Exploring Chronic Respiratory Disease Care using Statistical Modelling and Routine Data

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A thesis submitted for the degree of

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Abstract

Chronic respiratory disease represents a significant burden to healthcare services and wider society. Patients benefit from early diagnosis and effective disease management, yet few patients in England are receiving the recommended levels of care. NHS services are increasingly under pressure from an ageing population, as well as disruption following the COVID-19 pandemic, raising important questions about how services can evolve to improve efficiency and standard of care. This thesis explores chronic respiratory disease care using two contrasting approaches. First, Chapters 2 and 3 utilise routinely collected health data from the Morecambe Bay area and provide insight into the impact of a local integrated care initiative. Spatio-temporal methodology is used to model referrals to outpatient respiratory clinics and a thorough data review is conducted to consider the challenge of measuring diagnostic quality. These studies exemplify different approaches to overcoming barriers encountered when using routine data for research purposes. Second, Chapters 4 and 5 apply a discrete-event microsimulation model for chronic obstructive pulmonary disease in the Canadian population to questions in the field of health economics and outcomes research. Simulated data is used to analyse the impact of interventions, both for identifying patients at an earlier stage in the disease progression and earlier initiation of more intensive pharmacotherapy to improve patient quality-of-life. The discussion points of these studies link to key NHS goals for respiratory disease. This thesis demonstrates the role of both routine and simulated data in healthcare research by providing insight into service utilisation, diagnostics, earlier detection of disease, and therapeutic management. However, neither approach is without limitations. Future research could focus on further developing methods for synthetic data, a means of using simulation to enhance the rich routine data landscape in England in order for research to be carried out in a safe and effective way.

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List of abbreviations

CDW	Community Data Warehouse
COPD	Chronic Obstructive Pulmonary Disease
CRD	Chronic Respiratory Disease
EHR	Electronic Health Record
EPIC	Evaluation Platform in COPD
GLM	Generalised Linear Model
GLMM	Generalised Linear Mixed Model
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner / General Practice
HES	Hospital Episode Statistics
ILD	Interstitial Lung Disease
IMD	Index of Multiple Deprivation
LSOA	Lower Layer Super Output Area
MBCCG	Morecambe Bay Clinical Commissioning Group
MBRN	Morecambe Bay Respiratory Network
MCMC	Markov Chain Monte Carlo
MDT	Multidisciplinary Team
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
POHEM	Population Health Model
QALY	Quality-Adjusted Life-Year
QOF	Quality and Outcomes Framework
RCT	Randomised Controlled Clinical Trial
SDE	Secure Data Environment
UHMBT	University Hospitals of Morecambe Bay NHS Foundation Trust

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How do I acknowledge all of the people,
Who have contributed to an experience to any other unequal?
I have spent time reflecting, considering, and accounting,
So for one last time, let me share the View from the Mountain.

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Here I acknowledge that your LaTeX skills are superior to mine.
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Alas, my nine years at Lancaster University draws to a close,
I take my bow, and on to next chapters of motherhood I go.
- "But wait, your husband, mum, sister, don't they get a mention?!"
Let's be real, they'll never read this, but "thank you" for the sake of convention -
I have loved being a PhD student, no-doubt.
Thank you all. Over and out.

Declaration

I declare that the work presented in this thesis is the result of my own work. Collaborators are specifically indicated for each chapter. The material has not been submitted, either in whole or in part, for a degree at this, or any other university.

This thesis does not exceed the maximum permitted word length of 80,000 words including appendices and footnotes, but excluding the bibliography. An approximate estimate of the word count is: 40,956.

The research in this thesis using data from the Morecambe Bay Community Data Warehouse (Chapters 2 and 3) received ethical approval through the Health Research Authority and Health and Care Research Wales (IRAS project ID: 289188). The primary data of these studies are anonymised routinely collected NHS data so the ethical committees of Health Research Authority and Health and Care Research Wales waived the need for informed consent from subjects to participate. All methods were carried out in accordance with relevant guidelines and regulations.

This thesis comprises of four research papers. The publication status and specific contributions to each paper are as follows:

Chapter 2
Spatio-temporal modelling of referrals to outpatient respiratory clinics in the integrated care system of the Morecambe Bay area, England
Rachael Mountain, Jo Knight, Kelly Heys, Emanuele Giorgi, and Timothy Gatheral
Published in BMC Health Services Research (2024)
10.1186/s12913-024-10716-7
Contribution: Jointly developed study design and statistical methodology, built research data set, conducted the analysis, lead author of manuscript.

Chapter 3
Measuring diagnostic quality using routinely collected data
Rachael Mountain, Timothy Gatheral, Patrick Haslam, Kelly Heys, and Jo Knight
In preparation for submission
Contribution: Jointly decided analysis variables, built research data set, conducted data analysis, lead author of manuscript.

Chapter 4

Budget impact analysis of adopting primary care–based case detection of chronic obstructive pulmonary disease in the Canadian general population
Rachael Mountain, Dexter Kim, and Kate M. Johnson
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Contribution: Jointly developed study design and analysis plan, searched literature for parameter values, conducted the analysis, lead author of manuscript.

Chapter 5

Benefit-harm analysis of earlier initiation of triple therapy for prevention of acute exacerbation in patients with COPD
Rachael Mountain, Kevin I. Duan, and Kate M. Johnson
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Chapter 1

Introduction

1.1 Chronic respiratory disease

Chronic respiratory disease (CRD) is an umbrella term referring to diseases that affect the airways and other structures of the lungs. The four main CRDs in the UK are asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and interstitial lung disease (ILD). It is estimated that 15% of the population in England have a history of CRD and it is the fourth most common cause of death [1]. Whilst cause of disease varies by specific condition, common risk factors include tobacco smoke, air pollution, poor housing, and occupational hazards, contributing to CRD disproportionately affecting disadvantaged socio-economic groups [2, 3]. Preventable mortality from respiratory disease in the under 75 age demographic is almost three times higher in the most deprived areas of England compared to the least deprived [4].

CRD represents a substantial burden to society and healthcare services, particularly when poorly managed. Associated breathing difficulties and other symptoms can majorly impact on quality-of-life, with CRD accounting for 4.5% of all disability-adjusted life-years lost [5]. Between 2012 and 2019, non-elective hospital admissions for respiratory disease increased at three times the rate of all admissions generally, and are a key factor in the winter pressures faced by the National Health Service (NHS) in England [4, 6]. The direct cost of respiratory disease to the NHS is estimated at £9 billion each year, with £4.7 billion from asthma and COPD alone [7].

Two of the four chapters of this thesis focus on COPD due to its individual and prominent burden. COPD refers to a group of lung conditions characterised by persistent and progressive airflow obstruction. COPD is the third leading cause of death worldwide and has a prevalence of 1.9% in England [8, 9]. Clinical intervention is critical to reduce the burden of symptoms and to slow the progression of lung function decline through optimal preventative and therapeutic management, including smoking cessation, inhalers, influenza vaccinations, and pulmonary rehabilitation [10, 11]. Despite the opportunity to improve patient outcomes, COPD is notoriously underdiagnosed and poorly managed. It is estimated that two-thirds of people with COPD in England are currently undiagnosed, with this figure rising as high as 90% globally [12, 13]. Furthermore, COPD is a leading cause of potentially preventable emergency admissions [14]. COPD is an ambulatory sensitive condition meaning hospital admissions can be avoided through effective outpatient and community-based management. Yet a survey from 2022 found that only 18% of COPD patients in England are receiving the National Institute for Health and Care Excellence (NICE) recommended levels of care [11].

It is clear that care standards for CRD are lacking, an issue further exacerbated by the COVID-19 pandemic. During the pandemic, the diagnosis and management of chronic disease was critically disrupted due to reduced access to care, and studies have found that chronic lung conditions were among the worst affected [15, 16, 17]. Patients with chronic conditions are typically highly dependent on primary care for ongoing care and access to specialist services. Yet in the first three months of the pandemic, general practitioners (GPs) were advised to postpone routine referrals to free up the capacity of acute services for pandemic response, resulting in a 74% drop in routine referrals compared to the same period in 2019. Health testing in primary care, including key diagnostic tests, decreased by 80%, along with reductions in prescriptions, immunisations, and incidence rates [15, 16].

Nationally, there is considerable focus on improving standard of care for CRD patients, both to improve population health and to reduce the burden on NHS services. The NHS Long Term Plan recognises the need for improved diagnosis of respiratory disease in primary care [18], not only for timely treatment of individual patients, but also to reduce non-elective admissions and lengthy hospital stays. An estimated 80,000 admissions could be avoided by earlier intervention for respiratory disease [18]. The misdiagnosis between asthma and COPD is a

common problem due to the similarity in symptoms and the lack of consistent access in primary care to robust spirometry testing. The NHS Long Term Plan also prioritises improved upstream prevention for respiratory disease including smoking cessation and reducing air pollution, as well as supporting CRD patients to effectively self-manage their conditions through correct medication usage and increased access to pulmonary rehabilitation programmes [18]. Promoting integrated care, an organising principle for improving the coordination of care between different healthcare providers, is a key goal in NHS agenda to improve population respiratory health, a theme returned to and expanded upon in Chapters 2 and 3.

1.2 Healthcare under pressure

The NHS at "breaking point" is a phrase repeatedly seen in news headlines and media reports. The COVID-19 pandemic caused unprecedented disruption to all healthcare services and added pressure to a system already under strain [19]. Acute services are struggling to meet demand with outpatient waiting lists holding 7 million patients (representing 10.6% of the total population) compared to 4.4 million prior to the pandemic, emergency department waiting times exceeding 12 hours, and only 2.4 hospital beds per 1,000 population (compared to an average of 5 across Europe) [19, 20, 21]. In primary care, the number of GPs per 1,000 population fell from 0.52 in 2015 to 0.44 in 2023 whilst the average number of patients per GP increased by 17%. Further, newly qualified GPs are increasingly opting for part-time work due to unmanageable workloads [22]. A key factor behind struggling services is tight healthcare budgets, with knock-on effects to staff strikes and shortages [19]. Although spending increased in 2020/21 to aid pandemic response, UK health spending has slowed in the last decade compared to the long-term average with a cumulative under-spend of £322 billion since 2009/10 [23].

The contribution of chronic disease to the healthcare crisis is substantial. In the 1950s, a pivotal transition began in developed countries in the leading type of health problems experienced, away from acute diseases and toward chronic diseases [24]. Today, approximately 70% of health and social care expenditure in England is attributed to treatment and care for long-term conditions [25]. This focus is only set to continue with population growth and increases in life expectancy. It is estimated that by 2040, 9.1 million individuals in England will be living with a long-term condition, 2.5 million more than in 2019. Of the projected increase, 80%

is estimated to be from the over 70 age demographic [26]. Nations around the world face a similar crisis. For example in the US, 50% of the population are suspected to have a long-term condition with 86% of healthcare costs attributable to chronic disease [24].

The organisation and delivery of healthcare services is continually under review with considerable investment from the NHS into transformational change and new models of care [27, 28]. The COVID-19 pandemic prompted the publication of further NHS reports that discussed the unique opportunity to radically redesign services [29]. With a growing and ageing population, with increasingly complex healthcare needs, there is a need more than ever for optimal service design and effective care management, both to ensure the best possible outcomes for patients, as well as to reduce the pressure on services by minimising avoidable healthcare interactions [30]. Health and healthcare research plays a vital role by creating an evidence base to inform appropriate changes in policy and practice, providing key context to this thesis.

Each chapter addresses a different aspect of service delivery or patient care, and considers how the efficiency and effectiveness of CRD care can be maximised to relieve pressure on healthcare services. Key themes encountered in this thesis include: efficient care pathways (Chapters 2 and 3); diagnostic accuracy and timeliness (Chapters 3 and 4); improving patient outcomes to reduce the economic, social, and clinical burden of unplanned care (Chapters 4 and 5); and primary care-based initiatives (Chapters 2, 3, and 4).

1.3 Data and methods

This thesis uses two contrasting data methods for investigating optimal CRD care: routinely collected health data and simulated data. This subsection outlines the definition, strengths, and limitations of each approach.

1.3.1 Routinely collected health data

Routinely collected health data can be defined as health data collected primarily for purposes other than research. It is the information generated as a by-product of patients' interactions with healthcare services and organisations [31]. Routine

health data can be administrative or clinical in nature, examples include electronic health records, birth and death registries, and prescribing data. In the UK, this data is mainly produced by the NHS.

Routinely collected health data holds huge potential for health service and clinical research. Each patient interaction presents an opportunity to improve services and standard of care through data-driven analytics [32]. The use of routine health data in research has increased over time. In particular, the COVID-19 pandemic prompted governments around the world to utilise routine health information systems for disease surveillance and monitoring of health programmes, spotlighting the value of routine data [33]. The UK government recently commissioned a review "Better, Broader, Safer: Using Health Data for Research and Analysis" by Professor Ben Goldacre and Jessica Morley that sets out a practical vision for how the efficient and safe usage of health data can drive innovation in healthcare services [34].

1.3.1.1 Benefits

The potential of routine data for health research stems predominately from the vast amount of information it can contain, with a wide breadth of study variables and detailed medical histories. Combining information from different branches of healthcare through patient-level data linkage, for example using pseudonymised NHS Numbers, can allow a far more realistic and holistic view of patient care pathways. Linkage to other socio-economic, environmental, or geospatial datasets can further improve completeness and broaden the possibilities for research questions [35, 36].

Routine data can contribute toward reducing bias in an analysis. The large sample sizes typically found in routine data can offer large statistical power, are often representative of the population, and include patient groups that may be missed in randomised controlled clinical trial (RCT) recruitment [35, 31]. Routine data has additional practical benefits in terms of increasing the efficiency of the research process. Since the information is generated as a by-product of routine health interactions, it is a cost-effective method of data collection. Furthermore, valuable time spent recruiting and observing participants, as is required for RCTs and longitudinal cohort studies, is avoided.

1.3.1.2 Limitations

However, by definition, routine data has been collected for purposes other than research, and thus its nature can limit its application in research. The most common issues cited in the literature are associated with data quality, specifically misclassified or missing data, which creates a potential source of error and bias [35]. Clinicians play a vital role in determining the quality of routine data which can result in significant variation in the detail of information collected. The literature recognises the tension between the need to train and educate clinicians in the importance of high quality data recording, whilst not adding to already unmanageable workloads [37, 38, 39].

Beyond data quality issues, data access barriers are a significant limitation to routine data research. Access to routine data is necessarily limited to researchers for patient privacy and data confidentiality reasons. Furthermore, the routine data landscape in England is fragmented, with data often stored at NHS Trust or regional level. Larger, national routine databases exist such as the Clinical Practice Research Datalink, Optimum Patient Care Research Database, and Hospital Episode Statistics (HES), however accessing such databases can come at considerate expense both financially and in time taken to complete the application process. Fragmentation also occurs between organisations, preventing important linkage of data across healthcare tiers at a patient level [32, 36]. In line with the recommendations outlined in the Goldacre Review, the NHS has committed to funding Secure Data Environments (SDEs) with the aim of enhancing the usage of linked routine data for research whilst ensuring the highest levels of patient privacy and data ethics [34, 40]. SDEs are data storage platforms that allow researchers to access and analyse health data without themselves receiving a copy of the dataset. The NHS is piloting a national SDE, that has been used by the British Heart Foundation and Health Data Research UK for understanding the impacts of COVID-19, along with multiple sub-national SDEs [41].

The limitations of routine data under the themes of data recording practices and data access barriers are explored further in Chapter 3.

1.3.1.3 Use of routinely collected health data in this thesis

The Morecambe Bay Community Data Warehouse (CDW) is an SQL server owned and maintained by University Hospitals of Morecambe Bay NHS Foundation Trust (UHMBT). The CDW contains data from primary, secondary, and community care across the Morecambe Bay and uses pseudonymised NHS Numbers to allow patient-level linkage between data sets. Examples of data sets contained within the CDW include, hospital admissions, GP observations, prescriptions, and community care home visits. The CDW was set up with the aim of bringing together data from different tiers of care to support services and patients across the Morecambe Bay by generating analytics and business intelligence. Kelly Heys is the Head of Information at UHMBT and co-supervised this thesis.

Part of this thesis aims to utilise the CDW to investigate patterns in respiratory disease care in the Morecambe Bay area and provide insight into the impact of the Morecambe Bay Respiratory Network (MBRN) integrated care initiative. The CDW SQL servers were accessed via a secured NHS laptop and all data tables within the CDW were available for analysis. Further information regarding CDW data methods are described in Chapters 2 and 3.

1.3.2 Simulated data

Simulated data is artificial data that has been designed to resemble the properties and characteristics of real-world data. Simulated data encompasses a broad range of data-generating methods with varying levels of complexity, including Markov models, decision trees, and discrete event simulations [42]. Simulation models have a longstanding use in infectious disease research with the classical "S-E-I-R" (susceptible, exposed, infected, and removed) modelling approach for the transmission of infectious diseases [43], yet simulation models are also widely used in chronic disease management. For example, the Population Health Model (POHEM) was developed by Statistics Canada to simulate the life cycle of the Canadian population, primarily focusing on aspects of health. POHEM has been applied and extended for research into cardiovascular disease, cancer, osteoarthritis, and chronic neurological conditions [44]. Additionally, the United Kingdom Prospective Diabetes Study Outcomes Model (UKPDS-OM) predicts the risk and health outcomes for patients with type 2 diabetes with applications to health service

planning and economic analyses [45].

1.3.2.1 Benefits

Data is vital for health research and evidence-based policy. However, researchers can encounter data access barriers, particularly those associated with information governance, as discussed in the limitations section for using routine health data for research. Simulated data is being increasingly used in health research to boost the utility of confidential datasets whilst protecting patient privacy [46]. For example, synthetic data, a type of simulated data, aims to create an artificial copy of an existing dataset. The US Census Bureau defines synthetic data as "microdata records created by statistically modelling original data and then using those models to generate new data values that reproduce the original data's statistical properties" [47]. Since synthetic data does not exactly reproduce patient-level information, it does not require such strict access procedures. The NHS is currently piloting a new service for synthetic A&E data based on HES data [48, 49].

In addition to the benefits associated with overcoming data access and privacy issues, simulated data offers a variety of advantages. Simulation models can allow the evaluation of a wide range of scenarios. Analyses can be conducted for scenarios where real-world data does not exist or is insufficient, such as for new interventions or rare outcomes, as well as scenarios that would be practically infeasible in empirical studies, such as long-term study periods [50, 51]. A further benefit of simulation models is the ability to carry out sensitivity analysis. By systematically adjusting model assumptions, the degree to which an intervention depends on a given parameter can be assessed. This feature can be crucial for medical decision making and policy recommendations [50]. The practical benefits noted for routinely collected data, namely reduced time and economic costs compared to RCTs and cohort studies, similarly apply to simulated data.

1.3.2.2 Limitations

Simulated data, however, has several limitations. First, simulated data is, by nature, a simplified reproduction of a real-world scenario. The simulation will not reflect the true complexity of a process, which may result in an inaccurate representation of the effects in reality of an intervention or projection [42, 50]. Second, simulations can

be very computationally intensive, with run times taking up to weeks if the model uses large input data sets and complex statistical methods, or if a large number of scenarios are being considered. In such situations, the analysis may require high performance computers capable of parallel computing [50]. Finally, it is important to acknowledge that a simulation model is only as good as the data sources and statistical methods behind it. This limitation highlights the necessity of data quality checks prior to modelling, as well as vigorous internal and external model validation to evaluate the robustness of the outputs against real-world data.

1.3.2.3 Use of simulated data in this thesis

The Evaluation Platform in COPD (EPIC) is a deterministic discrete event microsimulation model for the development and progression of COPD in the Canadian general population aged ≥40 years [52, 53]. EPIC was created to be a population-based model for epidemiological projections and evaluation of a wide range of COPD policies in the Canadian context. EPIC is a whole disease model which refers to a modelling approach that incorporates events across the entire disease pathway, from incidence until death, within a single framework and with consistent assumptions [54]. Whole disease models are an innovative method in the field of medical decision making; they have a more flexible platform for exploring the decision space and are able to account for downstream consequences of intervention. In contrast, a de novo model that simulates a single scenario in a particular population is more likely to make simplifying assumptions that may impact on the robustness of the results [54, 55, 56].

EPIC is owned and maintained by the Respiratory Evaluation Sciences Program research group at University of British Columbia, Vancouver. Its use in this thesis was born out of a UKRI-Mitacs Globalink research placement within the group between September and December 2022. Part of this thesis aims to apply EPIC to two research questions focused around COPD diagnosis and management. Further details regarding EPIC methodology and features added to the model for the purpose of this research are provided in Chapters 4 and 5.

Although EPIC simulates within the context of the Canadian population and healthcare system, the results of these studies still hold relevance to healthcare in England and the NHS. The Canadian and British populations are comparable in terms of average age and life expectancy [57]. Canada and Britain both have

single-payer healthcare systems financed by the government, although in Canada the private sector delivers a large proportion of the care. Both countries spend approximately 12% of their gross domestic product on health, and face similar capacity challenges with comparable number of beds and GPs per population [23, 58, 59]. Further, the key discussion points to stem from these studies regarding suggestions for policy and best practice guidelines are not limited to the Canadian healthcare system.

1.4 Thesis structure and aims

The overarching aim of this thesis is to use statistical modelling and data exploration to investigate chronic respiratory care and health service delivery. This thesis takes two different approaches and geographical settings. The first two studies use routinely collected health data from the Morecambe Bay CDW to investigate respiratory care in the local area and the impact of the MBRN, a local integrated care initiative. These projects both encounter limitations of routine health data for research but take different strategies for overcoming the barriers. The second two studies use EPIC, a microsimulation model, to evaluate the impact of interventions for COPD care in the Canadian population. These analyses take a health economics and patient outcomes perspective and include recommendations for practice and policy. The primary aims for each study are listed below:

1. Spatio-temporal analysis of referrals to outpatient respiratory clinics to evaluate the impact of the MBRN model of care on secondary care service utilisation (Chapter 2).

2. To assess the capacity of routinely collected data for measuring diagnostic quality of CRD (Chapter 3).

3. Budget impact analysis to evaluate the affordability of a primary care-based case detection programme for COPD from the perspective of the Canadian healthcare system (Chapter 4).

4. Benefit-harm analysis to quantify the impact of earlier initiation of triple therapy, compared to current guideline recommendations, on COPD patients' quality-of-life (Chapter 5).

This thesis is arranged into four chapters. Chapter 4 has been published, Chapters 2 and 5 are under review, and Chapter 3 is being prepared for submission.

In Chapter 2 of this thesis, we present the findings from a spatio-temporal analysis of outpatient referrals between 2012-2020, accounting for MBRN intervention in 2017. This study proposes a methodological solution to limitations encountered with routinely collected primary care data.

Chapter 3 explores the capacity of routine data present in electronic health records for measuring diagnostic quality. This chapter has two parts. First, a broader but more brief discussion of the topic in the format of a research letter, and second, an extended report including specific findings relevant to MBRN stakeholders.

In Chapter 4, we present the results of a budget impact analysis of COPD case detection in primary care. This analysis estimates the cost to the Canadian healthcare system of an earlier detection programme for COPD and identifies specific barriers to its implementation.

Finally, Chapter 5 presents a benefit-harm analysis for earlier initiation of inhaled triple therapy for patients with COPD. This analysis weighs the benefit of reduced risk of acute exacerbation against the harm of increased risk of pneumonia adverse events associated with steroid-based treatment in different subgroups of COPD patients.

Chapter 2

Spatio-temporal modelling of referrals to outpatient respiratory clinics in the integrated care system of the Morecambe Bay area, England

BMC Health Services Research

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Abstract

Background: Promoting integrated care is a key goal of the NHS Long Term Plan to improve population respiratory health, yet there is limited data-driven evidence of its effectiveness. The Morecambe Bay Respiratory Network is an integrated care initiative operating in the North-West of England since 2017. A key target area has been reducing referrals to outpatient respiratory clinics by upskilling primary care teams. This study aims to explore space-time patterns in referrals from general practice in the Morecambe Bay area to evaluate the impact of the initiative.

Methods: Data on referrals to outpatient clinics and chronic respiratory disease patient counts between 2012-2020 were obtained from the Morecambe Bay Community Data Warehouse, a large store of routinely collected healthcare data. For analysis, the data is aggregated by year and small area geography. The methodology comprises of two parts. The first explores the issues that can arise when using routinely collected primary care data for space-time analysis and applies spatio-temporal conditional autoregressive modelling to adjust for data complexities. The second part models the rate of outpatient referrals via a Poisson generalised linear mixed model that adjusts for changes in demographic factors and number of respiratory disease patients.

Results: The first year of the Morecambe Bay Respiratory Network was not associated with a significant difference in referral rate. However, the second and third years saw significant reductions in areas that had received intervention, with full intervention associated with a 31.8% (95% CI 17.0-43.9) and 40.5% (95% CI 27.5-50.9) decrease in referral rate in 2018 and 2019, respectively.

Conclusions: Routinely collected data can be used to robustly evaluate key outcome measures of integrated care. The results demonstrate that effective integrated care has real potential to ease the burden on respiratory outpatient services by reducing the need for an onward referral. This is of great relevance given the current pressure on outpatient services globally, particularly long waiting lists following the COVID-19 pandemic and the need for more innovative models of care.

2.1 Introduction

Chronic respiratory disease (CRD) remains a leading cause of morbidity and mortality in the UK; it is estimated that 15% of the population have a history of CRD and it is the fourth most common cause of death in England [1, 2]. Respiratory disease disproportionately affects disadvantaged socio-economic groups due to the known links with risk factors such as smoking, air pollution, poor housing, and occupational hazards [3]. CRD represents a large burden on the NHS with estimated direct costs of £4.7 billion from asthma and chronic obstructive pulmonary disease (COPD) alone [4]. The pressure is set to increase with an ageing population [5] which raises questions about how respiratory services can be changed to be more efficient and provide the best possible care for patients.

Promoting integrated care is a key goal of the NHS Long Term Plan to improve population respiratory health [6]. Integrated care is an organising principle for care delivery that seeks to improve the quality of care for patients by providing services that are better coordinated and act in a joined-up way [7, 8]. Integrated care has been argued as the key to making the health and social care system more sustainable. Without integration patients are more likely to become lost in the system, needed services can be duplicated or delayed, and the potential for cost-effectiveness declines [9]. However, despite the large push toward building integrated systems of care across England in recent years, evaluations have historically produced mixed results [10, 11, 12]. Research suggests this could, at least partly, be caused by the challenge in selecting outcome measures that are able to quantify the success of complex and multi-faceted initiatives [10, 13, 14]. The issue is exacerbated by data access barriers, particularly access to data linked across healthcare tiers at patient level, that can limit the possibilities for evaluations [14, 15].

The North-West region has the highest under 75 mortality rate from respiratory disease in England, 44.7% compared to 33.6% country-wide [16]. Clinical commissioning groups were dissolved on 1st July 2022, but at the time of this analysis, they were NHS bodies responsible for the planning and commissioning of healthcare services for their local area in England. The Morecambe Bay Clinical Commissioning Group (MBCCG) in the North-West of England provided primary care for approximately 352,000 patients across 32 general practices (GPs) [17]. The majority of patients reside in Lancaster, South Lakeland, and Barrow-in-Furness,

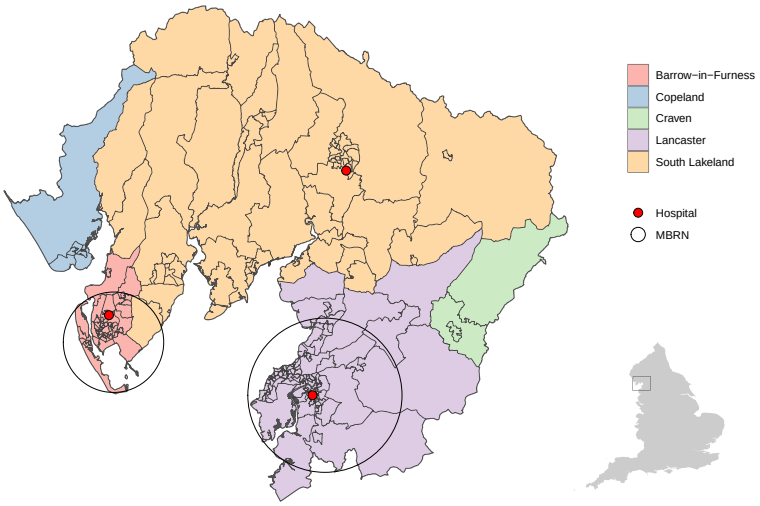

Figure 2.1: Map of the Morecambe Bay area shaded by local authority. Black circles show the approximate area of influence of the Morecambe Bay Respiratory Network.

covering both rural and urban town areas, as well as a range of socio-economic levels including some of the most deprived communities in the country [18].

The Morecambe Bay Respiratory Network (MBRN) is an integrated care initiative operating in the Morecambe Bay area that aims to improve the quality and efficiency of healthcare delivery for patients with the four most prevalent CRDs in the UK: asthma, COPD, bronchiectasis, and interstitial lung disease (ILD). The first phase of the initiative began in 2017, reaching 50% of the MBCCG population through 8 practices in the network, clustered predominately in the Lancaster and Barrow-in-Furness localities (Figure 2.1). A second phase in 2019 extended that reach to 65%, but this research focuses on phase one.

The MBRN evolved out of the vanguard programme for new care models, receiving approximately £1 million investment (£3 per patient per practice) from the MBCCG to develop a model of care that effectively used existing services to produce efficient outcomes [19, 20]. Given NHS consultant recruitment challenges in the area and nationally, models creating bespoke new services were unsuitable [20, 21] The core components of the MBRN model include an enhanced primary care team that has direct access to specialist investigation and is closely supported by secondary care expertise via monthly multidisciplinary meetings. This contrasts with other integrated respiratory initiatives, such as Knowsley Community Respiratory Service [22], also in the North-West region, that has moved acute services to the community rather

than empowering primary care to provide a higher level of clinical care. The MBRN promotes effective communication and shared pathways across healthcare tiers to ensure that patients receive consistent information and to remove unnecessary or duplicate appointments. A key metric for the MBRN has been the measured impact on outpatient referrals reflecting the goals of improved service efficiency, bringing care closer to the patient, and avoiding unnecessary referrals that increases pressure on outpatient services and wait time for all patients.

NHS England undertakes 125 million outpatient appointments a year [23]. The COVID-19 pandemic has added considerable pressure to an already strained system with 6 million people on the waiting list for elective care compared to 4.4 million prior to the pandemic. The waiting list is expected to continue to grow in the short term as patients come forward who have delayed seeking health advice or treatment during the pandemic [24]. The radical redesign of elective care is more essential now than ever to manage demand in a way that improves patient care as well as service efficiency [25]. There is a need to work with primary care to improve patient pathways to reduce the need for an onward referral and avoidable delays where possible [24].

The aim of this research is to provide a data-driven assessment of the impact of the MBRN using a source of routinely collected data that has not been extensively used in health service research. This analysis focuses on referrals to outpatient respiratory clinics, an outcome measure of key relevance both to the MBRN and wider NHS agenda. Existing quantitative evaluations of integrated care initiatives for respiratory disease often focus on hospital utilisation in terms of non-elective admissions, with mixed results [22, 26, 27, 28]. The literature on the impact to outpatient referrals is lacking. Evaluations for non-respiratory primary care enhanced initiatives have found evidence of a reduction in outpatient referrals, but these studies were restricted to short time frames (3-6 months) and did not account for other factors [29, 30]. The use of routinely collected data in this analysis facilitates a modelling approach that adjusts for demographic factors and changes in CRD patient count to closer study the underlying referral behaviour.

The remainder of the paper is structured as follows. After a brief overview of the modelling approach, we describe the routinely collected data source, including complexities and sources of missingness and the impact this may have on space-time analyses at small-area geography level. Next, we propose the methodology used that

has two parts:

1. Spatio-temporal extension of conditional autoregressive models to adjust for the complexities in the data prior to the primary analysis.
2. Generalised linear mixed model of outpatient referrals in the Morecambe Bay area over an eight year period.

We then present the results of the model output before providing a concluding discussion, relating back to the impact of the MBRN, the wider context of the demand on outpatient services, and the importance of robust data for healthcare evaluations.

2.2 Methods

The main outcome variable is annual rate of referrals from GP to outpatient respiratory clinics over an eight year study period (1st April 2012 - 31st March 2020) for 204 of the Lower-layer Super Output Areas (LSOAs) that lie within the MBCCG boundaries. LSOAs are small areas used for census geography in the UK that have an average population size of 1,500 [31]. The rate denominator of the outcome measure is number of diagnosed CRD patients to adjust for differences in patient count over space and time, and to avoid a model where referrals is acting as a proxy for prevalence. We consider data from adults aged 25 years or over. The 18-24 age bracket was excluded to reduce potential bias from the large student population in central Lancaster. Further, two LSOAs within the MBCCG boundaries were excluded due to the influence of Lancaster University.

