

**POPULATION-LEVEL STUDIES OF THE INCREMENTAL ECONOMIC BURDEN OF
SYSTEMIC AUTOIMMUNE RHEUMATIC DISEASES**

by

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES
(Pharmaceutical Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

April 2018

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Abstract

In systemic autoimmune rheumatic diseases (SARDs), immune dysregulation leads to systemic inflammation, organ damage, complications, and disability. I examined the longitudinal, incremental direct medical costs of newly-diagnosed SARDs, incremental productivity costs, and impact of socioeconomic status (SES) on costs, at the general population level.

Methods:

Nine population-based cohorts, one for each SARD, were identified from the administrative health databases of the province of British Columbia (BC), Canada. Nine non-SARD comparison cohorts were selected from the general population of BC, and matched to each SARD cohort on age, sex, and index-year.

Direct Medical Costs: Administrative data captured provincially-funded outpatient encounters and hospitalisations, and all dispensed medications. From these data, I estimated direct medical costs of each SARD and non-SARD cohort for up to five years after diagnosis/index date. I used generalised linear models to determine incremental costs of each SARD overall, and by SES group, controlling for covariates, and incremental costs of systemic lupus erythematosus (SLE, the most common SARD) before diagnosis.

Productivity Costs: Random sample of the population-based cohorts completed a survey on absenteeism and presenteeism (working at reduced levels/efficiency) from paid and unpaid

work. Survey data were used to determine adjusted, incremental lost productivity costs of three SARDs: SLE, systemic sclerosis (SSc), and Sjogren's (SjS).

Results:

Direct Medical Costs: I identified 8,858 incident adult SARD cases for the years 1996-2010 (79.8% female) and 32,727 non-SARDs (79.0% female). Adjusted mean per-person-year incremental costs (over-and-above non-SARDs') ranged from \$7,851 to \$54,061 2013 CDN, mainly from hospitalisations. For nearly every SARD, incremental costs of the low-SES exceeded the high-SES, by ~\$2,000-\$3,000 per-person-year. In each of the five pre-index years, adjusted costs for SLE were significantly greater than non-SLE; male sex and low SES were associated with greater costs among SLE.

Productivity Costs: 671 surveys were completed: SLE=167, SSc=42, SjS=90, and non-SARDs=375. Adjusted incremental productivity costs averaged \$4,494, \$3,582, and \$4,357 annually for SLE, SSc, and SjS, respectively. Major contributors were unemployment, presenteeism from paid work, and impairments with unpaid work.

Conclusion: These novel findings should inform health resource allocation, and ongoing research to improve outcomes and reduce costs in these chronic diseases.

Lay Summary

Systemic autoimmune rheumatic diseases (SARDs) are a group of inflammatory arthritides (including lupus) that cause organ damage and work disability. Most cost estimates were determined over short periods from highly-selected clinic settings, and the ‘extra’ costs from SARDs in Canada are unknown.

To address this, I used de-identified Ministry of Health data to study all BC adults newly-diagnosed with SARDs during 1996-2010, and a sample of BC residents without SARDs. I determined costs for outpatient care, hospitalisations, medications, and time lost from paid and unpaid work.

I studied 8,858 SARDs and 32,727 non-SARDs. After adjustment, ‘extra’ healthcare costs of SARDs (over-and-above costs of non-SARDs) averaged \$7,851-\$54,061 per-person-year, and were \$2,000-\$3,000 greater for patients of lower socioeconomic status. Extra costs of work loss averaged \$3,582-\$4,494 per-person-year, mainly from unpaid work impairments.

These estimates highlight the economic burden and unmet needs of these little-known chronic diseases, and will inform public healthcare spending.

Preface

I conceived and conducted each of the studies presented in this thesis, wrote the statistical code, analysed the data, interpreted the findings, and drafted and revised each chapter. While my supervisors (Dr. J. Antonio Aviña-Zubieta (JAA-Z) and Dr. Carlo A. Marra (CAM)) and other doctoral committee members (Dr. Larry Lynd, Dr. Jacek A. Kopec (JAK), and Dr. Mohsen Sadatsafavi (MS)) provided direction, support, and critical evaluation as is commensurate with a dissertation committee, I was responsible for the writing and final content of each chapter.

Some of the specific contributions of my supervisory committee are as follows: JAA-Z (as Principal Investigator) and CAM (as Co-Investigator) conceived and secured funding for the larger study of the disease and economic burden of SARDs, acquired the administrative data extracts, contributed to the design of the survey and collection of survey data, and gave input on my statistical analysis, interpretation of findings, and my manuscript/chapter drafts. JAK contributed to the design of the survey. MS consulted on the statistical analysis. All committee members provided valuable epidemiologic, statistical, economic, and/or clinical expertise.

All research was performed at the Collaboration for Outcomes Research and Evaluation, part of the Faculty of Pharmaceutical Sciences at The University of British Columbia, and Arthritis Research Canada, both located in the province of British Columbia, Canada. Ethical approval for this research was granted by Behavioural Research Ethics Board at The University of British Columbia: project title “Long-term health resource utilization and total economic burden following diagnosis of systemic autoimmune rheumatic diseases: a population-based

study” and certificate H12-03093. All inferences, opinions, and conclusions drawn in this thesis are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

- A portion of Chapter 1 has been published. McCormick N, Marra CA, Aviña-Zubieta JA. Productivity Losses and Costs in the Less-Common Systemic Autoimmune Rheumatic Diseases. *Curr Rheumatol Rep*. 2017 Nov;19(11).

I conceived the topic of the review, performed the literature search, reviewed the full-text of selected articles and extracted the data, interpreted the findings, and drafted and revised the manuscript. CAM and JAA-Z reviewed the manuscript draft for critically important content.

- A portion of Chapter 2 has been published. McCormick N, Reimer K, Famouri A, Marra CA, Aviña-Zubieta JA. Filling the gaps in SARDs research: collection and linkage of administrative health data and self-reported survey data for a general population-based cohort of individuals with and without diagnoses of systemic autoimmune rheumatic disease (SARDs) from British Columbia, Canada. *BMJ Open*. 2017 Jun 21;7(6):e013977.

I was involved in the study design, was primarily responsible for collecting, cleaning, and analysing the survey data, drafted most of the manuscript, and revised it. K. Reimer wrote part of the first draft of the manuscript, helped collect the survey data, and reviewed the manuscript draft for critically important content. A. Famouri helped collect the survey data and reviewed the manuscript draft for critically important content. CAM contributed to the study design and reviewed the manuscript draft for critically important content. JAA-Z acquired the data, contributed to study design, and reviewed the manuscript draft for critically important content.

- A version of Chapter 4 has been accepted for publication. McCormick N, Marra CA, Sadatsafavi M, Aviña-Zubieta JA. Incremental Direct Medical Costs of Systemic Lupus Erythematosus Patients in the Years Preceding Diagnosis: A General Population-Based Study. *Lupus*. Accepted 2018 March 8. doi: 10.1177/0961203318768882.

I designed the study, analysed the data, interpreted the findings, and drafted and revised the manuscript. CAM helped interpret the findings and reviewed the manuscript draft for critically important content. MS contributed to the statistical analysis and reviewed the manuscript draft for critically important content. JAA-Z acquired the data, helped interpret the findings, and reviewed the manuscript draft for critically important content.

- A version of Chapter 5 has been accepted for publication. McCormick N, Marra CA, Sadatsafavi M, Kopec JA, Aviña-Zubieta JA. Excess Productivity Costs of Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjogren's Syndrome: A General Population-Based Study. *Arthritis Care & Research*. Accepted 2018 March 23. doi: 10.1002/acr.23573.

I was involved in the study design, was primarily responsible for collecting, cleaning, and analysing the survey data and interpreting the findings, and drafted and revised the manuscript. CAM contributed to the study design, helped interpret the findings, and reviewed the manuscript draft for critically important content. MS contributed to the statistical analysis and reviewed the manuscript draft for critically important content. JAK contributed to the study design and reviewed the manuscript draft for critically important content. JAA-Z helped acquire the data, contributed to the study design, and reviewed the manuscript draft for critically important content.

Table of Contents

Abstract.....	ii
Lay Summary	iv
Preface.....	v
Table of Contents	viii
List of Tables	xiv
List of Figures.....	xvii
List of Abbreviations	xviii
Acknowledgements	xxii
1 . Introduction.....	1
1.1: Overview of epidemiology and economic burden	2
1.1.1 Epidemiology	2
1.1.2 Economic burden	3
1.2: Pathophysiology, manifestations, and treatments.....	4
1.2.1 Treatments.....	5
1.3: Burden of specific SARD diagnoses	6
1.3.1 Systemic lupus erythematosus (SLE)	6
1.3.2 Sjogren’s syndrome (SjS)	9
1.3.3 Systemic sclerosis (SSc)	10
1.3.4 Polymyositis and dermatomyositis (PM/DM)	12
1.3.5 Systemic vasculitides (SV)	13
1.3.6 Polyarteritis nodosa.....	13

1.3.7 Giant cell arteritis (GCA) and Takayasu's arteritis (Takayasu's)	14
1.3.8 Granulomatosis with polyangiitis (GPA).....	16
1.3.9 Eosonophilic granulomatosis with polyangiitis (EGPA).....	17
1.4 Costs of treatments for SARDs.....	17
1.4.1 Prescription medication costs and coverage in British Columbia, Canada	17
1.4.2 Current and anticipated costs	18
1.5 Direct medical costs in SARDs: a critical literature review	21
1.5.1 Research gaps.....	22
1.6 Productivity losses and costs in SARDS: a critical literature review	24
1.6.1 Research gaps.....	25
1.7 Impact of socioeconomic status on costs in SARDS.....	27
1.8 Summary of knowledge gaps and thesis objectives.....	29
1.9 Overview of thesis	31
2 . Methods.....	72
2.1 Data source.....	73
2.1.1 Medical Services Plan Consolidation File	74
2.1.2 Medical Services Plan Payment Information File (MSP).....	75
2.1.3 Discharge Abstract Database (DAD).....	76
2.1.4 PharmaNet.....	77
2.2 Study populations.....	78
2.2.1 SARD individuals	78
2.2.2 Comparison group.....	80
2.3 Healthcare utilisation and cost calculation	80

2.4 Independent variables (direct medical costs analysis)	82
2.4.1 Baseline comorbidities	82
2.4.2 Baseline healthcare resource utilisation.....	83
2.4.3 Baseline socioeconomic status.....	83
2.4.4 Urban/rural residence.....	84
2.5 Statistical analysis (direct medical costs analysis – Chapters 3 and 4).....	85
2.5.1 Unadjusted analysis (Chapters 3 and 4).....	88
2.5.2 Adjusted analysis – direct medical costs of SARDs after index date (Chapter 3).....	88
2.5.3 Adjusted analysis – direct medical costs of SLE prior to index date (Chapter 4)	91
2.6 Survey recruitment (productivity costs analysis).....	92
2.6.1 Study populations.....	92
2.6.2 Recruitment procedures	93
2.7 Data collection (productivity costs analysis)	94
2.7.1 Survey components	95
2.7.2 Protection of privacy and confidentiality.....	97
3 . Total and Incremental Direct Medical Costs in Systemic Autoimmune Rheumatic	
Diseases and the Influence of Socioeconomic Status: A Longitudinal Population-Based	
Study.....	101
3.1 Introduction.....	101
3.2 Methods.....	105
3.2.1 Data source.....	105
3.2.2 Study populations.....	105
3.2.3 Healthcare utilisation and cost calculation	107

3.2.4 Independent variables	108
3.2.4.1 Baseline comorbidities.....	108
3.2.4.2 Baseline healthcare resource utilisation.....	108
3.2.4.3 Baseline socioeconomic status.....	108
3.2.4.4 Urban/rural residence.....	109
3.2.5 Statistical analysis	110
3.3 Results.....	114
3.3.1 Longitudinal patterns in healthcare use and costs from diagnosis.....	114
3.3.2 Incremental costs	115
3.3.3 Impact of baseline socioeconomic status – neighbourhood-level.....	116
3.3.4 Impact of baseline socioeconomic status – individual-level.....	117
3.4 Discussion	119
3.4.1 Longitudinal costs	119
3.4.2 Comparisons with prior estimates.....	120
3.4.3 Impact of socioeconomic status	123
3.4.4 Measurement of socioeconomic status	127
3.4.5 Strengths and limitations.....	129
3.5 Conclusion	131
4 . Incremental Direct Medical Costs of Systemic Lupus Erythematosus Patients in the Years Preceding Diagnosis: A General Population-Based Study.....	172
4.1 Introduction.....	172
4.2 Methods.....	175
4.2.1 Data source.....	175

4.2.2 Study populations.....	175
4.2.3 Healthcare utilisation and costs	176
4.2.4 Independent variables	177
4.2.5 Statistical analysis.....	178
4.3 Results.....	180
4.3.1 Healthcare components.....	181
4.3.2 Impact of sex.....	182
4.3.3 Impact of socioeconomic status.....	183
4.4 Discussion.....	184
4.5 Conclusion	190
5 . Incremental Productivity Costs of Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjogren’s Syndrome: A General Population-Based Study	203
5.1 Introduction.....	203
5.2 Methods.....	205
5.2.1 Administrative data source	205
5.2.2 Study populations.....	205
5.2.3 Survey	206
5.2.4 Independent variables	209
5.2.5 Dependent variables.....	209
5.2.6 Cost calculation.....	211
5.2.7 Statistical analysis.....	211
5.3 Results.....	214
5.3.1 Unadjusted costs	215

5.3.2 Adjusted analyses: incremental productivity losses and costs.....	216
5.3.3 Determinants of productivity costs within SARDs.....	217
5.4 Discussion.....	218
5.5 Conclusion	225
6 . Discussion and Conclusion.....	251
6.1 Summary of thesis findings	251
6.2 Contribution and applications	253
6.2.1 Contribution	253
6.2.2 Applications	255
6.3 Policy implications and ongoing research	256
6.3.1 Socioeconomic status and incremental direct medical costs	257
6.3.2 Expediting diagnosis and treatment	259
6.3.3 Lost productivity costs.....	263
6.4 Strengths and limitations.....	265
6.5 Future directions	269
6.5.1 Linkage with data on emergency department visits.....	270
6.5.2 Linkage of survey and administrative data	270
6.5.3 Productivity costs among incident cohorts	271
6.6 Conclusion	273
References	275
Appendix.....	319
Appendix A: Survey	320

List of Tables

Table 1.1: Studies Reporting on the Total Direct Medical Costs of SARDs.....	33
Table 1.2: Studies Reporting on the Incremental or Attributable Direct Medical Costs of SARDs	40
Table 1.3: Studies Reporting on the Lost Productivity Costs of Systemic Lupus Erythematosus	45
Table 1.4: Studies Reporting on the Productivity Losses and Costs of SARDs (excluding SLE)	48
Table 2.1: International Classification of Diseases 9th (ICD-9) and 10th (ICD-10) Revision Diagnostic Codes for Systemic Autoimmune Rheumatic Diseases (SARDs).....	98
Table 2.2: Annual Cost-Per-Standard-Hospital-Stay Values Used to Compute Hospitalisation Costs.....	99
Table 2.3: Multiplier Values Used to Standardise Medical Costs to 2013 Canadian Dollars	100
Table 3.1: Baseline Characteristics of Individuals With and Without Systemic Lupus Erythematosus (SLE)	133
Table 3.2: Baseline Characteristics of Individuals With and Without Systemic Sclerosis (SSc)	135
Table 3.3: Baseline Characteristics of Individuals With and Without Sjogren's Syndrome (SjS)	137
Table 3.4: Baseline Characteristics of Individuals With and Without Polymyositis (PM)	139
Table 3.5: Baseline Characteristics of Individuals With and Without Dermatomyositis (DM).	141
Table 3.6: Baseline Characteristics of Individuals With and Without Polyarteritis Nodosa (PAN)	143

Table 3.7: Baseline Characteristics of Individuals With and Without Giant Cell Arteritis (GCA)	145
Table 3.8: Baseline Characteristics of Individuals With and Without Granulomatosis with Polyangiitis (GPA)	147
Table 3.9: Baseline Characteristics of Individuals With and Without Takayasu’s Arteritis	149
Table 3.10: Unadjusted Annual Overall Mean Per-Person Direct Medical Costs for each SARD and non-SARD Group, and Incremental Costs	151
Table 3.11: Predicted Costs for SARDs and Non-SARDs, and Predicted Incremental Costs of SARDs	160
Table 3.12: Predicted Incremental Costs of SARDs, by Neighbourhood Socioeconomic Group	163
Table 3.13: Predicted Incremental Costs of Systemic Lupus Erythematosus, Overall and by Neighbourhood-Level Socioeconomic Group, Before and After Adjustment for Individual-Level Socioeconomic Group	166
Table 4.1: Characteristics of Individuals With and Without SLE, Overall and by Sex	191
Table 4.2: Overall Annual Mean Per-Person Direct Medical Costs, Before and After Adjustment	193
Table 4.3: Adjusted Cost and Utilisation Ratios (95% CI) Associated with SLE Status	194
Table 4.4: Adjusted Cost and Utilisation Ratios (95% CI) Associated with Sex and Socioeconomic Status, among SLE only	196
Table 5.1: Participant Characteristics, by Cohort	227
Table 5.2: Employment and Productivity Outcomes	232
Table 5.3: Occupational Sectors of Employed Participants, and Corresponding Wages	238

Table 5.4: Results of Regression Analysis of Productivity Costs for Systemic Lupus Erythematosus (SLE)	239
Table 5.5: Results of Regression Analysis of Productivity Costs for Sjogren's Syndrome (SjS)	242
Table 5.6: Results of Regression Analysis of Productivity Costs for Systemic Sclerosis (SSc)	245
Table 5.7: Summary of Factors Significantly Associated with Productivity Costs within SARDs	249

List of Figures

Figure 3.1: Unadjusted Annual Mean-Per-Person Direct Medical Costs for SLE and Non-SLE over the First Five Years after Diagnosis/Index Date, Among all Individuals (left) and Individuals with Complete Five-Year Follow-Up (right)	168
Figure 3.2: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of SARDs, by Healthcare Component.....	169
Figure 3.3: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of Selected SARDs, by Neighbourhood Socioeconomic Group (Left=Low SES, Middle=Moderate SES, Right=High SES)	170
Figure 3.4: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of SLE by Neighbourhood Socioeconomic Group, Before (left) and After (right) Adjustment for Individual-Level Socioeconomic Status	171
Figure 4.1: Unadjusted Annual Mean Per-Person Outpatient and Prescription Medication Costs for SLE and Non-SLE.....	200
Figure 4.2: Unadjusted Annual Mean Per-Person Direct Medical Costs for SLE and Non-SLE Males and Females.....	201
Figure 4.3: Annual Frequencies of the Most Common Charlson-Romano Comorbidities for SLE and Non-SLE Males and Females (<i>Dementia, Liver Disease, Hemiplegia, Metastatic Cancer, and HIV Not Shown Due to Very Small Numbers</i>)	202
Figure 5.1: Breakdown of Lost Productivity Costs by Component, Among all Participants (left) and Employed Participants (right)	250

List of Abbreviations

Abbreviation	Definition
95% CI	95% credible interval
ACE-II inhibitor	angiotensin-converting-enzyme inhibitor
ACR	American College of Rheumatology
ANCA	anti-neutrophil cytoplasmic antibodies
BC	British Columbia
BMI	body mass index
cBMI	corrected body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CDN	Canadian dollars
CIHI	Canadian Institute for Health Information
CSRG	Canadian Scleroderma Research Group
CTD	connective tissue disease
CVA	cerebrovascular accident
DAD	Discharge Abstract Database
DINPIN	Drug Information Number/Product Information Number
DM	dermatomyositis
DMARD	disease-modifying anti-rheumatic drug
DU	digital ulcers
EGPA	Eosinophilic granulomatosis with polyangiitis
ER	emergency room

FCA	friction cost approach
GC	glucocorticoids
GCA	giant cell arteritis
GEE	generalised estimating equation
GLM	generalised linear model
GP	general practitioner
GPA	Granulomatosis with polyangiitis
HAQ-DI	Health Assessment Questionnaire Disability Index
HCA	human capital approach
HCQ	hydroxychloroquine
HBV	hepatitis B virus
ICD-9	International Classification of Diseases - Ninth Revision
ICD-10	International Classification of Diseases - Tenth Revision
IQR	interquartile range
LN	lupus nephritis
LNN	lupus nephritis-negative
MI	myocardial infarction
MPA	microscopic polyangiitis
MSP	Medical Services Plan
N	number of participants
NOC	National Occupational Classification
NPSLE	neuropsychiatric lupus

OA	osteoarthritis
OLS	ordinary least squares
OR	odds ratio
PAH	pulmonary arterial hypertension
PAN	polyarteritis nodosa
PDE-5 inhibitor	phosphodiesterase-5 inhibitor
PM	polymyositis
PM/DM	poly/dermatomyositis
PPV	positive predictive value
PsA	psoriatic arthritis
PY	person-year
QIC	quasi-likelihood information criterion
RA	rheumatoid arthritis
RIW	resource intensity weight
RR	relative risk/risk ratio
SARD	systemic autoimmune rheumatic disease
SD	standard deviation
SES	socioeconomic status
SER	standardised employment ratio
SjS	Sjogren's syndrome
pSjS	primary Sjogren's syndrome
sSjS	secondary Sjogren's syndrome

SLE	systemic lupus erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SSc	systemic sclerosis
dcSSc	diffuse cutaneous systemic sclerosis
lcSSc	limited cutaneous systemic sclerosis
STD	short-term disability
SV	systemic vasculitides
UK	United Kingdom
USA (or US)	United States of America
USD	United States dollars
VAS	visual analogue scale
VOLP	Valuation of Lost Productivity questionnaire
WPAI	Work Productivity and Activity Impairment questionnaire
WLQ	Work Limitations Questionnaire

Acknowledgements

Many thanks to all the individuals and organisations whose time, expertise, and support were essential to the success of these projects and my development as a researcher. I thank both my supervisors, Dr. Antonio Aviña-Zubieta and Dr. Carlo Marra, who devoted many hours and resources to my training, and afforded me key professional opportunities within and outside this project. Thank you as well to my supervisory committee members (Dr. Larry Lynd, Dr. Jacek Kopec, and Dr. Mohsen Sadatsafavi) who provided much guidance and encouragement over the course of my M.Sc. and Ph.D.

I am grateful to all the survey participants and their family members, with and without SARDs, who generously contributed their time and energy. I also thank the members of the SARDs Consumer Advisory Council (Ms. Lianne Gulka, Ms. Janis McCaffrey, Ms. Joyce Ma, Ms. Marilyn Muldoon, and Mr. Alan Pemberton) for participating in many teleconferences and helping develop the recruitment procedures, survey, and other study materials, and personnel at Population Data BC and the BC Ministry of Health who helped facilitate the data access and request-to-contact applications. Many scientists and personnel at Arthritis Research Canada tested the survey and provided logistical support, but I must particularly acknowledge Lindsay Belvedere, Kathryn Reimer, and Lynn Nowoselski, and volunteers Ali Famouri, Iman Sheriff, Shannon Percival Smith, and Sophia Sidi, for their time, skills, and efforts.

I thank Dr. Eric Sayre for his help with the cohorts and overall administrative data expertise, Dr. Wei Zhang for her help (and patience) with assembling the productivity questionnaires and interpreting the results, Ms. Salma Lalji for her enthusiastic assistance with designing and programming the online survey, and Dr. Wenjia Chen for her friendly assistance with implementing the adjusted cost analyses.

I was fortunate to belong to two excellent research groups, the Collaboration for Outcomes Research and Evaluation (CORE) and Arthritis Research Canada (ARC), and to receive incredible research and moral support from both, and from the Faculty of Pharmaceutical Sciences as a whole. I enjoyed serving on the executive of the Pharmaceutical Sciences Graduate Student Society (PharGS) and Canadian Arthritis Trainee Association (CATA), and being part of the Vancouver Health Economics Methodology Group (VanHEM), and also gained much from working with Dr. Patti Katz, Dr. Ed Yelin, Ms. Laura Trupin, and other Lupus Outcomes Study investigators at the University of California at San Francisco.

The research in this thesis was funded by the Canadian Arthritis Network/The Arthritis Society and the Canadian Institutes of Health Research, with support from The University of British Columbia and the Population Data BC Student Cost Waiver Program.

I am grateful for the training awards I received from the Canadian Institutes of Health Research (Frederick Banting and Charles Best Doctoral Research Award, two Institute Community Support Travel Awards, and Michael Smith Foreign Study Supplement), Rx&D Health Research Foundation (Pharmaceutical Sciences Research Scholarship), Arthritis Alliance of Canada (Ph.D. Student Award), Scleroderma Association of British Columbia, Faculty of Pharmaceutical Sciences (entrance scholarship and Dwivedi-Mitchell Graduate Award in Pharmaceutical Sciences), and The University of British Columbia (Four-Year Fellowship Tuition Award and Andrew Nord Fellowship in Rheumatology).

Finally, special thanks to my longstanding office/classmates (including Sharan Rai, Jenny Leese, Nicole Tsao, and Wenjia Chen), and to ZQ and my parents, aunts, uncles, and grandparents who supported me during my graduate studies and shared in the fun.

1. Introduction¹

Systemic autoimmune rheumatic diseases (SARDs) are a group of complex but relatively unknown chronic inflammatory arthritides. Immune dysregulation leads to systemic inflammation, organ damage, complications and comorbidities, disability, premature mortality, and reduced health-related quality-of-life(1–6). Though distinct disorders, SARDs are often studied together due to their shared etiology, pathophysiology, manifestations, and treatments. There are two main subtypes, the connective tissue diseases (SARDs-CTD) and systemic vasculitides (SARD-SV). Though the diagnoses included under the term SARDs can vary, the diagnoses included in this thesis are the following connective tissue disorders - adult forms of systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc), Sjogren's syndrome (SjS), polymyositis (PM), and dermatomyositis (DM) – and adult primary systemic vasculitides: polyarteritis nodosa (PAN), giant cell arteritis (GCA, sometimes referred to as temporal arteritis), Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), Takayasu's arteritis, and Eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as Churg-Strauss syndrome).

¹ A portion of this chapter has been published:

McCormick N, Marra CA, Aviña-Zubieta JA. Productivity Losses and Costs in the Less-Common Systemic Autoimmune Rheumatic Diseases. *Curr Rheumatol Rep*. 2017 Nov;19(11).

1.1: Overview of epidemiology and economic burden

1.1.1 Epidemiology

According to recent estimates sourced from provincial administrative health databases, the incidence of SARDs-CTD in the province of British Columbia (BC), Canada, is 44.3 cases per-100,000 person-years (PY)(7) (in 2007), with a prevalence of 388.6(7). SARDs-SV are less common, with reported incidence and prevalence in BC of 5.3 and 31.9 per-100,000(7), respectively. In 2007, when there were about 3.3 million adults in BC, our group estimated about 12,966 BC adults (0.39% of the BC population) had a form of SARDs-CTD, and 1,065 (0.03%) had a form of SARDs-SV(7). SARDs affect far fewer individuals than do other arthritides, including osteoarthritis (OA), gout, and rheumatoid arthritis (RA). In studies using the same administrative data sources and similar case definitions as the BC estimates for SARDs, the incidence of OA, gout, and RA in BC was 1,170(8), 290(9), and 58-68(10) per 100,000 PY, respectively, while prevalence was 10,780(8), 3,800(9), and 760(11) per 100,000 BC residents, respectively.

Broadly, SARDs predominantly affect females and mainly strike between the ages of 20 and 60, peak childrearing and career years. However, the incidence, prevalence, sex distribution, and age of onset do vary by subtype and specific diagnosis. The female predominance is more apparent in SARDs-CTD, with SLE, SSc, and SjS about six-times more prevalent in females than males(7,12). GCA affects about two-to-three times more females(13), while PAN(14), GPA(15), and EGPA(16) have a more even sex distribution. GCA strikes mainly those older than 50 years of age(15), while Takayasu's affects mainly young women(17).

SARDs can afflict any racial/ethnic group, though certain diagnoses are more frequent in certain groups. SjS and GPA are more common in those of White/Caucasian/European descent(15,18), and GPA appears to be more prevalent in Northern Europe than Southern Europe(19). Conversely, SLE and SSc tend to be more common in those of non-White/Caucasian races/ethnicities. Data from the United States (USA) suggests there is an increased prevalence of SLE among those of Hispanic(20,21), Middle-Eastern(22), Asian(20,21), and African-American(20,21,23–25) descent, as compared to Whites, and an increased prevalence of SSc among those of African American descent(26). Both US and Canadian data have shown a higher prevalence among Indigenous groups(25,27–30), those of Native American/Canadian, First Nations, Metis, or Aboriginal descent. In the Canadian province of Alberta, SLE and SSc were twice as prevalent among Indigenous females > 45 years of age than non-Indigenous females in the same age group(27), though the prevalence of PM/DM(31) did not differ between Indigenous and non-Indigenous groups.

1.1.2 Economic burden

In this thesis, I define economic burden as the direct medical costs and lost productivity costs. Direct medical costs are the costs paid for the provision of healthcare resources such as outpatient care, hospitalisations, and medications, while lost productivity costs (sometimes referred to as indirect costs) are the monetary value of production losses due to health. The following is a brief overview of what is known about the economic burden of SARDs, with a focus on Canada; in Sections 1.5 and 1.6, I provide a comprehensive review of all-known estimates as available from the published, English-language literature. All estimates are standardised to 2013 Canadian dollars. The most recent Canadian data (from a clinic-based

cohort) suggest the direct medical costs of prevalent SLE average **\$11,182** per-patient annually: **\$15,862** for severe disease and **\$6,237** for non-severe(32). The costs of prevalent SSc and PM/DM patients in the Canadian province of Quebec averaged **\$5,549**(33) and **\$4,412**(34), respectively, though the PM/DM estimate included only outpatient and hospitalisation costs, not medications. The direct medical costs of other SARDs have not been determined in the Canadian setting, though some estimates are available from other countries: annual direct medical costs averaged **\$6,118**(35) among a clinic-based cohort of prevalent SjS in the United Kingdom (UK), **\$7,195**(36) among a clinic-based cohort of prevalent Takayasu's arteritis in Italy, **\$42,638**(37) among prevalent GPA in the USA, and **\$42,252**(38) among newly-diagnosed GCA in the USA. As described in Section 1.6, there is a paucity of Canadian data on the lost productivity costs of SARDs, though four-year cumulative costs of SLE averaged **\$54,151**(39) and the costs of SSc were **\$14,775** per-year(35). Both estimates were from tertiary clinic cohorts.

1.2: Pathophysiology, manifestations, and treatments

SARDs are autoimmune diseases, meaning the body launches an immune response against its own organs, tissues, and blood vessels. Although the pathophysiology is not fully understood, a positive-feedback loop has been proposed for many SARDs wherein, upon the formation of immune complexes between auto-antibodies and auto-antigens, toll-like receptors stimulate innate immune cells to produce type I interferon(40). This triggers an adaptive immune response, with maturation and differentiation of (sometimes abnormal, pro-inflammatory) T-cells and B-cells(40). Generation of additional auto-antigens and auto-antibodies serves to maintain this loop by forming additional immune complexes, and stimulating further production of interferon gamma. The T-cells themselves can induce direct

tissue damage, and evidence suggests that the target organs and tissues may also induce and maintain the abnormal immune response(40)

This immune dysregulation (or “continuous immune activation”(40)), and uncontrolled inflammation, leads to a variety of constitutional symptoms (i.e. fatigue, fever, malaise, myalgia, arthralgia/arthritis)(41) and organ-specific manifestations, the extent of which depends on the specific SARD. For example, SLE can manifest in nearly every organ system while the other SARDs-CTD affect specific connective tissues: SjS the salivary, lachrimal, and other exocrine glands, SSc the skin, kidneys, gastrointestinal tract, and lungs, and PM/DM the muscle fibres and skin(40). The defining feature of SV is inflammatory narrowing and necrosis of the walls of specific blood vessels(41), which restricts blood flow, thereby damaging the target organs. In addition to these direct organ manifestations, SARDs are associated with a significantly increased risk of complications including myocardial infarction (MI), cerebrovascular accident (CVA), and venous thromboembolism(42–59); recent evidence even suggests those with SLE have worse functional outcomes and higher mortality after CVA than those without SLE(60). SARD patients have also been found to have an increased risk of comorbidities such as diabetes(61), chronic obstructive pulmonary disease(62), and certain cancers(63–76).

1.2.1 Treatments

To ameliorate the inflammation and underlying immune dysregulation, the mainstay therapies for SARDs are glucocorticoids (GC) and immune-modulating and immunosuppressing agents, many of which are also used to treat cancer and prevent (or address) rejection of transplanted organs and tissues. The immune-modulators used in SARDs include methotrexate,

azathioprine, and the anti-malarials hydroxychloroquine (HCQ) and chloroquine.

Immunosuppressants include cyclophosphamide, mycophenolate, ciclosporin, and tacrolimus.

GC are associated with an array of acute and chronic adverse effects including cataracts, hypertension, osteonecrosis, diabetes, and opportunistic infections(77–80). Thus, to avoid (or at least reduce) GC exposure, HCQ, immune-modulators, and immunosuppressants, so-called ‘steroid-sparing agents’, are used in place of (or alongside) GC. Moreover, as cyclophosphamide can cause infertility, gonadal failure, and bladder cancer, therapies such as mycophenolate(81) or rituximab(82) may be used instead. Biologics are used far less-frequently in SARDs than in other inflammatory arthritides, but three are indicated for SARDs in Canada: belimumab for SLE, rituximab for GPA, and (as of October 2017) tocilizumab for GCA.

1.3: Burden of specific SARD diagnoses

To help one appreciate the disease, healthcare, and productivity burden of SARDs, I provide below a brief description of the pathophysiology, epidemiology, and distinct clinical features and treatments for each. Where possible, I provide data from Canadian settings.

1.3.1 Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE), the prototypical SARD, is the most common and well-known of these disorders. SLE can manifest in nearly every organ system, though the main areas of involvement are the mucocutaneous, pleuropulmonary, musculoskeletal, cardiovascular, renal, haematological, and neuropsychiatric(83) systems. The two main mechanisms of SLE pathogenesis are deposition of immune complexes in body tissues (such as the skin and kidneys), and binding of circulating auto-antibodies against antigens present in specific tissues(84). These

processes cause tissue injury and further immune system activation and heightened repair response(84). SLE affects mainly females, with a mean age at diagnosis of around 30-35 years(85–88) among clinic-based cohorts, but older (around 45 to 50 years)(89–92) in population-based cohorts

According to a 2017 systematic review(93), the incidence of SLE in North America is up to three cases per-100,000 PY, with prevalence ranging between 30 and 60 cases per-100,000 adults. In Canada, the reported incidence of SLE has ranged from 2.8 per-100,000 PY(94) (in 2003 in the province of Quebec) to 14.1 per-100,000 PY(7) (in 2007 in BC), with prevalence ranging from 51.0(94) to 113.9 per-100,000(7). The authors of the aforementioned systematic review(93) concluded that the prevalence of SLE may indeed have increased over time, as supported by investigations from the UK, Scandinavia, and Minnesota, USA. However, the trends for incidence were less clear, with reports from the UK and Minnesota suggesting the incidence has decreased over time(93).

SLE generally has a relapsing-remitting course, with disease activity fluctuating over time. Clinically-significant increases in disease activity, which usually necessitate changes in treatment, are referred to as disease flares(95). However, a number of patterns have been observed, including long quiescent (no disease manifestations for at least one year) and chronic active (constantly active disease for at least one year)(96), and patients may switch between patterns over time(97). Though mortality has decreased over the decades(98–100), SLE is still associated with an approximately three-fold increased risk of mortality as compared to the general population(101,102).

The major therapeutic goals in the management of SLE, as identified by an international taskforce, are prevention of flares and damage accrual, achievement of complete remission of systemic symptoms and organ manifestations (or if not possible, then the lowest-possible level of disease activity), and addressing fatigue, pain, depression, and other aspects of health-related quality-of-life(103). Taskforce members suggested that hydroxychloroquine be used in all SLE patients who do not have an absolute contraindication, due to its role in reducing flares, preventing damage accrual, and reducing mortality(103).

Belimumab, which inhibits a B-cell stimulator protein, is indicated for reducing disease activity in adults with active, antibody-positive SLE when used alongside standard therapies(104), though was not trialed in lupus nephritis or neuropsychiatric lupus. The regulatory approval of belimumab in 2011 was met with great excitement since it was the first therapy in over 50 years that was developed specifically for SLE(105). However, given its high cost (about \$20,000 per-patient annually) and a lack of evidence that belimumab can reduce GC exposure or the risk of organ damage, Canada's health technology assessment agency, the Canadian Agency for Drugs and Technologies in Health (CADTH), recommended that belimumab not be listed by Canada's provincial and other publicly-funded drug plans(104). As such, it is not covered by the BC government(106), though is available to patients if they have coverage through private insurance or are willing to pay out-of-pocket. Though the 2017 British Society of Rheumatology guidelines(103) suggest using belimumab or rituximab for moderate to severe SLE (in the UK, limited public funding is available for SLE patients with refractory active disease(107,108)), rituximab is not licensed in Canada (or the UK) for the treatment of SLE.

1.3.2 Sjogren's syndrome (SjS)

Sjogren's syndrome has two forms: primary (pSjS, occurring on its own) and secondary (sSjS, occurring in conjunction with another rheumatic disease, such as SLE or rheumatoid arthritis). It is characterised by salivary gland dysfunction (resulting from autoimmune-mediated destruction of these glands), and chronic inflammation of the tear ducts (lacrimal glands), which reduce tear secretion and salivary flow(109). As such, the distinguishing features of SjS are ocular and oral dryness, which can damage the eyes, cause difficulty speaking or swallowing, and lead to oral candidiasis and tooth decay(109). Extraglandular manifestations include depression, fatigue, joint pain, dysphagia, peripheral neuropathy, and lung involvement(109). It is important to emphasise that while the manifestations of SjS may not seem life-threatening, SjS is associated with an increased risk of complications such as venous thromboembolism(110,111) and chronic obstructive pulmonary disease(62), and an increased risk of lymphoma(112–114).

Treatments for SjS include topical therapies, and systemic ones such as hydroxychloroquine(115). Topical therapies for ocular dryness include lubricating drops (to replace tears), and steroid- or ciclosporin-containing drops or ointments to reduce inflammation. High fluoride toothpastes, fluoride-containing mouthwashes or gels, saliva substitutes (sprays, gels, or rinses), and xylitol-containing chewing gum can promote good oral hygiene and relieve oral dryness by replacing or stimulating saliva production. Oral pilocarpine may be used to stimulate ocular and systemic secretions(115).

SjS affects about nine-times as many females as males(116), with a peak incidence during the sixth decade(117). In data from BC, the incidence of SjS (in 2007) was 4.3 per-

100,000 PY and prevalence was 21.3 per-100,000 overall, and 54.4 per 100,000 females aged \geq 45 years(7). Prevalence estimates for pSjS vary with the reference standard: lower when based upon fulfillment of classification criteria (22 per-100,000), as compared to a physician-recorded diagnosis (103 per-100,000), since many of the requisite tests for evaluating the criteria are not performed(118).

1.3.3 Systemic sclerosis (SSc)

Systemic sclerosis (SSc) is characterised by vasculopathy (affecting the small arteries, arterioles, and capillaries), and thickening and fibrosis of the skin and internal organs. Vascular injury usually occurs first: the vessel cells proliferate, and collagen and other extracellular matrix components accumulate, thickening the vessel walls and reducing blood flow(119). As such, Raynaud's phenomenon (pain, loss of sensation, and cyanosis in the fingertips, resulting from cold- or stress-induced vasospasm(120)) is usually the first clinical sign of SSc. Fibrosis occurs from tissue hypoxia, and excess deposition of collagen and other extracellular matrix components into the tissues, mainly the skin, lungs, heart, gastrointestinal tract, and tendon sheath(119). The manifestations of this vasculopathy and fibrosis include skin thickening and hardening, digital ulcers and gangrene, arthralgia and joint contractures, gastrointestinal disease, lung fibrosis or interstitial lung disease, pulmonary arterial hypertension (PAH), cardiac fibrosis, and scleroderma renal crisis(121). SSc has two major subsets, limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc), which are classified based on the degree of skin involvement. lcSSc affects the skin below the knees and elbows (as well as the face and neck), while dcSSc affects the torso and upper portions of the limbs(121). Although dcSSc is the more severe form of the

disease, and associated with elevated mortality(122,123), patients with either subset can suffer from lung disease and severe gastrointestinal manifestations.

Unlike most SARDs, GC are not widely used in SSc, and may actually increase the risk of scleroderma renal crisis(124). Instead, treatment depends on the organ systems affected. ACE-II inhibitors should be used to treat scleroderma renal crisis, but are not recommended as a preventative therapy, while methotrexate is used to treat skin manifestations, and cyclophosphamide for interstitial lung disease(124). Treatments for SSc-associated PAH include endothelin receptor antagonists (i.e. ambrisentan, bosentan, and macitentan), phosphodiesterase-5 (PDE-5) inhibitors (i.e. sildenafil, tadalafil), prostacyclin analogues (i.e. epoprostenol, treprostinil), and riociguat, the first of a new class of drug that stimulates soluble guanylate cyclase(124)). Due to their vasodilating action, many of these therapies, along with calcium channel receptor antagonists like nifedipine, are also used to heal or prevent the development of digital ulcers, and reduce the impact of Raynaud's. As detailed more in Section 1.4, these therapies for PAH can cost as much or more than biologic therapies, with annual costs (for the drug alone) ranging from about \$7,000 for sildenafil(125,126) to \$47,000 for macitentan(125), riociguat(126), and brand-name bosentan(125). Patients with severe lung disease may also be considered for lung transplant(120).

SSc is much rarer than SLE, affecting between 21.3 per-100,000 adults (in 2007 in BC)(7) and 44.3 per-100,000 (in 2003 in Quebec)(12), where it was most prevalent among females over 45 years of age (161.2 cases per 100,000)(12). The mean age at onset is 35-50 years(120).

1.3.4 Polymyositis and dermatomyositis (PM/DM)

Polymyositis (PM) and dermatomyositis (DM) are characterised by muscle inflammation, weakness, and fatigue, usually in the neck, shoulders, pelvis, and thighs(127). In DM, a rash is also present. These disorders can occur on their own, or in conjunction with other SARDs including SLE, SSc, and SjS. PM/DM are thought to result from a combination of immune-mediated attack of muscle fibers and capillaries, and non-immune processes(127). The muscle weakness and fatigue can develop over weeks or months, will progress if left untreated(127), and about one-third of patients will experience long-term disability to a certain extent(128). Treatment starts with high-dose GC, often in conjunction with an immune-suppressant or immune-modulator(127,128), after which the GC dose can be tapered, and the immune-suppressant/modulator eventually replaced by methotrexate(127,128). PM/DM are associated with an increased risk of MI, CVA, and venous thromboembolism(44,45), and malignancy(129), with the risk of cardiovascular complications in PM(44,45), and malignancy in PM and DM(129), greatest at the time of diagnosis

The mean age of onset is 50-60 years for PM and 45-65 years for adult DM(127). The reported Canadian prevalence of PM/DM combined has ranged from 21.5 per-100,000 individuals(130) (in 2003 in Quebec) to 33.8 per-100,000(31) (in 2007 among non-Indigenous Albertans), with a higher prevalence in females. In the only Canadian study reporting incidence data(7), the incidence rates were 1.4 and 1.0 per-100,000 PY for PM and DM, respectively, in BC over 1996-2007.

1.3.5 Systemic vasculitides (SV)

The defining feature of the systemic vasculitides (SV) is inflammation and necrosis of the walls of specific blood vessels. SV are classified according to the size and type of vessel affected, and the presence or absence of anti-neutrophil cytoplasmic antibodies (ANCA), which form against antigens within certain white blood cells (neutrophils and monocytes)(15). While there are many forms of SV, the ANCA-associated SV described in this thesis include Granulomatosis with polyangiitis (GPA) and Eosinophilic granulomatosis with polyangiitis (EGPA), while the ANCA-negative forms include polyarteritis nodosa (PAN), giant cell arteritis (GCA), and Takayasu's arteritis.

1.3.6 Polyarteritis nodosa

Polyarteritis nodosa (PAN) is an ANCA-negative SV affecting the small and medium-sized muscular arteries. There are three subsets: idiopathic generalised PAN (affecting the skin, nervous and cardiovascular systems, abdominal organs, and renal arteries(14)), cutaneous PAN (affecting only the skin and surrounding muscles, joints, and nerves(131)), and one induced by the hepatitis B virus (HBV). In HBV-associated PAN, antibodies form immune complexes with the viral antigens and deposit in blood vessels(131), damaging them and leading to further inflammation and immune system activation(14). Newly-diagnosed patients are treated with GC, sometimes in combination with cyclophosphamide(131,132); to clear the immune complexes, HBV-associated PAN is treated with GC, antivirals, and plasma exchange(82,132).

PAN typically strikes between the ages of 40 and 60(14) and is one of the rarest SV(131), with a reported incidence of 0.9 per million(133) and prevalence of 31 per million(134,135).

However, the incidence and prevalence in BC in 2007 were slightly higher: 6 per million and 40 per million, respectively(7).

1.3.7 Giant cell arteritis (GCA) and Takayasu's arteritis (Takayasu's)

Giant cell arteritis (GCA) and Takayasu's arteritis (Takayasu's) are both large-vessel vasculitides that may actually be subsets of one disorder(136). GCA (also known as temporal arteritis) is the most common form of SV in adults over 50 years of age(137). There were about 17.3 prevalent cases per 100,000 BC adults of any age in 2007, including 30.8 cases per 100,000 adults ≥ 45 years of age(7). The mean age of onset is about 79 years, and it strikes at least twice as many females than males(17). Indeed, in 2007 the incidence in BC was 2.7 per 100,000 PY overall: 3.8 in females and 1.6 in males(7). Takayasu's predominantly strikes females between the ages of 20 and 40, though there is a less of a female predominance in Western countries than in Asia(138). Moreover, findings from a Japanese survey suggest there is no age predominance in males(139). The incidence and prevalence of Takayasu's in BC in 2007 was 0.4 and 1.7 per 100,000, respectively(7).

GCA affects the medium- and large-sized muscular arteries, including the aorta and its branches like the temporal artery. The classic symptom is new-onset, continuous, severe headache (usually over the temporal or occipital lobes), while the most serious initial manifestation is vision loss (stemming from occlusion of the ciliary or retinal arteries) which can become permanent(13). Temporal artery biopsy is considered the gold-standard for establishing the diagnosis(13), but false-negatives results do occur(140); thus, in an effort to prevent vision loss, treatment is often started before a biopsy is conducted or results are available(141). Some

of the long-term consequences of GCA are aortic dissection/aneurysm and neuropathies(13), but studies of population-based cohorts do not indicate there is a significantly increased risk of mortality(142).

In Takayasu's, immune-mediated destruction of the walls of the aorta and other major arteries (including the coronary, pulmonary, and renal arteries) leads to stenosis, thrombosis, and vessel aneurysm and rupture(138), which limits blood flow to the target organs. Major complications include aortic regurgitation, hypertension, brain ischaemia, ischaemic heart disease, and aneurysm(139), and a major cause of death is renovascular hypertension(138). Most patients have relapsing-remitting or progressive disease(17), and in a report from the Mayo Clinic(143), mortality was three-times higher in Takayasu's than the general population (absolute mortality of 3% after 10 years, and 14% after 15 years, among the 79 patients followed).

Upon diagnosis with GCA or Takayasu's, patients are prescribed high-dose GC (40-60 mg of prednisone per day) for at least the first month, sometimes in conjunction with low-dose aspirin, after which time the GC dose can be tapered if symptoms have resolved(144,145). However, especially in the case of relapse, methotrexate or immunosuppressants may also be required(144,145).

1.3.8 Granulomatosis with polyangiitis (GPA)

A key feature of Granulomatosis with polyangiitis (GPA), formerly known as Wegener's disease, is the presence of inflammatory granulomatous lesions(146). It impacts the small- and medium-sized vessels, including arteries, arterioles, veins, and capillaries. There are two subsets, localised or limited, which affects the upper respiratory tract, and systemic or diffuse, which affects the lungs, kidneys and other vital organs, resulting in lung nodules, alveolar haemorrhage, glomerulonephritis, and skin lesions and ulcerations(146). Upon diagnosis or relapse, patients are started on a regimen of immune-suppressing (GC plus cyclophosphamide or rituximab for up to six months(147)) or immune-modulating therapies (GC plus methotrexate(82,147) or mycophenolate(82) for at least 12 months) to induce remission. Maintenance therapy (low-dose GC plus an immune-modulator or rituximab) is continued for at least 18 months once patients have achieved remission(147). Unlike belimumab, rituximab was recommended for listing on Canada's public drug formularies(148), and public coverage for rituximab in BC is available for eligible GPA patients upon special request(149).

Mortality is most elevated within the first six months after diagnosis (~10%), mainly from treatment-related infections, and remains somewhat elevated over the longer-term, due to infection, malignancy, and renal and cardiovascular disease(16). Still, evidence suggests that mortality in GPA and other ANCA-associated vasculitides has improved over time(150). Patients who survive the initial period after diagnosis often suffer from the effects of permanent organ damage to the lungs, kidneys, and sinuses(16).

GPA tends to strike between the ages of 45 and 60(146), with no sex predominance. In 2007, the incidence in BC was 2.2 per 100,000 PY overall (2.0 among males and 2.5 among females), while prevalence was 10.3 per 100,000 (10.0 among males; 10.7 among females)(7).

1.3.9 Eosonophilic granulomatosis with polyangiitis (EGPA)

Eosonophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, affects the small-to-medium-sized vessels, including the arterioles, venules, and capillaries, and is almost always accompanied by severe asthma(151). Vascular inflammation and necrotising vasculitis in EGPA restricts blood flow to the organs and tissues, including the respiratory, cardiovascular, gastrointestinal, and peripheral nervous systems(151). EGPA is uncommon, with a prevalence of between 2.4 and 6.8(151) per million adults, but is more frequent among asthmatics (i.e. 64 per million asthmatics and 1.8 per million non-asthmatics(152)). GPA and EGPA are similar: both affect the small vessels and granulomas form in both, with asthma and eosinophilia being the distinguishing features of EGPA. As the two have the same billing codes, they cannot be distinguished in the administrative data, so I will not be reporting on the direct medical costs of EGPA separately from GPA.

1.4 Costs of treatments for SARDs

1.4.1 Prescription medication costs and coverage in British Columbia, Canada

One motivation for learning more about the direct medical costs of SARD patients at present is the high cost of treatments (and treatment strategies) now emerging for SARDs. In Canada, publicly-funded healthcare is available to all residents, regardless of ability to pay. Each of the country's 13 provinces and territories administer their own healthcare systems which

cover the costs of all medically-necessary inpatient and outpatient care upfront, but prescription medication coverage is incomplete and varies by province. Moreover, there is no publicly-funded coverage for healthcare products available without a prescription including, for example, aspirin and most eye drops and oral care products used by individuals with SjS.

Through a program called Fair Pharmacare(153), the BC Ministry of Health provides some coverage for prescription medication costs, on the basis of household income. Individuals are responsible for the full cost of their prescription medications until they reach their annual deductible, after which Pharmacare will cover 70-75% of eligible prescription costs. If a household's annual prescription spending goes on to exceed a certain, household income-based threshold, Pharmacare will cover 100% of eligible costs for the rest of the year(153). Biologics and other high-cost medications are also covered on a case-by-case basis. Beyond this assistance, any remaining costs are paid by individuals out-of-pocket, or by private (often employer-based) insurance plans that many purchase or receive as an employment benefit. Thus, the costs for SARD treatments at present, and any increases in costs, impact many different payers: patients, their families, employers, private insurers, and the public healthcare system.

