



Managing complex pooled international cohort data in Stata:

Health-related quality of life (HRQoL) outcomes following injury in childhood and adolescence using EuroQol (EQ-5D) responses with pooled longitudinal data

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Article Health-Related Quality of Life (HRQoL) Outcomes Following Injury in Childhood and Adolescence Using EuroQol (EQ-5D) Responses with Pooled Longitudinal Data

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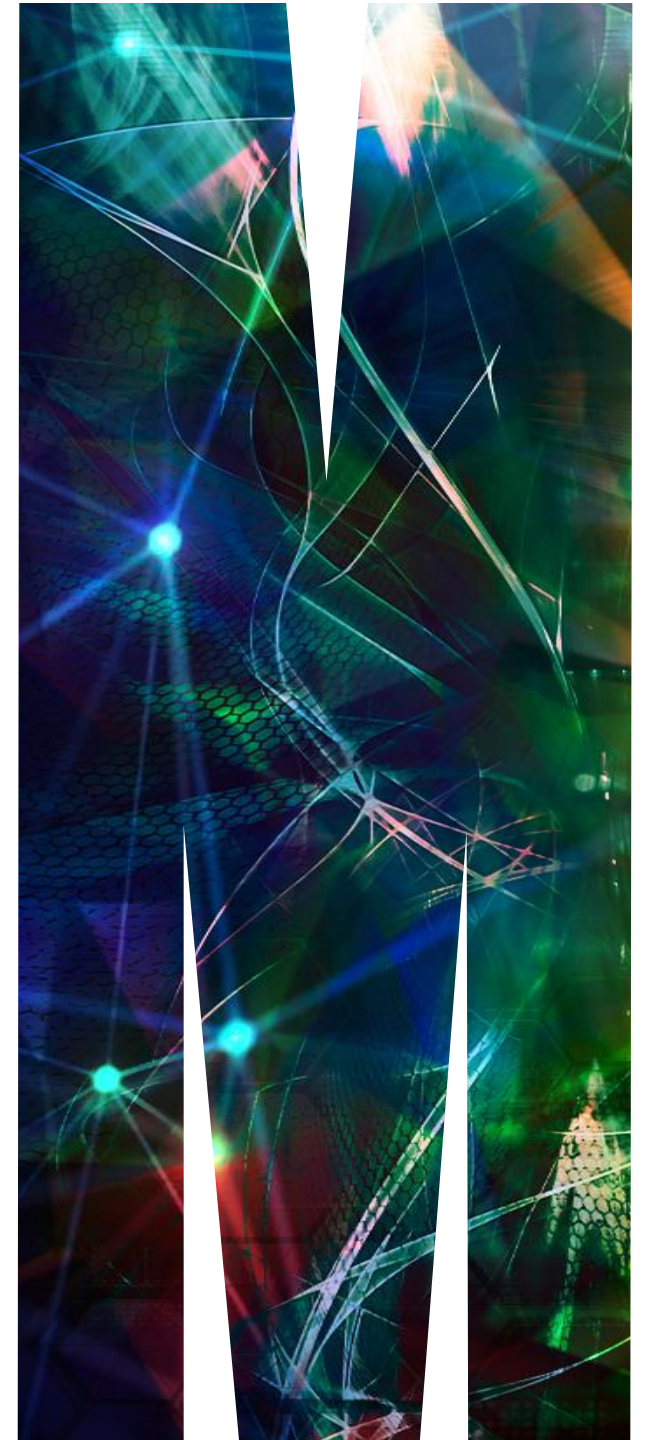
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Abstract: Background: Injury is a leading contributor to the global disease burden in children, affecting their health-related quality of life (HRQoL)—yet valid estimates of burden are absent. Methods: This study pooled longitudinal data from five cohort studies of pediatric injury survivors (5–17 years) at baseline, 1-, 4-, 6-, 12-, and 24- months ($n = 2334$). HRQoL post-injury was measured using the 3-level EQ-5D utility score (EQ-5D) and five health states (mobility, self-care, activity, pain, anxiety and depression (anxiety)). Results: Mean EQ-5D post-injury did not return to baseline level (0.95) by 24 months (0.88) and was lower for females over time (-0.04 , 95%CI -0.05 , -0.02). A decreased adjusted risk ratio over time (ARR) was observed for intentional injuries (pain: 0.85, 95%CI 0.73,0.98; anxiety: 0.62, 95%CI 0.49,0.78); spinal cord injuries (mobility: 0.61, 95%CI 0.45,0.83), self-care: 0.76, 95%CI 0.63,0.91, activity: 0.64, 95%CI 0.47,0.88); moderate/severe traumatic brain injury (activity: 0.83, 95%CI 0.71,0.96). ARRs were also low for certain fractures, with various health states affected. Conclusions: HRQoL outcomes over time for children and adolescents post-injury differed across key demographic and injury related attributes. HRQoL did not reach levels consistent with full health by 24 months with recovery plateauing from 6 to 24 months. Tailored interventions are required to respond to the varying post-injury recovery trajectories in this population.



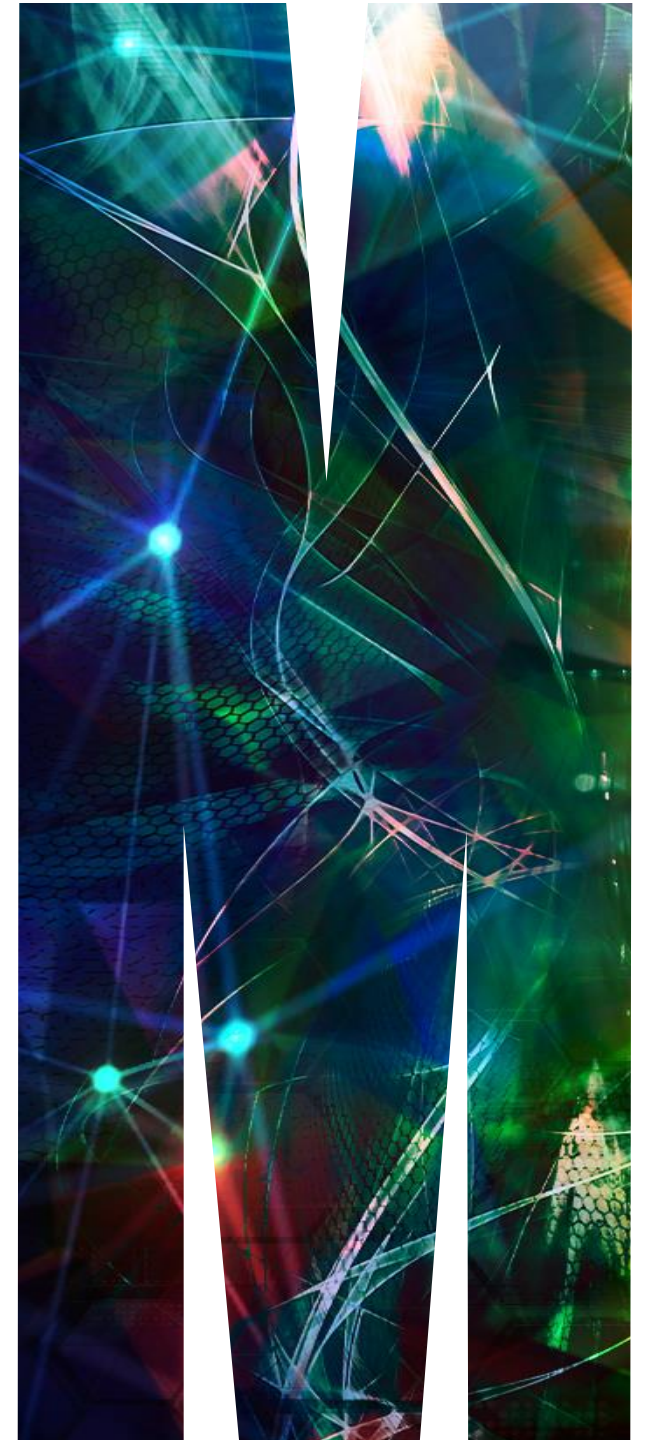
ACKNOWLEDGEMENT OF COUNTRY

We acknowledge the Traditional Owners of the land we are on today and pay respect to elders past, present and emerging and acknowledge any Aboriginal and Torres Strait Islander People with us today.