For the sake of brevity, in the remainder of the paper study years will be referenced by the start date. For example, the study year '2012' will refer to the period 1st April 2012 – 31st March 2013. Additionally, 'adults' will refer to individuals aged 25 years or over unless specified otherwise.

2.2.1 Primary data source

This study uses routinely collected NHS data stored in the Morecambe Bay Community Data Warehouse (CDW), a SQL Server owned and maintained by the University Hospitals of Morecambe Bay NHS Foundation Trust. The CDW contains

data from primary, secondary, and community care across Morecambe Bay and uses pseudonymised NHS Numbers to allow linkage between data sets at an individual level.

Referrals were identified from secondary care records of the three hospitals within the study area with outpatient respiratory services: Furness General Hospital in Barrow-in-Furness, Royal Lancaster Infirmary in Lancaster, and Westmorland General Hospital in South Lakeland (Figure 2.1). A relevant referral was defined as any new referral from GP to a respiratory, spirometry, oxygen, or lung clinic, for an adult residing in the study area. We excluded referrals to clinics for asthma biologics, respiratory postoperative, respiratory physiotherapy, sleep apnoea, and referrals made under the 'two-week wait' pathway for suspected respiratory cancer. Clinics were excluded if they were outside the scope of the MBRN (e.g., cancer), had their own existing referral pathway (e.g., sleep apnoea), or if the clinic did not exist for the entirety of the study period (e.g., asthma biologics) as this may confound results.

Primary care records were used to build a GP-registered population dataset of all adults residing in a study LSOA and registered at a MBCCG GP. An individual's entry date is defined as the most-recent of GP registration start date and their 25^{th} birthday. Although registration status is recorded in the CDW, registration end date is missing for all individuals who have left or died so we use last interaction with primary care (appointment, consultation, or medication issue) as a proxy. An individual's end date in the GP-registered population dataset, if relevant, is end date proxy or date of death.

CRD patients were identified from among the GP-registered population cohort by diagnoses recorded in primary care with a relevant asthma, COPD, bronchiectasis, or ILD SNOMED CT code. Relevant codes were identified using NHS Digital's SNOMED CT Browser [32]. The codes were then filtered with the aim of reflecting as closely as possible MBRN's own in-house patient registers. For an asthma diagnosis, an issuing of inhaled therapy in the past 12 months was used as an additional criterion. The Quality and Outcomes Framework guidelines require post bronchodilator spirometry for a COPD diagnosis [33]. We have not applied this criterion due to discrepancies in the recording of lung function test results in the CDW. A validation study found that using diagnoses codes alone gave a positive predictive value for true COPD of 86.5% and including spirometry results or

medications only marginally improved results [34]. Start and end dates for diagnoses are recorded in the CDW and applied here to estimate the number of respiratory patients for any given space-time unit. In the case of asthma diagnoses, the ceasing of inhaled therapy for a period of 12 months qualifies as an end date.

The primary care data in the CDW has missingness and complexities that introduce bias to the GP-registered population cohort, in turn impacting the CRD patient counts. The three main issues are:

1. Two of the 32 MBCCG GPs are not signed up to the CDW data sharing agreement and so we do not have access to primary care records for these patients. This creates spatially-correlated gaps in the data.

2. We use a proxy for GP registration end date but this will likely be earlier than the true de-registration date, resulting in an underestimate of the GP-registered population size at any given time.

3. For a given registration, only a patient's current address rather than entire address history is recorded and so movement of people within the MBCCG over time cannot be tracked. An individual's current address is assumed to be the residency for their entire registration period which may result in individuals being assigned to an incorrect space-time unit.

Each of these issues has a spatial and/or temporal dimension and could bias the analysis via the denominator of the outcome rate.

2.2.2 Secondary data sources

GP registration data from NHS Digital [35] was used to estimate the GP-registered population counts that would be observed in the CDW without the presence of bias and missingness. Since 2014, NHS Digital releases data on a quarterly basis at LSOA-level for total number of patients registered at each GP practice in England. An age breakdown is not provided at LSOA level due to possible identification of individuals when linked to other data sets. However, an age breakdown is provided for each distinct GP register. Therefore, for each of the 204 LSOAs in the study area, we estimate the number of adults registered at a MBCCG GP by multiplying the number from the LSOAs population registered at each relevant GP by the proportion

of that GP's register ages 25 years or over, then summing across all GPs. This is repeated for all quarterly releases, and the mean taken by study year.

The Office for National Statistics (ONS) publishes mid-year population estimates that are used for estimates of LSOA age and sex demographics [36]. Although the census population and GP-registered population are not identical, we use the ONS estimates since NHS Digital does not cover all study years. The MBCCG and LSOA boundaries are also available from ONS as shapefiles [37, 38]. The Open Source Routing Machine (OSRM) package in R Studio was used to construct variables for distance to healthcare services [39]. The road distance in kilometres (km) was calculated for all postcodes within the study area and then averaged by LSOA. The English Indices of Deprivation was used as a relative measure of deprivation at LSOA-level [18].

2.2.3 Statistical Analysis

2.2.3.1 Adjusting CRD patient count

We adjust the rate denominator, CRD patient count, for the previously described data complexities in the CDW GP registers by assuming that the population assigned to a given space-time unit by the CDW is representative of the corresponding true, unobserved GP-registered population. Then for study years 2014 onward, an estimate for the number of adult CRD patients is obtained for each LSOA by:

$$\hat{R}_{it} = \frac{R_{it}^{CDW}}{P_{it}^{CDW}} \times P_{it}^{NHS} \ , \tag{2.1}$$

where R_{it}^{CDW} is the CRD patient count from the CDW for LSOA i ($i = 1, \ldots, N$) and year t ($t = 1, \ldots, T$), P_{it}^{CDW} the GP-registered adult population count from the CDW, and P_{it}^{NHS} the GP-registered adult population estimate from NHS Digital. Since LSOA-level data is not available from NHS Digital pre-2014, we apply spatio-temporal modelling techniques to model the error in the primary care records of the CDW and to predict the NHS Digital figures for study years 2012 and 2013 based on the corresponding CDW count. Once the predictions are obtained, the adjustment in (2.1) can be applied.

The study period has $T = 8$ years (2012-2019), but for this model we also use data from 1$^{\text{st}}$ April 2020 to 31$^{\text{st}}$ March 2021 to improve prediction capacity. The outcome

variable is P_{it}^{NHS} for LSOA i ($i = 1, \ldots, N$) and year t ($t = 1, \ldots, T+1$). The counts are sufficiently large (mean = 1181, minimum = 681) to use a log-Gaussian model as an approximation to the Poisson. We include covariates for (natural logarithm of) CDW population count, P_{it}^{CDW}, and measurable sources of error namely time and proportion of LSOA population registered at a GP not included in the CDW data sharing agreement (calculated using NHS Digital data). A generalised linear model (GLM) was first explored. The residuals exhibited strong spatio-temporal correlation: Moran's I statistics computed on the residuals for each year separately produced values ranged from 0.23 to 0.33 with p-values less than 0.0001 in all years while the lag-1 temporal autocorrelation calculated for each LSOA separately yielded a mean of 0.3762 across all LSOAs.

We consider a model that captures the spatio-temporal autocorrelation via random effects assigned a spatio-temporal extension of conditional autoregressive (CAR) distributions, which are a type of Gaussian Markov random field. We assume the random effects to represent the unmeasured error in the CDW counts. Here we follow the model proposed by Rushworth et al. [40]. Let $S = (S_1, \ldots, S_{T+1})$ denote the set of random effects for time points $t = 1, \ldots, T+1$, where $S_t = (S_{1t}, \ldots, S_{Nt})$ is the vector of random effects for specific time point t. Then,

$$\begin{aligned} \log(P_{it}^{NHS}) &\sim \mathrm{N}\left(x_{it}^{\top}\beta + S_{it}, \sigma^2\right) \\ S_t|S_{t+1} &\sim \mathrm{N}\left(\rho_T S_{t+1}, \tau^2 Q(\rho_S, W)^{-1}\right) \qquad (t = 1, \ldots, T) \\ S_{T+1} &\sim \mathrm{N}\left(0, \tau^2 Q(\rho_S, W)^{-1}\right) . \end{aligned}$$

The vector x_{it} denotes the set of explanatory variables, β the corresponding regression parameters, and σ^2 the variance of the residual errors. For the distributions of the random effects, ρ_T denotes the temporal dependency parameter, ρ_S the spatial dependency parameter, τ^2 the conditional variance parameter, W an $N \times N$ neighbourhood matrix defined for the 204 non-overlapping spatial units that comprise the lattice data for this study, and Q the Leroux precision matrix [41]. Further detail for the spatio-temporal CAR model methodology can be found in the supporting information (Section 2.6).

The random effect for time point $T + 1$ is specified marginally since S_{T+2} is not observed. A typical first-order autoregressive process defines each value conditioned on the previous value. We condition in the reverse order since data is extracted from

the CDW retrospectively making the most recent data the most accurate and error accumulating as we go further back in time.

2.2.3.2 Modelling referrals to outpatient respiratory clinics

Let Y_{it} be the number of new referrals from GP to an outpatient respiratory clinic for LSOA i ($i = 1, \ldots, N$) and year t ($t = 1, \ldots, T$). The referral data is modelled using a Poisson generalised linear mixed model (GLMM) with a random intercept term for each LSOA, denoted by Z_i. The adjusted number of CRD patients from the first part of the methodology, $\hat{R}_{it}$, is included as an offset term to give a rate interpretation. Then,

$$\begin{aligned} Y_{it} &\sim \text{Poisson}\left(\hat{R}_{it} \exp\left(d_{it}^{\top}\gamma + Z_i\right)\right) \\ Z_i &\sim \text{N}\left(0, \kappa^2\right) , \end{aligned}$$

where d_{it} is the vector of explanatory variables, γ the corresponding regression parameters, and κ^2 the variance of the random effects for which we assume independence. A corresponding Poisson GLM was over-dispersed yet exploratory analysis carried out on the residuals did not provide evidence to support a more complex correlation structure for the random effects. Relevant results can be found in the supporting information (Section 2.6).

The covariate component of the GLMM is:

$$\begin{aligned} d_{it}^{\top}\gamma = \gamma_0 &+ \gamma_1 \, \texttt{Age}_{it}^{65-74} + \gamma_2 \, \texttt{Age}_{it}^{75+} + \gamma_3 \, \texttt{Male}_{it} + \gamma_4 \, \texttt{Distance}_i \\ &+ \gamma_5 \, \texttt{IMD}_i + \gamma_{6-12} \, \texttt{Year}_t + \gamma_{13} \, \texttt{MBRN}_{it} + \gamma_{14-20} \, \texttt{Year}_t * \texttt{MBRN}_{it} \ . \end{aligned}$$

The covariates $\texttt{Age}^{65-74}$, $\texttt{Age}^{75+}$, and `Male` are included to account for demographic differences in the LSOAs and respectively represent the proportion of the adult population in the 65-74 and 75+ age brackets, and proportion of the adult population that are male. Stepwise covariate selection (with age groups 25-39, 40-54, 55-64, 65-74, 75+) suggested the age groups included are the only ones that are predictive of referrals and have a distinct effect to each other. `Distance` represents the average car travel distance to the nearest hospital within the MBCCG providing respiratory outpatient services. `IMD` represents the Index of Multiple Deprivation (IMD) scores where a higher score indicates greater levels of deprivation. The IMD is updated

every 3-4 years thus we take the mean of the 2015 and 2019 scores for each LSOA.

To account for the effect of MBRN intervention, we calculate the percentage of an LSOAs GP-registered population that is registered at a GP that joined the MBRN in 2017, represented in the model by `MBRN`. This is calculated for all study years , even prior to MBRN introduction, to account for any baseline differences in health service utilisation for LSOAs that received MBRN intervention from 2017 onward. For the purpose of exploratory data analysis, we dichotomise the continuous `MBRN` variable so that an LSOA is classed as an 'MBRN LSOA' if `MBRN` $> 50\%$ and a 'Non-MBRN LSOA' otherwise.

`Year` represents the study year and `MBRN*Year` is an interaction term between study year and MBRN coverage, which will be the main indicator of the impact of the MBRN on outpatient referrals. Study year has been defined as a factor variable as opposed to a continuous covariate or a before/after MBRN indicator, in order to better study the evolution of MBRN impact since its initiation. For the sake of space, the factor levels have been grouped into one term in the above equation.

Additional descriptions of covariates used for both models can be found in the supporting information (Section 2.6).

2.2.3.3 Inference

The models are specified as Bayesian hierarchical models and parameter estimation carried out using Markov Chain Monte Carlo (MCMC) algorithms. For the spatio-temporal GP registration model, prediction for years 2012 and 2013 is carried out as part of model fit. The unobserved data are treated as missing values in the response vector and are estimated each iteration of the MCMC algorithm via the posterior predictive distribution to produce a posterior sample. When fitting the referrals model, to account for the uncertainty in the predictions, we randomly sample from the posterior samples for the predictions each iteration and recalculate the offset term. For further information on MCMC specifics, including prior distributions, we refer readers to the supporting information (Section 2.6). The significance of model covariates is tested at the 5% significance level using Bayesian credible intervals (CIs). A covariate is insignificant if the interval contains the null value. All statistical analysis was carried out in R Studio [42].

2.3 Results

2.3.1 Adjusting CRD patient count

Since the spatio-temporal model for patient count adjustment is not the main focus of this paper, we refer readers to the supporting information (Section 2.6) for extended results including covariate description, parameter estimates, prediction output, model validation, and MCMC diagnostics. Figure 2.2 and Table 2.1 are included here to highlight respectively the need and impact of the proposed adjustment modelling.

Figure 2.2 shows the spread of percentage change between the CDW GP-registered population counts and NHS Digital estimates for study years 2014-2019. As we go further back in time, the magnitude of the median percentage difference increases and there is increased variation in the degree of error. The plot shows an LSOA that is consistently a 50-60% underestimate in the CDW whilst other LSOAs have above a 30% overestimate in years 2014-2016, highlighting the error that can occur at both ends of the spectrum using CDW registration data.

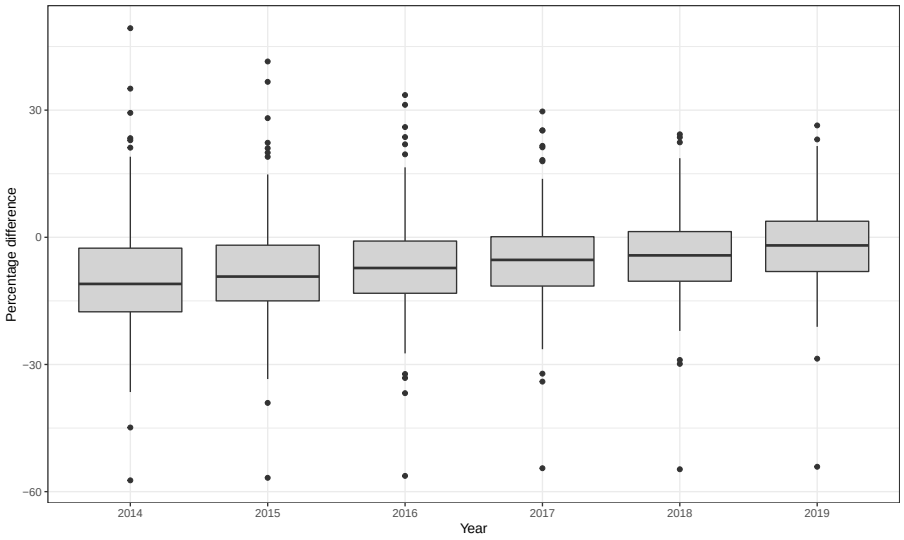

Figure 2.2: Boxplot showing the spread of relative difference between the CDW counts and NHS Digital estimates for adults registered at a MBCCG GP at LSOA-level. Percentage difference = (CDW − NHS)/NHS × 100. Data for years 2012 and 2013 are not available from NHS Digital.

Table 2.1 summarises the overall impact of the adjustment methodology on the total

number of CRD patient counts that is used as the denominator of the outpatient referral rate.

Table 2.1: Comparison of unadjusted (raw counts extracted from CDW) and adjusted (prevalence × GP-registered adult population) total CRD patients within the MBCCG by study year.

Year	Unadjusted	Adjusted	Percentage difference
2012	22,803	26,293	+15.3%
2013	23,747	26,962	+13.5%
2014	24,876	27,820	+11.8%
2015	25,936	28,477	+9.8%
2016	27,082	29,305	+8.2%
2017	28,234	29,975	+6.2%
2018	29,262	30,631	+4.5%
2019	30,902	31,715	+2.6%

2.3.2 Modelling referrals to outpatient respiratory clinics

Raw data

We first present data summary results. Table 2.2 shows a comparison of age, sex, distance to nearest hospital, and IMD score for LSOAs that received MBRN intervention in 2017 and those that did not. Populations of the MBRN LSOAs are on average younger, closer in distance to a major hospital, and have higher relative deprivation.

Table 2.2: Median (interquartile range) of covariates used in the outpatient referrals random intercept model for MBRN and non-MBRN intervention LSOAs.

	MBRN	Non-MBRN	Difference
Age 65-74	15.4 (12.1, 19.3)	18.5 (14.7, 21.0)	-3.1
Age 75+	12.6 (9.1, 16.6)	14.0 (11.3, 17.0)	-1.4
Male	47.7 (46.5, 49.0)	48.1 (46.8, 49.6)	-0.4
Distance	6.0 (2.4, 8.2)	11.0 (3.76, 20.4)	-5
IMD	19.5 (11.8, 31.6)	14.7 (10.0, 22.5)	4.8

A total of 8,897 referrals to outpatient respiratory clinics that fulfilled the inclusion criteria were extracted from secondary care records in the CDW. Table 2.3 documents the raw counts by study year and the average number of referrals per LSOA. The total number of new referrals from GP to respiratory outpatient clinics

displayed a consistent increasing trend up to 2016, but the counts in the years since the introduction of the MBRN (2017-2019) have not risen above 2016 levels.

Table 2.3: New referrals from GP to outpatient respiratory clinics for each study year.

Year	Total number of referrals	Average per LSOA
2012	968	4.75
2013	974	4.77
2014	1,039	5.09
2015	1,120	5.49
2016	1,218	5.97
2017	1,204	5.90
2018	1,165	5.71
2019	1,209	5.93

Additional data summaries can be found in the supporting information (Section 2.6).

Model output

Table 2.4 presents the parameter estimates for the GLMM.

The main indication of the effect of the MBRN are the interaction terms between MBRN coverage and year. Prior to MBRN intervention (2012-2016), the model output does not suggest a systematic difference in referral rates at baseline, after adjusting for all other covariates, for LSOAs that received higher percentages of MBRN intervention from 2017 onward. The MBRN main effect term (i.e., the effect in 2012) and the interaction term for 2015 are marginally significant, whilst the interactions terms for 2013, 2014, and 2016 are insignificant, at the 5% significance level.

The MBRN did not have a significant association with referral rate in the activation year (2017). In 2018, a 1% increase in percentage of the population registered at an MBRN GP was associated with a 0.04% decrease in rate of referral to outpatient respiratory clinics from GP. To put this figure in context, an LSOA with all its population registered at an MBRN GP (i.e., full intervention, `MBRN` = 100%) is associated with a 31.8% (95% CI 17.0-43.9) decrease in referral rate compared to an LSOA with none of its population registered at an MBRN GP (i.e., no intervention, `MBRN` = 0%), with all other covariates held constant. In 2019, the same 1% increase

is associated with a 0.05% decrease in referral rate, corresponding to a 40.5% (95% CI 27.5-50.9) decrease in referral rate for full MBRN intervention compared to no intervention.

The model output does not suggest a significant change in overall referral rate over time beyond what can be attributed to changes in demographic factors and the introduction of the MBRN. All levels of the year factor variable are insignificant except for 2016 which shows a marginally significant 9.1% increase in referral rate compared to 2012.

Table 2.4: The median relative risks (RR) and 95% credible intervals (CI) for the covariates included in the outpatient referrals random intercept model.

Parameter	**RR**	**95% CI**
Intercept	0.037	(0.035, 0.040)
Age 65-74	1.017	(1.008, 1.026)
Age 75+	1.009	(1.001, 1.016)
Male	1.016	(1.002, 1.028)
Distance to hospital	1.005	(1.001, 1.009)
IMD	0.998	(0.996, 0.999)
2013	0.965	(0.878, 1.054)
2014	0.991	(0.909, 1.078)
2015	1.030	(0.950, 1.128)
2016	1.091	(1.000, 1.191)
2017	1.049	(0.963, 1.149)
2018	0.975	(0.894, 1.064)
2019	0.961	(0.880, 1.049)
MBRN (*main effect*)	1.001	(1.000, 1.003)
MBRN 2013	0.998	(0.996, 1.000)
MBRN 2014	0.999	(0.997, 1.001)
MBRN 2015	0.998	(0.996, 1.000)
MBRN 2016	0.999	(0.997, 1.001)
MBRN 2017	0.999	(0.997, 1.001)
MBRN 2018	0.996	(0.994, 0.998)
MBRN 2019	0.995	(0.993, 0.997)

Figure 2.3 is an interaction plot providing an illustration of the effect of MBRN intervention over time. The plot is produced using the fitted model output and compares the predicted referral rate for an LSOA with full MBRN intervention (MBRN=100%) compared to an LSOA with no MBRN intervention (MBRN=0%). The rate of referral is predicted for each study year whilst all other covariates

including the offset term are fixed at their median values across the entire data set. In the baseline years (2012-2016) and in the activation year (2017), the credible intervals for the predictions consistently overlap, illustrating no systematic difference between intervention and non-intervention areas once all other covariates adjusted for. In 2018 and 2019, the intervals separate, with the non-intervention LSOA continuing in an upward trend and the intervention LSOA substantially decreasing. In 2019, the model predicts a median rate of 2.9 referrals per 100 CRD patients (95% CI 2.6-3.3) for full MBRN intervention compared to 4.3 per 100 CRD patients (95% CI 3.9-4.7) for no MBRN intervention.

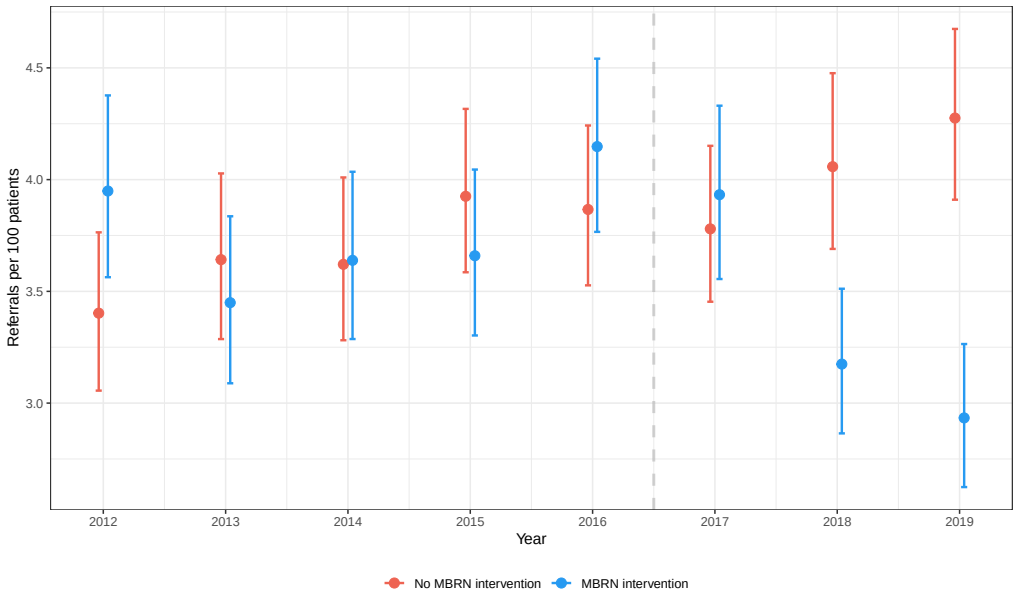

Figure 2.3: Interaction plot for the effect of the interaction term between year and MBRN on referral rate over time. The predicted number of referrals per 100 CRD patients is estimated for two levels of registration at an MBRN GP at LSOA-level: 0% ('No MBRN intervention') and 100% ('MBRN intervention'). The dashed line represents the introduction of the MBRN in 2017.

All other covariates included in the model are significant (Table 2.4). The covariates relating to age and sex demographics are positively associated with referral rate. For each 1% increase in the proportion of an LSOAs adult population in the 65-74 age bracket, a 1.7% increase in referral rate would be expected. For the 75+ age bracket, the analogous increase in referral rate is 0.9%. For each 1% increase in the proportion male, a 1.6% increase in referral rate would be expected. Distance to closest hospital is also positively associated with referral rate with an increase of 0.5% associated with a 1 km increase in road travel distance. The model results

suggest a negative relationship between referral rate and socio-economic deprivation. A 1 point increase in IMD score is associated with a 0.02% decrease in referral rate, equating to a referral rate 1.2 times higher for the least deprived LSOA in the study area compared to the most deprived.

The variance term for the random effects, κ^2, was estimated at 0.023, 95% CI (0.015, 0.033), supporting the need for a GLMM over a GLM.

Diagnostics for the MCMC algorithm can be found in the supporting information (Section 2.6).

2.4 Discussion

Integrated care is a broad concept with multi-faceted implications which presents a challenge for evaluators. This study considered the use of routinely collected data to provide a robust data-driven analysis of healthcare delivery that focuses on an outcome measure of relevance and adjusts for diversity in the study population. The results suggest the success of the MBRN model in reducing rates of new referrals to outpatient respiratory clinics from GP in areas that have received higher percentages of intervention compared to areas with lower intervention. Three years of full MBRN intervention was associated with a 40.5% decrease in referral rate, adjusted for changes in CRD patient count. [14, 43].

The first stage of the methodology in this paper applies existing saptio-temporal methodology to a new setting to model official statistics and predict beyond the published time frame at the required geography level based on error-filled routine data. In addition, we account for uncertainty in the predictions by using the full posterior predictive distributions in the model fit for the mixed Poisson model. The results from the first model illustrate the consequences of the issues described with the CDW GP registers. For example, LSOAs where a large proportion of the population is registered at a GP not in the CDW data sharing agreement can result in substantial underestimates of the true GP-registered population. In contrast, LSOAs that have undergone significant housing development can have an overestimate of the true GP-registered population in years prior to the building work. If individuals move into the houses from the local area, the CDW does not store the address history, thus assigning them to an address at a time before the housing existed. The methodology we have proposed could be used in other fields of research that use

time restricted official statistics such as further areas of health service provision, public health and social care, and the broader social sciences.

This research into outpatient referrals supports findings from systematic reviews that integrated care services for a specific chronic disease using an MDT approach with disease-specific specialist input is likely to be successful at reducing hospital activity [11, 44]. However, existing evaluations of integrated services for chronic respiratory disease commonly focus on COPD alone, and often target only the most high-risk patients to prevent non-elective hospital admissions [26, 27, 28]. The MBRN adds to the existing literature by showing the potential for effective integrated care with a broader patient scope and benefits to other aspects of healthcare service utilisation, namely outpatient attendances. It is not a given that empowering primary care will decrease outpatient service usage since integrated care initiatives can identify unmet needs in their populations, resulting in evaluations reporting an increase in total healthcare service usage [30]. In addition, an often cited limitation of integrated care evaluations is the short follow-up period [11], an issue found in the literature that considered the impact of enhanced primary care models on referrals. In this analysis, the effect of the MBRN progressively increased between 2017-2019 highlighting the importance of evaluating healthcare initiatives over sufficient time periods [14, 43]. Policymakers frequently want to see immediate results yet transformational changes in practice and work culture requires time to gain traction [45].

The model results identified a negative relationship between socio-economic deprivation and rate of referrals, after adjustment for CRD patient count. This finding supports existing literature that the most disadvantaged patient groups often have lower probabilities of attending specialist care [46, 47]. This study is unable to comment on the reason for the inequality in the MBCCG context; possible reasons include patient preference [46], lack of adequate communication or health literacy [48, 49], or differences in GP referral behaviour across the study area [50]. Existing research predominately does not find an association between socio-economic position and probability of visiting primary-care in developed countries, with some studies even reporting higher rates of attendance [46, 51]. There is an opportunity for integrated care services to reduce healthcare inequalities by training primary care to provide more specialist services.

Of the remaining covariates in the model, the 65-74 age bracket was at the greatest risk of higher rates of referrals followed by proportion male. Distance to hospital was

positively associated with rate of referral, which contrasts with existing research that links rurality with reduced access to services [52]. A probable explanation for this finding is the relative affluence of the rural areas in the MBCCG. We are unable to identify previous work in which outpatient referrals have been analysed at an LSOA-level in England. The study area contained 32 GPs but 204 LSOAs, hence using the small-area geography gave potential for insight into the contribution of other risk factors for rate of referral that may have been lost if covariates were averaged to GP-level. This is a particular issue in the MBCCG where several practises are made up of multiple sites. For example, Lancaster Medical Practice is comprised of eight separate sites spread over central Lancaster, serving a wide spectrum of patients, demographically and clinically speaking.

The recovery of elective care following the COVID-19 pandemic is not unique to the NHS but is affecting healthcare systems worldwide [53]. The NHS post-COVID recovery plan states the need for an increase in activity of 30% above pre-pandemic level by 2024/25 to reduce waiting times, but this goal has been met with scepticism in light of NHS staff shortages and recruitment challenges [24, 54, 55]. The MBRN model demonstrates that effective integrated care has real potential to optimise existing services and ease the burden on respiratory outpatient services by reducing the need for an onward referral through improved patient pathways, effective communication between healthcare tiers, and an upskilled primary care team. The results of this analysis suggest a potential reduction of 1.4 referrals per 100 CRD patients per year for an LSOA with full MBRN intervention comapred to no MBRN intervention. Applying this result to the MBCCG population that had an estimated 31,715 adults with a CRD diagnosis in 2019 (Table 2.1), this would equate to a difference of over 400 referrals a year; 930 referrals under full MBRN intervention compared to 1,356 under no MBRN intervention. Assuming a respiratory clinician has 2-3 4-hour clinics per week and assigns 30 minutes to a new patient [56], the reduction of over 400 new referrals per year in the MBCCG population would equate to approximately one fewer clinics per week, with no consideration made for the knock-on effect to follow-up appointments.

A key strength of the proposed methods is using number of diagnosed CRD patients as the referral rate denominator. Disease prevalence data is not always readily available particularly at small area geography level and changes in patient counts, beyond what is able to be accounted for through population growth and known

risk factors, can distort both space and time analyses of healthcare utilisation [57, 58]. The model in this paper controls for changes in the size of the patient cohort, allowing a closer study of the underlying referral behaviour.

Data is vital for understanding the impacts of health interventions and generating robust analytics to improve healthcare delivery [43, 59]. Access to the CDW facilitated the flexibility of this analysis and key strengths of the methodology, including choice of outcome measure, spatial unit, adjusting for changes in CRD patient size, a longer study period, and filtering referrals and patients at a finer scale to capture healthcare interactions of closest relevance to the MBRN. This research is the first extensive use of the CDW for health service research and has barely scratched the surface of its potential. The CDW uses pseudonymised NHS Numbers; linking data at a patient level and removing traditional data silos between different branches of healthcare has the potential to provide a far more realistic and holistic view of patient care pathways. There is a clear, high value in investing in databases and personnel to exploit the wealth of information available in routinely collected data to support evidence-based decision making [60, 61].

The limitations associated with routinely collected data are well-established [62, 63]. This research contributes to the existing literature by exploring limitations encountered when using primary care records for space-time analyses, particularly the difficulty in tracking movement of people. The methodology proposed to circumvent the issues identified is somewhat of a crude fix and relies on the assumption that the prevalence calculated from the CDW is representative of the true, unobserved adult population for the corresponding space-time unit. This assumption may not be reasonable for error introduced by movement of people due to the relationship between transiency and age. If an age breakdown was provided at LSOA-level by NHS Digital, then a more informed adjustment to CRD patient count could be considered. Nevertheless, the strong spatio-temporal correlation identified in the CDW error process may be useful for future research into methodology for improving analysis using routinely collected healthcare data.