1.4.2 Current and anticipated costs

The least expensive therapies used in SARDs are aspirin and GC, each of which cost less than \$10 (Canadian) for a 30-day supply in Canada(141) (excluding dispensing fees and any administration costs). Similarly, nifedipine(154) (main calcium channel blocker used in SSc), hydroxychloroquine, and azathioprine each cost less than \$25 per month, and methotrexate less than \$50 per month(81). The annual costs of these medications (again, excluding the dispensing

fee of approximately \$10 per-prescription) translate roughly to \$120 per-year for aspirin or GC, and \$300 per-year for nifedipine, hydroxychloroquine, or azathioprine.

Mycophenolate costs more, \$100 per-month, at minimum, for the drug alone(81), which translates roughly to \$1,200 per-year. Even still, the costs of the vasodilators used to treat digital ulcers and PAH in SSc, and the biologics indicated for use in SLE, GPA, and GCA, are considerably higher. According to CADTH, the **daily** cost for the different vasodilators ranges from \$19 for sildenafil(125,126) to \$27 for tadalafil(125,126), \$32 for generic bosentan(126), \$123 for ambrisentan(125,126), and \$128 for macitentan(125) and riociguat(126). Of note, bosentan recently went off patent, and the daily cost for brand-name bosentan is much higher, about \$128 per day(125). These daily costs translate roughly to \$6,935 per-year for sildenafil, \$9,855 for tadalafil, \$11,680 for generic bosentan, \$44,895 for ambrisentan, and \$46,720 per-year for macitentan, riociguat, and brand-name bosentan.

A four-week course of rituximab for the treatment of GPA costs about \$12,867, on-average(148), while cyclophosphamide, the alternative therapy, costs between \$128 and \$341 for a three-to-six month course of the oral formulation, and between \$115 and \$173(148) for the intravenous formulation. The biologic belimumab costs between \$18,018 to \$22,176 per-person during the first year of treatment for SLE, and \$15,616 to \$19,219 in subsequent years(104). Tocilizumab is still being reviewed by Canada's health technology assessment agency(155), but data from its other indications suggest it will cost approximately \$9,230 per-year, if administered every-other-week, and \$18,460 per-year if administered on a weekly basis(156).

Beyond their official indications, some of the above therapies are being investigated or used off-label for the treatment of other SARDs. These include rituximab(157,158) and belimumab(159) for SjS, rituximab for SLE(160,161) and SSc(162–164), and tocilizumab for Takayasu's(165) and possibly even PAN(166). Additional biologic therapies being considered or trialed for SARDs include abatacept for GCA(167) and Takayasu's(168), infliximab(169) for Takayasu's, and epratuzumab(170,171) and anifrolumab(172) for SLE, while two non-biologics, mycophenolate(173) and nintedanib(174), are being investigated for the treatment of interstitial lung disease in SSc. There is also growing interest in the use of autologous haematopoietic stem cell transplantation for severe, rapidly-progressing SSc(175–177). Making this option more widely available to Canadians would not only come at a high direct cost, but require considerable capital investment(177).

With this expanding use of biologics and other expensive therapies, the treatment costs of SARDs are likely to rise. Some of this cost increase may be worthwhile, if these treatments offer incremental health gains over existing therapies, or provide other benefits of value. One example is rituximab, which is more expensive than cyclophosphamide, and considered non-inferior for the treatment of GPA, but was recommended for listing by CADTH as a better option for patients who wish to preserve gonadal function or fertility(148). There may also be a decreased risk of malignancy with rituximab than with cyclophosphamide(178). But in order to allocate resources efficiently, decision-makers need high-quality evidence surrounding the economic burden of SARDs at the population level.

1.5 Direct medical costs in SARDs: a critical literature review

Due to the organ damage, complications, increased comorbidity rates, and adverse effects of the immune-modulating and immunosuppressive therapies needed to manage these chronic disorders, the direct medical costs of SARDs are likely substantial. I have summarised the published estimates of the all-cause (Table 1.1) and incremental or attributable (Table 1.2) direct medical costs of SARDs, as available in the peer-reviewed, English-language literature through September 2017, in Tables 1.1 and 1.2. All cost estimates in these tables have been standardised to 2013 Canadian dollars using exchange rates from the Bank of Canada(179) and the general component of the Canadian Consumer Price Index(180). To ensure comparability, these tables do not include estimates specific to children(181–183) or pregnant women(184), nor estimates that only include costs for a single healthcare component(185–191).

Even still, I located 45 studies with data on direct medical costs from 14 countries, with some including patients from multiple countries: Canada (n=7)(32–34,192–195), USA (n=22)(37,38,91,92,193,194,196–211), UK (n=6)(35,193,194,212–214), Germany (n=3)(213–215), Italy (n=3)(36,213,214), Sweden (n=3)(213,216,217), Hungary (n=2)(213,218), Spain (n=2)(213,214), France (n=2)(213,214), Hong Kong (n=2)(219,220), Taiwan (n=2)(221,222), South Korea(n=2)(223,224), Poland (n=1)(225), and Greece (n=1)(226) Thirty-two were on SLE(32,91,92,192–195,198,201–212,214–217,219–226), five on SSc(33,196,199,213,218), two were on SjS(35,227), two on PM/DM(34,197), and four reported on a form of SV(36–38,200). Three studies(200,215,216) reported only on the incremental or attributable costs of the SARD, and not the total (all-cause) medical costs incurred by SARD patients.

1.5.1 Research gaps

These estimates have been useful in raising awareness of the healthcare costs of patients with these little-known disorders, and major drivers and contributors of these costs. Higher costs were reported for SLE patients with flares(219) (especially severe flares(32,205,214)), renal(91,195,198,202,203,223,224,228) and neuropsychiatric(198,220) manifestations, and high levels of disease activity. In PM/DM(34), female sex and older age were associated with higher costs, and longer disease duration with lower costs, while in SjS(35), longer disease duration was associated with higher costs, as was poorer physical function. Moreover, studies that compared the costs of patients with different rheumatic diseases reported that hospitalisation rates were higher in SSc than in RA or psoriatic arthritis(218), and (early in the biologic era, at least), the healthcare costs of pSjS did not differ significantly from RA(35).

Still, there remain gaps in the literature that limit our understanding of the healthcare burden of SARDs, especially at the population-level. First, though some estimates of SjS, GCA, and GPA have emerged in recent years, the vast majority (32 of 45) were determined for SLE; there were only two studies of direct medical costs in each of SjS(35,227), PM/DM(34,197), and GCA(38,200), and one in each of GPA(37) and Takayasu's(36). Second, many estimates have been determined from small, clinic-based samples. A key advantage of clinic-based/disease registry data is the extent of clinical and patient-reported variables available. However, patients attending tertiary clinics may have more severe disease than patients followed by community-based providers, and these studies may only include patients who consent to participate. Thus, estimates from clinic-based cohorts are prone to selection bias. As well, since it can be hard to attribute healthcare utilisation to the patient's SARD, and these tertiary clinics and registries do

not usually collect comparable healthcare utilisation data on the general population, it is difficult (if not impossible) to determine the incremental burden of SARDs from these sources. Evidence suggests that computing only the costs of utilisation deemed attributable to the disease (i.e. only the costs of physician visits coded for the SARD, or for immune-modulating/suppressing medications) will underestimate the incremental healthcare costs imparted by a disease. The costs of complications associated with that disease, for example, will not be captured(229) using this approach. Administrative databases that capture healthcare utilisation from primary- and tertiary-care settings can be used to produce more comprehensive and generalisable estimates, though some databases cover only selected populations (i.e. the US Medicaid database(203,205), which covers only poor or disabled individuals, and the US Medicare database(208), which covers mainly those ≥ 65 years of age).

Third, most cost estimates for SARDs have been conducted on prevalent cohorts. These have limited generalisability since the costs of patients who consume a high level of healthcare resources around the time of diagnosis, and quickly succumb to the disease, will not be included. With prevalent cohorts, it is also difficult to determine the temporal relationship between many variables and costs. As detailed more in the Section 1.7, low socioeconomic status (SES) is associated with poorer clinical outcomes in SLE(230–235), and is likely associated with higher healthcare costs, but it may be unclear whether low SES contributed to poorer health (and higher costs), or resulted from it.

There is also a paucity of data on the long-term patterns of healthcare use and costs in SARDs, from the time of diagnosis-onwards, and in the years leading up to diagnosis. Such

information could inform those charged with health services delivery about the longitudinal patterns in costs or healthcare resource use, and guide the development of better models of care for SARDs. Knowledge of the healthcare utilisation and costs in the years leading to diagnosis could help evaluate the cost-effectiveness of emerging strategies to expedite diagnosis and initiation of treatment(236), and even slow(237) or prevent(236) their development via, for example, pre-emptive use of hydroxychloroquine. However, at the time of this writing, the longitudinal costs of SARDs had only been described in three reports: one on the costs of outpatient encounters and hospitalisations (but not prescription medications) for GCA patients before and after diagnosis(200), one on outpatient costs of SLE patients in the years leading up to diagnosis(191), and one on the costs of SLE patients for five years after diagnosis(203). The latter study, which was restricted to Medicaid beneficiaries, only assessed the costs of patients followed for the entire five years after diagnosis, and did not examine costs prior to diagnosis.

1.6 Productivity losses and costs in SARDS: a critical literature review

In addition to the increased levels of healthcare resource utilisation, the physical, psychological, and neurocognitive effects of SARDs also limit patients' participation in paid employment(238–245), family life(246–248), and other meaningful activities(249,250). Indeed, in earlier investigations of Canadian clinic-based cohorts, the lost productivity costs of SLE and SSc (monetary value of time lost from paid and unpaid work) exceeded direct medical costs by two- to three-fold(33,39,192). A systematic review and meta-analysis of 26 studies(238) reported that only 46% (95% CI: 40%-52%) of SLE were employed, while 34% (95% CI=24%-44%) were work disabled; what's more, these effects on productivity can strike early. For example, 21% of Chinese SLE patients became unable to work within two years of

diagnosis(251), and 22%(252) to 28%(241) of SSc patients (in Sweden and Canada, respectively) were work disabled within three years of diagnosis.

Building upon earlier reviews(253–255), I have tabulated the published estimates of the lost productivity costs of SLE in Table 1.3. For the other SARDs, I have tabulated the published (English-language) literature on productivity losses and costs through July 2017 (published(256) and summarised in Table 1.4), since, aside from two systematic reviews on productivity loss in SSc(257,258), and a narrative review on productivity loss in SV(259) (which only profiled two studies), these data have not been previously synthesised.

1.6.1 Research gaps

As with the literature on direct medical costs, these productivity studies have value, but are characterised by several limitations. Most estimates pertained to SLE; of 20 studies reporting lost productivity costs, 13 reported on SLE(39,91,192,209,211,212,215–217,219,220,224,243), five on SSc(33,199,213,218,260), one on SLE and SSc(261), and just one reported on the costs of SjS(262). There were no cost estimates for PM, DM, or any SV. Most were conducted on highly-selected, clinic based samples. This reduces their generalisability, and makes it difficult to determine the incremental productivity burden of SARDs over-and-above the general population. As well, although presenteeism (working, but at reduced level/efficiency) is a major driver of productivity loss, accounting for 41% of productivity costs in a study of Canadians with RA and OA(263), most estimates of paid work loss have only included absenteeism (i.e. hours or days of work missed).

Another issue has been the handling of productivity losses from unpaid work activities, including housework, yard work, child or elder care, studying, and volunteering. Some studies did not include unpaid work losses at all, while others have valued the time losses from unpaid work at a lower rate than paid work losses (replacement cost approach). From a societal perspective, there are costs associated with all forms of productivity loss, and such practices undervalue the economic contributions of work-disabled individuals (those unable to perform paid work, due to health) and those not-employed for other reasons, such as homemakers, students, and retirees. Eliciting unpaid work losses can also reveal the trade-offs some patients make between time spent on paid and unpaid work(264), and the resultant costs. Employment offers many benefits, and those with health impairments may continue in their paid work for personal and social rewards, to meet current financial needs, or remain eligible for pensions and insurance. But participation in paid work can leave them with limited time or capacity to complete household tasks, especially if their paid working tasks take longer to complete(264).

Finally, as with direct medical costs, there have been few longitudinal assessments of productivity costs and work cessation. Estimates of paid work loss from prevalent cohorts may be influenced by the ‘healthy-worker’ effect(265), wherein those with the greatest impairments died or left the paid workforce at an earlier time. Moreover, with cross-sectional studies of prevalent cohorts, it is unclear whether some of the main drivers of lost productivity (costs), including overweight(266)/increased body mass index(216), depression(266,267), and fatigue(241,266,268–271), contributed to productivity loss and work cessation, or developed afterwards (and perhaps even resulted from it). This, in turn, makes it difficult to identify factors that newly-diagnosed patients should modify to help preserve their productivity.

1.7 Impact of socioeconomic status on costs in SARDs

Better knowledge of the significant drivers (or predictors) of costs in SARDs may help reduce their burden if these drivers/predictors can be modified or addressed earlier-on. One potential driver in SARDs is socioeconomic status (SES), a known determinant of health status(272), healthcare costs(273), work disability(274), and mortality(275,276) in general populations. Some measures of SES include income level, educational attainment, occupation, and employment status. While these factors may not always be modifiable, evidence that lower-SES SARD patients are likely to have worse health or productivity outcomes, and incur higher costs, would at least provide the impetus to devote more resources towards reducing these disparities and costs.

Low SES (defined mainly as low education) has been associated with work disability or employment status in SLE(238), SSc(242,252,260,269), and SjS(277), though the impact of SES on productivity costs, especially those associated with presenteeism and unpaid work loss, is largely unknown. In SLE, there is a wide body of literature showing that low SES is associated with reduced access to specialist care(278), more avoidable hospitalisations(279), and higher levels of disease activity(230,280,281), damage(231,232,282,283), depressive symptoms(235), complications(234,284), and mortality(285–287). These associations have been observed across different countries, healthcare settings, and measures of SES including educational attainment(232,235,280,281), individual(231,234,235,282) and neighbourhood(235,285) income levels, and health insurance source/status(285). Beyond the financial barriers that low SES individuals may face in accessing healthcare (or health insurance), other mechanisms proposed for this relationship include higher levels of depressive symptoms or perceived stress(283)

among low-SES patients, and lower levels of social support or self-efficacy(288). The latter can impact health by decreasing one's ability to manage their disease, communicate effectively with their healthcare providers, or adhere to medical care(288).

As such, SES is likely a predictor of healthcare and productivity costs in SLE, but this has not been well-investigated, especially at the general population level. One study from the USA reported that higher neighbourhood income was associated with higher hospitalisation charges(186), and another, from South Korea(224), found that lower education was associated with lower direct (medical and nonmedical) costs, but income was not. Unfortunately, neither assessed the impact of SES at diagnosis, and little is known about the impact of SES on health outcomes or costs in other SARDs. Findings from one Canadian study of prevalent PM/DM(34), wherein patients in the highest income tertile had significantly-lower costs than others, suggest SES may be a significant driver of direct medical costs among the inflammatory myopathies. However, findings from a Canadian study of prevalent SSc(289), wherein low SES (defined as not completing high school) was not associated with mortality, suggests more investigation is needed. Prevalent cohorts make it hard to assess directionality. In the case of SES, lower levels of disease activity and higher levels of physical functioning have been predictive of work entry (becoming employed) in SLE(290). In turn, higher levels of depressive symptoms(290), and increases in disease activity and number of organ manifestations(291), have been predictive of work loss, which could reduce financial and social resources. Since early mortality is a feature of some SARDs, including SSc (5-year survival rate of 78%(123)) and GPA (1-year survival rates of 86%(292) to 88%(293); 5-year survival of 70%(294)), studies of prevalent cohorts are also subject to survival bias, with SES potentially having a different effect on those with longer

disease durations than those who succumb early-on. This could be why SES was not associated with mortality in the Canadian SSc cohort (mean disease duration 11.0 ± 9.5 years(289)).

Another unanswered question is how SES impacts the *incremental* costs of SARDs. Since low SES is associated with higher healthcare costs in the Canadian general population(273), low SES may well be associated with increased all-cause healthcare costs in SLE and other SARDs. However, knowledge of whether the incremental costs of SARDs differ across SES groups would inform policymakers about whether (and how much) the extra costs incurred by low-SES patients are the result of SARDs. This, in turn, could guide efforts to reduce socioeconomic disparities in health outcomes, and healthcare use and costs.

1.8 Summary of knowledge gaps and thesis objectives

Considering the intense inflammation and multiple systemic manifestations and complications of SARDs, their economic burden is likely considerable and complex. Of note, the treatment costs listed in Section 1.4 only included the costs of therapies used to manage the direct manifestations, and not the costs of other therapies used to prevent or manage the associated comorbidities and complications such as cardiovascular disease. The improvements in mortality over time and emergence of new therapies are positive developments, but do mean the economic impact of SARDs on healthcare systems and society is likely to increase alongside. More information on the current healthcare and lost productivity costs of individuals with SARDs, and key drivers and predictors of these costs, could help abate this burden. Specifically, this information could be used to develop better quality, more efficient models of care delivery for SARDs, identify and address disparities in healthcare and productivity outcomes and costs,

and make responsible, evidence-based decisions on the cost-effectiveness of new therapies and vocational interventions.

Unfortunately, our understanding of the long-term, population-level, incremental burden of SARDs is limited, especially in the Canadian setting. For example, there are no estimates of the incremental healthcare costs of any SARD in Canada, and transnational differences in healthcare delivery, labour practices, health and social insurance systems, and the cost and availability of medications, make it difficult to apply cost estimates from other countries.

In this thesis, I sought to address these research gaps by using administrative healthcare data from a single payer system (the province of British Columbia (BC), Canada), and prospectively-collected survey data from a sample of individuals in the administrative databases, to assess the **incremental economic burden** of SARDs at the **general population level**, and **impact of socioeconomic status** on costs. My specific objectives were to:

- (1) Determine the total and incremental healthcare use and costs of each SARD cohort during the first five years after diagnosis, from the public healthcare payer perspective **(Chapters 3 and 4)**;
- (2) Assess the total and incremental healthcare use and costs of SLE for the five years preceding diagnosis, from the public healthcare payer perspective **(Chapter 4)**;
- (3) Determine the total and incremental productivity losses and costs of SLE, SjS, and SSc, from the societal perspective **(Chapter 5)**;

- (4) Assess the impact of baseline socioeconomic status on the direct medical costs of SARDs, and impact of socioeconomic factors on productivity costs for SLE, SjS, and SSc (Chapters 3, 4, and 5).

1.9 Overview of thesis

This thesis is comprised of six chapters. Chapter 1, the current chapter, provides background knowledge about each SARD, and their current and prospective clinical, healthcare, and productivity impact. Within this chapter, I also review what is known from the published literature on the direct medical and productivity costs of SARDs, and determinants of costs. Chapter 2 outlines the main data sources and methods employed in addressing my research objectives, including the novel procedures used to collect survey data from a sample of individuals in the administrative databases.

Chapters 3, 4, and 5 are the analysis chapters. In Chapter 3, I use administrative health data from the province of BC to identify cohorts of BC residents newly-diagnosed with each of the nine SARDs over the years 1996-2010, and a comparison group (one for each SARD cohort), selected from a random sample of the BC population and matched on sex, age, and calendar-year of the SARD index date. From these data, I assess the mean all-cause direct medical costs for each SARD cohort during the first five years after diagnosis, and trends in these costs over time. I also determine the incremental direct medical costs of SARDs during this period (adjusted for covariates and unequal follow-up times) and assess the impact of low SES at diagnosis on these incremental costs.

In Chapter 4, I use this same data source to assess the year-to-year changes in the incremental costs of SLE during the five years leading up to diagnosis. To ensure five years of complete cost data for all individuals, this analysis was conducted only on SLE cases (and their matched non-SLE counterparts) diagnosed over the years 2001 through 2010. I also examine the impact of sex and SES on costs among SLE during this pre-index period.

In Chapter 5, I use the survey data collected from a subset of the population-based SARD and non-SARD cohorts to assess the incremental productivity losses and costs of the three most frequent SARD diagnoses, SLE, SjS, and SSc, and determinants of these costs.

Chapter 6 is a summary of the findings presented in this thesis, and key limitations and strengths of this work. In this final chapter I also describe the significance of my research contributions and their policy implications, and identify avenues for future research.

Table 1.1: Studies Reporting on the Total Direct Medical Costs of SARDs

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Poly/dermatomyositis								
Bernatsky(34)	2011	PM/DM	2003	1,102	Canada	administrative data	\$4,412	-
Furst(197)	2012	PM/DM	2003-2008	347	USA	administrative data	\$32,042	incident DM
				956			\$22,979	incident PM
				706			\$26,086	prevalent DM
				1,477			\$21,380	prevalent PM
Sjogren's syndrome								
Birt(227)	2017	SjS	2006-2011	10,414	USA	administrative data	\$22,117	-
Callaghan(35)	2007	SjS	2001	129	UK	clinic-based	\$6,118	-
Systemic Lupus Erythematosus								
Aghdassi(195)	2011	SLE	2004-2009	79	Canada	clinic-based	\$13,522	LN
				62			\$11,362	LNN
Bertsias(226)	2016	SLE		215	Greece	clinic-based	\$2,749	all
				67			\$5,118	severe
				148			\$1,676	non-severe
Carls(91)	2009	SLE	2000-2005	6,269	USA	administrative data	\$27,118	-
Chen(204)	2015	SLE	2007-2011	50,230	USA	administrative data	\$21,721	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Lupus Erythematosus								
Chiu(221)	2010	SLE	2000-2007	9,393	Taiwan	administrative data	\$1,715	year 2000
				15,463			\$1,965	year 2007
Chiu(222)	2016	SLE	2006-2010	22,258	Taiwan	administrative data	\$5,530	all incident cases
				3,738			\$3,438	no organ damage
Cho(224)	2014	SLE	2010-2011	201	South Korea	clinic-based	\$2,817	-
Clarke(192)	1993	SLE	1989-1990	164	Canada	clinic-based	\$9,434	year 1989
							\$11,563	year 1990
Clarke(193)	1999	SLE	1995-1997	229	Canada, USA, UK	clinic-based	\$7,179	Canada
				268			\$6,906	USA
				211			\$6,579	UK
Clarke(194)	2004	SLE	1995-2001	162	Canada, USA, UK	clinic-based	\$19,458	Canada, four-year cumulative
				157			\$24,860	USA, four-year cumulative
				166			\$21,671	UK, four-year cumulative

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Lupus Erythematosus								
Clarke(32)	2015	SLE	2007-2010	109	Canada	clinic-based	\$11,182	all
				56			\$15,862	severe
				53			\$6,237	non-severe
Doria(214)	2013	SLE	2008-2010	427	France, Germany, Spain, Italy, UK	clinic-based	\$5,204	all
				212			\$6,694	severe
				215			\$3,736	Non-severe
Furst(92)	2013	SLE	2003-2008	1,278	USA	administrative data	\$23,509	incident
				10,152			\$18,984	prevalent
Furst(198)	2013	SLE	2003-2008	907	USA	administrative data	\$41,031	LN
				1,062			\$37,193	NPSLE
Garris(207)	2013	SLE	2004-2008	2,990	USA	administrative data	\$34,430	two-year cumulative
Garris(208)	2015	SLE	2003-2007	6,707	USA	administrative data	\$19,368	-
Gironimi(201)	1996	SLE	1990-1991	174	USA	clinic-based	\$18,222	-
Jonsen(217)	2015	SLE	2003-2010	127	Sweden	clinic-based and administrative data	\$7,796	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Lupus Erythematosus								
Kan(205)	2013	SLE	2003-2009	14,777	USA	administrative data	\$43,199	-
Kan(206)	2013	SLE	2004-2011	178	USA	administrative data with clinical records	\$19,084	-
Li(203)	2009	SLE	1999-2005	2,298	USA	administrative data	\$20,538	Year 1
							\$19,585	Year 2
							\$23,218	Year 3
							\$27,090	Year 4
							\$30,457	Year 5
Narayanan(211)	2013	SLE	2004-2009	13,460	USA	administrative data	\$32,970	-
Oglesby(210)	2014	SLE	2000-2010	4,166	USA	administrative data	\$17,535	early SLE diagnosis
				4,166			\$22,577	late SLE diagnosis
Panopalis(209)	2008	SLE	2004-2005	812	USA	clinic-based	\$19,300	-
Park(223)	2015	SLE	2010	749	South Korea	clinic-based	\$3,588	-
Pelletier(202)	2009	SLE	2007-2008	15,590	USA	administrative data	\$15,265	all
				1,068			\$35,167	with nephritis
				14,522			\$13,801	without nephritis

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Lupus Erythematosus								
Śliwczyński(225)	2015	SLE	2008-2012	694	Poland	administrative data	\$796	year 2008
				878			\$889	year 2011
Sutcliffe(212)	2001	SLE	1995-1996	105	UK	clinic-based	\$7,681	-
Zhu(219)	2009	SLE	2005-2007	62	Hong Kong	clinic-based	\$21,538	with flare
				244			\$7,702	without flare
Zhu(220)	2009	SLE	2005-2007	306	Hong Kong	clinic-based	\$10,506	all
				83			\$15,721	NPSLE
				223			\$8,565	without NPSLE
Systemic Sclerosis								
Bernatsky(33)	2009	SSc	2007?	457	Canada	clinic-based	\$5,549	-
Furst(196)	2012	SSc	2003-2008	1,648	USA	administrative data	\$21,287	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Sclerosis								
Lopez-Bastida(213)	2016	SSc	2011-2013	147	Spain, Hungary, Germany, Italy, UK, Sweden, France	patient associations, disease registry	\$10,934	Spain
				38			\$1,575	Hungary
				65			\$22,433	Germany
				145			\$9,101	Italy
				24			\$10,276	UK
				23			\$12,803	Sweden
				147			\$10,959	France
Minier(218)	2010	SSc	2006?	80	Hungary	clinic-based	\$5,292	all
				20			\$6,261	dcSSc
				60			\$4,970	lcSSc
Wilson(199)	1997	SSc	1994	183	USA	administrative and patient-level data	\$9,719	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Systemic Vasculitis								
Babigumira(38)	2017	GCA	2008-2013	1,293	USA	administrative data	\$42,252	-
Krucichova(36)	2004	Takayasu's	1998-2000	67	Italy	clinic-based	\$7,195	all
				45			\$8,917	active
				26			\$2,343	inactive
Raimundo(37)	2015	GPA	2010-2013	2,784	USA	administrative data	\$42,638	12-month costs
				1,926			\$79,095	24-month costs

dcSSc=diffuse systemic sclerosis; DM=dermatomyositis; GCA=giant cell arteritis; GPA=Granulomatosis with polyangiitis;

lcSSc=limited cutaneous systemic sclerosis; LN=lupus nephritis; LNN=lupus nephritis-negative; NPSLE=neuropsychiatric lupus;

PM=polymyositis; SjS=Sjogren's syndrome; SLE=systemic lupus erythematosus; SSc=systemic sclerosis; UK=United Kingdom;

USA=United States of America

Table 1.2: Studies Reporting on the Incremental or Attributable Direct Medical Costs of SARDs

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall	Incremental ^a or Attributable ^b	Parameter
							Annual Mean Per-Patient Costs (2013 CDN)		
Poly/dermatomyositis									
Furst(197)	2012	PM/DM	2003-2008	347 DM; 1,041 non-DM	USA	administrative data	\$25,861	incremental	incident DM
				956 PM; 2,868 non-PM			\$16,931		incident PM
				706 DM; 2,118 non-DM			\$19,382		prevalent DM
				1,477 PM; 4,431 non-PM			\$14,909		prevalent PM
Sjogren's syndrome									
Birt(227)	2017	SjS	2006-2011	10,414	USA	administrative data	\$1,888	attributable	-
Callaghan(35)	2007	SjS	2001	129 SjS; 92 non-SjS	UK	clinic-based	\$3,463	incremental	
Systemic Lupus Erythematosus									
Bexelius(216)	2013	SLE	2011?	339	Sweden	clinic-based/patient-level	\$6,173	attributable	-
Carls(91)	2009	SLE	2000-2005	6,269 SLE; 6,269 non-SLE	USA	administrative data	\$17,018	incremental	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Incremental ^a or Attributable ^b	Parameter
Systemic Lupus Erythematosus									
Furst(92)	2013	SLE	2003-2008	1,278 SLE; 3,834 non-SLE	USA	administrative data	\$17,491	incremental	incident
				10,152 SLE; 30,456 non-SLE			\$12,664		prevalent
Furst(198)	2013	SLE	2003-2008	907 SLE; 2,721 non-SLE	USA	administrative data	\$34,476	incremental	LN
				1,062 SLE; 3,186 non-SLE			\$31,498		NPSLE
Garris(208)	2015	SLE	2003-2007	6,707 SLE and 13,414 non-SLE	USA	administrative data	\$11,736	incremental	-
Huscher(215)	2006	SLE	2002	844	Germany	national registry	\$5,799	attributable	-
Jonsen(217)	2015	SLE	2003-2010	127 SLE; 508 non-SLE	Sweden	clinic-based and administrative data	\$5,704	incremental	-

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall	Incremental ^a or Attributable ^b	Parameter
							Annual Mean Per-Patient Costs (2013 CDN)		
Systemic Lupus Erythematosus									
Kan(205)	2013	SLE	2003-2009	14,777 SLE; 14,262 non-SLE	USA	administrative data	\$11,319	incremental	-
Li(203)	2009	SLE	1999-2005	2,298 SLE; 2,298 non-SLE	USA	administrative data	\$8,722	incremental	Year 1
									Year 2
									Year 3
									Year 4
									Year 5
Narayanan(211)	2013	SLE	2004-2009	13,460 SLE; 13,460 non-SLE	USA	administrative data	\$6,224	incremental	-
Oglesby(210)	2014	SLE	2000-2010	4,166	USA	administrative data	\$2,697	attributable	early SLE diagnosis
				4166			\$3,544		late SLE diagnosis
Pelletier(202)	2009	SLE	2007-2008	1,068	USA	administrative data	\$7,451	attributable	LN
				14,522			\$2,855		LNN

First Author	Year of Publication	Diagnosis	Years of Data Collection	N Patients	Country	Data Source	Overall Annual Mean Per-Patient Costs (2013 CDN)	Incremental ^a or Attributable ^b	Parameter
Systemic Sclerosis									
Furst(196)	2012	SSc	2003-2008	1,648 SSc; 4,944 non-SSc	USA	administrative data	\$14,535	incremental	-
Systemic Vasculitis									
Babigumira(38)	2017	GCA	2008-2013	1,293 GCA; 6,465 non-GCA	USA	administrative data	\$20,380	incremental	-
Koster(200)	2017	GCA	1987-2017	147 GCA; 147 non-GCA	USA	administrative data	median=\$5,050	incremental	cumulative median difference in costs over five years
Raimundo(37)	2015	GPA	2010-2013	2,784	USA	administrative data	\$25,046	attributable	12-month costs
				1,926			\$46,078		24-month costs

dcSSc=diffuse cutaneous systemic sclerosis; DM=dermatomyositis; GCA=giant cell arteritis; GPA=Granulomatosis with polyangiitis;

lcSSc=limited cutaneous systemic sclerosis; LN=lupus nephritis; LNN=lupus nephritis-negative; NPSLE=neuropsychiatric lupus;

PM=polymyositis; SjS=Sjogren's syndrome; SLE=systemic lupus erythematosus; SSc=systemic sclerosis; UK=United Kingdom;

USA=United States of America

^aIncremental costs are the differences in mean per-person all-cause direct medical costs between those with and without a SARD (with or without adjustment for covariates)

^bAttributable costs are the mean per-person costs only for healthcare utilisation that was deemed SARDs-related

Table 1.3: Studies Reporting on the Lost Productivity Costs of Systemic Lupus Erythematosus

First Author	Year of Publication	Years of Data Collection	N Patients	Country	Study Population	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Bexelius (216)	2013	2011?	339	Sweden	clinic-based/patient-level	\$20,831	-
Campbell (243)	2009	2001	198 SLE; 299 non-SLE	USA	clinic-based	\$9,938	overall
						\$8,480	incremental
Carls (91)	2009	2000-2005	140 SLE; 140 non-SLE 260 SLE; 260 non-SLE	USA	administrative data	\$4,820	overall-absenteeism
						\$3,118	overall-STD
						-\$1,428	incremental-absenteeism
						\$4,512	incremental-STD
Cho (224)	2014	2010-2011	201	South Korea	clinic-based	\$5,129	-
Clarke (192)	1993	1989-1990	164	Canada	clinic-based	\$11,075	year 1989
						\$11,672	year 1990
Huscher (215)	2006	2002	844	Germany	national registry	\$11,845	FCA
						\$26,190	HCA

First Author	Year of Publication	Years of Data Collection	N Patients	Country	Study Population	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Jonsen(217)	2015	2003-2010	127 SLE; 508 non-SLE	Sweden	clinic-based and administrative data	\$20,399	overall
						\$13,122	incremental
Kawalec(261)	2015	2012	1,600	Poland	administrative data	\$5,884	Gross Domestic Product per capita
						\$14,169	Gross Value Added per worker
						\$4,333	Gross Income per worker
Narayanan(211)	2013	2004-2009	756 SLE; 756 non-SLE	USA	administrative data	\$1,745	overall absenteeism
						\$2,181	overall STD
						\$794	incremental absenteeism
						\$1,113	incremental STD
Panopalis(39)	2007	1995-2001	231	Canada, USA, UK	clinic-based	\$54,151	Canada
			269			\$76,129	USA
			215			\$62,364	UK
Panopalis(209)	2008	2004-2005	651	USA	clinic-based	\$13,210	-
Sutcliffe(212)	2001	1995-1996	105	UK	clinic-based	\$15,577	-

First Author	Year of Publication	Years of Data Collection	N Patients	Country	Study Population	Overall Annual Mean Per-Patient Costs (2013 CDN)	Parameter
Zhu(219)	2009	2005-2007	62	Hong Kong	clinic-based	\$7,349	with flare
			244			\$6,263	without flare
Zhu(220)	2009	2005-2007	306	Hong Kong	clinic-based	\$6,483	all
			83			\$8,758	NPSLE
			223			\$5,636	without NPSLE

FCA=friction cost approach; HCA=human capital approach; NPSLE=neuropsychiatric lupus; SLE=systemic lupus erythematosus;

STD=short-term disability; UK=United Kingdom; USA=United States of America

Incremental costs are the differences in mean per-person lost productivity costs between those with and without a SARD (with or without adjustment for covariates)

Table 1.4: Studies Reporting on the Productivity Losses and Costs of SARDs (excluding SLE)

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Polymyositis/Dermatomyositis (PM/DM)																
Regardt, 2016(295)	2012	Sweden	cross- sectional	self-report questionnaire or in-person interview	clinic-based	none	48: 23 DM and 25 PM	29 (60%)	54 (10)	9 (9)	12/48=25% on full-time sick leave, 21/48=44% working full- time, 15/48=31% working part-time	-	-	-	-	-
Rice, 2016(296)	1998-2014	United States	cross- sectional	healthcare and disability insurance claims	commercial health insurance beneficiaries aged 18-64 years	sample of beneficiaries without a diagnosis of PM or DM	611 PM/DM and 611 non- PM/DM	64% <i>among whole cohort, while disability data were only available for a subset</i>	49.4 (10.6) <i>among whole cohort, while disability data were only available for a subset</i>	n/a?	-	medically- related absenteeism: 10.7 days per-year for PM/DM vs. 9.5 for non- PM/DM disability leave: 6.8 days for PM/DM vs.	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
												6.0 for non-PM/DM total work loss: 17.5 days per-year for PM/DM vs. 15.5 for non-PM/DM				
Sjogren’s syndrome (SjS)																
Bowman, 2010(262)	2003-2005	United Kingdom	cross-sectional	self-report questionnaire	clinic-based	clinic-based sample of patients with RA; patients without SjS or RA recruited from a local general practitioner	84 pSjS, 87 RA, and 96 non-SjS	84 (100%)	60 (11)	7 (7)	26/84=31% of SjS and 68/96=71% of non-SjS employed (mean 26.7 and 33.3 hours worked per week); 15% of SjS and 49% of	annual mean hours of missed work: 35.8 (95% CI: - 3.3 - 74.9) for SjS and 22.5 (6.9 - 38.1) for non-SjS;	-	annual mean hours of household work loss: 146.3 (70.2 – 222.4) for SjS and 35.1 (-3.7 – 74) for non-SjS;	annual time losses from paid work: £6,155 to £11,612 for SjS and £540 to £2,937 for non-SjS; annual time losses from household work: £1,376	annual time losses from paid work: \$13,000 to \$24,525 for SjS and \$1,141 to \$6,203 for non-SjS; annual time losses from household work: \$2,906 to \$3,686 for SjS and \$697 to \$893 for non-SjS; annual time losses from paid work for carers: \$308

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											non-SjS employed full-time (mean 35.0 and 39.0 hours worked per week)	annual mean hours of missed work for carers: 10.5 (2.3 – 18.7) for SjS and 1.6 (-0.3 – 3.4) for non-SjS			to £1,745 for SjS and £330 to £423 for non-SjS; annual time losses from paid work for carers: £146 for SjS and £22 for non-SjS [2008 British pounds]	for SjS and \$46 for non-SjS
Mandl, 2017(297)	2001-2012	Sweden	Longitudinal	sick leave and disability pensions paid by the Swedish Social Insurance Agency	clinic-based	matched sample of the Swedish general population	51 pSjS and 204 non-SjS	50 (98%)	45.6 (11.3)	n/a (incident cohort)	26% WD at SjD diagnosis; RR (vs. general population) =1.30 (95% CI: 0.74-2.28)	at diagnosis: 6.2 days of sick leave or disability pension per-month; at 12 months: 9.2	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											37% WD at 12 months after diagnosis; RR=1.47 (0.83-2.61)	days per-month; at 24 months: 10.2 days per-month				
											41% WD at 24 months after diagnosis; RR=2.10 (1.34-3.30)					
Meijer, 2009(277)	n/a?	Netherlands	cross-sectional	self-report questionnaire	clinic-based	age- and sex-specific Dutch population data	195: pSjS=154 sSjS=41; 135 of working age: pSjS=109 and sSjS=26	179 (92%)	55.5 (15.0)	9.7 (8.8)	63/135=47% of SjS, 49/109=45% of pSjS and 14/26=54% of sSjS (vs. 2% of general population), receiving	15.6±39 days of sick leave per year, 14.7±37.8 for pSjS and 22.3±50.0 for sSjS	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											disability benefits; 69/135=51% were employed, 58/109=53% of pSjS and 11/26=42% of sSjS (vs. 83% of non-SjS)					
Segal, 2009(267)	2007	United States	cross-sectional	self-report questionnaire	clinic-based	unrelated friends (same sex and age) of patient members of the Sjogren’s Syndrome Foundation	277 pSjS and 606 non-SjS	90%	62 (12.6)	9.0 (8.4)	12% of SjS and 0% of non-SjS not employed due to disability	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Westhoff, 2012(268)	2009-?	Germany	cross-sectional	questionnaire	clinic-based	friends of the SjS cohort, of same sex and similar age	128 pSjS and 84 non-SjS	128 (100%)	50.2 (9.4)	n/a?	10.4% of SjS and 1.5% of non-SjS employed but on sick leave (p < 0.01); 28.3% of SjS and 10.7% of non-SjS retired early (p < 0.01)	19.8±30.6 days for SjS and 4.5±9 for non-SjS over past 6 months	-	-	-	-
Systemic Sclerosis (SSc)																
Bérezné , 2011(298)	2008-2009	France	cross-sectional	self-report questionnaire	clinic-based and French SSc patient association	none	189	164 (87%)	54.1 (13.3)	9.3 (8.4)	36/113=32% of working-age receiving full disability pension	-	mean SSc-related decrease in productivity of 3.4±3.8 over the past month (range 0-10)	mean hours of SSc-related household help per-month: paid=4.0 ±13.5	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
														(8.0±21.5 for those with DU and 2.0±6.3 for those without DU); unpaid=9.0 ±27 (18.7±40.8 for those with DU and 4.0±15 for those without DU)		
Bernatsky, 2009(33)	2007?	Canada	cross-sectional	self-report questionnaire	clinic-based	none	457: lcSSc=272 dcSSc=185	401 (88%)	55.1 (12.1)	10.5 (8.6)	-	-	-	-	\$13,415 overall (\$5,345 from paid work and \$8,070 from unpaid); \$11,277 for lcSSc (\$4,101	\$14,775 overall (\$5,887 from paid work and \$8,888 from unpaid); \$12,420 for lcSSc (\$4,517 from paid work and \$7,903 from unpaid);

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
															from paid work and \$7,176 from unpaid); \$16,416 for dcSSc (\$7,092 from paid work and \$9,324 from unpaid) [2007 CDN]	\$18,080 for dcSSc (\$7,811 from paid work and \$10,269 from unpaid)
Decuman, 2012(299)	2008-2009	Belgium	cross-sectional	self-report questionnaire	clinic-based	none	84	64 (76%)	47.8 (8.9)	56.5 months	47/84=56% made a work transition due to health: 34/84=40% stopped working, 13/84=15% reduced hours and/or changed jobs	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Hudson, 2009(241)	2004-2008	Canada	cross-sectional	self-report questionnaire	clinic-based	none	365	83%	WD: 50.2 (8.2); non-WD: 48.4 (9.4)	WD: 11.0 (8.6); non-WD: 9.0 (7.7)	133/365=36 % of working-age participants; 133/643=21 % of all participants	-	-	-	-	-
Kawalec, 2015(261)	2012	Poland	cross-sectional	sick leave and disability pensions paid by the Social Insurance Institution of Poland	population-based sample, from among virtually all working patients in the country	population-based samples of SLE and sarcoidosis	500	n/a?	n/a?	n/a?	-	-	-	-	€341 (Gross Income per worker); €4537 (Gross Domestic Product); €10,927 (Gross Value Added) [2012 Euros]	\$4,332 (Gross Income per worker); \$5,883 (Gross Domestic Product); \$14,168 (Gross Value Added)
López-Bastida, 2016(213) ^a	2011-2013	France, Germany, Hungary, Italy, Spain, Sweden,	cross-sectional	self-report questionnaire	national and regional patient associations, and Spanish	none	589 SSc and 57 carers	n/a?	50 (range 45-54)	n/a?	-	-	-	=	<u>Caregivers' time:</u> France: €1,875, Germany: €94,	<u>Caregivers' time:</u> France: \$2,431, Germany: \$770, Hungary: \$1,361, Italy: \$3,646, Spain: \$6,073, Sweden: \$0, UK: \$4,878

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
		United Kingdom			rare diseases registry										Hungary: €1,050, Italy: €2,812, Spain: €4,684, Sweden: €0, UK: €3,762 <u>Sick Leave:</u> France: €1,501, Germany: €1,369, Hungary: €20, Italy: €790, Spain: €1,445, Sweden: €2,558, UK: €4,912 <u>Early Retirement:</u> France: €8,123, Germany:	France: \$1,946, Germany: \$1,775, Hungary: \$1,469, Italy: \$1,024, Spain: \$1,874, Sweden: \$3,317, UK: \$6,369 <u>Early Retirement:</u> France: \$10,532, Germany: \$13,656, Hungary: \$2,906, Italy: \$1,181, Spain: \$7,822, Sweden: \$0, UK: \$12,359

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
															€0,532, Hungary: €2,241, Italy: €11, Spain: €6,033, Sweden: €0, UK: €0,532 [2012 Euros]	
Mau, 2005(245)	1993-2001	Germany	cross-sectional	self-report questionnaire	clinic-based	German population data	802	667 (83%)	47 (10)	n/a?	SER=0.77 (0.85 for males and 0.75 for females); adjusted RR for employment (vs. RA reference group) of 0.98 (disease duration ≤ 5 years) and	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											1.03 (disease duration > 10 years)					
Minier, 2010(218)	2006?	Hungary	cross-sectional	self-report questionnaire	clinic-based	clinic-based samples of patients with RA and PsA	80: 60 lcSSc and 20 dcSSc	72 (90%)	57.4 (9.6)	6.2 (6.6)	39/80=49% receiving disability benefits (vs. 35% of RA and 25% of PsA)	-	-	-	mean annual informal care: €246 overall, €197 for lcSSc and €393 for dcSSc mean annual disability pension: €5,305 overall, €5,025 for lcSSc and €6,142 for dcSSc	mean annual informal care: \$395 overall, \$316 for lcSSc and \$630 for dcSSc mean annual disability pension: \$8,508 overall, \$8,059 for lcSSc and \$9,850 for dcSSc mean annual sick leave: \$136 overall, \$178 for lcSSc and \$13 for dcSSc

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
															mean annual sick leave: €85 overall, €111 for lcSSc and €8 for dcSSc total lost productivity costs (sick leave and pension): €390 overall, €134 for lcSSc and €150 for dcSSc [2006 Euros]	total lost productivity costs: \$8,644 overall, \$8,237 for lcSSc and \$9,863 for dcSSc

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Morrisroe, 2016(300)	2007-2015	Australia	cross-sectional	self-report questionnaire	clinic-based	Australian population data	802	670 (84%)	employed: 50.4±10.7; not employed: 51.9±10.4	employed: 9.6±9.0; not employed: 11.1±10.9	160/802=20% not employed	-	-	-	-	-
Nguyen, 2010(301)	2007	France	cross-sectional	self-report questionnaire	clinic-based and French SSc patient association	none	87	72 (83%)	48.6 (8.5)	8.1 (6.4)	53/87=61% on full-time sick leave; 31/87=36% receiving disability benefits	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Ouimet, 2008(242)	2002-2003	Canada	cross-sectional	self-report questionnaire	clinic-based	clinic-based sample of patients with RA	61: 35 lcSSc and 26 dcSSc	52 (85%)	52.0 (1.2)	11.0 (1.2)	34/61=56% overall (95% CI: 43%-68%), vs. 36/104=35% (26%-44%) of RA 17/26=65% of dcSSc, 17/35=49% of lcSSc	-	-	-	-	-
Sandqvist, 2008(270)	n/a?	Sweden	cross-sectional	patient interview	clinic-based?	none	44 lcSSc	44 (100%)	median 52 (range 24-60)	median 8 (range 2-44)	23/44=52% on full or partial sick leave: 15/44=34% partial and 8/44=18% full sick leave or disability	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Sandqvist, 2010(271)	2008	Sweden	cross-sectional	self-report questionnaire	clinic-based?	none	57: 47 lcSSc and 10 dcSSc	53 (93%)	median 58 (IQR 47-62)	median 14 (IQR 9-19)	41/57=72% on full or partial sick leave: 20/57=35% partial and 21/57=37% on full sick leave or disability	-	-	-	-	-
Sandqvist, 2015(252)	2003-2009	Sweden	longitudinal	sick leave and disability pensions paid by the Swedish Social Insurance Agency	clinic-based	matched sample of the Swedish general population	32 SSc and 128 non-SSc	26 (81%)	median 48 (IQR=43-53)	n/a (incident cohort)	7/32=22% full-time WD after three years (4/8=50% of dcSSc and 3/24=13% of lcSSc); compared to reference group, OR for WD was	mean of 103±130 full or partial days for lcSSc over the first three years, and 190±151 for dSSc	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											0.95 (95% CI: 0.39-2.33) at baseline, 2.09 (1.17-3.73) after one year and 2.41 (1.28-4.55) after three years					

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Sharif, 2011(269)	1998-?	United States	Longitudinal	patient questionnaire	clinic-based	none	255	212 (83%)	non-WD at baseline: 45.3±13.0, WD at baseline: 50.9±12.5	non-WD at baseline: 2.41±1.61, WD at baseline: 2.71±1.57	124/255=49% working-age were WD at baseline; 35/131=27% became disabled, after mean 4.4±3.8 years of follow-up	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Singh, 2012(260)	2010?	United States	cross-sectional	self-report questionnaire	clinic-based	none	162	131 (81%)	51.8 (14.2)	7.6 (8.2)	39/162=24% WD due to SSc; 10/43=23% of lcSSc and 24/46=52% of dcSSc	mean 2.5±6.1 days of ≤ 50% productivity among all employed (n=60), 2.6±6.3 days per month among all employed (n=60), 3.5±7.8 for lcSSc and 1.5±2.9 for dcSSc; 24/60=40% missed ≥ 1 work day per month; 2.1±3.0 for lcSSc and 2.7±2.9 for dcSSc;	mean among all employed (n=60), 3.4±7.5 for lcSSc and 1.2±2.6 for dcSSc; mean 2.2±2.9 days where SSc interfered with productivity among all employed, 2.1±3.0 for lcSSc and 2.7±2.9 for dcSSc;	8.0±10.6 household work days missed among all, 6.2±9.4 for lcSSc and 10.9±11.8 for dcSSc, 8.9 for employed and 6.4 for not employed; 6.0±9.7 days of ≤ 50% productivity for household work among all, 5.5±9.5 for lcSSc and 7.3±10.7 for dcSSc;	mean income loss of \$897 (range \$127 to \$2,792) per month (\$10,764 annually) from absenteeism; \$3,577 ±\$1,303 per month (\$42,924 annually) for WD [2010 USD]	mean income loss of \$974 per month (\$11,686 annually) from absenteeism; \$3,883 per month (\$46,599 annually) for WD

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
														2.0±5.0 days with hired help, 1.4±4.0 for lcSSc and 2.7±6.2 for dcSSc 4.0±3.4 days where SSc interfered with household work productivity among all, 3.4±3.3 for lcSSc and 5.1±3.5 for dcSSc		

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Wilson, 1997(199)	n/a? (~1974-?)	United States	cross-sectional	self-report questionnaire	clinic-based	none	183	86%	n/a?	n/a?	18.8% on disability or sick leave	mean 2.1 days of paid work lost each year	-	mean 11.8 days of unpaid work (among unemployed) lost per year	mean total indirect costs of \$10,228 (\$8,392 for morbidity and \$1,835 for mortality); males: \$10,149 overall (\$8,393 for morbidity and \$1,756 for mortality); females: \$10,254 overall (\$8,392 for morbidity and \$1,862 for mortality) [1994 USD]	mean total indirect costs of \$20,026 (\$16,431 for morbidity and \$3,593 for mortality); males: \$19,871 overall (\$16,433 for morbidity and \$3,438 for mortality); females: \$20,077 overall (\$16,431 for morbidity and \$3,646 for mortality)

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
Systemic Vasculitis (SV)																
Basu, 2014(266)	n/a?	United Kingdom	cross-sectional	self-report questionnaire	clinic-based	none	208: 144 GPA, 40 MPA, 22 EGPA	109 (52.4%)	51.1 (12.3)	n/a?	54/208=26% not working due to health	-	-	-	-	-
Barra, 2016(302)	2012-2014	Canada	cross-sectional	self-report questionnaire	clinic-based	none	103: 32 GPA, 12 EGPA, 5 MPA, 24 GCA, 2 Takayasu's, 7 IgA vasculitis, 6 PAN, 4 Behcet's disease, 3 cryoglobulin aemic vasculitis, 2 hypocomplementemic urticarial vasculitis, 1 secondary vasculitis, 5	60%	58 (17)	4 (4)	22/103=21% (22/51=43% of working age) were WD due to SV: not working (n=13), early retirement (n=3), or working reduced hours (n=6)	-	mean work productivity loss due to health (measured by WLQ): 8.2%	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
							unclassifiabl e									
Boomsma, 1999, 2002 (244,303) ^b	n/a? (~1998)	Netherlands	cross-sectional	self-report questionnaire	clinic-based	clinic-based sample of patients with SLE	79 GPA	35 (44%)	60 (range 27 to 90)	median 5 years (range 0 to 25)	27% receiving disability benefits	-	-	-	-	-
Hoffman, 1998 (304)	n/a? (~1997)	United States	cross-sectional	self-report questionnaire	clinic-based	none	60 GPA	47%	54 (range 17-84)	median 5 years (range < 1 to 33)	11/35=31% of once-employed receiving disability benefits	-	-	-	-	-
Mau, 2005 (245)	1993-2001	Germany	cross-sectional	self-report questionnaire	clinic-based	German population data	385 GPA	189 (49%)	46 (11)	n/a	SER=0.76 (0.74 for males and 0.79 for females); adjusted RR for employment (vs. RA reference group) of 0.83 (disease	-	-	-	-	-

Study Characteristics							Characteristics of Study Population				Productivity Outcomes					
First Author, Year	Study Year(s)	Country	Design	Data Source	Study Population / Recruitment Source	Comparison Group	N Participants	N (%) Female	Mean (SD) Age, years	Mean (SD) Disease Duration, years	Work Disability (WD)	Paid Work Losses: Absenteeism	Paid Work Loses: Presenteeism	Unpaid Work Losses	Costs (as reported)	Costs (2013 CDN)
											duration ≤ 5 years) and 0.62 (disease duration > 10 years)					
Reinhold-Keller, 2002(305)	1996	Germany	cross-sectional	self-report questionnaire	clinic-based	none	60 GPA	34 (57%)	median 36 (range 17 to 48)	median 39 months (range 0 to 228)	16/60=27% unemployed due to GPA	median 14 workdays lost over past 12 months (range 0 to 18)	-	-	-	-

^aThis article reported on costs from each of the seven European countries that participated in this study. The findings from Spain(306) and France(307) are also reported separately.

