**This is an author’s draft of an article published in Injury 2016 47 pp1151-1157**

**Identifying gaps for research prioritization: Global burden of external causes of injury as reflected in the *Cochrane Database of Systematic Reviews***

**Structured Abstract:**

**Importance**: Burden of disease should impact research prioritization.

**Objective**:To analyze the *Cochrane Database of Systematic Reviews* (CDSR) and determine whether systematic reviews and protocols accurately represent disease burden, as measured by disability-adjusted life years (DALYs) from the Global Burden of Disease (GBD) 2010 Study.

**Methods**:Two investigators collected GBD disability metrics for 12 external causes of injury in the GBD 2010 Study. These external causes were then assessed for systematic review and protocol representation in CDSR. Data was collected during the month of April 2015. There were no study participants aside from the researchers.Percentage of total 2010 DALYs, 2010 DALY rank, and median DALY percent change from 1990 to 2010 of the 12 external causes of injury were compared with CDSR representation of systematic reviews and protocols. Data were analyzed for correlation using Spearman rank correlation.

**Results**:Eleven of the 12 causes were represented by at least one systematic review or protocol in CDSR; the category *collective violence and legal intervention* had no representation in CDSR. Correlation testing revealed a strong positive correlation that was statistically significant. Representation of *road injury*; *interpersonal violence*; *fire, heat, and hot substances*; *mechanical forces*; *poisonings*, *adverse effect of medical treatment*,and *animal contact* was well aligned with respect to DALY. Representation of *falls* was greater compared to DALY, while *self-harm*, *exposure to forces of nature*, and *other transport injury* representation was lower compared to DALY.

**Conclusions and Relevance**:CDSR representation of external causes of injury strongly correlates with disease burden. The number of systematic reviews and protocols was well aligned for seven out of 12 causes of injury. These results provide high-quality and transparent data that may guide future prioritization decisions.

**Introduction:**

Modern research is driven by many different incentives and motivations, making the allocation of available funding quite limited1. It is the duty of current health practitioners to pursue research endeavors based on sound data that reflects the need for such research2. Priorities must be set in place to guide practitioners toward conducting meaningful research that will benefit society. Cost is one of the major driving forces behind research, while other prioritization criteria include lack of economical interventions, opportunity for pioneering therapies, prevention of highly transmissible diseases, public interest, and burden of disease1-3.

Few efforts take place to drive agendas and prioritization of research specifically within the field of injuries and trauma. For example, a research agenda for geriatric emergency medicine was proposed by the Academy of Emergency Medicine4. The agenda authors sought to gather data on articles pertaining to trauma, using search terms of *penetrating wounds* and *non-penetrating wounds*. The goal was to provide a synthesis of current literature and suggest areas for further research. Furthermore, the Fogarty International Center of the National Institutes of Health assembled a global panel of trauma and injury experts to identify research and technological advancement needs to reduce the burden of trauma and injuries in low- and middle-income countries5. While both of the described efforts strove to develop research agendas and prioritization, neither takes into account the impact of injuries and trauma on particular populations. We hope to expand upon these efforts by providing transparent data on the global burden of injuries and trauma with corresponding systematic review representation.

The Global Burden of Disease (GBD) 2010 Study is a systematic assessment of the disability and mortality of major diseases and risk factors worldwide6. It is a collaborative effort of scientists and researchers from the World Health Organization (WHO), World Bank, Institute for Health Metrics and Evaluation (IHME), Harvard School of Public Health, and University of Auckland School of Population Health. GBD 2010 estimates the burden of 291 diseases and injuries in 187 countries from 1990 to 20107. The disability-adjusted life year (DALY) was developed as a standardized metric to compare burden across various disease states. The DALY metric is composed of years of life lost (YLL) due to disease-causing mortality and years lived with disability (YLD)8. This provides high-quality epidemiological data on health status that is independent of interest groups. GBD 2010 serves as a universal measurement to inform research output and determine efficacious and cost-effective interventions. DALY metrics are estimated for 12 external causes of injury based on prevalence and data availability.

Systematic reviews are crucial to evidence-based medicine and the reduction of disease burden in the community. By providing a summary of the highest-quality, current literature relevant to a research topic, systematic reviews are increasingly recognized as the pillar of research translation9. Topic coverage in high-quality systematic reviews may serve as a proxy of research prioritization. The Cochrane Collaboration is a group of 31,000 healthcare specialists whose purpose is to establish interventions and protocols of evidence-based medicine to assist healthcare professionals in clinical decision-making10,11. The *Cochrane Database of Systematic Reviews* (CDSR) consists of systematic reviews and protocols (proposals for future systematic reviews) covering a diversity of diagnostic, therapeutic, and epidemiological topics. As the gold standard of systematic reviews, Cochrane reviews represent the most current evidence to ensure applicability to health-care practitioners and organizations around the world10,11. However, information regarding the impact of disease burden on priority-setting of CDSR is lacking. This study will examine whether CDSR representation of 12 external causes of injury correlates with their respective disease burden as measured by GBD 2010.