FORMAT OF PRESENTATION

1. Background to this research
2. Complexities
 1. Data sets & challenges
 2. Measures & challenges
3. Models
4. Management
5. Results
6. Conclusion



Background

World Health Organisation (WHO)

- Injury is a leading contributor to the global disease burden in children, placing them at risk of long-term adverse impacts on their health-related quality of life (HRQoL)
- In 2016, WHO estimated that over 640,855 children under 15 years of age died due to an injury and between 10 to 30 million suffered a non-fatal injury
WHO Child Injury. http://www.who.int/violence_injury_prevention/child/injury/en/
- Injuries impact on health systems
 - Affects society at large, families, individuals and their quality of life
- Regardless of country's income, children from lower socioeconomic status are at highest risk

Background

- Patterns of injuries (and recovery) in children differ to adults:
 - Mechanism of injury
 - Pattern of injury
 - Childhood history
 - Examination and management of the injury
- Methods used to estimate burden **do not account for differences in patterns of injury and recovery between children and adults**
- **Need more empirical data** on postinjury disability in children to derive valid disability weights and describe the long-term individual and societal impacts of injury in the early part of life

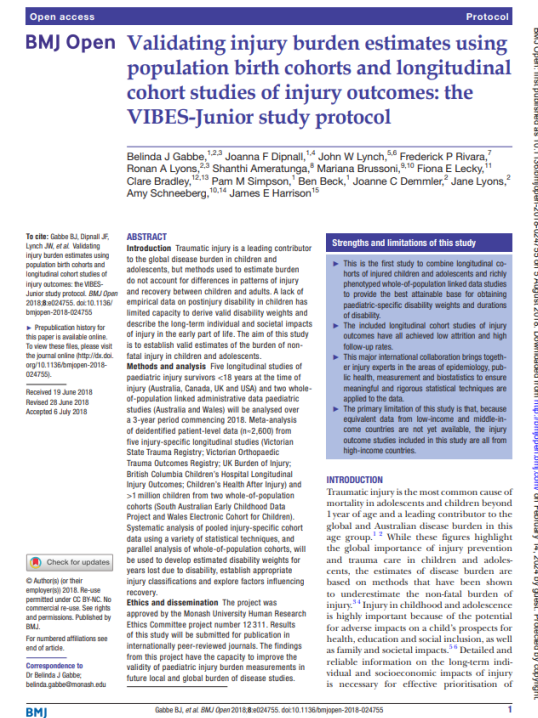
The VIBES-Junior Study

- The aim of the VIBES-Junior study is to **establish valid estimates of the burden of non-fatal injury in children and adolescents**

Ethics : Project approved by the Monash University Human Research Ethics Committee (project number 12311) and was conducted in compliance with the NHMRC National Statement on Ethical Conduct in Human Research (2007)—Updated 2018 and the ICH Guideline for Good Clinical Practice E6(R2).

Preventing Childhood Injuries (WHO)

<https://www.who.int/europe/activities/preventing-child-injuries>



Data

Data: 5 International cohorts in pooled analysis

- **Australia:**
 - The Victorian State Trauma Registry (**VSTR**)
 - Population-based trauma registry that captures data about all major trauma patients in the state of Victoria in Australia
 - The Victorian Orthopedic Trauma Outcomes Registry (**VOTOR**)
 - Clinical registry of orthopedic injuries, treatment, complications and outcomes based on admissions to four Australian centres
- **United States of America:**
 - The US Children's Health After Injury (**CHAI**) study
 - Children with mild, moderate and severe traumatic brain injury (TBI) or with upper extremity injuries who presented to a set of US hospitals
- **United Kingdom:**
 - The United Kingdom Burden of Injury (**UKBOI**)
 - Injured individuals with children recruited from emergency department (ED) presentations and hospital admissions in four UK centers
- **Canada:**
 - The British Columbia Children's Hospital Longitudinal Injury Outcomes (**BCCH-LIO**) study
 - Children who attended the British Columbia Children's Hospital in Canada for an injury
- **Data integration procedures were documented using DIPIT Protocol (i.e. Table of 10 steps)**



ABSTRACT

Introduction: The exponential increase in data, computing power and the availability of readily accessible analytical software has allowed organisations around the world to leverage the benefits of integrating multiple heterogeneous data files for enterprise-level planning and decision making. Benefits from effective data integration to the health and medical research community include more trustworthy research, higher service quality, improved personnel efficiency, reduction of redundant tasks, facilitation of auditing and more timely, relevant and specific information. The costs of poor quality processes elevate the risk of erroneous outcomes, an erosion of confidence in the data and the organisations using these data. To date there are no documented set of standards for best practice integration of heterogeneous data files for research purposes. Therefore, the aim of this paper is to describe a set of clear protocol for data file integration (Data Integration Protocol in Ten-steps; DIPIT) translatable to any field of research.

Methods and results: The DIPIT approach consists of a set of 10 systematic methodological steps to ensure the final data are appropriate for the analysis to meet the research objectives, legal and ethical requirements are met, and that data definitions are clear, concise, and comprehensive. This protocol is neither file specific nor software dependent, but aims to be transposable to any data-emerging situation to minimise redundancy and error and transitional to any field of research. DIPIT aims to generate a master data file that is of the optimal integrity to serve as the basis for research analysis.

Conclusion: With linking of heterogeneous data files becoming increasingly common across all fields of medicine, DIPIT provides a systematic approach to a potentially complex task of integrating a large number of files and variables. The DIPIT protocol will ensure the final integrated data is consistent and of high integrity for the research requirements, useful for practical application across all fields of medical research.