Other limitations of this research must be recognised. First, this is not a controlled study. The data summary results evidence that the MBRN reaches the most urbanised and deprived areas of the MBCCG. Access to a larger national or sub-national routine data source would facilitate a matched controlled study. However, exploratory analysis (found in the supporting information, Section 2.6) and the

interaction terms in the GLMM prior to MBRN introduction did not suggest a systematic difference in referral rates, once all else adjusted for, between intervention and non-intervention areas. Therefore, it is reasonable to attribute the dramatic decrease in referrals in 2018 and 2019 to the work of the MBRN. However, areas that have not received MBRN intervention may not have the same capacity for referral reduction due to potential differences in disease severity and patient need, which are not accounted for in the model. Second, in the GLMM, year is defined as a factor variable, adding to model complexity and forcing the relative risks to be compared to a baseline year, in this case 2012. The factor variable was selected as it captures the evolving and distinct impact of the MBRN in each intervention year. In contrast, other representations of time, such as a linear time trend or a before/after indicator variable, would assume a fixed trend across larger time periods. Due to the small temporal sample size, more advance time series modelling was not appropriate. Third, the study period was restricted by the introduction of the first COVID-19 lockdown in England, so we cannot comment on whether the reduction in referral rate was sustained. Finally, reason for referral is not documented in the secondary care records in the CDW therefore it is likely that the referrals modelled in this paper include irrelevant referrals. Access to unstructured data, such as referral letters, may minimise this source of bias. However, the clinic inclusion-exclusion criteria were determined in consultation with MBRN physicians to best capture referrals that aligned with MBRN priorities.

Future research should explore other impacts of the MBRN integrated care initiative. This analysis has focused on outpatient referrals given the relevance to MBRN goals and current healthcare pressures, as well as the gap in the integrated care evaluation literature. However, it is important to consider other measures, such as patient experience, standard of care received in primary care, and health outcomes, to provide a full-picture evaluation of an integrated care initiative. The associated cost to an initiative is a critical factor in decision-making for policy makers. The cost savings associated with reduced outpatient referrals have not been included in this study as these results may be misleading. The MBRN model has many facets beyond efficient referral pathways, thus a separate cost-effectiveness analysis that captures the initiatives complexity would be required.

2.5 Conclusion

Overall, our novel analysis demonstrates the use of large routinely collected data to robustly evaluate key outcome measures of integrated care, in this case, rate of referrals to outpatient services. The results of this study are of great relevance to current healthcare pressures across the globe, with large outpatient service backlogs and demand for innovative models of care. Future work should focus on assessing other measures appropriate to the MBRN to provide a full evaluation of the initiative's model of care.

2.6 Supporting information

This section is the contents of the supplementary material file that was submitted to BMC Health Services Research and appears online alongside the main article. Section 2.6.1 provides further detail of the steps that were taken when constructing the analysis data set from the CDW. Section 2.6.2 contains additional information of the spatio-temporal GP registration model that was omitted from the main article as this is not the primary focus of the research. Finally, Section 2.6.3 contains exploratory data analysis, MCMC methodology, and diagnostics relating to the outpatient referrals GLMM, to supplement the information given in the main article.

2.6.1 Primary data source

The construction of the population data set from the CDW is outlined in Section 2.2.1. In this section we provide additional detail of decisions made, for the sake of transparency:

- Duplicate NHS Numbers (most commonly caused by an individual being registered at more than one GP) with agreeing sex, date of birth, and date of death (if applicable), are assumed to be the same person, and the record with the most recent GP registration start date is taken as their current GP practice and address. If there is discrepancy then all records with the given NHS number are excluded.

- In order to be counted in a particular year, an individual's entry date must be prior to the half way point (1st October) of the given year and their end date after the halfway point. This was done to avoid overestimating the population count, particularly in areas with highly transient populations.

- For a given GP registration, only the individual's current address, rather than entire address history, is recorded. A change in address can only be identified if it is accompanied by a change in registered GP. Consequently, it is possible to observe "large" moves in people, but not "smaller" local moves. This is exacerbated by several GP practices in the MBCCG being made up of multiple sites. For example, Lancaster Medical Practice is comprised of eight sites spread over central Lancaster, hence an individual could move multiple times living in varied areas, demographically speaking, whilst remaining with

the same GP. In addition, since GP registration end date is missing, it is not possible to determine whether there are breaks between registrations, for example if an individual has moved out of the MBCCG then moved back in at a later date. Therefore, we only consider the most recent registration for each individual. Although this wastes some information, given the relatively short length of the study period it should only impact majorly on areas with transient populations which will have a spatial correlation.

- 'Regular' registrations only are considered. In England, a 'temporary' GP registration can be used whilst away from home for work, study, or on holiday, for up to three months. Individuals with a temporary registration remain registered with their permanent GP surgery during this time.

2.6.2 GP registration model

The primary focus of the main article is referrals to outpatient respiratory clinics and the impact of the MBRN, hence minimal focus is given to the extensive work carried out to model the GP-registered population. In this section we provide extended detail of the model, including motivation, exploratory analysis, methodology, and results. Some information from the main article has been duplicated for the sake of clarity and completeness.

2.6.2.1 Model motivation

For our study into referrals to outpatient respiratory clinics, it is crucial to adjust for patient burden to avoid producing a model that simply acts as a proxy for CRD prevalence. Our modelling approach includes CRD patient count as an offset term to express the rate of referral for each space-time unit in terms of number of CRD patients. Patients with a CRD diagnosis are identified from CDW primary care records. However, the number of patients registered at a MBCCG GP for a given space-time unit is open to multiple sources of error (Section 2.2.1) which will in turn bias the CRD patient count. NHS Digital has released GP-registered population data at LSOA level since 2014, allowing us to apply a correction to our CRD patient count for study years 2014-2019 (Section 2.2.3.1). However, NHS Digital has only released this data since 2014, whereas our study begins in 2012. The purpose of this model is to model the error process between the true GP-registered population

count taken from NHS Digital and the corresponding erroneous population count from the CDW. The model output allows us to predict the unobserved NHS Digital data for 2012 and 2013 and apply the correction to the CRD patient count. For our research into outpatient referrals, the GP registration model is a means to an end, but the methodology outlined could be applied to other research where official statistics are required beyond the time frame for which they have been reported.

2.6.2.2 Exploratory analysis

The outcome variable, denoted P_{it}^{NHS}, is the number of adults ≥ 25 years registered at an MBCCG GP for LSOA $i = 1, \ldots, N$ and year $t = 1, \ldots, T+1$, calculated from NHS Digital. Our study of outpatient referrals is over $T = 8$ study years (2012-2019), yet for this model we utilise data from the year 1st April 2020 - 31st March 2021. We recognise that including the 2020/21 year may introduce COVID-related bias (e.g., people may have been less likely to move house or relocate during the pandemic which would in turn affect GP registration) but it has been included to increase the sample size and improve the model's prediction capacity.

We first consider a GLM. The outcome counts are sufficiently large (mean = 1181, minimum = 681) to justify a log-Gaussian model as an approximation to the Poisson. The natural logarithm of CDW population count, from which we aim to predict the outcome variable for the unobserved years, is included as a covariate ($\log(\texttt{CDW})$). Additional covariates are included to adjust for known sources of error, namely year (`Year`) and proportion of the population registered at a GP not included in the CDW data sharing agreement (`Missing`). Table 2.5 provides further details of the variables used in analysis and Table 2.6 provides summary statistics. The GLM is of the form:

$$\log(P_{it}^{NHS}) = \beta_0 + \beta_1 \log(\texttt{CDW}_{it}) + \beta_2 \texttt{Year}_t + \beta_3 \texttt{Missing}_{it} .$$

Spatial autocorreltion was explored using Moran's I statistic computed on the GLM residuals for each year separately; the values ranged from 0.23 to 0.33 with p-values$<$0.0001 in all years. The lag-1 temporal autocorrelation calculated for each LSOA separately yielded a mean of 0.3762 across all LSOAs. Therefore, we pursued modelling approaches that would account for strong spatio-temporal correlation.

Table 2.5: Description of variables used in spatio-temporal GP registration model.

Variable	**Time varying (Y/N)**	**Source**	**Description**	**Notes**
GP-registered population	Y	NHS Digital	Average number of adults (25+ years) registered at a MBCCG GP for each LSOA inside the CCG boundaries	LSOA-level data released quarterly (1^{st} Jan, 1^{st} Apr, 1^{st} Jul, 1^{st} Oct) since January 2014. LSOA-level given for all-age only. GP-level given in five-year age brackets. Number 25 years or over estimated for each LSOA by multiplying the number registered at each GP by the proportion of that GPs register over 25. Estimates calculated for each quarter and averaged across study years. Only consider data for MBCCG GPs and LSOAs within the MBCCG. 'Regular' registrations only. 'Temporary' registrations are not counted in the NHS Digital data

CDW GP register counts	Y	CDW (primary care records)	Annualised count of the number of adults (25+ years) registered at a MBCCG GP for each LSOA inside the CCG boundaries	Entry date – most recent of study start date (01/04/12), 25th birthday, and GP registration start date. End date – earliest of date of death and GP registration end date proxy. If not relevant then 'NA'. 'Regular' registrations only. 'Temporay' registrations not included.
Year	Y	NA	Continuous variable form of year	Exploratory analysis suggested a linear trend between (natural logarithm of) GP-registered population and time, hence the use of a continuous form of year.
Missing GPs	Y	NHS Digital	Percentage of the LSOAs GP-registered population missing from the CDW as a result of GPs not in the data sharing agreement	Two GPs not in the data sharing agreement of the CDW. An additional GP closed in September 2015 (before the CDW was created), patients had to register at a new GP so these patients are "missing" pre-September 2015. Percentage calculated using LSOA-level GP registration data released by NHS Digital. We do with calculations with all-age data and assume this variable not to be correlated with age. As with the 'GP-registered population' variable, mean taken across quarters. For the study years 2012 and 2013, the 2014 value is used. Exploratory analysis suggests this variable does not fluctuate year-on-year.

Table 2.6: Summary statistics for covariates used in the GP registration model.

	Min	1st	Median	Mean	3rd	Max
NHS Digital	680.6	960.5	1102.5	1180.7	1356.5	2210.7
CDW	365	881	1048	1095	1272	2153
Proportion missing	0	0	0	0.022	0.017	0.555

2.6.2.3 Methodology

Model specification

Let $S = (S_1, \ldots, S_{T+1})$ be the set of random effects for time points $t = 1, \ldots, T+1$, where $S_t = (S_{1t}, \ldots, S_{Nt})$ is a vector of LSOA-level random effects for a given time point t. Then,

$$\log(P_{it}^{NHS}) \,|\, S_{it} \sim \mathrm{N}\left(x_{it}^T\beta + S_{it}, \sigma^2\right) ,$$

where x_{it} is the vector of explanatory variables, β the corresponding regression parameters, and σ^2 the variance of the residual errors. The model captures the spatio-temporal autocorrelation by assigning the random effects a spatio-temporal extension of conditional autoregressive (CAR) priors, which are a type of Gaussian Markov random field (GMRF). Here we follow the model proposed by Rushworth et al. [40],

$$\begin{aligned} S_t|S_{t+1} &\sim \mathrm{N}\left(\rho_T S_{t+1}, \tau^2 Q(\rho_S, W)^{-1}\right) \qquad t = 1, \ldots, T \\ S_{T+1} &\sim \mathrm{N}\left(0, \tau^2 Q(\rho_S, W)^{-1}\right) . \end{aligned} \tag{2.2}$$

The S_{T+1} is specified marginally since S_{T+2} does not exist. We condition in the reverse order since the unobserved data is the furthest back in time as opposed to a future event which is more typically seen in prediction modelling.

The random effects specified in (2.2) are non-separable in space and time. Temporal correlation is modelled in the conditional expectation via a first-order autoregressive process with dependency parameter ρ_T, whereas the spatial autocorrelation is induced via the precision matrix, Q. Numerous specifications for the precision matrix have been proposed in the CAR literature, but here we use that proposed by Leroux et al. [41], $Q(\rho_S, W) = \rho_S W + (1 - \rho_S)I$ where ρ_S is the spatial dependency parameter, I the $N \times N$ identity matrix, and W an $N \times N$ neighbourhood matrix defined for the 204 non-overlapping spatial units that comprise the lattice data for this study. Using the notation $i \sim j$ to mean "areas i and j share a common border"

and n_i to be the total number of neighbours for area i, the individual elements of W are:

$$w_{ij} = \begin{cases} n_i & \text{if } i = j \\ -1 & \text{if } i \sim j \\ 0 & \text{otherwise}\,. \end{cases}$$

Thus the precision matrix is a weighted average of the spatially dependent and independent structures, accommodating both weak and strong spatial autocorrelation [64]. The univariate full conditional distribution better illustrates the spatial relationship, and is given by,

$$S_{it}|S_{-i,t} \sim \mathrm{N}\left(\frac{\rho_S \sum_{j\sim i} S_{jt}}{n_i\rho_S + 1 - \rho_S}, \frac{\tau^2}{n_i\rho_S + 1 - \rho_S}\right)\,.$$

The subscript notation $_{-k}$ is used to mean "all elements except k", and so $S_{-i,t}$ is the vector of all random effects at time point t excluding area i.

MCMC methodology

Model fit was carried out by sampling from the posterior distribution of the parameters using MCMC methodology. It is assumed the reader has an understanding of the fundamentals of Bayesian inference and MCMC methods.

Prior distributions:
The random effects, S_{it} ($i = 1, \ldots, N$ and $t = 1, \ldots, T{+}1$), act as latent variables and the spatio-temporal CAR prior is described in (2.2). For the remaining parameters, we assume the following independent prior distributions:

$$\begin{aligned} \tau^2 &\sim \text{Inverse-Gamma}\,(a, b) \\ \sigma^2 &\sim \text{Inverse-Gamma}\,(c, d) \\ \rho_T &\sim \text{Unif}\,(0, 1) \\ \rho_S &\sim \text{Unif}\,(0, 1) \\ \beta &\sim \mathrm{N}\left(0, \lambda^2 I_4\right)\,, \end{aligned}$$

where $a = c = 1$, $b = d = 0.01$, $\lambda^2 = 1000$, and I_4 the 4-dimensional identity matrix.

Posterior distribution:
Let $\theta = (\beta, S, \tau^2, \sigma^2, \rho_T, \rho_S)$ be the vector of parameters to be estimated. The joint

posterior distribution is:

$$\begin{aligned}\pi\left(\theta|P\right) &\propto f\left(\log\left(P\right)|S\right) \times \prod_{t=1}^{T+1} \pi(S_t|S_{t+1}) \times \pi(\tau^2, \sigma^2, \rho_T, \rho_S, \beta) \\ &\propto \left(\sigma^2\right)^{-N(T+1)} \exp\left(-\frac{1}{2\sigma^2}\left(\log(P) - X\beta - S\right)^T \left(\log(P) - X\beta - S\right)\right) \\ &\quad \times det\left(\tau^2 Q^{-1}\right)^{-(T+1)/2} \exp\left(-\frac{1}{2\tau^2}\sum_{t=1}^{T+1}\left(S_t - \rho_T S_{t+1}\right)^T Q \left(S_t - \rho_T S_{t+1}\right)\right) \\ &\quad \times \pi(\tau^2, \sigma^2, \rho_T, \rho_S, \beta)\ .\end{aligned}$$

In the above we define $S_{T+2} = 0$ to simplify the posterior equation and write $\pi(\tau^2, \sigma^2, \rho_T, \rho_S, \beta)$ as shorthand for the prior distributions.

Updating algorithms:
The parameters $(\tau^2, \sigma^2, \rho_T)$ were updated via separate Gibbs samplers according to their full conditional posterior distributions:

$$\begin{aligned}\tau^2|P, \theta_{-\tau^2} &\sim \text{Inverse-Gamma}\left(a + \frac{N(T+1)}{2},\ b + \frac{1}{2}\sum_{t=1}^{T+1}\left(S_t - \rho_T S_{t+1}\right)^T Q \left(S_t - \rho_T S_{t+1}\right)\right) \\ \sigma^2|P, \theta_{-\sigma^2} &\sim \text{Inverse-Gamma}\left(c + \frac{N(T+1)}{2},\ d + \frac{1}{2}\left(\log(P) - X\beta - S\right)^T \left(\log(P) - X\beta - S\right)\right) \\ \rho_T|P, \theta_{-\rho_T} &\sim \text{Truncated-Normal}\left(\frac{\sum_{t=1}^{T+1} {S_t}^T Q S_{t+1}}{\sum_{t=1}^{T+1} {S_{t+1}}^T Q S_{t+1}},\ \frac{\tau^2}{\sum_{t=1}^{T+1} {S_{t+1}}^T Q S_{t+1}}\ ;\ 0, 1\right)\ ,\end{aligned}$$

where the parameters of the truncated normal distribution respectively correspond to the mean, variance, minimum value, and maximum value.

The parameter ρ_S was updated via a random walk Metropolis step. The tuning parameter was tuned to achieve an acceptance rate between 0.4 and 0.45.

The regression parameters, β, and latent variables, S, were updated jointly using GMRF full conditional sampling techniques outlined in Chapter 2 of Rue and Held (2005) [65]. To summarise, we define $\phi = (\beta, S)$ and so,

$$\boldsymbol{\phi}|P, \theta_{-\boldsymbol{\phi}} \sim \text{N}\left(\frac{1}{\sigma^2} V^{-1} A^T \log\left(P\right),\ V^{-1}\right)\ ,$$

where A is the design matrix and V the precision matrix for ϕ. We omit the

full specification of V^{-1}. To ensure V is singular, we enforce the linear constraint $\sum_i \phi_i = 0$. Sparse matrix methods combined with the algorithm for sampling from GMRFs under a linear constraint outlined on page 38 of Rue and Held (2005) were used to improve computational efficiency [65].

Inference

Inference was based on 2,000 independent samples obtained from 250,000 iterations of the algorithm with a burn-in of 50,000 and the remaining 200,000 thinned by a factor of 100 to remove any remaining autocorrelation. Convergence of the MCMC algorithm was established by the Gelman-Rubin convergence diagnostic calculated on three shorter chains to select a suitable length for the burn-in period. Trace plots, density curves, auto-correlation plots, and effective sample size (ESS) calculations were used to assess sufficient mixing of the final chain. The independent variables were standardised prior to model fit to reduce multicollinearity.

The unobserved data for years 2012 and 2013 (corresponding to years $t = 1, 2$) are treated as missing values in the response vector and are estimated each iteration of the MCMC algorithm according to the posterior predictive distribution:

$$\widehat{\log(P_{it})}|P \sim N\left(x_{it}^T\beta_0 + S_{it0},\, {\sigma^2}_0\right) \qquad t = 1, 2\ ,$$

where the subscript $_0$ has been used to denote the current values of the parameters at a given iteration.

2.6.2.4 Results

In preliminary runs of the MCMC algorithm, the temporal dependency parameter, ρ_T, was close to 1 (0.989), suggesting very strong temporal autocorrelation in the error process between NHS Digital data and the CDW. The model was repeated with ρ_T fixed at 1 which represents perfect temporal auotcorrelation. The Deviance Information Criterion (DIC), an indicator of model fit for hierarchical models, was equivalent (DIC=-7299) for the models with variable and fixed temporal dependency. Hence for sake of parsimony, we proceeded with the temporal parameter fixed at 1.

Model output

Table 2.7 shows the results of the model fit.

Table 2.7: Median parameter estimates, 95% credible intervals (CI), and effective sample size (ESS) for the spatio-temporal GP-registration model based on 2,000 independent MCMC samples.

Parameter	Coefficient	95% CI	ESS
ρ_s	0.353	(0.264, 0.450)	2000
σ^2	0.000173	(0.000144, 0.000207)	2138
τ^2	0.00263	(0.00226, 0.00303)	2000
β_0 (Intercept)	6.111	(6.088, 6.136)	1360
β_1 (log(CDW))	0.000839	(0.000817, 0.000860)	2000
β_2 (Year)	-0.0152	(-0.0173, -0.0130)	1535
β_3 (Missing GPs)	1.302	(1.203, 1.399)	2000

Figure 2.4 is a boxplot of the LSOA-level true GP-registered population; observed years are shaded in grey and the predicted years shaded in green. The predicted years are very similar to that of 2014. This is supported by census data over the same time period which shows a plateau in the total adult population between 2012-2014 (Figure 2.5). Although the census population is not identical to the GP-registered population, it is still a good indicator of overall trends [66].

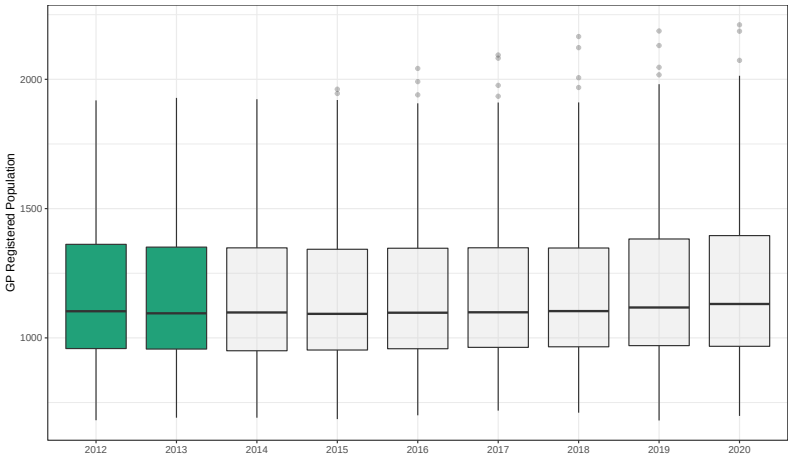

Figure 2.4: Spread of LSOA-level GP-registered adult (≥25) population from NHS Digital data for years 2014-2020 (shown in grey) and spatio-temporal model prediction results for years 2012-2013 (shown in green).

The predictive performance of the spatio-temporal model was by leave-one-out cross validation on the observed data (2014-2020). The mean absolute percentage error

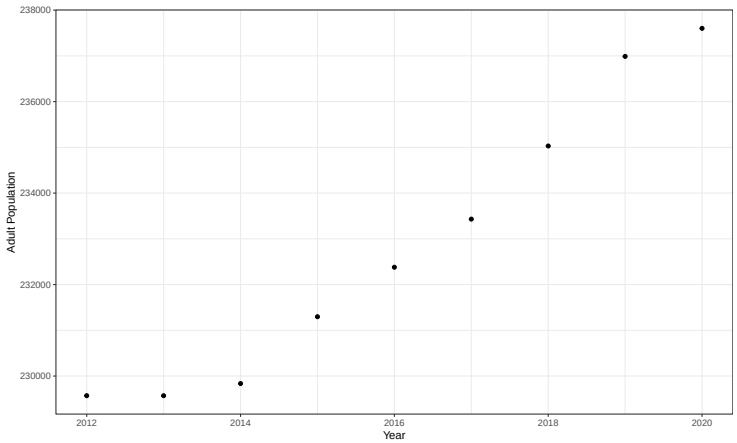

Figure 2.5: Total population size for the 204 study LSOAs according to ONS mid-year estimates.

(MAPE) was calculated for the predictions as well as the percentage of LSOA-level true values within the 95% credible intervals for the corresponding prediction (Figure 2.8). The model predicts well for years 2014-2019, with a maximum of three LSOAs falling outside the 95% CI. The year 2020 performs considerably worse compared to the others, likely due to impact of the COVID-19 lockdown on movement of people and GP registration behaviour.

Table 2.8: Mean absolute percentage error (MAPE) and proportion of true values that are within the 95% credible interval (CI) for each year predicted.

Year predicted	MAPE	LSOAs in 95% CI
2014	1.81	202 (99.0%)
2015	1.14	202 (99.0%)
2016	1.21	204 (100.0%)
2017	1.02	204 (100.0%)
2018	1.11	201 (98.5%)
2019	1.36	202 (99.0%)
2020	3.28	168 (82.4%)

MCMC diagnostics

Figures 2.6-2.8 show the traceplots and density curves for the parameters in the model and a subset of the latent variables. The ESS for the model parameters can be seen in Table 2.7, and the ESS for the latent variables had a median of 2,000 and a minimum of 1,104.

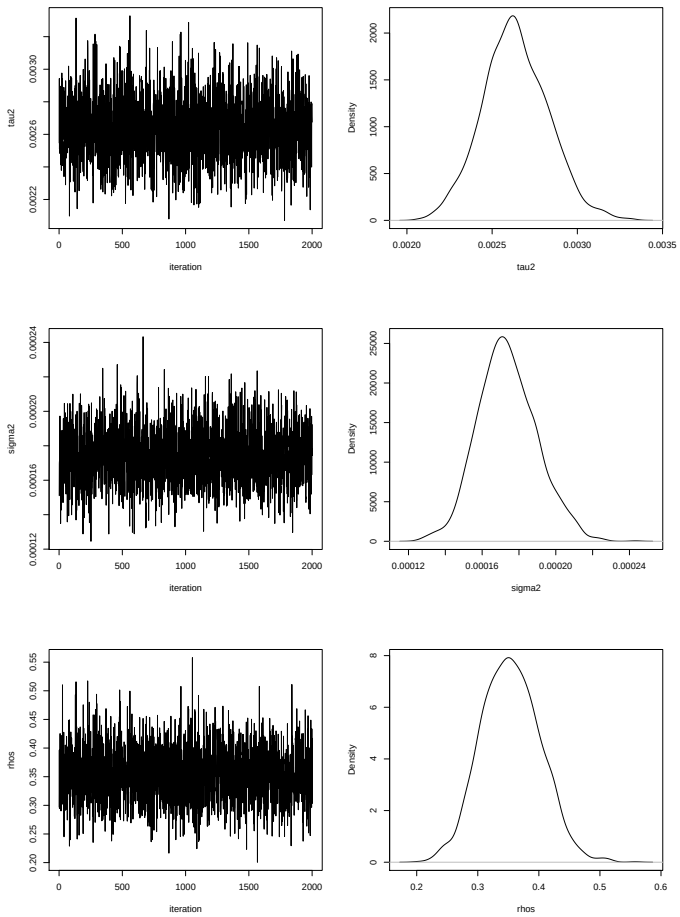

Figure 2.6: Diagnostic traceplots and density curves for $(\tau^2, \sigma^2, \rho_s)$ in the spatio-temporal GP registration model.

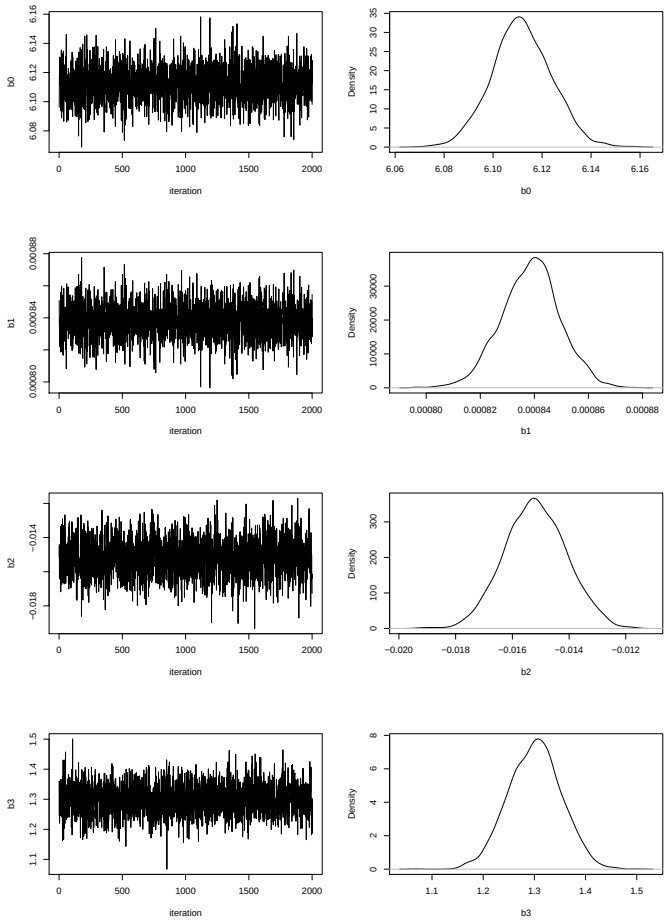

Figure 2.7: Diagnostic traceplots and density curves for the $\boldsymbol{\beta}$ parameters in the spatio-temporal GP registration model.

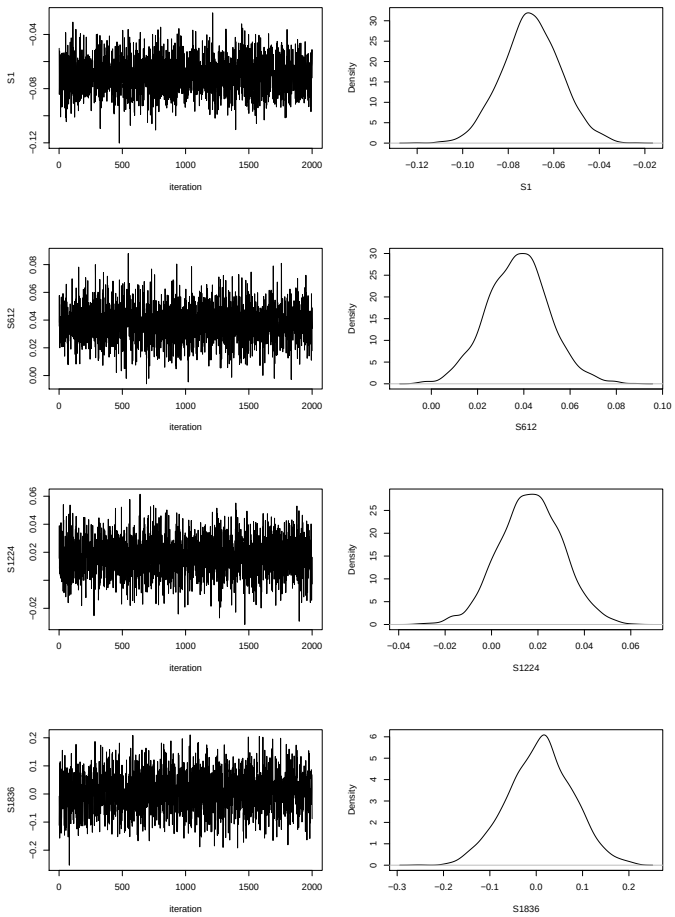

Figure 2.8: Diagnostic traceplots and density curves for a subset of the $\boldsymbol{S}$ latent variables in the spatio-temporal GP registration model.

2.6.3 Outpatient referrals model

This section supplements the main article by providing additional details of the GLMM for outpatient referrals. We first present exploratory data analysis results before describing the specifics of the MCMC algorithm used for model fit. The material is assumed to be read in conjunction with the main article.

2.6.3.1 Exploratory data analysis

Table 2.9 provides a summary of the variables used in the referrals model, including data source, general description, and additional notes.

Response variable

Figure 2.9 shows the time trend in the raw referral counts data by MBRN intervention status. For the sake of this figure, we dichotomiose the MBRN covariate so that an LSOA is classed as 'MBRN' if the proportion of the population registered at an MBRN GP $\geq 50\%$ and 'Non-MBRN' otherwise. Prior to the initiation of the MBRN, the time trends are quite similar between the two groups. Post-initiation, the MBRN areas show a dramatic decrease in annual number of referrals whilst non-MBRN areas continue in an upward trend. However, the patterns in this plot do not account for population growth or changes in the demographic or health structure of the populations.

Table 2.9: Description of variables used in the random intercept model of referrals to outpatient respiratory clinics.

Variable	**Time varying (Y/N)**	**Source**	**Description**	**Notes**
Outpatient referrals	Y	CDW (secondary care records)	Annualised count of number of referrals to outpatient respiratory clinics	New referrals from GP, for adults aged 25+ years residing within MBCCG boundaries. Clinic inclusion: respiratory, spirometry, lung, or oxygen clinics; nurse or consultant led; at Royal Lancaster Infirmary, Furness General Hospital, or Westmorland General Hospital. Clinic exclusion: post-op, rheumatology, physio, asthma biologics, or sleep clinics, and 2-week-wait cancer referrals.
CRD patients	Y	NHS Digital and spatio-temporal model output	Annualised count of number of patients with an asthma, COPD, bronchiectasis, or ILD diagnosis	Patients identified by relevant asthma, COPD, bronchiectasis, and ILD SNOMED CT codes. Additional criterion for asthma diagnosis is an inhaler prescription in the last 12 months.
Age	Y	ONS (mid-year estimates)	Percentage of adult (25+ years) population in a given age bracket.	Age brackets '65-74' and '75+' are used; covariate selection methods suggests these are the only relevant age groups.

