatient claims, “ER” = emergency room claims, “DAD” = discharge abstract database, “Radiology” = radiological examination claim in the context of any trauma diagnosis.

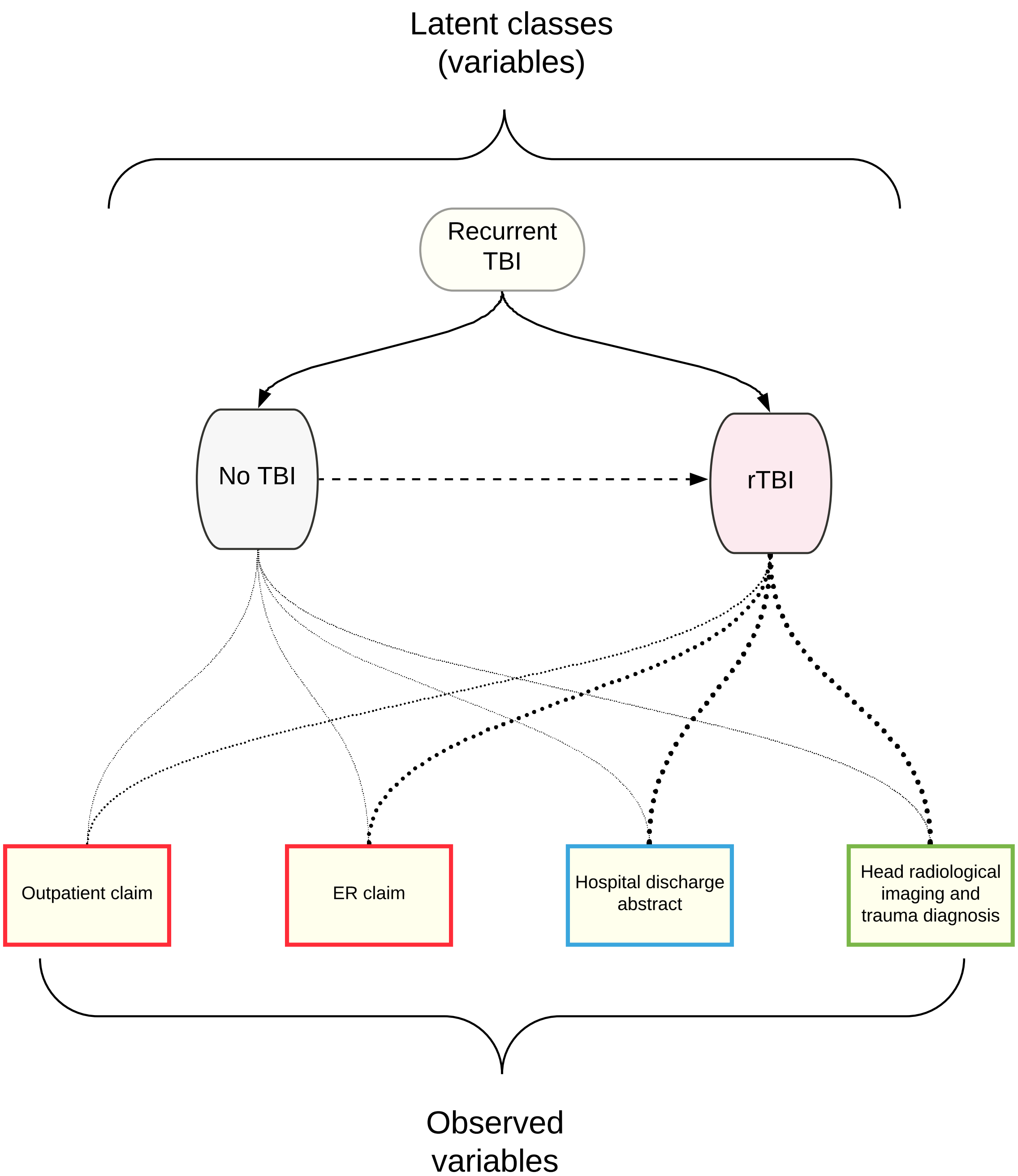
Appendix 7: Heuristic diagrams demonstrating the latent classes and the observed variables used in the incident TBI and rTBI analyses

7A:



This heuristic diagram outlines the incident TBI latent class analysis that was previously completed.[4] This model was used to predict 1000 cohorts of incident TBI patients across the three age groups in the main analysis. The incident cohorts were predicted into two severity classes: "mildest/more severe" and "most severe" incident TBI patients.