^bData from one study were reported across two manuscripts

95% CI: 95% confidence interval; dcSSc=diffuse systemic sclerosis; DU=digital ulcers; EGPA= Eosinophilic Granulomatosis with polyangiitis (Churg-Strauss syndrome); GCA=giant cell arteritis; GPA=Granulomatosis with polyangiitis; IQR=interquartile range; lcSSc=limited cutaneous systemic sclerosis; MPA=Microscopic polyangiitis; PsA=psoriatic arthritis; pSjS=primary Sjogren’s syndrome; PAN=polyarteritis nodosa; RA=rheumatoid arthritis; RR=relative risk; SER=standardised employment ratio; SLE=systemic lupus erythematosus; sSjS=secondary Sjogren’s syndrome; WLQ=Work Limitations Questionnaire

2. Methods²

In this thesis, I used administrative health data to identify cohorts of prevalent SARDs residing in the province of British Columbia (BC), Canada, the third most-populous province in the country, at any time during the years 1996 through 2010. From these data, I also established a matched comparison group for each SARD cohort, selected from a random sample of the BC population. For my analysis of direct medical costs, I captured healthcare utilisation data for the SARD and non-SARD cohorts from the provincial administrative data. These databases did not contain information on productivity, so I collected this information from a sample of these cohorts using a survey. I start this chapter by describing the administrative databases (Section 2.1) and how the population-based cohorts were identified (Section 2.2). In Sections 2.3 to 2.5, I describe how I analysed direct medical costs from the administrative data. In Section 2.6, I outline the procedures used to recruit a sample of the population-based SARD and non-SARD cohorts for the productivity survey, while in Section 2.7, I describe the components of the survey itself. Detailed information on how I analysed the survey data, and my findings on productivity costs, are reported in Chapter 5.

² A portion of this chapter has been published:

McCormick N, Reimer K, Famouri A, Marra CA, Aviña-Zubieta JA. Filling the gaps in SARDs research: collection and linkage of administrative health data and self-reported survey data for a general population-based cohort of individuals with and without diagnoses of systemic autoimmune rheumatic disease (SARDs) from British Columbia, Canada. *BMJ Open*. 2017 Jun 21;7(6):e013977.

2.1 Data source

The administrative data were sourced through Population Data BC, which uses population-based linkable administrative data files to capture provincially-funded/administered health care utilisation for virtually all BC residents. Healthcare systems in Canada are publicly-funded, with each of the country's 13 provinces and territories responsible for financing and administering their own systems. These are funded by the provinces/territories themselves, and by transfer payments from the federal government. All eligible BC residents and their dependents (including Canadian citizens, permanent residents, and those holding ≥ 6 -month study or work permits who live in BC) must enroll in the BC Medical Services Plan (MSP)(308). This entitles them to full, first dollar coverage (without co-payment) for all medically-necessary hospital and physician services, including outpatient medical visits, interventions, and investigations. The maximum monthly premium was \$75 per-adult in 2017 (in January 2018, this decreased by half, to \$37.50 per-month), and financial assistance is available(308). Moreover, while residents must pay out-of-pocket for non-medically-necessary items such as cosmetic procedures, and for most visits to allied health professionals, nearly all physician and hospital care are provided through the public system. A small number of elective surgeries are performed in privately-operated surgical centres, but there are no privately-operated acute-care hospitals. Thus, through these linked data, healthcare utilisation records are available for virtually all BC residents (population of approximately 4.6 million in the year 2013, with about 3.6 million adults(309)), though coverage for First Nations individuals (about 5% of the population(310)) is more limited. The exceptions are members of the Canadian Armed Forces, inmates of federal correctional facilities, and members of the Royal Canadian Mounted Police, all of whom receive healthcare coverage through the federal government(308). Numerous general population-based

studies have been successfully conducted using these databases(42,311–315). All inferences, opinions, and conclusions drawn in this thesis are mine, and do not reflect the opinions or policies of the Data Steward(s).

The linked healthcare utilisation datasets used in this thesis included the Medical Services Plan Payment Information File(316), the Discharge Abstract Database(317), and PharmaNet(318). These healthcare utilisation datasets were linked with demographic(319) and vital statistics data(320). Additional details about these datasets are provided in the paragraphs below. Population Data BC used Personal Health Numbers to link these data at the individual level, then released them in de-identified form, with health numbers and any other potentially-identifying information removed. Participant consent was not required for the analysis of direct medical costs, since it was conducted solely from the de-identified, routinely-collected administrative data. Ethical approval was granted by the Behavioural Research Ethics Board of The University of British Columbia (# H12-03093).

2.1.1 Medical Services Plan Consolidation File

This dataset contained demographic data for each individual, including their sex, date of birth, date their MSP enrollment started (if not continuously enrolled), number of days of MSP enrollment each year, and Forward Sorting Area (first three digits of the postal code of the address they had registered with MSP each year)(321). Through geographic coding, Population Data BC used this address to determine the health service delivery area, census division, and neighbourhood income level of each individual each year they were enrolled with MSP(321).

These data were also linked to the vital statistics files, which contained data on the date and cause of death for all deaths within BC(322).

2.1.2 Medical Services Plan Payment Information File (MSP)

This dataset contained records of provincially-funded outpatient medical visits, interventions, and investigations from 1990 through 2013(323). Specifically, it included records of virtually all services provided by fee-for-service practitioners, including office visits/consultations, care provided in acute care hospitals or long-term care facilities, and laboratory and diagnostic tests and procedures. Practitioners submit these records to MSP in order to receive payment for services rendered, which lends support to their completeness. The majority of practitioners were physicians, but there were also claims from midwives and supplemental benefits practitioners (i.e. physiotherapists, naturopathic doctors, chiropractors)(323). Of note, MSP stopped providing coverage for most supplemental benefit services on April 1, 2002, meaning there are few claims for these services in the MSP datafiles after this time(323). While some non-fee-for-service practitioners participate in ‘shadow billing’ (submitting a record of services rendered, without a claim for payment), most services provided by these practitioners were not captured. Records associated with a motor vehicle accident insurance claim or workers compensation claim (and thus not paid by the Medical Services Plan) were not captured either(323). But for every encounter that was captured in this dataset, up to five International Classification of Diseases Ninth Revision (ICD-9) diagnoses were recorded, along with the date of service, practitioner type/specialty, service provided, amount paid, and location of service (i.e. practitioner’s office, patient’s home, hospital, emergency room)(323).

2.1.3 Discharge Abstract Database (DAD)

The Discharge Abstract Database, or hospital separations file, contained records of provincially-funded inpatient and day hospital admissions and discharges from 1990 through 2013, for MSP beneficiaries hospitalised within and outside BC(324). Data on abortion procedures were not included(324). Hospital separations were processed internally, according to standardised national reporting requirements, then submitted to the Canadian Institute for Health Information (CIHI). Using hospital separations data collected from BC and the other Canadian provinces (except Quebec), they derived additional variables (including those used for costing) then sent the information back to the BC Ministry of Health. There were up to 25 diagnoses recorded for each hospitalisation, with the first or primary diagnosis indicating the condition most responsible for the patient's stay, or if there were multiple conditions, the one responsible for the greatest portion of the hospital stay or consumption of resources(325). For separations occurring before April 1, 2001, these diagnoses were recorded using ICD-9 codes only. From April 1, 2001 through March 31, 2007, provinces were transitioning to the ICD-10 system, so both ICD-9 and ICD-10 (ICD 9th and 10th Revision) codes were included for these separations, after which time only ICD-10 codes were recorded(324). As the Discharge Abstract Database did not contain data on ambulatory ('treat-and-release') emergency room visits, I could not tabulate the number or reasons for these visits. However, it has been reported that the costs for majority of these emergency room visits are captured in the outpatient billings and (in the case of hospital admissions through the ER) inpatient separations data(326).

2.1.4 PharmaNet

Included in PharmaNet were records of virtually all prescription medications dispensed by community and outpatient pharmacies (plus some medications dispensed during hospital emergency department visits) for all BC residents for the years 1996 through 2013. Prescriptions were included in database regardless of age or funding source (i.e. government subsidy/public insurance, private insurance, or out-of-pocket). This is an advantage over many Canadian provinces, including the two largest, Ontario(327,328) and Quebec(329), where prescription medication data are only available for selected populations, such as seniors and those receiving social assistance. However, PharmaNet did not include records of anti-retroviral medications, chemotherapy dispensed by the BC Cancer Agency, or medications, vitamins, minerals, or supplements purchased without a prescription(330). Of note, while medications dispensed during a hospitalisation were not recorded in PharmaNet, the costs for those medications were captured as part of the cost for the hospitalisation. Each dispensing record had information on the dispensing date, medication and dose dispensed (via the Drug Information Number/Product Information Number (DINPIN)), quantity and days' supply dispensed, and total drug cost and dispensing fee claimed by the pharmacist(330). There was also a variable indicating which type of publicly-funded coverage the individual was receiving, though not their actual income level. Most residents fell under Plan E or I (which provides partial coverage, based on household income(331,332)), but permanent residents of long-term care facilities and those receiving income assistance, for example, fell under other plans. This field was blank for prescriptions funded by the federal government, but dispensed to MSP beneficiaries, including those for First Nations individuals and dependents of members of the Royal Canadian Mounted Police.

2.2 Study populations

2.2.1 SARD individuals

From the administrative data files, population-based cohorts of all BC adults (aged ≥ 18 years) newly-diagnosed with a SARD from January 1, 1996 to through December 31, 2010 were assembled. SARD cases were identified using the ICD-9/10 diagnostic codes recorded for outpatient encounters and hospitalisations; specifically, either: (a) \geq two ICD-9 codes for SARDs \geq two months apart but within a two-year period by a non-rheumatologist physician; or (b) one ICD-9 code for SARDs by a rheumatologist; or (c) one ICD-9/10 recorded on an inpatient or day hospitalisation discharge abstract. The ICD code (listed in Table 2.1) could have been in any of the five diagnostic positions available in the outpatient billing data, or 25 positions available in the hospital separations data. In addition, GCA cases needed to be at least 40 years of age at diagnosis, and to have been dispensed a prescription for oral glucocorticoids between one month before, and six months following, the second GCA-coded encounter (or first encounter if diagnosed in hospital or by rheumatologist). The SARD index date was the date of the first SARD-coded encounter.

Since my direct costs analysis examined the costs of SARDs from the time of diagnosis, and prescription medication data were only available from 1996-onwards, I only included SARD cases who were incident (newly-diagnosed) for the period 1996-2010. Incident SARD cases were individuals with at least five years of follow-up in the databases prior to diagnosis, during which time they did not fulfill the case definition for that particular SARD in the outpatient or hospitalisation databases, although they could have had a single SARD-coded outpatient encounter with a non-rheumatologist physician. However, since I was unable to assess

productivity data from the time of SARD diagnosis (I collected these data prospectively during calendar years 2015 and 2016), all prevalent SARDs were potentially eligible for the productivity survey. Prevalent SARD cases were individuals who met the case definition for SARDs during the years 1990 (the outpatient and hospitalisation data were available from January 1, 1990-onwards) through 2010, and were still registered with MSP at any time during 1996 through 2010.

The validity of these case definitions for SARDs have been evaluated in a Canadian context, wherein the sensitivity for most SARDs was $\geq 88\%$ and positive predictive value was $\geq 57\%$ (333). Moreover, when similar criteria were used to identify GCA within the United Kingdom (UK) General Practice Research Database, the GCA diagnosis was confirmed in 91% of potential cases(334). The validity of these algorithms and diagnostic codes for GPA and Takayasu's is additionally supported by data from the UK(335,336), Sweden(76), and Finland(337). Nevertheless, to further improve specificity, potential SARD cases were excluded if they had at least two visits \geq two months apart (subsequent to the SARD index visit) with diagnoses of other inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies. An individual could be included in more than one SARD cohort (i.e. SLE and SjS); however, those meeting the criteria for both a connective tissue SARD and a form of systemic vasculitis were excluded.

Arthritis Research Canada statistician Dr. Eric C. Sayre used these definitions to identify the initial pool of eligible, prevalent SARD cases for the years 1996-2010, and exclude those with subsequent diagnoses of other inflammatory arthritides. From this pool, I created the final

cohorts of newly-diagnosed SARDs for the direct cost analysis, including only those with at least five-years' follow-up in the databases before diagnosis.

2.2.2 Comparison group

The non-SARD cohorts were established from data for a random sample of the BC population ($n \approx 400,000$) registered with MSP during the study period. I randomly-assigned each non-SARD individual an index date (from all possible dates from January 1, 1996 through December 31, 2010), and eliminated those whose random index date fell outside their actual follow-up period (i.e. after their death), or did not have continuous follow-up in the databases for five years prior to this index date. I then matched each SARD individual, without replacement, to a maximum of ten non-SARD individuals (maximum of five for SLE) based on age (\pm two years), sex, and calendar year of study entry, and eliminated any with a SARD diagnosis.

2.3 Healthcare utilisation and cost calculation

Individuals were followed from their index date for up to five years, or until death, de-registration from MSP, or December 31, 2013, whichever came first. All healthcare use captured in the databases from the index date through end-of-follow-up (for any reason, not just SARDs-related care) was included, and the unit costs summed. Costs were calculated in accordance with guidelines issued by Canada's health technology assessment agency, the Canadian Agency for Drugs and Technologies in Health (CADTH)(338). The unit cost of each outpatient encounter (available in the dataset) was the amount ('fee-item') paid to the practitioner by the BC Ministry of Health, as specified in the provincial fee-for-service agreement(323). There were thousands of distinct fee items, each one specific to the type and specialty of practitioner, service rendered,

and location of service (i.e. in-hospital vs. office visit), and more than one fee item could be billed for a single encounter.

The cost for each prescription medication (also available in the dataset) included the complete drug cost and dispensing fee. Cost data were available for most prescriptions but not all, namely those dispensed to individuals registered with MSP, but receiving federal prescription medication coverage, such as First Nations individuals and dependents of members of the Royal Canadian Mounted Police. To account for these potentially non-differentially missing cost data, I used the available cost data to compute the cost of each DINPIN-days' supply combination, and imputed that cost for *all* prescriptions.

Costs for inpatient and day hospitalisations (excluding in-hospital physician services billed to the medical services plan, as described above) were calculated using the Canadian Institute for Health Information (CIHI)'s well-established case-mix methodology(338), in which the resource intensity weight (RIW) of each hospitalisation is multiplied by the cost for a standard hospital stay in the province of British Columbia (Table 2.2). The RIW is a measure of the relative resource consumption of a hospitalisation, in relation to the provincial 'average' (for which the RIW would equal 1.0), and is determined annually by CIHI (using data from a sample of Canadian hospitals) based on the patient's age group (for adults, either 18-59 years, 60-79 years or ≥ 80 years) and case-mix group(338). There are 528 case-mix groups, each one pertaining to cases with similar diagnoses receiving similar interventions. For example, in 2013, the RIWs for the simple appendectomy case-mix group were 0.57984 for those aged 18-59 years,

0.66083 for those 60-79 years, and 0.87377 for those ≥ 80 years, while for the open cholecystectomy case-mix group, the respective RIWs were 1.21414, 1.32732 and 1.50784(339).

The cost for a standard hospital stay (previously known as the cost-per-weighted-case) is also determined by CIHI. Although I was computing costs for the years 1996 through 2013, CIHI does not make older cost-per-standard-hospital-stay values available to researchers. Thus, I extrapolated values for the earlier years (years 1996-2003) from a best-fit line I constructed from the published values (for fiscal years 2004-2005 to 2013-2014). The linear equation used to extrapolate the earlier values ($153.95 \times \text{year} - 304,015$) had an R^2 value of 0.9305. When multiplying the aforementioned RIW values for the simple appendectomy and open cholecystectomy case-mix groups by the year 2013 cost-per-standard-hospital-stay (\$5,816), the computed cost of those hospitalisations would be \$3,372, \$3,843, and \$5,082 for simple appendectomy in the 18-59, 60-79, and ≥ 80 years age groups, respectively, while the corresponding costs for open cholecystectomy would be \$7,061, \$7,720, and \$8,770.

All costs were adjusted for inflation and standardised to 2013 Canadian dollars using the general component of the Canadian Consumer Price Index (available from Statistics Canada(180) and provided in Table 2.3).

2.4 Independent variables (direct medical costs analysis)

2.4.1 Baseline comorbidities

A modified version of the Charlson-Romano comorbidity index for administrative data(340), one that excluded SARD diagnoses (ICD-9 710; ICD-10 M31, M32, M34, M35), was

calculated for the 365-day period before index date, and collapsed into categories of 0 or ≥ 1 .

When examining the incremental costs of SLE before diagnosis, I also calculated the comorbidity score for each pre-index year, from the comorbidities recorded during the prior 365 days. For example, when assessing the costs incurred during the final 365 days before diagnosis, I used the comorbidities recorded during the second-last 365-day period before diagnosis.

2.4.2 Baseline healthcare resource utilisation

The number of healthcare encounters in the 365 days before index date was included to control for individuals' baseline volume of healthcare resource utilisation. Since a single physician consultation may result in multiple records in the outpatient database (i.e. one for each service rendered or investigation ordered during that consultation), and individuals may have multiple admissions recorded during the same day if transferred between hospitals, I only included the first outpatient encounter or hospitalisation for each person each day. This variable was not included in the models examining costs for SLE in the years leading up to diagnosis.

2.4.3 Baseline socioeconomic status

As the administrative databases did not have information on absolute individual or household income level, occupation, or educational attainment, socioeconomic status (SES) was defined primarily using Statistics Canada neighbourhood income data, as per previous analyses(311,312,341–344). From self-reported annual household income data collected during the Canadian census, Statistics Canada calculates the mean equivalised per-person income in each neighbourhood (400 to 700-person census dissemination area, the approximate equivalent of a census block group in the United States(345)), then ranks all neighbourhoods within a larger

census area on income, and divides this list into fifths. Baseline neighbourhood SES was categorised according to the neighbourhood income level of the address recorded for each individual (by the provincial medical plan) during their index year. The five levels were collapsed into three neighbourhood SES groups: low SES (lowest- and second-lowest income groups), moderate SES (middle income group), and high SES (second-highest and highest income groups).

Since neighbourhood income data has shown poor agreement with self-reported income data for cohorts of diabetes, RA, and asthma⁽³⁴⁶⁾, the impact of individual-level SES was assessed in an exploratory analysis. I did not have access to data on absolute individual or household income, so individual-level SES was defined (as done previously⁽³¹²⁾) by whether the person was receiving income assistance from the provincial government. This assistance includes income support and 100% coverage for the costs of prescription medications and dispensing fees^(331,332); thus, receipt of income assistance was captured from the prescription medication datafiles. As someone may start receiving income assistance immediately following a SARD diagnosis, and I wanted to include the best-possible measure of SES at baseline (before diagnosis), receipt of income assistance was determined for the 365-days before index date. Due to the low numbers of SARD and non-SARD individuals receiving income assistance, this analysis was only conducted in SLE.

2.4.4 Urban/rural residence

Since urban/rural residence can impact the types of healthcare resources used by individuals with SARDs (potentially due to reduced access to specialty care in rural

areas(130,347)), urban/rural residence may also impact healthcare costs. Administrative data have been used to determine the incidence and prevalence of SARDs in several Canadian provinces, and in these studies, hospital separations data had greater sensitivity for cases living in rural areas (versus urban)(12,130). In turn, rheumatologist billings data had greater sensitivity for cases living in urban areas(12,348). For example, urban-dwelling SSc had 40% lower odds of being detected in the hospitalisation data, as compared to rural-dwelling SSc, and 1.5-times greater odds of being detected in the rheumatologist billings data(12). Thus, an indicator variable for urban/rural residence was included in the models. It was derived from the first three digits of the postal code recorded for each individual during their index year, wherein a second-digit of 0 indicated a rural address. This definition has been used in Canadian studies of urban-rural disparities in outcomes and patterns of care for heart failure(349) and prevalence and mortality rates in diabetes(350), and patterns of urban-rural migration following RA diagnosis(351). Moreover, similar percentages of the BC population have been classified as rural under both this definition (14.6%) and a census-based definition (15.5%), which defined rural as living outside the commuting zone of a larger urban centre (population $\geq 10,000$)(352).

2.5 Statistical analysis (direct medical costs analysis – Chapters 3 and 4)

As described by Glick *et al.*(353) and many others, medical cost data have features that necessitate special considerations in its analysis. These costs tend to follow a non-normal, right-skewed distribution, with a portion of individuals incurring costs that are higher than the average, though not in the extremes, and a small number of complex individuals incurring extremely high costs(353). At the same time, while negative cost values are not possible, a notable proportion of individuals will not consume any healthcare resources (or incur any costs). Thus, one must

account for both the skewness in these data and large number of zero values, and consider both the odds of utilisation, as well as the costs incurred by those with healthcare utilisation.

Approaches typically used in the analysis of continuous variables, such as *t*-tests, ANOVA, and ordinary least squares (OLS) regression models, are often not suitable for cost data since they assume a normal distribution and are sensitive to extreme values(353). Log-transformation of costs can make the distribution more normal, though not always, and zero-values will be undefined. When the arithmetic mean of the log-transformed data is exponentiated (converted back to the untransformed scale), what results is the geometric mean, which can be a downward-biased estimate of arithmetic mean(353). Moreover, when comparing costs between groups using univariable or log-transformed OLS regression analysis, the p-value for the difference in geometric mean costs may not be applicable to the difference in arithmetic mean costs(353).

A more suitable model for the analysis of cost data is the generalised linear model (GLM), since both the mean and variance can be modelled on the original scale. Instead of transforming the raw data, one specifies a link function that represents the relationship between the mean cost and the covariates, allowing zero-cost values to be included(353). When analysing cost data, one usually specifies a log-link, thus modelling the relationship between the log of the arithmetic mean cost and the covariates, and not mean of the log(cost), as happens in a log-transformed OLS model(353). In addition to the link function, a ‘family’ must also be specified, which represents the relationship between the variance and the mean. The choices of family include Gaussian (constant variance), Poisson (variance proportional to the mean), gamma

(variance proportional to the mean-squared), and inverse Gaussian (variance proportional to the mean-cubed). The modified Park's test(354) can be used to select the appropriate family, although misspecification of the family will not bias the results as long as the appropriate link function is specified(353).

Note that, despite the skewed nature of cost data, wherein estimates of median costs are usually lower than mean costs, my outcome measure in this thesis is arithmetic mean cost. This measure is more useful for healthcare decision making *because* it encompasses the costs of all individuals, including those in the right tail with extremely high costs. Cost effectiveness decisions are based upon the difference in the arithmetic mean cost of two interventions, and the difference in their mean effect. As well, when assessing a new programme or intervention, the total costs (number of individuals affected*per-person cost) need to be considered(355). If median values are used in this calculation instead of means, the total costs of the program will be underestimated (since they will not include the extremely high costs incurred by those outliers(355)), potentially leading to less-efficient allocation of scarce resources. Item 19 of the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement specifies that mean values of estimated costs should be reported, along with mean differences in costs between groups(356), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(357), and health technology assessment agencies in Canada(358), the UK(359), and Ireland(360), also recommend that mean costs/values be reported.

2.5.1 Unadjusted analysis (Chapters 3 and 4)

Unadjusted comparisons between each SARD cohort and its matched comparison group were made using chi-squared tests (for frequencies) and *t*-tests (for continuous variables). Unadjusted mean per-person healthcare use and costs for each year (365-day period) after index date (Years +1 to +5) were determined for each SARD and non-SARD cohort, as were annualised costs incurred over the whole five-year period. I also assessed healthcare use and costs for the SLE and non-SLE groups during each of the five years leading up to diagnosis/index date (Years -5 to -1). Knowing that the annual costs of individuals followed for shorter periods of time may differ from those with complete follow-up, separate estimates were also produced for individuals with the full five-years' of follow-up after diagnosis/index date.

2.5.2 Adjusted analysis – direct medical costs of SARDs after index date (Chapter 3)

Multivariable generalised linear models(361), adjusted for sex (reference=male), age at index year (centered to the mean), baseline comorbidity score, urban/rural residence (reference=urban), level of healthcare utilisation, year of follow-up (reference=first year after index date), and SES group (reference=highest), were then used to determine the relative levels of healthcare costs associated with SARDs. Odds of hospitalisation were determined with generalised logistic regression models, while utilisation ratios were determined from generalised negative binomial count models. Log-link and negative binomial distribution were specified in these multivariable cost models to account for skewness in these data.

The unit of analysis was person-year of follow-up, with each person contributing up to five observations, one for each year after their index date. To account for unequal follow-up

times within each year, I included an offset variable, equal to the log of the follow-up time contributed by the individual that year. All observations were entered into a single generalised estimating equation (GEE) model, which accounted for the correlation of data between SARD individuals and their matched non-SARD counterparts, and the multiple annual observations that each individual could contribute. Though I hypothesised that an autoregressive correlation structure was the best choice for these time-series data, I assessed the choice of correlation structure by comparing the QIC goodness-of-fit statistics derived from models where either a first-order autoregressive (higher correlation among observations closer together in time), unstructured (all possible correlations for within-subject observations are estimated), or exchangeable/compound structure (all observations within subjects are equally correlated)(362) was specified. While the parameter estimates from GEE models are robust to misspecification of the correlation structure(362), there can still be efficiency losses(363).

As many individuals did not incur costs for each healthcare component in each year (especially hospitalisation costs), two-part models were used. The first part (logistic regression model) assessed one's probability of incurring any cost in each year (i.e. being hospitalised at all), controlling for covariates, while the second part (linear regression model) assessed costs only among those with non-zero costs. Year*SARDs interaction terms were included in all models to assess whether the longitudinal patterns in utilisation and costs differed between those with and without SARDs, while SES*SARDs interactions were included to assess the impact of SES in those with and without SARDs. As I was examining the impact of *baseline* SES and urban/rural residence on longer-term costs, baseline values were used in all observations after diagnosis/index date, regardless of whether one changed neighbourhoods after index date.

The GLM models specified above generate estimates of relative costs between groups. A more relevant metric is the incremental cost, which is the difference in absolute direct medical costs between groups. To derive the adjusted value for this quantity, I used G-computation(364), as has been applied previously on these data(312). With this approach, multivariable regression models are used to predict costs for each individual multiple times, each time with the same person in a different disease (and SES) group, but with their other covariates set at the observed value. The difference between estimates represented the incremental costs, and per-person incremental costs were averaged across all individuals. Two sets of two-part regression models were constructed. In the first, costs were predicted for each person two times, coded once as SARD and once as non-SARD, and the incremental costs of SARDs was the mean difference in predicted costs when coded as SARD versus non-SARD. In the second set of models, costs were predicted for each person six times, once for each SARD-SES combination (SARD-low, SARD-moderate, SARD-high, non-SARD-low, non-SARD-moderate, and non-SARD-high). I used these estimates to determine the incremental costs of SARDs by SES group (i.e. difference in predicted costs when the person was coded as SARD-low-SES and non-SARD-low-SES). Parametric bootstrapping was used to derive 95% credible intervals (95% CI) for these estimates, and make inferences about the differences in mean all-cause costs for SARDs and non-SARDs, and mean incremental costs for the low-SES and high-SES groups. All analyses were generated using the SAS Enterprise software package, version 7.13 (SAS Institute Inc., Cary, NC, USA).

2.5.3 Adjusted analysis – direct medical costs of SLE prior to index date (Chapter 4)

My analysis of the direct medical costs of SLE in the years leading up to index date was conducted in a similar manner to the analysis of post-index direct medical costs just described.

The key differences are listed below:

- Since prescription medication data were only available from 1996-onwards, I only included individuals with an index date on-or-after January 1, 2001. This ensured five years of complete pre-index cost data for each person.
- I used multivariable two-part generalised linear models adjusted for sex (reference=male), age at index year (centered to the mean), and comorbidity score, urban/rural residence (reference=urban), and SES (reference=highest), but not level of healthcare utilisation or year of follow-up.
- When analysing post-index costs, all per-person-year observations (up to five per-person) were entered into a single GEE model, but when analysing pre-index costs, I constructed separate regression models for each year of study.
- I entered year-specific values for comorbidity score, urban/rural residence, and SES in the regression models for Years -5 through +1. For example, when assessing costs incurred during the final 365 days before SLE diagnosis (Year -1), I adjusted for comorbidities recorded during the second 365-day period before diagnosis (Year -2).
- Pre-index follow-up time was the same for all individuals (five full years), but post-index follow-up time could be less than one year if an individual died, was de-registered from MSP, or reached the end of the study period. To account for this, an offset variable (log of each person's follow-up time) was used in the negative binomial count models, while

the cost models for Years +1 through +5 (GLM with gamma distribution instead of negative binomial) only included individuals followed for that entire post-index year.

- Finally, I used five SES groups in this analysis instead of three (corresponding to each of the five Statistics Canada neighbourhood income quintiles), and assessed the impact of SES on *all-cause* medical costs *among* SLE instead of the *incremental* medical costs.

2.6 Survey recruitment (productivity costs analysis)

2.6.1 Study populations

The administrative health datasets described in Section 2.1 are released to researchers in a de-identified form, stripped of any names, addresses, or phone numbers that would allow researchers to identify or contact these individuals. However, there is a new process in BC where researchers may apply for access to the names and contact information of a sample of individuals in administrative health databases, for the sole purpose of recruiting them to participate in a specific health research study. This ‘Request-to-Contact’ application must be approved by a number of governing bodies, including the institutional research ethics board, the BC Ministry of Health’s Data Stewardship Committee, and the Office of the Information and Privacy Commissioner for BC.

Our group submitted such an application for this project, and upon receiving final approval from all governing bodies in April 2015, myself and Dr. Sayre assembled a subset of the prevalent SARD and comparison cohorts who were still registered with MSP in 2015. Included in the subset were 9,335 prevalent SARD cases (82.3% female, mean age in 2015 of 60 ± 15.8 years) and 55,431 matching non-SARD individuals (82.8% female, mean age 62.4 ± 16.0

years). The BC Ministry of Health selected a random sample (n=12,000) of these individuals, and on July 9, 2015, their names, addresses, and phone numbers were released to the research team. Although 6,000 of these individuals were selected because they met the case definition for SARDs in the administrative databases, and 6,000 were selected because they did not, the information on all 12,000 individuals was provided in a single file, and I was blinded to the disease status of each individual.

2.6.2 Recruitment procedures

The recruitment strategy was developed using the Dillman method(365), and adapted, where necessary, to meet Office of the Information and Privacy Commissioner regulations concerning the number of contacts that could be made, and timing and format of each contact. Potential participants were mailed an invitation package complete with a personalised letter of invitation from the Principal Investigator, a separate invitation from the BC Ministry of Health, two copies of the consent form, and an addressed, pre-paid envelope for returning one copy of the consent form. Included in the invitation letters and consent form were a description of the study, and how and why the recipient's name and contact information were disclosed to the research team. We emphasised the importance of having both people with and without SARDs participate, and described the measures in place to protect the privacy of each participant's personal information, including their disease status.

A \$2 coin was included in the invitation package as a token of appreciation for the recipient's time, and an incentive to participate. Small tokens (between \$1-\$5) delivered as part of the initial request to respond to mail questionnaires have been found to increase response

rates(366), whereas promises of tokens upon completion are less effective(365,367). All contacted individuals, regardless of whether they chose to participate in the study, were given the option of keeping the \$2, or mailing it back to the research team for donation to one of five SARD-related charities of their choice.

Individuals who wished to participate in the study were asked to review and sign the consent form, return one copy to the research team, and retain the other copy for their records. Potential participants who did not respond to the invitation package after two weeks were mailed a reminder letter. Four weeks after the invitation package was mailed, I was permitted to make up to two attempts to contact non-respondents by phone. This was critical as some individuals had moved (such that their address on file with the BC Ministry of Health was out-of-date), but could still be reached at the same phone number.

Recruitment was carried out in four mailouts (n=2,400 invitations total), starting with two pilot mailouts (n=200 invitation packages each), one in July 2015 (two weeks after receiving the contact information from the BC Ministry of Health), and one in September 2015. Two pilots were conducted to see if the recruitment process would be different outside of the summer months. The main mailouts (n=1,000 invitation packages each) commenced in November 2015 and March 2016. As such, survey data were collected from July 2015 through December 2016.

2.7 Data collection (productivity costs analysis)

The survey was distributed upon receipt of the completed consent form. Participants who opted to complete the survey online were e-mailed a link to the survey, along with a unique six-

digit username that allowed them to complete the survey over multiple sessions and save their responses as they went along. The online survey was developed using Sawtooth survey software (Sawtooth Software Inc., Orem, Utah, USA), and hosted on a secure webserver at The University of British Columbia. Participants who requested a paper survey were mailed a copy of the survey along with a prepaid return envelope. A copy of the paper survey is available in Appendix A. All participants were asked to complete and submit the survey within two weeks of receipt. Participants who did not submit the online survey within this time were sent an e-mail reminder, while those who did not return their paper survey were mailed a reminder letter. As requested by the Data Stewards, the reminders included explicit instructions on how participants could withdraw from the study, if they so desired. Follow-up phone calls were made to participants who did not return the survey within four weeks.

2.7.1 Survey components

The cross-sectional survey was self-administered, and comprised of six sections. The survey and other study documents were reviewed and pilot-tested by research staff at Arthritis Research Canada and volunteer members of the SARDs Consumer Advisory Council.

- **Section One:** Using questions from the Canadian Community Health Survey(368) and other established health research questionnaires, data were collected on sociodemographic variables (i.e. marital status, race, educational attainment, household income), health exposures and behaviours (i.e. height, weight, smoking history, alcohol use), diagnoses of SARDs and any other forms of arthritis and selected comorbid conditions, month and year of SARD diagnosis by a health professional (and start of symptoms), use of healthcare resources not captured in the provincial administrative

databases (i.e. non-prescription medications, complementary care, medical devices, visits to allied health professionals), and out-of-pocket costs.

- **Section Two:** The EQ-5D-5L instrument(369,370) was used to collect data on health-related quality-of-life. This instrument asked respondents to rate five separate dimensions of their health on that day: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents were also asked to rate their current health on a 100-point scale.
- **Section Three:** Data were collected on health status, including level of disability (using the Health Assessment Questionnaire Disability Index(371)), and severity of pain and fatigue over the past seven days (using a 100-point visual analogue scale).
- **Sections Four and Five:** Data on employment status, occupation, and lost productivity during the past seven days were collected using the Work Productivity and Activity Impairment (WPAI) questionnaire(372) in Section Four, and Valuation of Lost Productivity (VOLP)(373) questionnaire in Section Five. The WPAI has been used to assess productivity losses in SLE(374,375) and SSc(376). Two productivity questionnaires were included because the WPAI is fairly short (maximum of six questions presented over two pages), but only allows for the valuation of absenteeism from paid employment. The VOLP, a newer questionnaire which has been validated in a population of rheumatoid arthritis (RA) patients(377), and used to assess the productivity costs of RA(378) and asthma(379), allows for the valuation of productivity losses from paid and unpaid activities. It also considers the productivity losses experienced by the workplace when one member of the team is away from work or less productive.

- **Section Six:** Participants were asked if they were interested in receiving information about the results of the study, and about future health research studies conducted at The University of British Columbia. This served to facilitate the establishment of a population-based SARD cohort and comparison group for long-term study, although individuals will need to provide additional consent before participating in future research.

2.7.2 Protection of privacy and confidentiality

A number of measures were enacted to ensure the privacy of potential participants' personal information, and the security of data throughout the recruitment, data collection and analysis processes. All electronic information, including names, contact information, and survey data, remained in Canada, housed in encrypted, password-protected computerised files on secured network servers. Participants were only identified on study documents by a survey ID number; personal information (i.e. names, contact information) were not linked to survey results, nor administrative health data, at any time.

It was also important to ensure that an individual's disease status was not unwittingly revealed to the research team or other individuals during the recruitment process. To prevent this, the invitation letter was carefully worded to communicate that the individual had been randomly selected to participate in the study as someone who "may or may not" have been diagnosed with a SARD. Furthermore, when leaving phone messages for potential participants, the study was referred to only as a "health research study conducted at The University of British Columbia", without mention of the specific diagnoses under study.

Table 2.1: International Classification of Diseases 9th (ICD-9) and 10th (ICD-10) Revision Diagnostic Codes for Systemic Autoimmune Rheumatic Diseases (SARDs)

Diagnosis	ICD-9	ICD-10
All connective tissue diseases	710 710.X	M32.1 M32.8 M32.9 M34.X M35.0 M35.1 M33.0, M33.1, M33.9 M33.2
Systemic lupus erythematosus (SLE)	710.0	M32.1 M32.8 M32.9
Scleroderma/systemic sclerosis (SSc)	710.1	M34.X
Sjogren's syndrome (SjD)	710.2	M35.0
Dermatomyositis (DM)	710.3	M33.0, M33.1, M33.9
Polymyositis (PM)	710.4	M33.2
Polyarteritis nodosa (PAN)	446.0	M30.0
Granulomatosis with polyangiitis (GPA)	446.4	M31.3
Giant cell arteritis (GCA)	446.5	M31.5
Takayasu disease	446.7	M31.4

**Table 2.2: Annual Cost-Per-Standard-Hospital-Stay Values Used to Compute
Hospitalisation Costs**

Calendar Year	Cost of a Standard Hospital Stay
1996	\$3,093 ^a
1997	\$3,247 ^a
1998	\$3,401 ^a
1999	\$3,555 ^a
2000	\$3,709 ^a
2001	\$3,863 ^a
2002	\$4,017 ^a
2003	\$4,171 ^a
2004	\$4,325 ^b
2005	\$4,767 ^b
2006	\$4,802 ^b
2007	\$4,939 ^b
2008	\$5,166 ^b
2009	\$5,304 ^b
2010	\$5,589 ^b
2011	\$5,329 ^b
2012	\$5,804 ^b
2013	\$5,816 ^b

^aExtrapolated from the values provided for the years 2004-2013 by the Canadian Institute for Health Information

^bActual values provided by the Canadian Institute for Health Information(339)

Table 2.3: Multiplier Values Used to Standardise Medical Costs to 2013 Canadian Dollars

Calendar Year	Percent-Change from 2013	Multiplier
1996	0.38133	1.381327
1997	0.35841	1.358407
1998	0.34502	1.345016
1999	0.32185	1.321851
2000	0.28721	1.287212
2001	0.25562	1.255624
2002	0.22800	1.22800
2003	0.19455	1.194553
2004	0.17287	1.172875
2005	0.14766	1.147664
2006	0.12557	1.125573
2007	0.10135	1.101345
2008	0.07625	1.076249
2009	0.07343	1.073427
2010	0.05408	1.054077
2011	0.02419	1.024187
2012	0.00904	1.009039
2013	0	1

Source: Statistics Canada. *Table 326-0021 - Consumer Price Index (CPI), annual, Canada, All-items*: <http://www5.statcan.gc.ca/cansim/a26?id=3260021>

3. Total and Incremental Direct Medical Costs in Systemic Autoimmune Rheumatic Diseases and the Influence of Socioeconomic Status: A Longitudinal Population-Based Study

3.1 Introduction

Systemic autoimmune rheumatic diseases (SARDs) include systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma (SSc), Sjogren's syndrome (SjS), polymyositis (PM), dermatomyositis (DM), and the following forms of adult systemic vasculitides: polyarteritis nodosa (PAN), giant cell arteritis (GCA), Granulomatosis with polyangiitis (GPA), and Takayasu's arteritis. Immune dysregulation in SARDs leads to systemic inflammation, organ damage, and complications(42–51,53–56,58), including significantly increased risks of myocardial infarction, cerebrovascular accident, and venous thromboembolism. Due to the organ damage, complications, and adverse effects of immune-modulating and immunosuppressive therapies, the incremental direct medical costs of SARDs (additional costs for the provision of healthcare resources, over-and-above non-SARDs') are likely substantial. However, the long-term burden imparted by SARDs, especially at the population-level, is largely unknown.

To date, estimates of direct medical costs for SARDs have focussed mainly on SLE, and have been largely determined from patients with prevalent disease receiving care at tertiary centres. Such cost estimates have limited generalisability, since clinic-based samples tend to have more severe disease, and may not capture the costs of patients who consume a high level of

healthcare resources around the time of diagnosis. As well, tertiary centres and disease registries that collect data on SARDs typically do not collect comparable information on the general population. This makes it difficult (if not impossible) to determine the incremental burden of these disorders.

With prevalent cohorts, it is also difficult to determine the temporal relationships between many sociodemographic factors and costs, which have implications for health policy and clinical care. One factor of particular interest in SARDs is socioeconomic status (SES). Low SES is a well-recognised determinant of health status(272), healthcare costs(273), and mortality(275,276) in general populations, and is associated with poorer clinical outcomes in SLE, including higher levels of disease activity(230,280,281), damage(231,232,282,283), and depressive symptoms(235), and higher complication(234,284) and mortality(285–287) rates. These associations have been observed across different countries, healthcare settings, and measures of SES including educational attainment(232,235,280,281), individual(231,234,235,282) and neighbourhood(235,285) income levels, and health insurance source/status(285). Beyond financial barriers in accessing healthcare (or health insurance), lower levels of social support or self-efficacy among low SES patients(288), and higher levels of depressive symptoms or perceived stress(283), may also contribute to these disparities.

As such, SES is likely a predictor of healthcare costs in SLE (and perhaps other SARDs), but its impact has not been well-investigated, especially at the general population level. The few studies known to have assessed the impact of SES on costs in SARDs(34,186,224) were conducted on prevalent cases, which brings directionality into question, since low SES may

contribute to poorer health (and higher costs), or result from it. For example, lower levels of disease activity and higher levels of physical functioning have been predictive of work entry (becoming employed) in SLE(290), while higher levels of depressive symptoms(290), and increases in disease activity and number of organ manifestations(291), have been predictive of work loss. Studies of prevalent cohorts are also subject to survival bias; early mortality is a feature of some SARDs, especially SSc(123) and GPA(292–294), and low-SES ‘survivors’ may differ from low-SES patients who succumb to the disease early-on. Another key limitation is that the previous studies only assessed the impact of SES on the *all-cause* medical costs incurred by those with SARDs, not the incremental costs.

Finally, there is also a paucity of data on the long-term patterns of healthcare use and costs in SARDs, which could assist policymakers in developing better models of care. To my knowledge, such patterns in costs from diagnosis onwards have been described in only two reports at the time of this writing: one describing the costs of outpatient encounters and hospitalisations (but not prescription medications) for GCA patients before and after diagnosis(200), and one on the costs of SLE patients for the first five years after diagnosis(203). Unfortunately, the latter study was not generalisable to the Canadian population (it was conducted on a sample of Medicaid beneficiaries in the USA), and only assessed the costs of patients who were followed for the entire five years.

In this Chapter, I address these knowledge gaps by using administrative health databases from the province of British Columbia (BC), Canada, to assess the longitudinal, incremental direct medical costs of newly-diagnosed SARDs, mainly from the perspective of the public

healthcare payer. My specific objectives were to determine the total and incremental direct medical costs of each SARD cohort during the first five years after diagnosis, and assess the impact of baseline SES on the incremental costs of SARDs during this time.

3.2 Methods

3.2.1 Data source

The administrative health databases were sourced through Population Data BC, which uses population-based linkable administrative data files to capture provincially funded health care services including outpatient medical visits, interventions, and investigations(316), and hospital admissions and discharges(317), from 1990 through 2013, as well as demographic(319) and vital statistics data(320). Furthermore, it encompasses the comprehensive prescription drug database PharmaNet(318), which includes virtually all community-dispensed medications for all BC residents, regardless of age or funding source, for the years 1996 through 2013, though does not capture non-prescription/over-the-counter medications. Many general population-based studies have been successfully conducted using these databases(42,311–315).

3.2.2 Study populations

From the administrative data files, I assembled population-based cohorts of all BC adults (aged ≥ 18 years) newly-diagnosed with a SARD from January 1, 1996 through December 31, 2010. To ensure only incident cases were included, all individuals needed at least five years of follow-up in the databases prior to diagnosis, during which time they did not fulfill the case definition for that particular SARD in the outpatient or hospitalisation databases (which contained records of encounters from 1990-onwards). SARD cases were identified using International Classification of Diseases Ninth (ICD-9) and Tenth (ICD-10) Revision diagnostic codes recorded for outpatient encounters and hospitalisations; specifically, either: (a) \geq two ICD-9 codes for SARDs \geq two months apart but within a two-year period by a non-rheumatologist physician; (b) one ICD-9 code for SARDs by a rheumatologist; or (c) one ICD-9/10 code from

hospitalisation. The ICD codes (listed in Table 2.1) could have been in any of the five diagnostic positions available in the outpatient billing data, or 25 positions available in the hospital separations data. In addition, GCA cases needed to be at least 40 years of age at diagnosis, and to have been dispensed a prescription for oral glucocorticoids between one month before, and six months following, the second GCA-coded encounter (or first encounter if diagnosed in hospital or by rheumatologist). The SARD index date was the date of the first SARD-coded encounter.

The validity of these case definitions for SARDs have been evaluated in a Canadian context, wherein the sensitivity for most SARDs was $\geq 88\%$, specificity was $\geq 95\%$, and PPV was $\geq 57\%$ (333). Moreover, when similar criteria were used to identify GCA within the United Kingdom (UK) General Practice Research Database, the GCA diagnosis was confirmed in 91% of potential cases(334). Nevertheless, to further improve specificity, potential SARD cases were excluded if they had at least two visits \geq two months apart (subsequent to the SARD index visit) with diagnoses of other inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies.

The non-SARD cohorts were established from data for a random sample of the BC population ($n \approx 400,000$) registered with the provincial medical plan during the study period. I randomly-assigned each non-SARD individual an index date (from all possible dates during the period January 1, 1996 through December 31, 2010), and eliminated those whose random index date fell outside their actual follow-up period (i.e. after their death), or who did not have continuous follow-up in the databases for five years prior to this index date. I then matched each SARD individual, without replacement, to a maximum of ten non-SARD individuals (maximum

of five for SLE) based on age (\pm two years), sex, and calendar year of study entry, and eliminated any with a SARD diagnosis.

3.2.3 Healthcare utilisation and cost calculation

Individuals were followed from their index date for up to five years, or until death, de-registration from BC's universal health insurance provider, or December 31, 2013, whichever came first. All healthcare use captured in the databases from the index date through end-of-follow-up (for any reason, not just SARDs-related care) was included, and the unit costs summed. The unit cost of each outpatient encounter (available in the dataset) was the amount paid to the practitioner by the BC Ministry of Health, as specified in the provincial fee-for-service agreement. The cost for each prescription medication (also available in the dataset) included the complete drug cost and dispensing fee as listed on each dispensing record. Costs for inpatient and day hospitalisations were calculated using the Canadian Institute for Health Information (CIHI)'s well-established case-mix methodology(338), in which the resource intensity weight (RIW) of each hospitalisation (as determined by CIHI), the relative resource consumption in relation to the provincial 'average' (for which the RIW would equal 1.0), is multiplied by the cost for a standard hospital stay in the province of British Columbia. All costs were adjusted for inflation using the general component of the Canadian Consumer Price Index(180) (listed in Table 2.3) and are reported in 2013 Canadian dollars.

3.2.4 Independent variables

3.2.4.1 Baseline comorbidities

A modified version of the Charlson-Romano comorbidity index for administrative data(340), one that excluded SARD diagnoses (ICD-9 710; ICD-10 M31, M32, M34, M35), was calculated for the 365-day period before index date, and collapsed into categories of 0 or ≥ 1 .

3.2.4.2 Baseline healthcare resource utilisation

The number of healthcare encounters in the 365 days before index date was included to control for individuals' baseline volume of healthcare resource utilisation. Since a single physician consultation may result in multiple 'encounters' in the outpatient database (i.e. one for each service rendered or laboratory investigation ordered during that consultation), and individuals may have multiple hospital admissions recorded during the same day if they were transferred between hospitals, I only included the first outpatient encounter or hospitalisation for each person each day.

3.2.4.3 Baseline socioeconomic status

As the administrative databases did not have information on absolute individual or household income level, occupation, or educational attainment, SES was defined primarily using Statistics Canada neighbourhood income quintile data, as per previous analyses(311,312,341–344). From self-reported annual household income data collected during the Canadian census, Statistics Canada calculates the mean per-person income in each neighbourhood (400 to 700-person census dissemination area, the approximate equivalent of a census block group in the United States(345)), then ranks all neighbourhoods within a larger census area, and divides this

list into fifths. Baseline neighbourhood-level SES was grouped according to the income quintile of the address recorded for each individual (by the provincial medical plan) during their index year, and collapsed into three groups: low (two-lowest quintiles), moderate (middle quintile), and high SES (two-highest quintiles).

Since neighbourhood income data have shown poor agreement with self-reported income data(346) for cohorts of diabetes, RA, and asthma, the impact of individual-level SES was assessed in conjunction with neighbourhood SES in a secondary analysis. As I did not have access to data on absolute individual or household income, individual-level SES was defined (as done previously(312)) by whether or not the person was receiving income assistance benefits from the provincial government. These benefits include income support and 100% coverage for the costs of eligible prescription medications (including the dispensing fee)(331,332); thus, receipt of income assistance was captured from the prescription medication datafiles. As someone may start receiving income assistance upon SARD diagnosis, and I wanted to include the best-possible measure of SES at baseline (before diagnosis), receipt of income assistance was determined during the 365-days before index date. Due to the low numbers of SARD and non-SARD individuals receiving income assistance, this analysis was only conducted in SLE.

3.2.4.4 Urban/rural residence

Evidence suggests that urban/rural residence may impact the types of healthcare resources used by individuals with SARDs. When administrative data was used to assess the incidence and prevalence of different SARDs in Canada, hospital separations data had greater sensitivity for detecting cases in rural areas (versus urban)(12,130), while rheumatologist billings

data had greater sensitivity for cases in urban areas(12,348). Consequently, urban/rural residence may also impact costs (potentially confounding any associations between SES and costs), so an indicator variable for urban/rural residence was included. Urban/rural residence was categorised from the first three digits of the postal code recorded for each individual during their index year, with a second-digit of 0 indicating a rural address. This definition has been used in Canadian studies of urban-rural disparities in outcomes and patterns of care for heart failure(349) and prevalence and mortality rates in diabetes(350), and urban-rural migration following RA diagnosis(351).