Sex	Y	ONS (mid-year estimates)	Percentage of adult (25+ years) population that are male	
IMD score	Y	Ministry of Housing, Communities & Local Government	Index of Multiple Deprivation (IMD) score from English Indices of Deprivation	The IMD is update every 3-4 years. The mean of the 2015 and 2019, the two publications within the study period, indices was taken.
Distance to hospital	N	OSMR	Travel distance (km) by car to the nearest hospital within the MBCCG	Hospitals considered: Royal Lancaster Infirmary, Furness General Hospital, and Westmorland General Hospital. Distances were calculated using open source routing software in R Studio. Distances were calculated for all 11,594 (as of 14/01/22) postcodes in the study area and then averaged by LSOA.
Year	Y	NA	Factor variable form of year	Factor form used as opposed to continuous to better study the evolution of the MBRN in the three years since initiation.

MBRN intervention	Y	NHS Digital	Percentage of GP-registered population registered at an MBRN GP	This is calculated for each year regardless of whether the MBRN was yet active in order to account for baseline differences in the areas that have and have not received MBRN intervention. For study years prior to MBRN introduction (2012-2016), the covariate is calculated as the percentage of the population registered at a GP that goes on to join the MBRN in 2017. Percentage calculated using LSOA-level GP registration data released by NHS Digital. We do with calculations with all-age data and assume this variable not to be correlated with age. As with the 'GP-registered population' variable, mean taken across quarters. For the study years 2012 and 2013, the 2014 value is used. Exploratory analysis suggests numbers registered at each GP does not fluctuate year-on-year.

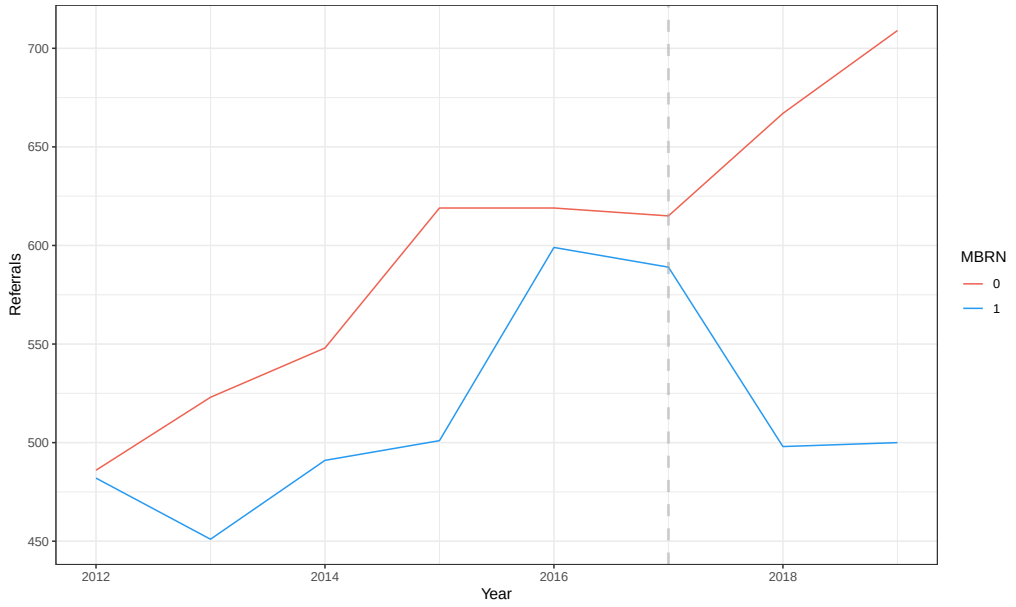

Figure 2.9: Annual number of referrals for intervention and non-intervention areas. The MBRN covariate has been dichotomised at the 50% mark. The grey dashed line represents the introduction of the MBRN in 2017.

Explanatory variables

Table 2.10 provides summary statistics of the covariates used in the final model for referrals to outpatient respiratory clinics.

Table 2.10: Summary of model covariates over all space-time units. All values are percentages, except the distance variable which is in kilometres.

	Min	**1st quartile**	**Median**	**Mean**	**3rd quartile**	**Max**
65-74	4.40	13.73	16.42	16.88	20.52	32.70
75+	2.33	9.90	13.54	14.09	16.79	34.71
Male	40.19	46.63	47.88	48.20	49.43	65.66
Distance	0.87	3.31	6.81	9.42	13.27	38.16
IMD	3.62	10.84	16.72	22.62	29.19	77.84
MBRN	0	0.20	51.46	50.93	99.90	100.00

Table 2.11 shows the change in mean of all time-varying covariates: both age variables show a mostly increasing trend, indicative of an ageing population, and percentage male has increased marginally. The proportion of the population registered at a GP that joined the MBRN in 2017 remained mostly constant between 2014-2017 before increasing in 2018. MBRN coverage is unobserved for study years

2012 and 2013 as NHS Digital did not release LSOA-level data until 2014. In the final model, we assume the 2012 and 2013 values to be equal to 2014. Note that IMD is not included in Table 2.11 since it is not time varying.

Table 2.11: Mean of time varying GLMM covariates by study year.

Year	**65-74**	**75+**	**Male**	**MBRN**
2012	16.0	13.5	48.0	-
2013	16.5	13.7	48.0	-
2014	16.8	13.9	48.0	50.7
2015	17.0	14.0	48.3	50.7
2016	17.2	14.1	48.3	50.8
2017	17.3	14.2	48.3	50.8
2018	17.2	14.5	48.4	51.4
2019	17.1	14.8	48.4	51.6

Figures 2.10 and 2.11 both illustrate the spread of the MBRN. Since the MBRN covariate is time-varying we used 2017 data only for these plots. The MBRN covariate is defined as percentage of the total population (Table 2.10), yet 84% of the data points are either less than 1% or greater than 99%, with an overall median of 51.5% (Figure 2.10). Lancaster is the only area that has had widespread full coverage (Figure 2.11), this is because all GPs in this area are part of larger, multi-site practices. The LSOAs with 0% coverage account for a greater proportion of the MBCCG spatially speaking, due to the differences in population density (illustrated by the sizes of the LSOAs), and yet phase 1 of the MBRN reached 50% of the total MBCCG population.

Overdispersion

We first considered a Poisson GLM to model referrals, with covariates included as described in the main article. The model was overdispersed ($\text{mean}(Y_{it}) = 5.5 < 10.0 = \text{var}(Y_{it})$; residual deviance $= 2092 > 1707 = q(0.95, df = 1612)$ and random effects models were next considered. An analysis of the residuals did not suggest any significant spatial or temporal correlation. Moran's I statistic was insignificant for study years 2012-2017 and suggested only a weak spatial correlation at the 5% significance level for 2018 and 2019 (Moran's I = 0.10 and 0.15 respectively). Therefore, it was concluded that a more complex spatial correlation structure was not necessary and an independent random intercept model was used.

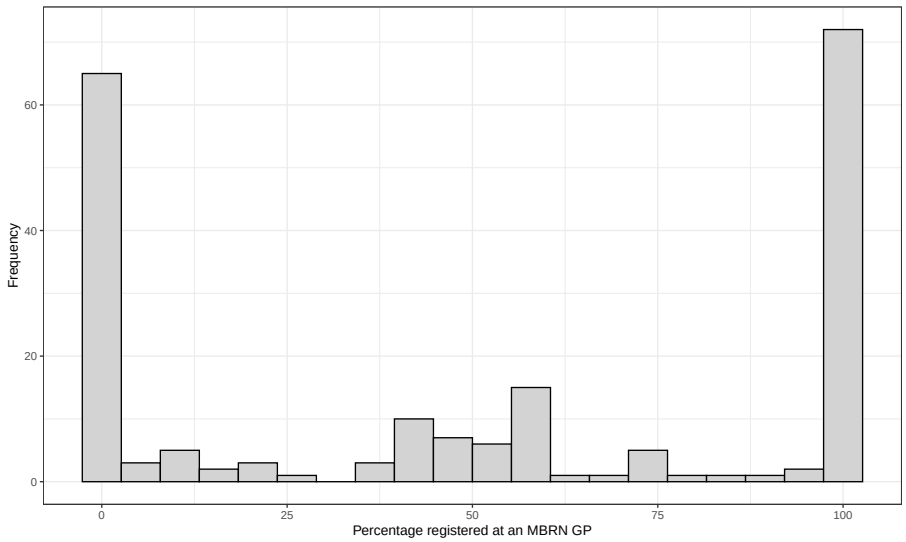

Figure 2.10: Histogram showing the distribution of the proportion of the popualtion registered at an MBRN GP in 2017.

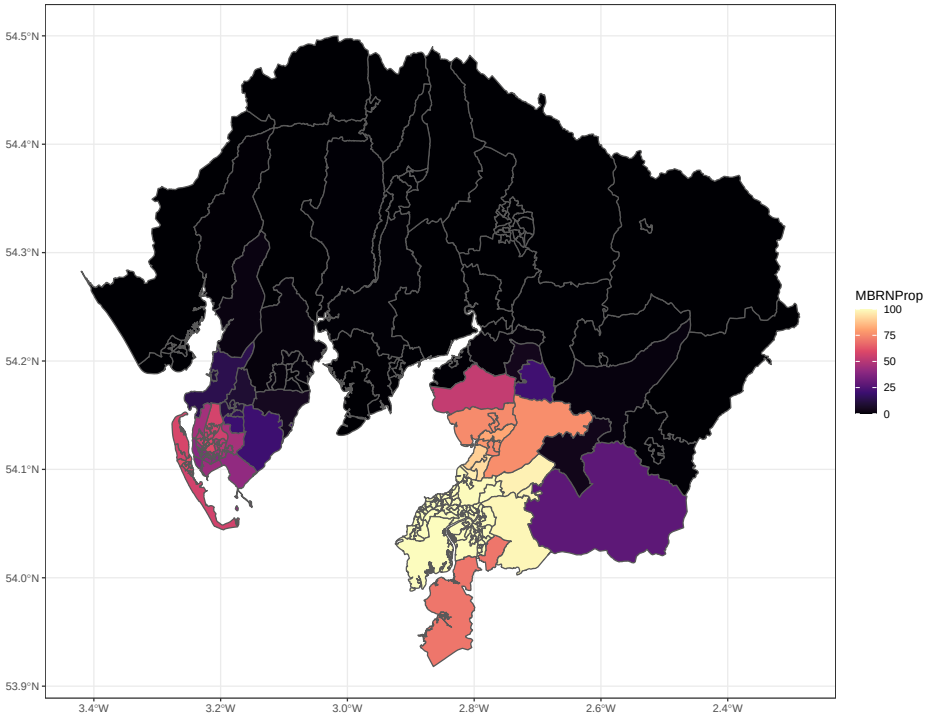

Figure 2.11: Choropleth map of percentage of LSOA population registered at a GP that joined the MBRN in 2017.

2.6.3.2 MCMC methodology

Prior distributions:
The random effects, Z_i $(i = 1, \ldots, N)$, act as latent variables and have independent Normal$(0, \kappa^2)$ priors, as described in the main article. For the remaining parameters, the following priors were used:

$$\begin{aligned} \kappa^2 &\sim \text{Gamma}\,(a, b) \\ \gamma &\sim \text{N}\left(0, \lambda^2 I\right) \ , \end{aligned}$$

where $a = 1$, $b = 0.01$, $\lambda^2 = 1000$, and I_p is a p-dimensional identity matrix with p being the number of regression parameters in the referrals model.

Posterior distribution:
Let $\theta = (\gamma, Z, \kappa^2)$ be the vector of parameters to be estimated. The joint posterior distribution is:

$$\begin{aligned} \pi\left(\theta|Y\right) \propto \exp &\left(\sum_{i=1}^{N} \sum_{t=1}^{T} \left[y_{it}^T d_{it} \gamma + y_{it}^T z_i - \exp(\log(R_{it}) + d_{it}\gamma + z_i) \right] \right) \\ &\times \left(\kappa^2\right)^{-N/2} \exp\left(-\frac{1}{2\kappa^2} \sum_{i=1}^{N} z_i^2 \right) \\ &\times \pi(\kappa^2, \gamma) \ , \end{aligned}$$

where $\pi(\kappa^2, \gamma)$ represents the corresponding prior distributions.

Updating algorithms:
The parameter κ^2 was updated via a Gibbs sampler according to the its full conditional posterior distribution:

$$\kappa^2 | Y, \theta_{-\kappa^2} \sim \text{Inverse-Gamma}\left(a + \frac{N}{2},\ b + \frac{1}{2} \sum_{i=1}^{N} z_i^2 \right) \ .$$

The regression parameters, γ, and latent variables, Z, were updated jointly. If we let $\psi = (\gamma, Z)$, the posterior distribution for ψ is:

$$\pi(\psi|Y, \kappa^2) \propto \exp\left(-\frac{1}{2}\psi^T Q \psi + Y^T B \psi - \mathbf{1}^T \exp(\log(R) + B\psi) \right) \ , \tag{2.3}$$

where Q is a diagonal matrix of the prior precision and B is the design matrix for ψ. The distribution in (2.3) does not have a tractable form but can be approximated to a GMRF using the methodology in e.g., Chapter 4 of Rue and Held (2005) [65]. The GMRF approximation, which we will denote by $q(.)$, is then used as a proposal distribution in a Metropolis-Hastings step.

We omit the full calculations, but in brief, the approximation uses a second-order Taylor's expansion of the log of the posterior in (2.3) about the current value of ψ, say ψ_0. Then,

$$\pi(\psi|Y,\kappa^2) \approx q(\psi|Y,\kappa^2,\psi_0) \propto \exp\left(-\frac{1}{2}\psi^T C\psi + b\psi\right) \sim N\left(C^{-1}b, C^{-1}\right) \ ,$$

where the matrix C and vector b are functions of ψ_0:

$$\begin{aligned} b &= \left(\log \pi(\psi_0|Y,\kappa^2)\right)' - \left(\log \pi(\psi_0|Y,\kappa^2)\right)'' \psi_0 \\ C &= -\left(\log \pi(\psi_0|Y,\kappa^2)\right)'' \ . \end{aligned}$$

To improve the accuracy of the approximation, the expansion is repeated, with each successive expansion performed around the mean of the previous approximation i.e. the first expansion is around ψ_0, the second expansion is around $\mu_1 = C^{-1}(\psi_0)b(\psi_0)$, the third expansion is around $\mu_2 = C^{-1}(\mu_1)b(\mu_1)$, and so on. Preliminary runs of the algorithm found five expansions to be sufficient. Once the approximation is complete, a proposed value, say ψ^*, can be sampled from the GMRF according to the same methodology in Section 2.6.2.3. As with the spatio-temporal GP registration model, we impose the linear constraint $\sum_i \psi_i = 0$ to ensure the precision matrix of the GMRF is invertible.

The acceptance probability of the Metropolis-Hastings step is,

$$\alpha = \min\left\{1, \frac{\pi(\psi^*|Y,\kappa^2)q(\psi_0|\psi^*)}{\pi(\psi_0|Y,\kappa^2)q(\psi^*|\psi_0)}\right\} \ .$$

Note that the above also requires a Taylor's expansion of $\pi(\psi^*|Y,\kappa^2)$ around ψ^* in order to evaluate $q(\psi_0|\psi^*)$. This is also iterated to improve the accuracy.

Finally, at each iteration of the MCMC algorithm, we randomly sample from the posterior predictions of P_{it}^{NHS} for study years 2012 and 2013, and update the offset term according to the correction formula in Section 2.2.3.1. Using this method, we

use the entire posterior predictive sample, as opposed to a point estimate such as the mean of the sample, and thus account for the uncertainty in the predictions.

Inference

Inference was based on 2,000 independent samples obtained from 25,000 iterations of the algorithm, with a burn-in of 5,000 and the remaining 20,000 thinned by a factor of 10. Similarly to the registration model, convergence was established by the Gelman-Rubin convergence diagnostic. Trace plots, density curves, auto-correlation plots, and ESS calculations were used to assess sufficient mixing of the chain. Continuous explanatory variables were standardised prior to model fit to reduce multicollinearity.

2.6.3.3 MCMC diagnostics

Figures 2.12-2.14 show the traceplots and density curves for the parameters in the model. Since there are 21 regression coefficients and 204 latent variables, only a subset of the plots are displayed. The ESS for κ^2 was 1,432. The ESS for the regression coefficients had a median of 2,000 and a minimum of 1,863, and the latent variables had a median of 2,000 and a minimum of 1,231.

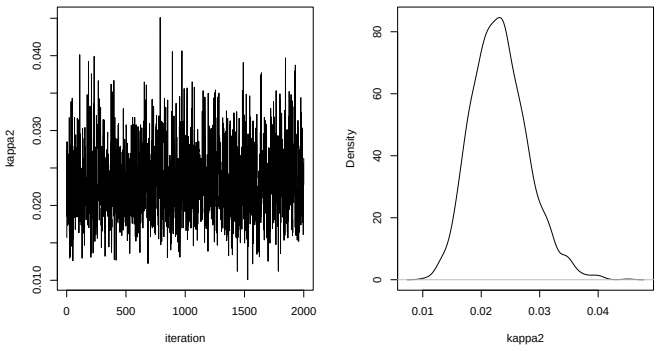

Figure 2.12: Diagnostic traceplots and density curves for κ^2 in the random intercept outpatient referrals model.

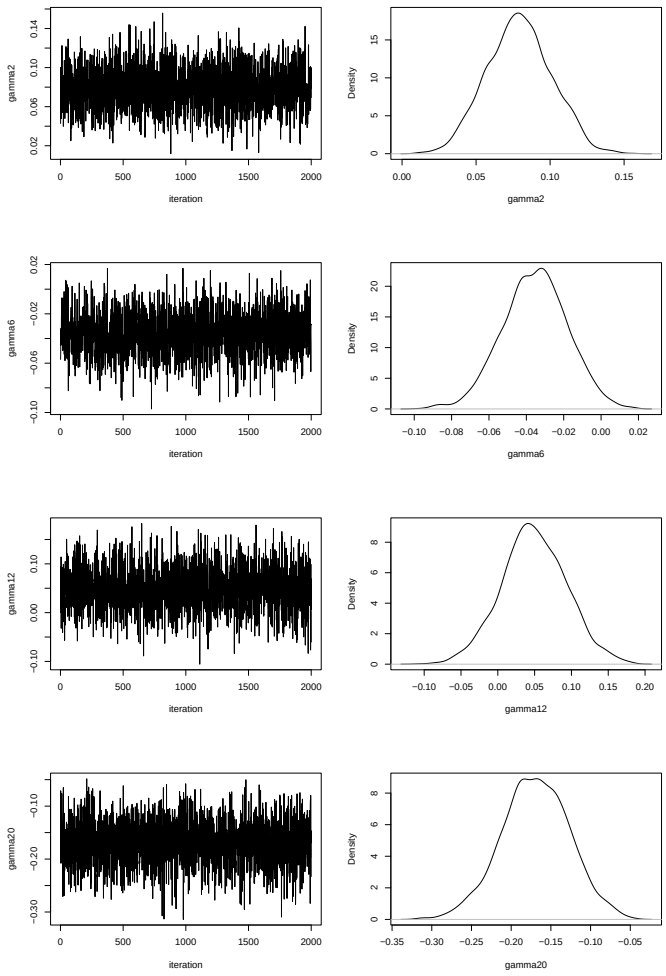

Figure 2.13: Diagnostic traceplots and density curves for a subset of the regression coefficients, $\boldsymbol{\gamma}$, in the random intercept outpatient referrals model.

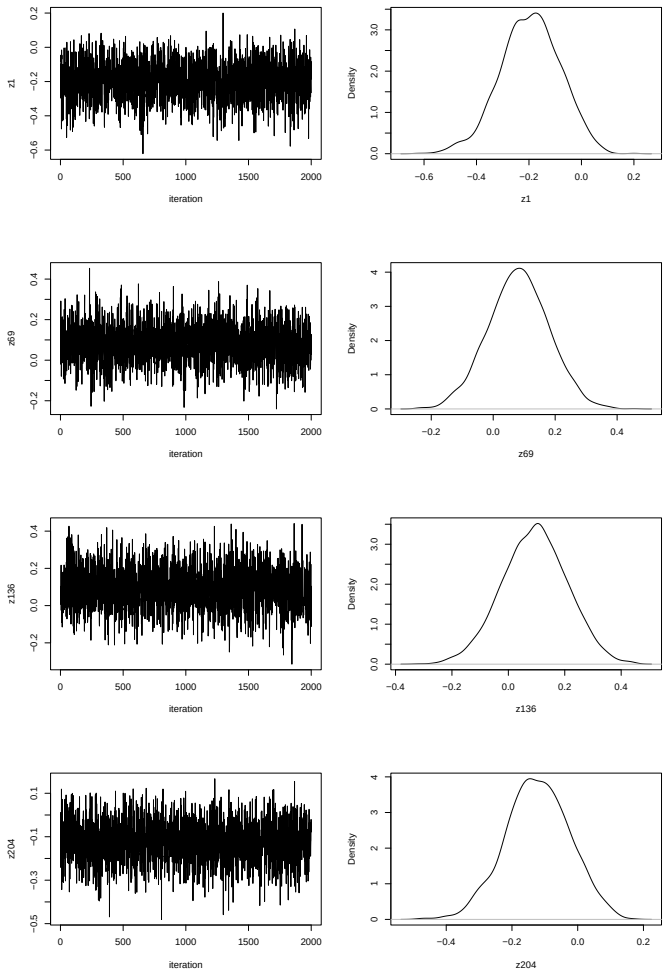

Figure 2.14: Diagnostic traceplots and density curves for a subset of the $\boldsymbol{Z}$ latent variables in the random intercept outpatient referrals model.

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Chapter 3

Measuring diagnostic quality: The capacity of routinely collected data and the role of integrated care initiatives

Alternative title: Ulysses

3.1 Research letter

Measuring diagnostic quality using routinely collected data

In preparation for submission

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3.1.1 Introduction

The demand on diagnostic services in England has risen year-on-year. The National Health Service (NHS) has identified the need for radical investment and reform of diagnostic services, both to prevent missed or delayed diagnoses, and to transform the process itself that can be duplicative and inefficient. New service delivery recommendations emphasise virtual consultations and community diagnostics to relieve pressure on acute services, an issue only exacerbated by the COVID-19 pandemic. There is considerable focus on the robust diagnosis of respiratory disease, with targets to reduce variation in spirometry testing nationally through improved training of primary care personnel.

However, there is currently no widely accepted approach for evaluating diagnostic performance. Measuring diagnostic quality must consider more than whether the final diagnosis is correct, but also the efficiency, timeliness, and rigorousness of the process. There is opportunity for advanced analytic methods able to incorporate a spectrum of information and account for the dynamic nature of the diagnostic process. Such methods would require appropriate input data sources with clinically rich information and linkage across healthcare tiers [1].

Routinely collected health data holds huge potential for clinical research. Each patient interaction presents an opportunity to improve services and standard of care through data-driven analytics. However, the nature of routine data can limit its applications in research. The availability and quality of all variables required for analysis must first be assessed to evaluate the capacity of the data in answering the intended research question.

Existing literature recognises the challenges of using routine data for evaluating diagnostics due to incomplete and erroneous coding, with an emphasis on the critical role of physicians in influencing the quality of routine data for research purposes [2, 3]. This study aimed to extend the discussion of the suitability of routine data for measuring diagnostic quality by considering the problem in the context of a specific data source and disease area. We aimed to illustrate key barriers using electronic health records (EHRs) from the Morecambe Bay Community Data Warehouse (CDW) applied to chronic respiratory disease (CRD).

3.1.2 Methods

This report retrospectively analysed primary and secondary care data from the Morecambe Bay CDW, an SQL Server owned by the University Hospitals of Morecambe Bay NHS Foundation Trust. The CDW uses pseudonymised NHS Numbers to individually link healthcare data across the Morecambe Bay, north-west England, covering 3 hospitals, 32 general practices (GPs), and a population exceeding 360,000. Patient demographic information was obtained from GP records.

CRD diagnoses (asthma, chronic obstructive pulmonary disease [COPD], bronchiectasis, and interstitial lung disease [ILD]) were identified from GP records by the first recording of a relevant SNOMED diagnosis code between 01/07/18-30/06/23. Only patients aged ≥35 years at time of diagnosis and with ≥12 months of continuous medical records prior to diagnosis were considered. If an individual had more than one CRD diagnosis, these were treated as distinct events.

For each qualifying diagnosis, we extracted potential events in the diagnostic pathway in the six-month period prior to diagnosis. By 'diagnostic pathway', we are referring to the chain of events leading up to diagnosis. We obtained information for: respiratory symptoms (cough, wheeze, dyspnoea, sputum, chest pain, fatigue, and weight loss) recorded in GP records using SNOMED codes; diagnostic tests conducted in both primary and outpatient care settings, using SNOMED codes and procedure names respectively; and secondary care utilisation, specifically outpatient respiratory clinic attendance, inpatient admissions using ICD-10 codes, and emergency department visits with mention of respiratory problems. All SNOMED and ICD-10 codes used in this research are available at: `https://doi.org/10.17635/lancaster/researchdata/651`.

Exploratory analysis was performed to evaluate the quality of the data.

3.1.3 Results

A total of 5,922 CRD diagnosis events (43.4% COPD, 32.9% asthma, 13.6% bronchiectasis, 10.1% ILD) from 5,435 individuals were included in this study. Table 3.1 summarises the data findings including stratification by diagnosis.

Table 3.1: Summary of extracted data variables for CRD diagnoses. All figures are percentages unless specified otherwise.

	All (n=5,922)	**COPD (n=2,573)**	**Asthma (n=1,949)**	**Bronchiectasis (n=803)**	**ILD (n=597)**
Demographics					
Age (mean ± s.d.)	65.4 ± 13.3	66.3 ± 12.1	59.4 ± 13.6	71.4 ± 11.2	72.5 ± 11.8
Male	49.9	50.3	44.3	51.2	64.2
Symptom information					
Dyspnoea	36.1	38.4	31.1	38.9	39.4
Cough	22.2	22.4	21.5	27.0	16.9
Sputum	14.4	16.2	10.0	21.2	11.9
Wheeze	12.7	12.0	17.3	10.3	4.2
Other [a]	8.0	9.4	4.8	9.7	9.5
Symptom absence	17.4	17.6	18.3	16.9	14.1
None	47.5	47.0	49.9	44.0	46.2
Selected diagnostic tests					
Blood test	63.6	65.3	53.1	74.7	76.2
Chest x-ray	41.1	44.0	31.0	53.1	45.4
Spirometry [b]	36.1	41.3	36.5	26.8	24.3
Peak expiratory flow	34.4	35.0	34.9	27.8	39.5
Oximetry	32.2	31.5	28.3	39.0	39.2
Reversibility [b]	23.2	28.4	24.6	13.6	9.5
Other lung function	22.6	27.8	19.6	21.4	38.4
Other	4.0	2.8	2.2	9.5	7.7
None	17.1	15.0	25.2	10.1	8.5
Secondary care utilisation					
Outpatient clinic	26.3	22.4	12.6	44.2	63.5
Inpatient admission	17.1	17.9	8.9	23.7	32.0
Emergency department	9.3	10.3	6.0	11.8	11.7
None	60.8	62.6	78.6	41.3	21.1

[a] 'Other' symptoms are chest pain, fatigue, and weight loss.
[b] Spirometry is any evidence of spirometry being carried out whereas reversibility is when the spirometry has been specified as post-bronchodilation.

Symptom recording

Almost half of diagnoses had no SNOMED-coded symptom information in the six months prior to diagnosis. Absence of symptoms cannot safely be inferred from absence of symptom recording. Other explanations include incomplete data recording, symptoms were not discussed, or an incidental diagnosis occurred following an unlinked medical event. The explicit recording of symptom absence was low, only 17.4%.

Removing patients without symptom information recorded from further analysis could induce bias by excluding milder or asymptomatic cases. Less obvious bias may result from demographic variability due to differences in data recording by GP sites. When aggregated at GP-level, the percentage of diagnoses without symptom information ranged from 30.1%-83.7%.

Diagnostic tests

At least one diagnostic test was identified for 82.9% of diagnoses, but issues arise with interpreting results. X-ray imaging was the second most common test ordered prior to CRD diagnosis with highest rates seen for bronchiectasis. However, scan imagery and associated reports are not available in the CDW to interpret results. Descriptive SNOMED codes such as 'Chest x-ray abnormal' exist yet lack clinical detail and had only been used in 4.9% of chest x-rays.

There was evidence of post-bronchodilator spirometry ('reversibility') for 28.4% of COPD diagnoses. Yet only 50.3% of this group had numeric results for both pre- and post-bronchodilation stored under explicit and easily identifiable SNOMED codes (e.g., 'Forced expiratory volume in one second/forced vital capacity ratio before[after] bronchodilator'). In 23.0% of cases, numeric results were missing altogether, potentially recorded in free text.

There is lack of data pertaining to the motivation for a diagnostic test. Blood tests were the most common test ordered, yet these could have been ordered for purposes other than CRD diagnosis.

Forming care pathways

We present evidence of care across the healthcare tiers. In total, 39.2% of diagnostic pathways included secondary care services with higher percentages observed for rarer diseases. However, the CDW does not contain free text fields, referral letters, or clinician reports. Without a connecting narrative, there is uncertainty in which healthcare events are part of the same chain of care and have contributed toward a diagnosis, similar to the issue of motivation behind diagnostic tests.

Suspected cases

Our analysis only included cases that result in diagnosis. However, we can infer that identifying suspected cases (where a patient is suspected of having a disease but is not diagnosed either because the diagnosis was ruled out or the patient was not adequately followed up) presents a challenge. There are SNOMED codes for 'Suspected asthma' and 'Suspected COPD', but these had only been used in 13.6% and 6.4% of asthma and COPD diagnoses respectively. No equivalent codes exist for the rarer diseases, bronchiectasis and ILD. Other variables could act as proxies, including diagnostic tests, symptoms, referrals, or a combination, but there are other conditions for which such events could apply.

3.1.4 Discussion

This report has evaluated and illustrated the capacity of routinely collected health data for measuring diagnostic quality using examples from the Morecambe Bay CDW and CRD. Routine health data holds huge potential to provide feedback for transforming diagnostic services to meet increasing demand and improve standard of care. However, by exploring data quality in a specific setting we have identified data-level barriers that must first be addressed to assess diagnostic performance. These issues also generalise beyond the scope of this project. The issues identified can be broadly grouped into two themes: data recording practices and data access barriers.

Data recording

Data with rich clinical information such as GP observations will be essential to understanding diagnostic quality [1]. However, our findings support previous literature that there are fundamental problems at the data recording level [2, 3, 4]. Without consistent and high-quality data recording, both over time and between GPs, we are unable to distinguish incomplete data collection from incomplete diagnostic pathways. Standardising data recording practices in primary care will be paramount to facilitating high-quality evidence-based health services research and we present specific recommendations regarding standardisation.

First, standardisation is needed in terms of the information to be recorded for each diagnosis. The consideration of symptoms is a likely first event in a diagnostic pathway, yet our results show this information is substantially under-recorded in primary care, particularly symptom absence. Other potentially key information, including commentary on scan imagery and codes indicating suspected disease face similar barriers of inconsistent usage.

Second, standardisation regarding the specific SNOMED codes used. SNOMED is the most comprehensive clinical terminology product globally and a critical tool for research with primary care EHRs. However, the hierarchy of the coding system creates multiple ways of recording similar information. The use of ambiguous codes can lead to misclassification by a researcher, or the information being missed altogether [4], as illustrated by post-bronchodilation spirometry results.

Data access

Access to individually linked data will be crucial to the task of measuring diagnostic quality [1]. Health data research in England is moving in the direction of wider access to individually linked data with recommendations outlined in the Goldacre Review and the recent funding of NHS Secure Data Environments to centralise health data sub-nationally. This study supports existing recommendations by demonstrating the proportion of diagnostic pathways that traverse healthcare tiers. The fragmentation of data across different health systems is an established barrier to research with routine data and prevents a full picture of patients' healthcare journeys [5].

Unstructured data, including free text fields, narrative reports, and referral letters, is needed to improve clarity and completion of the diagnostic pathway, yet access to

unstructured data is often limited to researchers in accordance with information governance. We recommend the further development of methods for drawing structured data from free text, such as natural language processing (NLP). NLP could be used both to withdraw information from historical data to supplement gaps in structured data, including clinical motivation and narrative to link events, as well as implemented in current EHR systems to support real-time coding of structured data to improve usage of correct clinical coding [2, 6].