7B:



This heuristic diagram demonstrates the two latent classes used in the present rTBI analysis. The predicted incident TBI cohorts, described in the previous heuristic diagram, were used to complete this analysis.

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Chapter 7: Discussion and conclusion

The TBI burden in populations across the globe continues to lead to important disability and mortality. An accurate portrait of the true injury burden has been challenging due to limitations in methods for conducting surveillance accurately and efficiently. Public health stakeholders and researchers have called the TBI burden on society a "silent epidemic", due to its persistent underestimation.[9,40] In addition, recurrent cases, which have been largely ignored in the TBI surveillance literature, add an additional burden.[132] However, a prerequisite to adequately capturing the rTBI burden, is to accurately measure the burden related to incident TBI.

This thesis addressed each of these issues by providing the tools for TBI and public health stakeholders to conduct accurate and efficient TBI/rTBI surveillance using administrative health data. First, I assessed the accuracy of widely used ICD-based TBI surveillance case definitions for incident TBI, across the full spectrum of injury.[131] Then, I shed light on the current knowledge regarding rTBI epidemiology and risk factors in the general population through a systematic review of the literature, while identifying methodological limitations that needed to be addressed.[132] Finally, I used the knowledge from these two last studies to assess the accuracy of rTBI surveillance case definitions in administrative health data.

Summary of research findings

The first manuscript demonstrated that using administrative health data to perform incident TBI surveillance underestimates the true TBI incidence. In this study, I used ICD-based TBI surveillance case definitions to ensure that the results would be applicable across jurisdictions where similar data are available. I circumvented the problem of underestimating the true injury burden by correcting for the inherent measurement error when using administrative health data.

To correct for measurement error, I used Bayesian latent class analysis, which allowed me to avoid the problem of having to define a gold standard for TBI. As previously mentioned, a gold standard for TBI diagnosis does not exist, and therefore validly assessing the true measurement error is not feasible if an imperfect reference standard is used. Furthermore, I was able to stratify patients into categories of injury severity by using the patterns of care at the time of their incident TBI. This study also demonstrated secular trends in the performance of case definitions to detect TBI, which must be accounted for to appropriately adjust for measurement error that varies over time. As such, this study demonstrated that administrative health data can be used to conduct surveillance for TBI accurately and efficiently, provided that measurement error is accounted for.

The second manuscript synthesized knowledge on the epidemiological characteristics of rTBI in the general population. Previously, most literature on this topic focused on athlete populations, and therefore the rTBI burden in the general population was not well-characterized. This study demonstrated that the literature on rTBI has important methodological flaws, which stem mainly from limitations in adequately defining rTBI in various data sources. In addition, many studies were not population-based, which limited the generalizability of the findings. Several risk factors associated with rTBI were identified, such as increasing age, male sex, higher severity index TBI, alcohol intoxication, prior history of TBI, and lower socio-economic status. However, there was important heterogeneity demonstrated across studies for the association measures of these risk factors. Furthermore, my meta-regression analysis emphasized that the use of administrative health data, compared to other data sources such as cohort studies and trauma registries, tend to provide higher rTBI risk estimates even when controlling for follow-up time. Many studies also reported that rTBI most often occurs within the first 6 months after an incident TBI. In short, this systematic review demonstrated that our current knowledge on the epidemiological characteristics of rTBI in the general population is limited by a lack of methods that allow us to conduct surveillance accurately and efficiently.

The third manuscript in this thesis addressed limitations identified in the systematic review on rTBI. I again used Bayesian latent class models to estimate the accuracy of widely available ICD-based TBI case definitions in administrative health to detect rTBI in a population-based sample. Given that I used a Bayesian approach, I was able to propagate the uncertainty from my analysis on incident TBI (Manuscript 1) through to my final analysis on rTBI. I also stratified my analysis by the severity of the index TBI, since the latent class model from Manuscript 1 was able to provide this information. In doing so, I was able to demonstrate that a higher severity index TBI is associated with a higher risk of rTBI. I was also able to demonstrate that male sex is associated with a higher risk of rTBI in children and adults, but that elderly females have a higher risk than males. The explanation for this phenomenon is not clear, but these findings have not been reported in the literature since previous analyses were not stratified by age groups.[132] I also demonstrated, after correcting for measurement error, that the median time to rTBI is the shortest in adults (75 days) and slightly longer in children and the elderly (120 and 109 days, respectively). This median time was significantly shorter when it was not adjusted for the measurement error in detecting both incident and recurrent TBI. This finding in turn explains why administrative health data overestimate the true rTBI burden, as I showed in my meta-regression analysis from Manuscript 2. The 1-year rTBI incidence I estimated was 4.48 per 100 person-years, compared to a crude estimate of 8.03 per 100 person-years. Administrative health data can provide a complete record of health care utilization by patients, and therefore follow-up for incident TBI can often be mistaken as rTBI events. By adjusting for this measurement error through latent class analysis, I was able to at least partially address this limitation. In short, administrative health data overestimate the rTBI burden if measurement error is not accounted for. However, they remain a powerful resource for efficient rTBI surveillance across jurisdictions.

