

# Contents

## Part I Setting the Stage: Rationale Behind and Challenges to Health Data Analysis

<b>1</b>	<b>Objectives of the Secondary Analysis of Electronic Health Record Data</b> . . . . .	3
1.1	Introduction . . . . .	3
1.2	Current Research Climate . . . . .	3
1.3	Power of the Electronic Health Record . . . . .	4
1.4	Pitfalls and Challenges . . . . .	5
1.5	Conclusion . . . . .	6
	References . . . . .	7
<b>2</b>	<b>Review of Clinical Databases</b> . . . . .	9
2.1	Introduction . . . . .	9
2.2	Background . . . . .	9
2.3	The Medical Information Mart for Intensive Care (MIMIC) Database . . . . .	10
2.3.1	Included Variables . . . . .	11
2.3.2	Access and Interface . . . . .	12
2.4	PCORnet . . . . .	12
2.4.1	Included Variables . . . . .	12
2.4.2	Access and Interface . . . . .	13
2.5	Open NHS . . . . .	13
2.5.1	Included Variables . . . . .	13
2.5.2	Access and Interface . . . . .	13
2.6	Other Ongoing Research . . . . .	14
2.6.1	eICU—Philips . . . . .	14
2.6.2	VistA . . . . .	14
2.6.3	NSQUIP . . . . .	15
	References . . . . .	16

- 3 Challenges and Opportunities in Secondary Analyses of Electronic Health Record Data** . . . . . 17
  - 3.1 Introduction . . . . . 17
  - 3.2 Challenges in Secondary Analysis of Electronic Health Records Data . . . . . 17
  - 3.3 Opportunities in Secondary Analysis of Electronic Health Records Data . . . . . 20
  - 3.4 Secondary EHR Analyses as Alternatives to Randomized Controlled Clinical Trials . . . . . 21
  - 3.5 Demonstrating the Power of Secondary EHR Analysis: Examples in Pharmacovigilance and Clinical Care . . . . . 22
  - 3.6 A New Paradigm for Supporting Evidence-Based Practice and Ethical Considerations . . . . . 23
  - References. . . . . 25
- 4 Pulling It All Together: Envisioning a Data-Driven, Ideal Care System** . . . . . 27
  - 4.1 Use Case Examples Based on Unavoidable Medical Heterogeneity . . . . . 28
  - 4.2 Clinical Workflow, Documentation, and Decisions . . . . . 29
  - 4.3 Levels of Precision and Personalization . . . . . 32
  - 4.4 Coordination, Communication, and Guidance Through the Clinical Labyrinth. . . . . 35
  - 4.5 Safety and Quality in an ICS . . . . . 36
  - 4.6 Conclusion . . . . . 39
  - References. . . . . 41
- 5 The Story of MIMIC** . . . . . 43
  - 5.1 The Vision . . . . . 43
  - 5.2 Data Acquisition . . . . . 44
    - 5.2.1 Clinical Data . . . . . 44
    - 5.2.2 Physiological Data . . . . . 45
    - 5.2.3 Death Data. . . . . 46
  - 5.3 Data Merger and Organization . . . . . 46
  - 5.4 Data Sharing . . . . . 47
  - 5.5 Updating . . . . . 47
  - 5.6 Support . . . . . 48
  - 5.7 Lessons Learned . . . . . 48
  - 5.8 Future Directions . . . . . 49
  - References. . . . . 49
- 6 Integrating Non-clinical Data with EHRs** . . . . . 51
  - 6.1 Introduction . . . . . 51
  - 6.2 Non-clinical Factors and Determinants of Health . . . . . 51
  - 6.3 Increasing Data Availability . . . . . 53
  - 6.4 Integration, Application and Calibration . . . . . 54