Limitations

In this study, diagnosis events were identified by the first recording of a relevant SNOMED diagnosis code. This method was selected based on previous validation studies for identifying respiratory disease patients from EHRs, yet these studies deal only with whether the patient has the disease in question, and not the precise time of diagnosis. Patients can be treated for a condition before a diagnosis code is recorded. Alternatively, a code may be recorded when it is in fact only a working diagnosis due to financial incentives such as the Quality and Outcomes Framework (QOF) in England. Suspected disease SNOMED codes do not qualify for QOF patient registers, a possible explanation for their low usage in our data. This source of uncertainty is a limitation of our study. Since we look at the six months prior to diagnosis, our results may change under different definitions of time of diagnosis. However, it is also an issue beyond the scope of this study and the problem links into the data recording theme. Established coding practices combined with validation studies are required for accurately identifying time of diagnosis in EHRs [7]

Other limitations include the fact that the data explorations have been kept brief and more patterns in the data could be uncovered by exploring relationships with, for example, age, sex, and time. Second, we used a 5-year study period which covers the COVID-19 pandemic, a time of significant disruption to healthcare services. However, both pre- and post-pandemic data is included to minimise bias. Finally, we have focused on a specific case study and have not explored the generalisability of our results to other routine data sources or disease areas.

3.1.5 Conclusion

Measuring diagnostic quality using routinely collected data will require improvements in data recording and data access. A standardisation of data recording practices in primary care is needed to promote consistent, high-quality, and easily interpretable data. However, even with perfect coding, structured EHRs leave gaps in the diagnostic pathway. Unstructured data present in healthcare documents combined with NLP methodology may provide solutions.

This study demonstrates the importance of effective feedback loops between researchers and healthcare professionals for increasing the capacity of routine data for research. It is critical to provide those on the frontlines of data collection with an understanding of how data will appear in EHR databases, targeted areas for recording improvement, and motivation of what could be achieved with better data.

3.2 A report to the Morecambe Bay Respiratory Network

The capacity of routinely collected data to measure diagnostic quality and evaluate the impact of integrated care: A report to the MBRN

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Executive summary

The NHS Long Term Plan outlines aims to improve the robust recognition and diagnosis of respiratory disease, with a focus on reducing the variation in access to spirometry testing. Broader NHS agenda is increasingly centred on community-based care through new service delivery models to relieve pressure on acute services.

The Morecambe Bay Respiratory Network (MBRN), an integrated care initiative in the Morecambe Bay area, has targeted improved diagnostic standards. The MBRN's service model allows a higher standard of clinical care closer to home through an enhanced primary care service, whilst streamlining access to specialist services via monthly multidisciplinary team meetings. It was hoped that this thesis would be able to evaluate the MBRN's impact on patient diagnostic pathways.

The main findings of this report presented in Section 3.2.3 detail the barriers encountered in using routine data from the Morecambe Bay Community Data Warehouse (CDW) to measure diagnostic quality. The discussion is structured by topic, including constructing diagnostic pathways, symptoms, and diagnostic tests. To aid in extending our findings to other field of research, we additionally propose a thematic framework:

- **Data recording** – foundational issues at the recording level, specifically how data is inputted into electronic health records by general practitioners.
- **Data access** – limitations arising from data availability.
- **Broader study design considerations** – such as the impact of COVID-19.

Despite the limitations encountered, Section 3.2.4 presents findings from the data relevant to MBRN stakeholders. These results are exploratory only but are provided to demonstrate the often-unconsidered potential of integrated care initiatives to facilitate greater research capacity of routine data via standardisation of care pathways and promoting high-quality data recording practices.

The report concludes with recommendations for future research into diagnostic quality, specifically standardising data recording practices in primary care, validation studies for time of diagnosis, and access to free-text data for insight into the complexities of the diagnostic process. Regarding the MBRN, access to MDT data linked with patient records will be critical for future evaluations of the intervention.

3.2.1 Introduction

The NHS Long Term Plan identifies the need for radical investment and reform of diagnostic services to not only prevent missed or delayed diagnoses but also to transform the diagnostic process itself that can be duplicative and inefficient [8]. The demand on diagnostic services has risen year on year with a knock-on effect to waiting times, an issue only exacerbated by the COVID-19 pandemic [9]. Recent NHS England reports outline recommendations for new service delivery models with an emphasis on virtual consultations and community diagnostics to relieve pressure on acute services [10]. There is considerable focus on the robust recognition and diagnosis of respiratory disease, with targets to reduce the variation in the quality of spirometry testing across the country through improved training of personnel in primary care [8].

The Morecambe Bay Respiratory Network (MBRN)

The key component of the MBRN integrated care service model is to enhance and upskill primary care teams to provide a higher level of clinical care to patients. The following elements specifically relate to diagnostics:

- Multidisciplinary team (MDT) meetings – primary care is supported by secondary care expertise and expanded community teams via monthly MDT meetings where patients are discussed from diagnostic and management perspectives. Specialist input is received at an earlier stage in the patient pathway, improving diagnostic accuracy as well as service efficiency by reducing inappropriate referrals.

- Direct referrals – GPs have direct access to lung function testing. This means that GPs can refer directly to lung function clinics rather than first referring to a respiratory medicine clinic, then the patient receiving an onward referral for testing. The aim is to improve the efficiency of the diagnostic process by ensuring patients have all appropriate tests completed before being discussed at an MDT or seen in clinic if necessary.

- Diagnostic template – the MBRN diagnostic template covers key areas of diagnostic relevance for chronic respiratory disease (CRD) namely symptoms, medical and family histories, risk factors, diagnostic tests, and follow up

plan. Usage of the template should aid in standardising diagnostic practice across GPs and improve diagnostic accuracy by ensuring all clinically relevant features are considered. A copy of the template can be found in Appendix A.1.

- Training – alongside the informal training opportunities through the MDT meetings GPs receive additional training and education via the MBRN, including in spirometry.

Project background

An original aim of this thesis was:

"Using national standards and guidelines, develop classification algorithms to understand the features of diagnostic quality for the four main CRDs (asthma, chronic obstructive pulmonary disease [COPD], bronchiectasis, and interstitial lung disease [ILD]). Identify areas of good practice and areas that may require improved training in respiratory care and support from population health strategies."

In brief, to achieve this aim we planned to develop an algorithm that identifies from the data key risk factors, symptoms, tests results, and other healthcare interactions, that are associated with each of the four main CRD diagnoses. This could then be compared to national diagnostic standards and guidelines to assess the standard of practice and identify any improvements made by the MBRN. However, to undertake this work, a more fundamental question first needed to be answered: "How do we define a good diagnosis and how can it be measured using routinely collected data?". Addressing this question is the overarching objective of this report.

Despite the need for radical reform of diagnostic services, there is currently no widely accepted measurement approach for evaluating diagnostic performance. To be clear, in this report we use diagnostic performance and diagnostic quality to refer to the entire journey of a patient being diagnosed, as opposed to the accuracy of diagnostic instruments. There is opportunity for advanced analytic methodology that incorporates a spectrum of information and accounts for the dynamic nature of the diagnostic process. However, such methods would require appropriate input data sources with clinically rich information, particularly symptoms, and linkage across healthcare tiers [1].

Routinely collected health data holds huge potential for epidemiological and clinical

research. Routine data can offer large statistical power, are often representative of a population, have detailed medical histories, and linkage with other data sources can improve completeness [11, 12]. However, the nature of routine data can limit its applications in research, with common issues associated with misclassified and missing data. Any research using routine data must consider both the availability and quality of all variables required for analysis to assess the capacity and fitness-for-purpose of the data in answering the intended research question [13, 14].

Existing literature recognises the challenges of using routine data to measure diagnostic performance due to incomplete and erroneous coding, with an emphasis on the critical role of physicians in influencing the quality of routine data for research purposes [2, 3, 6]. Suggested solutions include improved standardisation of clinical coding, a culture of change in physicians' attitudes toward high-quality recording practices, and increased validation of coding used for research [1, 3, 6]. However, to the best of our knowledge, no studies have provided a thorough examination of a routine data source or considered the issues in the context of a specific disease.

The content of this report has been used to achieve two outcomes. First, to extend the existing discussion of measuring diagnostic quality with routine data by providing an in-depth examination of key barriers and illustrating with specific examples using electronic health records (EHRs) from the Morecambe Bay Community Data Warehouse (CDW) applied to CRD. Second, to provide a response to MBRN stakeholders regarding the feasibility of the originally planned research question, specifically evaluating the impact of the MBRN on diagnostic performance.

3.2.2 Methods

This report uses primary and secondary care data from the Morecambe Bay CDW linked at patient-level via pseudonymised NHS Numbers. Incidences of CRD (asthma, COPD, bronchiectasis, and ILD) diagnoses between 2015-2022, for adults $\geq$35 years at time of diagnosis, were identified from primary care records using SNOMED CT codes. Unless specified otherwise, we consider diagnosis events, not individuals. For example, if an individual has both an asthma and COPD diagnosis in their medical history these are counted as two distinct diagnosis events. For each disease and individual combination, only the first occurrence of a diagnosis is considered.

Data variables that could either be indicators of diagnostic quality or be associated with the diagnostic process were extracted from primary and secondary care records, including symptoms, diagnostics tests, secondary care utilisation, and MBRN intervention. Quantitative exploratory analysis was carried out to assess the availability, identifiability, completion, and missingness of these variables. All SNOMED and ICD-10 codes used for analysis are available at: `https://doi.org/10.17635/lancaster/researchdata/651`.

The data presentations in this report include temporal trends, but also focus on diagnoses made in 2022 to provide a picture of the most up-to-date diagnostic practices since diagnostic technologies and best practice guidelines change over time. Findings from 2022 may be vulnerable to COVID-19 related bias and Appendix A.2 provides additional results to consider this impact on the data presentations and subsequent conclusions.

3.2.3 Generalisable issues

In this section, we consider different barriers to measuring diagnostic quality using routine data. Although we illustrate with examples from CRD in the Morecambe Bay area, the issues discussed are generalisable to other disease areas, as well as research using routine data more broadly. The section is structured by topic. However, we also propose a thematic framework for thinking through the issues raised, specifically whether the issue is linked to data recording practices, data access, or is a broader study design consideration. Table 3.2 provides an overview of the topics and themes that will be encountered to help orientate the reader.

Table 3.2: Topics discussed in Section 3.2.3 with crosses indicating the relevant themes.

Topic	**Data recording**	**Data access**	**Broader study design consideration**
Constructing diagnostic pathways	X	X	X
Symptom recording	X		
Diagnostic tests	X	X	
Suspected cases	X		
Identifying local intervention	X	X	X
Control group		X	X
COVID-19			X

3.2.3.1 Constructing patient diagnostic pathways

By 'diagnostic pathway' we are referring to the chain of events leading up to diagnosis. Two examples are provided in Tables 3.3 and 3.4. The pathways were constructed by first identifying patients according to the criteria outlined in Section 3.2.2 then extracting any respiratory-related activity from primary or secondary care prior to the diagnosis.

Table 3.3 shows the pathway for a COPD diagnosis. The patient only interacted with primary care prior to diagnosis and there is a good level of detail with risk factors, symptoms, and diagnostic tests recorded.

Table 3.3: Example of a diagnostic pathway for COPD diagnosis.

Date	Age	Category	Observation	Result/additional detail
2013-01-29	55	Risk factor	Current smoker	Light (1-9 cigs/day)
2014-12-23	57	Risk factor	Current smoker	Moderate (10-19 cigs/day)
2016-04-05	59	Test	Chest X-ray	
2016-04-26	59	Symptom	Chesty cough	
2016-04-26	59	Test	Spirometry	
2016-04-26	59	Test	FEV_1/FVC ratio	67.620
2016-04-26	59	Test	FEV_1/FVC ratio post bronchodilator	65.980
2016-04-26	59	Test	Spirometry reversibility negative	
2016-05-11	59	Risk factor	Current smoker	
2016-05-11	59	Symptom	Wheeze absent	
2016-05-11	59	Symptom	Medical Research Council Breathlessness Scale	Grade 3
2016-05-11	59	Test	Spirometry	
2016-05-11	59	Test	Post bronchodilator spirometry	
2016-05-11	59	Test	FEV_1/FVC ratio	69.790
2016-05-11	59	Diagnosis	COPD	

The pathway shown in Table 3.4 is for a bronchiectasis diagnosis. Compared to Table 3.3, the pathway is shorter and less detailed in terms of symptoms and tests, but we see the patient interacting with both inpatient and outpatient services in the months prior to diagnosis.

These pathways were constructed on an ad-hoc basis for illustration. Producing a rigorous algorithm to construct diagnostic pathways from EHRs for research purposes raises key questions that first need addressing.

Table 3.4: Example of a diagnostic pathway for bronchiectasis diagnosis.

Date	Age	Category	Observation	Result/additional detail
2013-11-19	85	Risk factor	Non-smoker	Never smoked tobacco
2014-11-04	86	Diagnosis	Asthma	
2015-04-21	87	Inpatient	Emergency admission	Asthma, unspecified
2015-06-05	87	Test	Chest X-ray	
2015-06-09	87	Referral	Referred from GP	
2015-06-30	87	Diagnosis	Acute asthma exacerbation	
2015-07-03	87	Outpatient	Seen in respiratory clinic	No procedures recorded
2015-07-29	87	Diagnosis	Bronchiectasis	

i. Identifying time of diagnosis

For research using primary care records, SNOMED CT is a crucial tool for identifying patients with a specific condition. SNOMED CT is the most comprehensive clinical terminology product globally and allows patient problem lists of current diagnoses to be maintained by general practices [15]

However, primary care records show that patients can be treated for a condition for years before a diagnosis code is recorded, resulting in a diagnosis time later than the truth. A partial solution has been implemented in the BREATHE recommended codes for asthma and COPD found via the Health Data Research Phenotype Library [16]. These codes allow observations that indicate ongoing treatment such as 'COPD annual review' and 'Under care of specialist asthma nurse' to qualify as a diagnosis. These codes were implemented for further analysis, along with our own constructed lists for bronchiectasis and ILD.

Alternatively, a relevant SNOMED code may be recorded as a working diagnosis. For example, in the case of COPD, a GP may record a diagnosis code to ensure the patient is listed on the Quality and Outcomes Framework (QOF) COPD patient register whilst diagnostic tests are carried out. If the suspected diagnosis is ruled out, the active code should be removed from the patients record, but this may not always happen. The recording of diagnosis codes as a working diagnosis can result in a diagnosis time earlier than the truth if the clinical diagnosis is later confirmed, or even a false detection if the diagnosis is later ruled out. Validation studies for identifying patients from EHRs attempt to circumvent this issue by considering algorithms with additional criteria along with diagnostic codes such as prescriptions, diagnostic tests, and/or symptoms [11, 13, 17]. However, in the case of COPD, validation studies recommend the use of diagnosis codes alone and

found that including test results or medications only marginally improved results [17]. Nevertheless, these validation studies consider only the question of whether an individual has the condition in question as opposed to the exact time of diagnosis, which is critical for studying patient diagnostic pathways.

ii. Defining the start and end of the diagnostic pathway

This can be undertaken in two ways:

1. Event-based – the pathway starts with a certain event, such as a risk factor (although this could occur years prior; in Table 3.3 the first smoking observation occurs over three years prior to COPD diagnosis) or the recording of a relevant symptom (poor symptom recording is discussed in Section 3.2.3.2) and ends with diagnosis.

2. Time-based – the pathway includes events within a certain window of time, for example, the six months prior to diagnosis. The appropriate window of time would vary by disease and should account for factors associated with the wider healthcare environment such as outpatient referral waiting times. To adjust for the possibility of codes being recorded as a working diagnosis, the end point of the diagnostic pathway could be set beyond the recording of a qualifying diagnosis code. However, this could result in the diagnostic pathway including treatment-related events.

iii. Selecting events relevant to the diagnostic pathway

The diagnostic process is often not confined to a single episode of care but will traverse multiple appointments and even healthcare tiers. Relevant events could include risk factors and symptoms recorded in primary care, diagnostic tests in primary or secondary care, referrals to outpatient clinics, A&E presentations, and admissions to hospital. The CDW does not contain free text fields, referral letters, or clinician reports, linking to the data access theme of our thematic framework (Table 3.2). Without an accompanying narrative it is difficult to determine which interactions are part of the same chain of care and hence which events have contributed toward a diagnosis (this is further discussed Section 3.2.3.3). For example, in Table 3.4, the hospital admission for asthma may have triggered a chain of events leading to the bronchiectasis diagnosis 10 months later, or it may

have been an independent event.

3.2.3.2 Symptom recording

The presentation of a symptom is a likely first event in a diagnostic pathway. For research using claims-based data, the lack of symptom information has been highlighted as a major barrier to measuring diagnostic quality [1]. The CDW provides clinically rich information from primary care observations data, avoiding the data access issue, yet there is a more fundamental problem at the recording-level, aligning with the data recording theme of our proposed framework (Table 3.2). For the diagnosis of CRD, we consider cough, wheeze, sputum, breathlessness, chest pain, weight loss, and fatigue as relevant symptoms, following clinician input. Figure 3.1 shows the percentage of CRD diagnoses made in 2022 with recorded symptom information in the six months prior to the first recording of a diagnosis code. In the six months prior to diagnosis, 46% of diagnoses had no symptom information recorded. Note that symptom information includes the recorded absence of a symptom (e.g., 'No wheeze' or 'Weight normal'). The explicit recording of symptom absence was present in just 20% of diagnostic pathways.

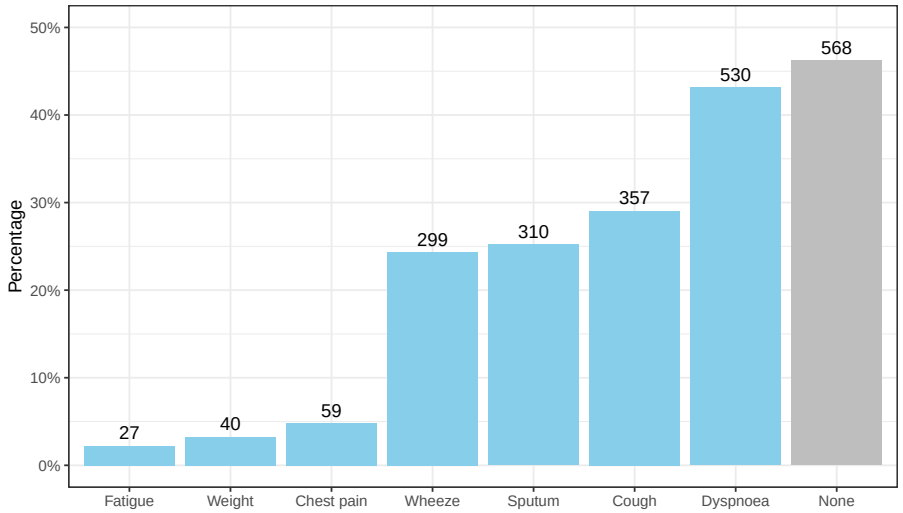


Figure 3.1: Percentage of diagnoses 2022 (n=1,229) with symptom information recorded in the six months prior to diagnosis. Labels above bars show the frequency.

However, we cannot infer absence of symptoms from absence of symptom recording. Some of the 46% will be asymptomatic cases that have been diagnosed following an incidental diagnostic test or other healthcare interaction, but many will likely

be the result of incomplete data recording, or even that the symptom was not discussed between patient and practitioner. It is not possible to distinguish between these events from the data. Performing diagnostic pathway analysis on the subset of patients that have a symptom recorded could induce bias by excluding milder or asymptomatic cases, but also in terms of location and demographics since data recording practices are likely to vary by GP (see Section 3.2.4.2, for example).

A standardisation of the diagnostic process, including the recording of presence and absence of key symptoms, would facilitate defining the diagnostic pathway and identifying instances where symptom information is not being taken into consideration for diagnosis [3, 6].

3.2.3.3 Diagnostic tests

The diagnostic process, particularly diagnostic testing, often traverses healthcare tiers. Thus, an immediate barrier to constructing diagnostic pathways is being able to integrate different sources of healthcare data at patient-level [1]. This research uses the CDW, a store of primary, secondary, and community care data that can be individually linked via pseudonymised NHS Numbers. However, issues arise with both identifying tests relevant to the diagnostic pathway and with interpreting the test results, preventing critical judgement on diagnostic quality.

i. Identifying relevant tests

Potentially relevant diagnostic tests for each of the four CRDs were advised by clinician expertise. Tests carried out in primary care were identified using SNOMED CT codes and tests carried out in secondary care were identified by searching procedure names. Using this method, we identified diagnostic tests carried out for each patient in the six months prior to diagnosis. However, uncertainty remains surrounding the motivation behind a test since not all diagnostic tests are specific to one disease or even to a small group of conditions. As discussed in Section 3.2.3.1, without free text fields to provide clinician commentary on the decision-making process, there can be ambiguity in clinical coding as to why a given test was ordered [18]. As an illustration, Figure 3.2 shows the percentage of CRD diagnoses made in 2022 that have evidence of each test in the six months prior to diagnosis. The four most common tests, each with approximately 60% completion, are blood tests.

Given the older demographic of CRD patients and probable comorbidities, a blood test could have been ordered for other purposes and may not be part of the chain of events contributing toward diagnosis.

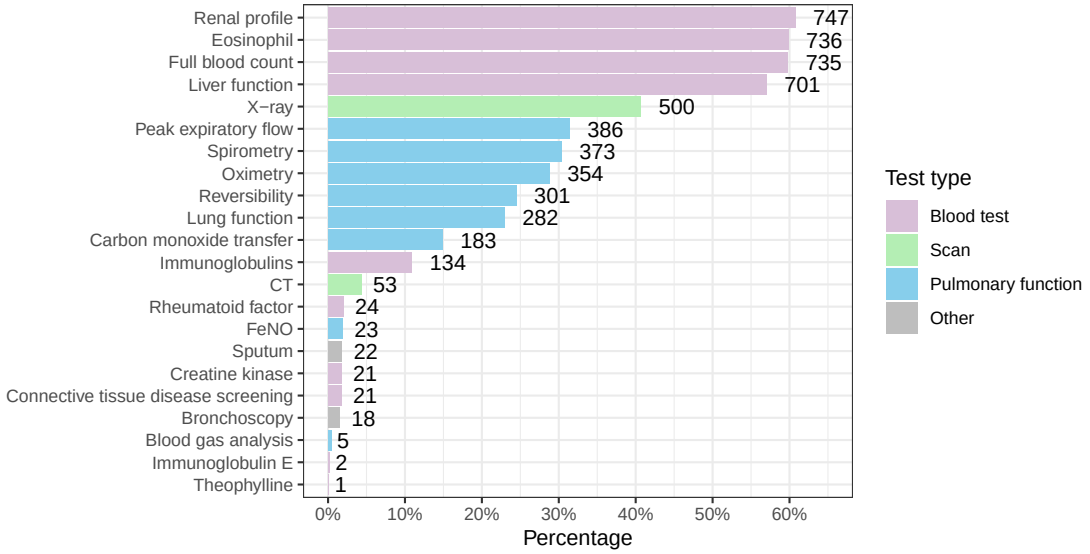


Figure 3.2: Percentage of diagnoses in 2022 (n=1,229) with evidence of each diagnostic test in the six months prior to diagnosis. Labels next to bars show the frequency.

ii. Interpreting test results

SNOMED CT is advertised as a comprehensive clinical terminology product [15], yet the fine granularity of the codes can create multiple ways of recording similar information. When unspecific or ambiguous codes are used, information, although recorded, can become unusable to a researcher [2]. As an example, COPD can only be confirmed by a post-bronchodilator spirometry result of FEV_1/FVC ratio < 0.7 [19]. This is often referred to as a test of reversibility since if lung function (measured by FEV_1/FVC) is not improved ("reversed") by administering a bronchodilator then this is indicative of COPD. The underutilisation of spirometry for diagnosing COPD is a global issue with an estimated 60%-70% of COPD patients lacking this test in their medical records [20]. In our data, only 29% of COPD patients diagnosed in 2022 had evidence of a test of reversibility being administered in the six months prior to diagnosis, which is consistent with the literature. However, of that 29%, only 27% had the numeric test results recorded under the explicit SNOMED codes 'FEV_1/FVC ratio before bronchodilator' and 'FEV_1/FVC ratio after bronchodilator'. Many GPs, although recording that post-bronchodilator

spirometry was being carried out, instead used the unspecific 'FEV_1/FVC ratio' code to record both the before and after bronchodilator results, as illustrated in Table 3.5. The three observations have the same time stamp since it corresponds to the time the GP saves the appointment notes, and so the before and after bronchodilator results become indistinguishable.

Table 3.5: An illustration of spirometry results for COPD diagnosis being recorded under unspecific SNOMED codes.

Date/time	**Observation**	**Results**
2018-03-21 10:34:51	FEV_1/FVC ratio	0.63
2018-03-21 10:34:51	Post-bronchodilator spirometry	
2018-03-21 10:34:51	FEV_1/FVC ratio	0.71

Even when results have been explicitly recorded, numeric results do not always have a clear and decisive cut-off. For example, COPD is defined by a post-bronchodilator FEV_1/FVC ratio < 0.7. In contrast, an asthma diagnosis typically requires a peak expiratory flow test [19], the interpretation of which is dependent on what's 'normal' for the individual which may not be identifiable from EHRs.

X-ray and scan imagery are not typically available in EHR databases used by researchers. After blood tests, x-ray imaging is the most common test used for CRD diagnosis (Figure 3.2) and is crucial for diagnosing bronchiectasis and ILD. Descriptive SNOMED codes such as 'Chest x-ray abnormal' exist yet lack the rich clinical detail that could be provided by free text fields or the scan image itself, and would be susceptible to inconsistent data recording practices, as seen in other areas.

3.2.3.4 Suspected disease

In the issues discussed so far, the data presentations have been limited to cases that result in a diagnosis, which would be a major source of bias in any further analysis. The pathway taken for suspected cases of a disease where the patient is not diagnosed, either because the diagnosis was ruled out or the patient was not adequately followed up, speak just as loudly to the question of diagnostic quality. However, identifying suspected cases is not a straightforward task. For CRD, there are SNOMED codes for 'Suspected asthma' and 'Suspected COPD', but no equivalent for the rarer diseases, bronchiectasis and ILD. Furthermore, using this method would rely on consistent and widespread recording of suspected codes which is currently lacking. Only 15% of asthma patients and 8% of COPD patients

had the corresponding suspected disease code anywhere in their records. A possible explanation for the low usage of suspected disease codes is the preference of GPs to use diagnosis codes as a working diagnosis to ensure the patient is on the relevant QOF register whilst tests are carried out to confirm the diagnosis. This issue was discussed briefly in Section 3.2.3.1. Other variables could act as proxies for suspected disease, such as key diagnostic tests, symptoms, referral to other services, or a combination, but there are other conditions for which such events could apply.

3.2.3.5 Identifying local intervention

Interventions introduced locally will not have a unique associated SNOMED code, creating a barrier for researchers restricted to structured data in EHRs. An intended aim of this project was to evaluate the impact of the MBRN care model on diagnostic quality. However, key elements of the MBRN diagnostic pathway are either challenging to identify or unavailable in the CDW. The two examples given below highlight the importance of collaboration between clinician and researcher, and links to all the issues considered in our thematic framework (Table 3.2). If studies are to be designed that can effectively evaluate healthcare interventions, those responsible for service design need an understanding of the availability and format of structured EHR databases commonly used by researchers.

i. MBRN diagnostic template

The MBRN diagnostic template (Appendix A.1) was introduced in 2017. The template has been circulated to all GPs in the Morecambe Bay area, but we would expect its usage to be higher amongst MBRN GPs. The template includes the SNOMED code for 'Initial respiratory assessment' for administrative purposes and it was hoped this code could identify template usage. Figure 3.3 shows the annual usage of the code has increased dramatically since template introduction yet was also used frequently pre-intervention.

To identify authentic uses of the template, additional codes from the template recorded in the same appointment as the 'Initial respiratory assessment' code were considered with the intention of applying a threshold. The template has a theoretical maximum of 48 codes in one use if all are relevant and able to be carried out. Figure 3.4 shows the annual average number of additional codes between 1991-2022.

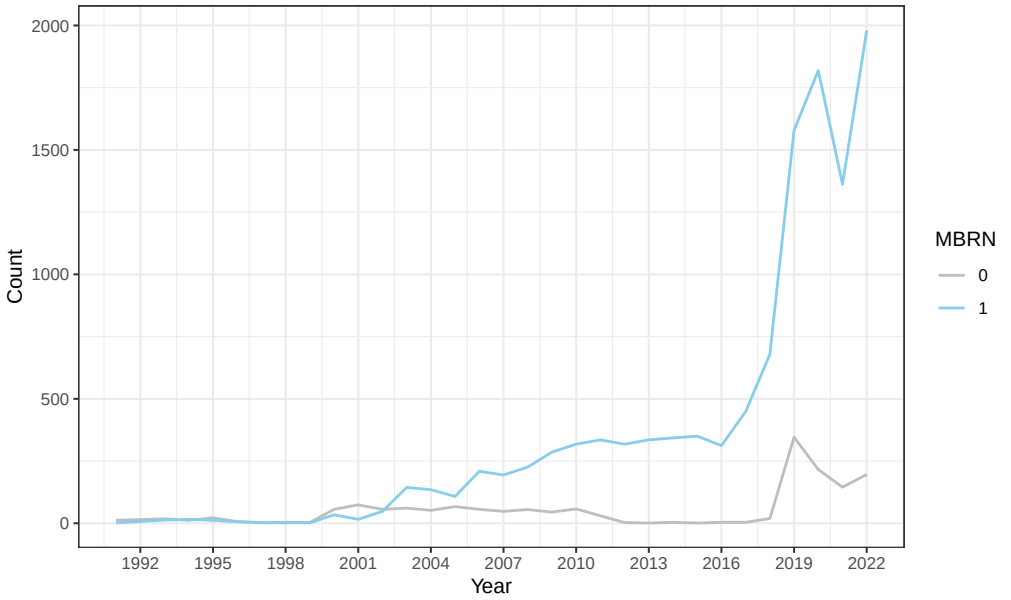


Figure 3.3: Number of initial respiratory assessment codes recorded between 1991-2022 by GP MBRN status.

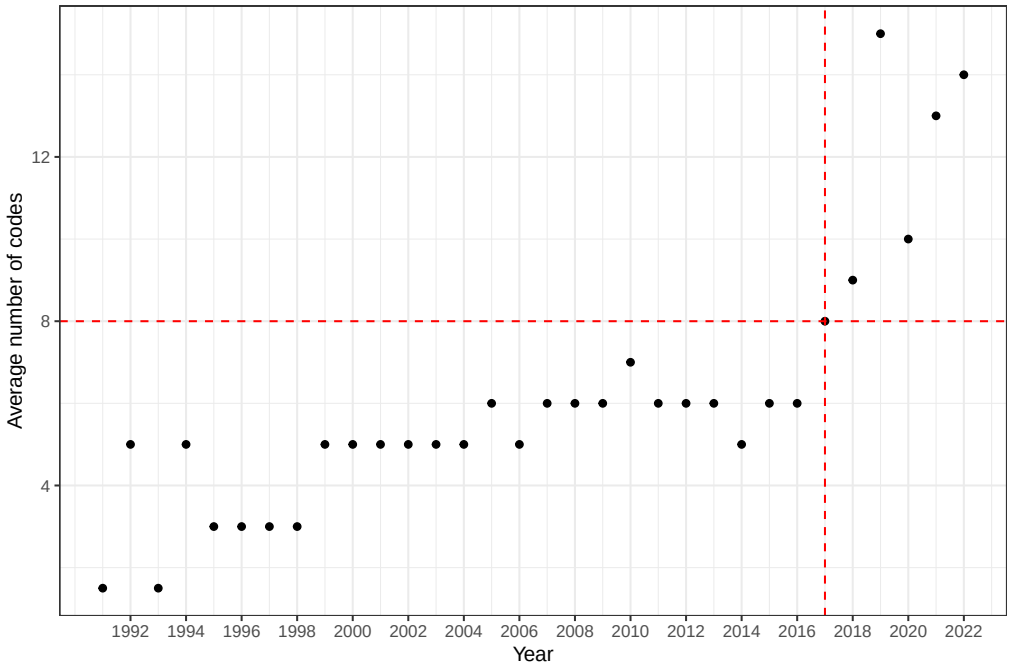


Figure 3.4: Median number of additional template codes recorded during same appointment as initial respiratory assessment code between 1991-2022.

From these results, a sensible threshold could be eight i.e., template usage would be identified by the recording of 'Initial respiratory assessment' plus eight other codes during the same appointment that correspond to fields of the MBRN template. Applying this criterion reduces the estimated number of templates completed from 7,760 to 5,657 between 2017-2022.