Limitations

Each manuscript in this thesis had its respective limitations that were described in Chapters 4-6. Across these manuscripts, there are some common limitations that should be acknowledged to properly interpret the main conclusions of this thesis.

Generalizability/external validity of findings

In Manuscripts 1 and 3, I used a 25% random sample of the Census Metropolitan Area (CMA) of Montreal population to estimate the accuracy of administrative health data case definitions to detect incident TBI and rTBI. Clearly, the health care utilization patterns of this population are not necessarily the same as in other jurisdictions, or even in the greater Province of Quebec. The case definitions based on the patterns of care by TBI patients depend on how a health care system is organized and the health care policies that are in place in a given jurisdiction. For example, in Quebec, the Ministry of Health and Social Services developed guidelines for selecting TBI patients that require a transfer to a designated neurotrauma centre and follow-up care.[133] Such guidelines influence the patterns of care patients will experience. Therefore, the response patterns to the case definitions I used to detect TBI in administrative health data may be different than in other jurisdictions where such policies are not in place, or where the adherence to such policies is different. In addition, the CMA of Montreal is a predominantly urban population, although it also includes some rural areas.[102] The urban versus rural setting can have an impact on the epidemiologic characteristics of TBI, which would in turn influence the performance of the case definitions that I used.[14,104] However, many epidemiologic studies in developed countries have demonstrated that the epidemiology of TBI shares many similar characteristics across jurisdictions, which may limit the influence of this limitation.[31] Also, international guidelines have been developed for the management of TBI, and these guidelines should help to standardize patterns of care for TBI patients across jurisdictions.[134] Nonetheless, the parameter estimates should be interpreted with caution and applied in populations that share similar characteristics.

Assumptions used in Bayesian latent class analyses

In Manuscripts 1 and 3, the use of Bayesian latent class analysis was contingent on several assumptions that may limit the validity of my findings.

First, I used prior information to constrain certain parameters to allow the models to converge and to avoid the problem of label switching previously described.[122] I tried to use the least informative prior information as possible to limit the influence that they would have on the overall conclusions of the study. In addition, I conducted multiple sensitivity analyses that varied these prior distributions within reasonable ranges, with little impact on the overall conclusions of each study.

Second, conditional dependence between case definitions, given injury status, in the latent class analyses can bias the parameter estimates I provided. In Manuscript 1, I used 5 case definitions where the diagnosis of TBI, through ICD codes, were provided by different individuals. For example, the outpatient physician claim was provided by a family provider, the emergency room claim by an emergency room physician, the inpatient claim by an admitting physician, the discharge abstract database by a medical archivist, and the radiological examination claim by a radiologist. Nonetheless, the diagnosis by one physician can influence the diagnosis of another physician, and therefore conditional dependence is still possible. In Manuscript 1, I assessed for residual correlation between pairs of case definitions and I also used Bayesian *p* values to assess whether the observed counts of patients with a pair of positive case definitions was systematically higher or lower than the model prediction.[135,136] In both instances, there was no evidence of poor model fit or of any significant residual correlation. A similar approach was used in Manuscript 3, where only 4 case definitions were used. In that study, there was also no evidence of residual correlation between pairs of case definitions.