3.2.5 Statistical analysis

Mean per-person healthcare use and costs for each year (365-day period) after index date (Years +1 to +5) were determined for each SARD and non-SARD cohort. Knowing that the annual costs of individuals followed for shorter periods of time may differ from those with complete follow-up, separate estimates were also produced for individuals with the full five-years' of follow-up after diagnosis/index date.

Unadjusted comparisons between each SARD cohort and its matched comparison group were made using chi-squared tests (for frequencies) and *t*-tests (for continuous variables). Multivariable generalised linear models (GLM)(361), adjusted for sex (reference=male), age at index year (centered to the mean), baseline comorbidity score, urban/rural residence (reference=urban), level of healthcare utilisation, year of follow up (reference=first year), and SES group (reference=highest), were then used to determine the adjusted relative levels of

healthcare costs associated with SARDs. Log-link and negative binomial distribution were specified in these multivariable cost models to account for skewness in these data.

The unit of analysis was person-year of follow-up, with each person contributing up to five observations, one for each year after index date. To account for unequal follow-up times within each year, I included an offset variable, equal to the log of follow-up time contributed by the individual that year. All observations were entered into a single generalised estimating equation model (with autoregressive correlation structure), which accounted for the correlation of data between SARD individuals and their matched non-SARD counterparts, and the multiple annual observations that each individual could contribute.

As many individuals did not incur costs for each healthcare component in each year (especially hospitalisation costs), two-part models were used to account for the zero-inflated nature of the data. The first part (logistic regression model) assessed one's probability of incurring any cost in each year (i.e. being hospitalised at all), controlling for covariates, while the second part (negative binomial GLM) assessed costs only among those with non-zero costs. Year*SARDs interaction terms were included in all models to assess whether the longitudinal patterns in costs differed between those with and without SARDs, while SES*SARDs interactions were included to assess the impact of SES in those with and without SARDs. As I was examining the impact of *baseline* SES and urban/rural residence on longer-term costs, baseline values were used in all observations, regardless of whether the individual changed neighbourhoods during the study period.

The GLM models above generate estimates of relative costs (cost ratios) between groups. A more relevant metric is the incremental cost, which is the difference in absolute direct medical costs between groups. To derive the adjusted value for this quantity, I used G-computation(364), as has been applied previously on these data(312). With this approach, multivariable regression models are used to predict costs for each individual multiple times, each time with the same person in a different disease (and SES) group, but with their other covariates set at the observed value. The difference between estimates represented the incremental costs, and per-person incremental costs were averaged across all individuals. Two sets of two-part regression models were constructed. In the first, costs were predicted for each person two times, coded once as a SARD and once as a non-SARD, and the incremental costs of SARDs was the mean difference in predicted costs for the SARD and non-SARD groups. In the second set of models, costs were predicted for each person six times, once for each SARD-SES combination (SARD-low, SARD-moderate, SARD-high, non-SARD-low, non-SARD-moderate, and non-SARD-high). I used these estimates to determine the incremental costs of SARDs by SES group (i.e. difference in predicted costs when the person was coded as SARD-low-SES versus non-SARD-low-SES).

The impact of individual- and neighbourhood-level SES was compared in an exploratory analysis where I assessed changes in the predicted incremental costs of SLE (overall, and by SES group) after individual-level SES was added to the model. Substantial changes in predicted costs would suggest the two SES measures influence costs in separate ways.

Parametric bootstrapping was used to derive 95% credible intervals (95% CI) for these estimates, and make inferences about any differences in mean costs between SARDs and non-

SARDs, and incremental costs between the low- and high-SES groups. All analyses were generated using the SAS Enterprise software package, version 7.13.

3.3 Results

Altogether, I included 8,858 newly-diagnosed adult SARD cases for the years 1996-2010 (79.8% female) and 32,727 non-SARDs (79.0% female) from the general population. Baseline characteristics of each SARD and comparison cohort are shown in Tables 3.1 to 3.9.

3.3.1 Longitudinal patterns in healthcare use and costs from diagnosis

Annual mean per-person costs for each SARD and comparison cohort, for each of the five years after diagnosis, are shown in Table 3.10, and illustrated for SLE in Figure 3.1. While the magnitude of costs differed among diagnoses (highest in GPA, \$38,197 per-person, and lowest in SjS, at \$11,630 per-person), a similar pattern was observed across all SARDs with costs highest during the first year after diagnosis (Year +1). Mean per-person costs decreased sharply in the second year after diagnosis (Year +2), and, in general, were relatively stable in Years +3 and +4, before increasing slightly between Years +4 and +5 (Figure 3.1, left). For example, Year +1 costs in SLE averaged \$13,038 per-person (61% from hospitalisations, 23% outpatient, and 16% from medications), then decreased by 42% the next year to \$7,570 (42% from hospitalisations, 28% outpatient, and 30% medications). This pattern was not exhibited by the comparison cohorts, whose costs increased slightly from Years +1 to +2 (Table 3.10).

The biggest cost contributor during Year +1 was hospitalisations, with the percent-contribution ranging from 57% of costs for SSc to 74% of costs for DM and GPA.

Hospitalisation rates were highest in Year +1; for example, 38% of SLE and 47% of SSc had at least one inpatient admission during Year +1, while in Year +2, only 18% of SLE and 23% of SSc were hospitalised. Day hospitalisations were a minor contributor, accounting for less than

5% of costs each year in the SARD and non-SARD groups. Outpatient encounters were the second-highest cost contributor during Year +1 (15% of costs in GPA, and 23% of costs in each of SLE, SjS, and Takayasu's), followed by prescription medications. Among non-SARDs, the three components each accounted for about one-third of costs in Year +1 (with ~8% of non-SARDs hospitalised at least once) and this changed little in subsequent years.

When I restricted the analysis to just those individuals with full follow-up over the five years, the absolute costs were lower, but the same patterns were observed. For example, Year +1 costs in SLE patients with full follow-up (n=2,954, 63% of the entire SLE cohort) averaged \$9,809 (compared to \$13,038 among the whole cohort), and decreased by 36% the following year to average \$6,279 (Figure 3.1, right).

3.3.2 Incremental costs

Displayed in Table 3.10 are the annual, unadjusted incremental costs of each SARD (difference in mean per-person costs between SARDs and non-SARDs) during each year of follow-up. Unadjusted incremental costs were highest during Year +1, ranging from \$8,551 per-person for SjS to \$34,734 for GPA. Hospitalisations accounted for about two-thirds of the incremental costs during this first year (i.e. \$7,132 in SLE), while the contribution from medications was relatively small (i.e. \$1,294 in SLE, 12% of all incremental costs).

The predicted per-person-year costs for each SARD and non-SARD group, and adjusted incremental costs of each SARD, averaged over the first five years after diagnosis, are shown in Table 3.11. Estimates were adjusted for sex, age, SES, urban/rural location, and baseline

comorbidities and healthcare utilisation, and accounted for unequal follow-up times and the odds of incurring any cost during each year. Incremental costs ranged from \$7,851 in SjS, to \$10,078 in SLE, and \$54,061 in GPA (Figure 3.2), and were lower when restricting to individuals with full five-year follow-up (i.e. for SLE: \$4,850 vs. \$10,078 among all individuals).

Hospitalisations accounted for the majority of incremental costs in all SARDs (about 85-90%), with about 10% from outpatient encounters and less than 5% from prescription medications. However, hospitalisations contributed less to the incremental costs of SLE (75% among all SLE, with 17% from outpatient) and SSc (76%, with 14% from outpatient). Among those with SLE followed for the entire five years after diagnosis, hospitalisations accounted for 55% of incremental costs, and outpatient 28%. Absolute incremental medication costs were just \$319 in SjS, and \$456 in GCA, but higher in SSc (\$1,554) and GPA (\$1,947).

3.3.3 Impact of baseline socioeconomic status – neighbourhood-level

Shown in Table 3.12 and Figure 3.3 are the predicted incremental per-person-year costs of SARDs, by SES group, and the excess in incremental costs for low-SES individuals (difference in predicted incremental costs between the low and high SES). In every SARD except PM, overall incremental direct medical costs were significantly greater for the low SES group (versus the high SES). This excess in costs averaged approximately \$2,000 per-person-year in each of SLE, SjS, and SSc, \$2,790 in GCA, and \$2,917 in GPA, but was considerably higher in PAN, Takayasu's (~\$6,000 per-person-year in each), and DM (\$8,414 per-person-year), the three smallest cohorts (n=331 DM, n=210 PAN, and n=50 Takayasu's). Incremental hospitalisation costs were significantly greater for each of the low-SES SARD groups (compared to the high SES), except PM. However, the impact of SES on outpatient and medication costs

was more variable. Incremental outpatient costs were significantly greater for most low-SES SARD groups except GCA and GPA, where predicted mean incremental costs were actually greater for the high-SES than the low-SES (by \$12 and \$77 per-person-year, respectively). The biggest excesses in incremental medication costs were observed for SLE (\$40 more per-person-year than the high-SES), GPA (\$47 more), and Takayasu's (\$226 more), while for SSc, predicted medication costs for the high-SES *exceeded* the low-SES by \$41 per-person-year (mean excess of -\$41, 95% CI: -\$122 to -\$12).

3.3.4 Impact of baseline socioeconomic status – individual-level

For SLE, I also examined the impact of neighbourhood-level SES on incremental costs before and after controlling for a measure of individual-level SES (receiving income assistance or not). Eight percent of SLE (n=392) and 4.7% of non-SLE (n=1,098) received income assistance benefits during the year before index date, and 64% of these SLE (65% of non-SLE) were also in the low neighbourhood-level SES group.

As shown in Table 3.13, there was little change (maximum 5% increase) in the overall predicted costs for SLE and non-SLE after individual-level SES was added to the model. The excess in predicted incremental costs between the low- and high-SES neighbourhood groups did decrease, by \$373 per-person-year (from \$1,922 in the original model to \$1,549). Excess hospitalisation costs decreased by 17% (from \$1,770 to \$1,463), as did excess outpatient costs (from \$111 to \$92), but there was a greater change in excess medication costs. Predicted incremental medication costs were \$40 *more* per-person-year among the low SES (versus the high SES) before individual-level SES was included, and \$7 *less* per-person year afterwards.

This stemmed mainly from increased costs for the high SES group (Figure 3.4). For example, predicted medication costs for the low SES group were \$798 beforehand and \$808 afterwards, while predicted costs for the high SES group were \$757 beforehand and \$815 afterwards.

3.4 Discussion

In this first-ever population-based, Canadian longitudinal analysis, all-cause annual direct medical costs for SARD patients during the first five years after diagnosis averaged between \$7,885 and \$18,998 per-person-year (among SjS and GPA, respectively). Per-person costs for SARDs peaked during the first year after diagnosis (ranging from \$11,630 for SjS to \$38,197 for GPA), decreased sharply the following year, by 38% (in SjS) to 68% (in GPA), then stabilised. Adjusted annualised costs for individuals with SARDs exceeded those of the sex- and age-matched non-SARD cohorts by \$7,851 to \$54,061 per-person, on-average (again, among SjS and GPA, respectively). Moreover, in nearly every SARD, predicted incremental costs were significantly greater among patients of low socioeconomic status than those of high socioeconomic status.

3.4.1 Longitudinal costs

The high costs incurred by SARD patients during Year +1 are likely related to the volume of healthcare resources consumed in establishing the diagnosis, and intense management (oftentimes in hospital) required initially upon diagnosis. The subsequent decrease in healthcare use and costs is likely due to the disease becoming controlled. It has been observed in SLE that disease activity decreases during the first year after diagnosis(88,380), and remains low(380), while disease damage increases over the first five years(380), potentially from extended use of GC(380); similar longitudinal cost trends have been reported in conditions outside of SARDs including diabetes(381,382), heart failure(383), and coeliac disease(384). Moreover, while the absolute costs were lower, the same pattern in costs was observed when restricting to individuals contributing five full years of follow-up. This implies that the decrease in costs from Years +1 to

+2 cannot be attributed simply to a small number of complex cases incurring high costs around time of diagnosis, and dying shortly after.

3.4.2 Comparisons with prior estimates

As nearly all published cost estimates for SARDs have been cross-sectional, it is difficult to compare these longitudinal estimates with those in previous studies. Li *et al.*(203) used Medicaid data (a selected sample) to assess the direct medical costs of 2,298 incident SLE and 2,298 matched non-SLE for the first five years after diagnosis. While the absolute costs reported in that US study were far greater than those here, the longitudinal pattern (decrease from Year +1 to Year +2) was similar to what I observed, with hospitalisation rates for that SLE cohort also highest during Year +1 (24.4%). Of note, that Medicaid study only included individuals with full five-year follow-up, although it was mentioned that Year +1 costs amongst patients with only one year of follow-up were about 55% greater than those for patients with five years of follow-up (about \$25,000 vs. \$16,089 2006 USD).

My longitudinal findings for SLE are also consistent with those of a longitudinal, population-based study of healthcare utilisation (but not costs) for incident SLE in another Canadian province(90). There, the mean annual number of physician visits for SLE was highest during Year +1, then decreased over time, while for the non-SLE comparison group, utilisation increased gradually over time. Specifically, there were substantial decreases in visits to rheumatologists, internists, and other specialist physicians, while visits to family physicians decreased by only 9%. The numbers of ambulatory emergency department visits (which I could not tabulate) and hospital admissions were also highest in the period early after diagnosis.

The second longitudinal study of costs available for comparison, published in 2017 by Koster *et al.*(200), used population-based data from the Mayo Clinic in Rochester, Minnesota, USA, to examine the annual direct medical costs of 147 newly-diagnosed GCA, and 147 matched non-GCA. Combined costs for GCA were significantly greater than non-GCA during the final month before diagnosis, and each of the first four years after diagnosis, but not the fifth year. Of note, hospitalisation costs alone were not significantly different for GCA and non-GCA at any point during the study period. These findings differ somewhat from mine, as I found that unadjusted per-person costs for GCA were significantly higher than non-GCA during each of the first five years after diagnosis, and their predicted hospitalisation costs were significantly greater than non-GCA. However, their estimates did not include costs for prescription medications, and their summary measure (median difference in costs between GCA/non-GCA pairs each year) and analytical approach, differed from mine. Indeed, the standard and least-biased cost measure for economic evaluations is the arithmetic mean cost, not median cost, with health technology assessment agencies in Canada(358), the UK(359), and Ireland(360) all recommending that mean costs/values be reported. Although estimates of mean medical costs are usually higher than median costs, mean costs are more useful for healthcare decision making *because* they encapsulate the costs of all individuals, including those few patients with very high costs(355).

While, to my knowledge, the studies by Li *et al.*(203) and Koster *et al.*(200) are the only longitudinal cost estimates currently available, several estimates have been produced (from US commercial claims databases) of the unadjusted, incremental costs of SLE during just the first year after diagnosis. All cost estimates listed here have been converted to 2013 Canadian dollars (CDN). In a study by Carls *et al.*(91), total healthcare costs averaged approximately \$27,118

2013 CDN, and incremental costs (difference between SLE and non-SLE) averaged \$17,018, while in a study by Furst *et al.*(92), total and incremental costs averaged \$23,509, and \$17,491, respectively. Oglesby *et al.*(210) also determined the costs of newly-diagnosed SLE (\$17,535 to \$22,577 2013 CDN), and while they did not examine costs for a non-SLE comparison group, the SLE-attributable costs of their cohort averaged between \$2,697 and \$3,544. In additional studies using US commercial claims data, total and incremental costs for incident DM averaged \$32,042 and \$25,861, respectively, during Year +1, while total and incremental costs for incident PM were \$22,979 and \$16,931, respectively(197). Year +1 costs of newly-diagnosed GCA and SjS averaged \$42,25(38) and \$22,117(227), respectively. For SSc and other forms of SV, published estimates are only available for prevalent cases (Table 1.1 and Table 1.2).

Variation in these cost estimates may arise from differences in patient populations between studies. My estimates for SSc and PM/DM were lower than prior estimates from Canada(33,34), but those were conducted on prevalent cohorts, and the authors acknowledge they may not reflect the higher costs of patients with new-onset disease. Since a considerable proportion of individuals with diffuse SSc (the more severe subset) die soon after diagnosis (five-year cumulative survival of 69.6% for diffuse SSc and 90.9% for limited SSc in a recent meta-analysis(122)), cost estimates of SSc are particularly prone to survival bias. Differences in prices and practices of healthcare delivery between countries may also contribute to variation in estimates. My unadjusted estimates were far lower than those determined from US commercial claims databases, likely due to the higher costs of delivering healthcare in the US(201); others have attributed variation in the costs of SSc across European countries to trans-national variation in the amount of care delivered in hospital settings versus community settings(307).

3.4.3 Impact of socioeconomic status

My most compelling finding was that the incremental costs of SARDs were significantly-greater (by about \$2,000 to \$3,000 per-person-year, on-average) for those in the low SES group at diagnosis, compared to high SES. Excess incremental costs were even greater in PAN (\$6,263 per-person-year), Takayasu's (\$5,992 per-person-year), and DM (\$8,414 per-person-year), though those figures should be viewed with caution considering the small numbers of patients in those cohorts. Hospitalisations were the major contributor, but low-SES was still associated with greater outpatient and medication costs with, for example, \$111 and \$77 per-person-year excesses in incremental outpatient costs for low-SES SLE and SSc, and a \$47 per-person-year excess in incremental medication costs for low-SES GPA. These differences across SES groups are striking since the outcome was *incremental costs*, 'extra' costs from SARDs that remained after the removal of 'background' medical costs incurred by those in the general population (along with the 'background' (273) impact of SES on costs in the general population). In sum, these findings suggest that SES influences not just all-cause medical costs, but more specifically, the costs incurred for the management and treatment of SARDs and associated complications.

Very few studies have reported on the relationship between SES and healthcare costs in SARDs. Although higher neighbourhood income was associated with higher hospitalisation charges among SLE patients in the USA(186), and lower education was associated with lower direct (medical and nonmedical) costs among SLE in South Korea(224), neither study assessed the impact of SES at diagnosis, nor the impact of SES on the *incremental* costs of SLE. Still, my findings are consistent with the well-established association between low SES and poorer clinical outcomes specific to SLE, including disease activity and damage(230,231,235), development of

lupus nephritis(284), and SLE-related mortality(285). The body of published literature for SSc is much smaller, and more mixed. In a study from the Canadian Scleroderma Research Group (CSRG), being in the highest income tertile was associated with a higher volume of physician visits for any reason ($>$ or ≤ 6 per-year)(385), but SES (measured by educational attainment) was not associated with all-cause healthcare costs(33). Another CSRG study looked at the impact of education (high school completion) on organ damage and mortality in SSc(289), and found no significant relationship. But unlike mine, those investigations were conducted on prevalent cohorts (mean disease duration of 9.7(385) to 11(289) years), and are likely subject to survival bias. SES may have more of an impact on outcomes (and thus healthcare costs) earlier-on in the disease course. This supposition is supported by the fact that the mortality rate during the first 12 months after diagnosis was considerably higher among the low-SES members of my SSc cohort than the high-SES (15.5% of the low-SES SSc died versus 7.9% of the high-SES; rates of 17.2 and 8.3 deaths per 100-person-years). There are little published data on the impact of SES in the other SARDs, though high SES (specifically, high neighbourhood income level) was associated with significantly lower physician and hospitalisation costs among prevalent PM/DM in the Canadian province of Quebec(34).

My research was observational and retrospective, and while I controlled for age, sex, and measures of baseline comorbidities, urban/residence, and baseline healthcare utilisation, my findings are still subject to residual confounding. While this novel relationship between SES and incremental costs should be assessed in other population-based cohorts, moving forward, research should also focus on why low-SES individuals seem to incur more costs from SARDs, and how these disparities could be mitigated. BC has a universal, publicly-funded healthcare

system where physician and hospital care are accessed without co-payment, and income-based subsidies are available for prescription medications. Thus, if baseline SES does have an independent effect on the incremental costs of SARDs, it would impact patients in ways other than their ability to purchase health care, especially physician and hospital care.

Low-SES individuals may put off seeking care for initial symptoms, or experience organisational barriers in accessing specialty or follow-up care, which delays diagnosis and initiation of treatment until the point where hospitalisation is required. In the SLE and SjS cohorts, low SES patients were more likely than the high SES to be identified from hospitalisation data (versus physician billings data), controlling for urban/rural residence, age, sex, comorbidities, and baseline levels of healthcare utilisation (OR=1.42 (95% CI=1.22-1.65) for SLE and 1.47 (95% CI=1.07-2.02) for SjS). Low household income has been associated with delayed presentation to rheumatology care among paediatric SLE patients in the USA(386), and while that may be less of an issue in BC, where access to primary and specialist care is more universal, socioeconomic disparities in specialist care and receipt of treatment have been reported for other arthritides in BC. Among rheumatoid arthritis patients, high SES was associated with higher odds of receiving specialist care, or treatment with DMARDs(11), while among osteoarthritis patients, the highest-SES individuals were more likely to see an orthopaedic surgeon, and undergo total joint arthroplasty(311).

Differences in health behaviours may also contribute to this disparity in costs since, in general populations(387–389), and SLE specifically(234), smoking and obesity rates tend to be higher in low SES groups. Smoking has been associated with poorer SARD-specific health

outcomes, including higher levels of disease activity in SLE(390), and poorer digital ischaemic (391,392) and respiratory(393) outcomes in SSc. In turn, SLE disease activity, and SSc disease activity and severity, have been associated with higher direct medical costs(218,253). While the role of body mass index (BMI) on SLE-specific outcomes is not clear(394), higher BMI did increase the risk for hospitalisation for SLE flare in one Canadian study(395). Unfortunately, as I did not have information on smoking or BMI in the administrative data, I could not assess the prevalence of these factors across SES groups or their impact on costs.

Additionally, SARDs are associated with an elevated risk of certain cardiovascular complications, including myocardial infarction (MI), stroke, and venous thromboembolism(42–51,53–56,58), and it is possible that the low-SES SARD patients in my cohort developed more of these complications than the high SES. Support is provided by findings from the Hopkins Lupus Cohort(234), where the lowest-income White SLE patients had approximately three-times greater odds of MI and cerebrovascular accident (CVA) than the highest-income Whites, and from the UK(396), where GCA patients living in the most deprived areas had an increased risk of CVA and cardiovascular disease than the least-deprived. Assessing the risk of complications between SES groups was beyond the scope of my thesis, but should be investigated in future studies. If low-SES SARD patients do have an excess risk of these costly complications, targeted efforts to mitigate these risks may help reduce disparities in outcomes and costs.

The role of race/ethnicity also bears consideration since SLE and SSc are more prevalent among those of African(20,21,23–26), Hispanic(20,21,25), and Aboriginal descent(27–29), groups that tend to be more socioeconomically disadvantaged and have poorer health outcomes.

In a study from the Canadian province of Manitoba(28), Aboriginal patients with SLE had higher levels of disease activity at diagnosis than Caucasian patients, accumulated more damage over time, and had higher mortality. However, evidence suggests it is income level, and not ethnicity, that contributes to the higher damage accrual(231) and mortality(397) observed in these SLE patients, although race and genetics may be a determinant of the clinical course of SSc(398). Unfortunately, as with health behaviours, information on race/ethnicity was not available in the administrative data, so its impact could not be assessed.

3.4.4 Measurement of socioeconomic status

My findings on the impact of SES must be considered in light of the complexities of defining and measuring SES. Because my administrative data did not contain information on absolute individual or household income, educational attainment, or occupation, SES was defined primarily by neighbourhood income level. This measure has been used in other studies from BC(311,312), and one strength is that it is a measure of relative income, within one area of the province. Due to regional variations in housing prices and other aspects of cost-of-living, categories of absolute household income may not be a reliable measure of financial resources.

It is certainly possible that the high-cost individuals residing in low-income neighbourhoods may not have had low incomes themselves, and vice-versa. Two studies from BC compared census-derived income groupings with actual household income data, and agreement between the two was fair/poor(346,399). In the first(399), the highest kappa values (measure of agreement, beyond that expected by chance, between neighbourhood income decile and household income as reported on tax returns) were 0.26 overall, and 0.31 among non-seniors

(considered as fair agreement(400)). In the second study(346), which included cohorts of RA (79% female, mean age 61.2 ± 13.8), diabetes (48% female, mean age 56.9 ± 13.1), and asthma (64% female, mean age 36.8 ± 8.4), the self-reported household income grouping tended to be lower than the area-derived income grouping, with intra-class correlation coefficients ranging from 0.15 (95% CI=0.03-0.28) for RA to 0.29 (95% CI=0.17-0.39) for asthma (correlation coefficients of < 0.40 were considered as poor agreement). Agreement was poorest for those in the lowest self-reported income group. However, those authors(346) point out that one's current level of household income may not be the best measure of overall SES, especially if one or more household members are retired. Moreover, particularly in a universal healthcare setting, neighbourhood-level factors such as walkability, levels of crowding and noise, and distance from healthcare services, may have a greater influence on health outcomes and costs than individual/household income. Additional support is provided by the Lupus Outcomes Study(235) in the US, where there were similar associations between SES and levels of disease activity, physical functioning, and depressive symptoms when SES (poverty status) was measured at the individual- and neighbourhood-level.

Still, in an exploratory analysis, I compared estimates of the incremental costs of SLE before and after income assistance (a proxy of individual-level SES) was added to the models. Nearly two-thirds of income assistance recipients were also in the low neighbourhood-SES group. After controlling for individual-level SES, the excess in incremental hospitalisation and outpatient costs for the low neighbourhood-SES patients (over-and-above the high-SES) decreased by 17% (by \$307 and \$19 per-person-year, respectively), while the excess in medication costs decreased by 119%, from +\$40 to -\$7. This suggests that individual-level SES

(at least, how it was defined in this study) had little influence on the incremental outpatient and hospitalisation costs of SLE *beyond* neighbourhood-level SES. Individual-level SES had a greater impact on incremental medication costs, with predicted incremental costs increasing by \$58 per-person-year among the high neighbourhood-SES, and \$10 per-person-year among the low neighbourhood-SES. However, this may be an artifact of using income assistance (which was captured from the prescription medication dataset) to classify individual SES. Income assistance recipients were those dispensed at least one prescription coded as Plan C (income assistance plan) during the 365-days before index date, while the ‘non-recipient’ group was comprised of those with and without any prescriptions, and included those dispensed prescriptions under other BC public plans, and federal plans. Nevertheless, these findings still provide evidence of an association between low SES (whether measured at the individual or area level) and an excess in the incremental medical costs of SLE.

3.4.5 Strengths and limitations

The strengths and limitations of this analysis stem mainly from the administrative data source. Some of the limitations discussed earlier include the absence of data on race/ethnicity, educational attainment, absolute individual/household income, and health behaviours. Data on disease-specific measures such as disease activity, damage, and serological markers, were not available either, nor were patient-reported outcome measures. Thus, I was unable to determine the incremental costs associated with more severe disease, as has been done by other groups(32,214,219,220), or assess the impact of patient-reported outcomes (such as physical functioning and fatigue) on costs.

My SARD cohorts were identified from ICD codes, and the diagnoses were not clinically confirmed. However, most were identified by a rheumatologist or hospitalisation (including 85% of SLE, 88% of GPA, and 91% of SSc), and studies assessing the validity of these codes and algorithms have generally supported their use in identifying SARDs. In another Canadian province (Nova Scotia), Bernatsky *et al.*(333) assessed an algorithm nearly identical to the one I used, and the reported sensitivity and specificity for most SARDs were $\geq 88\%$ and $\geq 95\%$, respectively. In a subsequent assessment of several case definitions for SLE in the Nova Scotia databases, the definition closest to the one I used had a sensitivity of 85%, specificity of 98%, and positive predictive value of 91%(401). There is additional evidence from Europe supporting the validity of diagnostic codes for GCA(334), GPA(76,336,337), and Takayasu's(335).

To ensure only incident cases were included, all individuals were required to have five years of follow-up in the databases before index date, during which time they did not meet the case definition for the SARD in question. The mean age at diagnosis for my SLE cohort (49.9 years) is higher than often reported in clinic-based studies(209,231,380), but consistent with that reported for population-based cohorts of newly-diagnosed SLE in multiple countries(59,89–92,202,203,210). It may be that individuals with late-onset SLE (≥ 50 years of age at diagnosis), a subset associated with milder disease, including lower disease activity(402–407), fewer flares(407), and less renal involvement/nephritis(402–408), are under-represented in clinic-based cohorts.

This analysis was conducted mainly from the provincial healthcare system (payer) perspective, but I nevertheless acknowledge my estimates do not include costs for healthcare

utilisation not funded by the provincial government (aside from filled prescriptions, whose costs are captured regardless of payer), and not captured in the databases, including non-prescription medications, complementary therapies, and most allied health visits after April 2002.

Still, accessing administrative data from a single-payer healthcare system allowed me to study nearly all newly-diagnosed individuals who sought care for SARDs in the province over 15 years, regardless of age, employment status, urban/rural residence, disease severity, or care provider (i.e. rheumatologist, nephrologist, or general practitioner). I was able to capture their longitudinal healthcare costs, including virtually all community-dispensed prescription medications (regardless of age or funding source), right from diagnosis. This is an improvement upon registries and clinic-based inception cohorts, where patients may be enrolled up to 15 months after diagnosis(380), and those who die shortly after diagnosis may not be enrolled at all. The databases also allowed me to compare the costs of SARD cases to a sample of the general population, which served to enhance the external validity of my findings.

3.5 Conclusion

In this chapter, I reported on the total and incremental healthcare utilisation and direct medical costs of SARDs at the general population level. I found costs are highest in the first year after diagnosis, with the majority of costs from hospitalisations, decrease sharply in the second year, then remain relatively stable for the next three years. A similar pattern was observed among individuals followed for the entire five-year period. This is encouraging and suggests the decrease in costs during Year +2 is likely due to stabilisation of the disease and fewer hospitalisations, and not just removal of high-cost individuals due to mortality. These cost

estimates will serve as the benchmark for future studies, and could contribute to cost-effectiveness analyses of new therapies or models of care for SARDs, particularly in the Canadian setting.

Using data from the SARD and non-SARD individuals, I also determined the adjusted, incremental per-person-year healthcare costs of SARDs overall, and by SES group. After adjustment for age, sex, urban/rural residence, baseline comorbidities, and baseline healthcare utilisation, and accounting for unequal follow-up times, the incremental costs of SARDs ranged from \$7,851 to \$54,061 per-person-year. More importantly, I found these incremental costs (costs for SARDs over-and-above those expected for the general population) tended to be higher among individuals of low socioeconomic status. Research should now focus on identifying the reasons for this variation (i.e. delayed diagnosis or gaps in care for SARDs, higher rates of SARDs-associated complications), and how to reduce these disparities and mitigate the burden of these chronic diseases.

In the next chapter, I assess the incremental healthcare utilisation and direct medical costs of SLE patients over the five years leading up to diagnosis. Specifically, I build on this work on the impact of low SES after diagnosis, and assess the impact of SES on costs for SLE in each of the five years before diagnosis. I also investigate the impact of sex on these costs.

Table 3.1: Baseline Characteristics of Individuals With and Without Systemic Lupus Erythematosus (SLE)

	SLE	Non-SLE	p-value
N	4,679	23,219	-
N (%) Female	4,004 (86%)	19,851 (86%)	0.89
Mean (SD) Age	49.9 (16.0)	50.0 (15.6)	0.72
Median (IQR) Age	50 (13)	50 (12)	0.74
N (%) Rural Residence	695 (15%)	2,732 (12%)	< 0.01*
Mean (SD) Charlson-Romano Comorbidity Score	0.43 (0.50)	0.13 (0.34)	< 0.01*
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	26.8 (21.3)	11.6 (11.9)	< 0.01*
Mean (SD) Months of Follow-Up (maximum 60)	51.5 (15.5)	56.9 (7.3)	< 0.01*
N (%) Complete Five-Year Follow-up	2,954 (63%)	17,981 (77%)	< 0.01*
N (%) Deaths During Follow-Up	701 (15%)	360 (2%)	< 0.01*
Source of Diagnosis, N (%)			
Hospitalisation	1,287 (28%)	-	-
Physician Billings - Rheumatologist	2,720 (58%)	-	-
Physician Billings - Other Physician	690 (15%)	-	-

	SLE	Non-SLE	p-value
Socioeconomic Status, N (%)			
Low	1938 (41%)	9,244 (40%)	< 0.01*
Moderate	981 (21%)	4,599 (20%)	
High	1,760 (38%)	9,371 (40%)	

Table 3.2: Baseline Characteristics of Individuals With and Without Systemic Sclerosis (SSc)

	SSc	Non-SSc	p-value
N	1,230	12,271	-
N (%) Female	1,011 (82%)	10,083 (82%)	0.98
Mean (SD) Age	57.4 (0.41)	57.3 (0.13)	0.75
Median (IQR) Age	58 (21)	58 (21)	0.72
N (%) Rural Residence	203 (17%)	1,455 (12%)	< 0.01
Mean (SD) Charlson-Romano Comorbidity Score	0.46 (0.50)	0.16 (0.37)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	28.1 (21.7)	12.8 (12.6)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	45.9 (19.5)	56.9 (7.4)	< 0.01
N (%) Complete Five-Year Follow- up	617 (50%)	9,530 (78%)	< 0.01
N (%) Deaths During Follow-Up	373 (30%)	311 (3%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	517 (42%)	-	-
Physician Billings - Rheumatologist	605 (49%)	-	-
Physician Billings - Other Physician	115 (9%)	-	-

	SSc	Non-SSc	p-value
Socioeconomic Status, N (%)			
Low	478 (39%)	4,843 (39%)	0.68
Moderate	258 (21%)	2,444 (20%)	
High	494 (40%)	4,983 (41%)	

Table 3.3: Baseline Characteristics of Individuals With and Without Sjogren's Syndrome (SjS)

	SjS	Non-SjS	p-value
N	1,120	11,156	
N (%) Female	983 (88%)	9,795 (88%)	0.97
Mean (SD) Age	57.6 (14.8)	57.4 (14.5)	0.61
Median (IQR) Age	58 (20)	57 (20)	0.53
N (%) Rural Residence	159 (14%)	1,340 (12%)	0.03)
Mean (SD) Charlson-Romano Comorbidity Score	0.44 (0.50)	0.17 (0.34)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	27.2 (21.1)	12.9 (12.6)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	49.9 (15.7)	55.8 (8.0)	< 0.01
N (%) Complete Five-Year Follow-up	582 (52%)	7,559 (68%)	< 0.01
N (%) Deaths During Follow-Up	201 (18%)	328 (3%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	273 (24%)	-	-
Physician Billings - Rheumatologist	732 (65%)	-	-
Physician Billings - Other Physician	116 (10%)	-	-

	SjS	Non-SjS	p-value
Socioeconomic Status, N (%)			
Low	446 (40%)	4,540 (41%)	0.76
Moderate	213 (19%)	2,149 (19%)	
High	461 (41%)	4,465 (40%)	

Table 3.4: Baseline Characteristics of Individuals With and Without Polymyositis (PM)

	PM	Non-PM	p-value
N	427	4,254	-
N (%) Female	245 (57%)	2,447 (58%)	0.95
Mean (SD) Age	61.6 (15.0)	61.4 (14.8)	0.77
Median (IQR) Age	63 (22)	63 (20)	0.76
N (%) Rural Residence	59 (14%)	537 (13%)	0.46
Mean (SD) Charlson-Romano Comorbidity Score	0.49 (0.50)	0.19 (0.39)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	33.0 (21.4)	13.5 (14.2)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	42.4 (21.6)	56.5 (8.1)	< 0.01
N (%) Complete Five-Year Follow-up	183 (43%)	3,243 (76%)	< 0.01
N (%) Deaths During Follow-Up	156 (37%)	171 (4%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	194 (45%)	-	-
Physician Billings - Rheumatologist	155 (36%)	-	-
Physician Billings - Other Physician	80 (19%)	-	-

	PM	Non-PM	p-value
Socioeconomic Status, N (%)			
Low	198 (46%)	1,680 (39%)	0.02
Moderate	76 (18%)	881 (21%)	
High	153 (36%)	1,693 (40%)	

Table 3.5: Baseline Characteristics of Individuals With and Without Dermatomyositis (DM)

	DM	Non-DM	p-value
N	331	3,292	-
N (%) Female	211 (64%)	2,104 (64%)	0.95
Mean (SD) Age	57.4 (16.1)	57.2 (16.0)	0.88
Median (IQR) Age	58 (24)	58 (24)	0.92
N (%) Rural Residence	51 (15%)	408 (12%)	0.11
Mean (SD) Charlson-Romano Comorbidity Score	0.47 (0.50)	0.17 (0.38)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	30.1 (20.3)	12.8 (14.0)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	41.5 (22.6)	56.7 (8.1)	< 0.01
N (%) Complete Five-Year Follow-up	146 (44%)	2,511 (76%)	< 0.01
N (%) Deaths During Follow-Up	118 (36%)	97 (3%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	150 (45%)	-	-
Physician Billings - Rheumatologist	123 (37%)	-	-
Physician Billings - Other Physician	61 (18%)	-	-

	DM	Non-DM	p-value
Socioeconomic Status, N (%)			
Low	148 (45%)	1,300 (40%)	0.15
Moderate	59 (18%)	681 (21%)	
High	123 (37%)	1,310 (40%)	

Table 3.6: Baseline Characteristics of Individuals With and Without Polyarteritis Nodosa (PAN)

	PAN	Non-PAN	p-value
N	210	2,099	-
N (%) Female	131 (62%)	1,309 (62%)	> 0.99
Mean (SD) Age	65.9 (16.3)	65.8 (16.2)	0.92
Median (IQR) Age	69.5 (22)	70 (22)	0.86
N (%) Rural Residence	29 (14%)	262 (13%)	0.59
Mean (SD) Charlson-Romano Comorbidity Score	0.53 (0.50)	0.23 (0.42)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	33.9 (24.5)	14.7 (13.7)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	42.8 (21.4)	55.8 (9.0)	< 0.01
N (%) Complete Five-Year Follow-up	93 (44%)	1,519 (72%)	< 0.01
N (%) Deaths During Follow-Up	70 (33%)	142 (7%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	78 (37%)	-	-
Physician Billings - Rheumatologist	81 (39%)	-	-
Physician Billings - Other Physician	51 (24%)	-	-

	PAN	Non-PAN	p-value
Socioeconomic Status, N (%)			
Low	79 (38%)	85 (41%)	0.33
Moderate	40 (19%)	443 (21%)	
High	91 (43%)	800 (38%)	

Table 3.7: Baseline Characteristics of Individuals With and Without Giant Cell Arteritis (GCA)

	GCA	Non-GCA	p-value
N	844	8,214	-
N (%) Female	608 (72%)	5,952 (72%)	0.79
Mean (SD) Age	76.4 (9.1)	75.5 (8.9)	0.01
Median (IQR) Age	78 (12)	77 (12)	< 0.01
N (%) Rural Residence	122 (14%)	1,003 (12%)	0.06
Mean (SD) Charlson-Romano Comorbidity Score	0.53 (0.50)	0.29 (0.45)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	31.5 (19.0)	17.4 (15.5)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	39.5 (21.2)	53.7 (12.3)	< 0.01
N (%) Complete Five-Year Follow-up	296 (35%)	5,610 (68%)	< 0.01
N (%) Deaths During Follow-Up	389 (46%)	1,135 (14%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	401 (48%)	-	-
Physician Billings - Rheumatologist	235 (28%)	-	-
Physician Billings - Other Physician	212 (25%)	-	-

	GCA	Non-GCA	p-value
Socioeconomic Status, N (%)			
Low	342 (41%)	3,528 (43%)	0.04*
Moderate	151 (18%)	1,626 (20%)	
High	351 (42%)	3,060 (37%)	

Table 3.8: Baseline Characteristics of Individuals With and Without Granulomatosis with Polyangiitis (GPA)

	GPA	Non-GPA	p-value
N	472	4,710	-
N (%) Female	248 (53%)	2,472 (52%)	0.98
Mean (SD) Age	60.9 (16.4)	60.8 (16.3)	0.89
Median (IQR) Age	63 (22)	63 (23)	0.86
N (%) Rural Residence	69 (15%)	603 (13%)	0.27
Mean (SD) Charlson-Romano Comorbidity Score	0.56 (0.50)	0.20 (0.40)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	35.3 (30.4)	13.4 (13.3)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	42.9 (22.2)	55.9 (8.8)	< 0.01
N (%) Complete Five-Year Follow-up	229 (49%)	3,487 (74%)	< 0.01
N (%) Deaths During Follow-Up	161 (34%)	215 (5%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	329 (70%)	-	-
Physician Billings - Rheumatologist	93 (20%)	-	-
Physician Billings - Other Physician	55 (12%)	-	-

	GPA	Non-GPA	p-value
Socioeconomic Status, N (%)			
Low	206 (44%)	1,885 (40%)	0.25
Moderate	88 (19%)	991 (21%)	
High	178 (38%)	1,834 (39%)	

Table 3.9: Baseline Characteristics of Individuals With and Without Takayasu's Arteritis

	Takayasu's arteritis	Non-Takayasu's arteritis	p-value
N	50	500	-
N (%) Female	41 (82%)	410 (82%)	> 0.99
Mean (SD) Age	51.9 (20.6)	51.9 (20.3)	0.99
Median (IQR) Age	50.5 (34)	51 (35.5)	0.99
N (%) Rural Residence	7 (14%)	52 (10%)	0.44
Mean (SD) Charlson-Romano Comorbidity Score	0.60 (0.49)	0.16 (0.37)	< 0.01
Mean (SD) Number of Healthcare Visits Prior to Diagnosis	35.9 (32.1)	13.1 (13.1)	< 0.01
Mean (SD) Months of Follow-Up (maximum 60)	46.4 (19.4)	56.9 (7.3)	< 0.01
N (%) Complete Five-Year Follow-up	27 (54%)	399 (80%)	< 0.01
N (%) Deaths During Follow-Up	13 (26%)	16 (3%)	< 0.01
Source of Diagnosis, N (%)			
Hospitalisation	23 (46%)	-	-
Physician Billings - Rheumatologist	24 (48%)	-	-
Physician Billings - Other Physician	< 6	-	-

	Takayasu’s arteritis	Non-Takayasu’s arteritis	p-value
Socioeconomic Status, N (%)			
Low	25 (50%)	202 (40%)	0.42
Moderate	9 (18%)	103 (21%)	
High	16 (32%)	195 (39%)	

Values not reported for cell sizes < 6

Table 3.10: Unadjusted Annual Overall Mean Per-Person Direct Medical Costs for each SARD and non-SARD Group, and Incremental Costs

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Systemic Lupus Erythematosus: All Individuals						
1	\$13,038	-	\$2,431	-	\$10,607	5.4
2	\$7,570	-42%	\$2,647	9%	\$4,923	2.9
3	\$7,192	-5%	\$2,698	2%	\$4,494	2.7
4	\$6,768	-6%	\$2,720	1%	\$4,047	2.5
5	\$7,183	6%	\$2,791	3%	\$4,392	2.6
Five-Year Average	\$8,514	-	\$2,653	-	\$5,861	3.2
Systemic Lupus Erythematosus: Individuals with Five Years' Follow-Up						
1	\$9,809	-	\$2,216	-	\$7,593	4.4
2	\$6,279	-36%	\$2,383	8%	\$3,896	2.6
3	\$5,897	-6%	\$2,480	4%	\$3,417	2.4
4	\$6,114	4%	\$2,661	7%	\$3,453	2.3
5	\$6,569	7%	\$2,850	7%	\$3,719	2.3
Five-Year Average	\$6,939	-	\$2,519	-	\$4,420	2.8

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Systemic Sclerosis: All Individuals						
1	\$17,354	-	\$2,925	-	\$14,428	5.9
2	\$10,621	-39%	\$3,099	6%	\$7,522	3.4
3	\$10,628	0%	\$3,174	2%	\$7,454	3.3
4	\$11,116	5%	\$3,270	3%	\$7,846	3.4
5	\$9,593	-14%	\$3,456	6%	\$6,137	2.8
Five-Year Average	\$12,234	-	\$3,177		\$9,057	3.9
Systemic Sclerosis: Individuals with Five Years' Follow-Up						
1	\$10,530	-	\$2,614	-	\$7,916	4.0
2	\$6,616	-37%	\$2,829	8%	\$3,786	2.3
3	\$7,103	7%	\$2,941	4%	\$4,163	2.4
4	\$8,010	13%	\$3,182	8%	\$4,828	2.5
5	\$8,615	8%	\$3,455	9%	\$5,160	2.5
Five-Year Average	\$8,181	-	\$3,005	-	\$5,176	2.7

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Sjogren’s Syndrome: All Individuals						
1	\$11,630	-	\$3,079	-	\$8,551	3.8
2	\$7,159	-38%	\$3,302	7%	\$3,857	2.2
3	\$7,165	0%	\$3,370	2%	\$3,795	2.1
4	\$6,907	-4%	\$3,347	-1%	\$3,560	2.1
5	\$5,506	-20%	\$3,277	-2%	\$2,229	1.7
Five-Year Average	\$7,885	-	\$3,274	-	\$4,611	2.4
Sjogren’s Syndrome: Individuals with Five Years’ Follow-Up						
1	\$6,845	-	\$2,734	-	\$4,111	2.5
2	\$4,818	-30%	\$2,962	8%	\$1,856	1.6
3	\$5,414	12%	\$3,081	4%	\$2,332	1.8
4	\$5,952	10%	\$3,369	9%	\$2,583	1.8
5	\$5,828	-2%	\$3,423	2%	\$2,404	1.7
Five-Year Average	\$5,773	-	\$3,115	-	\$2,658	1.9

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Polymyositis: All Individuals						
1	\$24,619	-	\$3,352	-	\$21,267	7.3
2	\$13,518	-45%	\$3,807	14%	\$9,711	3.6
3	\$11,426	-15%	\$3,926	3%	\$7,499	2.9
4	\$11,148	-2%	\$3,845	-2%	\$7,303	2.9
5	\$11,251	1%	\$3,898	1%	\$7,353	2.9
Five-Year Average	\$15,326	-	\$3,761	-	\$11,565	4.1
Polymyositis: Individuals with Five Years' Follow-Up						
1	\$16,427	-	\$2,935	-	\$13,492	5.6
2	\$6,860	-58%	\$3,243	11%	\$3,617	2.1
3	\$7,781	13%	\$3,585	11%	\$4,196	2.2
4	\$7,254	-7%	\$3,645	2%	\$3,609	2.0
5	\$8,611	19%	\$3,899	7%	\$4,712	2.2
Five-Year Average	\$9,403	-	\$3,463	-	\$5,94	2.7

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Dermatomyositis: All Individuals						
1	\$27,012	-	\$3,104	-	\$23,908	8.7
2	\$11,194	-59%	\$3,492	12%	\$7,703	3.2
3	\$11,408	2%	\$3,492	0%	\$7,916	3.3
4	\$8,823	-23%	\$3,647	4%	\$5,176	2.4
5	\$6,583	-25%	\$3,700	1%	\$2,883	1.8
Five-Year Average	\$14,430	-	\$3,480		\$10,950	4.1
Dermatomyositis: Individuals with Five Years' Follow-Up						
1	\$19,984	-	\$2,843	-	\$17,142	7.0
2	\$7,063	-65%	\$3,250	14%	\$3,813	2.2
3	\$5,491	-22%	\$3,394	4%	\$2,097	1.6
4	\$6,087	11%	\$3,523	4%	\$2,564	1.7
5	\$5,951	-2%	\$3,783	7%	\$2,167	1.6
Five-Year Average	\$8,964	-	\$3,360		\$5,604	2.7

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Polyarteritis Nodosa: All Individuals						
1	\$24,709	-	\$4,101	-	\$20,608	6.0
2	\$13,179	-47%	\$4,049	-1%	\$9,131	3.3
3	\$12,523	-5%	\$4,906	21%	\$7,618	2.6
4	\$8,320	-34%	\$5,017	2%	\$3,303	1.7
5	\$8,049	-3%	\$4,730	-6%	\$3,319	1.7
Five-Year Average	\$14,440	-	\$4,551		\$9,889	3.2
Polyarteritis Nodosa: Individuals with Five Years' Follow-Up						
1	\$15,613	-	\$3,141	-	\$12,471	5.0
2	\$7,761	-50%	\$3,444	10%	\$4,317	2.3
3	\$6,397	-18%	\$3,997	16%	\$2,400	1.6
4	\$6,026	-6%	\$4,509	13%	\$1,517	1.3
5	\$7,570	26%	\$4,809	7%	\$2,761	1.6
Five-Year Average	\$8,684	-	\$3,983	-	\$4,701	2.2

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Giant Cell Arteritis: All Individuals						
1	\$20,781	-	\$4,866	-	\$15,916	4.3
2	\$11,640	-44%	\$5,302	9%	\$6,338	2.2
3	\$11,003	-5%	\$5,751	8%	\$5,253	1.9
4	\$9,893	-10%	\$5,592	-3%	\$4,301	1.8
5	\$9,536	-4%	\$5,495	-2%	\$4,041	1.7
Five-Year Average	\$13,503	-	\$5,401	-	\$8,102	1.6
Giant Cell Arteritis: Individuals with Five Years' Follow-Up						
1	\$11,971	-	\$3,675	-	\$8,297	3.3
2	\$8,556	-29%	\$4,219	15%	\$4,337	2.0
3	\$8,110	-5%	\$4,928	17%	\$3,182	1.6
4	\$9,857	22%	\$5,128	4%	\$4,729	1.9
5	\$9,410	-5%	\$5,460	6%	\$3,949	1.7
Five-Year Average	\$9,582	-	\$4,683	-	\$4,899	2.0

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Granulomatosis with Polyangiitis: All Individuals						
1	\$38,197	-	\$3,462	-	\$34,734	11.0
2	\$12,341	-68%	\$3,729	8%	\$8,612	3.3
3	\$11,943	-3%	\$3,962	6%	\$7,980	3.0
4	\$11,162	-7%	\$3,831	-3%	\$7,331	2.9
5	\$13,378	20%	\$3,999	4%	\$9,379	3.3
Five-Year Average	\$18,998	-	\$3,789	-	\$15,209	5.0
Granulomatosis with Polyangiitis: Individuals with Five Years' Follow-Up						
1	\$27,316	-	\$2,903	-	\$24,413	9.4
2	\$9,793	-64%	\$3,226	11%	\$6,567	3.0
3	\$9,685	-1%	\$3,428	6%	\$6,256	2.8
4	\$10,236	6%	\$3,587	5%	\$6,649	2.9
5	\$13,459	31%	\$4,003	12%	\$9,456	3.4
Five-Year Average	\$14,128	-	\$3,432	-	\$10,696	4.1

Year After Diagnosis /Index Date	Mean Per-Person Costs	Annual %-Change	Mean Per-Person Costs	Annual %-Change	Unadjusted Incremental Costs	Unadjusted Cost Ratio
	SARD		Non-SARD			
Takayasu’s Arteritis: All Individuals						
1	\$21,927	-	\$3,724	-	\$18,203	5.9
2	\$10,899	-50%	\$2,742	-26%	\$8,158	4.0
3	\$7,174	-34%	\$3,576	30%	\$3,599	2.0
4	\$12,627	76%	\$3,829	7%	\$8,798	3.3
5	\$8,414	-33%	\$3,264	-15%	\$5,151	2.6
Five-Year Average	\$12,821	-	\$3,429	-	\$9,392	3.7
Takayasu’s Arteritis: Individuals with Five Years’ Follow-Up						
1	\$13,603	-	\$2,920	-	\$10,683	4.7
2	\$6,366	-53%	\$2,446	-16%	\$3,920	2.6
3	\$5,571	-12%	\$2,769	13%	\$2,802	2.0
4	\$8,637	55%	\$3,322	20%	\$5,314	2.6
5	\$9,326	8%	\$3,099	-7%	\$6,227	3.0
Five-Year Average	\$8,696	-	\$2,911	-	\$5,785	3.0