However, an immediate issue with applying an additional code threshold is we are essentially creating a subset of 'good' template usage. By removing those we deem to be ingenuine uses of the template, we will likely also remove many poor uses of the template, which could introduce bias into further analysis.

ii. MBRN MDT meetings

The MDT meetings are the central element to the MBRN model and represent a critical step in the MBRN diagnostic pathway. During these meetings, suspected diagnoses are discussed with specialist input to avoid secondary care utilisation where possible. The MBRN maintains their own records for when a patient was presented at a meeting and the subsequent outcomes of the discussion. However, this data is not available in the CDW, preventing accurate identification of patients cared for under the MBRN model. A partial solution in this instance could be for the MBRN to record the 'Multidisciplinary meeting' SNOMED code in patients' primary care records when discussed at an MDT. A researcher with knowledge of the MBRN meeting dates would then at least be able to identify with reasonable certainty when a patient was discussed, even if they do not have access to the meeting outcomes.

3.2.3.6 Control group

Routinely collected health data, by definition, is not collected for the primary purpose of research. A consequence of this can be a lack of control group when aiming to evaluate the effectiveness of healthcare interventions. For this specific research, a control group for the MBRN intervention population is particularly important to control for changes in diagnostic practice and data recording practice over time, as well as the interruption to healthcare services caused by the COVID-19 pandemic (see Section 3.2.3.7).

The CDW is a regional database covering healthcare interactions within the

Morecambe Bay area only. The Morecambe Bay has an adult (≥35 years) population size over 260,000 which, numerically speaking, is quite large, yet the populations that have and have not received MBRN intervention are not comparable groups (Table 3.6). The MBRN intervention population is on average younger, living in more urban areas, and significantly more deprived, with 27.3% of its adult (≥35) population in the bottom two deciles of the Index of Multiple Deprivation (IMD) compared to just 0.3% for the non-MBRN intervention population. The COPD prevalence is significantly greater for the MBRN intervention population, which is to be expected given the higher rate of key risk factors, namely smoking and deprivation.

Larger, national routine health data sources exist, such as secondary care data from NHS Digital's Hospital Episode Statistics (HES) [21] and the Clinical Practice Research Datalink (CPRD) which includes primary care data for 18 million currently registered patients across the UK [22] and would likely be able to provide an effective control group for the MBRN intervention population. However, such databases can come at considerable expense both financially and in time taken to complete the application process, linking into the data access theme in our proposed thematic framework (Table 3.2).

3.2.3.7 COVID-19 pandemic

The COVID-19 pandemic caused obvious, significant disruption to all healthcare services [23, 24]. The impact to the management and diagnosis of chronic disease in primary care was substantial with decreases in the number of referrals, medical tests, prescriptions, immunisations, and incidence rates [25, 26]. Studies have found chronic lung conditions, particularly COPD, to be amongst the worst affected [26, 27]. Further, the pandemic has changed the way patients access healthcare services, including style of consultation with GPs [28, 29]. The MBRN is now facing a considerably different healthcare environment than when the initiative began. Since diagnostics is a dynamic field, any analysis on diagnostic quality would benefit from using the most recent data to reflect current diagnostic technology and best practice guidelines [1]. Therefore, a study of diagnostic performance and the impact of the MBRN may be best attempted in the future to allow the data to stabilise post-pandemic.

Table 3.6: Population demographics table for Morecambe Bay GP registered adult (age $\geq$ 35) population (n=264,626) as of January 2023.

	Non-MBRN (n=96,990)	**MBRN (n=167,636)**	**p-value**
Age			
Mean ± sd	60.3 ± 14.6	58.5 ± 14.7	<0.0001
35-49 (%)	26.0	31.3	
50-64 (%)	35.1	34.3	<0.0001
65-79 (%)	28.2	25.2	
80+ (%)	10.7	9.2	
Sex			
Male (%)	48.8	49.4	<0.0001
Socioeconomic deprivation			
IMD deciles 1-2 (%)	0.3	27.3	
IMD deciles 3-4 (%)	7.5	21.1	
IMD deciles 5-6 (%)	31.9	18.1	<0.0001
IMD deciles 7-8 (%)	44.2	20.4	
IMD deciles 9-10 (%)	15.6	12.9	
Smoking status			
Current smoker (%)	10.3	16.0	
Ex-smoker (%)	41.6	41.0	<0.0001
Never smoker (%)	46.0	41.1	
Missing (%)	2.1	1.9	
Location			
Urban (%)	31.8	67.8	<0.0001
CRD prevalence			
Asthma (%)	11.3	12.0	<0.0001
COPD (%)	2.5	4.4	<0.0001
Bronchiectasis (%)	0.8	0.9	0.21
ILD (%)	0.5	0.5	0.50

3.2.4 Results for the MBRN

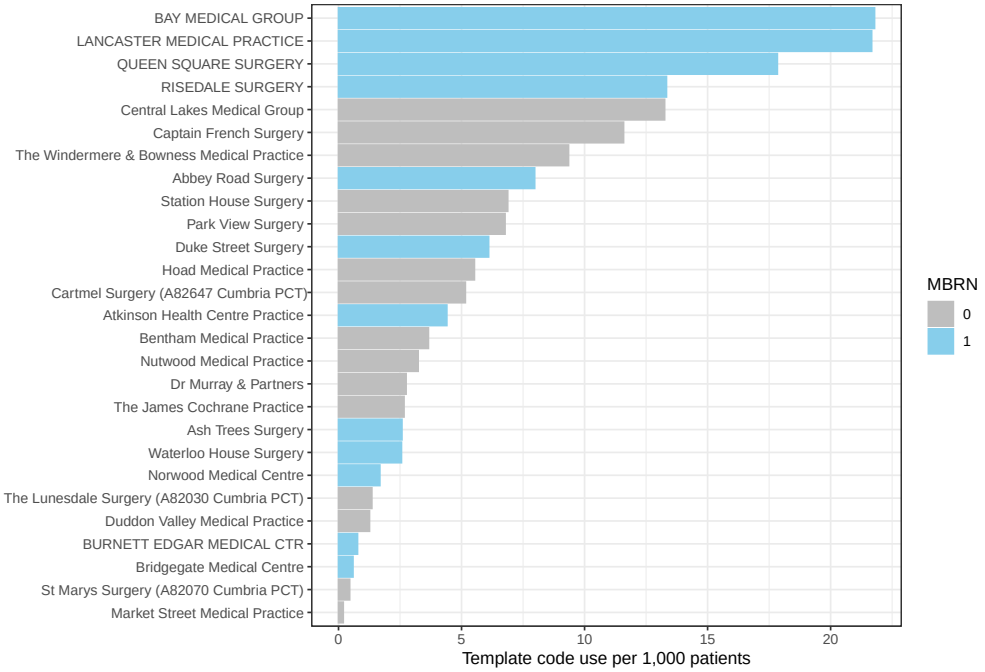
Section 3.2.3 described different barriers to researching diagnostic quality with routine data, discussing the broader issues under a thematic framework. This section presents exploratory results from the data relevant to the MBRN. The findings are not what we originally aimed to achieve but have been useful for our stakeholders.

3.2.4.1 MBRN Diagnostic Template

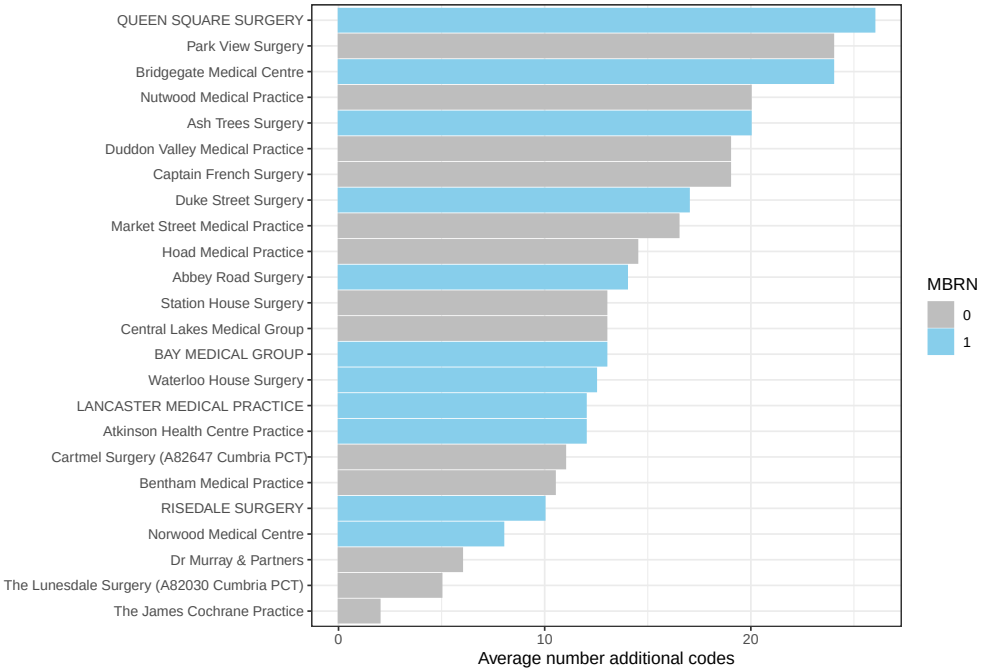
The MBRN diagnostic template examples one method through which standardisation of care and coding practices could be achieved. When used correctly and consistently, clinically relevant information required for analysing diagnostic quality is recorded, and addresses some of the challenges discussed in this report. The template includes fields for the presence and absence of symptoms (Section 3.2.3.2), uses explicit SNOMED codes for recording test results (Section 3.2.3.3), and its usage could provide some indication of GP diagnostic suspicion (Section 3.2.3.4). Sections 3.2.4.2 and 3.2.4.3 include results for specific fields of the template.

The effectiveness of the template in transforming both diagnostic and data recording practices critically depends on successful uptake by GPs. The MBRN template has been circulated to all GPs within the Morecambe Bay area, but we would expect its usage to be higher amongst MBRN GPs. Figure 3.5a shows considerable variation in the number of recordings of the 'Initial respiratory assessment' code by GP in 2022, standardised for GP patient list size. The results show that MBRN GPs are generally using the template at a higher rate compared to non-MBRN GPs. Bay Medical Group has the highest rate of template usage with 29 uses per 1,000 patients, followed by Lancaster Medical Practice and Queen Square Surgery with 21 and 17 uses per 1,000 patients respectively. These three GPs are all based in the Lancaster area and are significant contributors to the MBRN.

However, rate of usage does not equate to consistent template completion. Figure 3.5b shows the average number of additional template codes recorded in the same appointment as a recording of the 'Initial respiratory assessment' code by GP. The results do not have as clear a divide by MBRN status compared to Figure 3.5a. Queen Square Surgery has the highest number of additional codes with a median of 26 (theoretical maximum of 48), whereas Bay Medical Group and Lancaster Medical Practice are in the bottom half with just 13 and 12 additional codes respectively.



(a) Number of initial respiratory assessment codes recorded per 1,000 patients.



(b) Median number of additional codes recorded during the same appointment as a recording of initial respiratory assessment.

Figure 3.5: Results for MBRN template usage in 2022 by GP.

3.2.4.2 Symptom recording

Using the method described in Section 3.2.3.5 to identify authentic uses of the MBRN diagnostic template, symptom information had been recorded in 87% of uses. However, given that the method used essentially creates a subset of good template usage, we also examined temporal trends in symptom information recording in the six months prior to diagnosis for all CRD diagnoses, split by MBRN GP status. Figure 3.6 shows that MBRN GPs had better, symptom recording, even prior to intervention in 2017 and maintained their rate throughout the COVID-19 pandemic. In contrast, non-MBRN GPs saw some improvements up until 2019, but regressed over the pandemic. Number of diagnoses in 2022 with symptom information recorded in the previous six months was 60% for MBRN GPs yet only 39% for non-MBRN GPs.

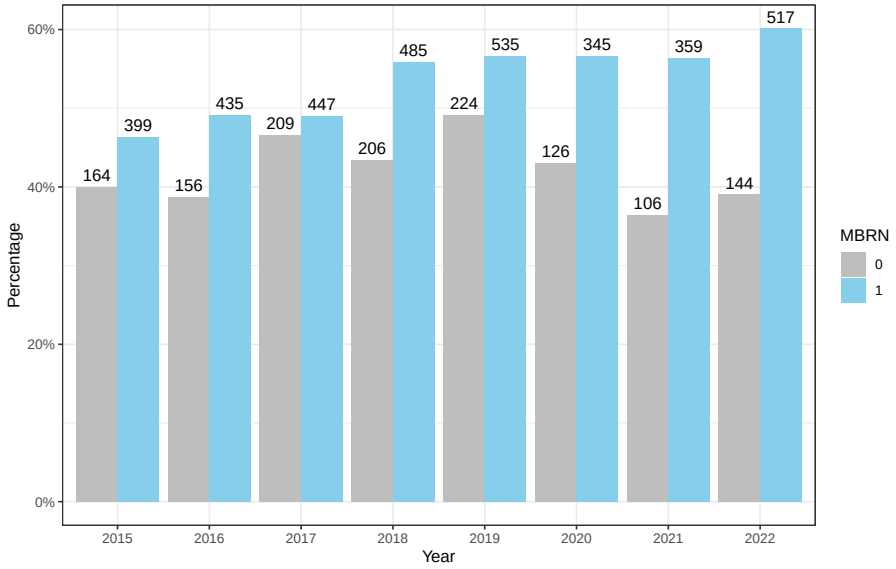


Figure 3.6: Percentage of diagnoses with a symptom recorded in the six months prior to diagnosis between 2015-2022 and by GP MBRN status. Labels above bars show the frequency.

In Section 3.2.3.2 it was reported that 46% of diagnoses made in 2022 had no symptom information recorded in the six months prior to diagnosis. Figure 3.7 shows this result varies between 8% and 93% when aggregated at GP level. In fact, the average of 46% is considerably weighted by Bay Medical Group and Lancaster Medical Practice, the two largest GPs in the Morecambe Bay, and part of the MBRN. Seven of the eight lowest results are from practices within the MBRN network.

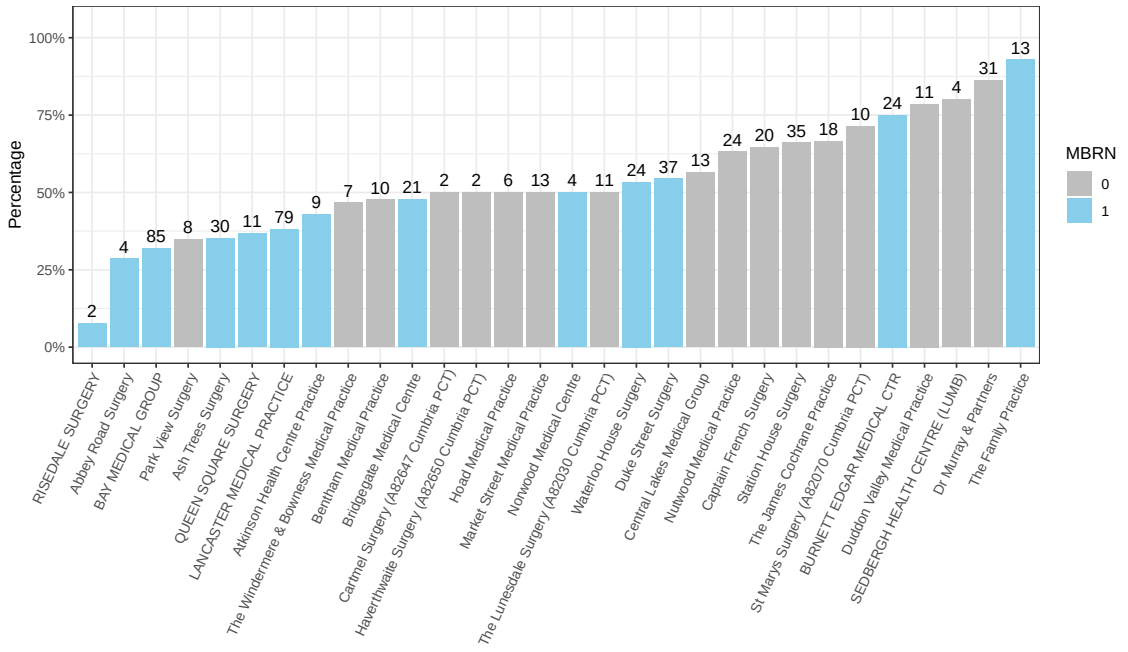


Figure 3.7: Percentage of diagnoses in 2022 with no symptom information recorded in the previous six months by GP. Labels above bars show the frequency.

3.2.4.3 Spirometry results for COPD diagnoses

The need for improved spirometry access and the goals of the MBRN have already been discussed in Section 3.2.1 and Section 3.2.3.3. In brief, the underutilisation of spirometry for diagnosing COPD is a global issue, a key reason being the lack of equipment and trained personnel in primary care. National agenda from the NHS has set targets to improve the quality of spirometry testing across the country. The MBRN model aims to address these issues by upskilling GPs, including spirometry training, to provide a higher level of clinical care.

For authentic uses of the template resulting in a COPD diagnosis within six months of template completion, post-bronchodilator spirometry is present in 70% of cases, all of which have results recorded using unambiguous SNOMED codes due to template design (Appendix A.1). Spirometry is not suitable for all patients and lung function testing was restricted during the COVID-19 pandemic, which may explain some of the 30% without evidence of the test. As explained in the previous section, the method used for identifying template usage is biased toward good completion, and so we also examine temporal trends in spirometry and reversibility tests in the six months prior to diagnosis for all COPD diagnoses, split by MBRN GP

status. 'Spirometry' includes any evidence of the test being carried out whereas 'reversibility' are the instances where it has been specified as post-bronchodilation. Figure 3.8 shows that MBRN GPs display an increasing trend in spirometry and reversibility following intervention in 2017. There was a decrease in test utilisation during the COVID-19 pandemic, but with evidence of recovery by 2022. In comparison, non-MBRN GPs fared worse during the pandemic with spirometry utilisation reaching approximately 10% in 2021, with little improvement in 2022.

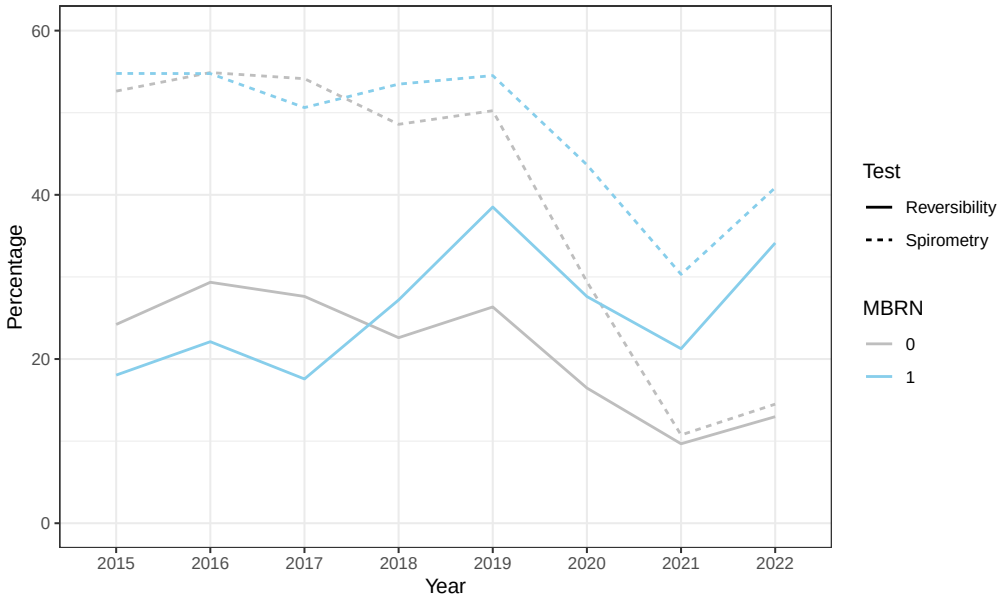


Figure 3.8: Percentage of COPD diagnoses by GP MBRN status with evidence of spirometry and post-bronchodilator spirometry in the six months prior to diagnosis between 2015-2022.

Section 3.2.3.3 showed that only 27% of COPD diagnoses with evidence of a test for reversibility additionally had clearly identifiable numeric results. Figure 3.9 shows how this percentage varies over time and by GP MBRN status. The results shows a clear increase in the percentage of identifiable post-bronchodilator numeric results among MBRN GPs since the introduction of the initiative in 2017. Non-MBRN GPs were also displaying an increasing trend until 2020, but have significantly decreased over the COVID-19 pandemic.

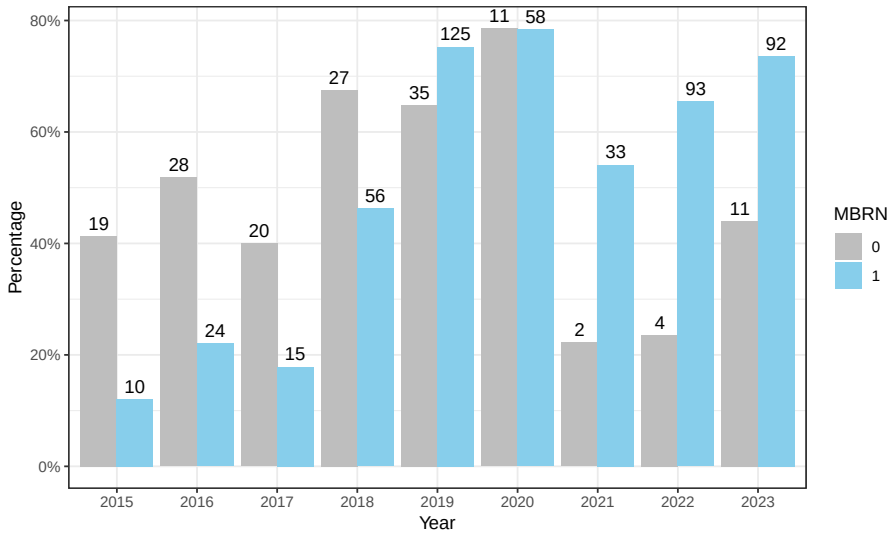


Figure 3.9: Percentage of COPD diagnoses between 2015-2022 with evidence of reversibility and clearly identifiable numeric test results in the six months prior to diagnosis. Labels above bars show the frequency.

3.2.4.4 COVID-19 pandemic

Longitudinal results presented in this report (e.g., Figures 3.6, 3.8, and 3.9) suggest a greater continuation of care to MBRN GPs during the COVID-19 pandemic, with results returning, if not improving upon, pre-pandemic levels by 2022. This could provide evidence of the benefit of effective integrated care during times of crises to healthcare services. However, given the lack of comparability between the MBRN and non-MBRN populations (Section 3.2.3.6), we cannot safely attribute these differences to the influence of MBRN intervention alone.

3.2.4.5 Direct referrals

MBRN GPs have direct access to lung function clinics (see Section 3.2.1 for further details) which are identifiable in outpatient data in the CDW from 2020 onward. Use of this facility should produce a more efficient diagnostic process by ensuring patients have all appropriate information required by the clinician in place before being discussed at an MDT or seen in clinic if necessary.

Relevant direct referrals were identified from CDW outpatient attendance tables by the following criteria: clinic names with the term 'lung function', new referrals (as opposed to follow-up), and general practice as the referral source.

Between 2020-2022, MBRN GPs made 740 direct referrals to lung function clinics. Of the 740 patients, 675 have a CRD diagnosis in their medical records, but only 171 occurred within six months of being seen in the lung function clinic. This suggests that the majority of referrals are treatment-related rather than diagnostic-related. It would be possible, and potentially insightful, to do a closer examination of the 171 patients directly referred for lung function testing in the six months prior to diagnosis. However, in the MBRN model, direct referrals and MDT meetings work in unison; a patient is first directly referred for testing then all appropriate results are presented at an MDT meeting and discussed with specialist input. Without access to MDT records (see Section 3.2.3.5) we only have a partial picture of the MBRN diagnostic pathway and thus any inference on the direct referrals alone would be considerably limited in its ability to evaluate MBRN impact.

However, direct referrals to lung function clinics remain a key element to the MBRN model. Here we present summary data comparing outpatient service utilisation in the six-month period before and after the lung function clinic appointment for patients referred directly and indirectly (e.g., from a respiratory clinic or from A&E). The following results only consider appointments up to 30$^{\text{th}}$ June 2022, since we look at the six-month period following the appointment. We do not restrict to appointments that can be linked to a diagnosis event for the sake of a larger samples size.

Table 3.7 shows that patients directly referred are less likely to have been seen in a respiratory clinic in the six months prior to the lung function clinic appointment (p-value < 0.0001), as would be expected for a direct referral. Table 3.8 shows that patients directly referred are also less likely to be seen in a respiratory clinic in the six months following the lung function appointment (p-value < 0.0001). Only 20% of patients directly referred are seen in a respiratory clinic in the six months following lung function testing, compared to 59% for indirect referrals. This suggests the effectiveness of the MBRN model in streamlining care pathways and improving service efficiency.

Table 3.7: Frequency table for direct referrals to lung function clinic against respiratory outpatient clinic attendance in the six months prior to the appointment.

	Not seen in respiratory clinic	**Seen in respiratory clinic**
Indirect referral	309	757
Direct referral	652	74

Table 3.8: Frequency table for direct referrals to lung function clinic against respiratory outpatient clinic attendance in the six months following the appointment.

	Not seen in respiratory clinic	Seen in respiratory clinic
Indirect referral	435	631
Direct referral	579	147

3.2.4.6 Rare disease

An increase in the (diagnosed) prevalence of rare disease could be indicative of improved diagnostic quality, particularly under the MBRN model where GPs receive additional training and have access to specialist expertise via MDT meetings. For CRD, the rare diseases we consider are complex asthma and ILD.

i. Complex asthma

Severe asthma is not well coded in primary care records. There are only 59 patients with the 'Severe asthma' SNOMED code in the CDW for adults ≥35 years, the earliest usage dating back to 1972. We instead use referrals to severe asthma and asthma biologics (a treatment option for certain types of complex asthma) clinics as a proxy. Table 3.9 shows the number of referrals to these clinics between 2018-2022 by GP MBRN status. Prior to 2018, total referral counts are less than 10 per year thus have been excluded. The results do not provide strong evidence that the MBRN has driven an increase in diagnosed complex asthma. Non-MBRN GPs accounted for a greater proportion of the referrals between 2018-2020 despite having a smaller asthma cohort (Table 3.6). Although this relationship has reversed in 2021-2022, the results may be affected by the COVID-19 pandemic (Section 3.2.3.7).

Table 3.9: Number of referrals to complex asthma and asthma biologics clinics by GP MBRN status between 2018-2022.

	2018	2019	2020	2021	2022
Non-MBRN	12	25	44	16	30
MBRN	8	25	33	42	52
Total	20	50	77	58	82

An issue related to these results, is that the CDW only has data for referrals made into the University Hospitals of Morecambe Bay NHS Foundation Trust. Patients in the Lancaster area (which has received MBRN intervention) may choose to attend clinics at Royal Preston Hospital, part of Lancashire Teaching Hospitals NHS

Foundation Trust, over Lancaster Royal Infirmary, if the waiting lists are shorter. In comparison, patients in the more northern parts of the Morecambe Bay area (which has not received MBRN intervention) do not have other hospitals in proximity thus their care is more likely to be kept within the Trust, and hence within the data.

ii. ILD

Figure 3.10 shows the number of ILD patients between 2015-2022 among patients registered at MBRN and non-MBRN GPs. The gap between MBRN and non-MBRN GPs is more pronounced from 2018 onward, following MBRN intervention. MBRN GPs saw a significant rise in diagnosed cases in 2021, and similarly for non-MBRN GPs in 2022, which may support evidence in the literature of the association between COVID-19 and lung fibrosis [30].

However, simple examinations of rare disease prevalence cannot alone be an indicator of diagnostic quality and should not be entirely attributed to an intervention such as the MBRN. Modelling disease prevalence would require a more sophisticated model to account for changes in population demographics, risk factors, and other changes in diagnostic practice outside that of the MBRN. Given the, naturally, small samples sizes for these rare diseases within the Morecambe Bay, this type of modelling approach would benefit from a larger, perhaps national, dataset, an issue touched upon in Section 3.2.3.6.

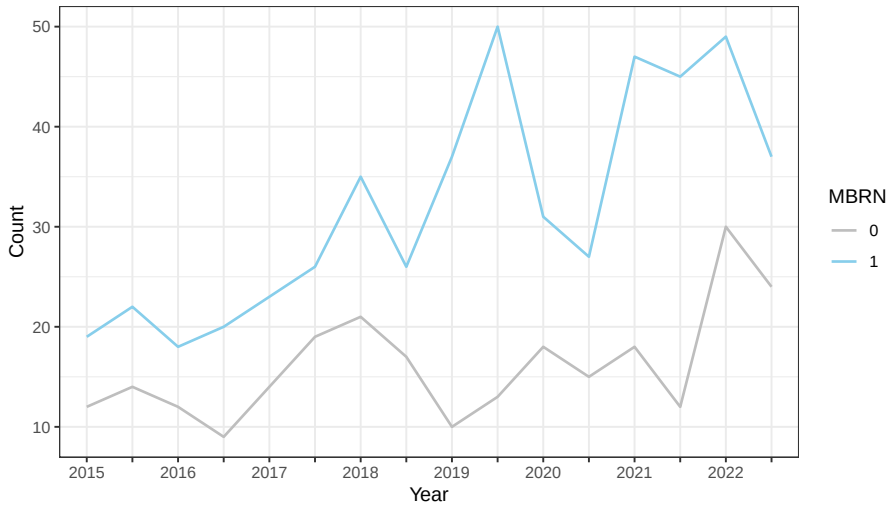


Figure 3.10: Number of diagnosed ILD patients by GP MBRN status 2015-2022.

3.2.5 Discussion

This report has considered the capacity of routinely collected health data for measuring diagnostic quality. The diagnostic process is complex and multi-faceted which certainly presents an opportunity for advanced analytic methods, however, routine data is not yet fit for the task. This research examined the limitations associated with relevant data variables, which are generalisable beyond the scope of this project. We have proposed a thematic framework for grouping the barriers encountered, specifically whether they can be linked to data recording practices, data access, or broader study design considerations. The themes we assigned to each topic is specific to this project and may vary in different study environments and data access agreements. The framework can be used and adapted by other researchers working with routine health data as a tool for thinking through barriers to research.

The key strength of this study is the illustration of the issues using a specific data source and disease area. Our findings support existing literature that a standardisation of coding in primary care is paramount to facilitating high-quality evidence-based health services research [4, 31], yet many of these articles fail to provide targeted areas for improvement or motivation as to what could be achieved with better data [3, 6]. Using the example of CRD in the Morecambe Bay area and data from the CDW, we have highlighted specific issues that need addressing, including: consistent recording of both symptoms and their absence in primary care to distinguish incomplete data collection from incomplete diagnostic pathways; the use of unambiguous SNOMED codes to prevent recorded information, such as test results, becoming unusable by a researcher; and an established method for recording patients suspected of a given disease, and when the diagnosis has been ruled out, to avoid a biased analysis limited to patients that are eventually diagnosed. This research demonstrates the importance of effective feedback loops between researcher and healthcare professionals on the frontlines of data collection for increasing the capacity of routine data for research purposes.

The secondary aim of this report was to respond to the feasibility of the original thesis project plan, particularly with regards to MBRN intervention. The broader challenges to measuring diagnostic quality still apply, yet there are additional barriers specific to evaluating the impact of the MBRN. We have shown the MBRN diagnostic template to be challenging, although not impossible, to identify, and

MDT data to be unavailable in the CDW. Without access to this information, we cannot form MBRN diagnostic pathways. The lack of sufficient control group is also a considerable challenge; in seeking to improve diagnostic quality, the MBRN has consequently improved coding standards, creating their own confounder. Therefore, evaluating the impact of the MBRN on diagnostic quality may require a larger, perhaps national, data set. Nonetheless, there have been positive results reported regarding the MBRN, including symptom recording and usability of post-bronchodilator spirometry results. These results are a small but important demonstration of the benefits of coding standardisation, through simple means such as a diagnostic template, as well as the role integrated care initiatives could play in facilitating high-quality research. The inferred reduced secondary care utilisation from direct referrals to lung function clinics also lends evidence to improved service efficiency through integrated care.

This study has many limitations. First, the data explorations presented are necessarily brief to cover the numerous data variables suggested by clinical expertise as relevant to the diagnostic process. There is admittedly far more that could be done to uncover patterns in the data, such as relationships by age, sex, GP, and specific disease type. Second, we identified diagnosis events by the first recording of a relevant SNOMED code then looked at the previous six months for diagnostic-related activity. In this report, we recognise the uncertainty in defining the diagnostic pathway and our results may change under different definitions. Third, the interruption of the COVID-19 pandemic to healthcare provision has been highlighted as a barrier to researching diagnostic quality for CRD, but it also will have impacted all the exploratory results presented. Finally, although the use of a specific case study is a key strength of this project, we are unable to comment on the generalisability of our results to other routine data sources or disease areas.