Third, the number of latent classes used in each analysis was also investigator-dependent and can have an impact on the results. In Manuscript 1, my *a priori* hypothesis was that the 5 case definitions I used could cluster patients into 3 severity classes of TBI (4-class model). I used model fit strategies to assess whether models with 2 and 3 classes would provide an adequate fit. These models had poorer model fit than the 4-class model. In addition, a 5-class model would not converge without additional informative prior information, which was not available in the literature. Furthermore, the latent class model does not provide a label for each class. The class-specific sensitivity of each case definition provides a portrait of how the class is labelled. Based on the results I obtained, it was clear that the 3 classes represented patients that had the "mildest" TBI (mainly outpatient visits), "more severe" TBI (patients presenting to the emergency room), and "most" severe (hospitalized patients). However, the labels represent a spectrum of injury severity and do not match the standard methods of classifying the severity of TBI patients, such as the Glasgow Coma Score, and should not be interpreted as such.[49] In Manuscript 3, the sparsity of data from the predicted cohorts from Manuscript 1 made it difficult for models with more than 2 classes to converge. As such, a 2-class model was used, and model fit assessments were adequate. Thus, larger studies are needed to further evaluate the other classes or severities of rTBI.

Comprehensiveness of surveillance using administrative health data:

Manuscripts 1 and 3 used administrative health data to conduct TBI and rTBI surveillance. By using multiple overlapping sources of administrative health data, I was able to comprehensively assess the TBI and rTBI burden. However, patients that did not seek medical care were not included since, by definition, there would not be any claims or hospitalization data for these individuals. As such, the estimates from these studies should be interpreted as representative of patients seeking medical care. The population-based cohort study in New Zealand by Feigin et al. demonstrated that only 1% of patients in their cohort study of TBI patients were self-referrals that would not be captured through comprehensive administrative health data that includes outpatient visits, imaging claims, emergency room visits, inpatient claims and hospitalization data.[14] Nonetheless, it must be acknowledged that although the methods I present improve the accuracy of TBI surveillance, the injury burden is still likely to be larger than measured.

Implications and future directions for TBI surveillance and epidemiologic research

The knowledge and methods regarding TBI and rTBI surveillance generated through this thesis are relevant to surveillance researchers, public health authorities, and decision-makers.

TBI and rTBI surveillance:

In Canada, the Public Health Agency of Canada completed the "Mapping Connections" study in 2014 that brought together several research groups to provide a portrait of the burden of neurological disease in Canada.[7] They assessed the incidence, prevalence, and economic impact of neurological diseases in the Canadian population. As in other studies on TBI surveillance, they acknowledged that current methods used to conduct TBI surveillance yield underestimates of the true injury burden.[14,33,36,56] As such, information regarding its economic impact also needs to be interpreted as an underestimation. The information I provided through my first manuscript fills these knowledge gaps by providing the tools to conduct accurate TBI surveillance using widely available administrative health data. Public health authorities can use the accuracy measures (sensitivity and specificity) of different case definitions I assessed to adjust their crude incidence estimate. Since I assessed the accuracy of 5 case definitions that identify TBI across the full spectrum of care, different health authorities can make use of a single data source/case definition and still adjust their incidence estimates. This approach to conducting surveillance allows public health authorities to conduct accurate surveillance efficiently across the full injury spectrum, by avoiding the costs related to having to undertake cohort studies to assess the TBI burden.[27] Similarly, these stakeholders will also have the information to assess the rTBI burden in the general population. Thus, comprehensive and accurate TBI burden assessments are now feasible using resources that are readily available. These accurate estimates of TBI and rTBI incidence can also be used in economic analyses on the impact of TBI on the general population to make those analyses more representative of the true TBI burden on society.

I also identified important secular trends in the performance of certain case definitions, which should be accounted for in surveillance studies since these changes over time can have important impacts on estimates of injury burden. Furthermore, the characteristics of the rTBI burden in the general population were previously not comprehensively described. However, the systematic review on the topic provided important information on risk factors that can help in identifying patients at risk of rTBI. All of these improvements in incident TBI and rTBI surveillance methodology and knowledge are critical to decision-makers that need to justify the allocation of health care resources for prevention and care of TBI patients, which is necessary to better control the injury burden.