Table 3.11: Predicted Costs for SARDs and Non-SARDs, and Predicted Incremental Costs of SARDs

	Overall	Outpatient	Medication	Hospitalisation
Systemic Lupus Erythematosus (SLE)				
SLE	\$12,787	\$2,614	\$1,841	\$8,333
Non-SLE	\$2,709	\$866	\$1,057	\$786
Difference, 95% CI	\$10,078 (\$2,062-\$32,254)	\$1,747 (\$762-\$4,342)	\$784 (\$203-\$2,541)	\$7,547 (\$898-\$25,823)
Systemic Sclerosis (SSc)				
SSc	\$19,415	\$3,314	\$2,711	\$13,389
Non-SSc	\$3,257	\$1,045	\$1,157	\$1,056
Difference, 95% CI	\$16,157 (\$3,473-\$43,899)	\$2,270 (\$838-\$5,794)	\$1,554 (\$362-\$4,956)	\$12,333 (\$2,040-\$34,043)
Sjogren's Syndrome (SjS)				
SjS	\$11,268	\$2,257	\$1,585	\$7,426
Non-SjS	\$3,417	\$1,048	\$1,265	\$1,104
Difference, 95% CI	\$7,851 (\$1,278-\$26,218)	\$1,209 (\$433-\$3,281)	\$319 (\$88-\$994)	\$6,323 (\$697-\$22,396)
Polymyositis (PM)				
PM	\$36,043	\$4,482	\$2,074	\$29,488
Non-PM	\$3,914	\$1,152	\$1,336	\$1,426
Difference, 95% CI	\$32,129 (\$4,810-\$82,161)	\$3,330 (\$978-\$8,685)	\$738 (\$68-\$2,560)	\$28,061 (\$3,400-\$71,995)

	Overall	Outpatient	Medication	Hospitalisation
Dermatomyositis (DM)				
DM	\$46,338	\$6,089	\$2,681	\$37,569
Non-DM	\$3,689	\$1,075	\$1,443	\$1,171
Difference, 95% CI	\$42,649 (\$4,884-\$99,304)	\$5,014 (\$1,249-\$12,581)	\$1,237 (\$71-\$4,194)	\$36,398 (\$2,857-\$85,341)
Polyarteritis Nodosa (PAN)				
PAN	\$41,527	\$4,850	\$1,663	\$35,014
Non-PAN	\$4,607	\$1,247	\$1,400	\$1,960
Difference, 95% CI	\$36,920 (\$3,336-\$97,233)	\$3,603 (\$993-\$9,584)	\$263 (\$3-\$1,059)	\$33,054 (\$2,092-\$95,137)
Giant Cell Arteritis (GCA)				
GCA	\$28,857	\$4,112	\$1,944	\$22,801
Non-GCA	\$5,570	\$1,399	\$1,488	\$2,682
Difference, 95% CI	\$23,287 (\$4,168-\$47,100)	\$2,713 (\$915-\$6,346)	\$456 (\$184-\$1,103)	\$20,119 (\$2,875-\$40,690)

	Overall	Outpatient	Medication	Hospitalisation
Granulomatosis with Polyangiitis (GPA)				
GPA	\$57,832	\$7,034	\$3,177	\$47,621
Non-GPA	\$3,772	\$1,117	\$1,230	\$1,424
Difference, 95% CI	\$54,061 (\$6,330-\$125,917)	\$5,917 (\$1,597-\$15,827)	\$1,947 (\$404-\$6,123)	\$46,197 (\$3,070-\$106,027)
Takayasu's arteritis				
Takayasu's	\$21,149	\$5,189	\$3,754	\$12,206
Non-Takayasu's	\$4,684	\$1,303	\$1,857	\$1,524
Difference, 95% CI	\$16,465 (\$2,741-\$60,656)	\$3,887 (\$1,343-\$14,162)	\$1,897 (\$438-\$9,622)	\$10,682 (\$1,316-\$52,701)

All differences were statistically-significant

Table 3.12: Predicted Incremental Costs of SARDs, by Neighbourhood Socioeconomic Group

	Overall	Outpatient	Medication	Hospitalisation
Systemic Lupus Erythematosus (SLE)				
Low	\$11,146	\$1,805	\$798	\$8,544
Moderate	\$9,584	\$1,730	\$806	\$7,048
High	\$9,225	\$1,694	\$757	\$6,773
Difference (Low – High), 95% CI	\$1,922 (\$327-\$5,645)	\$111 (\$47-\$266)	\$40 (\$11-\$131)	\$1,770 (\$254-\$5,246)
Systemic Sclerosis (SSc)				
Low	\$17,425	\$2,296	\$1,509	\$13,619
Moderate	\$15,086	\$2,313	\$1,674	\$11,099
High	\$15,430	\$2,219	\$1,550	\$11,661
Difference (Low – High), 95% CI	\$1,995 (\$401-\$4,753)	\$77 (\$28-\$198)	-\$41 (-\$122 - -\$12)	\$1,958 (\$391-\$4,681)
Sjogren’s Syndrome (SjS)				
Low	\$8,976	\$1,239	\$323	\$7,414
Moderate	\$7,180	\$1,195	\$335	\$5,650
High	\$6,978	\$1,183	\$308	\$5,487
Difference (Low – High), 95% CI	\$1,997 (\$268-\$6,176)	\$56 (\$21-\$147)	\$14 (\$4-\$45)	\$1,927 (\$237-\$5,986)

	Overall	Outpatient	Medication	Hospitalisation
Polymyositis (PM)				
Low	\$31,766	\$3,347	\$711	\$27,708
Moderate	\$32,895	\$3,361	\$848	\$28,686
High	\$32,140	\$3,290	\$713	\$28,136
Difference (Low – High), 95% CI	-\$374 (-\$2,695 - \$228)	\$57 (-\$11-\$151)	-\$3 (-\$5 - \$2)	-\$428 (-\$2,862 - \$203)
Dermatomyositis (DM)				
Low	\$48,109	\$5,095	\$1,228	\$41,785
Moderate	\$37,870	\$5,094	\$1,369	\$31,407
High	\$39,694	\$4,877	\$1,179	\$33,639
Difference (Low – High), 95% CI	\$8,414 (\$900-\$17,172)	\$218 (\$54-\$548)	\$50 (-\$3 - \$203)	\$8,147 (\$802-\$16,550)
Polyarteritis Nodosa (PAN)				
Low	\$39,828	\$3,650	\$266	\$35,912
Moderate	\$37,075	\$3,604	\$306	\$33,165
High	\$33,565	\$3,549	\$233	\$29,783
Difference (Low – High), 95% CI	\$6,263 (\$568-\$13,847)	\$101 (\$27-\$269)	\$33 (\$0-\$138)	\$6,129 (\$520-\$13,528)

	Overall	Outpatient	Medication	Hospitalisation
Giant Cell Arteritis (GCA)				
Low	\$24,634	\$2,710	\$461	\$21,463
Moderate	\$22,993	\$2,699	\$474	\$19,819
High	\$21,844	\$2,722	\$440	\$18,681
Difference (Low – High), 95% CI	\$2,790 (\$426-\$5,491)	-\$12 (-\$28 - -\$4)	\$21 (\$9-\$45)	\$2,782 (\$417-\$5,480)
Granulomatosis with Polyangiitis (GPA)				
Low	\$55,276	\$5,869	\$1,904	\$47,503
Moderate	\$54,774	\$5,957	\$2,197	\$46,620
High	\$52,359	\$5,946	\$1,857	\$44,557
Difference (Low – High), 95% CI	\$2,917 (\$180-\$6,905)	-\$77 (-\$205 - -\$21)	\$47 (\$5 - \$162)	\$2,946 (\$171-\$6,959)
Takayasu's arteritis				
Low	\$19,711	\$4,035	\$2,053	\$13,624
Moderate	\$16,066	\$3,619	\$1,922	\$10,525
High	\$13,719	\$3,891	\$1,827	\$8,001
Difference (Low – High), 95% CI	\$5,992 (\$969-\$22,437)	\$143 (\$36-\$416)	\$226 (\$26-\$569)	\$5,623 (\$886-\$21,087)

Bold values are statistically-significant differences; 95% CI: 95% credible interval

Table 3.13: Predicted Incremental Costs of Systemic Lupus Erythematosus, Overall and by Neighbourhood-Level Socioeconomic Group, Before and After Adjustment for Individual-Level Socioeconomic Group

	Overall	Outpatient	Medication	Hospitalisation
Before Adjustment for Individual-Level SES				
SLE	\$12,787	\$2,614	\$1,841	\$8,333
Non-SLE	\$2,709	\$866	\$1,057	\$786
Difference, 95% CI	\$10,078 (\$2,062-\$32,254)	\$1,747 (\$762-\$4,342)	\$784 (\$203-\$2,541)	\$7,547 (\$898-\$25,823)
Low	\$11,146	\$1,805	\$798	\$8,544
Moderate	\$9,584	\$1,730	\$806	\$7,048
High	\$9,225	\$1,694	\$757	\$6,773
Difference (Low – High), 95% CI	\$1,922 (\$327-\$5,645)	\$111 (\$47-\$266)	\$40 (\$11-\$131)	\$1,770 (\$254-\$5,246)

	Overall	Outpatient	Medication	Hospitalisation
After Adjustment for Individual-Level SES				
SLE	\$13,087	\$2,631	\$1,818	\$8,638
Non-SLE	\$2,639	\$862	\$998	\$779
Difference, 95% CI	\$10,448 (\$2,088-\$34,037)	\$1,769 (\$768-\$4,415)	\$820 (\$208-\$2,777)	\$7,859 (\$904-\$27,203)
Low	\$11,276	\$1,816	\$808	\$8,652
Moderate	\$10,134	\$1,757	\$859	\$7,518
High	\$9,728	\$1,724	\$815	\$7,189
Difference (Low – High), 95% CI	\$1,549 (\$248-\$4,569)	\$92 (\$39-\$221)	-\$7 (-\$24 - -\$2)	\$1,463 (\$204-\$4,369)

All differences were statistically-significant

95% CI: 95% credible interval

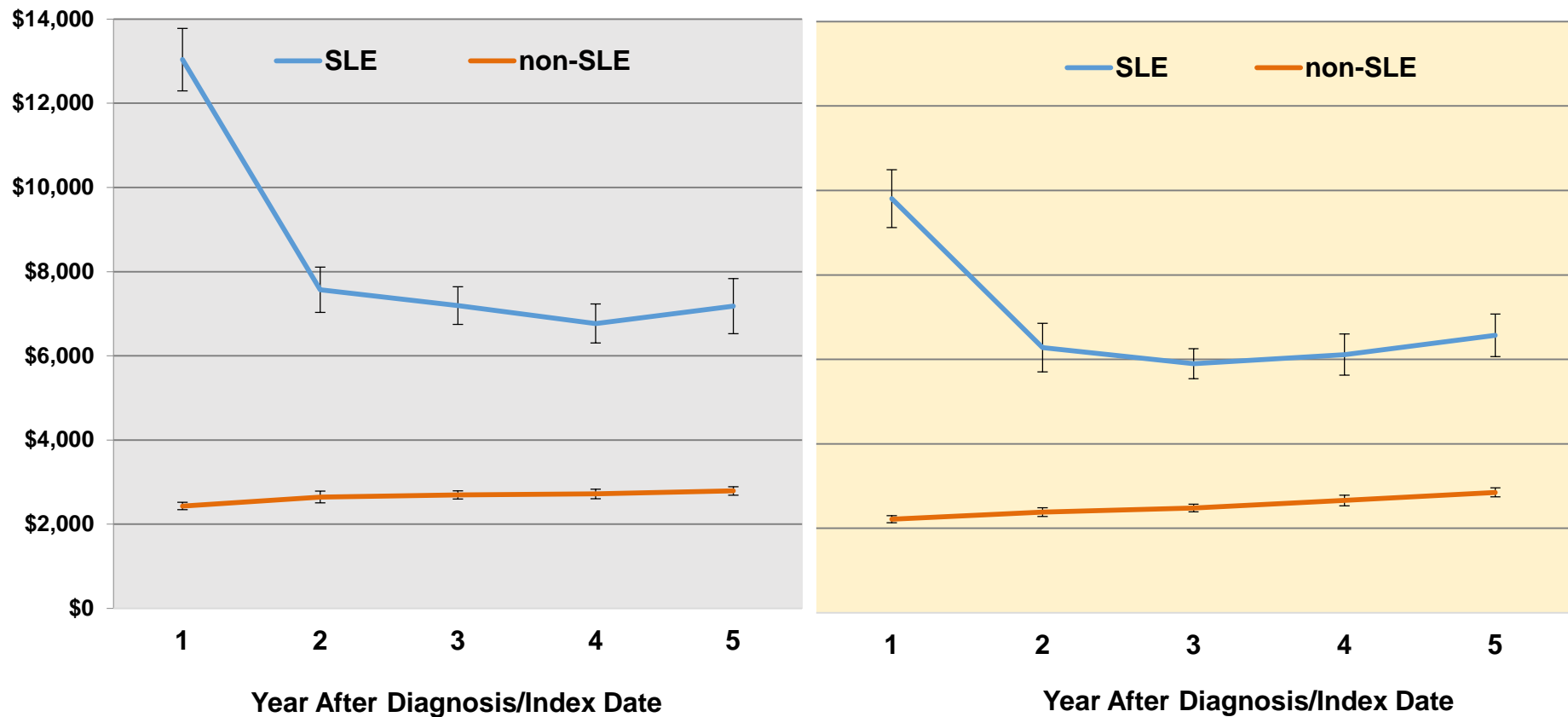


Figure 3.1: Unadjusted Annual Mean-Per-Person Direct Medical Costs for SLE and Non-SLE over the First Five Years after Diagnosis/Index Date, Among all Individuals (left) and Individuals with Complete Five-Year Follow-Up (right)

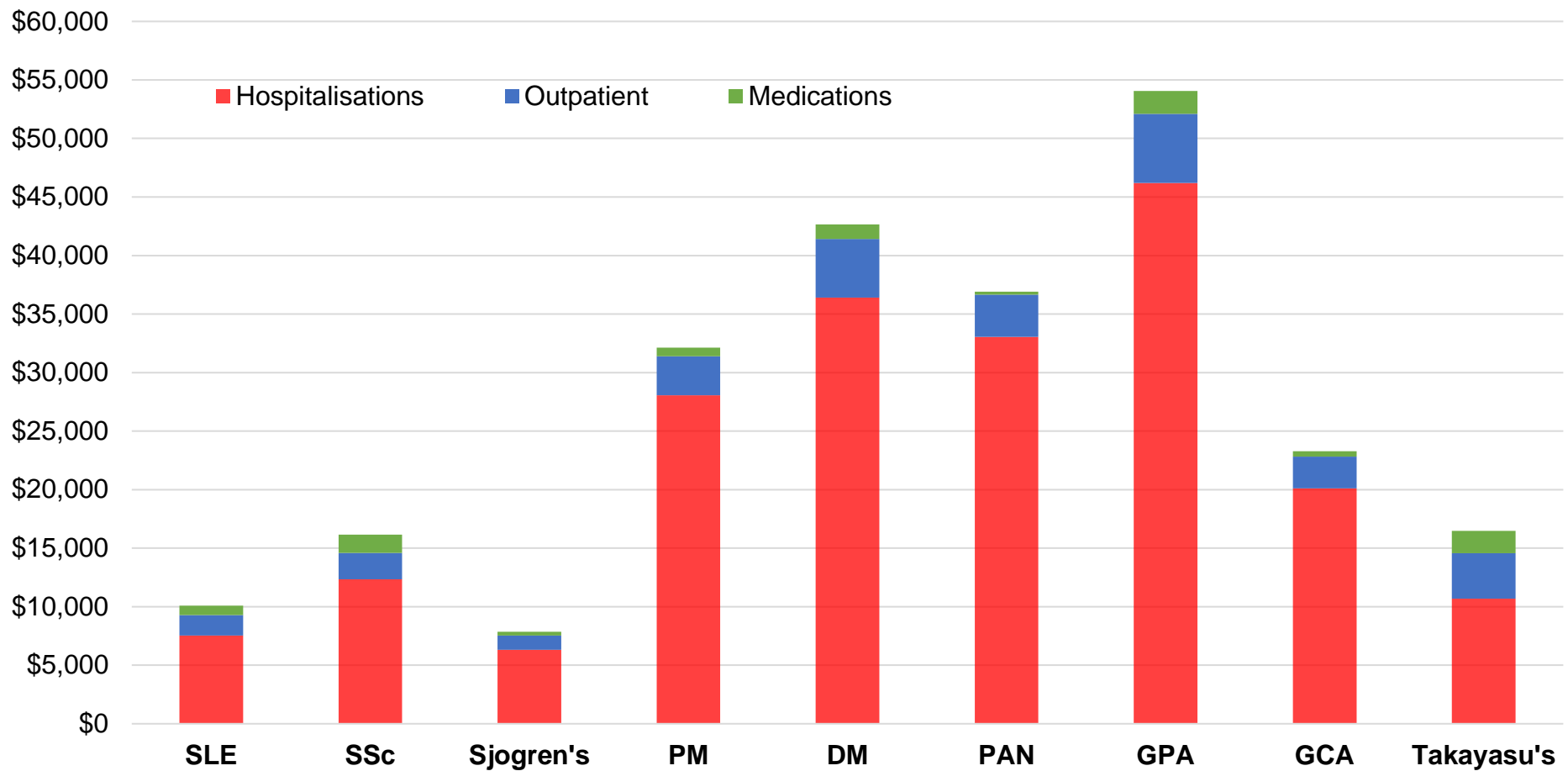


Figure 3.2: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of SARDs, by Healthcare Component

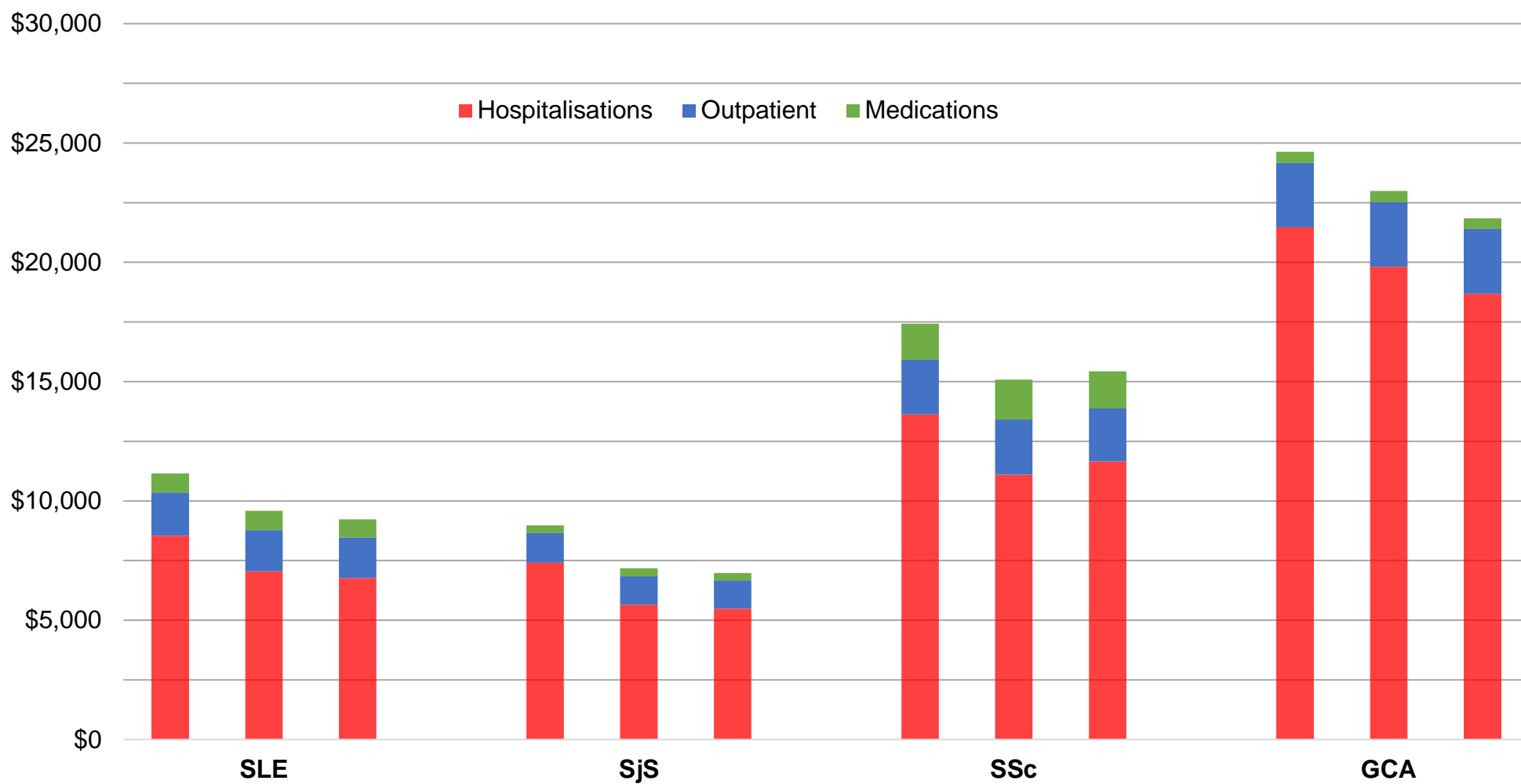


Figure 3.3: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of Selected SARDs, by Neighbourhood Socioeconomic Group (Left=Low SES, Middle=Moderate SES, Right=High SES)

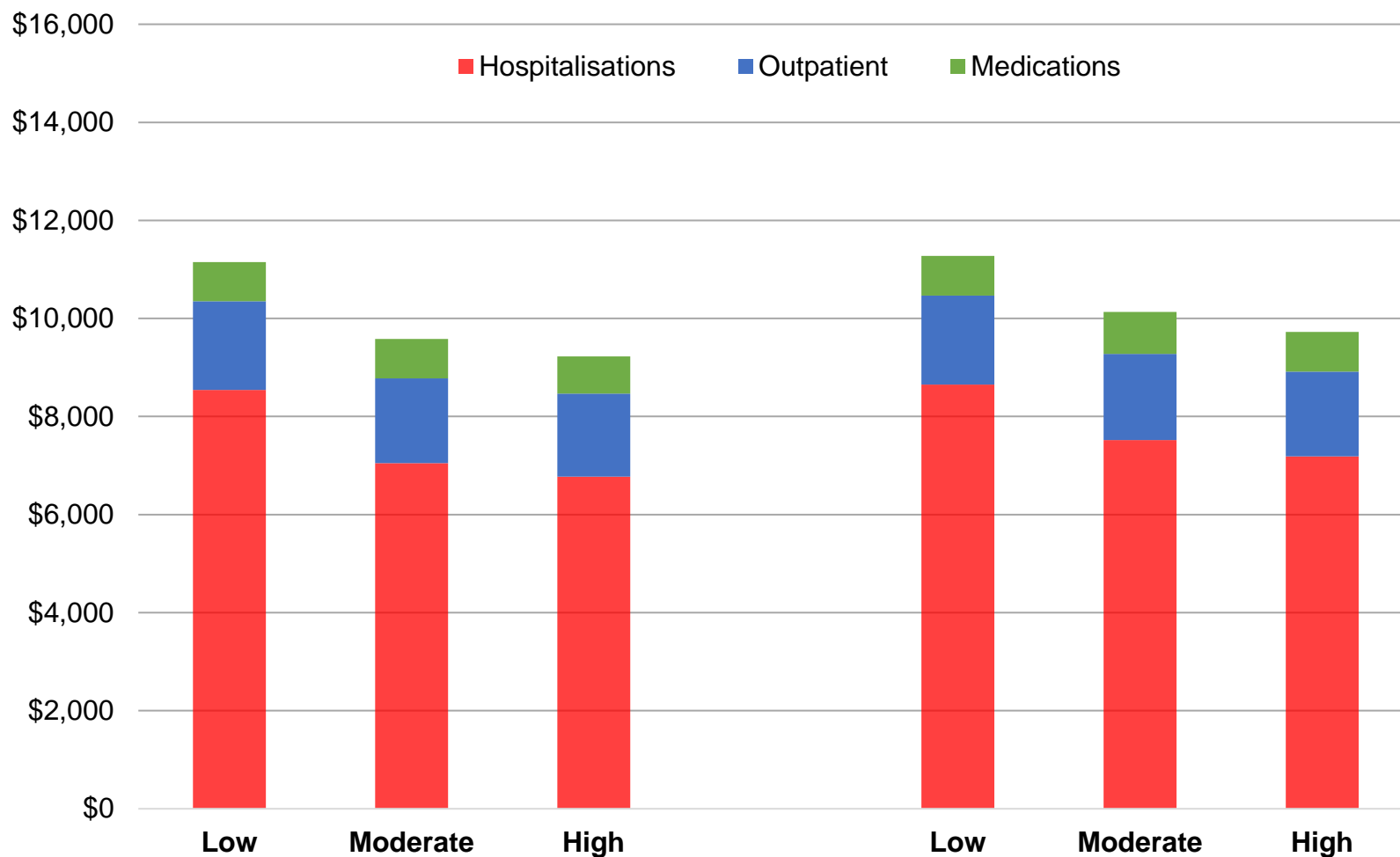


Figure 3.4: Predicted Incremental Mean Per-Person-Year Direct Medical Costs of SLE by Neighbourhood Socioeconomic Group, Before (left) and After (right) Adjustment for Individual-Level Socioeconomic Status

4. Incremental Direct Medical Costs of Systemic Lupus Erythematosus Patients in the Years Preceding Diagnosis: A General Population-Based Study³

4.1 Introduction

According to a recent systematic review(93), about three of every 100,000 North Americans are diagnosed with systemic lupus erythematosus (SLE) each year, and up to six per-100,000 Europeans. This disease tends to start slowly and insidiously, with SLE-associated autoantibodies present many years(409,410) before symptom-onset or diagnosis. Though complete SLE is characterised by intense inflammation, organ damage, and a high comorbidity burden(63), the early manifestations are often non-specific, typically involving arthritis(411,412) and photosensitivity(411), which makes diagnosis difficult.

The time from initial symptoms to formal diagnosis (accumulation of four American College of Rheumatology (ACR) Classification Criteria(413)) spans, on average, two years(414), but can be longer without the classic malar rash or symptoms suggestive of life-threatening organ involvement(412). During this time, however, the inflammatory effects of SLE are already setting in. Evidence suggests there is an elevated risk of cardiovascular disease(415) during this

³ A version of this chapter has been accepted for publication:

McCormick N, Marra CA, Sadatsafavi M, Aviña-Zubieta JA. Incremental Direct Medical Costs of Systemic Lupus Erythematosus Patients in the Years Preceding Diagnosis: A General Population-Based Study. *Lupus*. Accepted 2018 March 8. doi: 10.1177/0961203318768882.

period and, by the time of diagnosis, many patients already have renal disease(416,417), including nephritis(88,418).

The investigation of initial symptoms and management of serious health events preceding diagnosis is likely associated with additional medical costs. However, while several estimates are available on the costs of SLE patients following diagnosis(91,92,203), little is known about the years prior. Two recent analyses of primary care data in the United Kingdom (UK) reported substantial increases (65%(89) and 71%(419)) in primary care visits between the second and first year prior to SLE diagnosis. In the only report I could find on healthcare *costs* before diagnosis, which described the pre-diagnosis (pre-index) cost patterns in Taiwan(191), mean per-person costs for outpatient care more than doubled from the fifth to first year before diagnosis. Unfortunately, that study did not assess hospitalisation or medication costs, and their findings may not be generalisable to other countries or healthcare systems. Moreover, the impact of factors like socioeconomic status (SES) and sex on pre-index costs is also unknown. These are of interest since lower SES has been associated with reduced access to care and poorer outcomes(288) later-on in the disease course, and males tend to accrue damage more quickly than females(420). Males are also more likely to have renal and cardiovascular disease at the time of diagnosis(421).

Knowledge of the pre-index healthcare utilisation and costs of SLE patients across multiple settings, not just primary care, would give policymakers more information about the real burden of this disease. It would also inform emerging strategies to expedite diagnosis and

initiation of treatment, and even slow(237) or prevent the development of complete SLE in those at high risk(236), with pre-emptive hydroxychloroquine therapy.

To generate such knowledge, I used routinely-collected administrative healthcare data from a single-payer setting capturing the entire population to estimate the incremental healthcare burden of SLE in the five years before diagnosis, and year following, and assess the impact of sex and socioeconomic status on costs.

4.2 Methods

4.2.1 Data source

The province of British Columbia (BC), Canada, has a publicly-funded, universal healthcare system through which all legal residents receive medically-necessary outpatient and hospital care. The administrative data were sourced through Population Data BC, which uses population-based linkable administrative data files to capture records of all provincially-funded healthcare services, including all outpatient medical visits, interventions, and investigations(316), and hospitalisations(317), from 1990 through 2013, as well as demographic(319) and vital statistics data(320). Furthermore, it includes data on nearly all community-dispensed prescription medications for all BC residents, regardless of age or funding source, from 1996 through 2013(318). Numerous general population-based studies have been successfully conducted using these databases(49,311,312).

4.2.2 Study populations

From the administrative data files, we assembled a population-based cohort of all BC adults (aged ≥ 18 years) newly-diagnosed with SLE from January 1, 2001 through December 31, 2010. SLE cases were identified using International Classification of Diseases Ninth/Tenth (ICD-9/10) Revision diagnostic codes (710.0/M32) recorded for outpatient encounters and hospitalisations as follows: (a) \geq two ICD-9 codes for SLE \geq two months apart but within a two-year period by a non-rheumatologist physician (excluding codes recorded for laboratory tests and other diagnostic encounters); (b) one ICD-9 code by a rheumatologist; or (c) one ICD-9/10 code from a hospitalisation. The code could have been in any of the five diagnostic positions in the

outpatient billing data or in any of the up to 25 positions in the hospitalisation data. The first SLE-coded encounter was considered the index date. Potential cases were excluded if they had at least two visits \geq two months apart (subsequent to the SLE index encounter) with diagnoses of other inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies. The validity of this case definition has been evaluated in another Canadian province with reported sensitivity of 85% and specificity of 98% (401).

The non-SLE group was selected from a random sample of the BC population whom I randomly-assigned an index date among all possible dates within the study period. Those whose random date fell outside of their actual follow-up (i.e. after their death) were eliminated. From this pool, I selected up to five individuals per SLE case, matched (without replacement) on age (\pm two years), sex, and calendar-year of study entry, and eliminated any with an SLE diagnosis.

4.2.3 Healthcare utilisation and costs

To ensure only incident cases were included, all individuals (SLE and non-SLE) needed at least five years of registration in the databases prior to meeting the case definition for SLE. This ‘run-in’ period also ensured there were complete healthcare utilisation and cost data for the preceding five years. Thus, all healthcare utilisations captured in the databases from five years prior to index date and for up to five years after index date (or until the earliest of death, de-registration from BC’s universal health insurance provider, or December 31, 2013) were included, and unit costs summed. Though this chapter focusses on the pre-index period, costs were computed from Year -5 (fifth year before diagnosis) through Year +5 (fifth year after

diagnosis). Costs were computed in accordance with guidelines issued by Canada's health technology assessment agency, the Canadian Agency for Drugs and Technologies in Health(338). The unit cost of each outpatient encounter (available in the dataset) was the amount paid to health care providers by the BC Ministry of Health. The costs for each prescription (also available in the dataset) included the complete drug cost and dispensing fee. Costs for inpatient and day hospitalisations were calculated using the Canadian Institute for Health Information (CIHI)'s well-established case-mix methodology(338), in which the resource intensity weight (RIW) of each hospitalisation (provided by CIHI), the relative resource consumption in relation to the provincial 'average' (for which the RIW would equal 1.0), is multiplied by the cost of a 'standard' hospital stay in the province each year. All costs were adjusted for inflation using the general component of the Canadian Consumer Price Index (listed in Table 2.3), and reported in 2013 Canadian dollars.

4.2.4 Independent variables

A modified version of the Charlson-Romano comorbidity index for administrative data(340), one excluding diagnoses of SLE and other systemic autoimmune rheumatic diseases, was calculated for each 365-day period before index date, and collapsed into categories of 0 or \geq 1. For example, when assessing costs incurred during the final 365 days before SLE diagnosis (Year -1), I adjusted for comorbidities recorded during the second 365-day period before diagnosis (Year -2).

SES was defined using Statistics Canada neighbourhood income quintile data, as per previous analyses(311,312). SES was grouped according to the income quintile of the address recorded for each individual (by the provincial medical plan) in each study year. Urban/rural residence was defined using the first three digits of the postal code of this address (second-digit of 0 indicating a rural address).

4.2.5 Statistical analysis

Unadjusted comparisons between SLE and non-SLE individuals (and between male and female SLE) were made using chi-squared tests and *t*-tests. Mean per-person healthcare use and costs for each year (365-day period) were then determined for the (pre)-SLE and non-SLE cohorts. Along with mean annual costs, I also examined which inpatient and outpatient diagnoses were recorded most-frequently for the cohorts each year, and determined the prevalence of individual Charlson-Romano comorbidities in each pre-index year. Multivariable generalised linear models (GLM), adjusted for sex, age at index year, and year-specific comorbidity score, urban/rural residence, and SES, were then used to determine the relative utilisation and costs associated with SLE each year. Negative binomial count models were used to compare volumes of outpatient encounters and dispensed medications. Log-link and gamma distribution were specified in the cost models to account for skewness in these data(361).

The unit of analysis was person-year of follow-up. Thus, separate regression models were constructed for each year before diagnosis/index date and the year after. Pre-index follow-up time was the same for all individuals (five full years), but post-index follow-up time could be

less than one year for some individuals who might have died or reached the end of the study period. To account for this, an offset variable (log of each person's follow-up time) was used in the count models, while the post-index cost models only included individuals followed for the entire post-index year. As some individuals did not incur healthcare costs during each follow-up year, two-part models(361) were used for cost calculation. The first part (a logistic regression model) assessed one's probability of incurring any healthcare costs that year, controlling for covariates, while the second part (a gamma GLM) assessed costs only among those with non-zero costs. Similar models assessed the impact of sex and SES on costs within the SLE cohort.

To derive the incremental costs, which is the difference in costs between the SLE and the comparison group from the two-part model, I used G-computation(364), as has been applied previously on these data(312). With this approach, multivariable regression models are used to predict costs for each individual multiple times, each time with the same person in a different disease or sociodemographic group, but with their other covariates the same. The difference between estimates (i.e. predicted costs as if the same person did and did not have SLE) represented the incremental costs when the status of the variable changed (i.e. an individual was in the non-SLE or the SLE group), and per-person incremental costs were averaged across all individuals followed for the entirety of each year, with 95% credible intervals derived through parametric bootstrapping. Analyses were generated using the SAS Enterprise software package, version 7.13.

4.3 Results

I identified 3,632 newly-diagnosed SLE patients for the years 2001-2010 (86% female, mean age 49.6 ± 15.9) and 18,060 non-SLE individuals (mean age 49.8 ± 15.4). Two-thirds of SLE were diagnosed by a rheumatologist on an outpatient basis, with an additional 20% diagnosed in hospital (Table 4.1). SLE males were slightly older, on average, than SLE females (49.1 vs. 52.9 years, $p < 0.01$), as were non-SLE males and females, and males had a higher comorbidity score at diagnosis. Otherwise, males and females were nearly identical with regards to urban/rural residence, SES distribution, and source of SLE diagnosis

Costs for SLE in first year after diagnosis (Year +1) averaged \$12,019 per-person with 58% from hospitalisations, 24% outpatient, and 18% from prescription medications. Mean per-person costs for non-SLE were about five-fold lower, \$2,412 per-person. In the five years leading up to diagnosis, the average year-over-year increase in costs was 35% for the SLE cohort and 7% for non-SLE. However, the largest annual increases for SLE were observed in the final two years before diagnosis: 39% and 97%, respectively (Table 4.2).

After adjustment for sex, age, urban/rural residence, SES, and comorbidity burden in each preceding year, costs were significantly greater for SLE than non-SLE each year (Table 4.3). Incremental costs of SLE (difference in costs between SLE and non-SLE, controlling for covariates) rose over time from \$1,131 in Year -5 to \$1,536 (Year -3), \$3,473 (Year -1), and \$6,474 in the year after SLE diagnosis (Table 4.2).

4.3.1 Healthcare components

During the final two years before diagnosis, costs for outpatient consultations and investigations rose by 39% and 35%, respectively (Figure 4.1). For outpatient investigations specifically, the biggest increase occurred between Years -2 and -1 (by 47%, from \$468 to \$690 per-person). Prescription medication costs increased the most (by 33%) between Years -1 and +1. Day hospitalisations accounted for just 2-4% of costs each year.

The percentage of SLE with an inpatient hospitalisation was 10-12% in Years -5 to -2, 18% in the year before diagnosis, and 31% the year after, while only 6-7% of non-SLE were hospitalised each year. Among SLE, the most frequent reasons for hospitalisation during Year -1 (based upon the primary discharge diagnosis) were circulatory (mainly heart failure, pericardial, myocardial infarction, and phlebitis/thrombophlebitis), respiratory (mainly pneumonia, pleural effusion, and interstitial lung disease), and gastrointestinal conditions (mainly abdominal/pelvic pain, intestinal obstruction, bleeding, gastroenteritis, and gallstones). Among non-SLE, maternity care accounted for nearly one-quarter of admissions, while the other most-frequent reasons for hospitalisation were gastrointestinal (mainly intestinal obstruction, gallstones, and appendicitis) and circulatory conditions (mainly ischaemic heart disease and myocardial infarction).

The median number of physician consultations increased from 9 (IQR=4-16) in Year -5, to 11 (IQR=6-20) in Year -2, 15 (IQR=9-25) in Year -1, and 18 (IQR=11-30) in Year +1. For general practitioners (GPs) specifically, median consultations for SLE were 6 (IQR=3-12) in

Year -5, 8 (IQR=4-14) in Year -2, and 10 in Years -1 and +1; non-SLE had a median of 5 GP consultations in each of these years. Thirty-four percent of those eventually diagnosed with SLE visited a rheumatologist in the year before SLE diagnosis, and 84% the year after. The most common diagnoses recorded for these rheumatologist encounters during Year -1 were for diffuse connective tissue disease (29%), rheumatoid arthritis (14%), other/unspecified arthropathies (10%), other/unspecified joint/soft tissue disorders (8.4%), and erythematous conditions (5.3%).

4.3.2 Impact of sex

Starting from Year -4, unadjusted annual mean per-person costs for SLE males were about 25% greater than SLE females (Figure 4.2). In the year after SLE diagnosis, their costs were 68% greater (\$18,433 vs. \$10,945). Following adjustment, male sex was associated with significantly-greater costs among SLE in Years -2, -1, and +1 (Table 4.4). Hospitalisations were a major contributor, with males having greater odds of hospitalisation than females in the year before diagnosis (odds ratio (OR)=1.49, 95% CI=1.19-1.88), and significantly-greater hospitalisation costs the year after. Conversely, among non-SLE, male sex was associated with significantly lower costs over Years -5 to +1. In absolute terms, predicted incremental costs for SLE males (over-and-above SLE females') were \$540 per-person in Year -2, \$1,385 in Year -1, and \$2,288 in Year +1.

Figure 4.3 shows the annual prevalence of most Charlson-Romano comorbidities during the pre-index period, among males and females with and without SLE. For diabetes,

cerebrovascular disease, myocardial infarction, heart failure, and renal disease, prevalence increased over time for SLE (more so for SLE males than females), but was stable for non-SLE.

4.3.3 Impact of socioeconomic status

Among SLE, being in the lowest-SES group was associated with significantly-greater healthcare costs in Years -4, -2, -1, and +1 (Table 4.4). The second-lowest group also had significantly-greater costs in Years -2 and +1. Outpatient costs contributed, but hospitalisations were the major driver in Year +1. The lowest-SES had greater odds of being diagnosed in hospital (OR=1.45, 1.12-1.88), and, as compared to others diagnosed in hospital, incurred greater costs for this index hospitalisation (adjusted cost ratio=1.33, 1.05-1.68).

4.4 Discussion

To the best of my knowledge, these are the first-known estimates of outpatient, hospitalisation, and medication costs before SLE diagnosis. With access to routinely-collected healthcare utilisation data for virtually all residents of the province, I assessed the incremental costs among 3,632 SLE patients before and after diagnosis. Though index-year costs were nearly four-times greater for SLE than the non-SLE group, SLE patients had significantly-greater costs, in all of these components, during each of the five years before diagnosis.

The largest increases in utilisation and costs occurred in the two years before diagnosis, which is consistent with oft-reported span of two years, on-average, from symptom onset to SLE diagnosis(414). However, individuals with SLE also incurred greater costs than non-SLE in the third, fourth, and fifth years before diagnosis, and had more comorbidities recorded in the pre-index period. These findings suggest the rise in incremental costs over time is not solely from consultations and investigations involved in confirming the diagnosis, and rather indicate the broader, systemic aspect of inflammation affecting multiple organs.

Though these findings may not be generalisable to SLE patients in all countries or healthcare settings, they are consistent with previous, more limited assessments of pre-index use and costs in SLE. Two studies were conducted using primary care data from the UK Clinical Practice Research Datalink. In one(419), the median number of primary care visits for SLE patients increased from six per-year (Years -5, -4, and -3) to seven (Year -2), and 12 in the year before diagnosis. Conversely, visits for the non-SLE comparison group (median 3) were

unchanged(419). The second UK study(89) reported an increase in median annual consultations from one (4 to 4.5 years before diagnosis, IQR=0-17), to 23 in Year -2 (IQR=11-43), and 38 in Year -1 (IQR=23-61). A third study, conducted in Taiwan(191), found that pre-index outpatient costs were significantly greater for SLE than non-SLE, even eight years beforehand. The annual median number of ambulatory care encounters was significantly greater for SLE each year, and rose from 1 (Year -8) to 11 (Year -5), 13 (Year -2), and 22 in Year -1(191). Similar findings on incremental pre-index costs have been reported for rheumatoid arthritis (RA) patients in Taiwan(422), and psoriatic arthritis(423) and RA(424) patients in Denmark. In the latter study, costs for RA patients were significantly-greater than the general populations', even 11 years before diagnosis.

Despite conducting this study within a publicly-funded healthcare system covering all residents of the province, I found that low SES was independently associated with increased healthcare costs among SLE, especially in the final two years before diagnosis. Specifically, the lowest-SES group had greater outpatient costs than the highest-SES, were more likely to be diagnosed in-hospital, and incurred greater hospitalisation costs at diagnosis. These higher costs around the time of diagnosis align with my findings from Chapter 3, wherein the incremental costs of SLE were significantly-greater among the low-SES SLE patients versus the high-SES. Since there are no private acute-care hospitals in BC, these differences in hospitalisation rates and costs cannot be attributed to the highest-SES patients obtaining care outside the public system. It is possible, however, that the lowest-SES individuals face difficulties in accessing care that eventually land them in hospital at the time of diagnosis, requiring more complex care.

Low household income has been associated with delayed presentation to rheumatology care among paediatric SLE patients in the United States(386), something that warrants further exploration in adult SLE. While this may be less of an issue within Canada's single-payer system where access to primary and specialist care is more universal, a pan-Canadian study of juvenile idiopathic arthritis similarly found that children whose parents were highly educated also had shorter times from symptom onset to consultation with a paediatric rheumatologist(425)

Another striking finding was SLE males having significantly-higher costs than SLE females in this period, even after adjustment for age, urban/rural residence, and SES. Unlike the SES groups, males and females were quite similar regarding the sources of diagnosis; however, SLE males did have a significantly-higher pre-index comorbidity burden than females, including more diagnoses recorded for diabetes, renal disease, and cardiovascular disease in the years leading up to index date. There is disagreement in the literature about whether males (particularly Caucasians) tend to be diagnosed at an older age than females, and have a different, perhaps more severe, form of lupus with associated increased mortality(426). But it has been reported that males are more likely to have renal disease at SLE diagnosis(416,417), and accrue organ damage at a higher rate than females(417,420). Evidence also suggests that, among those with confirmed SLE, cardiovascular disease/damage is higher in males (421,427,428). If males also have more organ damage and comorbidities in the pre-index period, this may explain why pre-index healthcare costs were higher for males. Although costs in each pre-index year (and Year +1) were adjusted for the Charlson-Romano comorbidity score for the previous 365-days, there may have been residual differences in comorbidity burden between the sexes.

Though sex-specific data on pre-index comorbidities in SLE are not available, evidence does suggest that, overall, SLE patients have an increased inflammatory disease burden before diagnosis. In clinical studies, many patients have had nephritis(88,418) or other forms of renal disease(416,417) at diagnosis, and while SLE patients are known to have an elevated risk of cardiovascular events immediately following diagnosis(49), increased cardiovascular disease before SLE diagnosis has also been reported. Among members of the multinational SLICC cohort, prevalence of myocardial infarction around the time of SLE diagnosis (between five years before, and two years following) exceeded the figure reported for the general population (4.8% vs. 0.7%)(429). In a population-based study in rural Wisconsin, USA, SLE patients had 3.8-times greater odds of cardiovascular disease in the two years prior to diagnosis, versus a sex- and age-matched sample from the general population. This included three-times greater odds of both heart failure and ischaemic heart disease, and five-times greater odds of stroke(415). Increased cardiovascular disease has also been observed in the years preceding diagnosis of RA(430,431) and psoriatic arthritis(423), and diabetes has been associated with subsequent diagnosis of RA(432,433). It was beyond the scope of this analysis to evaluate the risks of incident comorbid conditions in the pre-index period, and the increased prevalence observed over time could reflect the development of new conditions, increased severity of pre-existing conditions (increasing the complexity and cost of care for these conditions and others), or even unconfirmed diagnoses and ‘rule-out’ encounters. However, any additional healthcare encounters for SLE patients during this time (even for unconfirmed diagnoses), and associated costs, are still part of the incremental burden of SLE.

Several mechanisms have been proposed for the concurrence of SLE and these other inflammatory diseases. As mentioned by the SLICC investigators, early autoimmunity and early atherosclerosis may develop at the same time, but through independent processes(429); alternatively, early subclinical autoimmunity may actually contribute to early subclinical atherosclerosis(429). The Wisconsin investigators suggested atherosclerosis may accelerate prior to full onset of SLE, but also acknowledged that formal diagnosis of SLE may have been delayed in their cohort due to its older age, rural nature, and higher percentage of males(415). Renal disease, meanwhile, is likely an early manifestation of undiagnosed (or unconfirmed) SLE itself.

These novel estimates should inform current healthcare decision-making, and efforts to expedite SLE diagnosis and treatment, or, in high-risk individuals, even prevent it from developing. One early or potentially pre-emptive treatment is hydroxychloroquine (HCQ). Persistent use of HCQ in newly-diagnosed patients has been associated with a longer clinically quiescent phase(434), and early initiation of HCQ (after initial symptoms, but before accumulation of \geq four ACR criteria) has been shown to delay the accumulation of additional criteria(237). Moreover, these efforts could be cost-saving: a retrospective analysis of US commercial claims data(210) found that ‘early’ diagnosis of SLE (within six months of symptom onset) was associated with fewer flares, and lower levels of post-diagnosis healthcare costs, compared to those diagnosed 6-12 months after symptom onset. However, the possible harms and added costs of any early treatment efforts (including the consequences of treating false-positive cases of SLE) warrant careful evaluation.

The administrative healthcare data imparted both strengths and limitations to this analysis. Although SLE patients were identified from ICD codes, and the diagnoses were not clinically confirmed, 86% were identified by a rheumatologist or hospitalisation, and the case definition has a reported specificity of 98% and positive predictive value of 91% in the Canadian setting(401). Moreover, I helped ensure only truly incident SLE were included by requiring five years' pre-index follow-up time without meeting the case definition for SLE. As I did not have access to medical records, I could not assess whether the SLE index date coincided with patients' fulfilling at least four ACR classification criteria, but the temporal cost patterns observed (costs rising in the final two years before diagnosis, and peaking the year after diagnosis) do lend support and are consistent with previous reports(191,419). Although all individuals had five years of follow-up prior to index date, a small number of individuals were not followed through the end of the first year after index date due to death or de-registration from the provincial health insurance plan. To account for these unequal follow-up times, my regression analyses for Year +1 costs only included individuals followed for the entirety of Year +1, thus excluding 158 SLE (69% female, with 149/158=94% dying) and 57 non-SLE (89% female, with 22/57=39% dying). However, this exclusion likely made my analyses more conservative since nearly all of these SLE died, and they likely incurred very high healthcare costs just prior to their deaths.

Despite these limitations, the routinely collected data allowed me to identify virtually all newly-diagnosed SLE in the province (regardless of age, employment, urban/rural residence, or disease severity) and capture their pre-index healthcare utilisation from all settings (not just primary care) with minimal selection and recall bias. My estimates include the costs for all

provincially-funded fee-for-service outpatient encounters and hospitalisations, and virtually all community-dispensed prescriptions, regardless of age or funding. However, I acknowledge these estimates do not include items not captured in the databases (and not funded by the province) such as non-prescription medications and most allied health visits.