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Table 1 – Mixed Methods Data Integration

DIPIT Step	Action	Settings	Method
1	Define the data requirements	<ul style="list-style-type: none"> Define research objectives Establish files to integrate Access data source 	VOST-UNOT Act 1 Characteristics and Features which are physical and operational following following study in individual and substances.
2	Establish ethical, legal and privacy issues	Establish ethical, legal and privacy issues for each data file to integrate	The project was approved by the Monash University Human Research Ethics Committee (HREC) and the Victorian Department of Health (VDOH) Human Research Ethics Committee (HREC) and the Victorian Department of Health (VDOH) Human Research Ethics Committee (HREC) and the Victorian Department of Health (VDOH) Human Research Ethics Committee (HREC).
3	Order the files to integrate	Set up a download for all files to be integrated, incorporating all file names	Performance a Master Data file in the Microsoft Excel spreadsheet file in the State and the Central Data file
4	Establish the file format	Assess the download in step 3 to determine the file format for each file integrated and the final master file	NA
5	Define the variables of interest	Create a table containing the variables of interest for research contrasting as a minimum: <ul style="list-style-type: none"> Final variable name Original variable name Source file of variable Predefined label for variable Description of variable 	Table created as part of investigation leading analysis – November 2013
6	Set up linked file integration	Create a table containing the variable(s) link and linkage method(s) used containing as a minimum: <ul style="list-style-type: none"> Link variable(s) Method of linkage Assessment used (if applicable) 	Table appended onto Link VLA Buffer Content_Link_Produced file
7	Document the integration path	Document the review of the path that the integration to include is a minimum: <ul style="list-style-type: none"> The structure of the source files The source of the Master file format as a standard file format The variables of interest to be retained The variables standard naming format The merge of all files into the Master file A list of results of the key variables, and naming data analysis 	Table (Table 1) referred to in Step 3. The integration path only only variables taken from Source File. The integration path only only variables taken from Source File. The integration path only only variables taken from Source File. The integration path only only variables taken from Source File. The integration path only only variables taken from Source File.
8	Flatten the type of integration	Document on Flatten type of integration: <ul style="list-style-type: none"> one-to-one many-to-one one-to-many 	Integration used was according to linking list provided across each variable.
9	Document the integration outcome	Define linkage equity success <ul style="list-style-type: none"> Variable name Source of variable Assess file attachment 	NA
10	Check variables and naming file	Final file name should be included as a minimum: <ul style="list-style-type: none"> Analysis of key variable(s) Missing data analysis 	Table of key variables finally reviewed by the research team in November 2014. Final Table 1 required for integration as part of research – included missing data analysis.

Data

Table 1. Specific details of VIBES-Junior cohorts.

Study & Setting	Month/Year & Participants	Inclusion Criteria & Injury Diagnosis Coding	Post-Injury Follow-Up Time Point EQ-5D Measures & Mode of Interview
VSTR Australia	03/2009 to 03/2017 <i>n</i> = 824, 5–16 years	In hospital death, ISS > 12, ICU admission or urgent surgery, met burns criteria 20–29% full/partial thickness. ICD-10-AM	EQ-5D total score and items at 6, 12 and 24 months. Telephone
VOTOR Australia	03/2009 to 03/2017 <i>n</i> = 502, 16–17 years	16+ years of age, orthopedic injury admission >24 h or death ICD-10-AM	EQ-5D total score and items at 6, 12 and 24 months. Telephone
CHAI United States of America	03/2007 to 09/2008 <i>n</i> = 635, 5–17 years	Presentation to ED or hospital admission for either a TBI or an upper extremity injury ICD-9 mapped to ICD-10	PedsQL scores mapped to EQ-5D total score at 3, 12, and 24 months. Online, telephone and postal
UKBOI United Kingdom	09/2005 to 04/2007 <i>n</i> = 174, 5–17 years	Presentation to ED or hospital admission. ICD-10	EQ-5D total score and items at 1, 6 and 12 months. Postal
BCCH-LIO Canada	02/2011 to 12/2013 <i>n</i> = 199, 5–16 years	Presentation to ED or hospital admission. ICD-10	EQ-5D total score and items at 1, 4, and 12 months. Postal and online

Measures

Demographics

- Baseline measures:
 - Sex
 - *Male, female*
 - Three age groups to align with the World Health Organization (WHO) classification within the age band of our pooled cohort
 - *5–9 years, 10–14 years, 15–17 years*
 - Measure of socio-economic status (SES) collapsed from quintiles into tertiles (*low, moderate, high*)
 - **Challenge:** SES differed
 - **Australia:** Quintiles of the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) area-based measure released by the Australian Bureau of Statistics;
 - **USA:** Quintiles created from principal components analysis using income and education variables
 - **UK:** Quintiles from Townsend Deprivation Score reversed so that higher quintiles reflect higher SES;
 - **Canada:** Initially contained quintiles Quintile of Annual Income Per Person Equivalent (QAIPPE) area-based measure released by Statistics Canada.

Measures

Injury

- **Mechanism** of injury was dichotomized:
 - *Transport injuries (motor vehicle occupant, pedestrian, or on a motorcycle or bicycle)*
 - *Non-transport injuries (falls, struck by/against an object or person, and other mechanisms)*
- **Challenge:** Inclusion criteria differed where some did/did not include ED admission:
 - So included a **Emergency Department (ED) / Hospital admission** measure:
 - 0 for *ED presentation and discharge*
 - 1 = Hospital admission
- **Injury Severity Score (ISS)** is the most widely used to assess trauma severity collapsed into tertiles for each cohort
 - *Low, Mid, High*
- **Intent** of injury was grouped into three groups:
 - *Intentional (including self-harm, maltreatment and interpersonal violence,*
 - *Unintentional*
 - *Intent not known*

Measures

Comorbidities

- Comorbidities present at the time of injury was based on the 27 health conditions described by Mitchell et al. and were collapse into two groups
 - No comorbidities
 - ≥ 1 comorbidities

Mitchell, R.J.; Curtis, K.; Braithwaite, J. *Health outcomes and costs for injured young people hospitalised with and without chronic health conditions. Injury* 2017, 48, 1776–1783.

Diagnoses

- **Challenge:** Diagnoses and external cause codes were classified using different International Classification of Disease (ICD) so used ICD-10:
 - **Australia, UK & Canada:** ICD 10th Revision (ICD-10)
 - **USA:** ICD 9th Revision (ICD-9) mapped to the ICD-10
- All diagnosis codes were then mapped to the 2013 Global Burden of Disease (GBD) study injury health states

Original article

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The global burden of injury: incidence, mortality, disability-adjusted life years and time trends from the Global Burden of Disease study 2013

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/injury-2015-041616>).

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ABSTRACT The Global Burden of Diseases (GBD), Injuries, and Risk Factors study used the disability-adjusted life year (DALY) to quantify the burden of diseases, injuries, and risk factors. This paper provides an overview of injury estimates from the 2013 update of GBD, with detailed information on incidence, mortality, DALYs and rates of change from 1990 to 2013 for 26 causes of injury, globally, by region and by country. **Methods** Injury mortality was estimated using the extensive GBD mortality database, corrections for ill-defined cause of death and the cause of death ensemble modelling tool. Morbidity estimation was based on inpatient and outpatient data sets, 26 cause-of-injury and 47 nature-of-injury categories, and seven follow-up studies with patient-reported long-term outcome measures. **Results** In 2013, 973 million (uncertainty interval (UI) 942 to 993) people sustained injuries that warranted some type of healthcare and 4.8 million (UI 4.5 to 5.1) people died from injuries. Between 1990 and 2013 the global age-standardised injury DALY rate decreased by 31% (UI 26% to 35%). The rate of decline in DALY rates was significant for 22 cause-of-injury categories, including all the major injuries.

Conclusions Injuries continue to be an important cause of morbidity and mortality in the developed and developing world. The decline in rates for almost all injuries is so prominent that it warrants a general statement that the world is becoming a safer place to live in. However, the patterns vary widely by cause, age, sex, region and time and there are still large improvements that need to be made.