6.5 A Well-Connected Empowerment. . . . . 57

6.6 Conclusion . . . . . 58

References. . . . . 59

**7 Using EHR to Conduct Outcome and Health Services Research. . . . . 61**

7.1 Introduction . . . . . 61

7.2 The Rise of EHRs in Health Services Research . . . . . 62

7.2.1 The EHR in Outcomes and Observational Studies. . . . . 62

7.2.2 The EHR as Tool to Facilitate Patient Enrollment in Prospective Trials . . . . . 63

7.2.3 The EHR as Tool to Study and Improve Patient Outcomes. . . . . 64

7.3 How to Avoid Common Pitfalls When Using EHR to Do Health Services Research . . . . . 64

7.3.1 Step 1: Recognize the Fallibility of the EHR. . . . . 65

7.3.2 Step 2: Understand Confounding, Bias, and Missing Data When Using the EHR for Research . . . . . 65

7.4 Future Directions for the EHR and Health Services Research. . . . . 67

7.4.1 Ensuring Adequate Patient Privacy Protection. . . . . 67

7.5 Multidimensional Collaborations. . . . . 67

7.6 Conclusion . . . . . 68

References. . . . . 68

**8 Residual Confounding Lurking in Big Data: A Source of Error . . . . . 71**

8.1 Introduction . . . . . 71

8.2 Confounding Variables in Big Data . . . . . 72

8.2.1 The Obesity Paradox. . . . . 72

8.2.2 Selection Bias . . . . . 73

8.2.3 Uncertain Pathophysiology . . . . . 74

8.3 Conclusion . . . . . 77

References. . . . . 77

**Part II A Cookbook: From Research Question Formulation to Validation of Findings**

**9 Formulating the Research Question. . . . . 81**

9.1 Introduction . . . . . 81

9.2 The Clinical Scenario: Impact of Indwelling Arterial Catheters. . . . . 82

9.3 Turning Clinical Questions into Research Questions. . . . . 82

9.3.1 Study Sample . . . . . 82

- 9.3.2 Exposure . . . . . 83
- 9.3.3 Outcome . . . . . 84
- 9.4 Matching Study Design to the Research Question . . . . . 85
- 9.5 Types of Observational Research . . . . . 87
- 9.6 Choosing the Right Database . . . . . 89
- 9.7 Putting It Together . . . . . 90
- References. . . . . 91
- 10 Defining the Patient Cohort . . . . . 93**
  - 10.1 Introduction . . . . . 93
  - 10.2 PART 1—Theoretical Concepts . . . . . 94
    - 10.2.1 Exposure and Outcome of Interest. . . . . 94
    - 10.2.2 Comparison Group . . . . . 95
    - 10.2.3 Building the Study Cohort. . . . . 95
    - 10.2.4 Hidden Exposures . . . . . 97
    - 10.2.5 Data Visualization . . . . . 97
    - 10.2.6 Study Cohort Fidelity . . . . . 98
  - 10.3 PART 2—Case Study: Cohort Selection. . . . . 98
  - References. . . . . 100
- 11 Data Preparation. . . . . 101**
  - 11.1 Introduction . . . . . 101
  - 11.2 Part 1—Theoretical Concepts . . . . . 102
    - 11.2.1 Categories of Hospital Data. . . . . 102
    - 11.2.2 Context and Collaboration . . . . . 103
    - 11.2.3 Quantitative and Qualitative Data . . . . . 104
    - 11.2.4 Data Files and Databases. . . . . 104
    - 11.2.5 Reproducibility . . . . . 107
  - 11.3 Part 2—Practical Examples of Data Preparation . . . . . 109
    - 11.3.1 MIMIC Tables. . . . . 109
    - 11.3.2 SQL Basics . . . . . 109
    - 11.3.3 Joins . . . . . 112
    - 11.3.4 Ranking Across Rows Using a Window  
Function . . . . . 113
    - 11.3.5 Making Queries More Manageable Using  
WITH . . . . . 113
  - References. . . . . 114
- 12 Data Pre-processing. . . . . 115**
  - 12.1 Introduction . . . . . 115
  - 12.2 Part 1—Theoretical Concepts . . . . . 116
    - 12.2.1 Data Cleaning . . . . . 116
    - 12.2.2 Data Integration. . . . . 118
    - 12.2.3 Data Transformation . . . . . 119
    - 12.2.4 Data Reduction . . . . . 120