**Methods:**

The following 12 external causes of injury were analyzed in GBD 2010: *road injury*; *other transport injuries*; *falls; fire, heat, and hot substances*; *poisonings*; *mechanical* *forces*; *adverse effects of medical treatment*; *animal contact*; *self-harm*; *interpersonal violence*; *exposure to forces of nature*; *collective violence and legal intervention*. The category of *other transport injuries* includes injuries caused by watercrafts, airways, ships, airplanes, and railways. Keywords and synonyms from ICD-10 code definitions, as defined by GBD 2010, were used to generate search terms for each of the 12 causes. Search terms were entered into the CDSR “title, abstract, keywords” search function12. Upon reviewing search results within CDSR, systematic reviews and protocols were matched to a corresponding injury or trauma based on subject content and study objectives. In order to be included, a review or protocol must have included the particular external cause of injury as a primary outcome and predominant focus of the subject content, study objectives, and results. Data was also collected on type of publication (systematic review or protocol), Cochrane review group responsible for publication, date of online publication, and the number of trials included in each systematic review. Two authors (CK and BA) collected data independently in February 2015 with final consensus during April 2015. Institutional board review approval was not required since the study solely used data in the public domain and no living subjects.

Methods used by GBD 2010 to measure DALY metrics have been previously described and are available for public access6,13,14. The following two DALY metrics were collected for each of the 12 external causes of injury: percent of total 2010 DALYs (of all 291 diseases studied by GBD) and 2010 DALY rate per 100,000 persons (see Table 1). CDSR representation and DALY metrics were compared using a Spearman rank correlation. Rho, a measure of correlation was determined, along with a two-tailed p-value, which tests the null hypothesis of no correlation. In addition, a data plot was created with the number of review and protocol titles and percent of total 2010 DALYs for each of the 12 external causes of injury to generate a line of best fit with a coefficient of determination (R2). The trend line allowed for spatial demonstration of over- or under-representation of injuries and trauma in CDSR in relation to disease burden.

**Results:**

Search terms for the 12 external causes of injury yielded a total of 646 review and protocol titles, of which 459 were ultimately excluded due to lack of abstract content, objectives, or results focus on the particular cause of injury (see Table 2). A compiled list of all included and excluded reviews and protocols for the 12 external causes of injury can be found in eTables 1 and 2. It should be noted that the Cochrane Library search function provides a list of all review and protocol titles that include a particular search term at least once in the abstract. For this reason, the use of general search terms such as, ‘fall’ and ‘car’ yielded extraneous titles that were irrelevant and excluded. The overall proportion of retained initial ‘hits’ was 29% and ranged from 0% for *collective violence and legal intervention* to 78% for *interpersonal violence*.

A total of 187 reviews and protocols were included to represent the 12 external causes of injury. The Cochrane Injuries Group published the majority of the titles (n = 115). Other Cochrane Groups that contributed to CDSR representation of the 12 causes are as follows: Bone, Joint and Muscle Trauma Group (30); Developmental, Psychosocial and Learning Problems Group (15); Wounds Group (9); Musculoskeletal Group (7); Depression, Anxiety, and Neurosis Group (6); Oral Health Group (5); Eyes and Vision Group (4); Stroke Group (3); Anaesthesia Group (3); HIV/AIDS Group (3); Neonatal Group (2); Dementia and Cognitive Improvement Group (2); Back Group (2); Pain, Palliative, and Supportive Group (2); Drugs and Alcohol Group (2); Public Health Group (1); Drugs and Alcohol Group (1); Peripheral Vascular Diseases Group (1); Hypertension Group (1); Hepato-Biliary Group (1); Effective Practice and Organisation of Care Group (1); Renal Group (1); Occupational Safety and Health Group (1); Childhood Cancer Group (1); Pregnancy and Childbirth Group (1); Incontinence Group (1); Infectious Diseases Group (1); Skin Group (1); Gynaecological Group (1). The majority of reviews and protocols covering the 12 causes of injury were published in 2000 to 2010 (n = 133), followed by 2011 to 2015 (94). Only 4 reviews and protocols were published prior to 2000.

*Falls* and *road injury* had the greatest representation in CDSR with 45 and 44 titles, respectively (see Table 2, Figure 1). These two causes also had the greatest cumulative number of studies informing the systematic review evidence-base (911 and 515, respectively). *Falls* had disproportionately greater CDSR representation compared to its disease burden.