INTRODUCTION Since the late 1940s the use of epidemiological analyses to assess the gains of prevention of injury has been advocated, reflecting the changing view of injuries as preventable events.¹ These epidemiological analyses entail the use of data to quantify the injury problem and assess causative factors to guide the development of preventive measures and to enable periodic evaluation of the effectiveness of instituted prevention programmes.¹ For many decades, injury epidemiologists have largely relied on mortality data.² However, since the launch of

Linked

► <http://dx.doi.org/10.1136/injury-2015-041616>

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BMJ

Haagsma JA, et al. *Inj Prev* 2016;22:3–18. doi:10.1136/injury-2015-041616

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Inj Prev: first published as 10.1136/injury-2015-041616 on 3 December 2015. Downloaded from <http://injury.bmj.com/> on February 14, 2024 by guest. Protected by copyright.

GBD 2013 Study

- Contained tables related to injury health state classifications to enable cross-walking from the ICD-10 codes to the GBD injury groups
- GBD 2013 Injury groups were in order of severity and collapsed into 17 binary variables indicating the presence or absence of that injury

GBD 2013 Injury Groups

- | | |
|---|---|
| 1. Spinal cord lesion | 10. Burns (including lower airways) |
| 2. Fracture of femur | 11. Fracture of vertebral column |
| 3. Fracture of patella, tibia, fibula, or ankle | 12. Asphyxiation, non-fatal submersion |
| 4. Moderate to severe TBI | 13. Contusion, open wound |
| 5. Crush injury, fracture foot/hand bones | 14. Other injuries of muscle & tendon and other dislocations |
| 6. Internal hemorrhage in abdomen or pelvis | 15. Fracture of clavicle, scapula, or humerus |
| 7. Minor TBI | 16. Fracture of radius or ulna |
| 8. Fracture of pelvis | 17. Other. (I.e. included injuries such as amputation of one limb/toe, poisoning, injured nerves, environmental factors, injured nerves, dislocation of shoulder/hip/knee, fracture of ribs/sternum/skull/face bone, foreign body in ear/gastrointestinal or urogenital system, superficial injury, and injury to eyes) |
| 9. Severe chest injury | |

Outcomes

Outcome Measure

- Generic and easily administered multi-attribute utility instruments such as the EUROQOL 5 Dimension (EQ-5D) have been used for both recovery and health economic analyses

Overall EQ-5D utility score

- Score derived according to a set of weights (country specific) that reflect, on average, people's preferences about how good or bad the health state is
- Values are anchored at 1 (full health) and 0 (a state as bad as being dead) as required by their use in economic evaluation
- Negative values represent health states regarded as “worse than a state that is as bad as being dead”
- **Challenge: Australia, UK & Canada:** Collected the EQ-5D outcomes at multiple time points after injury but **USA:** Collected the Pediatric Quality of Life Inventory (PedsQL)
 - Responses to these questions were mapped to the EQ-5D using the algorithm developed by **Khan et al.**
Khan, K.A.; Petrou, S.; Rivero-Arias, O.; Walters, S.J.; Boyle, S.E. Mapping EQ-5D utility scores from the PedsQL™ generic core scales. Pharmacoeconomics 2014, 32, 693–706.
- **Challenge:** Country-specific weights - needed to develop own Stata program (i.e. ado) for to provide the, then, recent Australian weights

Outcomes

Three-level EQ-5D scale (EQ-5D-3L)

- Three level measure: *No problems, Some problems, Extreme problems*
- **Five health states** measured:
 1. Mobility
 2. Self-care
 3. Activity
 4. Pain
 5. Anxiety & Depression
- **Challenge:** Due to low frequency across the three categories a binary measure was created:
 - 1 = No problems
 - 0 = Problems (some/extreme)
- **Challenge:**
 - As there was no map available of the individual EQ-5D-3L health state questions from the PedsQL, the US cohort was excluded from this analysis

Models

- Missing data on the covariates included in the models was quantified and found to be acceptable at <5%

Tabachnick, B.G.; Fidell, L.S. Using Multivariate Statistics, 6th ed.; Pearson: Boston, MA, USA, 2013. Newman, D.A. Missing data: Five practical guidelines. Organ. Res. Methods 2014, 17, 372–411

- Mixed Effects (ME) linear regression modelled EQ-5D utility

- Estimated average EQ-5D and 95% CI

ME linear example:

$$y = X\beta + Zu + \epsilon$$

- ME modified Poisson modelled the five binary EQ-5D health state items

- Estimated relative risks (RR) and 95%CI for each binary outcome

Zou, G. A modified poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 2004, 159, 702–706

- Predicted margins across time estimated and graphed

- ME regression models uses as has been shown to be flexible in handling missing data compared to using multiple imputation which has been found to potentially produce unstable results

Twisk, J.; de Boer, M.; de Vente, W.; Heymans, M. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. J. Clin. Epidemiol. 2013, 66, 1022–1028

- Time was treated as a discrete categorical variable in the models, requiring no assumptions to be made about its mathematical function

Management

Storage:

- All data was stored in the Monash Safe eResearch Platform (SeRP)
 - Restricted access based on ethics approval
 - Secure separate study drive to store study data
 - Analysis performed in user drive so that study data kept separate

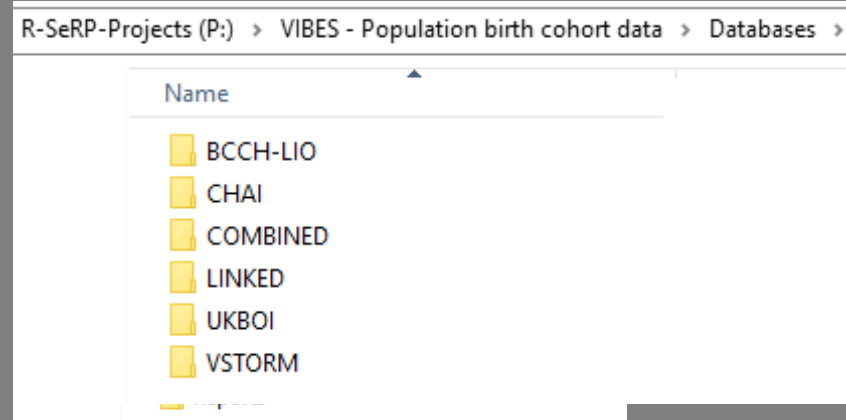
Stata Projects & Do Files:

- Stata V16 was used to manage the data and run the analysis and ensure reproducibility
 - A VIBES-Junior Stata Project file was set up for the data management
 - folders were set up to indicate:
 - Stages of each cohort preparation
 - Pooling of cohort data
 - Stages of analysis
 - Do files were grouped and numbered accordingly

Storage

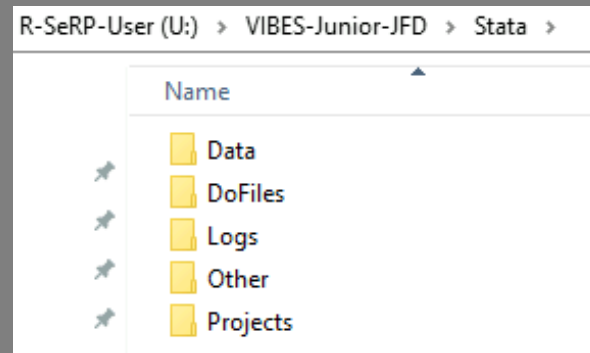
Project Drive P:\

- Restricted (read)
- Secure



User Drive U:\

- Read/write
- Personal



Projects & Do Files

The screenshot shows the 'Do-file Editor - Untitled' window. The menu bar includes File, Edit, View, Language, Project, and Tools. The Project pane on the left shows a tree view with 'Combined' selected, containing subfolders 'Data' and 'DoFiles'. The main editor area shows a single line of code: '1'. The Properties pane at the bottom left shows details for the 'Combined' project, including its name, type, location, relative path, and full path. The status bar at the bottom right indicates 'Line: 1, Col: 1 CAP NUM OVR'.