12.3	PART 2—Examples of Data Pre-processing in R . . . . .	121
12.3.1	R—The Basics . . . . .	121
12.3.2	Data Integration . . . . .	129
12.3.3	Data Transformation . . . . .	132
12.3.4	Data Reduction . . . . .	136
12.4	Conclusion . . . . .	140
	References . . . . .	141
<b>13</b>	<b>Missing Data . . . . .</b>	<b>143</b>
13.1	Introduction . . . . .	143
13.2	Part 1—Theoretical Concepts . . . . .	144
13.2.1	Types of Missingness . . . . .	144
13.2.2	Proportion of Missing Data . . . . .	146
13.2.3	Dealing with Missing Data . . . . .	146
13.2.4	Choice of the Best Imputation Method . . . . .	152
13.3	Part 2—Case Study . . . . .	153
13.3.1	Proportion of Missing Data and Possible Reasons for Missingness . . . . .	153
13.3.2	Univariate Missingness Analysis . . . . .	154
13.3.3	Evaluating the Performance of Imputation Methods on Mortality Prediction . . . . .	159
13.4	Conclusion . . . . .	161
	References . . . . .	161
<b>14</b>	<b>Noise Versus Outliers . . . . .</b>	<b>163</b>
14.1	Introduction . . . . .	163
14.2	Part 1—Theoretical Concepts . . . . .	164
14.3	Statistical Methods . . . . .	165
14.3.1	Tukey’s Method . . . . .	166
14.3.2	Z-Score . . . . .	166
14.3.3	Modified Z-Score . . . . .	166
14.3.4	Interquartile Range with Log-Normal Distribution . . . . .	167
14.3.5	Ordinary and Studentized Residuals . . . . .	167
14.3.6	Cook’s Distance . . . . .	167
14.3.7	Mahalanobis Distance . . . . .	168
14.4	Proximity Based Models . . . . .	168
14.4.1	k-Means . . . . .	169
14.4.2	k-Medoids . . . . .	169
14.4.3	Criteria for Outlier Detection . . . . .	169
14.5	Supervised Outlier Detection . . . . .	171
14.6	Outlier Analysis Using Expert Knowledge . . . . .	171
14.7	Case Study: Identification of Outliers in the Indwelling Arterial Catheter (IAC) Study . . . . .	171
14.8	Expert Knowledge Analysis . . . . .	172

14.9	Univariate Analysis . . . . .	172
14.10	Multivariable Analysis . . . . .	177
14.11	Classification of Mortality in IAC and Non-IAC Patients . . . . .	179
14.12	Conclusions and Summary . . . . .	181
	Code Appendix . . . . .	182
	References. . . . .	183
<b>15</b>	<b>Exploratory Data Analysis . . . . .</b>	<b>185</b>
15.1	Introduction . . . . .	185
15.2	Part 1—Theoretical Concepts . . . . .	186
15.2.1	Suggested EDA Techniques. . . . .	186
15.2.2	Non-graphical EDA. . . . .	187
15.2.3	Graphical EDA . . . . .	191
15.3	Part 2—Case Study. . . . .	199
15.3.1	Non-graphical EDA. . . . .	199
15.3.2	Graphical EDA . . . . .	200
15.4	Conclusion . . . . .	202
	Code Appendix . . . . .	202
	References. . . . .	203
<b>16</b>	<b>Data Analysis. . . . .</b>	<b>205</b>
16.1	Introduction to Data Analysis . . . . .	205
16.1.1	Introduction. . . . .	205
16.1.2	Identifying Data Types and Study Objectives . . . . .	206
16.1.3	Case Study Data . . . . .	209
16.2	Linear Regression . . . . .	210
16.2.1	Section Goals. . . . .	210
16.2.2	Introduction . . . . .	210
16.2.3	Model Selection. . . . .	213
16.2.4	Reporting and Interpreting Linear Regression . . . . .	220
16.2.5	Caveats and Conclusions . . . . .	223
16.3	Logistic Regression. . . . .	224
16.3.1	Section Goals. . . . .	224
16.3.2	Introduction . . . . .	225
16.3.3	$2 \times 2$ Tables . . . . .	225
16.3.4	Introducing Logistic Regression. . . . .	227
16.3.5	Hypothesis Testing and Model Selection . . . . .	232
16.3.6	Confidence Intervals . . . . .	233
16.3.7	Prediction . . . . .	234
16.3.8	Presenting and Interpreting Logistic Regression Analysis. . . . .	235
16.3.9	Caveats and Conclusions . . . . .	236
16.4	Survival Analysis . . . . .	237
16.4.1	Section Goals. . . . .	237
16.4.2	Introduction . . . . .	237

- 16.4.3 Kaplan-Meier Survival Curves. . . . . 238
- 16.4.4 Cox Proportional Hazards Models. . . . . 240
- 16.4.5 Caveats and Conclusions. . . . . 243
- 16.5 Case Study and Summary. . . . . 244
  - 16.5.1 Section Goals. . . . . 244
  - 16.5.2 Introduction. . . . . 244
  - 16.5.3 Logistic Regression Analysis. . . . . 250
  - 16.5.4 Conclusion and Summary. . . . . 259
- References. . . . . 261
- 17 Sensitivity Analysis and Model Validation. . . . . 263**
  - 17.1 Introduction. . . . . 263
  - 17.2 Part 1—Theoretical Concepts. . . . . 264
    - 17.2.1 Bias and Variance. . . . . 264
    - 17.2.2 Common Evaluation Tools. . . . . 265
    - 17.2.3 Sensitivity Analysis. . . . . 265
    - 17.2.4 Validation. . . . . 266
  - 17.3 Case Study: Examples of Validation and Sensitivity Analysis. . . . . 267
    - 17.3.1 Analysis 1: Varying the Inclusion Criteria of Time to Mechanical Ventilation. . . . . 267
    - 17.3.2 Analysis 2: Changing the Caliper Level for Propensity Matching. . . . . 268
    - 17.3.3 Analysis 3: Hosmer-Lemeshow Test. . . . . 269
    - 17.3.4 Implications for a ‘Failing’ Model. . . . . 269
  - 17.4 Conclusion. . . . . 270
  - Code Appendix. . . . . 270
  - References. . . . . 271