Epidemiologic research

As previously mentioned, improvements in TBI surveillance improve the assessment of the injury burden, which helps inform public health policy and resource allocation. However, the improved TBI surveillance methodology provided in this thesis is also a powerful tool for epidemiologic researchers assessing the impact of interventions that mitigate the risk of TBI, rTBI, or adverse consequences related to such injuries. By addressing measurement error inherent in administrative health data to detect TBI/rTBI cases, investigators now have the tools to provide higher quality research that produces more precise and valid inferences. For example, studies assessing the impact of public health interventions, such as helmet laws and concussion prevention policies, on the occurrence of TBI may result in invalid inference if measurement error is not accounted for.[137,138] In such studies, the incidence of TBI is assessed before and after an intervention is implemented, such that inference on the effect of the intervention can be established. As I demonstrated, the accuracy of certain case definitions varies over time, through secular trends, which requires researchers to adjust for this time-varying measurement error that could lead to overestimates or underestimates of the true impact of an intervention. In addition, the estimates of the association between an intervention and an outcome may be falsely more precise if this measurement error is not accounted for. I demonstrated this finding in Manuscript 1, where the crude TBI incidence estimate had a much narrower credible interval than the measurement error-adjusted estimate. As such, the inferences of these studies may be invalid or overly precise, which can lead individuals to interpret these results with a false sense of their efficacy or inefficacy.

The improved methods developed to identify TBI and rTBI patients in administrative health data are also useful to researchers investigating adverse events related to the occurrence of TBI. To achieve the latter, investigators must identify incident TBI (or rTBI) patients to form a cohort of patients they can follow until the adverse consequences of interest are observed. Recently, the association between TBI and suicide has garnered much interest, since large population-based studies have demonstrated heterogeneous magnitudes of association between TBI and suicide.[66–69] In three of these studies, the lower limit of the confidence interval for the association measure between TBI occurrence and suicide was close to the null. Cohorts of TBI patients were ascertained using ICD-based case definitions, as I have used in this thesis. Given that the positive predictive value (the probability of having TBI given being positive to a case definition) of these case definitions can be as low as 45%, an important proportion of the constructed TBI cohort may not be true cases of TBI. This phenomenon leads to nondifferential misclassification of the exposure (TBI) and would tend to bias the estimated association measure towards the null.[139] As such, the association between TBI and adverse outcomes such as depression, suicide, or dementia may be even larger than reported.[68,69,140] However, the precision in these estimates is falsely reassuring since not accounting for measurement error leads to narrower confidence intervals. As such, these results should be interpreted with that consideration in mind. Therefore, investigators should make the effort to construct valid TBI cohorts probabilistically if administrative health data are used to conduct etiologic research. They could do so using the approach I used to predict cohorts of incident TBI patients in Manuscript 3. In short, measurement error adjustment in TBI etiologic research is necessary to provide valid inferences and is feasible using case definition accuracy parameters. The resources used to conduct these studies are limited, and providing the most valid inferences that account for the uncertainty in the precision of estimates is critical to using research resources efficiently.[97]

The systematic review on rTBI also emphasized that the quality of the literature on rTBI surveillance is currently low due to poor internal and external validity, which has been addressed by the study conducted in Manuscript 3. However, studies assessing interventions that mitigate the risk of rTBI were not identified. I have demonstrated that up 50% of recurrence occur within the first 4 months after incident TBI. As such, interventions that mitigate rTBI risk must be provided shortly after index TBI to prevent these recurrent injuries, which are associated with greater disability when they are closer in time to the index injury.[77] This thesis has provided epidemiologic researchers with the tools to construct valid TBI cohorts and accurately identify rTBI patients in administrative health data by adjusting for measurement error. Thereafter, assessing health care policies that impact the risk of recurrence, such as the implementation of clinical guidelines on the management of TBI patients, through counselling and referral to rehabilitation services, would be feasible.[141] Preliminary research I conducted on the impact of being treated in a specialized neurotrauma centre as opposed to a non-specialized centre for mild TBI suggested that being treated in specialized neurotrauma centre is associated with a lower risk of rTBI. However, this study needs to employ the measurement error adjustments, as mentioned above, before final conclusion can be confirmed. Thereafter, identifying the mediators that may mitigate this decrease in rTBI risk in patients treated in specialized centres would require further investigation so that specific interventions can be implemented.

Conclusion

This thesis provides new evidence and methods to improve TBI surveillance and research across incident and recurrent cases, such that the “silent epidemic” can be exposed. Stakeholders in TBI surveillance can now accurately and efficiently conduct TBI surveillance and provide decision-makers with the information they need to allocate resources to TBI prevention, care, and research. In addition, investigators can use the results from this thesis to conduct higher quality epidemiologic research on interventions that may mitigate the risk of TBI and rTBI. Further research on such interventions, especially to control rTBI which often occurs within months of an index injury, are necessary. With each of these steps forward in improving the quality of surveillance and research, the TBI burden on society will be better understood.

Chapter 8: References

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