The screenshot shows a file explorer view of a project structure. The root folder is 'Combined', which contains a 'Data' folder and a 'DoFiles' folder. The 'Data' folder contains subfolders '1 Source', '2 Combined', '3 ISS', '4 Pooled', '5 ME Models', and '6 Graphs Main Manuscripts'. The 'DoFiles' folder contains subfolders '1. General', '2. Mapping EQ5D', '3. Comorbidities', '4. ISS', '5. Pooled', and '6. Mixed Models'. The '5. Pooled' folder is highlighted and contains subfolders 'a. Combining' and 'b. Pooled', along with a file named 'MASTER_Combined_Setup.do'.

Preventing Childhood Injuries (WHO)

<https://www.who.int/europe/activities/preventing-child-injuries>

Projects & Do Files

The screenshot shows the Stata software interface. On the left is the 'Project' pane with a tree view of folders. The 'DoFiles' folder is expanded, showing sub-folders 1 through 6, with folder 5 'Pooled' further expanded to show sub-folders 'a. Combining' and 'b. Pooled'. The 'b. Pooled' folder contains several do files, including 'MASTER_Combined_Setup.do'. On the right is the 'MASTER_Combined_Setup' do file editor, showing the following code:

```
1  *** COMBINING COHORT ***
2  sysdir set PLUS "c:\ado\plus"
3  sysdir set PERSONAL "U:\ado\plus"
4
5  version 16
6
7  *path for do files
8  global path "U:\VIBES-Junior-JFD\Stata\DoFiles\"
9
10 *Create frames used in do files
11 frame create VSTORM
12 frame create CHAI
13 frame create UKBOI
14 frame create BCCH
15 frame create POOLED
16
17 frame create comorbid
18 frame create issNew
19
20 cd "$path\Combined"
21
22 do "Combined_Setup_VSTORM.do"
23 do "Combined_Setup_CHAI.do"
24 do "Combined_Setup_UKBOI.do"
25 do "Combined_Setup_BCCH.do"
26
27 *** POOLED DATA
28 do "Combined_Setup_POOLED.do"
29
30 frame drop VSTORM
31 frame drop CHAI
32 frame drop UKBOI
33 frame drop BCCH
34 frame drop comorbid
35 frame drop issNew
```

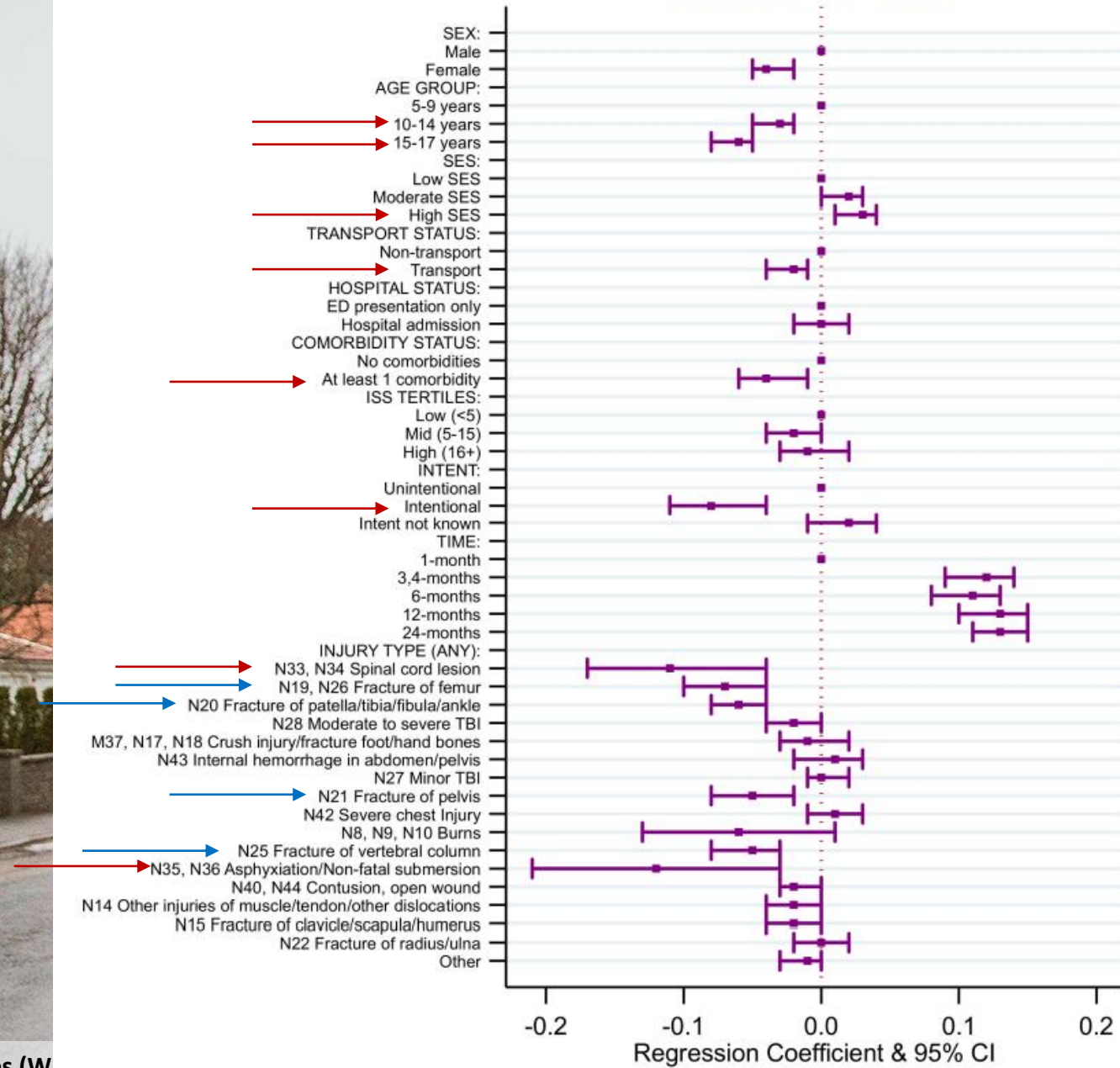
The screenshot shows a project tree view. The '6. Mixed Models' folder is expanded to show sub-folders 'a Setup', 'b Table1 notes, T-Tests', 'c Missing Data Analysis', and 'd Final Models'. The 'd Final Models' folder is further expanded to show sub-folders 'A EQ5D', 'B PEDSQL', and 'e Sensitivity'. The 'A EQ5D' folder is highlighted with a red box, showing sub-folders '1 Original_Ages', '2 AgeSexInteraction', and '3 WHO_Ages'.