**Part III Case Studies Using MIMIC**

- 18 Trend Analysis: Evolution of Tidal Volume Over Time for Patients Receiving Invasive Mechanical Ventilation. . . . . 275**
  - 18.1 Introduction. . . . . 275
  - 18.2 Study Dataset. . . . . 277
  - 18.3 Study Pre-processing. . . . . 277
  - 18.4 Study Methods. . . . . 277
  - 18.5 Study Analysis. . . . . 278
  - 18.6 Study Conclusions. . . . . 280
  - 18.7 Next Steps. . . . . 280
  - 18.8 Connections. . . . . 281
  - Code Appendix. . . . . 282
  - References. . . . . 282

- 19 Instrumental Variable Analysis of Electronic Health Records . . . . .** 285
  - 19.1 Introduction . . . . . 285
  - 19.2 Methods . . . . . 287
    - 19.2.1 Dataset. . . . . 287
    - 19.2.2 Methodology . . . . . 287
    - 19.2.3 Pre-processing . . . . . 290
  - 19.3 Results . . . . . 291
  - 19.4 Next Steps . . . . . 292
  - 19.5 Conclusions . . . . . 293
  - Code Appendix . . . . . 293
  - References. . . . . 293
  
- 20 Mortality Prediction in the ICU Based on MIMIC-II Results  
from the Super ICU Learner Algorithm (SICULA) Project . . . . .** 295
  - 20.1 Introduction . . . . . 295
  - 20.2 Dataset and Pre-preprocessing. . . . . 297
    - 20.2.1 Data Collection and Patients Characteristics . . . . . 297
    - 20.2.2 Patient Inclusion and Measures . . . . . 297
  - 20.3 Methods . . . . . 299
    - 20.3.1 Prediction Algorithms . . . . . 299
    - 20.3.2 Performance Metrics . . . . . 301
  - 20.4 Analysis . . . . . 302
    - 20.4.1 Discrimination . . . . . 302
    - 20.4.2 Calibration. . . . . 303
    - 20.4.3 Super Learner Library . . . . . 305
    - 20.4.4 Reclassification Tables. . . . . 305
  - 20.5 Discussion. . . . . 308
  - 20.6 What Are the Next Steps? . . . . . 309
  - 20.7 Conclusions . . . . . 309
  - Code Appendix . . . . . 310
  - References. . . . . 311
  
- 21 Mortality Prediction in the ICU . . . . .** 315
  - 21.1 Introduction . . . . . 315
  - 21.2 Study Dataset . . . . . 316
  - 21.3 Pre-processing . . . . . 317
  - 21.4 Methods . . . . . 318
  - 21.5 Analysis . . . . . 319
  - 21.6 Visualization. . . . . 319
  - 21.7 Conclusions . . . . . 321
  - 21.8 Next Steps . . . . . 321
  - 21.9 Connections . . . . . 322
  - Code Appendix . . . . . 323
  - References. . . . . 323



- 22 Data Fusion Techniques for Early Warning of Clinical Deterioration** . . . . . 325
  - 22.1 Introduction . . . . . 325
  - 22.2 Study Dataset . . . . . 326
  - 22.3 Pre-processing . . . . . 327
  - 22.4 Methods . . . . . 328
  - 22.5 Analysis . . . . . 330
  - 22.6 Discussion. . . . . 333
  - 22.7 Conclusions . . . . . 335
  - 22.8 Further Work . . . . . 335
  - 22.9 Personalised Prediction of Deteriorations . . . . . 336
  - Code Appendix . . . . . 337
  - References. . . . . 337
  
- 23 Comparative Effectiveness: Propensity Score Analysis** . . . . . 339
  - 23.1 Incentives for Using Propensity Score Analysis . . . . . 339
  - 23.2 Concerns for Using Propensity Score . . . . . 340
  - 23.3 Different Approaches for Estimating Propensity Scores . . . . . 340
  - 23.4 Using Propensity Score to Adjust for Pre-treatment Conditions . . . . . 341
  - 23.5 Study Pre-processing. . . . . 343
  - 23.6 Study Analysis . . . . . 346
  - 23.7 Study Results . . . . . 346
  - 23.8 Conclusions . . . . . 347
  - 23.9 Next Steps . . . . . 347
  - Code Appendix . . . . . 348
  - References. . . . . 348
  