4.5 Conclusion

In this population-based analysis, the healthcare and economic impact of SLE was evident long before the diagnosis was recorded. Even in the fifth year before diagnosis, members of the SLE cohort were more likely to be hospitalised than non-SLE, and incurred greater direct medical costs: \$1,131 more per-person, on-average. I hope this work will increase recognition of the early healthcare costs of SLE, including the impact of low socioeconomic status and early comorbidities, and spur efforts to mitigate this burden. In the next chapter, I move from direct medical costs to an examination of the incremental productivity losses and costs for a subset of the population-based SARD cohorts

Table 4.1: Characteristics of Individuals With and Without SLE, Overall and by Sex

	All SLE	All Non-SLE	p-value ($\alpha=0.05$)	Female SLE	Male SLE	Female Non-SLE	Male Non-SLE
N	3,632	18,060	-	3,111	521	15,459	2,601
N (%) Female	3,111 (86%)	15,459 (86%)	0.93	-	-	-	-
Mean (SD) Age at Diagnosis	49.6 (15.9)	49.8 (15.4)	0.60	49.1 (15.6)	52.9 (17.1)*	49.2 (15.1)	53.0 (17.0)*
Mean (SD) Comorbidity Score	0.42 (0.49)	0.14 (0.35)*	< 0.01	0.40 (0.49)	0.50 (0.50)*	0.13 (0.34)	0.17 (0.37)*
N (%) Rural Residence at Diagnosis	538 (15%)	2,108 (12%)*	< 0.01	459 (15%)	79 (15%)	1,784 (12%)	324 (12%)
Mean (SD) Months of Follow-Up After Diagnosis/Index Date (maximum 60)	52.4 (13.8)	56.2 (7.7)*	< 0.01	53.1 (13.0)	48.2 (17.5)*	56.2 (7.7)	55.7 (8.0)*
N (%) with Full Five- Years' Post-Index Follow-Up	2,238 (62%)	12,935 (72%)*	< 0.01	1,981 (64%)	257 (49%)*	11,177 (72%)	1,758 (68%)*

	All SLE	All Non-SLE	p-value ($\alpha=0.05$)	Female SLE	Male SLE	Female Non-SLE	Male Non-SLE
N (%) Died During Post-Index Follow-Up	415 (11%)	256 (1%)*	< 0.01	304 (10%)	111 (21%)*	196 (1%)	60 (2%)*
Source of Diagnosis							
Rheumatologist	2,395 (66%)	-	-	2,058 (66%)	337 (65%)	-	-
Hospitalisation	727 (20%)	-	-	613 (20%)	114 (22%)	-	-
Other Physician	522 (14%)	-	-	449 (14%)	73 (14%)	-	-
Socioeconomic Group							
1=Lowest	774 (21%)	3,599 (20%)		668 (21%)	106 (20%)	3,113 (20%)	486 (19%)
2	713 (20%)	3,619 (20%)		601 (19%)	112 (22%)	3,099 (20%)	520 (20%)
3=Middle	771 (21%)	3,567 (20%)	0.02*	672 (22%)	99 (19%)	3,036 (20%)	531 (20%)
4	722 (20%)	3,658 (20%)		617 (20%)	105 (20%)	3,120 (20%)	538 (21%)
5=Highest	652 (18%)	3,612 (20%)		553 (18%)	99 (19%)	3,087 (20%)	525 (20%)

*statistically-significant difference between SLE and non-SLE (or females and males), at $\alpha=0.05$

Table 4.2: Overall Annual Mean Per-Person Direct Medical Costs, Before and After Adjustment

Year Before/After Index Date	SLE	Non-SLE	Unadjusted Incremental Costs of SLE	Adjusted Incremental Costs^a (95% CI)
-5	\$3,073	\$1,686	\$1,386	\$1,131 (\$592-\$2,657)
-4	\$3,416	\$1,856	\$1,560	\$1,316 (\$658-\$3,309)
-3	\$3,682	\$1,911	\$1,771	\$1,536 (\$754-\$4,017)
-2	\$4,409	\$2,092	\$2,317	\$2,015 (\$986-\$4,941)
-1	\$6,111	\$2,247	\$3,864	\$3,473 (\$1,661-\$8,666)
+1	\$12,019	\$2,412	\$9,607	\$6,474 (\$3,220-\$15,437)

^aDetermined using two-part models: a logistic regression model for the odds of incurring non-zero costs, and generalised linear model with gamma distribution and log-link predicting costs for those with non-zero costs; adjusted for age, sex, previous year's modified Charlson comorbidity score, urban/rural residence and neighbourhood socioeconomic status

95% CI=95% credible interval

Table 4.3: Adjusted Cost and Utilisation Ratios (95% CI) Associated with SLE Status

Year Before/After Diagnosis/ Index Date	Outpatient			Medications		Inpatient Hospitalisations	
	Overall Costs ^a	Outpatient Encounters ^b	Outpatient Costs ^a	Dispensed Prescription Medications ^b	Medication Costs ^a	Odds of Inpatient Hospitalisation ^c	Inpatient Hospitalisation Costs (among those with non- zero costs) ^c
-5	1.62 (1.55-1.69)	1.44 (1.40-1.48)	1.61 (1.56-1.67)	1.48 (1.42-1.55)	1.56 (1.48-1.63)	1.51 (1.33-1.72)	1.11 (1.01-1.23)
-4	1.66 (1.59-1.73)	1.46 (1.41-1.50)	1.64 (1.58-1.70)	1.52 (1.46-1.58)	1.58 (1.51-1.66)	1.40 (1.24-1.59)	1.25 (1.14-1.36)
-3	1.74 (1.66-1.81)	1.48 (1.44-1.53)	1.68 (1.62-1.74)	1.50 (1.44-1.57)	1.57 (1.49-1.64)	1.52 (1.34-1.72)	1.30 (1.18-1.42)
-2	1.89 (1.81-1.98)	1.58 (1.54-1.63)	1.81 (1.75-1.88)	1.67 (1.60-1.74)	1.72 (1.64-1.80)	1.66 (1.48-1.87)	1.38 (1.26-1.52)
-1	2.42 (2.32-2.53)	1.99 (1.94-2.05)	2.40 (2.31-2.48)	1.71 (1.64-1.78)	1.72 (1.65-1.80)	2.62 (2.35-2.91)	1.39 (1.27-1.52)
+1	3.52 (3.36-3.68)	2.43 (2.36-2.50)	2.92 (2.81-3.02)	1.97 (1.89-2.06)	2.12 (2.03-2.22)	4.52 (4.09-4.99)	1.75 (1.61-1.90)

*adjusted for age at diagnosis, sex, previous year's modified Charlson comorbidity score, urban/rural residence and neighbourhood socioeconomic group; All values are statistically-significant ($\alpha=0.05$)

^aDetermined using a generalised estimating equations (linear) model, with gamma distribution and log-link

^bDetermined using a generalised estimating equations (count) model, with negative binomial distribution

^cDetermined using two-part models: a logistic regression model for the odds of incurring non-zero costs, and generalised linear model with gamma distribution and log-link predicting costs for those with non-zero costs

Table 4.4: Adjusted Cost and Utilisation Ratios (95% CI) Associated with Sex and Socioeconomic Status, among SLE only

Year Before/ After Diagnosis	Independent Variable	Outpatient			Medications		Inpatient Hospitalisations	
		Overall ^a	Outpatient Encounters ^b	Outpatient Costs ^a	Dispensed Prescription Medications ^b	Medication Costs ^a	Odds of Inpatient Hospitalisation ^c	Inpatient Hospitalisation Costs (among those with non-zero costs) ^c
-5	Male Sex	1.02 (0.91-1.14)	0.83 (0.77-0.90)	0.85 (0.77-0.93)	0.87 (0.79-0.97)	1.20 (1.06-1.35)	1.24 (0.92-1.68)	0.97 (0.76-1.23)
	Female Sex	-	-	-	-	-	-	-
	(reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.08 (0.96-1.22)	1.04 (0.96-1.13)	1.04 (0.94-1.15)	1.15 (1.03-1.29)	1.03 (0.91-1.17)	1.16 (0.83-1.62)	1.06 (0.81-1.40)
	2	1.02 (0.90-1.15)	1.05 (0.97-1.14)	1.03 (0.93-1.13)	1.25 (1.12-1.40)	1.01 (0.89-1.15)	0.95 (0.67-1.36)	1.12 (0.84-1.49)
	3=Middle SES	0.92 (0.82-1.04)	0.93 (0.86-1.01)	0.91 (0.82-1.01)	0.95 (0.85-1.06)	0.93 (0.81-1.05)	1.05 (0.74-1.48)	0.94 (0.72-1.24)
	4	0.86 (0.76-0.97)	0.94 (0.86-1.02)	0.92 (0.83-1.02)	0.96 (0.86-1.07)	0.90 (0.79-1.03)	0.83 (0.58-1.20)	0.84 (0.62-1.12)
-4	5=Highest SES	-	-	-	-	-	-	-
	(reference)	-	-	-	-	-	-	-
	Male Sex	1.12 (1.00-1.25)	0.86 (0.80-0.93)	0.93 (0.84-1.02)	0.83 (0.75-0.92)	1.16 (1.03-1.31)	1.25 (0.93-1.67)	1.25 (0.99-1.58)
	Female Sex	-	-	-	-	-	-	-
	(reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.34 (1.19-1.51)	1.13 (1.04-1.22)	1.13 (1.03-1.25)	1.55 (1.38-1.73)	1.34 (1.18-1.52)	1.37 (0.97-1.96)	1.11 (0.83-1.49)
	2	1.12 (1.00-1.26)	1.05 (0.97-1.14)	1.03 (0.93-1.13)	1.23 (1.10-1.38)	1.08 (0.95-1.23)	1.50 (1.06-2.14)	0.96 (0.72-1.28)
	3=Middle SES	1.01 (0.90-1.14)	0.96 (0.89-1.04)	0.93 (0.84-1.03)	1.13 (1.01-1.26)	1.07 (0.94-1.22)	1.23 (0.86-1.77)	0.91 (0.67-1.22)
	4	1.18 (1.04-1.33)	1.06 (0.97-1.15)	1.07 (0.97-1.19)	1.28 (1.14-1.43)	1.07 (0.94-1.22)	1.38 (0.96-1.98)	1.08 (0.80-1.47)
	5=Highest SES	-	-	-	-	-	-	-
	(reference)	-	-	-	-	-	-	-

Year Before/ After Diagnosis	Independent Variable	Outpatient			Medications		Inpatient Hospitalisations	
		Overall ^a	Outpatient Encounters ^b	Outpatient Costs ^a	Dispensed Prescription Medications ^b	Medication Costs ^a	Odds of Inpatient Hospitalisation ^c	Inpatient Hospitalisation Costs (among those with non-zero costs) ^c
-3	Male Sex	1.11 (0.99-1.24)	0.86 (0.80-0.93)	0.91 (0.83-1.00)	0.84 (0.75-0.93)	1.09 (0.97-1.23)	1.08 (0.80-1.46)	1.61 (1.24-2.09)
	Female Sex (reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.03 (0.91-1.16)	1.07 (0.98-1.16)	1.02 (0.92-1.13)	1.34 (1.19-1.49)	1.19 (1.05-1.35)	0.95 (0.69-1.33)	0.83 (0.63-1.08)
	2	0.83 (0.74-0.94)	1.01 (0.93-1.10)	0.95 (0.85-1.05)	1.18 (1.05-1.33)	1.05 (0.92-1.20)	0.80 (0.57-1.13)	0.64 (0.48-0.86)
	3=Middle SES	0.78 (0.69-0.88)	0.93 (0.85-1.01)	0.86 (0.77-0.95)	1.00 (0.89-1.12)	0.91 (0.80-1.04)	0.76 (0.54-1.08)	0.70 (0.52-0.95)
	4	0.92 (0.82-1.04)	1.03 (0.95-1.12)	1.00 (0.90-1.10)	1.09 (0.97-1.22)	1.00 (0.88-1.14)	1.03 (0.74-1.44)	0.81 (0.61-1.08)
	5=Highest SES (reference)	-	-	-	-	-	-	-
-2	Male Sex	1.15 (1.02-1.28)	0.88 (0.82-0.95)	0.91 (0.83-1.00)	0.80 (0.72-0.89)	1.13 (1.01-1.28)	1.15 (0.87-1.51)	1.48 (1.16-1.89)
	Female Sex (reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.16 (1.03-1.30)	1.15 (1.07-1.25)	1.15 (1.04-1.26)	1.34 (1.20-1.51)	1.07 (0.94-1.21)	1.25 (0.92-1.71)	1.09 (0.83-1.43)
	2	1.15 (1.02-1.30)	1.12 (1.03-1.21)	1.09 (0.99-1.21)	1.33 (1.18-1.49)	0.88 (0.77-1.00)	1.26 (0.92-1.74)	1.28 (0.97-1.69)
	3=Middle SES	0.94 (0.83-1.06)	0.97 (0.89-1.04)	0.91 (0.83-1.01)	0.96 (0.85-1.07)	0.83 (0.73-0.95)	0.92 (0.66-1.29)	1.21 (0.90-1.64)
	4	1.07 (0.95-1.21)	1.08 (0.99-1.16)	1.08 (0.98-1.19)	1.08 (0.96-1.21)	0.88 (0.78-1.00)	1.00 (0.72-1.39)	1.54 (1.14-2.06)
	5=Highest SES (reference)	-	-	-	-	-	-	-

Year Before/ After Diagnosis	Independent Variable	Outpatient			Medications		Inpatient Hospitalisations	
		Overall ^a	Outpatient Encounters ^b	Outpatient Costs ^a	Dispensed Prescription Medications ^b	Medication Costs ^a	Odds of Inpatient Hospitalisation ^c	Inpatient Hospitalisation Costs (among those with non-zero costs) ^c
-1	Male Sex	1.24 (1.12-1.37)	0.99 (0.93-1.05)	1.07 (0.99-1.15)	0.82 (0.74-0.90)	0.99 (0.89-1.10)	1.49 (1.19-1.88)	1.05 (0.87-1.28)
	Female Sex (reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.16 (1.04-1.29)	1.16 (1.09-1.25)	1.11 (1.02-1.21)	1.53 (1.38-1.71)	1.12 (1.00-1.26)	1.17 (0.90-1.53)	1.12 (0.89-1.41)
	2	1.12 (1.00-1.25)	1.14 (1.06-1.22)	1.09 (1.00-1.18)	1.46 (1.31-1.63)	1.05 (0.93-1.18)	1.05 (0.80-1.38)	1.25 (0.98-1.58)
	3=Middle SES	0.88 (0.79-0.98)	1.02 (0.95-1.09)	0.96 (0.89-1.04)	1.12 (1.00-1.25)	0.96 (0.85-1.08)	0.81 (0.61-1.07)	0.98 (0.76-1.26)
	4	0.92 (0.82-1.03)	1.01 (0.94-1.08)	0.96 (0.89-1.05)	1.17 (1.04-1.30)	0.95 (0.84-1.07)	0.85 (0.64-1.14)	1.18 (0.91-1.53)
	5=Highest SES (reference)	-	-	-	-	-	-	-
+1	Male Sex	1.24 (1.11-1.38)	1.13 (1.06-1.21)	1.08 (1.00-1.16)	0.92 (0.83-1.01)	1.18 (1.06-1.32)	1.11 (0.89-1.37)	1.37 (1.13-1.64)
	Female Sex (reference)	-	-	-	-	-	-	-
	1=Lowest SES	1.25 (1.11-1.42)	1.15 (1.06-1.24)	1.11 (1.02-1.20)	1.55 (1.39-1.73)	1.10 (0.97-1.24)	1.68 (1.31-2.14)	0.97 (0.79-1.20)
	2	1.19 (1.05-1.35)	1.14 (1.05-1.23)	1.11 (1.02-1.21)	1.42 (1.27-1.59)	1.16 (1.03-1.32)	1.60 (1.25-2.05)	0.88 (0.71-1.09)
	3=Middle SES	0.89 (0.79-1.01)	0.95 (0.88-1.03)	0.94 (0.87-1.02)	1.04 (0.93-1.15)	0.95 (0.84-1.07)	1.07 (0.83-1.37)	0.78 (0.62-0.98)
	4	0.98 (0.87-1.11)	1.01 (0.93-1.09)	1.07 (0.98-1.16)	1.13 (1.01-1.26)	0.94 (0.83-1.06)	1.16 (0.90-1.49)	0.81 (0.65-1.02)
	5=Highest SES (reference)	-	-	-	-	-	-	-

*adjusted for age at diagnosis, previous year's modified Charlson comorbidity score, and urban/rural residence

Bold values are statistically-significant ($\alpha=0.05$)

^aDetermined using a generalised estimating equations (linear) model, with gamma distribution and log-link

^bDetermined using a generalised estimating equations (count) model, with negative binomial distribution

^cDetermined using two-part models: a logistic regression model for the odds of incurring non-zero costs, and generalised linear model with gamma distribution and log-link predicting costs for those with non-zero costs

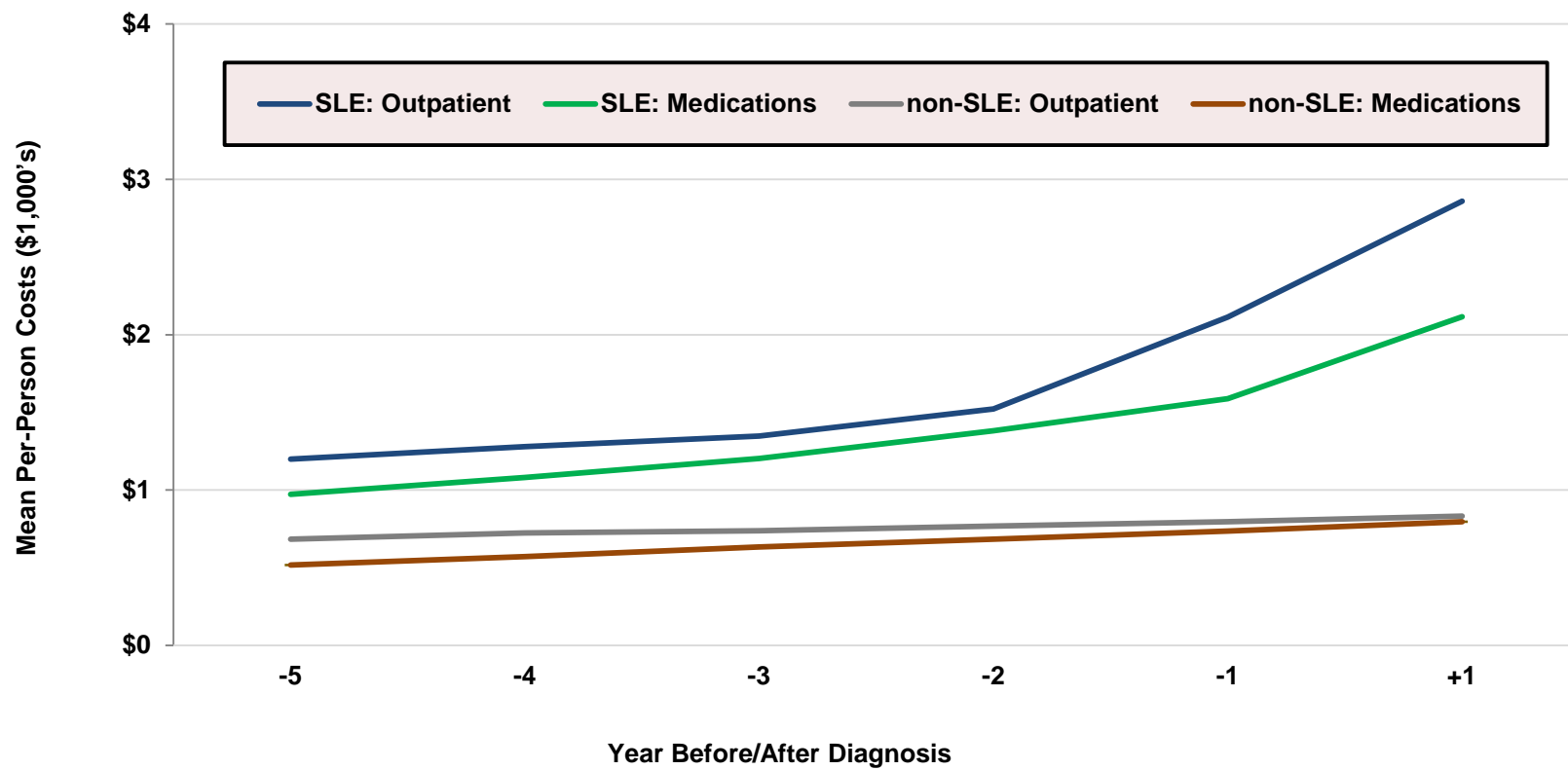


Figure 4.1: Unadjusted Annual Mean Per-Person Outpatient and Prescription Medication Costs for SLE and Non-SLE

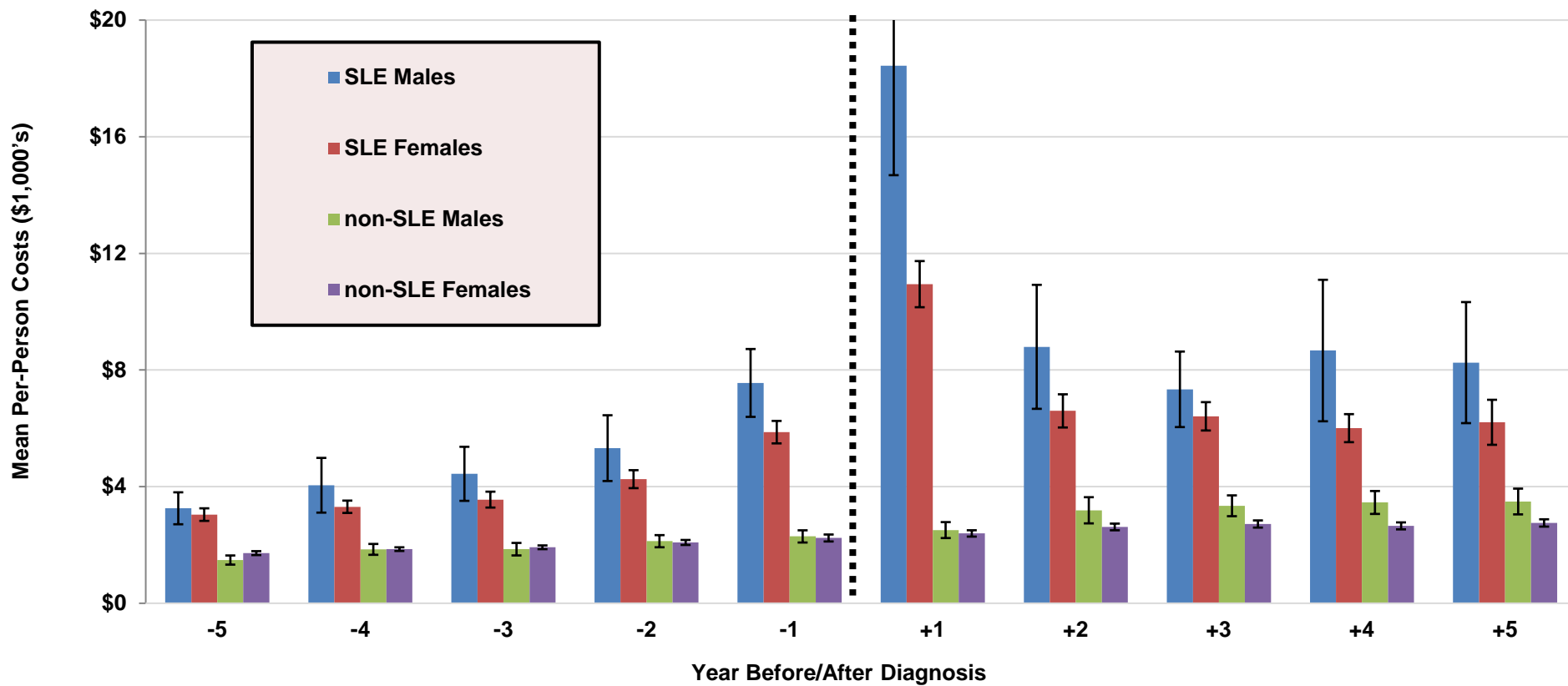


Figure 4.2: Unadjusted Annual Mean Per-Person Direct Medical Costs for SLE and Non-SLE Males and Females

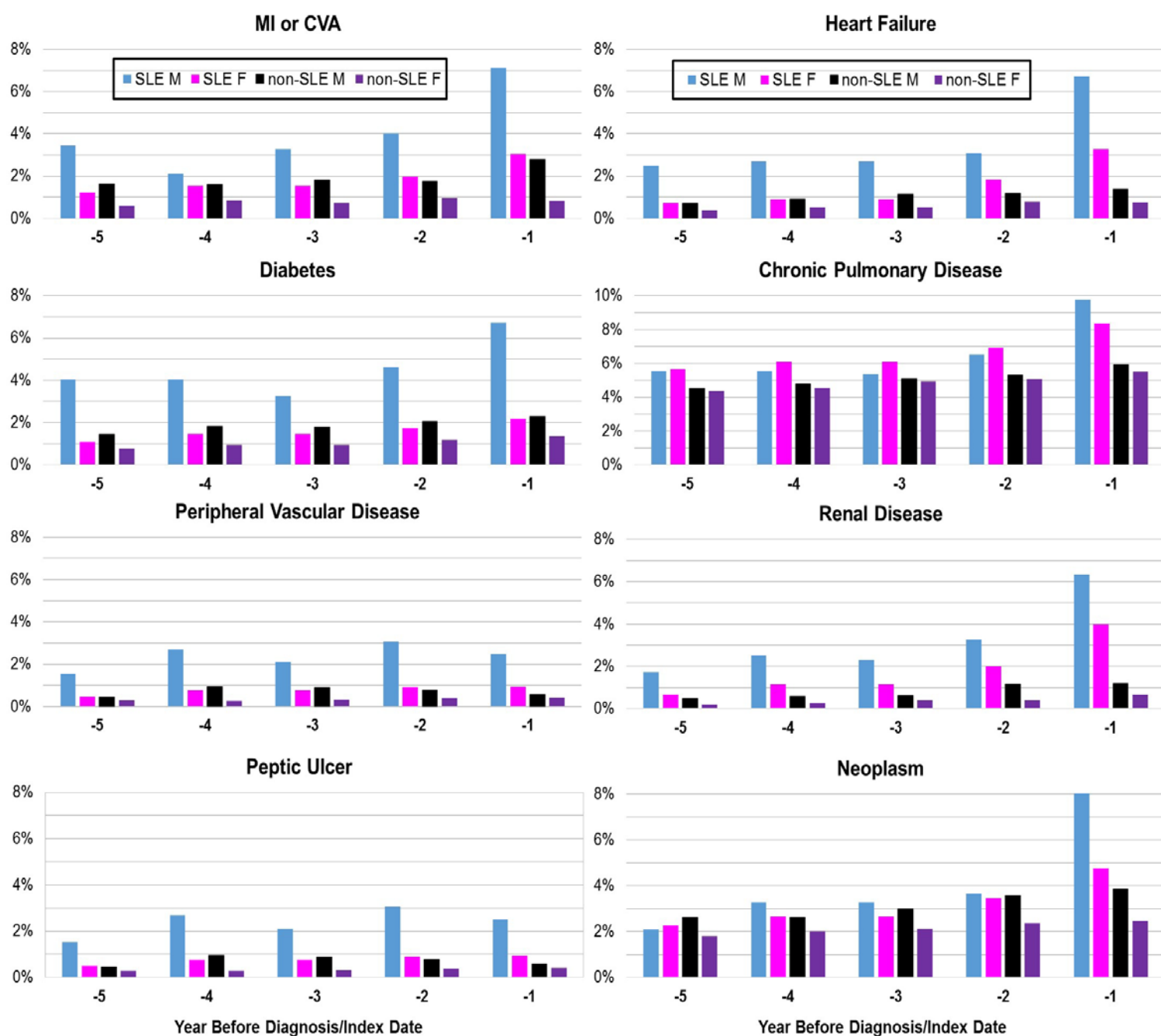


Figure 4.3: Annual Frequencies of the Most Common Charlson-Romano Comorbidities for SLE and Non-SLE Males and Females (*Dementia, Liver Disease, Hemiplegia, Metastatic Cancer, and HIV Not Shown Due to Very Small Numbers*)

5. Incremental Productivity Costs of Systemic Lupus

Erythematosus, Systemic Sclerosis, and Sjogren's Syndrome: A General Population-Based Study⁴

5.1 Introduction

Systemic autoimmune rheumatic diseases (SARDs) includes systemic lupus erythematosus (SLE), Sjogren's syndrome (SjS), systemic sclerosis/scleroderma (SSc), poly- and dermatomyositis, and forms of adult systemic vasculitis. Immune dysregulation in SARDs leads to systemic inflammation, organ damage, and an array of physical, psychological, and neurocognitive manifestations which can reduce patients' functional status, health-related quality-of-life(3–5), and participation and performance in paid and unpaid work(290,435,436). Approximately two to five of every 1,000 Canadians have been diagnosed with a SARD(347), and while many of these individuals do not participate in paid work (meta-analyses suggest that 54% of SLE(238) and 37% of SSc(258) are not employed), those who are employed may still experience challenges and limitations(437,438) that reduce their workplace productivity.

⁴ A version of this chapter has been accepted for publication:

McCormick N, Marra CA, Sadatsafavi M, Kopec JA, Aviña-Zubieta JA. Excess Productivity Costs of Systemic Lupus Erythematosus, Systemic Sclerosis, and Sjogren's Syndrome: A General Population-Based Study. *Arthritis Care & Research*. Accepted 2018 March 23. doi: 10.1002/acr.23573.

In Canadian clinic-based cohorts, lost productivity costs have averaged \$55,827 over four years for SLE(39), and \$18,639 and \$12,804 per-year for diffuse and limited SSc, respectively(33), while annual lost productivity costs for SjS in the United Kingdom (UK) averaged between \$16,392 and \$29,072(262) (all converted to 2015 Canadian dollars). Unfortunately, these clinic-based estimates have limited generalisability, and population-level cost estimates are lacking, especially outside SLE. Furthermore, previous studies have mostly failed to incorporate presenteeism (working, but at a reduced level/efficiency), a key driver of productivity costs in other arthritides(263), and time lost from unpaid work. When taking a societal perspective, one should consider the costs of productivity loss from paid and unpaid work. Consequently, excluding unpaid productivity losses will undervalue the time contributions of work-disabled individuals (those not employed for pay, due to health), homemakers, and retirees. It also fails to capture the costs for individuals who remain employed, but have difficulty performing their unpaid work activities(264).

To address these gaps, I used administrative databases to establish population-based SARD and matched non-SARD cohorts from one Canadian province, British Columbia (BC). A random sample of each cohort was invited to complete a cross-sectional survey on their paid and unpaid work. These data were used to compare weekly hours of lost productivity for those with and without a SARD diagnosis, and associated costs, from a societal perspective, at the general population level. This chapter focusses on the most-frequent diagnoses in the cohort, SLE, SSc, and SjS.

5.2 Methods

5.2.1 Administrative data source

Publicly-funded health care (including rheumatologist and other specialty care) is available to all legal residents of the province of BC (population ~4.5 million). Population Data BC uses population-based linkable administrative data files to capture provincially funded healthcare services, including all fee-for-service outpatient encounters(316) and hospitalisations(317) since 1990, and limited demographic(319) and vital statistics data(320).

5.2.2 Study populations

From the administrative data files, a population-based cohort was assembled of all adults who sought care for SARDs during the years 1990 to 2010, and were still registered with the provincial medical insurance plan at some point during 1996 to 2010. SARDs were identified from International Classification of Diseases Ninth/Tenth (ICD-9/10) Revision diagnostic codes (listed in Chapter 2, Table 2.1) recorded for outpatient encounters and hospitalisations: (a) \geq two ICD-9 codes for SARDs \geq two months apart but within a two-year period by a non-rheumatologist physician; (b) one ICD-9 code from a rheumatologist; or (c) one ICD-9/10 code from a hospitalisation. The SARD index date was the date of the first SARD-coded encounter. When the validity of this case definition was assessed in another Canadian province (with the gold standard being the clinical diagnosis recorded for patients attending a tertiary rheumatology clinic)(333), the majority of administrative database diagnoses were true-positives (positive predictive values of 57% for SLE, 63% for SSc, and 73% for SjS). However, to increase certainty in the SARD diagnoses in my study, potential SARD cases were excluded if they had at

least two visits \geq two months apart (subsequent to the SARD index visit) with diagnoses of other inflammatory arthritides, including rheumatoid arthritis, psoriatic arthritis, and spondyloarthropathies.

To establish the non-SARD comparison cohort, our group received data for a random sample of ~400,000 BC residents registered with the provincial medical plan during the study period. These individuals were assigned a random index date, and any individuals who met the case definition for SARDs were removed. We selected up to 10 individuals per SARD case, matched on age, sex, and calendar year of index date.

5.2.3 Survey

Productivity data are not available in the administrative health databases, so this information was collected from SARD and non-SARD individuals directly via a survey completed on paper or online. Administrative datafiles are released to researchers in de-identified form, stripped of any names, addresses, or phone numbers that would allow researchers to identify or contact these individuals. However, I recruited members of the SARD and non-SARD cohorts to complete the survey using a new 'Request-to-Contact' scheme which grants researchers access to names and contact information for a sample of individuals in the BC administrative databases. Our group chose this method of recruitment to obtain more representative samples of people with and without SARDs than would be achieved from recruiting online or from tertiary clinics.

The recruitment and data collection procedures for the survey have been published(439), and are detailed in Section 2.6 of Chapter 2. Briefly, upon final approval of our Request-to-Contact application in April 2015, we assembled a subset of the SARD and non-SARD cohorts (those still registered with the provincial medical plan in 2015) and submitted their Study IDs to the BC Ministry of Health. Included in the subset were 9,335 prevalent SARD cases (82.3% female, mean age in 2015 of 60 ± 15.8 years) and 55,431 matching non-SARD individuals (82.8% female, mean age 62.4 ± 16.0 years). The BC Ministry of Health selected a random sample ($n=12,000$) of these individuals, and on July 9, 2015, their names, addresses, and phone numbers were released to the research team, though their administrative database Study IDs were not. Although 6,000 of these individuals were selected because they had met the case definition for SARDs in the administrative databases, and 6,000 were selected because they had not met the definition, the information on all 12,000 individuals was provided in a single file, and I was blinded to the each person's disease status.

Participants were recruited by mail. From the list of 12,000 potential participants, I randomly selected a total of 2,400 names and mailed each person an invitation package. Four mailouts were conducted over an eight-month period; I started with two pilot mailouts ($n=200$ packages each), conducted in July and September 2015, while the two main mailouts ($n=1,000$ packages each) were conducted in November 2015 and March 2016. Individuals who wished to participate were asked to mail their signed consent form back to the research team. Those who requested a paper survey were mailed a copy of the survey, along with a prepaid return envelope, while the other participants were e-mailed a link to the online survey along with a unique, six-

digit access code. Potential participants who did not respond to the invitation package were mailed a reminder letter after two weeks, and phoned after four weeks. Similar follow-up procedures were employed after the survey was distributed to consenting participants.

The survey, which was pilot-tested among research staff and volunteer members of the SARD Consumer Advisory Council at Arthritis Research Canada, took about 30 minutes to complete. Those completing the online version could do so over multiple sessions and save their responses as they went along. The components of the survey are described in more detail in Section 2.7 of Chapter 2, and a copy of the survey is available in Appendix A. Briefly, it was comprised of six sections collecting data on sociodemographics, health status, behaviours, and health-related quality-of-life, levels of pain, fatigue, and functional disability, and participation in paid and unpaid work activities.

Importantly, since I did not have access to the diagnoses recorded for participants in the administrative databases, the disease status of each participant was based on self-report. Specifically, the survey asked participants whether they had been diagnosed by a health professional with each SARD. Those reporting at least one diagnosis were classified as SARDs, and the rest as non-SARDs, with the SLE, SSc, and SjS groups consisting of individuals reporting these respective diagnoses. Participants could be included in more than one SARD group (i.e. SLE and SjS). In a Canadian study of individuals diagnosed with SARDs (including SLE, SSc, SjS, and poly/dermatomyositis), ‘other disease’ controls (individuals diagnosed with haemolytic anaemia, multiple sclerosis, thyroid disease, or type I diabetes), and ‘healthy’

controls, a similarly-worded question demonstrated both high sensitivity (100% for each SARD) and high specificity (ranging from 95% for SLE to 100% for SSc) as compared to the diagnoses captured from medical record review(440).

5.2.4 Independent variables

Sociodemographic variables included gender, age, marital status (living with a partner yes/no), race/ethnicity (collapsed into White/non-White), children at home (yes/no), educational attainment, and household income level.

Disease duration was equal to the number of years between self-reported year of diagnosis by a health professional, and year 2015. Health status and behavioural data included height, weight, smoking status (ever vs. never) and pack-years, number of comorbidities (0, 1, 2, or ≥ 3), and levels of functional disability (using the Health Assessment Questionnaire Disability Index(371)), pain, fatigue, and health-related quality-of-life (using the EQ-5D-5L(369), scored according to the United States and Canadian(370) algorithms). Data on height and weight were used to calculate a raw body mass index value and determine overweight ($\geq 25 \text{ kg/m}^2$) and obesity ($\geq 30 \text{ kg/m}^2$) status. Sex-specific correction equations(441) were also implemented to correct for the tendency to overestimate height and underestimate weight in self-report.

5.2.5 Dependent variables

My primary outcome was incremental hours of productivity loss for SARDs and associated costs. I also computed the proportions of working-age individuals (aged < 65 years)

that were work-disabled (not working due to health), and assessed determinants of productivity costs and work disability among SARDs. ‘Incremental’ losses and costs refer to the differences in lost productive time (and monetary value of that time) between the diseased group and matched group from the general population. Following adjustment for measured confounders, such differences in productivity remove ‘background’ productivity losses/costs in the general population and provide estimates that can be attributable to the disease of interest.

Employment and productivity data were collected using two instruments, Work Productivity and Activity Questionnaire (WPAI)(372) and Valuation of Lost Productivity (VOLP)(377). Responses to questions from the WPAI were used to determine absenteeism (# hours missed from work over the past seven days, due to health) and presenteeism from paid work (# hours worked over the past seven days*percentage-impairment while working, due to health), while time loss from unpaid work was determined from the VOLP. Specifically, the VOLP asked about hours of paid and unpaid help received (for household chores, yard/maintenance work, shopping/errands, childcare, and voluntary activities) over the past seven days, due to health. This approach captures productivity losses only from essential, time-sensitive tasks, not all time available in the day for unpaid work(264). Both instruments asked about productivity losses due to any health problem, not just SARDs.

WPAI considers productivity losses as hours of lost labour input by an individual worker, but the VOLP allows for the consideration of the lost output of a worker and their colleagues when that individual is away from work or less productive. To do so, the VOLP asks about job

and workplace characteristics; specifically, how often one works in a team, size of their team, and substitutability. A multiplier value (≥ 1) is derived from the responses, with hours of lost output equal to the product of hours of lost input and this multiplier. Separate multipliers are calculated for absenteeism (among employed participants reporting absenteeism) and presenteeism (among those reporting presenteeism).

5.2.6 Cost calculation

Based on their stated job, participants were matched to one of ten sectors in Canada's National Occupational Classification(442). Hours of lost productivity were multiplied by the sector-specific hourly wage(443) to compute weekly lost productivity costs. More information on these sectors and the average wages is available in Table 5.3. If the participant was not in the paid workforce, or did not state their occupation, the overall average hourly wage for Canada in October 2015 (\$25.38) was used (opportunity cost approach). All costs are expressed in 2015 Canadian dollars.

5.2.7 Statistical analysis

Group characteristics were compared (each SARD group versus the non-SARDs) using *t*-tests and chi-squared tests. Unadjusted estimates of productivity losses and costs were produced for each of the four groups (SLE, SSc, SJS, and non-SARDs), and stratified by employment status, with the differences between each SARD group and the non-SARDs taken as the unadjusted incremental productivity losses and costs of SARDs. One member of the SSc cohort was not employed but reported very high unpaid productivity losses (196 hours per-week; this

was confirmed to be a special case and not an error), so SSc estimates are presented with and without this extreme observation. Some individuals reported multiple SARD diagnoses (i.e. SLE and SSc), and while this might be considered as ‘overlap syndrome’, I included these individuals in each applicable SARD group since I sought to compare the productivity losses of each SARD diagnosis with the non-SARD group, not losses between different SARDs.

Productivity costs were initially expressed as raw estimates (hours*hourly wage). Then, in a secondary analysis, I also applied the average multipliers (as done previously(444), calculated among all eligible participants) to the initial estimates of absenteeism and presenteeism from paid work. Multipliers were not applied to unpaid productivity losses. I additionally performed a secondary analysis which included, for work-disabled individuals, the costs of lost productivity from paid work. Briefly, I used data from a Canadian time use survey (Statistics Canada’s General Social Survey(445)) to impute the number of hours these individuals would have spent in paid work (average of 3.18 hours per-day*7 days=22.28 hours per-week), and multiplied these hours by the overall hourly wage in Canada (\$25.38).

Raw estimates of productivity costs were subsequently adjusted for potential confounders (factors that can affect the risk and severity of the diseases, and independently impact productivity). These included sociodemographic factors and comorbidity burden, but not health status measures (i.e. fatigue, disability) or behaviours which were likely to be mediators rather than confounders. However, as SARDs can increase the risk of certain comorbidities (thus placing comorbidity burden on the pathway between SARD status and productivity loss),

analyses were also conducted without adjustment for comorbidity score. I constructed separate sets of regression models for each SARD and aspect of productivity loss (absenteeism, presenteeism, any paid loss, any unpaid loss, and any paid or unpaid loss). As many individuals reported no productivity loss for an eligible category, two-part models were used. The first part, multivariable logistic regression model, assessed (for each aspect of productivity loss) the probability of incurring any time loss/cost. The second, a generalised linear model (with log-link and gamma distribution), estimated the time losses and costs expected for those with time loss/costs > 0 .

I subsequently used G-computation(364) to estimate the absolute time loss/costs expected for each group, and incremental costs of SARDs. With this approach, odds and time loss/costs were predicted for each person two times, once with them coded as having the SARD and once as non-SARDs, but with their other covariates the same. The final estimate for each iteration (SARD- and non-SARD-coded observation for each person) was the product of their predicted odds and predicted hours/costs. The difference between estimates for each person (i.e. predicted odds*costs when coded as SLE, and when coded as non-SARDs) represented the incremental costs of SARDs, with per-person predicted incremental costs averaged across all eligible individuals. Parametric bootstrapping (100 replications each) was used to produce 95% credible intervals (95% CI). Due to small sample sizes, determinants of productivity costs within each SARD were assessed with correlational and univariable analysis rather than multivariable models. Analyses were conducted using SAS Enterprise Guide version 4.3.

5.3 Results

From 2,400 invitations distributed, 743 consents were received (31%) and another 645 (27%) formally refused to participate. Surveys were completed by 671 of the 743 consenting individuals, with 69% online and 31% paper-based. Forty-four percent ($n=296$) reported at least one SARD diagnosis, with the other 375 classified as non-SARDs. SLE was the most common diagnosis (56%), followed by SjS (30%), and SSc (14%), while $\leq 5\%$ of respondents had been diagnosed with any of the other SARDs. Characteristics of the SLE, SSc, SjS, and non-SARD groups are shown in Table 5.1. Sociodemographics and health behaviours were generally comparable, although the SLE were slightly younger than non-SARDs (mean age 54.6 ± 13.1 vs. 57.8 ± 11.7) and the SLE and SjS had larger proportions of females than non-SARDs.

Similar percentages of working-age SSc, SjS, and non-SARDs (54-58%) were employed for pay, though somewhat fewer SLE were employed (46%). The mean number of hours worked by employed individuals over the past week was also comparable across the four groups (ranging from 26.5 ± 16.6 among employed SjS to 29.3 ± 16.6 among non-SARDs). But while similar percentages of SARDs and non-SARDs were (not)-employed, about twice as many working-age SARDs than non-SARDs were work disabled (not-employed, due to health). Table 5.3 breaks down the occupational sectors for employed members of each group, and corresponding average wages used to compute costs. The majority of SLE (59%) were in business, healthcare, or management occupations, while 52% of SjS were in business or educational/social services/law. The most common sector for non-SARDs was business (25%), with an additional 14% to 17% in each of healthcare, education/social services/law, sales/service, and management.

For absenteeism and presenteeism combined, productivity losses did not differ between any SARD group and non-SARDs. Weekly hours of absenteeism (among all employed individuals) averaged 2.4, 2.5, 4.0, and 3.1 in SLE, SSc, SjS, and non-SARDs respectively. However, presenteeism rates were higher in SARDs, and SLE and SjS reported significantly greater levels of impairment in paid work (percent impairment: SLE=21% and SjS=33%, vs. 14% for non-SARDs).

Each SARD group averaged more unpaid time loss (hours of paid and unpaid help received) than non-SARDs (Table 5.2), though only 44-50% of each SARD group, and 25% of non-SARDs, reported any unpaid productivity loss. Most help was provided by family members (81% for SjS, 87% for SSc and non-SARDs, and 89% for SLE).

5.3.1 Unadjusted costs

Average weekly costs for time lost from paid work were \$216, \$158, \$297 and \$187 for SLE, SSc, SjS, and non-SARDs, respectively (Table 5.2), with presenteeism accounting for 64-69% of costs in SARDs and 53% in non-SARDs. When extrapolated (multiplied by 52), these estimates translate to \$11,206 per year for SLE, \$8,200 for SSc, \$15,434 for SjS, and \$9,703 for non-SARDs.

Data from the VOLP were used to calculate multipliers representing the impact of the respondent's absence from paid work (or reduced productivity at work) on their workplace's productivity. Average multipliers were 1.77 ± 1.44 for absenteeism and 1.54 ± 1.10 for

presenteeism. Thus, a one-hour absence from work was valued at 1.77-times the person's hourly wage. When these multipliers were applied to paid productivity losses, mean costs were \$347, \$255, \$482, and \$307 per-week for SLE, SSc, SjS, and non-SARDs, respectively (Table 5.2).

Altogether, unadjusted per-person lost productivity costs from paid and unpaid work, as averaged among all participants, were \$301 in SLE, \$353 in SSc (\$240 excluding outlier), \$271 in SjS, and \$149 in non-SARDs. These weekly estimates translate to \$15,636 per-year for SLE, \$18,361 for SSc (\$12,501 without outlier), \$14,092 for SjS, and \$7,743 for non-SARDs. Unpaid work loss accounted for 31-47% of costs for employed SARDs, and just 21% for employed non-SARDs (Figure 5.1). When I imputed time loss from paid work for work-disabled individuals (Table 5.2), annual lost productivity costs averaged \$23,774 for SLE, \$23,962 for SSc (\$18,236 excluding outlier), \$19,599 for SjS, and \$11,144 for non-SARDs.

5.3.2 Adjusted analyses: incremental productivity losses and costs

After adjustment, SLE had 2.4-times greater odds of work disability than non-SARDs (95% CI=1.4-4.1) and 2.0-times greater odds of experiencing any paid or unpaid productivity loss (Table 5.4), while odds were 1.8-times greater for SjS (Table 5.5) and 2.6-times greater for SSc (Table 5.6). The two-part regression model predicted time loss and costs for each group, while accounting for the probability of reporting any loss, and adjusting for age, gender, race/ethnicity, marital status, children at home, education, and comorbidity burden. Altogether, incremental productivity loss (adjusted difference between SARDs and non-SARDs, from any paid or unpaid work) averaged 3.5, 3.2, and 3.4 hours per-week for SLE, SSc, and SjS,

respectively, with corresponding costs of \$86, \$69, and \$84 per-person. Estimates of incremental costs were larger (\$126, \$84, and \$107 per-week, respectively) when comorbidity score was removed from the models. For unpaid work losses specifically, adjusted incremental costs averaged \$127 per-week for SLE, \$100 for SSc, and \$82 for SjS. When stratified by working status, absolute costs for unpaid work loss were lower among employed individuals than those not-employed, but in each stratum (employed and not-employed), SARDs were still associated with significantly-greater costs than non-SARDs (Tables 5.4, 5.5, and 5.6).

5.3.3 Determinants of productivity costs within SARDs

In univariable analyses, having ever-smoked was associated with 2.1-times greater odds of work disability among SLE (95% confidence interval=1.0-4.5), and greater unpaid productivity costs for SSc (cost ratio=1.99 [95% CI=1.10-3.59]). Conversely, completion of a university degree was associated with 61% lower-odds of work disability among SLE (OR=0.39 [95% CI=0.16-0.96]), 45% lower costs from unpaid productivity loss among SLE (cost ratio=0.55, 0.33-0.93), and 73% lower absenteeism costs among SSc (cost ratio=0.27, 0.11-0.65). Functional disability, pain, and fatigue scores were significantly correlated with productivity costs in SLE and SjS (Table 5.7). High household income was associated with lower levels of unpaid productivity costs in SSc (cost ratio=0.48, 0.27-0.86) and SjS (0.39, 0.23-0.65), while being overweight was associated with greater absenteeism costs in SSc (cost ratio=3.77, 1.27-11.23), and unpaid productivity costs in SLE (1.67, 1.05-2.63) and SjS (1.96, 1.14-3.39).

5.4 Discussion

These are the first population-based estimates of the incremental lost productivity costs of SLE, SSc, and SjS. My annualised estimates suggest those with SLE, SSc, or SjS will incur an additional \$4,494, \$3,582, and \$4,357, respectively, in lost productivity costs each year, over-and-above a similar person without a SARD diagnosis. Estimates were even larger (\$6,530, \$4,379, and \$5,554, respectively) without adjustment for the elevated comorbidity burden present in SARD patients. Though work disability was more common among the SARD cohorts than non-SARDs (36% of SLE, 32% SSc, and 30% of SjS unable to work due to health, versus 18% of non-SARDs), SARD individuals who remained employed still had more impairment at work (presenteeism) than non-SARDs, and this accounted for 36-44% of their productivity costs.

There were no substantive differences in the mean hours worked, or hours or costs of absenteeism, among employed members of the four groups. This finding is congruent with a Canadian cohort of rheumatoid, psoriatic, and osteoarthritis (mean age 51 years, 79% female)(263), where presenteeism accounted for 81% of costs, and absenteeism just 19%. While it is tempting to infer that SARDs do not adversely impact individuals' attendance at work, this was a prevalent cohort with rather established disease (mean disease duration of 18 years in SLE, 13 in SSc, and 12 in SjS), and 30% to 36% of SARDs described themselves as work-disabled. Thus, a more likely explanation is a 'healthy-worker' effect(265), wherein those with the greatest impairments left the paid workforce at an earlier time.

Although the survey did not ask about employment status at diagnosis or subsequent job changes, this supposition is supported by findings from other cohorts. In a Chinese cohort of SLE(251), those who remained employed since diagnosis did not report a significant change over time in the mean hours worked per day. Among Lupus Outcomes Study participants who remained employed continuously since SLE diagnosis, there was little change in hours of paid work per-week (decrease of 5%) or per-year (decrease of 1%)(446). Those investigators suggest that SLE patients are more likely to leave the workforce entirely than reduce their hours or make other job changes(446). Similar findings have been reported in SSc, where the majority of health-related work transitions for one cohort were complete work stoppages rather than reductions in hours or job changes(299), and in SjS, where employed SjS did not differ significantly from non-SjS in mean hours of paid work(268), or time absent from work(262). There is disagreement in the literature about whether to include, for work disabled individuals, the costs of (potential) time loss from paid work. From a societal perspective, doing so may overestimate costs since, upon work cessation, that person's job will eventually be filled (and their productivity taken-over) by someone who was previously unemployed(447). Still, when I did include these costs in a secondary analysis (based upon a conservative 22.28 hours of lost paid-work time each week), mean per-person lost productivity costs increased by 39% among SjS (\$377 vs. \$271 per-week without imputed costs), 46% among SSc (\$351 vs. \$240), and 52% among SLE (\$457 vs. \$301 per-week).

Comparisons of my annualised cost estimates with those from prior studies are complicated by heterogeneity in the source populations, productivity components included, and

approaches to measuring and valuing time loss. For example, my absenteeism estimates included only time actually missed from scheduled work, while others(39,262) have included the additional hours participants reported they *would be* working if they did not have health problems. Moreover, use of service-sector (replacement) wages to value unpaid work, as others have done(33), will produce more conservative estimates compared to sector-specific wages, while asking about the *number of days* an individual was unable to work(33) may overestimate the *total hours* of lost productivity in a given week. Still, my extrapolated annual predictions for SSc and SjS (\$12,501 and \$14,092, respectively) are similar to those for a Canadian cohort of SSc (\$15,232 converted to 2015 CDN)(33) and UK cohort of SjS (\$16,392)(262).

Unpaid work loss was a major contributor, even among employed individuals. After adjustment, employed SLE and SjS averaged about three more hours of unpaid productivity loss per week than employed non-SARDs. Furthermore, unpaid work losses accounted for 41% of costs for employed SLE, but just 21% for non-SARDs. It is important to recognise that many individuals with health impairments remain employed and do complete their paid work tasks, but with less time or capacity for housework and other unpaid work activities(264). Although the majority of household help was provided by family members, at no direct cost, there is still a societal cost associated with this additional time expenditure.

While absenteeism from paid work is more straightforward to measure (i.e. hours/days of missed work), presenteeism and unpaid work loss can vary depending on how they are operationalised. In a comparison of four presenteeism instruments completed by Canadians with

rheumatoid arthritis or osteoarthritis(448), the one I used (WPAI) had the least amount of missing data, but also produced the highest estimates. I measured unpaid productivity losses using a question from the Health and Labour Questionnaire(449) (and included in the VOLP) that asks about hours of paid or unpaid help received because of health issues. This more conservative approach aims to measure time lost only from essential tasks, not all time available for unpaid work. It assumes individuals experiencing health impairments will not obtain extra help for tasks that are optional or can be put off(264). Thus, time loss from presenteeism may have been overestimated, and time loss from unpaid work underestimated. Though only about half of the SARD cohorts, and one-quarter of non-SARDs, reported any unpaid productivity loss, these proportions are congruent with a prior VOLP study (of employed individuals with early RA) in which 32% reported unpaid productivity loss(377). Moreover, I do not believe the degree of over/under-estimation would differ between SARDs and non-SARDs.