Results

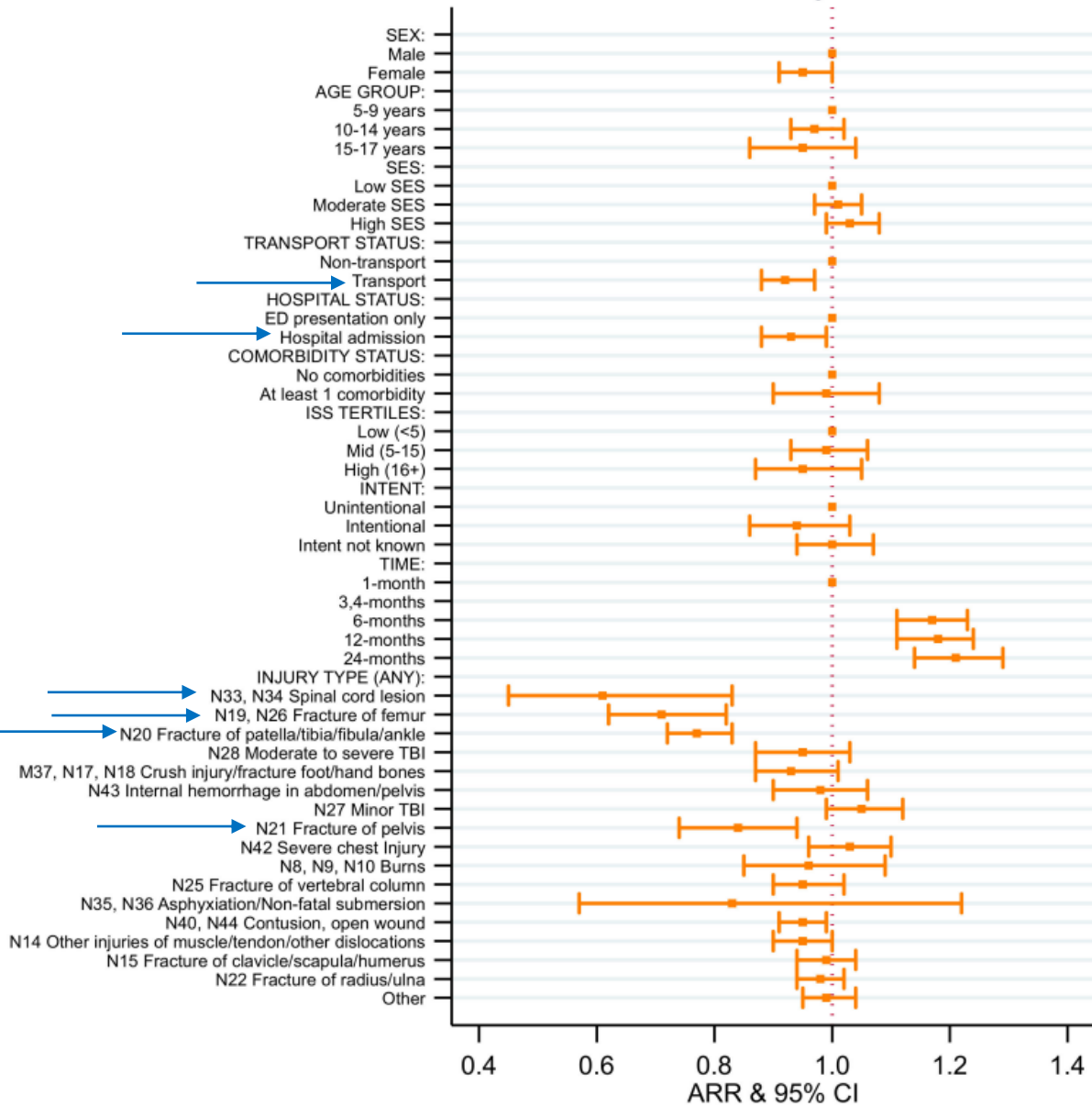
- 2,334 children and adolescents were included in the pooled analysis
 - Majority male (73%)
 - Mean age of 13.6 years (SD = 3.5)
 - 62% from moderate to high SES
 - 63% had a non-transport related injury
 - 73% had a hospital admission
 - 92% had no comorbidities recorded at the time of their injury