Correlation testing between DALY and CDSR title representation demonstrated rho = 0.77, two-tailed p = 0.003, indicating a strong positive correlation that was statistically significant. CDSR representation of *road injury*; *interpersonal violence*; *fire, heat, and hot substances*; *mechanical forces*; *poisonings*, *adverse effect of medical treatment*,and *animal contact* was well aligned with DALY metrics. Representation of *falls* was greater than the corresponding DALY metric, while *self-harm*, *exposure to forces of nature*, and *other transport injury* representation fell below the corresponding DALY metrics (see Figure 1).

**Discussion:**

Eleven of the 12 external causes of injury analyzed in GBD 2010 were represented by at least one review or protocol in CDSR. *Collective violence and legal intervention*, which includes violence between nations, states, terror groups, or gangs such as war, was not matched with a review or protocol in CDSR. The results of our statistical analysis demonstrate a strong positive correlation between representation of causes of injury in CDSR and respective disease burden. This may indicate that prioritization efforts by Cochrane review groups, particularly the Injuries Group responsible for the majority of publications, strongly considers disease burden when setting research priorities. The GBD database is becoming the preeminent global epidemiological data source15. Findings reported here are consistent with reports of weak association between global burden of disease and the number of published randomized trials16 and moderate correlation between systematic reviews and DALYS across the entire Cochrane Database of Systematic Reviews17. In addition, most reviews and protocols from our analysis were up-to-date with all but four published after 2000 and 50% in the last five years. The availability of systematic reviews that summarize the most current literature is paramount for clinical decision-making.

***Conditions for which CDSR representation was greater than disease burden***

*Falls* was the only cause of injury with CDSR representation that exceeded its disease burden. Out of all 291 conditions studied by GBD 2010, falls are responsible for 1.43% of disease burden. Falls are an important clinical presentation with an array of etiologies and consequences involving multiple medical specialties such as internal medicine, geriatrics, orthopedic surgery, neurology, and stroke services. This diversity was reflected in the Cochrane review groups responsible for titles covering *falls*: Bone, Joint and Muscle Trauma Group (n =24); Musculoskeletal Group (7); Injuries Group: 6; Stroke Group (3); Eyes and Vision Group (2); Oral Health Group (1); Hypertension Group (1); and Back Group (1). This array of specialties yielded reviews covering diverse aspects of falls including prevention, surgical intervention, special considerations in the elderly population, and adverse events such as traumatic brain injury, rehabilitation, and osteoporosis.

***Conditions for which CDSR representation was lower than disease burden***

*Self-harm* had the second greatest disease burden of the 12 causes of injury (1.48%), but the fourth lowest number of systematic reviews and protocols (5). *Exposure to forces of nature* (such as heat wave, earthquake, blizzard, and tornado) and *other transport injuries* (injuries due to watercrafts, aircrafts, and railways) each had only one review in CDSR. The one review on *other transport injuries*, which examined DVT prophylaxis in airline passengers, was based on 10 studies, while the review on *exposure to forces of nature*, which attempted to examine the impact of electric fans during heatwaves, found no published or un-published studies in the literature on this topic. Clearly, there is a paucity of high-quality data from the medical research community on these potentially catastrophic conditions.

***Limitations and Future Directions***

There is some degree of subjectivity in assigning each systematic review or protocol to a particular cause or condition, which we attempted to address with data collection by two independent authors. CDSR provides systematic reviews and protocols based on published and unpublished literature meeting pre-specified eligibility criteria for a particular topic, making meta-analyses impossible for certain topics which do not contain research-based evidence in the literature18. Furthermore, a systematic review may synthesize many interventions (“lumping”) or be divided into several different reviews of individual interventions (“splitting”). This was especially applicable for several reviews published by the Cochrane Injuries Group, such as “Home safety education and provision of safety equipment for injury prevention” which covered *fire, heat and hot substances*; *poisonings*; *mechanical forces*; and *interpersonal violence* and was assigned to all four causes of injury.

This study is part of a larger series intended to map all 291 diseases studied by GBD to representation in major research databases19,20,21,22. It would also be valuable to compare topic prioritization in other databases to CDSR, such as the Database of Abstracts and Reviews of Effects (DARE), Medline, Health Systems Evidence, and Web of Science, to provide further insight into whether research priorities are appropriately matched to corresponding disease burden.

**Conclusions:**

Clinicians and researchers rely on databases such as the Cochrane Library, to inform the public for the prevention and treatment of injury. Thus, prioritization methodology of major research databases is directly relevant to clinicians and researchers alike.

Disease burden should be considered in research prioritization. Established criteria have been identified by the Cochrane Collaboration to guide prioritization efforts regarding decisions to register a new title or update an existing review23. Many variables play a part in research prioritization including cost, disease transmissibility, vulnerability of populations, and public interest. There is a lack of transparency in many organizations regarding criteria used to drive prioritization decisions. This study sought to provide transparent data evaluating priority setting of Cochrane systematic reviews. Clinicians see the impact of injury at the individual patient level on a daily basis. The GBD Study provides both detailed view of the burden of injury and a novel tool for injury research prioritization.