This analysis was not well situated to identify determinants of productivity losses and costs *among* SARDs but, consistent with other studies(216,238,241,268,269), I did find that levels of functional disability, pain, and fatigue were associated with greater productivity losses/costs, as were past-or-present smoking and being overweight. Other studies of SLE have found obesity to be associated with decreased odds of employment(450), and higher body mass index with greater lost productivity costs(216). I also found that completion of a university degree was associated with decreased odds of work disability in SLE, and decreased unpaid productivity costs. Lower education has been associated with employment and disability status in prior studies of SLE(446,451,452), SSc(260,269) and SjS(277), and with greater unpaid

productivity losses(453) and costs(39) in SLE. It was been suggested that higher education may allow individuals to hold jobs that offer more flexibility(240) or other accommodations(454) conducive to employment. I acknowledge these were cross-sectional associations from unadjusted analyses, and their independent impact requires further investigation. Overweight and fatigue may be markers of more severe disease (in the case of SLE, high-dose GC used to manage severe disease may contribute to obesity) or comorbidity burden, although these factors were significant in previous studies that controlled for disease duration(216,241,450), comorbidities(216,241,268,450), disease severity(241,268,450), and medication use(216,268,450).

Still, it encouraging to think that, especially among newly-diagnosed individuals, modifications in these factors may attenuate future productivity losses. For example, several educational, psychological, and exercise interventions have been effective at reducing fatigue in SLE and SjS(455,456). Furthermore, while some may not wish to disclose their SARD diagnosis to their employers, increasing access to (and uptake of) workplace accommodations such as flexible hours(438,454), training for a different position(454), or (mainly for individuals with SSc) office heaters to ameliorate the impact of Raynaud's, and voice-recognition software to reduce time spent keyboarding(438), may help preserve these individuals' productivity and ability to work.

Many of this study's strengths and limitations stem from recruiting SARD and non-SARD participants from population-based cohorts. This is an improvement upon clinic-based

cohorts, whose members are likely to have more severe disease, and more productivity loss, than others with SARDs. To the other extreme, cohorts recruited exclusively online may not be representative either, as they tend to have a higher-than-average level of education(307,375), while commercial insurance databases only cover employed individuals, and do not contain data on presenteeism or unpaid work loss. Recruiting a comparison group from the general population is also an improvement upon ‘friend’ controls(268,452), who may not be representative of others in the population. Privacy regulations limited my ability to compare those who did and did not participate, but I know the participants were somewhat younger, on-average, than the initial survey sample (mean ages 57.8 versus ~61 years), and there were more females. Nonetheless, the same differences were observed for those with and without a SARD diagnosis.

As mentioned, the cohorts had rather established disease, so these findings may not represent the productivity impact on newly-diagnosed individuals at present. Small sample sizes, and even smaller numbers of employed participants (especially for SSc), limited my assessment of productivity losses from paid work, and determinants of productivity costs within SARDs. Although my analysis was focussed on time loss, costs, and employment status, I nevertheless acknowledge data were not collected on items such as workplace discrimination, job security, the potential for career advancement, workplace accommodations, or reductions in hours or career changes. These outcomes are important, and should be examined in future population-based studies of SARDs.

The data were self-reported, and the SARD diagnoses were not clinically confirmed (nor did I compare the self-reported diagnoses with those recorded in the administrative data), but participants were asked to only report diagnoses from a health professional. There are limited data available on the accuracy of self-reported diagnoses of SARDs, especially outside SLE, and among the published studies, the specificity and positive predictive values have varied depending on the composition of the source population. For example, confirmation rates were low for self-reported diagnoses of SLE (10/48=21%), SSc (1/6=17%), and SjS (11/29=38%) in the Women's Health Cohort Study(457), which recruited from a large sample of female health professionals, without regards to disease status. However, in Canadian studies of first-degree relatives of SLE patients (and matched population controls)(458), and SARD patients attending tertiary clinics (along with 'other disease' and healthy controls)(440), populations with a higher expected prevalence of SARDs, confirmation rates and specificity values were much higher (i.e. confirmation rates of 86-100% among the first-degree relatives(458)). This lends support to the accuracy of the self-reported diagnoses in my study since, instead of sampling from the community-at-large (where the prevalence of SARDs is low), I recruited from cohorts that had already met a validated case definition for SARDs.

Productivity costs were determined using occupation-specific wages (where available), though I used wages specific to one of ten broad occupational categories (i.e. healthcare, sales and service), and did not account for variation within those categories (i.e. within the sales and service category, the average wage for a childcare worker would be less than for an insurance salesperson). However, this would only meaningfully impact my estimates of incremental costs

if those with SARDs tended to be in lower-wage job groups than those without. The productivity questionnaires have been used and validated in populations of SLE(374,375), SSc(376), and RA(377,378), and Canadian research supports the validity of self-reported smoking data(459).

Despite these limitations, this study makes several unique contributions in highlighting the societal burden of SARDs. It is the first-known analysis of the incremental productivity costs of SSc, first population-level analysis of productivity costs in SjS, and one of few SLE estimates to include presenteeism in paid work, and time lost from unpaid work. The VOLP allowed me to estimate the costs of paid work loss for the respondent, and their workplace. Furthermore, I minimised equity concerns by including time spent in paid and unpaid work, using opportunity costs to value unpaid work losses, and applying sector-specific wages instead of sex-specific ones.

5.5 Conclusion

These comprehensive, more generalisable estimates can serve as the benchmark for ongoing assessments, and could be incorporated in economic evaluations of interventions aimed at improving health and vocational outcomes in SLE, SSc, or SjS. They also underscore the need for clinicians and researchers to look beyond paid work absences when evaluating the impact of the disease on patients' productivity and quality of life. Though productivity costs and gains are not usually considered in the (public payer) health system perspective, they are

important to patients(460), and I hope these findings will inform the agenda for ongoing research in these little-known disorders.

Table 5.1: Participant Characteristics, by Cohort

Mean (SD) or N (%)	Systemic Lupus Erythematosus	p-value (vs. non-SARDs)	Systemic Sclerosis	p-value (vs. non- SARDs)	Sjogren's Syndrome	p-value (vs. non- SARDs)	Non-SARDs
N	167	n/a	42	n/a	90	n/a	375
Female	157 (94%)	0.01	37 (88%)	0.73	87 (97%)	0.01	323 (86%)
Current Age, years	54.6 (13.1)	< 0.01	59.5 (12.0)	0.37	58.2 (12.6)	0.82	57.8 (11.7)
Age at Diagnosis, years	36.5 (13.7)	n/a	46.3 (14.0)	n/a	46.4 (12.7)	n/a	n/a
Disease Duration, years	17.6 (9.9)	n/a	13.0 (11.9)	n/a	11.7 (8.3)	n/a	n/a

Mean (SD) or N (%)	Systemic Lupus Erythematosus	p-value (vs. non-SARDs)	Systemic Sclerosis	p-value (vs. non- SARDs)	Sjogren’s Syndrome	p-value (vs. non- SARDs)	Non-SARDs
SOCIODEMOGRAPHICS							
White/Caucasian	122 (73%)	< 0.01	38 (90%)	0.32	68 (76%)	0.04	318 (85%)
Living with Partner	116 (69%)	0.89	31 (74%)	0.61	58 (64%)	0.30	262 (70%)
Living with Children	61 (37%)	0.34	11 (26%)	0.42	23 (26%)	0.21	121 (32%)
Educational Attainment							
High School or Less	52 (32%)	0.30	14 (33%)	0.59	18 (20%)	0.04	117 (31%)
Some Post-Secondary	70 (43%)		18 (43%)		45 (50%)		139 (37%)
University Degree	41 (25%)		10 (24%)		27 (30%)		117 (31%)
Household Income Level							
< \$40,000	42 (29%)	0.74	12 (30%)	0.80	26 (30%)	0.35	88 (26%)
\$40,000-\$80,000	43 (29%)		13 (33%)		31 (36%)		110 (32%)
> \$80,000	62 (42%)		15 (38%)		29 (34%)		145 (42%)

Mean (SD) or N (%)	Systemic Lupus Erythematosus	p-value (vs. non-SARDs)	Systemic Sclerosis	p-value (vs. non- SARDs)	Sjogren's Syndrome	p-value (vs. non- SARDs)	Non-SARDs
HEALTH STATUS							
Functional Disability (HAQ-DI score)	0.70 (0.64)	< 0.01	0.93 (0.70)	< 0.01	0.71 (0.64)	< 0.01	0.42 (0.56)
Pain (<i>range 0-100</i>)	38 (25)	< 0.01	39 (28)	0.03	39 (27)	< 0.01	29 (28)
Fatigue (<i>range 0-100</i>)	52 (27)	< 0.01	47 (27)	0.01	54 (28)	< 0.01	34 (29)
EQ-5D-5L							
VAS (<i>range 0-100</i>)	68 (20)	< 0.01	68 (17)	0.10	66 (20)	< 0.01	73 (19)
Health State Utility, Canadian norms	0.72 (0.22)	< 0.01	0.70 (0.22)	0.02	0.71 (0.23)	< 0.01	0.78 (0.21)
Health State Utility, United States norms	0.73 (0.19)	< 0.01	0.68 (0.20)	< 0.01	0.71 (0.18)	< 0.01	0.78 (0.19)
Comorbidity Score (<i>range 0-3</i>)	2.1 (1.1)	< 0.01	2.0 (1.0)	0.07	2.2 (1.1)	< 0.01	1.7 (1.2)

Mean (SD) or N (%)	Systemic Lupus Erythematosus	p-value (vs. non-SARDs)	Systemic Sclerosis	p-value (vs. non- SARDs)	Sjogren's Syndrome	p-value (vs. non- SARDs)	Non-SARDs
HEALTH BEHAVIOURS							
Cigarette Smoking							
Ever-Smoker	75 (45%)	0.49	19 (46%)	0.80	35 (39%)	0.10	181 (48%)
Pack-Years of Smoking (among ever-smokers)	14.3 (14.7)	0.31	15.7 (21.2)	0.81	15.1 (17.0)	0.63	17.0 (21.3)
Years Since Cessation (among ex-smokers)	9.1 (12.6)	0.05	15.7 (17.4)	0.23	10.2 (14.9)	0.35	12.2 (14.6)
Body Weight							
Body Mass Index (BMI)	25.8 (6.7)	0.60	25.0 (6.0)	0.27	26.6 (5.9)	0.55	26.2 (6.2)
Corrected Body Mass Index (cBMI)	27.3 (6.4)	0.71	26.8 (4.8)	0.44	27.8 (6.2)	0.73	27.5 (6.1)
Overweight (BMI ≥ 25 kg/m²)	80 (48%)	0.54	19 (46%)	0.54	47 (52%)	0.88	191 (51%)
Obese (BMI ≥ 30 kg/m²)	35 (21%)	0.72	8 (20%)	0.65	21 (23%)	0.88	84 (23%)

Mean (SD) or N (%)	Systemic Lupus Erythematosus	p-value (vs. non-SARDs)	Systemic Sclerosis	p-value (vs. non- SARDs)	Sjogren's Syndrome	p-value (vs. non- SARDs)	Non-SARDs
Overweight (cBMI \geq 25 kg/m²)	92 (56%)	0.30	23 (56%)	0.59	57 (63%)	0.62	225 (60%)
Obese (cBMI \geq 30 kg/m²)	43 (26%)	0.79	9 (22%)	0.47	29 (32%)	0.34	101 (27%)

Bolded values indicate statistically-significant differences between each SARD and non-SARDs

HAQ-DI=Health Assessment Questionnaire Disability Index), range 0-3

EQ-5D-5L=EuroQoL instrument (measure of health status and health-related quality-of-life)

VAS=visual analogue score, range 0-100

BMI=body mass index

cBMI=BMI corrected for underestimation of weight and overestimation of height in self-report

Table 5.2: Employment and Productivity Outcomes

Mean (SD) or N (%)	Systemic Lupus Erythematosus (n=167)	p-value (vs. non- SARDs)	Systemic Sclerosis (n=42)	p-value (vs. non-SARDs)	Sjogren's Syndrome (n=90)	p-value (vs. non- SARDs)	Non-SARDs (n=375)
EMPLOYMENT STATUS							
Employed for Pay^a	59 (46%)	0.03	14 (56%)	0.83	30 (54%)	0.53	146 (58%)
Work Disabled^a	46 (36%)	< 0.01	8 (32%)	0.10	17 (30%)	0.04	46 (18%)
Hours Worked, past 7 days^b	28.2 (16.2)	0.64	29.2 (20.3)	0.98	26.5 (16.6)	0.38	29.3 (16.6)
PAID WORK: ABSENTEEISM							
Any Absenteeism, past 7 days^b	19 (30%)	0.02	< 6	0.13	12 (36%)	0.01	26 (16%)
Hours, past 7 days^b	2.4 (6.2)	0.58	2.5 (6.1)	0.80	4.0 (8.2)	0.62	3.1 (9.6)
Costs^b	\$66.01 (166.1)	0.56	\$51.44 (107.3)	0.60	\$107.80 (227.1)	0.69	\$87.34 (273.1)
Costs, with multiplier^b	\$116.80 (293.9)	0.56	\$91.06 (189.9)	0.60	\$190.70 (402.00)	0.69	\$154.60 (483.3)

Mean (SD) or N (%)	Systemic Lupus Erythematosus (n=167)	p-value (vs. non- SARDs)	Systemic Sclerosis (n=42)	p-value (vs. non-SARDs)	Sjogren's Syndrome (n=90)	p-value (vs. non- SARDs)	Non-SARDs (n=375)
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PAID WORK: PRESENTEEISM

%-Impairment in

Paid Work, past 7 days^c	0.21 (0.23)	0.02	0.18 (0.20)	0.56	0.33 (0.29)	< 0.01	0.14 (0.20)
Any							
Presenteeism, past 7 days^c	38 (67%)	0.06	10 (83%)	0.04	25 (83%)	< 0.01	77 (52%)
Hours, past 7 days^c	5.8 (6.3)	0.07	5.4 (4.2)	0.46	7.6 (8.6)	0.01	4.1 (6.2)
Costs^c	\$165.30 (205.2)	0.04	\$141.70 (94.6)	0.49	\$208.00 (244.0)	0.01	\$107.30 (169.6)
Costs, with multiplier^c	\$254.50 (316.0)	0.04	\$218.30 (145.7)	0.49	\$320.20 (375.8)	0.01	\$165.20 (261.2)

Mean (SD) or N (%)	Systemic Lupus Erythematosus (n=167)	p-value (vs. non- SARDs)	Systemic Sclerosis (n=42)	p-value (vs. non-SARDs)	Sjogren's Syndrome (n=90)	p-value (vs. non- SARDs)	Non-SARDs (n=375)
PAID WORK: ABSENTEEISM AND PRESENTEEISM							
Any Absenteeism or Presenteeism, past 7 days ^b	41 (65%)	0.09	11 (69%)	0.21	27 (82%)	< 0.01	84 (53%)
Hours, past 7 days ^b	7.7 (9.4)	0.63	6.6 (7.0)	0.92	10.9 (11.6)	0.08	6.9 (11.8)
Costs ^b	\$215.50 (293.1)	0.55	\$157.70 (141.6)	0.74	\$296.80 (336.6)	0.09	\$186.60 (337.9)
Costs, with multiplier ^b	\$347.10 (480.6)	0.63	\$254.80 (235.7)	0.72	\$481.90 (556.2)	0.11	\$307.40 (576.1)
Costs, including work disability ^d	\$364.30 (282.9)	0.01	\$293.60 (227.2)	0.72	\$386.60 (301.7)	0.02	\$267.90 (338.9)

Mean (SD) or N (%)	Systemic Lupus Erythematosus (n=167)	p-value (vs. non- SARDs)	Systemic Sclerosis (n=42)	p-value (vs. non-SARDs)	Sjogren's Syndrome (n=90)	p-value (vs. non- SARDs)	Non-SARDs (n=375)
UNPAID WORK							
Any Unpaid Productivity Loss ^e	83 (50%)	< 0.01	21 (50%)	< 0.01	40 (44%)	< 0.01	93 (25%)
Hours, past 7 days ^e	8.5 (21.8)	< 0.01	11.4 (31.4) 6.9 (11.7)	< 0.01 < 0.01	6.4 (13.1)	< 0.01	2.6 (7.5)
Costs ^e	\$219.40 (554.2)	< 0.01	\$293.00 (795.9) \$178.80 (296.6)	< 0.01 < 0.01	\$162.10 (331.0)	< 0.01	\$69.31 (199.9)

Mean (SD) or N (%)	Systemic Lupus Erythematosus (n=167)	p-value (vs. non- SARDs)	Systemic Sclerosis (n=42)	p-value (vs. non-SARDs)	Sjogren's Syndrome (n=90)	p-value (vs. non- SARDs)	Non-SARDs (n=375)
PAID AND UNPAID WORK							
Any Productivity Loss, past 7 days ^e	104 (62%)	< 0.01	26 (62%)	0.01	53 (59%)	< 0.01	148 (39%)
Hours, past 7 days ^e	11.4 (22.8)	< 0.01	13.9 (31.4) <i>9.5 (12.8)</i>	< 0.01 <i>0.05</i>	10.4 (15.9)	< 0.01	5.5 (12.0)
Costs ^e	\$300.70 (597.7)	< 0.01	\$353.10 (792.3) <i>\$240.40 (310.7)</i>	< 0.01 <i>0.10</i>	\$271.00 (412.8)	< 0.01	\$148.90 (341.9)
Costs, including work disability ^f	\$457.20 (682.1)	< 0.01	\$460.80 (817.5) <i>\$350.70 (404.0)</i>	< 0.01 <i>0.04</i>	\$376.90 (462.7)	< 0.01	\$214.30 (393.5)

Italicised values are estimates after the removal of the outlier

Statistically significant differences between SARDs and non-SARDs are in bold

Values not reported for cell sizes < 6

^aAmong participants aged < 65 years

^bAmong employed participants

^cAmong employed participants who attended work in the past seven days

^dSum of actual costs of paid productivity loss incurred by employed participants, and imputed costs of paid productivity loss for work-disabled participants (< 65 years of age and not employed, due to health)

^eAmong all participants

^fSum of actual costs of unpaid productivity loss for all participants, actual costs of paid productivity loss incurred by employed participants, and imputed costs of paid productivity loss for work-disabled participants (< 65 years of age and not employed, due to health)

Table 5.3: Occupational Sectors of Employed Participants, and Corresponding Wages

National Occupational Sector	Average Hourly Wage (2015 Canadian dollars)	N (%) Participants		
		Systemic Lupus	Sjogren's Syndrome	Non-SARDs
		Erythematosus (SLE) (n=63)	(n=33)	(n=160)
0=Management	\$39.21	7 (11%)	< 6	22 (14%)
1=Business, finance, and administration	\$25.10	18 (29%)	9 (27%)	40 (25%)
2=Natural and applied sciences	\$35.02	< 6	0	< 6
3=Health	\$29.55	12 (19%)	< 6	23 (14%)
4=Education, law, and social, community, and government services	\$30.68	7 (11%)	8 (24%)	23 (14%)
5=Art, culture, recreation, and sport	\$24.02	< 6	< 6	< 6
6=Sales and service	\$16.64	7 (11%)	< 6	27 (17%)
7=Trades, transport, and equipment operators	\$25.42	< 6	< 6	< 6
8=Natural resources and agriculture	\$23.10	< 6	0	0
9=Manufacturing and utilities	\$21.18	< 6	0	< 6
missing	\$25.38 ^a	< 6	< 6	13 (8%)

^aOverall average hourly wage in Canada

Values not reported for cell sizes < 6; data not reported at all for systemic sclerosis due to small cell sizes (n < 6) in each sector

Table 5.4: Results of Regression Analysis of Productivity Costs for Systemic Lupus Erythematosus (SLE)

	ALL			EMPLOYED			NOT-EMPLOYED		
	SLE (n=167)	Non-SARDs (n=375)	Difference	SLE (n=63)	Non-SARDs (n=160)	Difference	SLE (n=104)	Non-SARDs (n=215)	Difference
Work Disabled									
(Y/N)^a	2.4 (1.4-4.1)	-	-	-	-	-	-	-	-
Any									
Absenteeism	-	-	-	1.7 (0.78-3.7)	-	-	-	-	-
(Y/N)^b									
Costs of				\$58	\$93	-\$35			
Absenteeism^c	-	-	-	(\$2-\$139)	(\$3-\$233)	(-\$97 - -\$1)	-	-	-
Any									
Presenteeism	-	-	-	1.3 (0.66-2.4)	-	-	-	-	-
(Y/N)^b									
Costs of				\$134	\$102	\$32			
Presenteeism^c	-	-	-	(\$57-\$266)	(\$41-\$207)	(\$16-\$59)	-	-	-
Any Paid Work									
Loss* (Y/N)^b	-	-	-	1.2 (0.63-2.4)	-	-	-	-	-

	ALL			EMPLOYED			NOT-EMPLOYED		
	SLE	Non-SARDs	Difference	SLE	Non-SARDs	Difference	SLE	Non-SARDs	Difference
	(n=167)	(n=375)		(n=63)	(n=160)		(n=104)	(n=215)	
Costs of Paid				\$175	\$206	-\$31			
Work Loss^c	-	-	-	(\$54-\$348)	(\$60-\$419)	(-\$71 - -\$6)	-	-	-
Any Unpaid									
Work Loss	2.7 (1.8-4.1)	-	-	2.3 (1.1-4.7)	-	-	3.0 (1.8-5.1)	-	-
(Y/N) ^b									
Costs of Unpaid	\$203	\$76	\$127	\$141	\$54	\$87	\$248	\$92	\$156
Work Loss^c	(\$26-\$530)	(\$7-\$217)	(\$19-\$310)	(\$7-\$399)	(\$2-\$175)	(\$5-\$228)	(\$42-\$653)	(\$11-\$251)	(\$30-\$418)
Any Paid or									
Unpaid									
Productivity	2.0 (1.3-3.0)	-	-	1.6 (0.78-3.1)	-	-	3.0 (1.8-5.1)	-	-
Loss (Y/N)^b									
Hours of									
Productivity	9.68	6.17	3.51	11.04	9.39	1.65	9.66	3.60	6.06
Loss^c	(3.09-18.92)	(1.55-13.79)	(1.54-5.87)	(3.61-20.57)	(2.71-18.15)	(0.72-2.56)	(1.67-25.22)	(0.44-9.41)	(1.20-15.65)

	ALL			EMPLOYED			NOT-EMPLOYED		
	SLE	Non-SARDs	Difference	SLE	Non-SARDs	Difference	SLE	Non-SARDs	Difference
	(n=167)	(n=375)		(n=63)	(n=160)		(n=104)	(n=215)	
Costs of									
Productivity	\$254	\$167	\$86	\$299	\$262	\$36	\$248	\$92	\$156
Loss^c	(\$75-\$535)	(\$39-\$392)	(\$36-\$154)	(\$91-\$616)	(\$73-\$563)	(\$16-\$59)	(\$42-\$653)	(\$11-\$251)	(\$30-\$418)

Bolded differences are statistically-significant

*Absenteeism or presenteeism

^aCalculated amongst those < 65 years of age

^bFrom the first part of the two-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable

^cFrom the second part of the two-part model: generalised linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable

Table 5.5: Results of Regression Analysis of Productivity Costs for Sjogren's Syndrome (SjS)

	ALL			EMPLOYED			NOT EMPLOYED		
	SjS (n=90)	Non-SARDs (n=375)	Difference	SjS (n=33)	Non-SARDs (n=160)	Difference	SjS (n=57)	Non-SARDs (n=215)	Difference
Work Disabled									
(Y/N) ^a	1.8 (0.85-3.6)	-	-	-	-	-	-	-	-
Any									
Absenteeism	-	-	-	2.1 (0.86-5.2)	-	-	-	-	-
(Y/N) ^b									
Costs of				\$88	\$99	-\$11			
Absenteeism^c	-	-	-	(\$16-\$229)	(\$15-\$257)	(-\$61 - \$1)	-	-	-
Any									
Presenteeism	-	-	-	2.9 (1.2-7.0)	-	-	-	-	-
(Y/N) ^b									
Costs of				\$188	\$98	\$90			
Presenteeism^c	-	-	-	(\$88-\$424)	(\$37-\$247)	(\$51-\$168)	-	-	-
Any Paid Work									
Loss* (Y/N)^b	-	-	-	3.2 (1.2-8.6)	-	-	-	-	-

	ALL			EMPLOYED			NOT EMPLOYED		
	SjS	Non-SARDs	Difference	SjS	Non-SARDs	Difference	SjS	Non-SARDs	Difference
	(n=90)	(n=375)		(n=33)	(n=160)		(n=57)	(n=215)	
Costs of Paid				\$258	\$196	\$61			
Work Loss^c	-	-	-	(\$110-\$460)	(\$71-\$408)	(\$18-\$113)	-	-	-
Any Unpaid									
Work Loss	2.0 (1.2-3.3)	-	-	3.5 (1.5-8.1)	-	-	1.5 (0.78-2.9)	-	-
(Y/N)^b									
Costs of Unpaid	\$152	\$70	\$82	\$120	\$55	\$65	\$183	\$82	\$101
Work Loss^c	(\$30-\$345)	(\$12-\$172)	(\$18-\$185)	(\$3-\$392)	(\$1-\$205)	(\$2-\$179)	(\$30-\$477)	(\$12-\$212)	(\$18-\$266)
Any Paid or									
Unpaid									
Productivity	1.8 (1.1-3.1)	-	-	4.8 (1.6-14.7)	-	-	1.5 (0.78-2.9)	-	-
Loss (Y/N)^b									
Hours of									
Productivity	9.16	5.74	3.42	14.24	8.98	5.26	7.09	3.16	3.92
Loss^c	(3.44-15.62)	(1.77-11.02)	(1.69-4.81)	(6.20-21.83)	(3.59-15.80)	(1.87-7.65)	(1.23-17.45)	(0.49-7.79)	(0.74-9.73)

	ALL			EMPLOYED			NOT EMPLOYED		
	SjS	Non-SARDs	Difference	SjS	Non-SARDs	Difference	SjS	Non-SARDs	Difference
	(n=90)	(n=375)		(n=33)	(n=160)		(n=57)	(n=215)	
Costs of									
Productivity	\$239	\$155	\$84	\$378	\$248	\$130	\$183	\$82	\$101
Loss^c	(\$82-\$434)	(\$43-\$317)	(\$39-\$124)	(\$160-\$600)	(\$89-\$457)	(\$42-\$204)	(\$30-\$477)	(\$12-\$212)	(\$18-\$266)

Bolded differences are statistically-significant

*Absenteeism or presenteeism

^aCalculated amongst those < 65 years of age

^bFrom the first part of the two-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable

^cFrom the second part of the two-part model: generalised linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable

Table 5.6: Results of Regression Analysis of Productivity Costs for Systemic Sclerosis (SSc)

	ALL			EMPLOYED			NOT EMPLOYED		
	SSc (n=42)	Non-SARDs (n=375)	Difference	SSc (n=16)	Non-SARDs (n=160)	Difference	SSc (n=26)	Non-SARDs (n=215)	Difference
Work Disabled									
(Y/N) ^a	2.6 (0.94-6.9)			-	-	-	-	-	-
Any									
Absenteeism	-	-	-	2.3 (0.70-7.3)	-	-	-	-	-
(Y/N) ^b									
Costs of				\$81	\$86	-\$5			
Absenteeism^c	-	-	-	(\$7-\$226)	(\$6-\$239)	(-\$33 - \$4)	-	-	-
Any									
Presenteeism	-	-	-	1.7 (0.56-5.2)	-	-	-	-	-
(Y/N) ^a									
Costs of				\$115	\$98	\$17			
Presenteeism^c	-	-	-	(\$44-\$289)	(\$32-\$256)	(\$8 - \$35)	-	-	-
Any Paid Work									
Loss* (Y/N)^b	-	-	-	1.8 (0.56-5.7)	-	-	-	-	-

	ALL			EMPLOYED			NOT EMPLOYED		
	SSc	Non-SARDs	Difference	SSc	Non-SARDs	Difference	SSc	Non-SARDs	Difference
	(n=42)	(n=375)		(n=16)	(n=160)		(n=26)	(n=215)	
Costs of Paid				\$169	\$186	-\$17			
Work Loss^b				(\$72-\$302)	(\$65-\$355)	(-\$65 - \$10)			
Any Unpaid	3.0 (1.5-5.8)						2.4 (0.98-5.9)		
Work Loss				5.1 (1.6-15.7)	-	-		-	-
(Y/N)^b	2.7 (1.4-5.3)	-	-				2.0 (0.82-5.1)		
	\$260	\$73	\$187				\$389	\$86	\$303
Costs of Unpaid	(\$63-\$902)	(\$14-\$245)	(\$48-\$660)	\$100	\$58	\$42	(\$73-\$1,413)	(\$12-\$292)	(\$62-\$1,071)
Work Loss^c				(\$5-\$332)	(\$2-\$220)	(\$3-\$99)			
	\$169	\$69	\$100				\$239	\$80	\$159
	(\$33-\$411)	(\$10-\$190)	(\$22-\$235)				(\$37-\$648)	(\$10-\$248)	(\$27-\$432)
Any Paid or Unpaid	2.8 (1.4-5.5)	-	-	5.7 (1.2-27.1)	-	-	2.4 (0.98-5.9)	-	-

	ALL			EMPLOYED			NOT EMPLOYED		
	SSc	Non-SARDs	Difference	SSc	Non-SARDs	Difference	SSc	Non-SARDs	Difference
	(n=42)	(n=375)		(n=16)	(n=160)		(n=26)	(n=215)	
Productivity	<i>2.6 (1.3-5.2)</i>						<i>2.0 (0.82-5.1)</i>		
Loss (Y/N)^b									
	12.72	5.61	7.11				15.19	3.30	11.88
Hours of	(5.89-19.50)	(1.82-10.15)	(4.07-10.37)				(3.01-52.00)	(0.48-10.67)	(2.54-38.55)
Productivity				11.62	8.58	3.04			
				(5.77-17.65)	(3.56-15.49)	(0.47-5.48)			
Loss^c	8.76	5.57	3.19				9.31	3.11	6.20
	(3.46-14.43)	(1.55-11.03)	(1.79-4.35)				(1.35-23.98)	(0.36-8.12)	(1.01-15.94)
Costs of	\$329	\$151	\$178				\$389	\$86	\$303
Productivity	(\$142-\$520)	(\$45-\$292)	(\$97-\$260)	\$288	\$238	\$51	(\$73-\$1,413)	(\$12-\$292)	(\$62-\$1,071)
				(\$118-\$465)	(\$83-\$417)	(-\$19 - \$130)			
Loss^c	\$220	\$151	\$69				\$239	\$80	\$159
	(\$80-\$399)	(\$39-\$317)	(\$30-\$102)				(\$37-\$648)	(\$10-\$248)	(\$27-\$432)

Italicised values are estimates after the removal of the outlier

Bolded differences are statistically-significant

*Absenteeism or presenteeism

^aCalculated amongst those < 65 years of age

^bFrom the first part of the two-part model: logistic regression (expressed as odds ratio) with occurrence of productivity loss as the dependent variable

^cFrom the second part of the two-part model: generalised linear model (log-link and gamma distribution) with hours of productivity loss (or costs) as the dependent variable

Table 5.7: Summary of Factors Significantly Associated with Productivity Costs within SARDs

	Systemic Lupus Erythematosus	Systemic Sclerosis	Sjogren's Syndrome
Costs of Absenteeism			
University degree	-	0.27 (0.11-0.65) ^a	-
Overweight	-	3.77 (1.27-11.23) ^a	-
Costs of Paid Work Loss			
Pain score	0.40 (< 0.01) ^b	-	0.38 (0.03) ^b
Fatigue score	0.34 (0.01) ^b	-	0.36 (0.04) ^b
Functional disability (HAQ-DI) score	0.34 (0.01) ^b	-	0.40 (0.02) ^b
Costs of Unpaid Work Loss			
University degree	0.55 (0.33-0.93) ^a	-	-
High household income (> \$80,000)	-	0.48 (0.27-0.86) ^a	0.39 (0.23-0.65) ^a
Overweight	1.67 (1.05-2.63) ^a	-	1.96 (1.14-3.39) ^a
Past-or-present smoking	-	1.99 (1.10-3.59) ^a	-
Comorbidity score	0.20 (0.01) ^b	-	-
Pain score	0.31 (< 0.01) ^b	-	0.39 (< 0.01) ^b
Fatigue score	0.22 (< 0.01) ^b	-	0.34 (< 0.01) ^b
Functional disability (HAQ-DI) score	0.41 (< 0.01) ^b	-	0.42 (< 0.01) ^b

^aUnadjusted cost ratio and 95% confidence interval, as determined from a generalised linear model (log-link and gamma distribution); ^bPearson correlation coefficient and p-value
HAQ-DI=Health Assessment Question Disability Index

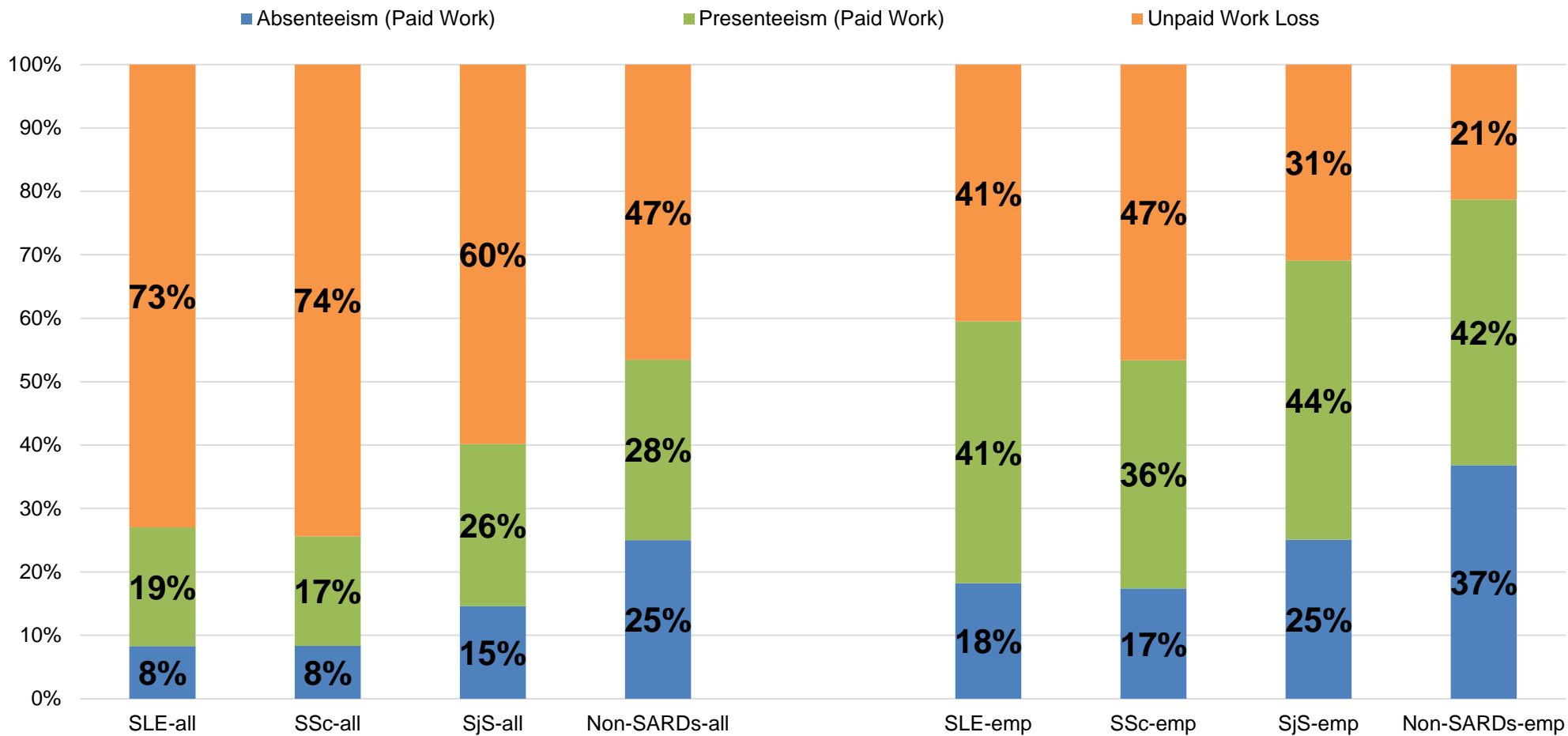


Figure 5.1: Breakdown of Lost Productivity Costs by Component, Among all Participants (left) and Employed Participants (right)

6. Discussion and Conclusion

In this final Chapter I briefly summarise the principal findings of this thesis, describe their implications and potential applications, discuss the key strengths and weaknesses, and propose some future studies that could extend this work.

6.1 Summary of thesis findings

This thesis examined several important gaps in our knowledge about the economic burden of systemic autoimmune rheumatic diseases (SARDs), especially outside of systemic lupus erythematosus (SLE). Although my three analysis chapters had somewhat different study populations and analytical approaches, the common aims were to assess the **incremental** economic burden of SARDs at the **general population level**, and assess the **impact of low socioeconomic status (SES)** on this burden.

For the studies presented in Chapters 3 and 4, I used administrative health data from the province of British Columbia (BC), Canada, to establish incident cohorts of each of nine SARDs over the period 1996 to 2010, and sex- and age-matched non-SARD comparison groups selected from the general population. In Chapter 3, I used the administrative data to determine the mean per-person direct medical costs for each cohort and comparison group over the first five years after diagnosis. These costs were highest during the first year after diagnosis (ranging from \$11,630 for Sjogren's syndrome (SjS) to \$38,197 for Granulomatosis with polyangiitis (GPA)), decreased substantially between the first and second year, and remained relatively stable for the following three years.

I subsequently used two-part generalised linear models to predict the incremental costs of SARDs (overall, and by SES group) during these first five years, while controlling for covariates and unequal follow-up times. Adjusted mean per-person-year incremental costs ranged from \$7,851 for SjS to \$54,061 for GPA, with the majority from hospitalisations. Moreover, for every SARD except polymyositis, predicted *incremental* costs for the low-SES group were significantly-greater than the high-SES. This ‘excess’ in incremental costs (difference in mean per-person-year incremental costs between the low-SES and high-SES groups) averaged about \$2,000 per-person-year for SLE, systemic sclerosis (SSc), and SjS, \$2,790 for giant cell arteritis (GCA), and \$2,917 for GPA. Though driven mainly by hospitalisation costs, outpatient costs also contributed to this excess in incremental costs.

In Chapter 4, I investigated the incremental direct medical costs of SLE patients over the five years leading up to diagnosis, and five years following. While adjusted mean per-person costs were significantly greater for SLE than non-SLE in each study year, the largest year-over-year increases were in the final two years before diagnosis date. In the last two years before SLE diagnosis, and most years after, being in the lowest-SES group was associated with significantly-greater healthcare costs. I also found that male SLE patients had significantly-greater costs than female SLE in the last two years before diagnosis, and the year following.

I rounded out this work in Chapter 5 by examining the incremental lost productivity costs of prevalent SARDs in BC. The administrative health databases in BC do not contain productivity data, but I was able to collect these data by surveying a sample of the original

population-based SARD and non-SARD cohorts. Following adjustment, the incremental costs of SLE, SSs, and SjS (the three-most common diagnoses in the survey subsample) were \$86, \$69, and \$84 per-week, respectively (over-and-above the costs for non-SARDs), equivalent to \$4,494, \$3,582, and \$4,357, respectively, per-year. Most productivity loss from paid work was from presenteeism, not absenteeism. However, about twice as many SARDs as non-SARDs were work disabled (30-36% of SARDs, 18% of non-SARDs), and it was unpaid work loss that accounted for the majority of lost productivity costs among SARDs. Results from univariable analyses suggested completion of university was associated with lower odds of work disability and lost productivity costs, while smoking and overweight were associated with greater costs.

6.2 Contribution and applications

6.2.1 Contribution

When developing policy, setting priorities for research and care, and allocating public dollars, healthcare decision makers in Canada should draw upon generalisable, population-level cost estimates. Due to transnational differences in healthcare delivery, health insurance systems, and drug access and prices, population-based estimates from Canadian settings are preferable to inform Canadian decision-making. Before I undertook this thesis, there existed only one population-based estimate of the direct medical costs of any SARD in Canada (which did not include medication costs), and there were no Canadian data on the longitudinal costs of incident SARD patients, or the incremental healthcare or productivity costs of SARDs.

To address these and other knowledge gaps, our group established one of the world's first population-based SARD cohorts. I accessed 18 years of administrative health data for this unique cohort (plus a random sample of the general population to act as a comparison group), estimated the annual outpatient, hospitalisation, and prescription medication costs for the first five years after SARD diagnosis, and determined productivity costs for a sample of the cohorts. With this work, I overcame many of the limitations of previous studies, developed and implemented a novel method of recruitment, and generated new knowledge. The survey data were collected through one of the first 'request-to-contact' endeavors for any disease group in Canada, and I have demonstrated that directly contacting individuals from administrative databases is a feasible way of recruiting general population-based samples of disease and non-disease groups of comparable size, sex, and age, while minimising privacy concerns. In doing so, I added to our knowledge of the productivity impact of SARDs, producing the first-known population-level estimates of productivity costs in SjS, the first estimates of the incremental productivity costs of SSc, and among the first estimates of the incremental costs of paid and unpaid work loss in SLE. The survey also enabled me to collect information not available in the administrative databases, including sociodemographic variables, health status and behaviours, and patient-reported outcomes, which will serve to enhance future population-level health research in SARDs and beyond.

In addition, my estimates of the incremental direct medical costs and productivity costs were determined using more rigorous statistical techniques than have often been employed in SARDs, thus minimising statistical bias (deviation from the 'true' value). Some studies have

computed the costs incurred by patients only for SARDs-related care(37,202,210,216,227), but evidence from other chronic inflammatory conditions(229,461) suggests such estimates of ‘disease-related’ costs do not capture the added costs for managing complications of the disease. Others have compared the mean per-person costs of matched SARD and non-SARD cohorts, but without further adjustment for confounding(91,203,208). I instead used two-part generalised linear models (which modelled both the probability of incurring any healthcare or productivity cost, and the expected cost itself), and G-computation techniques, to predict the policy-relevant, absolute, extra costs resulting from SARDs.

6.2.2 Applications

The cost estimates I produced will be useful in raising awareness of the burden of SARDs in Canada, and should inform ongoing research, priority-setting, and decision-making. Some high-cost, mainly biologic, therapies are being investigated or used off-label in SARDs, including rituximab(160,161) and anifrolumab(172) in SLE, rituximab(157,158) and belimumab(159) in SjS, abatacept(168) and tocilizumab(165) in Takayasu’s, and rituximab(162–164) and nintedanib in SSc(174). As well, there is growing interest in the use of autologous haematopoietic stem cell transplantation for patients with severe and rapidly-progressing SSc(175–177). Even if some of these new treatments provide incremental clinical or quality-of-life benefits, their implementation will be scrutinised (justifiably) due to their increased cost relative to current treatments. I anticipate my estimates could be incorporated into formal cost-effectiveness analyses of these interventions in SARDs, or otherwise assist those deciding whether these therapies should be made available to Canadians through public or private

insurance plans. As a timely example, Health Canada has just approved tocilizumab to be used for the treatment of GCA(462), a therapy far more expensive than glucocorticoids, the mainstay therapy, and CADTH is now deciding whether it should be listed on Canada's publicly-funded drug formularies for this purpose(155). My cost estimates could be used to populate an economic model to help determine the value for money for this agent.

I expect my analysis of productivity costs will bring attention to the incremental productivity burden SARDs impart on patients, employers, and Canadian society, including the significant contribution from 'hidden' or under recognised sources like presenteeism and impairment with unpaid work activities. CADTH(358), along with national health technology assessment agencies in Australia(463), Ireland(360), and the United Kingdom (UK)(359), make their evaluations from a health system (payer) perspective, and so do not consider productivity gains or costs in their decision-making. However, productivity outcomes are important to patients, and my findings show there is a need to develop and implement strategies to mitigate and prevent productivity loss in SARDs. They also reinforce the importance of including paid and unpaid productivity loss, and changes in productivity and employment, as outcome measures in clinical research (which has been done in trials of rheumatoid arthritis (RA)(378,464,465)), and the monitoring of patients' disease status and well-being in clinical practice.

6.3 Policy implications and ongoing research

Although I did not conduct a full economic evaluation, several aspects of my findings, including the impact of SES on the incremental costs of SARDs, and their incremental

productivity burden, should be of interest to policymakers, and warrant further investigation.

These aspects are detailed below.

6.3.1 Socioeconomic status and incremental direct medical costs

Prior to this work, very little was known about the impact of SES on direct medical costs in SARDs, especially among incident cases. In Chapter 4, I found that low SES was associated with significantly-greater *all-cause* direct medical costs (among SLE) during the fourth, second, and first years before diagnosis, and most years after. Moreover, in Chapter 3, I analysed the costs of each SARD and corresponding non-SARD cohort together and found that low SES had a striking effect on the *incremental* costs of most SARDs. This was mainly (though not entirely) from incremental hospitalisation costs. Given that low SES has been associated with poorer health⁽²⁷²⁾ and greater healthcare costs⁽²⁷³⁾ in the general population, my Chapter 4 findings (though the first of their kind) were not unexpected. My findings from Chapter 3, however, provide evidence that the greater costs incurred by low-SES SARD patients are not simply a reflection of the socioeconomic cost gradient seen in general populations. Instead, low-SES patients appear to incur greater costs for the management and treatment of SARDs and associated complications.

This is noteworthy given these studies were conducted in a publicly-funded healthcare setting where healthcare coverage is available to all legal residents, medically-necessary outpatient and hospital care are obtained without co-payments, and income-based subsidies are available for health insurance premiums and prescription medication costs. As such, these SES

disparities cannot be attributed to the individual's ability to pay for medical care directly. Instead, two alternative (though potentially overlapping) explanations for these cost disparities pertain to differences in health status and behaviours between SES groups, and access to (or receipt of) care. Regarding health status and behaviours, I proposed in Chapter 3 that smoking or obesity rates may have been greater among the low-SES SARD patients, a phenomenon that has been observed in general populations(387–389), and in SLE specifically(234). Smoking and elevated body mass index (BMI) have been associated with poorer health outcomes specific to SARDs, including higher levels of SLE disease activity(390) and hospitalisation for lupus flare(395). Severe flare(32,205,214) and greater disease activity(253) have, in turn, been associated with higher costs. Unfortunately, the BC administrative databases do not contain information on smoking or BMI, so I could not assess the prevalence of smoking or obesity across SES groups or their impact on costs, but this should be examined in future (preferably population-based) studies where such data are available. If these factors are more prevalent in lower-SES SARD patients, initiatives to modify these factors may improve SARD-specific outcomes, and be cost-saving.

On a related note, the risk of certain cardiovascular complications is elevated in SARDs(42–59), and the low-SES SARD patients may have developed more of these complications (and incurred more costs) than the high-SES. Support is provided by findings from the Hopkins Lupus Cohort in the United States (USA), where SLE patients in the lowest-income group had increased risks of cerebrovascular accident (CVA) and myocardial infarction(234), and the UK Clinical Practice Research Datalink, where GCA patients living in

the most deprived areas had an increased risk of CVA and cardiovascular disease(396). As with health behaviours, the presence of any socioeconomic differences in these risks should be examined in future population-based studies. If present, targeted efforts to prevent these complications may be a means of reducing the medical costs from SARDs.

SARD patients from lower socioeconomic groups may also experience barriers or gaps in care that ultimately contribute to the accrual of more costs. Though SARDs-specific data are not available, such gaps in care have been reported for other forms of arthritis in BC. In one population-based study, RA patients of higher SES were more likely to receive specialist care, and to receive guideline-based DMARD treatment, adjusting for regional variation and (in the DMARD analysis) physician specialty(11). In another population-based study, of osteoarthritis, low neighbourhood-level SES was associated with fewer consultations with an orthopaedic surgeon, and fewer joint replacement surgeries, even after adjustment for comorbidities(311).

6.3.2 Expediting diagnosis and treatment

As I studied cohorts of newly-diagnosed SARDs, delays in diagnosis and the initiation of treatment may have contributed to the cost disparities I observed. The low-SES SLE (defined as the lowest-SES quintile in Chapter 4, and the two-lowest quintiles in Chapter 3) and SjS patients had significantly-greater odds of being diagnosed with their SARD in hospital, controlling for age, comorbidities, urban/rural residence, and other covariates. Low SES individuals may put off seeking care for initial symptoms, or experience organisational barriers in accessing specialty or follow-up care, that land them hospital at the time of diagnosis, requiring more complex care.

Low household income has been associated with delayed presentation to rheumatology care among paediatric SLE patients in the United States(386). While access to primary and specialist care is more universal within the Canadian healthcare system, such socioeconomic disparities have been reported in pan-Canadian studies of inflammatory arthritis. Children with juvenile idiopathic arthritis whose parents were highly-educated had shorter times from symptom onset to consultation with a paediatric rheumatologist(425), while low income was associated with a longer time to diagnosis among adults with RA(466). Moreover, in a UK study of GCA, increased symptom duration (before initiation of treatment) appeared to mediate the relationship observed between low SES and the development of more ischaemic complications(467).

Since the endpoint measured in this thesis was costs, and not health outcomes, I do not know if the greater costs incurred by the low SES patients resulted from them having poorer clinical outcomes that required more expensive treatment and care. This should be examined in future studies. It is possible that clinical outcomes were similar across SES groups, but low SES patients consumed more unnecessary or ‘low-value’ healthcare resources. However, one would expect such ‘low-value’ utilisation to occur in the outpatient setting, and for medications, while low SES was associated with a substantial excess in the incremental costs for inpatient hospitalisations.

With that in mind, strategies to reduce the time to diagnosis may be a means of reducing the incremental costs of newly-diagnosed SARDs, and socioeconomic disparities in these costs. In Chapter 4, my analysis of pre-index costs, I found that SLE had significantly-greater adjusted

costs than non-SLE during each pre-index year, even in the fifth year before SLE diagnosis. Early initiation of hydroxychloroquine (HCQ) in SLE (after initial symptoms, but before accumulation of \geq four ACR criteria) has been shown to delay the accumulation of additional criteria(237), while persistent use of HCQ in newly-diagnosed patients has been associated with a longer clinically quiescent phase(434). Thus, earlier initiation of HCQ among SLE or 'pre-SLE' could be cost effective. Additional support is provided by a retrospective analysis of US commercial claims data(210) wherein 'early' diagnosis of SLE (within six months of symptom onset) was associated with fewer flares, and lower levels of post-diagnosis healthcare costs, compared to those diagnosed 6-12 months after symptom onset. However, the possible harms and added costs of HCQ or other pre-emptive treatments (including the consequences of treating false-positive cases of SLE) will require careful evaluation. Such evaluation could be conducted, in part, with the longitudinal, population-based, routinely-collected data used in this thesis.

Still, with the lack of definitive diagnostic tests for SARDs, the variable and non-specific nature of the initial symptoms, and shortage of rheumatologists in many areas of Canada(468), earlier diagnosis will not be easy to achieve. Due to the low sensitivity and specificity for detecting connective tissue diseases, Choosing Wisely committees in Canada(469) and the USA(470) advise against using ANA tests to screen for SLE or other connective tissue diseases in patients without specific signs or symptoms. UK researchers recently developed a risk-prediction model to help reduce delay in SLE diagnosis among patients presenting to primary care, and while model discrimination was good and specificity was high (90-95%), SLE is relatively uncommon, which rendered the sensitivity and positive predictive value (PPV) of the

model rather low (24-34%, and 0.07-0.09%, respectively)(419). SLICC investigators have suggested that the presence of autoimmune disease be considered in patients with premature atherosclerotic disease(429). This may be especially key for identifying SLE in males, who are more likely than females to have cardiovascular or renal disease at the time of SLE diagnosis(416,417,420,421,471,472).