- 24 Markov Models and Cost Effectiveness Analysis: Applications in Medical Research** . . . . . 351
  - 24.1 Introduction . . . . . 351
  - 24.2 Formalization of Common Markov Models . . . . . 352
    - 24.2.1 The Markov Chain . . . . . 352
    - 24.2.2 Exploring Markov Chains with Monte Carlo Simulations . . . . . 353
    - 24.2.3 Markov Decision Process and Hidden Markov Models. . . . . 355
    - 24.2.4 Medical Applications of Markov Models. . . . . 356
  - 24.3 Basics of Health Economics . . . . . 356
    - 24.3.1 The Goal of Health Economics: Maximizing Cost-Effectiveness . . . . . 356
    - 24.3.2 Definitions . . . . . 357
  - 24.4 Case Study: Monte Carlo Simulations of a Markov Chain for Daily Sedation Holds in Intensive Care, with Cost-Effectiveness Analysis . . . . . 359

- 24.5 Model Validation and Sensitivity Analysis  
for Cost-Effectiveness Analysis. . . . . 364
- 24.6 Conclusion . . . . . 365
- 24.7 Next Steps . . . . . 366
- Code Appendix . . . . . 366
- References. . . . . 366
- 25 Blood Pressure and the Risk of Acute Kidney Injury  
in the ICU: Case-Control Versus Case-Crossover Designs. . . . . 369**
- 25.1 Introduction . . . . . 369
- 25.2 Methods . . . . . 370
  - 25.2.1 Data Pre-processing . . . . . 370
  - 25.2.2 A Case-Control Study . . . . . 370
  - 25.2.3 A Case-Crossover Design . . . . . 372
- 25.3 Discussion. . . . . 374
- 25.4 Conclusions . . . . . 374
- Code Appendix . . . . . 375
- References. . . . . 375
- 26 Waveform Analysis to Estimate Respiratory Rate . . . . . 377**
- 26.1 Introduction . . . . . 377
- 26.2 Study Dataset . . . . . 378
- 26.3 Pre-processing. . . . . 380
- 26.4 Methods . . . . . 381
- 26.5 Results . . . . . 384
- 26.6 Discussion. . . . . 385
- 26.7 Conclusions . . . . . 386
- 26.8 Further Work . . . . . 386
- 26.9 Non-contact Vital Sign Estimation . . . . . 387
- Code Appendix . . . . . 388
- References. . . . . 389
- 27 Signal Processing: False Alarm Reduction . . . . . 391**
- 27.1 Introduction . . . . . 391
- 27.2 Study Dataset . . . . . 393
- 27.3 Study Pre-processing. . . . . 394
- 27.4 Study Methods . . . . . 395
- 27.5 Study Analysis . . . . . 397
- 27.6 Study Visualizations . . . . . 398
- 27.7 Study Conclusions . . . . . 399
- 27.8 Next Steps/Potential Follow-Up Studies . . . . . 400
- References. . . . . 401

- 28 Improving Patient Cohort Identification Using Natural Language Processing . . . . . 405**
  - 28.1 Introduction . . . . . 405
  - 28.2 Methods . . . . . 407
    - 28.2.1 Study Dataset and Pre-processing . . . . . 407
    - 28.2.2 Structured Data Extraction from MIMIC-III Tables . . . . . 408
    - 28.2.3 Unstructured Data Extraction from Clinical Notes . . . . . 409
    - 28.2.4 Analysis . . . . . 410
  - 28.3 Results . . . . . 410
  - 28.4 Discussion. . . . . 413
  - 28.5 Conclusions . . . . . 414
  - Code Appendix . . . . . 414
  - References. . . . . 415
- 29 Hyperparameter Selection. . . . . 419**
  - 29.1 Introduction . . . . . 419
  - 29.2 Study Dataset . . . . . 420
  - 29.3 Study Methods . . . . . 420
  - 29.4 Study Analysis . . . . . 423
  - 29.5 Study Visualizations . . . . . 424
  - 29.6 Study Conclusions . . . . . 425
  - 29.7 Discussion. . . . . 425
  - 29.8 Conclusions . . . . . 426
  - References. . . . . 427
- Erratum to: Secondary Analysis of Electronic Health Records . . . . . E1**