Our findings suggest possible future directions for research into diagnostic quality with routine data, other than the required improvements to data recording practices. First, validation studies for coding accuracy is key for research using routinely collected data [32, 33]. Although there have been numerous validation studies published for using EHRs to accurately identify CRD patients [17, 13], to the best of our knowledge, there have been no such studies conducted for time of diagnosis. Not until we have an accurate time of diagnosis can we meaningfully begin the discussion of defining the diagnostic pathway. Second, the CDW has important characteristics

that will be crucial for measuring diagnostic quality, including cross healthcare tier data and detailed clinical information, such as GP observations. However, the diagnostic process is complex and much depends on the thought process or motivation of the responsible healthcare professional. Data sources that include free text data, narrative reports, and scan imagery, combined with machine learning and natural language processing methodology, could provide valuable insight into clinical logic.

3.2.6 Conclusion

Measuring the performance of the diagnostic process using EHRs will rely on consistent and high-quality data recording which are currently lacking in routine data. Poor recording of both symptoms and their absence in primary care records is a critical barrier to defining diagnostic pathways and must improve to distinguish incomplete data collection from incomplete diagnostic pathways. There is a need to standardise coding practices as the fine granularity of SNOMED codes can prevent clear interpretation. In addition, validation studies have been published for accurately identifying CRD patients from EHRs, yet similar studies for time of diagnosis could aid in distinguishing diagnostic and treatment events. The MBRN diagnostic template demonstrates the often-unconsidered potential of integrated care initiatives to facilitate greater research capacity of routine data via standardisation of care pathways and promoting high-quality data recording practices. However, even with perfect coding, EHRs do not capture the clinical logic that accompanies decisions made by healthcare professionals. Free text data, narrative reports, and scan imagery along with machine learning and natural language processing methodology may provide solutions.

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Chapter 4

Budget impact analysis of adopting primary care–based case detection of chronic obstructive pulmonary disease in the Canadian general population

CMAJ Open

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Abstract

Background: An estimated 70% of Canadians with chronic obstructive pulmonary disease (COPD) are undiagnosed, creating a barrier to early intervention. There is growing interest in the value of primary care-based opportunistic case detection for COPD. We build on a previous cost-effectiveness analysis by evaluating the budget impact of adopting COPD case detection in the Canadian general population.

Methods: We used a validated discrete-event microsimulation model of COPD in the Canadian general population ≥40 years to assess the costs of implementing eight primary care-based case detection strategies over five-years (2022-2026) from the healthcare payer perspective. Strategies varied in eligibility criteria (based on age, symptoms, or smoking history) and testing technology (COPD Diagnostic Questionnaire [CDQ] or screening spirometry). Costs were determined from Canadian studies and converted to 2021 Canadian dollars. Key parameters were varied in one-way sensitivity analysis.

Results: All strategies resulted in higher total costs compared to routine diagnosis. The most cost-effective scenario (the CDQ for all patients) had an associated total budget expansion of $423 million, with administering case detection and subsequent diagnostic spirometry accounting for 86% of costs. This strategy increased the proportion of COPD individuals diagnosed from 30.4% to 37.8% and resulted in 4.6 million referrals to diagnostic spirometry. Results were most sensitive to uptake in primary care.

Interpretation: Adopting a national COPD case detection programme would be an effective method for increasing diagnosed COPD dependent on successful uptake, but it will require prioritisation by budget holders and substantial additional investment to improve access to diagnostic spirometry.

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) affects 2.6 million Canadians and is the third leading cause of death worldwide [1, 2]. Quality-of-life for COPD patients can be significantly impaired by the burden of symptoms and subsequent exacerbations, affecting their ability to partake in daily activities [3]. Diagnosis is critical for clinical intervention to reduce symptoms and the risk of exacerbations through optimal preventative and therapeutic management, particularly smoking cessation [4]. Despite major social and clinical implications, 70% of Canadians with COPD remain undiagnosed and experience worse long-term health outcomes through late recognition of their condition [5, 6]. Although COPD is recognized as an ambulatory-sensitive condition meaning hospitalisations can be avoided through optimal outpatient management, one-third of patients are initially diagnosed in hospital following an exacerbation-related admission [7, 8]. Guidelines recommend against screening of asymptomatic adults due to lack of evidence that diagnosis before symptom development improves patient outcomes. However, asymptomatic is an ambiguous concept; 50% of adults with airflow obstruction fail to report symptoms or mask symptoms by limiting physical activity [9, 10]. Given the substantial burden associated with undiagnosed COPD, there is a need for further research into alternative earlier detection strategies [11, 12, 13]. Emerging evidence from clinical trials and modelling studies demonstrates that targeted, opportunistic case detection in primary care improves long-term patient outcomes and is likely to be cost-effective [14, 15, 16]. A recent cost-effectiveness analysis by Johnson et al. (2021) evaluated primary care-based COPD case detection strategies in the general Canadian population. At a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) gained, case detection with symptom and risk factor-based questionnaires or screening spirometry was cost-effective. The highest value strategy was regularly administering the COPD Diagnostic Questionnaire (CDQ) at three-year intervals to all patients $\geq$40 years during routine primary care interactions [16].

However, given the high prevalence of undiagnosed COPD, investment in a national COPD case detection programme would require significant allocation of healthcare resources. In a time of intense pressure on healthcare budgets, we must consider the affordability of an intervention as well as its value. The aim of our study was to build on a previous cost-effectiveness analysis by evaluating the budget impact of adopting

primary care-based COPD case detection in the general Canadian population [16]. We assessed total medical costs from the healthcare payer perspective of implementing eight case detection strategies that vary in their eligibility criteria and testing technology over a five-year time horizon between 2022 and 2026.

4.2 Methods

This study was designed in accordance with ISPOR (The Professional Society for Health Economics and Outcomes Research) best practice guidelines for budget impact analysis [17].

4.2.1 Setting

Our analysis is from the perspective of the Canadian healthcare system and considers a five-year study period between 2022 and 2026. The total population of Canada was 38.9 million in 2022 with a median age of 41 years, based on Statistics Canada projections [18]. The target population for case detection intervention was the general Canadian population aged ≥40 years, of size 19.8 million in 2022 [18]. The eligible population was the subset of the target population that was eligible for case detection, which varied by strategy. We report the budget impact for the target population for comparability between strategies with different eligibility criteria. Our analysis was implemented in an open population, meaning individuals enter and exit the target population throughout the time horizon.

4.2.2 Analytic framework

We used the Evaluation Platform in COPD (EPIC), a previously validated deterministic discrete-event microsimulation model of COPD in the general Canadian population aged ≥40 years. EPIC simulates the development and progression of COPD across the entire disease pathway, including demographics of the general Canadian population, smoking prevalence, COPD occurrence, symptoms, primary care visits, COPD diagnosis, lung function decline, exacerbations, COPD-related and background mortality, medical costs, and QALYs over a lifetime horizon [19]. EPIC uses data from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study, a national prospective cohort of patients with COPD and at-risk of COPD,

to model community diagnosis, primary care utilisation, and respiratory symptoms [20]. Smoking status is based on Population Health Model (POHEM), a validated microsimulation model developed by Statistics Canada [21]. Each component of EPIC has passed rigorous tests of internal and external validity [19, 16] (Appendix B.1) and EPIC is an open-source R package [22].

This analysis simulated within EPIC the implementation of COPD case detection administered during routine primary care visits over a five-year time horizon (2022-2026).

4.2.3 Case detection

We evaluated eight case detection strategies used in the cost-effectiveness analysis by Johnson et al. (2021), all of which were found to be cost-effective at a WTP of $50,000/QALY (Table 4.1). We did not consider repeat testing of the same individual at specified intervals due to the short time horizon and to show the costs of a single implementation of each strategy. Strategies are grouped according to their eligibility criteria for selecting patients to receive case detection, either all patients (S1), symptomatic patients (any one of cough, phlegm, wheeze, or dyspnoea) (S2), or patients aged ≥50 years with a smoking history (S3). The testing technologies considered are the CDQ [23] and the hand-held flow meter [24], which performs screening spirometry based on the ratio of forced expiratory volume in 1 second to forced expiratory volume in 6 seconds <0.7. All scenarios were compared to a baseline scenario of no case detection.

Although we replicated all eight strategies reported by Johnson et al. (2021), our reporting focuses on S1a (CDQ ≥17 points for all patients), the highest value strategy identified at a WTP threshold of $50,000/QALY gained. However, guidelines suggest that interventions with a large budgetary impact should be subject to lower cost-effectiveness thresholds [25]. We reanalyzed the cost-effectiveness plane in Johnson et al. (2021) (Appendix B.2) and found that the WTP threshold must be reduced to $25,000/QALY for S1a to no longer be the preferred strategy, at which point S3b (CDQ ≥16.5 points for patients ≥50 years with a smoking history) becomes most cost-effective. Therefore, for comparison, we also discuss results for S3b.

Table 4.1: Summary of case detection strategies evaluated.

Testing technology	**Eligibility criteria**	**Sensitivity (%)** [a]	**Specificity (%)** [a]
(S1) All patients			
S1a: CDQ $\geq$ 17 points	None	91.0	49.0
S1b: Flow meter (with bronchodilator)		80.0	94.0
S1c: CDQ $\geq$ 17 points + Flow meter (with bronchodilator)		72.0	97.0
(S2) Symptomatic patients			
S2a: Flow meter (without bronchodilator)	$\geq$1 respiratory symptom [b]	81.5	88.9
(S3) Smoking history			
S3a: CDQ $\geq$ 19.5 points	Past or current smoker Age $\geq$50 years	64.5	65.2
S3b: CDQ $\geq$ 16.5 points		87.5	38.8
S3c: Flow meter (without bronchodilator)		79.9	84.4
S3d: CDQ $\geq$ 17 points + Flow meter (with bronchodilator)		74.4	97.0

CDQ - COPD Diagnostic Questionnaire

[a] Sensitivity and specificity values are derived from the literature and further details have been provided previously [16]. Sensitivity and specificity values relate to the outcome of the case detection test only; patients testing positive are then referred for diagnostic spirometry which we assume to have 100% accuracy.

[b] Respiratory symptoms defined as the presence of chronic cough in the absence of a cold, any wheeze, phlegm in the absence of a cold, or dyspnoea, measured using the Medical Research Council dyspnoea scale with a score of 2-5 indicating the presence of dyspnoea, in the past year.

To be eligible for case detection, individuals must fulfill the eligibility criteria and have visited primary care in the previous year (Figure 4.1). Patients testing positive at case detection were referred to outpatient diagnostic spirometry, which we assumed to have 100% accuracy. We modelled gradual market penetration by assuming a linear uptake from 5% in 2022 to 25% in 2026, based on participation in lung and colon cancer screening programmes [26, 27]. Throughout the simulation, patients could also be diagnosed with COPD at primary care visits without the use of case detection or following an exacerbation-related hospital admission (Appendix B.1).

4.2.4 Inputs

We include direct COPD healthcare costs only (Table 4.2). Costs were converted to 2021 Canadian dollars ($) using the healthcare component of the Consumer Price Index [28] and were not discounted over the time horizon [17].

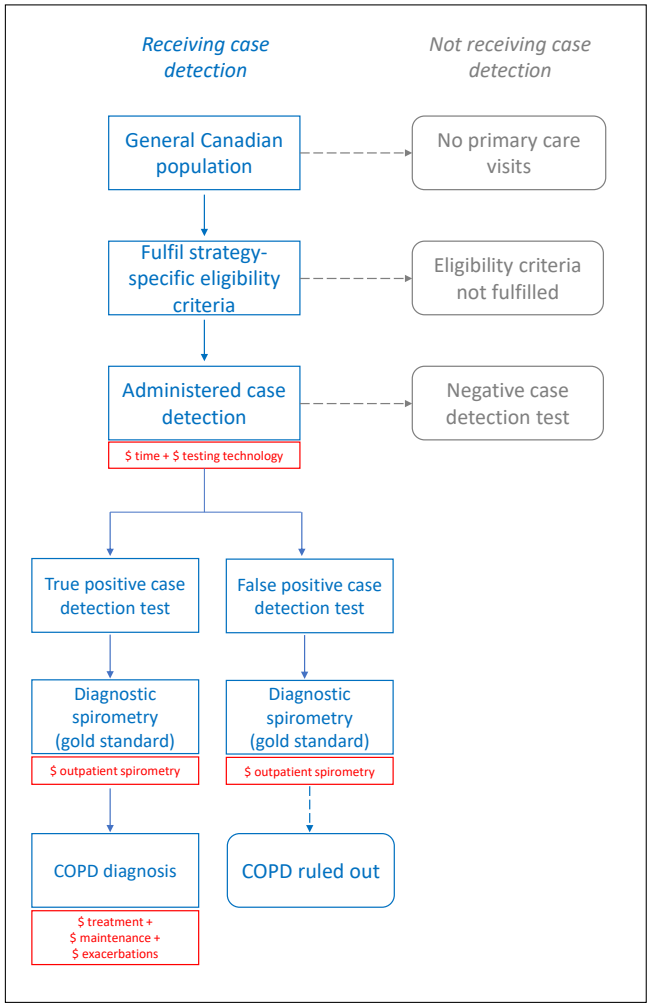


Figure 4.1: Schematic for administration of case detection programmes. Individuals receiving case detection are shown in blue, those not receiving case detection are shown in grey. Costs associated with case detection, diagnosis, and treatment are included in red.

Administering case detection was costed at 34% of a 15-minute routine primary care visit [42, 43]. The CDQ is only assigned the time-related cost whereas flow meter strategies incur the additional cost of screening spirometry. Outpatient diagnosis includes the cost of diagnostic spirometry plus a primary care visit to interpret the results. Unit costs of utilisation were determined from the British Columbia fee schedule [29].

Within EPIC, inhaled therapies are assigned to individuals according to the Global Initiative for COPD (GOLD) ABCD criteria following diagnosis or an exacerbation [44]. Average annual costs of treatment with inhaled therapies were determined from medication dispensation records in British Columbia health administrative data [30].

Table 4.2: Costs and parameter input values relevant to evaluation of case detection.

Item	Value	References
Global parameters		
Time horizon	5 years	
Population size	19.8 million	[18]
Case detection initial uptake	0.05	[26]
Annual increase in case detection uptake	0.05	
Discount for costs	0	[17]
Case detection costs		
Time-related cost for administration	$11.91	[29]
Flow meter with bronchodilator	$18.90	
Flow meter without bronchodilator	$12.77	
Outpatient diagnosis	$62.19	
Treatment		
Costs (annual per-patient) [a]		
SABA	$55.17	[30]
LAMA	$366.55	
LAMA/LABA	$670.44	
ICS/LAMA/LABA	$1,185.23	
NRT	$382.63	[31]
Rate reduction for exacerbations		
SABA	0	
LAMA	0.22	[32]
LAMA/LABA	0.23	[33]
ICS/LAMA/LABA	0.34	[34]
NRT odds ratio for successful smoking cessation	1.38	[35, 36]
Medication adherence [b]	0.7	
Exacerbation costs [c]		
Mild	$31.68	[37, 38]
Moderate	$793.08	
Severe	$10,063.13	
Very severe	$22,033.60	
Maintenance costs (annual per-patient) [d]		
GOLD 1	$147.48	[39, 40]
GOLD 2	$360.49	
GOLD 3	$943.83	
GOLD 4	$1,286.84	

CDQ - COPD Diagnosis Questionnaire; NRT - Nicotine Replacement Therapy; SABA - Short-acting beta-agonists; LAMA - Long-acting muscarinic antagonist; LABA - Long-acting beta-agonist; ICS - Inhaled corticosteroids; GOLD - Global Initiative for COPD.
General EPIC model parameters have been reported previously [19, 16].
[a] Annual per-patient treatment costs are weighted by adherence (70% in the base case analysis).
[b] Medication adherence of 70% means that out of 100 patient-years in which a patient was eligible for a medication, they only took the medication (and thus received the benefit) in 70 patient-years.
[c] Mild exacerbations are an intensification of symptoms that does not require an encounter with the healthcare system and so are only assigned the cost of increased medication; moderate exacerbations are when the patient visits a physician or emergency department but is not hospitalised; severe exacerbations are assumed to result in a hospital admission, and very severe exacerbations in admission to the intensive care unit.
[d] Maintenance costs are those that accrue outside of episodes of exacerbations and include physician visits, rehabilitation programmes, laboratory tests and devices, and oxygen therapy. Treatment costs have been deducted from maintenance costs to avoid double counting [41].

Three months of nicotine replacement therapy (NRT) was administered to all newly diagnosed patients who were current smokers. The associated effect of treatment on health outcomes is summarised in Table 4.2. Adherence to both treatments was set at 70%. We assume 100% public drug coverage since all provinces have full coverage for adults ≥65 years which will account for most COPD patients [45].

The medical costs of exacerbations and background medical costs (outside of exacerbations and treatment) were determined from published Canadian studies and applied by exacerbation severity and GOLD grade [37, 38, 39, 40].

4.2.5 Analysis

Budget impact was calculated for each strategy and year as the difference in total costs from the baseline scenario, where negative budget impact indicates additional healthcare resources are required (budget expansion). We also evaluated cost subcategories of case detection, treatment (inhaled therapies and NRT), and exacerbation-related hospitalisations. In addition, we evaluated the performance of each strategy by reporting the size of the eligible population, number of case detections administered, number of referrals to outpatient diagnostic spirometry, and number of additional true COPD diagnoses.

We conducted one-way sensitivity analysis to assess the impact of model assumptions. We evaluated low case detection uptake (2% to 10% range; 2%/year increase) and high uptake (8% to 40% range; 8% /year increase) scenarios. We ran separate analyses for reduced adherence to inhaled therapies of 0.5 and 0.3, following previous population assessments, and removing the administration of NRT following diagnosis since guidelines recommend smoking cessation for all current smokers irrespective of COPD diagnosis [46, 44]. Further analysis was conducted with an age limit ≥75 years for case detection.

4.3 Results

The starting population size was 19.8 million for adults ≥40 years of age. Over the time horizon, 2.3 million individuals entered the model and 940,000 left from death/emigration. At baseline the COPD prevalence among Canadians aged ≥40 years was 11.9% and 30.4% of individuals with COPD were diagnosed. These are

similar to the COPD prevalence (11.2%) and proportion diagnosed (29.7%) observed in the CanCOLD study [5, 47] (Appendix B.1).

The most inclusive strategies (S1 – all patients ≥40 years) resulted in 40.4% of the target population administered case detection after five years, compared to 16.7% under the least inclusive strategies (S3 – patients ≥50 years with a smoking history) (Table 4.3). In S1a (CDQ ≥17 points for all patients), an additional 145,700 individuals with COPD were diagnosed after five years compared to routine diagnosis in the no case detection scenario, which increased the proportion of COPD individuals diagnosed to 37.8% (from 30.4%) by 2026. The diagnosed proportion increased to 34.1% under S3b (CDQ ≥16.5 points for patients ≥50 with a smoking history). However, S1a also resulted in 4.6 million referrals to diagnostic spirometry, 96% of which were false positives.

Table 4.3: Five-year (2022-2026) cumulative results on scope and performance of case detection strategies. Percentages are the proportion of the target population, unless specified otherwise.

	Eligible [a]	**Administered case detection**	**Referred for OP spirometry**		**Additional diagnoses** [b]
			True positives (% of tested)	**False positives (% of tested)**	
(S1) All patients					
S1a: CDQ ≥ 17	20,468,000 (92.4%)	8,947,300 (40.4%)	175,400 (2.0%)	4,468,000 (49.9%)	145,700 (0.66%)
S1b: Flow meter			85,000 (0.9%)	772,100 (8.6%)	67,700 (0.31%)
S1c: CDQ ≥ 17 + Flow meter			58,100 (0.6%)	412,900 (4.6%)	44,600 (0.20%)
(S2) Symptomatic patients					
S2a: Flow meter	18,760,100 (84.7%)	5,792,300 (26.2%)	87,000 (1.5%)	1,161,600 (20.1%)	69,800 (0.32%)
(S3) Smoking history					
S3a: CDQ ≥ 19.5	8,486,300 (38.3%)	3,705,900 (16.7%)	28,000 (0.8%)	1,382,600 (37.3%)	22,000 (0.10%)
S3b: CDQ ≥ 16.5			87,000 (2.3%)	2,117,800 (57.1%)	76,300 (0.34%)
S3c: Flow meter			55,100 (1.5%)	748,900 (20.2%)	47,000 (0.21%)
S3d: CDQ ≥ 17 + Flow meter			42,400 (1.1%)	184,600 (5.0%)	35,300 (0.16%)

OP – outpatient. Results based on a single run of EPIC per scenario.
[a] Eligible defined as meeting the eligibility criteria and having visited primary care within the same year over the time horizon.
[b] Additional diagnoses compared to routine diagnosis under the baseline scenario of no case detection, after 5 years.

All strategies resulted in higher total costs compared to no case detection (Table 4.4). The greatest budget expansion was $423 million for S1a, with 86% of costs

attributed to administering case detection and subsequent diagnostic spirometry. The corresponding results for S3b were $195 million and 83%. The costs of case detection began to plateau by the end of the time horizon as the proportion of eligible patients not already tested was depleted, whereas treatment costs continued to increase as more patients were diagnosed (Figure 4.2). Minor cost-savings were observed from exacerbation-related admissions and outpatient care from fewer mild and moderate exacerbations, respectively saving $6 million/year and $12 million/year under S1a by 2026.

Table 4.4: Total budget impact (no case detection – case detection) results. Negative budget impact indicates budget expansion.

Outcome	**S1a**	**S1b**	**S1c**	**S2a**	**S3a**	**S3b**	**S3c**	**S3d**
No case detection strategy costs (million $)								
Case detection: physician time [a]				0				
Case detection: use cost [a]				0				
Treatment				2,300				
Hospitalisation				4,786				
Outpatient [b]				7,666				
Total				14,752				
Case detection strategy costs (million $)								
Case detection: physician time [a]	107	107	107	69	44	44	44	44
Case detection: use cost [a]	293	228	314	155	89	139	99	132
Treatment	2,365	2,325	2,312	2,329	2,306	2,337	2,321	2,314
Hospitalisation	4,772	4,779	4,780	4,779	4,781	4,777	4,779	4,780
Outpatient [b]	7,637	7,649	7,652	7,648	7,660	7,649	7,654	7,657
Total	15,175	15,087	15,165	14,980	14,880	14,947	14,898	14,927
Budget impact (million $)								
Case detection: physician time [a]	-107	-107	-107	-69	-44	-44	-44	-44
Case detection: use cost [a]	-293	-228	-314	-155	-89	-139	-99	-132
Treatment	-65	-25	-12	-29	-6	-37	-21	-14
Hospitalisation	13	7	6	7	5	9	7	6
Outpatient [b]	29	17	14	18	7	17	12	9
Total	-423	-335	-412	-228	-128	-195	-146	-175

Results based on a single run of EPIC per scenario.
[a] Case detection costs have been split by time (time-related cost of GP implementing case detection) and use cost (cost of Flow Meter technology and outpatient spirometry diagnosis).
[b] Outpatient care are the remaining costs not included in case detection, treatment or hospitalisation and includes COPD maintenance costs, routine diagnosis, and costs associated with mild and moderate exacerbations which are assumed not to result in hospitalisation.

Sensitivity analysis showed minimal change in the ranking of strategies across analyses (Figure 4.3). Total budget impact decreased by a maximum of 4.5% when NRT was removed or medication adherence was decreased since case detection administration, which comprises the majority of costs, was unaffected. Results were most affected by uptake, with higher uptake rates (8% to 40% range; 8% /year)

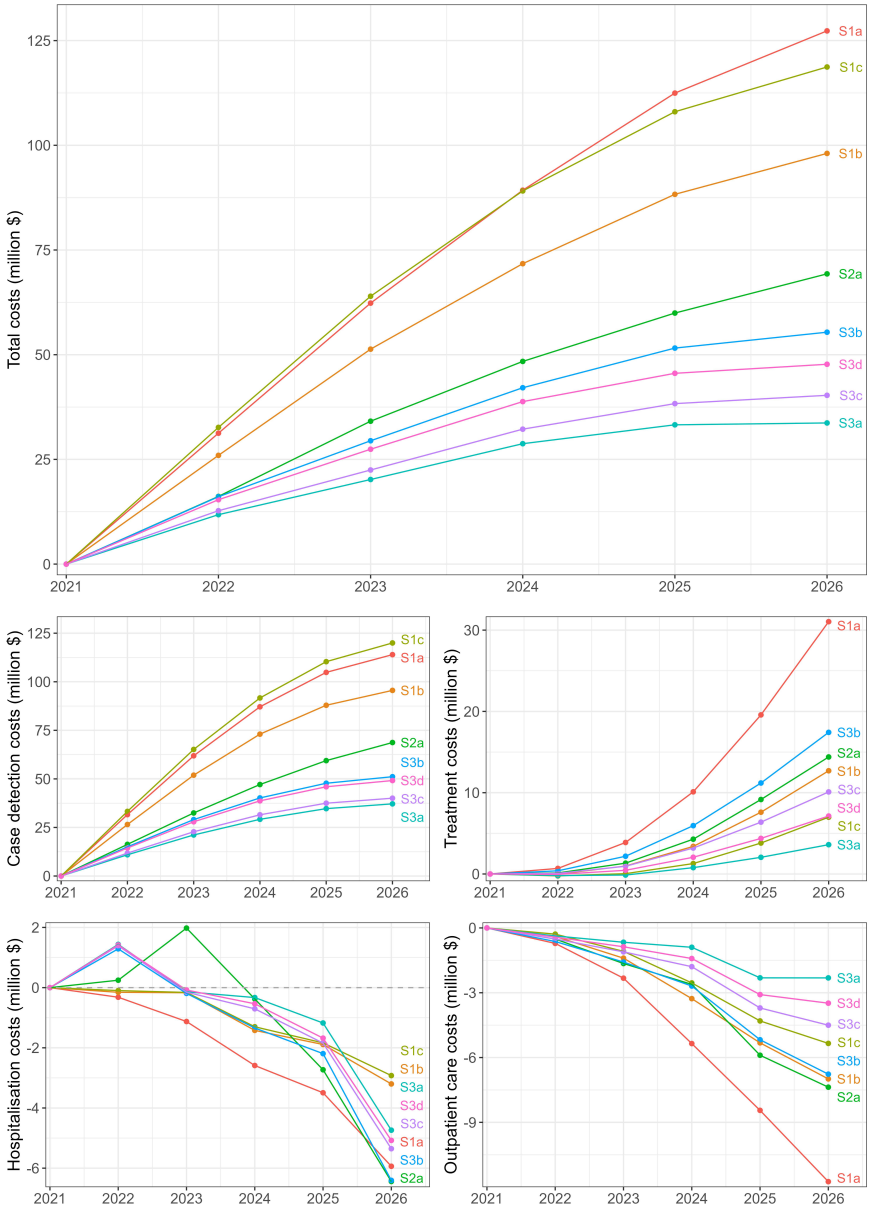


Figure 4.2: Annual total (top), case detection (middle left), treatment (middle right), hospitalisation (bottom left), and outpatient care (bottom right) additional costs (million $) compared to no case detection baseline scenario. Negative additional costs indicate cost savings.

S1a CDQ ≥ 17 points for all patients; S1b flow meter (with bronchodilator) all patients; S1c CDQ ≥ 17 points + flow meter (with bronchodilator) all patients; S2a flow meter (without bronchodilator) among symptomatic patients; S3a CDQ ≥ 19.5 points among patients aged ≥50 years with a smoking history; S3b CDQ ≥ 16.5 points among patients aged ≥50 years with a smoking history; S3c flow meter (without bronchodilator) among patients aged ≥50 years with a smoking history, S3d CDQ ≥ 17 points + flow meter (with bronchodilator) among patients aged ≥50 years with a smoking history. Results based on a single run of EPIC per scenario. Corresponding results tables can be found in Appendix B.3

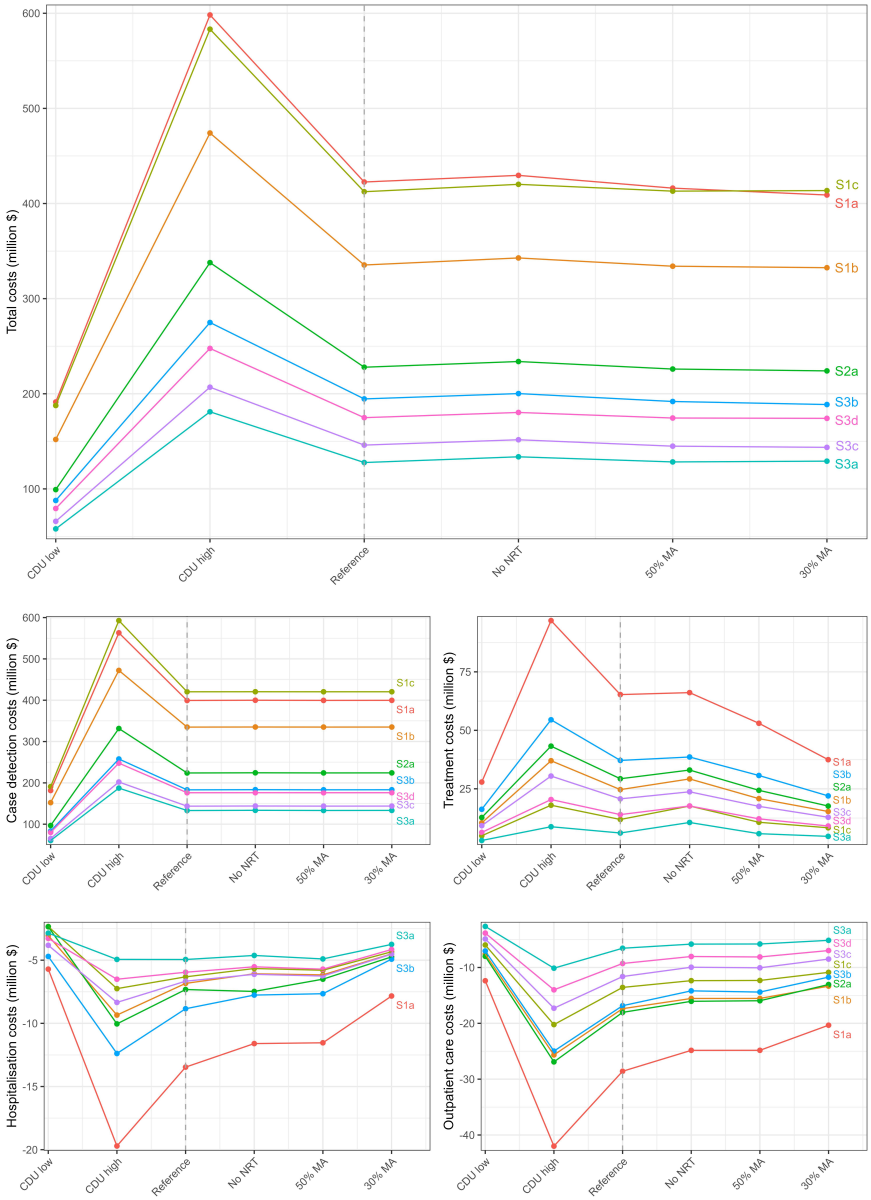


Figure 4.3: Sensitivity analysis of total additional costs of case detection strategies compared to no case detection. Negative additional costs indicate cost savings. Grey dashed line indicates the reference case analysis.
CDU – case detection uptake (low uptake defined as 2% to 10% range with 2%/year increase and high uptake as 8% to 40% range with 8% /year increase); NRT – nicotine replacement therapy; MA – medication adherence. S1a CDQ $\geq$ 17 points for all patients; S1b flow meter (with bronchodilator) all patients; S1c CDQ $\geq$ 17 points + flow meter (with bronchodilator) all patients; S2a flow meter (without bronchodilator) among symptomatic patients; S3a CDQ $\geq$ 19.5 points among patients aged $\geq$50 years with a smoking history; S3b CDQ $\geq$ 16.5 points among patients aged $\geq$50 years with a smoking history; S3c flow meter (without bronchodilator) among patients aged $\geq$50 years with a smoking history, S3d CDQ $\geq$ 17 points + flow meter (with bronchodilator) among patients aged $\geq$50 years with a smoking history. Results based on a single run of EPIC per scenario.

resulting in greater budget expansion ($598 million under S1a) but also a greater proportion of COPD patients diagnosed (40.1% by 2026 under S1a) compared to the reference analysis. Sensitivity analysis results for upper age limit are presented in Appendix B.5.