**References:**

[1] Andrews J. Prioritization Criteria Methodology for Future Research Needs Proposals Within the Effective Health Care Program. United States: Agency for Healthcare Research and Quality; 2013.

[2] Tromp N, Baltussen R. Mapping of multiple criteria for priority setting of health interventions: an aid for decision makers. *BMC Health Serv Res* 2012;**12**: 454.

[3] Gillum LA. NIH disease funding levels and burden of disease. *PLoS One* 2011;**6**(2): e16837.

[4] Wilber S, Gerson L. A Research Agenda for Geriatric Emergency Medicine. *Acad Emerg Med* 2003;**10**(3): 251-60.

[5] Hofman K, Primack A, Keusch G, Hrynkow S. Addressing the Growing Burden of Trauma and Injury in Low- and Middle-Income Countries. *Am J Public Health* 2005;**95** (1):13-7.

[6] Vos T, Flaxman A, Naghavi M, Lozano R, Michaud C, Ezzat M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 disease and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2163-96.

[7] Murray C, Phil D, Lopez A. Measuring the Global Burden of Disease. *N Engl J Med. 2013;***369**(5): 448-57.

[8] Reidpath D, Allotey P, Kouame A, Cummins RA. Measuring health in a vacuum: examining the disability weight of the DALY. *Health Policy Plan* 2003;**18**(4): 351-6.

[9] Grimshaw JM, Eccles MP, Lavis JN, Hill SJ, Squires JE. Knowledge translation of research findings. *Implement Sci*. 2012;**7**:50.

[10] The Cochrane Collaboration. About the Cochrane Library. <http://www.cochrane.org/cochrane-reviews/about-cochrane-library>.

[11] The Cochrane Collaboration. About Cochrane systematic reviews and protocols. http://www.cochrane.org/cochrane-reviews.

[12] The Cochrane Collaboration. Search the Cochrane Library. http://www.thecochranelibrary.com/view/0/ccochnewsearch.html.

[13] Institute for Health Metrics and Evaluation. GBD Compare. http://vizhub.healthdata.org/gbd-compare/.

[14] Institute for Health Metrics and Evaluation. GBD 2010 Arrow Diagram. http://vizhub.healthdata.org/irank/arrow.php.

[15] Shiffman J. Knowledge, moral claims and the exercise of power in global health. *Int J Health Policy Manag* 2014;**3**(6):297-9/

[16] Emdin CA, Odutayo A, Hsiao AJ, Shakir M, Hopewell S, Rahimi K, et al. Association between randomised trial evidence and global burden of disease: cross sectional study (Epidemiological Study of Randomized Trials—ESORT). *BMJ* 2015;**350** :h117.

[17] Yoong SL, Hall A, Williams CM, Skelton E, Oldmeadow C, Wiggers K, et al. Alignment of systematic reviews published in the Cochrane Database of Systematic Reviews and the Database of Abstracts and Reviews of Effectiveness with global burden of disease data: a bibliographic analysis. *J Epidemiol Community Health* 2015 Apr 17/ pii: jech-2014-205389. doi: 10.1136/jech-2014-20539. [Epub ahead of print]

[18] The Cochrane Collaboration. Cochrane handbook for systematic reviews of interventions. http://handbook.cochrane.org.

[19] Karimkhani C, Boyers LN, Prescott L, Welch V, Delamare FM, Nasser M, et al. Global Burden of Skin Disease as Reflected in Cochrane Database of Systematic Reviews. *JAMA Dermatol* 2014;**150**(9):945-51.

[20] Boyers LN, Karimkhani C, Hilton J, Richheimer W, Dellavalle RP. Global burden of eye and vision disease as reflected in the Cochrane Database of Systematic Reviews. *JAMA Ophthalmol* 2015;**133**(1):25-31.

[21] Pederson H, Okland T, Boyers LN, Karimkhani C, Rosenfeld RM, Nasser M, et al. Identifying otolaryngology systematic review research gaps: comparing global burden of disease 2010 results with Cochrane database of systematic reviews. *JAMA Otolaryngol Head Neck Surg* 2015;**141**(1): 67-72.

[22] Cochrane Agenda and Priority Setting Methods Group: Global Burden of Disease (GBD) – Cochrane Project. http://capsmg.cochrane.org/global-burden-disease-gbd-cochrane-project.

[23] The Cochrane Collaboration. Cochrane Injuries Group Prioritisation Strategy. <http://injuries.cochrane.org/sites/injuries.cochrane.org/files/uploads/Prioritisation%20strategy.pdf>.