Less is known about the existence of sociodemographic or socioeconomic delays in diagnosis and treatment of other SARDs, how diagnosis might be expedited, and the potential added value. Canadian Scleroderma Research Group investigators initially identified female sex as being associated with a longer time to diagnosis in diffuse cutaneous SSc(473), but this was attenuated in a subsequent analysis conducted with a larger sample size(474). A study from northern Saskatchewan (Canada) found that individuals with GPA and other forms of renal-associated vasculitis living in rural areas had a significantly longer time from symptom onset to diagnosis (mean 1.3 ± 0.94 vs. 3.5 ± 3.8 months), and higher levels of disease activity at diagnosis, than those living in the main metropolitan area(475). In a UK analysis of healthcare utilisation for GPA (and non-GPA controls) in the five years prior to diagnosis, the biggest predictor of GPA diagnosis was a high-volume of healthcare utilisation during the final 12 months (≥ 30 primary or secondary care encounters, ≥ 20 primary care consultations, or visits to ≥ 4 different specialty clinics), rather than primary care consultations for any specific clinical symptoms or features(476). Those authors suggested that efforts to expedite the diagnosis of GPA should focus on those most-frequently visited specialties (ear-nose-and-throat, ophthalmology, rheumatology, gastroenterology, and urology) rather than primary care(476).

Regarding SjS, two serologic markers (hypergammaglobulinaemia and hypocomplementaemia) were predictive of progression to SjS (fulfillment of \geq two of three ACR classification criteria) among an international cohort of individuals with suspected SjS(477). Unfortunately, while pre-emptive treatment was not the focus of that study, examination of those who did receive immune-modulators/immune-suppressants suggested those treatments did not impact progression to SjS. For GCA, it has been suggested(467) that public awareness campaigns, like those used in stroke, may help increase awareness of the symptoms of GCA, and need for prompt medical attention to prevent vision loss and other serious complications. The fact that GCA patients enrolled in a fast-track referral pathway at one UK hospital had reduced odds of vision loss (compared to a historical cohort)(478) provides additional support that increased public and health professional awareness of GCA, along with streamlined referral processes, may be helpful in reducing complications.

6.3.3 Lost productivity costs

The productivity burden of SARDs was substantial, even among my less-selected, population-based sample. This suggests that more needs to be done to improve productivity outcomes in patients with these chronic diseases. From a policy standpoint, individuals with SARDs should be supported in their efforts to remain employed (in their current position, or a more suitable one), while employers should be encouraged to hire qualified individuals with chronic diseases such as SARDs, and provide the accommodations needed for them to be (or stay) productive. Work cessation is costly for individuals (due to lost income and employment benefits) and employers, who incur costs directly (to hire and train replacement workers) and

indirectly (from reductions in productivity during this transition or ‘friction’(479) period). Since poor health can negatively impact productivity (for example, in the Lupus Outcomes Study, both increased disease activity, and the development of organ manifestations, increased the risk of work loss(291)), prevention and improved management of the acute manifestations and complications of SARDs may benefit productivity alongside. Still, my review of the literature(256) (summarised in Chapter 1) suggested that the main drivers of lost productivity are often not disease activity or other disease-specific items, but rather more generalised factors such as pain, fatigue, depression, and cognitive dysfunction. Thus, increased availability and uptake of workplace accommodations (i.e. flexibility in work hours or location(438,454), voice-recognition software to reduce keyboarding time(438), training for a different position(454)) may help individuals with SARDs manage these factors and remain employed and productive.

Some vocational interventions to prevent work loss in arthritis have been developed, including “Work-It”(480), a program for those with self-reported arthritis, rheumatologic conditions, or chronic low-back pain, and “Making it Work”(481), a program based at Arthritis Research Canada for individuals with RA, psoriatic arthritis, spondyloarthropathies, and SLE. While these programs are still being evaluated, the initial assessments show some promise: Work-It was deemed feasible to implement, and efficacious at reducing work cessation, though did not reduce limitations while performing work(482), and Making It Work participants reported decreases in the extent to which fatigue interfered with work(483). If these programs are eventually deemed to be efficacious and cost-effective, my thesis findings would provide additional support for them to be made more widely available to individuals with SARDs.

Finally, in assessing the determinants of productivity loss among SARDs, I found that completion of a university degree was associated with decreased odds of work disability in SLE, and increased productivity costs in SLE and SSc. While these were cross-sectional relationships, and I did not adjust for potential confounders, they are consistent with other reports(238,260,269). Since higher education may allow individuals to hold jobs that offer more flexibility(240) or other accommodations(454) known to foster employment for people with SARDs, this finding provides additional incentive to support newly-diagnosed patients in completing their education.

6.4 Strengths and limitations

The research discussed in this thesis must be considered in light of its strengths and limitations, with one overarching limitation being its observational nature. For one, though my direct cost analyses were adjusted for age, sex, and measures of baseline comorbidities, urban/rural residence, and healthcare utilisation, my findings are still subject to residual confounding. Thus, I cannot definitively say that low SES is a causal contributor to the incremental direct medical costs of SARDS.

As discussed in previous chapters, many of the specific strengths and limitations stem from the population-based nature of the data that were analysed. The SARD cohorts were identified from ICD codes recorded in the administrative data, and self-report diagnoses in the survey, and disease status was not clinically-confirmed. However, I used an established case definition to identify SARDs in the administrative data, and findings from Canada(333,401) and

Europe(76,334–337), including the UK General Practice Research Database(334–336), support the validity of the algorithms and diagnostic codes used. In the Canadian studies, potential cases of SARDs(333) or SLE-specifically(401) were identified from administrative physician billings and hospital discharge data covering all residents of the province of Nova Scotia. The administrative data diagnoses were compared to those recorded by rheumatologists in the charts of patients seen at The Arthritis Centre of Nova Scotia (the gold standard). In the SARDs study, by Bernatsky *et al.*(333), positive predictive value (PPV) ranged from 57% (for SLE) to 73% (for SjS), while in the SLE study, by Hanly *et al.*(401), the comparative PPV was 91%. It must be recognised that PPV is prevalence-dependent, and only patients seen at The Arthritis Centre (and thus more likely to receive a clinical diagnosis of a SARD than would a sample of the general population) were included in those two validation studies. But while the PPVs may have been overestimated, the specificity in the Bernatsky *et al.*(333) study in particular (73% for SLE, 95-96% for the other SARDs) was likely an underestimate, since, for each SARD, there were more false-positive diagnoses recorded than would be expected among the general population: they only included individuals with at least one SARD ICD code, and most of the false-positives (for a particular SARD) did receive a clinical diagnosis for another SARD or a related rheumatic disease(333). Of note, the comparative specificity for SLE was much higher (98%) in the Hanly *et al.*(401) study, whose control cohort consisted of patients seen at The Arthritis Centre, but without an administrative data diagnosis for either SLE or another connective tissue disease.

Unlike assessments of clinical outcomes, where specificity is key, mine was a population-level analysis of healthcare use and costs for which sensitivity was more important. Adding

prescription medication use to the case definition for every SARD may have increased specificity, but sensitivity would have decreased alongside. My capturing patients who obtained care in a variety of settings, with varying levels of health resource consumption, made my estimates less biased and more generalisable. Studying only patients attending tertiary clinics would likely overestimate costs, since they tend to be more complex (often with more severe disease) and thus have higher levels of healthcare utilisation. Disease severity aside, patients attending academic/tertiary clinics may also consume more healthcare resources as a result of being treated by ‘expert’ physicians with a special interest in their SARD(35).

When analysing the survey data, I was blinded to the diagnoses recorded in the administrative data, and so classified each participant’s disease status from their self-reported diagnoses. There are little data available on the accuracy of self-reported diagnoses for SARDs, especially outside SLE. Confirmation rates were low for self-reported diagnoses of SLE (10/48=21%), SSc (1/6=17%), SjS (11/29=38%), and PM/DM (1/23=4%) in the Women’s Health Cohort Study(457), but were much higher in Canadian studies of first-degree relatives of SLE patients (plus matched population controls)(458), and SARD patients recruited from tertiary clinics (plus ‘other disease’ and ‘healthy’ controls)(440). Among the first-degree relatives, confirmation rates were 88% for self-reported SLE (15/17 records reviewed), 100% for SSc (3/3), and 86% for SjS (6/7 records reviewed). A key determinant of the accuracy of these diagnoses is the expected prevalence of the condition in the study population. Since Women’s Health Cohort participants were recruited from a large sample of female health professionals, without regards to their disease status, the expected accuracy of their self-reported SARD

diagnoses would be lower than those of first-degree relatives of SLE patients, who are much more likely to have a connective tissue disease. This lends support to the accuracy of the self-reported diagnoses in my study since, instead of sampling from the community-at-large (where the prevalence of SARDs is low), I recruited from population-based cohorts that had already met a validated case definition for at least one SARD. Moreover, participants were asked to only report diagnoses of SARDs and other conditions that had been given by a health professional.

As the information in the databases were collected for administrative, and not research, purposes, detailed clinical and health behaviour data were not available, nor were any patient-reported outcome measures. This meant, for example, I could not distinguish between diffuse and limited subsets of SSc, or assess the impact of disease activity or cigarette smoking on direct medical costs. Still, the administrative data source lent this research some key strengths. The databases captured the day-to-day healthcare resource utilisation of nearly all residents of the province (population ~3.5 million adults(309)) for more than 15 years. Included were data on virtually all community-dispensed prescription medications, regardless of payer, and all provincially-funded inpatient hospitalisations and fee-for-service outpatient encounters, though not outpatient care provided on a contract or salary basis. This enhanced the generalisability of my findings within the province and country (though they may not be generalisable to SARD patients in different countries and healthcare settings), and allowed me to assess incremental costs on a longitudinal basis, right from diagnosis, with a larger sample than would be possible from many clinic-based settings. This is an improvement upon disease registries and clinic-based inception cohorts, where patients may be enrolled up to 15 months after diagnosis (as in

the SLICC cohort(380)), and those who remain severely ill or die shortly after diagnosis may not be enrolled at all. Furthermore, I was able to collect data from a random sample of the SARD and non-SARD individuals in these databases, allowing me to assess the incremental productivity impact of SARDs with minimal selection bias.

6.5 Future directions

The findings I presented in my analysis chapters generated new questions and hypotheses about the economic burden of SARDs that should be addressed in future studies. Some of these I described in **Section 6.3** when discussing the policy implications of my findings on the direct medical costs of SLE before diagnosis, and impact of SES on the additional costs from SARDs:

- Examining (preferably at the population level) the prevalence of smoking and elevated BMI across SES groups, and their impact on the incremental costs of SARDs (**page 258**)
- Examining (at the population level) the risks of costly cardiovascular complications and other poor clinical outcomes across SES groups in SARDs (**pages 258-259**)
- Assessing the impact of early hydroxychloroquine exposure (prior to, or upon, diagnosis) on downstream outcomes and costs in SLE patients overall, and by SES (**page 261**)

I now discuss three additional data linkage studies, the findings of which may help us understand and mitigate the burden of SARDs:

6.5.1 Linkage with data on emergency department visits

In another Canadian province, a population-based cohort of newly-diagnosed SLE had significantly more emergency room (ER) visits than non-SLE(90). I did not have access to data on ambulatory ER visits, but these have recently become available, which will allow us to tabulate ER utilisation for the SARD cohort, and cost-out these visits over time. Since ER visits are more expensive than office visits, and often avoidable (potentially reflecting poor access to appropriate outpatient care, or transitions between care settings(484)), reducing ER visits for SARDs could help improve care and save costs. Moreover, there likely exist socioeconomic disparities in emergency department use among SARDs, since these have been reported among the Canadian general population(485–487). As such, clinicians and policymakers would benefit from specific estimates of the incremental volume and costs of ER visits for those with SARDs, reasons for these visits, and characteristics of patients who frequent the ER.

6.5.2 Linkage of survey and administrative data

While survey participants were recruited from amongst the SARD and non-SARD cohorts identified in the administrative data, survey data were not linked with administrative data for this thesis. However, I have been granted approval for this, and my next step is to link and analyse these data together. This will allow me to assess how key sociodemographic, socioeconomic, and health behaviour variables (as collected in the survey) are associated with levels of healthcare utilisation and costs. In particular, it will provide greater insight into which socioeconomic measures (i.e. neighbourhood income level, household income level, or

educational attainment) are associated with healthcare costs, and the potential mechanisms; for example, if smoking or obesity rates are greater in the lower-SES members of these cohorts.

Two potential caveats will be the small number of survey participants (n=671) relative to subjects in the databases (thousands), and time lag between when the administrative and survey data were collected. However, many of the variables are truly time-invariant (i.e. race/ethnicity) or otherwise unlikely to change over short periods of time (i.e. educational attainment, past-or-present smoking status). With regards to sample size, survey data may eventually be imputed for the entirety of each SARD and non-SARD cohort, enhancing research into the rarer SARDs.

6.5.3 Productivity costs among incident cohorts

My survey was novel in many respects, but gaps still exist in our understanding of the productivity burden of SARDs. For one, I was unable to recruit sufficient numbers of individuals with the less-common SARDs (PM, DM, and SV), so their productivity costs remain unknown. As it was a cross-sectional survey, I was unable to assess changes in productivity over time, and any correlations between these changes and levels of pain, fatigue, or health-related quality-of-life. Moreover, while I observed that levels of pain, fatigue, and functional disability were associated with work disability and productivity costs, it is unclear when these factors became elevated in relation to work cessation or decrements in productive time.

I am currently conducting a follow-up survey (administered approximately one year after the initial survey), which will provide some information on changes in both productivity and

patient-reported outcomes over time. However, the survey participants tended to be older, with established disease (mean disease durations of 18, 13, and 12 years in SLE, SSc, and SjS, respectively), so I do not anticipate substantial changes in their productivity costs or employment status. Since mortality is elevated in SLE(488) and SSc(123), especially early-on(123), findings from these prevalent cohorts are also subject to survival bias. As work disability can strike quickly (about one-quarter of patients with early SSc in both Canada(241) and Sweden(252) were work disabled), work transitions and longitudinal patterns in productivity loss should ideally be assessed in a cohort of newly-diagnosed SARDs. Although early disease manifestations may impact productivity even before the diagnosis is confirmed, this would minimise the ‘healthy worker effect’(265) wherein those with the greatest impairments (health impairments, workplace barriers, or both) are likely to leave the paid workforce at an earlier time, and those still employed are likely to have milder or better-controlled disease.

Importantly, the longitudinal study of incident cohorts would also help identify true predictors of work disability and productivity impairment. I did not ask participants about their employment status at diagnosis or subsequent work transitions, and even if I did, I did not have access to data on time-varying factors like body mass index or levels of fatigue at the time of diagnosis. With knowledge of these true predictors, newly-diagnosed patients could be offered tailored interventions to help keep them in the workforce, if they so desire, and maintain their levels of productivity in paid and unpaid activities. For example, some non-pharmacologic interventions have been effective at reducing fatigue in SLE(456) and SjS(455).

Logistical issues prevented me from recruiting incident patients from the administrative databases for this study; for one, there is a few-years' lag between when the initial diagnosis is made (and first recorded in the database), and when researchers can access the datafiles containing that diagnosis and request an individual's contact information. Thus, in order to study cohorts of incident SARDs and ensure generalisability of the results, participants would need to be recruited from a variety of sources, including tertiary clinics, academic and community rheumatology practices, support groups, and online networks. The self-reported data collected from these individuals soon after diagnosis could eventually be linked to their administrative health data for the same period of time. For the less common SARDs, recruitment from multiple provinces may be needed to achieve sufficient sample size.

6.6 Conclusion

In this thesis, I assessed the population-level economic burden of systemic autoimmune rheumatic diseases (SARDs) in the province of British Columbia (BC), Canada. In doing so, I provided some of the first estimates of the longitudinal, incremental direct medical costs of SARDs over the first five years after diagnosis, incremental direct medical costs of systemic lupus erythematosus (the most common SARD) in the years leading up to diagnosis, and the incremental lost productivity costs of SARDs. These figures provide a benchmark for ongoing assessments of the burden of SARDs, and will guide decision making surrounding the many biologic medications and other interventions emerging for the treatment, and possibly the prevention, of these diseases. Although there exist many unmet medical needs in SARDs, most

of the new therapies will be considerably more expensive than the immune-modulators and immunosuppressants used currently, and their value for public money needs to be evaluated.

One of my key findings was that, even in a publicly-funded, universal healthcare system where medically-necessary care is accessed without co-payments, low socioeconomic status (SES) at the time of SARD diagnosis was associated with significantly-greater odds of hospitalisation during the first five years after diagnosis, and significantly-greater *incremental* healthcare costs. This generated additional questions and hypotheses on the mechanisms of this relationship, including potential gaps in SARD-related care for low-SES patients, which should be investigated as means of minimising disparities and reducing the economic burden of SARDs.

My research on the lost productivity costs of SARDs illustrated the substantial impact SARDs can have on employment and the performance of paid and unpaid work, as compared to the general population. These findings underscore the need for policies and interventions/accommodations to help patients become and remain employed (if they so desire), and productive in their paid and unpaid work activities. They also illustrate how performance of both paid and unpaid work should be included as outcome measures in research studies, and the ongoing clinical assessment of SARD patients. All-in-all, the research presented in this thesis is an important first step in improving our understanding of the economic burden of these cunning, lifelong diseases.

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3

Appendix



**Uncovering the Costs
Of Rare Diseases –
Systemic Autoimmune
Rheumatic Diseases (SARDs)**

Survey #1

Dear <Participant Name>:

This is the first of two surveys we are asking you to complete. There are questions about your background and health, and your involvement in many paid and unpaid activities. This survey may take 30 minutes to complete, and you may complete it in one or more sessions.

The questions are important to help us understand the economic impact of systemic autoimmune rheumatic diseases (SARDs). Individuals with these lifelong disorders may be unable to work or participate in other meaningful activities, at great financial cost to themselves, their family members, employers, and the larger Canadian economy.

Because SARDs are considered rare, their heavy impact on patients and society is underappreciated. By completing this survey to the best of your ability, and providing as much information as you can, you can help us increase awareness of the costs of SARDs.

Please remember, all information you provide will be kept confidential, and will be accessed only by the study team. Specifically, your workplace will not have access to this information. You do not have to provide any information you do not wish to.

If you have any questions about this study, please contact Natalie McCormick at **604-207-4045** or toll-free at **1-844-307-0400** or e-mail sardsurvey@arthritisresearch.ca. Collect calls are accepted.

Once again, thank you for participating in this study.

SECTION 1: YOUR BACKGROUND AND HEALTH

Please write in or check ☒ the appropriate answer:

Your Background and General Information

1. What is your year of birth?

Year			

2. Are you male or female?

☐ Male ☐ Female

3. People living in BC come from many different racial and cultural backgrounds. We are asking about your background because SARDs can affect people of some racial backgrounds differently than others.

To what racial or cultural groups do you belong? (Please check all that apply)

- ☐ Caucasian/White
- ☐ South Asian (e.g. Indian, Pakistani, Sri Lankan, Bangladeshi)
- ☐ East Asian (e.g. Chinese, Korean, Taiwanese, Vietnamese, Filipino, Cambodian, Malaysian, Laotian, Singaporean, Thai, Japanese)
- ☐ African, Caribbean, or Black
- ☐ Latino/Hispanic
- ☐ Arabic
- ☐ Aboriginal
- ☐ Other (please specify in the box below):

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- ☐ I prefer not to answer this question

4. What is your marital status?

- ☐ Married
- ☐ Common-law
- ☐ Widowed
- ☐ Separated
- ☐ Divorced
- ☐ Single, never married

- ☐ I prefer not to answer this question

5(a). Do you have any children?

- ☐ Yes (*please continue to 5(b)*)
- ☐ No (*please skip to Question 6*)

- ☐ I prefer not to answer this question (*please skip to Question 6*)

5(b). How many children do you have?

		Total Number of Children
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- ☐ I prefer not to answer this question (*please skip to Question 6*)

5(c). How many children currently live with you?

		Total Number of Children
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- ☐ I prefer not to answer this question (*please skip to Question 6*)

6(a). Did you graduate from high school (secondary school)?

- ☐ Yes (*please continue to 6(b)*)
- ☐ No (*please continue to 6(c)*)
- ☐ I prefer not to answer this question (*please continue to Question 7*)

6(b). What is the highest degree, certificate, or diploma you have obtained?

- ☐ No post-secondary degree, certificate, or diploma
- ☐ Trade certificate or diploma from vocational school or apprenticeship
- ☐ Non-university certificate or diploma from a community college, CEGEP, school of nursing, etc.
- ☐ University certificate below bachelor's degree
- ☐ Bachelor's degree
- ☐ University degree or certificate above bachelor's degree

Please continue to Question 7

- ☐ I prefer not to answer this question (*please skip to Question 7*)

6(c). What is the highest grade of elementary or high school you have completed?

- ☐ Grade 8 or lower
- ☐ Grade 9-10
- ☐ Grade 11-12
- ☐ I prefer not to answer this question (*please skip to Question 7*)

7. **Studies have found that income level can sometimes impact the healthcare people receive, though not always. Therefore, we would like to ask you about your approximate household income. This information is also important for statistical purposes, and will help us analyze the data.**

What is your best estimate of the total income received by all household members (from all sources, before taxes and deductions) in the past 12 months?

- ☐ \$0.00-\$19,999
- ☐ \$20,000-\$39,999
- ☐ \$40,000-\$59,999
- ☐ \$60,000-\$79,999
- ☐ \$80,000-\$99,999
- ☐ \$100,000-\$149,999
- ☐ \$150,000 and over
- ☐ I prefer not to answer this question

Your Health

8. **How tall are you without shoes on?**

	feet			inches
--	------	--	--	--------

OR

			cm
--	--	--	----

- ☐ I prefer not to answer this question

9. **How much do you weigh?**

			lbs
--	--	--	-----

OR

			kg
--	--	--	----

- ☐ I prefer not to answer this question

10. **In general, would you say your health is:**

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ I prefer not to answer this question

11(a). Do you, or have you ever, smoked cigarettes, cigars, and/or pipes?

- ☐ Yes, I currently smoke (*please continue to 11(b)*)
- ☐ Yes, I used to smoke (*please continue to 11(c)*)
- ☐ No (*please continue to Question 12*)
- ☐ I prefer not to answer this question (*please skip to Question 12*)

11(b). i. For how many years have you smoked?

		Total Number of Years
--	--	--------------------------

ii. How many cigarettes (or packages) do you smoke per day?

		Individual Cigarettes
--	--	--------------------------

OR

		Whole Packages
--	--	-------------------

please continue to Question 12

- ☐ I prefer not to answer this question (*please skip to Question 12*)

11(c). i. For how many years did you smoke?

		Total Number of Years
--	--	--------------------------

ii. How many cigarettes (or packages) did you smoke per day?

		Individual Cigarettes
--	--	--------------------------

OR

		Whole Packages
--	--	-------------------

iii. How many years ago did you quit?

		Years Ago
--	--	-----------

- ☐ I prefer not to answer this question (*please skip to Question 12*)

12. **During a typical week, how much time (i.e. the total for the entire week) do you spend on each of the following activities? If you don't spend any time on an activity, please write "0".**

	Minutes per Week
Stretching or strengthening exercise	
Walk for exercise	
Swimming or aquatic exercise	
Bicycling (including stationary, exercise bikes)	
Other aerobic exercise equipment (e.g. stair climber, elliptical, or skiing machines)	
Other aerobic exercise (<i>please specify</i>)	

☐ I prefer not to answer this question

13(a). In the past 12 months, have you had a drink of beer, wine, liquor, or any other alcoholic beverages?

By 'drink', we mean one bottle or can of beer (or glass of draft), one glass of wine or a wine cooler, or one drink or cocktail with 1 ½ oz. of hard liquor.

- ☐ Yes (please continue to 13(b))
- ☐ No (please skip to Question 14)
- ☐ I prefer not to answer this question (please skip to Question 14)

13(b). How often do you drink alcoholic beverages?

- ☐ Less than once a month
- ☐ Once a month
- ☐ 2 to 3 times a month
- ☐ Once a week
- ☐ 2 to 3 times a week
- ☐ 4 to 6 times a week
- ☐ Every day
- ☐ I prefer not to answer this question (please skip to Question 14)

13(c). On days when you do drink alcoholic beverages, how many drinks do you usually have?

	Number of Drinks
Beer (1 drink=12 oz. can or bottle)	
Wine (1 drink=6 oz. glass)	
Hard liquor, cocktails, or cordial (1 drink=1 ½ oz. liquor)	

- ☐ I prefer not to answer this question (please skip to Question 14)

- 14. We would like to ask about certain chronic health conditions which you may have. We are interested in “long-term conditions” which are expected to last, or have already lasted, 6 months or more.**

Please indicate (Yes, No, or Don't Know) whether you have been FORMALLY DIAGNOSED by a health professional with each of the following conditions:

	Yes	No	Don't Know
Asthma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Fibromyalgia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Arthritis, excluding fibromyalgia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Back problems, excluding fibromyalgia and arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High cholesterol	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Migraine headaches	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chronic bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heart disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Intestinal or stomach ulcers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Effects of a stroke	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Urinary incontinence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bowel disorder such as Crohn's disease, ulcerative colitis, Irritable Bowel Syndrome, or bowel incontinence	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Alzheimer's disease or any other dementia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Liver disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kidney or bladder disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anaemia or blood disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Osteoporosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- 15. In addition to the conditions in the previous question (#14), please indicate (Yes, No, or Don't Know) whether you have been FORMALLY DIAGNOSED by a health professional with each of the following conditions:**

	Yes	No	Don't Know
Rheumatoid arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psoriatic arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ankylosing spondylitis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Osteoarthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Systemic lupus erythematosus (SLE)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sjogren's Syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Scleroderma/Systemic sclerosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If Yes, which form do you have? *(please check one)*

- ☐ Diffuse
☐ Limited
☐ I don't know

Polymyositis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dermatomyositis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Polyarteritis nodosa	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Giant cell arteritis/temporal arteritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Granulomatosis with Polyangiitis (Wegener's)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Takayasu's arteritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Churg-Strauss syndrome	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Gout	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

16. For **EACH** condition in the previous question (#15) that you have been diagnosed with, please tell us when you were **diagnosed by a health professional** and when you **first had symptoms**:

Condition	Date of Diagnosis		Start of Symptoms	
	Year	Month (if known)	Year	Month (if known)
Rheumatoid arthritis				
Psoriatic arthritis				
Ankylosing spondylitis				
Osteoarthritis				
Systemic lupus erythematosus (SLE)				
Sjogren's Syndrome				
Scleroderma / Systemic sclerosis				
Polymyositis				
Dermatomyositis				
Polyarteritis nodosa				
Giant cell arteritis/ temporal arteritis				
Granulomatosis with Polyangiitis (Wegener's)				
Takayasu's arteritis				
Churg-Strauss syndrome				
Gout				

17. Please indicate (Yes, No, or Don't Know) whether you have seen, or talked to, each of the following types of medical doctors about your physical, emotional, or mental health in the past 6 months:

	Yes	No	Don't Know
Family doctor or general practitioner	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rheumatologist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kidney specialist (nephrologist)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Any other medical doctor or specialist (eg. surgeon, allergist, orthopaedist, or psychiatrist)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

18(a). Please indicate (Yes, No, or Don't Know) whether you have seen, or talked to, each of the following health professionals about your physical, emotional, or mental health in the past 6 months:

	Yes	No	Don't Know
Eye specialist (ophthalmologist or optometrist)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Nurse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dentist, dental hygienist, or orthodontist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chiropractor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Physiotherapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Massage therapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Social worker or counsellor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Audiologist, speech or occupational therapist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Dietician	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Podiatrist	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

18(b). Did you pay anything to see or talk to any of these health professionals?

- ☐ Yes (*please continue to 18(c), on next page*)
- ☐ No (*please skip to Question 19*)
- ☐ I don't know (*please skip to Question 19*)
- ☐ I did not see or talk to any of these health professionals (*please skip to Question 19*)
- ☐ I prefer not to answer this question (*please skip to Question 19*)

18(c). Please list the total amount you paid, after any reimbursement from the government or a health insurance plan, to see or talk to each of these health professionals over the past 6 months. If you did not see them, or did not pay anything, please write "0".

	Estimated Cost (total over past 6 months)
Eye specialist (ophthalmologist or optometrist)	\$
Nurse	\$
Dentist, dental hygienist, or orthodontist	\$
Chiropractor	\$
Physiotherapist	\$
Massage therapist	\$
Social worker or counsellor	\$
Audiologist, speech or occupational therapist	\$
Dietician	\$
Podiatrist	\$

19(a). Over the past 6 months, have you rented or bought any medical equipment or devices (e.g. eyeglasses, contact lenses, hearing aids, wheelchair, kitchen aids)?

- ☐ Yes (*please continue to 19(b)*)
- ☐ No (*please skip to Question 20*)
- ☐ I don't know (*please skip to Question 20*)
- ☐ I prefer not to answer this question (*please skip to Question 20*)

19(b). Over the past 6 months, about how much did you pay in total for these items?

Estimated Total Cost (over past 6 months): \$

20(a). Over the past 6 months, have you paid for any home-help (e.g. cooking, cleaning, caregiver, child/elder care, yard work, maintenance)?

- ☐ Yes (please continue to 20(b))
- ☐ No (please skip to Question 21)
- ☐ I don't know (please skip to Question 21)

- ☐ I prefer not to answer this question (please skip to Question 21)

20(b). Over the past 6 months, about how much did you pay in total for home-help?

Estimated Total Cost (over past 6 months):

\$	
----	--

21. In the past 4 weeks, how many different medications have you taken on an average day?

- ☐ None
- ☐ 1
- ☐ 2
- ☐ 3 or more

- ☐ I prefer not to answer this question

22. In the past 4 weeks, how often have you taken pain medication? (e.g. acetaminophen (Tylenol), ibuprofen (Advil), naproxen (Aleve), celecoxib (Celebrex), diclofenac, oxycontin)

- ☐ Never
- ☐ Less than once a week
- ☐ About once a week
- ☐ Two to three times a week
- ☐ Four to six times a week
- ☐ Once a day
- ☐ More than once a day

- ☐ I prefer not to answer this question

23(a). Over the past 6 months, have you used any prescription medications?

- ☐ Yes *(please continue to 23(b))*
- ☐ No *(please skip to Question 24)*
- ☐ I don't know *(please skip to Question 24)*

- ☐ I prefer not to answer this question *(please skip to Question 24)*

23(b). Over the past 6 months, about how much did you pay in total for your prescriptions, after any reimbursement from the government or a health insurance plan?

Estimated Total Cost (over past 6 months):

\$	
----	--

24(a). Over the past 6 months, have you used any non-prescription medications, vitamins, minerals, or supplements?

- ☐ Yes *(please continue to 24(b))*
- ☐ No *(please skip to Question 25)*
- ☐ I don't know *(please skip to Question 25)*

- ☐ I prefer not to answer this question *(please skip to Question 25)*

24(b). Over the past 6 months, about how much did you pay in total for your non-prescription medications, vitamins, minerals, or supplements?

Estimated Total Cost (over past 6 months):

\$	
----	--

25(a). Over the past 6 months, have you used any complementary methods of care (e.g. naturopathic doctor, herbal medications, homeopathic medications, acupuncture, Traditional Chinese Medicine, healing touch)?

- ☐ Yes (*please continue to 25(b)*)
☐ No (*please skip to Question 26*)
☐ I don't know (*please skip to Question 26*)
☐ I prefer not to answer this question (*please skip to Question 26*)

25(b). Please indicate (Yes, No, or Don't Know) whether you have used each of the following complementary methods of care over the past 6 months:

	Yes	No	Don't Know
Naturopathic doctor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Herbal medications	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Homeopathic medications	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Acupuncture	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Traditional Chinese Medicine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Healing touch	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypnosis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other (<i>please specify</i>):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

25(c). Over the past 6 months, about how much did you pay in total for ALL of the complementary methods of care you used (not just those listed above), after any reimbursement from the government or a health insurance plan?

Estimated Total Cost (over past 6 months):

\$	
----	--

26(a). Over the past 6 months, did you have to pay any other costs (e.g. transportation, meals, overnight accommodation, parking, or childcare) when attending medical appointments or getting medical treatments?

- ☐ Yes (please continue to 26(b))
- ☐ No (please skip to Question 27)
- ☐ I don't know (please skip to Question 27)
- ☐ I prefer not to answer this question (please skip to Question 27)

26(b). Over the past 6 months, about how much did you pay in total for these items, after any reimbursement from the government or other sources?

Estimated Total Cost (over past 6 months):

\$	
----	--

27. Please indicate (Yes, No, or Don't Know) whether you have EVER taken each of the following medications:

	Yes	No	Don't Know
Prednisone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Methotrexate (Rheumatrex)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Leflunomide (Arava)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sulfasalazine (Salazopyrin)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Azathioprine (Imuran)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hydroxychloroquine (Plaquenil)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chloroquine (Aralen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cyclophosphamide (Procytox, Cytosan)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cyclosporine (Sandimmune, Neoral)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mycophenolate mofetil (CellCept)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- ☐ I prefer not to answer this question

- 28. For each of the following medications, please indicate (Yes, No, or Don't Know) whether or not you are taking them NOW or HAVE taken them over the past 6 months:**

	Yes	No	Don't Know
Prednisone	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Methotrexate (Rheumatrex)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Leflunomide (Arava)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sulfasalazine (Salazopyrin)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Azathioprine (Imuran)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hydroxychloroquine (Plaquenil)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chloroquine (Aralen)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cyclophosphamide (Procytox, Cytoxan)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cyclosporine (Sandimmune, Neoral)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Chlorambucil (Leukeran)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Mycophenolate mofetil (CellCept)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ I prefer not to answer this question

- 29. Please indicate (Yes, No, or Don't Know) whether you have EVER taken each of the following medications (biologic drugs):**

	Yes	No	Don't Know
Rituximab (Rituxan)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Etanercept (Enbrel)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Infliximab (Remicade)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Belimumab (Benlysta)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adalimumab (Humira)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anakinra (Kineret)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Golimumab (Simponi)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tocilizumab (Actemra)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abatacept (Orencia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Certolizumab (Cimzia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ustekinumab (Stelara)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

☐ I prefer not to answer this question

30. We are interested in why you were prescribed these medications. If you have EVER taken any of the drugs listed in the previous question (#29), was it because you had:

	Yes	No	Don't Know
Arthritis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Psoriasis	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Inflammatory bowel disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lung disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Brain involvement	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cutaneous vasculitis (inflammation of blood vessels in the skin)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Other: (Please specify)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<div style="border: 1px solid black; height: 20px; width: 460px;"></div>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- ☐ I have never taken any of the medications listed in the previous question (#29)
- ☐ I prefer not to answer this question

31. For each of the following medications (biologic drugs), please indicate (Yes, No, or Don't Know) whether or not you are taking them NOW or HAVE taken them over the past 6 months:

	Yes	No	Don't Know
Rituximab (Rituxan)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Etanercept (Enbrel)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Infliximab (Remicade)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Belimumab (Benlysta)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adalimumab (Humira)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Anakinra (Kineret)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Golimumab (Simponi)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Tocilizumab (Actemra)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Abatacept (Orencia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Certolizumab (Cimzia)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Ustekinumab (Stelara)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- ☐ I prefer not to answer this question

****END OF SECTION 1****

SECTION 2: HEALTH STATUS – EQ-5D

Under each heading, please check the **ONE** box that best describes your health **TODAY**

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES (*e.g. work, study, housework, family or leisure activities*)

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

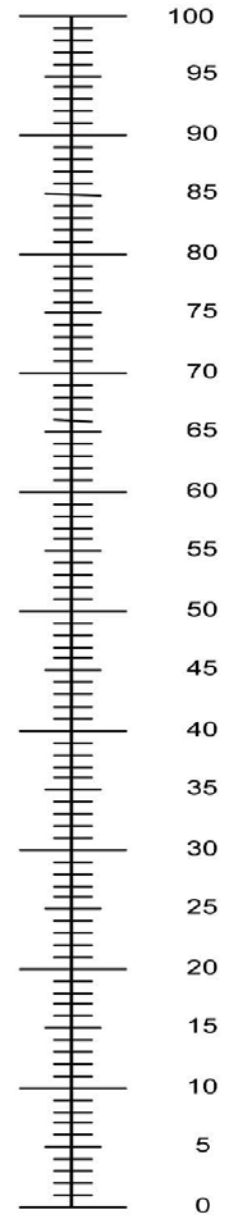
- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

We would like to know how good or bad your health is **TODAY**.

- This scale is numbered from **0** to **100**.
- **100** means the **best** health you can imagine.
- **0** means the **worst** health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY=

The best health
you can imagine



The worst health
you can imagine

****END OF SECTION 2****

SECTION 3: HEALTH STATUS: HAQ

In this section we are interested in learning about your ability to function in daily life.

1. For each category, please check the one response that best describes your usual abilities **OVER THE PAST WEEK:**

	NO DIFFICULTY	SOME DIFFICULTY	MUCH DIFFICULTY	UNABLE TO DO
Dressing and Grooming				
Dress yourself, including tying shoelaces and doing-up buttons	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Rising				
Stand up from an armless chair	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Eating				
Cut your meat	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new carton of milk	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking				
Walk outdoors on flat ground	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five stairs	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. Please check whether you **usually** (more than 50% of the time) use any of the following AIDS OR DEVICES for any of the activities listed in the previous question:

	Yes	No
Canes	<input type="checkbox"/>	<input type="checkbox"/>
Walker	<input type="checkbox"/>	<input type="checkbox"/>
Crutches	<input type="checkbox"/>	<input type="checkbox"/>
Wheelchair/scooter	<input type="checkbox"/>	<input type="checkbox"/>
Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc)	<input type="checkbox"/>	<input type="checkbox"/>
Special or built-up utensils	<input type="checkbox"/>	<input type="checkbox"/>
Special or built-up chair	<input type="checkbox"/>	<input type="checkbox"/>
Other: <i>(Please specify)</i>	<input type="checkbox"/>	<input type="checkbox"/>

3. For each of the following activities, please check whether you **usually** (more than 50% of the time) need help from another person:

	Yes	No
Dressing and grooming	<input type="checkbox"/>	<input type="checkbox"/>
Rising	<input type="checkbox"/>	<input type="checkbox"/>
Eating	<input type="checkbox"/>	<input type="checkbox"/>
Walking	<input type="checkbox"/>	<input type="checkbox"/>

4. For each category, please check the one response that best describes your usual abilities **OVER THE PAST WEEK:**

	NO DIFFICULTY	SOME DIFFICULTY	MUCH DIFFICULTY	UNABLE TO DO
Hygiene				
Wash and dry your entire body	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Take a bath	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get on and off the toilet	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Reach				
Reach and get down a 5lb object (for example, a bag of sugar from just above your head)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bend down to pick up clothing from the floor	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Grip				
Open car doors	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open jars which have been previously opened	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn taps on and off	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Activities				
Run errands and shop	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of a car	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do chores such as vacuuming, housework, or light gardening	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

5. Please check whether you **usually** (more than 50% of the time) use any of the following AIDS OR DEVICES for any of the activities listed in the previous question:

	Yes	No
Raised toilet seat	<input type="checkbox"/>	<input type="checkbox"/>
Bathtub seat	<input type="checkbox"/>	<input type="checkbox"/>
Jar opener (for jars previously opened)	<input type="checkbox"/>	<input type="checkbox"/>
Bathtub bar	<input type="checkbox"/>	<input type="checkbox"/>
Long-handled appliance for reach	<input type="checkbox"/>	<input type="checkbox"/>
Long-handled appliance in bathroom	<input type="checkbox"/>	<input type="checkbox"/>
Other: <i>(Please specify)</i>	<input type="checkbox"/>	<input type="checkbox"/>

6. For each of the following activities, please check whether you **usually** (more than 50% of the time) need help from another person:

	Yes	No
Hygiene	<input type="checkbox"/>	<input type="checkbox"/>
Reach	<input type="checkbox"/>	<input type="checkbox"/>
Gripping and opening things	<input type="checkbox"/>	<input type="checkbox"/>
Errands and chores	<input type="checkbox"/>	<input type="checkbox"/>

7. We are interested in learning whether or not you are affected by pain:

How much pain have you had **OVER THE PAST WEEK:**

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE
THE SEVERITY OF THE PAIN

NO PAIN

SEVERE PAIN

0

100

8. We are also interested in learning whether or not you are affected by fatigue:

How much of a problem has fatigue or tiredness been for you **OVER THE PAST WEEK:**

PLACE A VERTICAL (|) MARK ON THE LINE TO INDICATE
THE SEVERITY OF THE FATIGUE

NO FATIGUE

SEVERE FATIGUE

0

100

****END OF SECTION 3****

SECTION 4: PRODUCTIVITY LOSSES – WPAI

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. Please fill in the blanks or circle a number, as indicated.

We assure you, your workplace will not have access to this information.

1. Are you currently employed (working for pay)?

¹ ☐ Yes

² ☐ No If No, check “No” and skip to question 6, on next page

The next questions (Questions 2-6) are about the **past seven days**, not including today.

- 2. During the past seven days, how many hours did you miss from work because of your health problems?** Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.

		Number of Hours
--	--	----------------------------

- 3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?**

		Number of Hours
--	--	----------------------------

- 4. During the past seven days, how many hours did you actually work?**

		Number of Hours
--	--	----------------------------

(If “0”, skip to Question 6, on next page.)

5. During the past seven days, how much did your health problems affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	_____ 0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from working
--	---------------------------------	--

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	_____ 0 1 2 3 4 5 6 7 8 9 10	Health problems completely prevented me from doing my daily activities
--	---------------------------------	--

CIRCLE A NUMBER

****END OF SECTION 4****

SECTION 5: PRODUCTIVITY LOSSES – VOLP

Please remember, your workplace will not have access to this information.

1. Which of the following best describes your current employment status? (*check one only*)

- 1 ☐ Working full time as an employee (*please skip to Question 6, on page 32*)
- 2 ☐ Working part time as an employee (*please skip to Question 6, on page 32*)
- 3 ☐ Self-employed (*please skip to Question 6, on page 32*)
- 4 ☐ On official work disability (*please continue to Question 2*)
- 5 ☐ Unemployed but looking for work (*please continue to Question 2*)
- 6 ☐ Unemployed but not looking for work (*please continue to Question 2*)
- 7 ☐ Retired (*please continue to Question 2*)
- 8 ☐ Housewife / househusband (*please continue to Question 2*)
- 9 ☐ Other (*please specify in the box below, then continue to Question 2*)

2. Is your current unemployment status mainly due to YOUR HEALTH? (*please think of any physical, mental, or emotional problems or symptoms*)

- 1 ☐ Yes
- 2 ☐ No

3. Do you feel well enough to work if a job is available?

- 1 ☐ Yes, I am able to work full time
- 2 ☐ Yes, but I am only able to work part time
- 3 ☐ No, I am unable to work at all

4. During the past 7 days, how many hours have you spent on:

	Number of hours in the past 7 days
Housework (e.g. preparing meals, cleaning the house, washing clothes)	
Shopping (e.g. shopping for the daily groceries, other types of shopping, going to the bank or post office)	
Odd jobs and chores (e.g. house repairs, gardening, fixing the car)	
Doing things for or with your own children (e.g. caring for them, taking them to school, helping with homework)	
Voluntary activities	
Total time spent on these unpaid work activities	

5(a). During the past 7 days, have you had help with any of your household tasks (cleaning the house, shopping, taking care of the children) due to YOUR HEALTH?
(please think of any physical, mental, or emotional problems or symptoms)

- 1 ☐ Yes (please continue to 5(b))
- 2 ☐ No (please skip to Section 6, on page 37)

5(b). Please list the number of hours of help you received during the past 7 days, from each of the following sources. If you did not receive any help from a source, please write "0".

	Number of hours in the past 7 days
Family members (e.g. partner, children)	
Others (e.g. neighbours or volunteers)	
Paid help	

****END OF SECTION 5** - please skip to Section 6, on page 37**

6. Please state your job title (If you have more than one job, please report only on your main job — the job at which you spend the majority of work hours). For example, primary school teacher, chartered accountant, cashier:

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7. What kind of business, industry or service is your working organisation? Please give details. For example: construction, primary school, hospital, police, farm, shoe shop, food wholesale, factory:

--

8. On average, how many days do you work per week at this job?

	Number of Days per Week
--	----------------------------

9. On average, how many hours do you work per week at this job?

		Number of Hours per Week
--	--	-----------------------------

10. In the past 3 months, how many work days in total have you been absent from work because of YOUR HEALTH (any physical, mental, or emotional problems or symptoms)? Please include **work days** you missed due to your health, and/or **partial work days** where you went in late or left early due to your health (e.g. doctor appointments); DO NOT include any work days you missed to participate in this study

		Number of Days
--	--	-------------------

11. In the past 7 days, have you gone to work?

- 1 ☐ Yes (please continue to Question 12)
2 ☐ No (please skip to Question 15, on next page)

12. Think of all the work you have completed **during the past 7 days**. Would you complete the same work in **less time** if you did NOT experience any health problems? (*i.e. any physical, mental, or emotional problems or symptoms*)

- 1 ☐ Yes (*please continue to Question 13*)
 2 ☐ No (*please skip to Question 15*)

13. If yes, please indicate the time you took to complete all your work in the **past 7 days** and the time you would take to complete the same work if you did NOT experience any health problems:

	Number of hours in the past 7 days
(a) Time taken to complete all of my work during the past 7 days	
(b) Time I would take to complete the same work if I did NOT experience any health problems (<i>should be less than (a)</i>)	

14. In the **past 7 days**, to what extent was your performance at work affected by YOUR HEALTH while you were working? (*please think of any physical, mental, or emotional problems or symptoms*)

My health had no effect on my work 0 1 2 3 4 5 6 7 8 9 10 I could not do any work at all due to my health

CIRCLE A NUMBER

15. During the **past 7 days**, how many hours have you spent on:

	Number of hours in the past 7 days
Housework (<i>e.g. preparing meals, cleaning the house, washing clothes</i>)	
Shopping (<i>e.g. shopping for the daily groceries, other types of shopping, going to the bank or post office</i>)	
Odd jobs and chores (<i>e.g. house repairs, gardening, fixing the car</i>)	
Doing things for or with your own children (<i>e.g. caring for them, taking them to school, helping with homework</i>)	
Voluntary activities	
Total time spent on these unpaid work activities	

16(a). During the past 7 days, have you had help with any of your household tasks (cleaning the house, shopping, taking care of the children) due to YOUR HEALTH? *(please think of any physical, mental, or emotional problems or symptoms)*

- 1 ☐ Yes *(please continue to 16(b))*
 2 ☐ No *(please skip to Question 17)*

16(b). Please list the number of hours of help you received during the past 7 days, from each of the following sources. If you did not receive any help from a source, please write "0".

	Number of hours in the past 7 days
Family members (e.g. partner, children)	
Others (e.g. neighbours or volunteers)	
Paid help	

17. During your most recent period of absence due to YOUR HEALTH (any physical, mental, or emotional problems or symptom), was your work *(check one only)*:

- 1 ☐ Taken over by others
 2 ☐ Partly taken over by others and partly postponed until I returned
 3 ☐ Postponed until I returned
 0 ☐ Do not know

18. Who mainly took over your work during your most recent period of absence due to YOUR HEALTH? *(check one only)*

- 1 ☐ Co-workers
 2 ☐ Supervisors
 3 ☐ Temporary worker(s)/additional staff hired from outside agencies to do my work
 4 ☐ No one
 0 ☐ Do not know

19. Imagine if you are at work but YOUR HEALTH affects your ability to complete your work, will your work be *(please think of any physical, mental, or emotional problems or symptoms) (check one only):*

- 1 ☐ Taken over by others
- 2 ☐ Partly taken over by others and partly postponed until later (i.e., I will do it later)
- 3 ☐ Postponed until later (i.e., I will do it later)
- 0 ☐ Do not know

20. If you are at work but YOUR HEALTH affects your ability to complete your work, who mainly takes over the work you cannot complete? *(check one only)*

- 1 ☐ Co-workers
- 2 ☐ Supervisors
- 3 ☐ Temporary worker(s)/additional staff hired from outside agencies to do my work
- 4 ☐ No-one
- 0 ☐ Do not know

21. How often do you need to work with your co-workers as a team? *(by team, we mean 'a group of people who work/act together for a common purpose (e.g. projects and tasks)') (check one only)*

- 1 ☐ None of the time *(please skip to Question 24, on next page)*
- 2 ☐ A little of the time *(please continue to Question 22)*
- 3 ☐ Some of the time *(please continue to Question 22)*
- 4 ☐ Most of the time *(please continue to Question 22)*
- 5 ☐ All the time *(please continue to Question 22)*

22. For the time you are working with a team, how many co-workers do you usually work with as a team? *(if you are working with more than one team, please focus on the team you spend the most time with. Please DO NOT include yourself)*

Please write down a specific number such as '4' or a range such as '8–12'

	Number of Co-Workers
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23. For the time you are working with a team, how important are you to the function of your team? (if you are working with more than one team, please focus on the team you spend the most time with) (check one only)

- ☐ 1 My team can **function as usual** when I am absent, or when I am present but less productive (e.g. *this might be appropriate for a person who works in a team picking crops in a field. Each person in the team picks crops all by himself or herself*)
- ☐ 2 My team's function can **be affected a little bit** when I am absent, or when I am present but less productive
- ☐ 3 My team's function can **be somewhat affected** when I am absent, or when I am present but less productive
- ☐ 4 My team's function can **be affected quite a lot** when I am absent, or when I am present but less productive
- ☐ 5 My team **cannot function** when I am absent, or when I am present for work but less productive (e.g. *this might be appropriate for the conductor of an orchestra where the orchestra can't play without the conductor and the conductor is useless without the orchestra*)

24. Can any of your co-workers do your work? (check one only)

- ☐ 1 There are co-workers who can complete my work in **the same amount of time** as me
- ☐ 2 My co-workers can complete my work in **a little bit more time** than me
- ☐ 3 My co-workers can complete my work in **somewhat more time** than me
- ☐ 4 My co-workers can complete my work in **a lot more time** than me
- ☐ 5 None of my co-workers can do my work

25. Does your working organisation hire temporary (i.e., temp) workers from external agencies who do the same or similar work as you do?

- ☐ 1 Yes (please continue to Question 26)
- ☐ 2 No (please skip to Section 6, on next page)

26. Can any of the temp workers hired from external agencies do your work? (check one only)

- ☐ 1 Temp workers can complete my work in **the same amount of time** as me
- ☐ 2 Temp workers can complete my work in **a little bit more time** than me
- ☐ 3 Temp workers can complete my work in **somewhat more time** than me
- ☐ 4 Temp workers can complete my work in **a lot more time** than me
- ☐ 5 It is impossible to find any temp workers who can do my work

****END OF SECTION 5****

SECTION 6: FINAL QUESTIONS

1. Would you be interested in receiving information about the results of this study?

- ☐ Yes
☐ No

2. Would you be interested in receiving information about participating in other health-related research conducted by researchers at the University of British Columbia?

- ☐ Yes
☐ No

3. If you answered YES to questions 1 or 2 above, please provide your e-mail address below in order for us to contact you about this study or future health-related research studies that you may be interested in:

E-mail address:

**Thank you for completing this survey!
We look forward to your continued participation.**

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