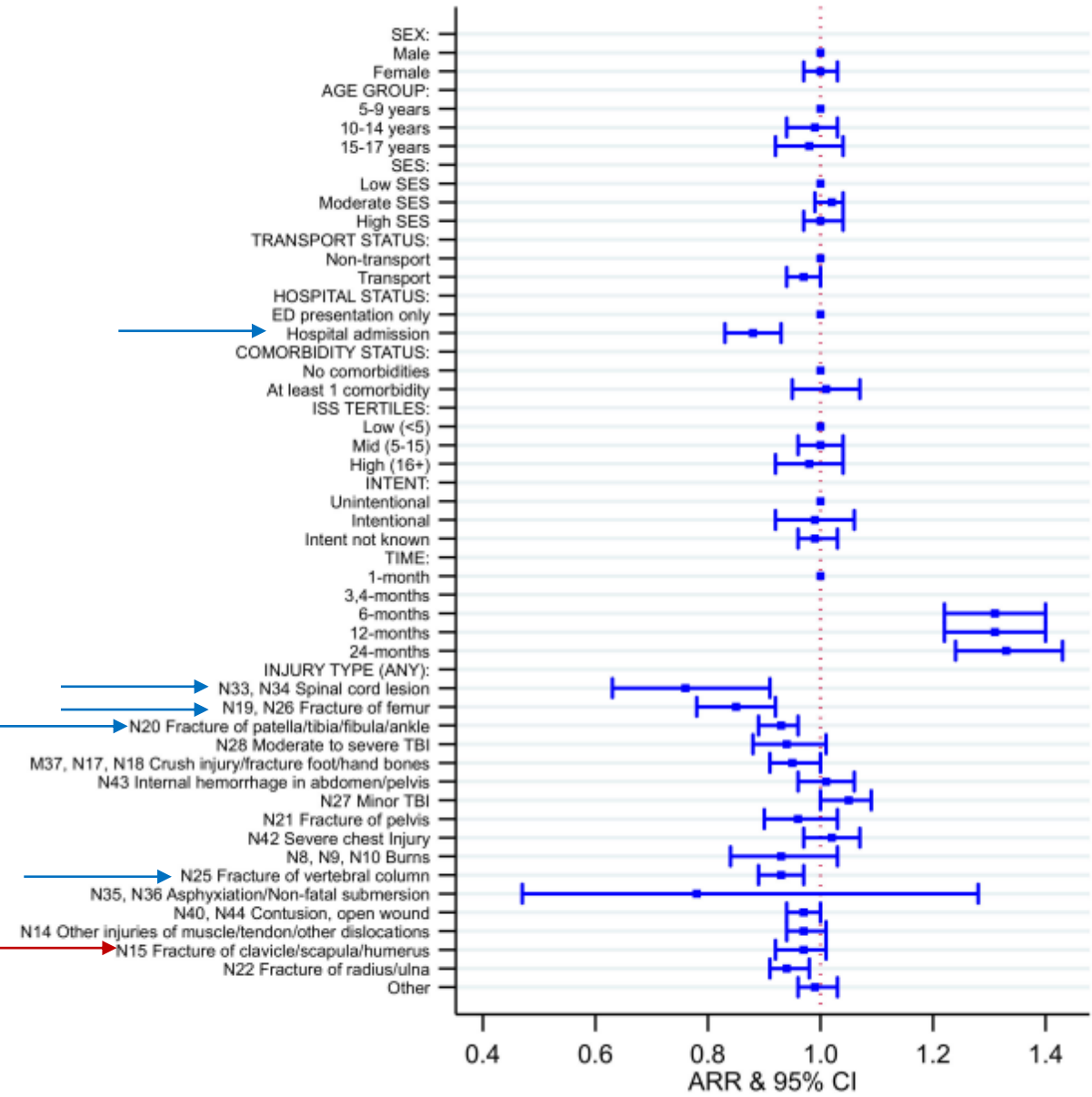
EQ-5D Utility Score



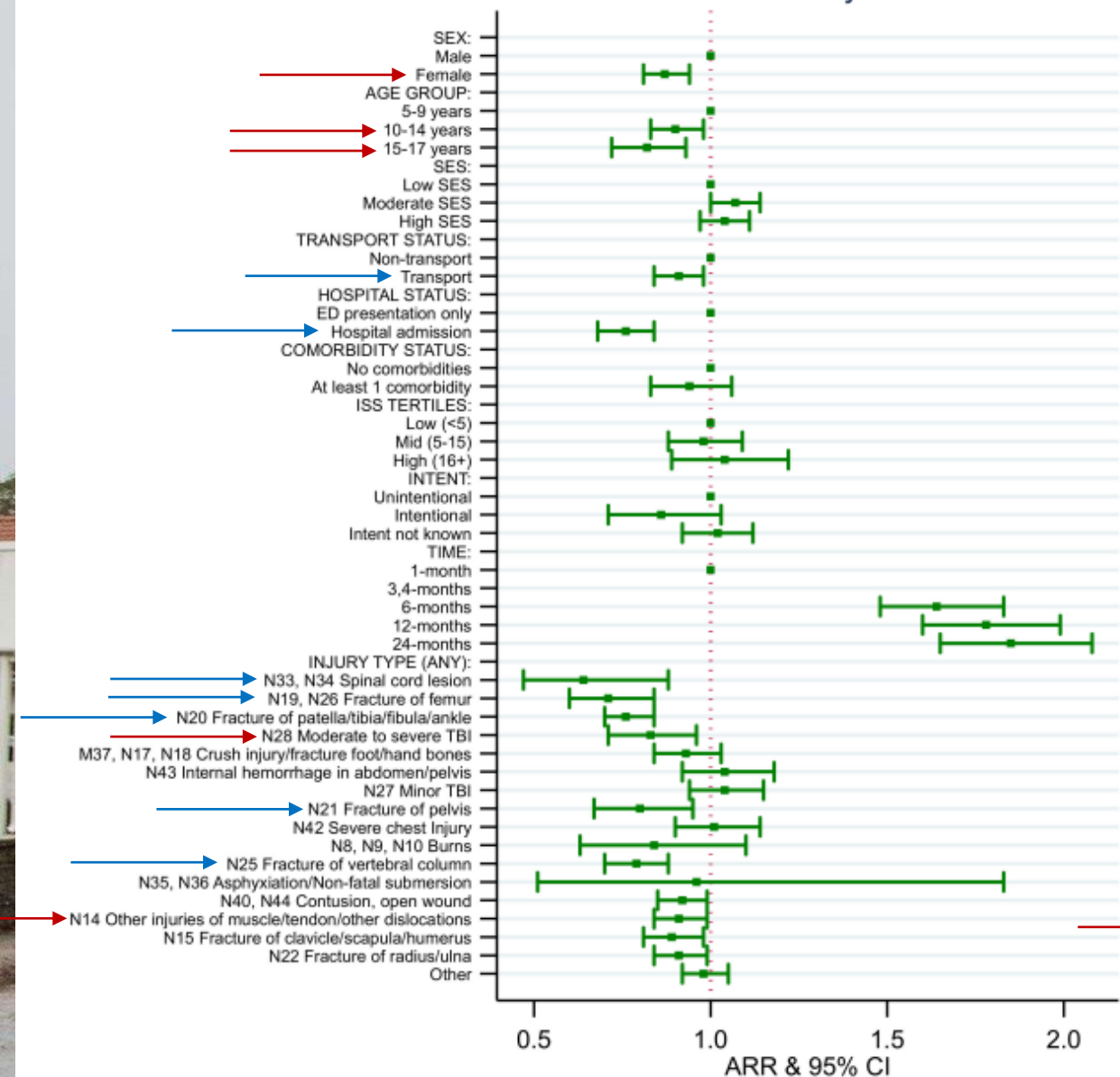
Mobility



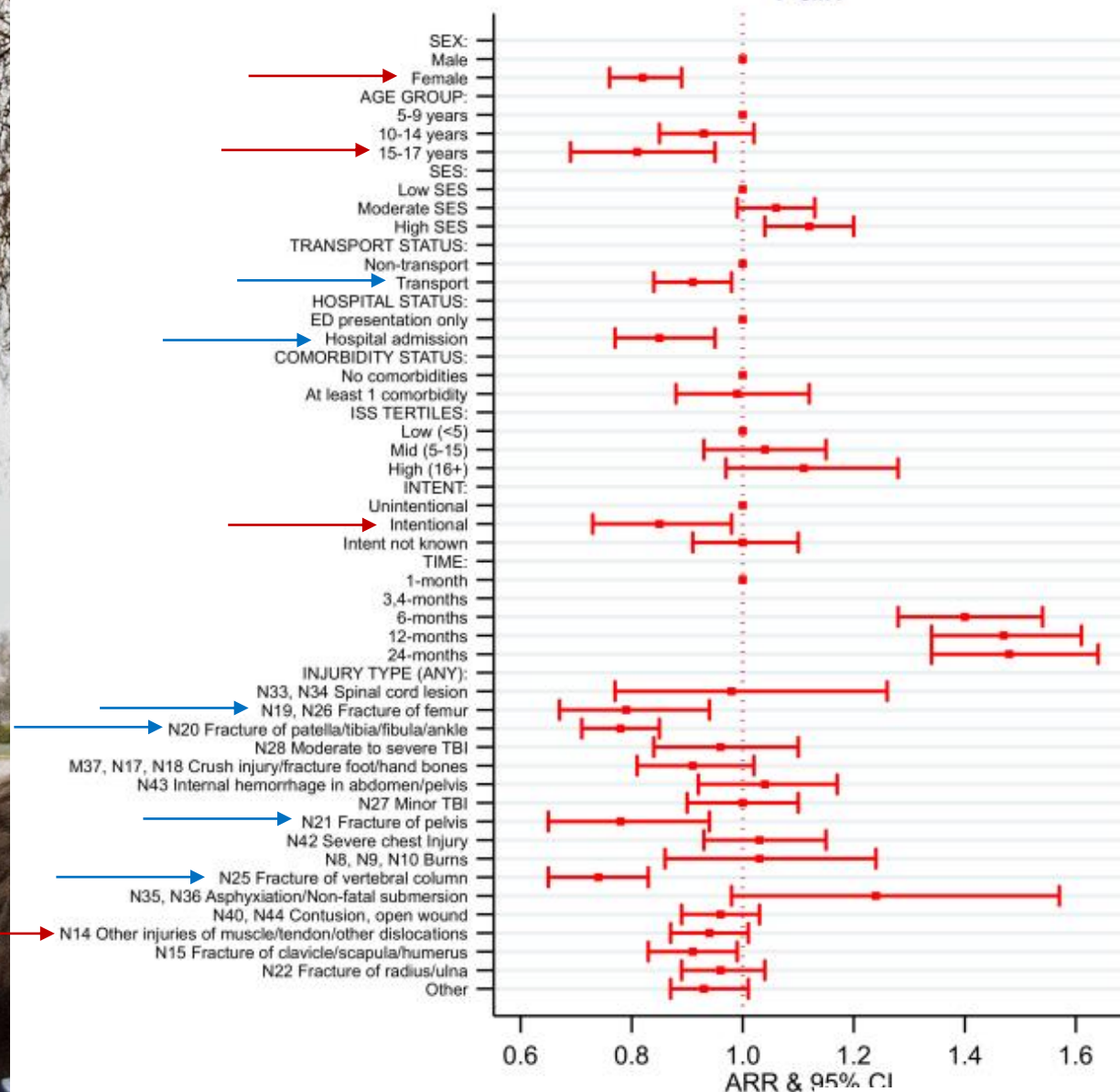
Self-Care



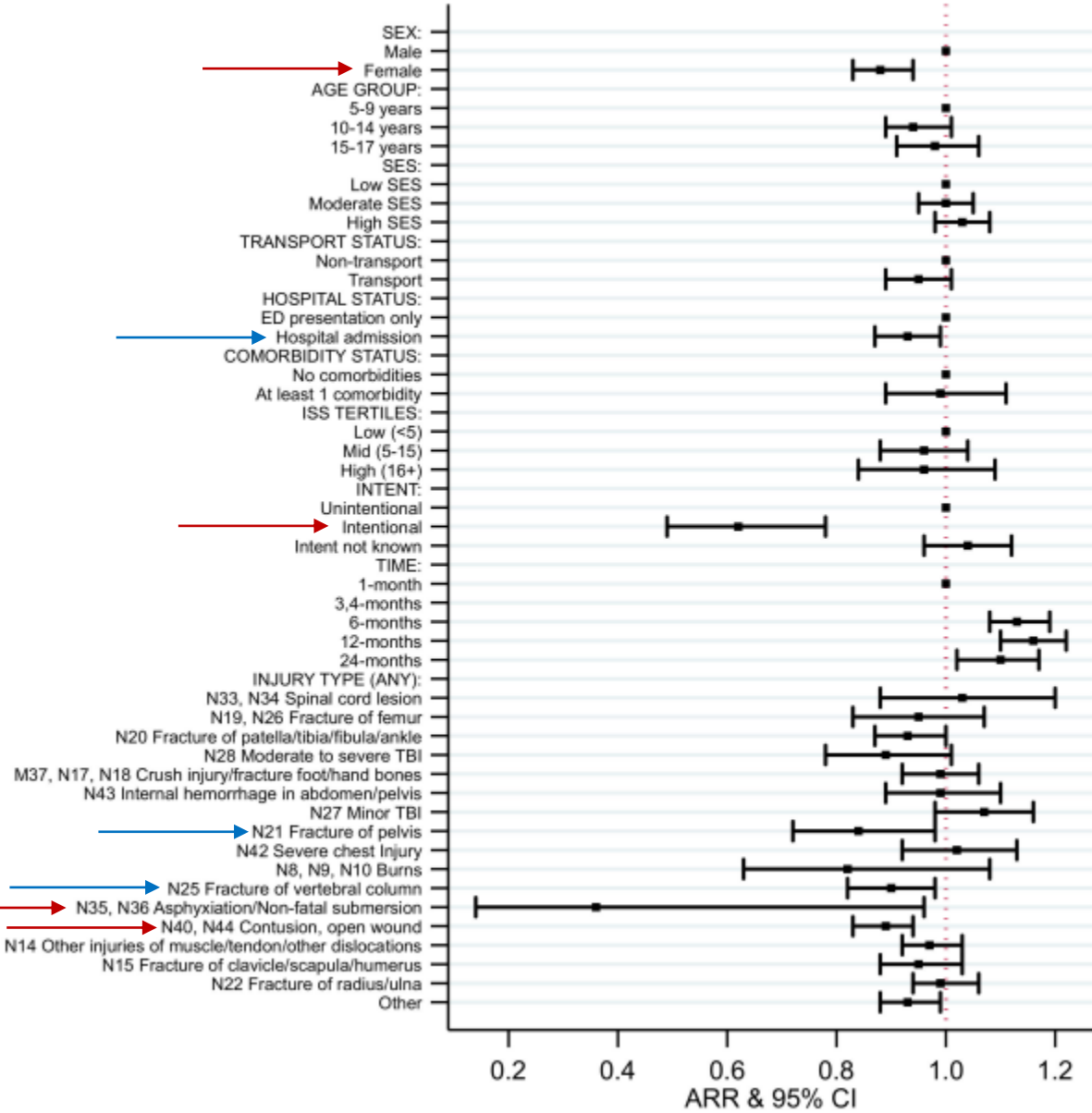
Activity



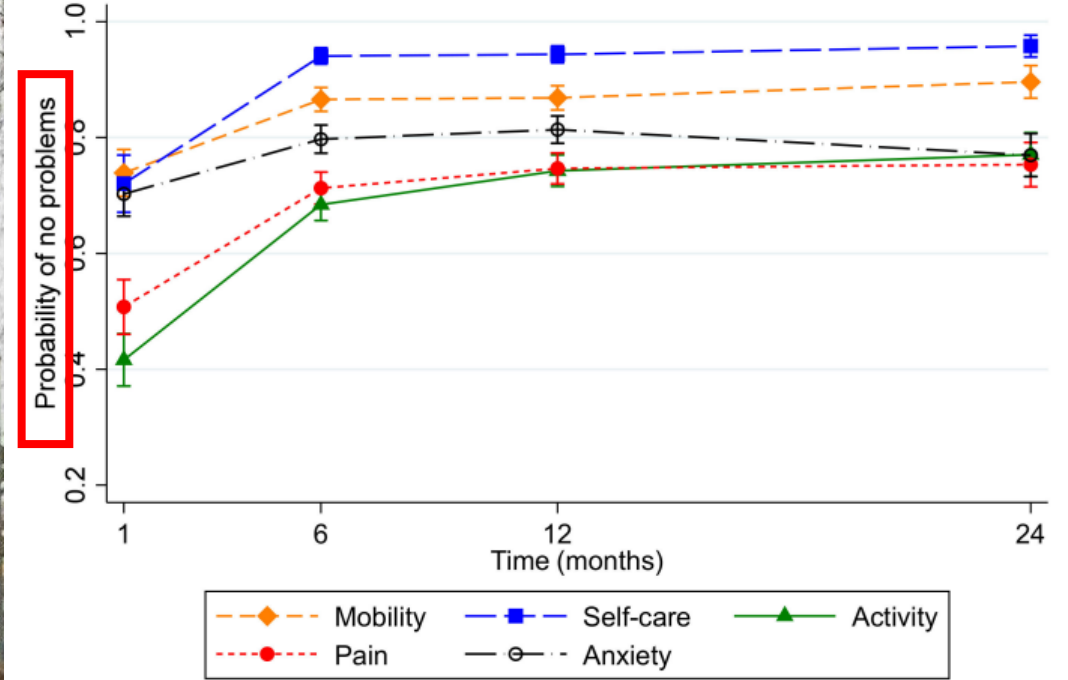
Pain



Anxiety & Depression



EQ-5D Health States



Conclusion

- HRQoL outcomes over time for children and adolescents post-injury differed across key demographic and injury related attributes
- HRQoL did not reach levels consistent with full health by 24 months with recovery plateauing from 6 to 24 months
- Tailored interventions are required to respond to the varying post-injury recovery trajectories in this population
- Systematic management procedures and use of Stata projects, structured do files make it easy to
 - Manage the complexities of pooling different cohort data
 - Replicate the results of this complex study
- Refer to article for extended Discussion including strengths and limitations

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