4.4 Discussion

We used a validated whole disease microsimulation model to evaluate the budget impact to the Canadian healthcare system of adopting primary care-based early detection strategies for COPD. We have created a web app which allows readers to modify cost and uptake inputs and examine their impact on results (`https://resplab.shinyapps.io/bia-copd-mountain-2023/`). Questionnaire-based testing for all patients ≥40 years during routine primary care visits, although most effective at increasing the diagnosed prevalence, would have a large budgetary impact of $423 million over five years, with budget expansion largely attributed to case detection and subsequent outpatient diagnosis. Total healthcare spending in Canada was estimated at $331 billion in 2022, representing 12.2% of the country's GDP [48]. Implementing a country-wide COPD case detection programme would require significant additional investment of healthcare resources, accounting for an estimated 0.04% of the healthcare budget per year by 2026. If the budget impact of a more inclusive strategy is deemed too high, then we must accept a lower threshold for cost-effectiveness. At a reduced WTP, the CDQ at a low threshold remains the preferred testing technology but paired with stricter eligibility criteria (≥50 years with a smoking history) with a budget impact of $195 million.

This study is the first budget impact analysis of COPD case detection strategies and contributes an important affordability and feasibility assessment. Our analysis is monetary-focused and only captures benefits that result in cost-savings. Therefore, it is important to keep the results in the context of the preceding and complimentary cost-effectiveness analysis that established the value of the strategies considered in terms of QALYs gained by patients diagnosed earlier through case detection versus monetary costs less than the conventional WTP threshold [16]. Other existing literature has evaluated the performance of COPD case detection in improving long-term patient outcomes [14, 15, 16]. We provide additional evidence showing that case detection can be a successful method for reducing the prevalence of undiagnosed COPD when applied to a large population, dependent on strategy selected and rate

of uptake. Strategies targeting a more limited population increase the proportion of diagnosed patients by a smaller proportion, but the total budgetary impact is smaller.

Our results highlight the need for increased diagnostic spirometry capacity, which may be the greatest barrier to implementing COPD case detection. A COPD diagnosis can only be confirmed using spirometry yet there is massive underutilisation of this diagnostic test globally [49, 50]. In Canada, estimates for the proportion of patients with a community diagnosis of COPD who have never received spirometry range from 30-42% [50, 51]. A principal reason for this is lack of equipment and trained personnel for spirometry in primary care where 80% of patients with COPD in Canada are managed [39]. Primary care practitioners often refer patients to specialised pulmonary function laboratories, which can have long waiting lists and create further access barriers for rural and remote parts of Canada [52, 53]. Most strategies considered in this analysis would require at least one million diagnostic spirometry tests over five years, which we assume to be referred to outpatient services. Future research and discussions must consider solutions for upskilling primary care to perform diagnostic spirometry if COPD case finding strategies in the entire Canadian population are to be feasible.

This study has several limitations. First, our analysis based uptake on general population participation in lung and colon cancer screening in Canada [26, 27]. Spirometry is a comparatively less invasive procedure so may have higher uptake, but given major issues with spirometry access, we do not exceed 40% per year as the upper limit in sensitivity analyses [51]. Nonetheless, sensitivity analysis shows uptake to be a significant determinant in affordability and our analysis should be updated when results from empirical studies are available. Second, our model only accounts for the effect of inhaled therapies on exacerbation rate and not the indirect improvement in lung function [54, 55]. We may observe more cost-saving if this latter mechanism was accounted for as patients would be less likely to progress to more severe disease stages. Third, there is uncertainty in how the time-related cost would be billed. Since we assume case detection to be administered during routine primary care visits, it may not result in budget impact if it does not result in an increase in the length or number of appointments. Conversely, this time cost captures the opportunity cost for time spent administering COPD case detection during primary care visits. We separate out the time-related cost in our budget impact results

for full transparency. Finally, EPIC is a deterministic model which means we are unable to explore uncertainty in the input parameters through probabilistic sensitivity analysis, however, results from one way sensitivity analyses are reported.

4.5 Conclusion

Adopting a national primary care-based case detection programme for COPD will require prioritisation by budget holders and significant additional investment to facilitate access to diagnostic spirometry. Case detection is an effective method for increasing the proportion of COPD patients diagnosed but depends on uptake of the programme in primary care.

4.6 Supporting information: Extended statistical methodology

The budget impact analysis was submitted and published in CMAJ Open, the Canadian Medical Association's open access journal. Therefore, the paper appropriately focused on the health economics and application of results. However, the analysis was carried out using an advanced statistical simulation model that underwent adaptation and development specifically for the purpose of this research. This report is supplementary to the main article and provides an extended explanation of the statistical methodology. We begin with an overview of the Evaluation Platform in COPD (EPIC) [19, 16] before detailing adaptations I made to EPIC during my time within the Respiratory Evaluation Sciences Program research group at University of British Columbia, Vancouver, funded by the UKRI-Mitacs Globalink research exchange scheme. The changes include necessary expansions to model inputs and outputs to accommodate the analysis design, and the development of a new model setting to allow identical baseline values across different intervention strategies, which will be of benefit to future research using EPIC. It is assumed that the reader has first read the main article.

4.6.1 What is EPIC?

EPIC is a deterministic discrete-event microsimulation model for the development and progression of COPD in the Canadian general population aged ≥40 years. EPIC was a nationally funded research project involving stakeholders from a variety of disciplines including statistics, data science, medicine, epidemiology, economics, and health policy. The aim of EPIC was to create a population-based COPD model for epidemiological projections and evaluation of a wide range of COPD policies in the Canadian context [19].

Key words:

- Deterministic – a given initial state will always produce the same output.
- Discrete-event – operates as an ordered sequence of events in time.
- Microsimulation – simulates events at an individual person level.

EPIC is a "whole disease" model which refers to a modelling approach that incorporates events across the entire disease pathway within a single framework and with consistent assumptions [56]. Compared to a de novo approach, whole disease models have a more flexible platform for exploring the decision space and are able to account for downstream consequences of intervention. This enables a more realistic estimation of costs and can improve efficient allocation of funds as well as overall disease management [56, 57, 58].

Events are incorporated into EPIC through a series of modules: (1) demographics of the general Canadian population, (2) smoking prevalence, (3) COPD occurrence, (4) symptoms, (5) primary care visits, (6) COPD diagnosis, (7) lung function decline, (8) exacerbations, (9) COPD-related and background mortality, and (10) medical costs and quality adjusted life-years. Figure 4.4 provides a simplified diagram of the EPIC model. An optional additional module for case detection was developed for the cost-effectiveness analysis that this budget impact analysis builds upon [19, 16]. Each module uses statistical modelling (e.g., linear models, generalised linear models, random effects model, cox proportional hazards models) fit to a range of Canadian data sources including clinical trials, longitudinal cohort studies, and administrative data. Parameter values are taken from published Canadian studies and reports. Where appropriate data or literature is not available, parameters have been fine-tuned until outputs reflect overall population trends.

EPIC is an open-source model available as an R package, but the model itself runs in C++.

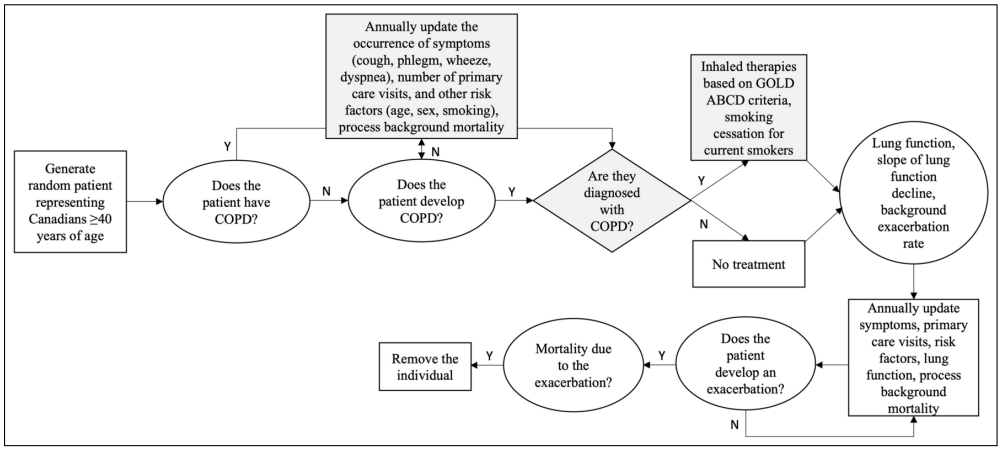


Figure 4.4: Schematic illustration of the Evaluation Platform in COPD (EPIC). Diagram from Johnson et al. (2021) [16].

4.6.2 Summary of minor changes to EPIC

Since EPIC was also used for the previous cost-effectiveness analysis by Johnson et al. (2021), all the major modelling components for case detection were already developed. However, a few minor adaptions were required to accommodate the budget impact study design.

Additional outputs

This study is the first time EPIC has been used for a cost-focused analysis. Furthermore, annual results are crucial for a budget impact analysis whereas some of the existing outputs in EPIC were only available cumulatively across the entire model time horizon. Therefore, additional outputs were added to provide costs by the required subcategories, and relevant results at an annual level.

Additional functionality to the case detection module

Two changes were made to the case detection module.

First, simulations in EPIC start in 2015 due to the incorporation of population projections from POHEM within the population demographics module. Previously, the case detection module could either be on for the entire model time horizon or off for the entire model time horizon, whereas for the budget impact analysis we needed case detection intervention to begin in 2022. Therefore, functionality was added to turn case detection on and off at user defined years. Turning case detection off is not needed for the budget impact analysis but was included to provide greater generalisability to other analyses where you may want to study the effects in the years following a short-term intervention.

Second, we needed to model gradual market penetration of the case detection strategy in primary care as rate of uptake would have a significant impact on costs. This was achieved by changing the probability of case detection from a scalar (in the cost-effectiveness analysis the probability of case detection is assumed fixed across the time horizon) to a vector of length equal to the time horizon. The user can then set the probability for each year of intervention individually.

4.6.3 Development of new setting

The most substantial change to EPIC was the addition of a new model setting that was developed to address a specific problem in the budget impact analysis but could be useful for any analysis that introduces an intervention or requires comparison across different scenarios/strategies.

The problem

There are two features of EPIC relevant to this problem. First, simulations start in 2015, and second, EPIC simulates person-by-person i.e., a given agent's pathway is simulated from creation to death (or end of model time horizon) before the next agent's pathway begins. As a result, the pre-intervention period in the budget impact analysis (2015-2021) was different across the nine scenarios considered (nine being one baseline no case detection scenario plus eight case detection strategy scenarios). By "different", we mean they have different simulation paths and produce different outputs. Setting seed in R does not fix the problem.

To explain why this occurs, let us simplify the problem by considering just two scenarios, one in which no case detection is introduced and one in which questionnaire-based case detection for all patients is introduced. These are strategies 'S0' and 'S1a' respectively, continuing notation from the main article. Assuming we set seed in R, when EPIC is initialised the first agent created in both scenarios will be identical. Further, the sequence of events for this agent from 2015-2021 will be identical since so far there is no difference between the two simulations. However, when we reach 2022, in the S1a simulation, case detection is introduced into the population and let's assume that this agent is both eligible and selected. The agent will then interact with the case detection module and randomness will be encountered that is not present in the S0 scenario. The set seed has now "broke" because S1a is a few "random steps" ahead of S0. This isn't a problem for the first agent; we of course want the simulation path to be different between the two scenarios following case detection – that's the whole point of an intervention! The problem arises when we move on to the second agent. Since the two simulation scenarios are now at different positions in the sequence of random numbers set by R, the second agent created will be totally different between the two scenarios (and will obviously then have different simulation paths). The same will be true for every

other agent simulated.

In certain analyses, this would potentially not be an issue. With a large enough sample size, the variation would even out, and EPIC would still produce very similar overall results. For example, even if the exact number of agents alive and the exact number of agents with COPD varies slightly across scenarios, we would still expect the COPD prevalence to be very similar. However, in a budget impact analysis the baseline values (results for 2021) should be identical. Figure 4.5 shows the equivalent results as Figure 4.2, but prior to the implementation of the new setting. The results show that the budget impact in 2021 is not equal to zero, illustrating the difference between simulation scenarios even prior to intervention. The hospitalisation costs and outpatient care costs plots (bottom row of Figure 4.5) show the most random fluctuation. These costing subgroups are driven by exacerbations which are rarer events and hence the most vulnerable to stochastic variation. Furthermore, the hospitalisation costs from 2022-2026 could misleadingly suggest that case detection is resulting in greater hospitalisation costs, when in fact there were greater hospitalisation costs in the baseline year as well, potentially resulting from the baseline scenario (S0) simulating a comparatively less severe COPD patient mix.

The solution

A few solutions were first considered but quickly dismissed:

- Simulate year-by-year instead of person-by-person – this would involve an extensive rewrite of all model code.
- Begin simulations in 2022 instead of 2015 – this is not possible due to the way population projections are incorporated.
- Run multiple simulations for each scenario and take the average (like an MCMC approach) – could theoretically work but would be extremely computationally intensive given the number of strategies, the time horizon, and population size. Even with high-performance computing, it would likely take weeks to run a large enough number of simulations for each scenario.

A solution was found by taking a closer look at the sources of randomness within EPIC and considering how to control the pre-intervention period.

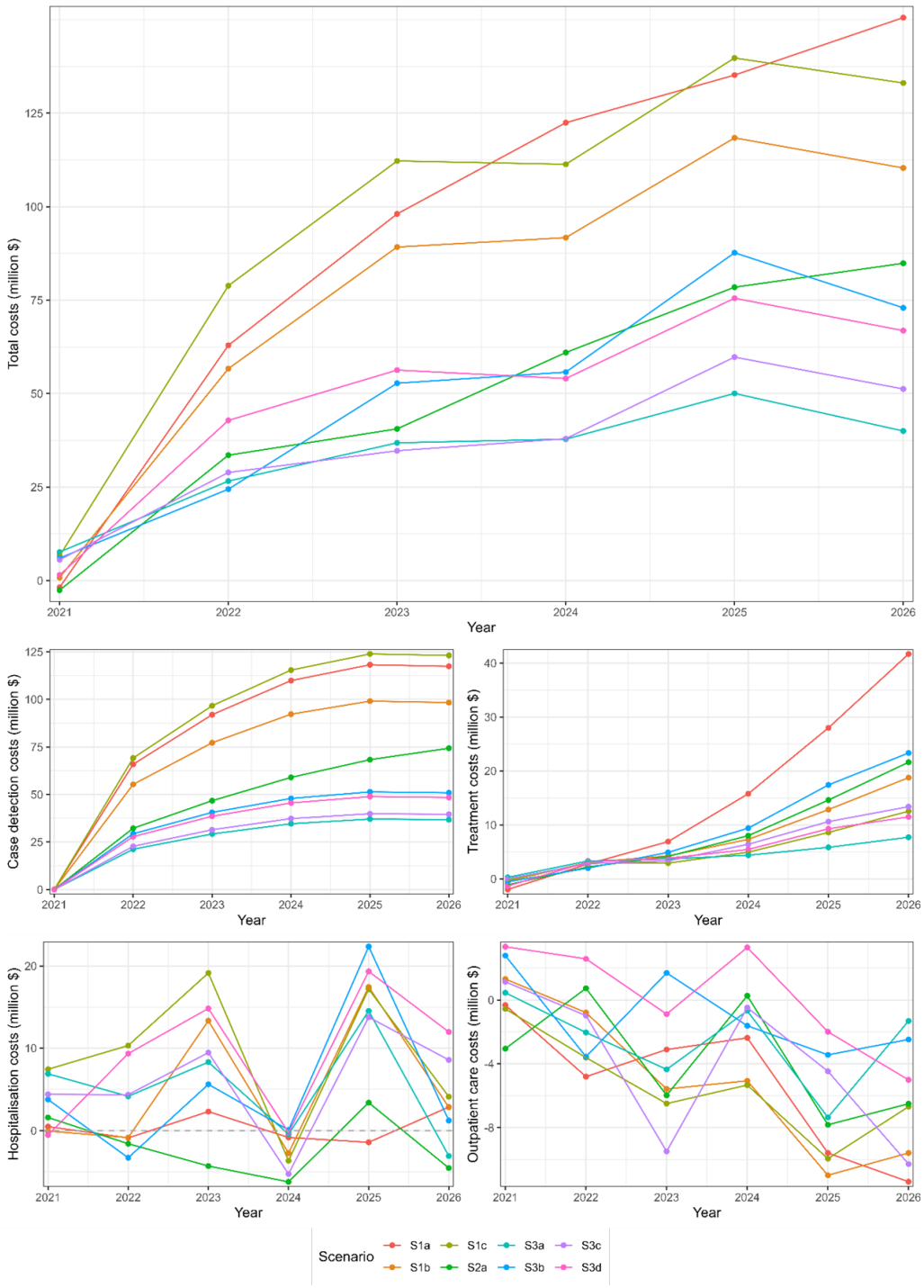


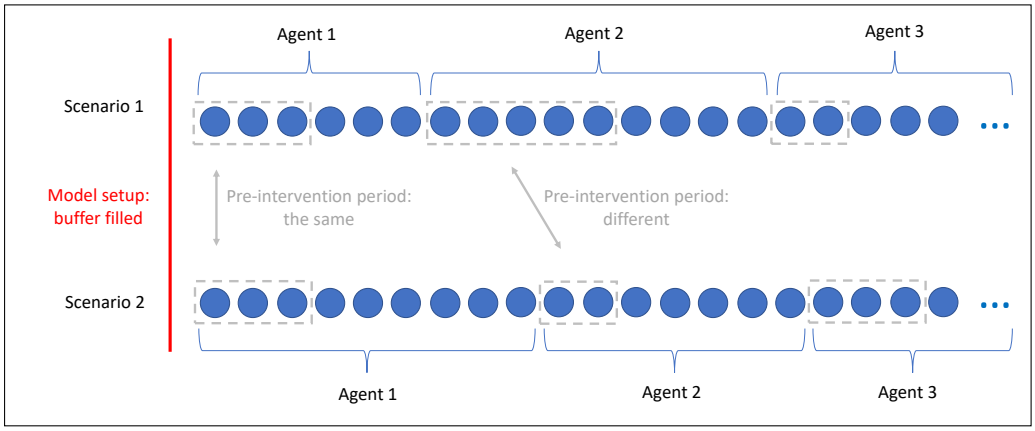
Figure 4.5: Annual total (top), case detection (middle left), treatment (middle right), hospitalisation (bottom left), and outpatient care (bottom right) additional costs (million $) compared to no case detection baseline scenario. Negative additional costs indicate cost savings. Analogous to Figure 4.2 but prior to the implementation of the new setting.

Within EPIC, randomness is introduced via random sampling from five statistical distributions:

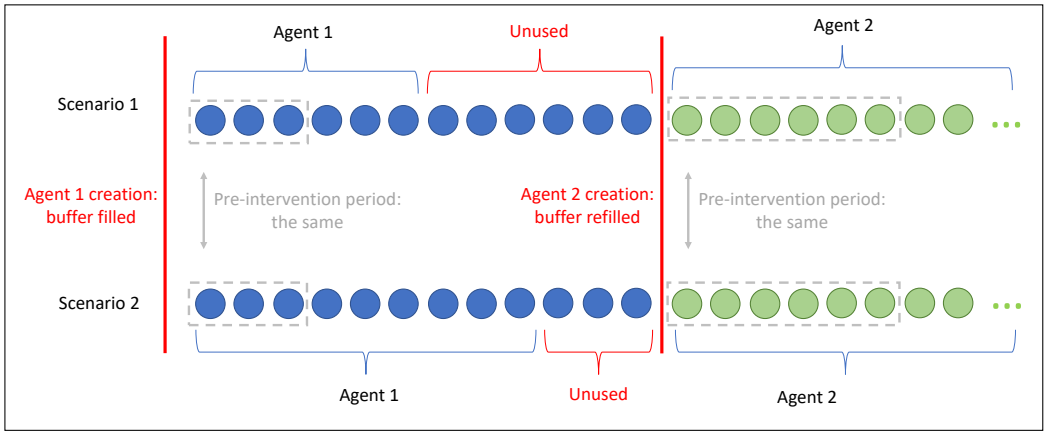
- Normal$(0, 1)$ – used to simulate patient characteristics that assume a normal distribution e.g., height and weight
- Uniform$(0, 1)$ – used to accept/reject events with a given probability
- Exponential(1) – used to simulate time to events
- Multivariate-Normal(μ, Σ) – where μ is the mean vector and Σ the covariance matrix; used to model presentation of respiratory symptoms (cough, wheeze, phlegm, and sputum)
- Gamma(α, β) – where α is the shape parameter and β the scale parameter; used for simulating number of primary care visits per year.

The normal, uniform, and exponential distributions are by far the most used (numerous times per agent per year). For the sake of efficiency in C++, random variables from these distributions are batch sampled at model setup and stored in a buffer. The default batch size is 50,000 but can be adjusted in model settings. When a sample from one of the distributions is needed during simulation, a value is taken from the respective buffer starting from the first value and working systematically through until all the values have been used. When every value in the buffer has been used, another batch is sampled.

To overcome the problem of different pre-intervention simulation paths, we instead refill the buffers immediately before each agent creation (regardless of whether all the values in the buffer have been used). This solution relies on the assumption that the user sets seed in R and that the buffers are appropriately sized as to not need refilling other than at agent creation. Corresponding agents across different scenarios will then have identical buffers and hence will have the same sequence of events pre-intervention. Once case detection is reached, the simulation paths of corresponding agents across different scenarios may diverge, but this will have no effect on the next agent. Referring back to the explanation of the problem in Section 4.6.3, by refilling before each agent creation it's as if every agent is the first agent. Figure 4.6 provides a simplified diagram that is intended to illustrate how the sequence of random numbers are realigned at each agent creation to produce



(a) Existing method in EPIC: buffers refilled only when needed.



(b) Newly developed method: buffers refilled at start of each agent creation.

Figure 4.6: Schematic comparing different methods of refilling random number buffers. Circles represent a random event in an agent's simulation pathway.

identical pre-intervention pathways. Note that if an agent does not interact with the case detection module in any of the scenarios, then that agent's simulation path will be identical for the entire time horizon across all scenarios. This has the additional benefit of reducing overall stochastic variation across scenarios allowing for a more accurate assessment of the effects of intervention (comparing Figure 4.5 of this report with Figure 4.2 illustrates the reduction in stochastic variation).

However, the multivariate normal (MVN) and gamma distributions do not use the buffer approach. These distributions are used less frequently (at most once per agent per year) and the parameters are not fixed but instead must be calculated based on patient-level characteristics. Therefore, these distributions are only sampled as and when needed.

We can convert both distributions over to the buffer system by using knowledge of statistical distributions.

For the MVN distribution, we apply the following result:

Result 1. *Let $y \sim MVN(\mu, \Sigma)$ and $x \sim MVN(0, I_d)$ where I_d is the d-dimensional identity matrix. Then $y = \mu + Lx$ where L is the Cholesky decomposition of Σ.*

So, when the MVN distribution is needed, μ and Σ (and hence L) can be calculated as previously. Then, x is a 4-dimensional vector (since there are 4 respiratory symptoms included within EPIC) of independent Normal$(0, 1)$ random variables which can be taken from the Normal$(0, 1)$ buffer.

For the gamma distribution, we first note that the shape parameter, α, can only ever be one of two values depending on the agents COPD status. These values are known at model setup. Hence, we create two gamma buffers Gamma$(\alpha_1, 1)$ and Gamma$(\alpha_2, 1)$ and apply the following result:

Result 2. *Let $X \sim Gamma(\alpha, 1)$. Then $X\beta \sim Gamma(\alpha, \beta)$.*

So, when the gamma distribution is needed, the scale parameter, β, can be calculated as previously. Then a Gamma$(\alpha, 1)$ random variable is drawn from the appropriate buffer, depending on the agents COPD status, and multiplied by the scale parameter.

Refilling the buffers at each agent creation comes at a major cost to model efficiency. The efficiency can be improved my minimising the batch size. As already mentioned, the default batch size is 50,000 which is excessive for one agent. Temporary counting functions were added into EPIC to count the number of times each distribution was being used per agent. Simulations were then run for 1,000,000 agents over varying time horizons to calculate the smallest possible batch sizes (as a function of the time horizon) needed to guarantee the buffers won't need refilling mid-agent pathway. These were the findings:

- Gamma – used at most once per agent per year. The two gamma buffers can use the same batch size. Batch size = time horizon + 1 *

- Normal – used at most eight times per agent per year. Batch size = 8 × (time horizon + 1) *
- Exponential – median used is 5.8 (IQR 5.5, 5.9) per agent per year but can get extreme results of up to 50 per agent per year (caused by agents experiencing large number of exacerbations). Batch size = 60 × time horizon has proved sufficient
- Uniform – median used is 8.7 (IQR 7.8, 9.7) per agent per year but similarly can get extreme results of up to 102 per agent per year. Batch size = 110 × time horizon has proved sufficient.

* *The + 1 is required since a given time horizon equates to time horizon + 1 simulation years as a baseline year zero is also simulated.*

These batch sizes are specific to the case detection analysis and would potentially need refining if applied to other analyses.

However, even with batch sizes minimised, the run time is approximately tripled compared to when the buffers are only refilled as needed. Therefore, the commands for refilling the buffers at agent creation have been wrapped in an if/else statement and the option to turn on this functionality included in model settings so that there is only a cost to model efficiency when necessary for the analysis.

4.7 References

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Chapter 5

Benefit-harm analysis of earlier initiation of triple therapy for prevention of acute exacerbation in patients with COPD

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Abstract

Rationale: Reducing the risk of exacerbation is a fundamental goal in managing stable COPD. Guidelines recommend triple therapy (inhaled corticosteroids, long-acting muscarinic antagonists, and long-acting beta-agonists [ICS/LAMA/LABA]) only as a step-up from dual therapy (LAMA/LABA) for patients at continued high risk of exacerbation, due to the trade-off of an increased risk of pneumonia associated with ICS-containing therapies. However, there is little evidence on the optimum timing of initiating triple therapy.

Objectives: To perform a benefit-harm analysis to evaluate the net benefit of earlier initiation of triple therapy for the prevention of acute exacerbations in patients with COPD, compared to standard timing recommended in current guidelines.

Methods: We used a validated whole disease microsimulation model of COPD in the Canadian general population aged ≥40 years to determine the benefit-harm of earlier initiation of triple therapy over a 20-year time horizon, compared to standard care. We assessed net change in quality-adjusted life-years (QALYs) from the reduction in risk of acute exacerbations and the increased risk of treatment-related pneumonia in subgroups of patients with COPD defined by exacerbation history, symptoms, and disease severity. Model parameters were determined from clinical trials and other published literature. Key parameters were varied in one-way sensitivity analysis.

Results: In patients at high risk of acute exacerbation (54.7% female, mean age 74.0, 68% GOLD grade I-II), earlier initiation of triple therapy was associated with a net QALY gain of 4.8 per 100 COPD patients over 20 years, compared to standard care. The net QALY gain increased to 5.9 per 100 patients in the subgroup of patients with a high symptom burden (mMRC≥2). Earlier initiation remained net beneficial in all subgroup and sensitivity analysis scenarios.

Conclusions: Modelling suggests that earlier initiation of triple therapy is likely to be net beneficial for patients at high risk of acute exacerbation, with an even greater benefit to patients with a high symptom burden. Further clinical research is needed to verify these findings in empirical studies.

5.1 Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide and significantly impairs quality-of-life [1]. Patients with COPD experience periods of acute symptom worsening, known as exacerbations, representing a major cause of hospitalisations. Reducing the risk of exacerbation is a fundamental goal in managing stable COPD to prevent accelerated deterioration of lung function, health status, quality-of-life, and mortality [2, 3, 4]. Maintenance pharmacotherapy with inhaled corticosteroids, long-acting muscarinic antagonists, and long-acting beta-agonists (ICS/LAMA/LABA), referred to as "triple therapy", is recommended for patients at continued risk of acute exacerbations despite dual therapy (LAMA/LABA) [2, 5]. Large randomised controlled trials have demonstrated the effectiveness of triple therapy in reducing the risk of acute exacerbations in patients with moderate to very severe COPD and a history of exacerbation [6, 7, 8]. However, ICS-containing therapies carry a number of risks, with varying degrees of evidence. Increased risk of pneumonia is most strongly associated with ICS use [9], though other potential risks such as osteoporosis, glycemic control, and cataracts have been observed in observational studies [10, 11, 12]. As a result of the trade-off between exacerbations and possible adverse outcomes associated with ICS, ICS-containing regimens, and specifically triple therapy, are not recommended until later stages of disease [2, 5].

Currently, little evidence exists comparing different approaches to the timing of triple therapy initiation. Therefore, the primary aim of this study was to perform a benefit-harm analysis to determine the net benefit of earlier initiation of triple therapy for the prevention of acute exacerbations in patients with COPD, compared to standard timing recommended in current guidelines [2, 5]. Net benefit analysis is a quantitative method for assessing whether the benefits of treatment outweigh the harms of side effects using a single measure, quality-adjusted life-years (QALYs), to inform clinical decision making [13]. We assessed net change in QALYs from the reduction of exacerbation risk and the increased risk of treatment-related pneumonia in subgroups of patients with COPD defined by exacerbation history, symptoms, and disease severity over a 20-year time horizon.

5.2 Methods

We performed a benefit-harm analysis of earlier initiation of triple therapy for prevention of acute exacerbation in patients with COPD. The benefit (reduction in exacerbation rate) of triple therapy and its harm (increased risk of pneumonia) were measured by net change in QALYs over 20 years. The time horizon was varied in sensitivity analysis. We chose pneumonia as the principal risk to include in our model given the strength of evidence linking triple therapy to pneumonia [14, 15, 16]. Other potential risks of ICS have weaker evidence from observational evidence [10, 11, 12] and were not included due to a lack of randomised evidence that ICS/LAMA/LABA is associated with an increased risk of adverse events other than pneumonia when compared to LAMA/LABA therapy [14, 15, 16].

Following Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Canadian Thoracic Society (CTS) guidelines, the target population was COPD patients on a single inhaler agent and at high risk of acute exacerbation, defined as $\geq$2 moderate or $\geq$1 severe exacerbations in the previous 12 months [2, 5]. This corresponds to groups C and D of the GOLD "ABCD" assessment tool, which the most recent GOLD 2023 report has proposed combining into a single "frequent exacerbator (group E)" category [17].

In the standard care scenario, patients fulfilling the eligibility criteria were assigned dual (LAMA/LABA) therapy. Patients remaining at high risk of acute exacerbation despite treatment with dual therapy were then stepped up to triple (ICS/LAMA/LABA) therapy. In the earlier initiation scenario, patients fulfilling the exacerbation eligibility criteria skipped dual therapy and were directly assigned triple therapy in the first instance of meeting the exacerbation criteria. The treatment pathways are shown in Figure 5.1.

5.2.1 Model

We used the Evaluation Platform in COPD (EPIC), a previously developed and validated deterministic discrete-event microsimulation model of COPD in the general Canadian population aged $\geq$40 years [18, 19, 20, 21]. EPIC simulates the development and progression of COPD through a series of interacting modules, including demographics of the general Canadian population, smoking prevalence,

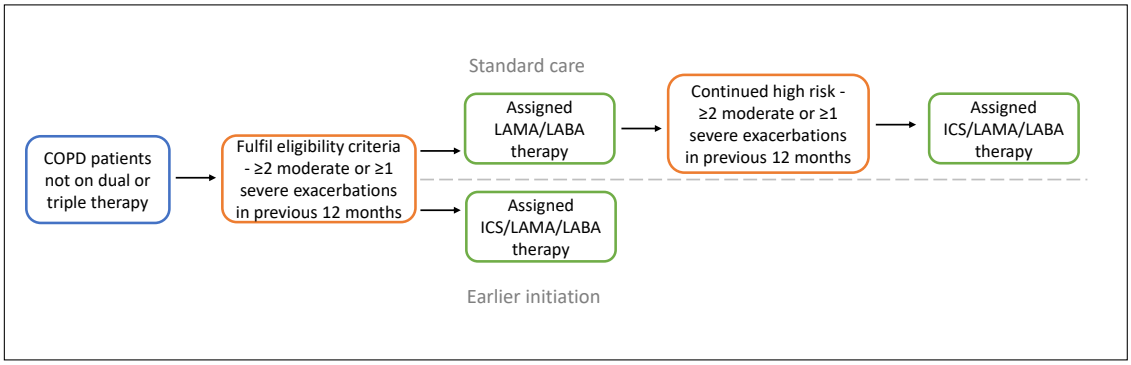

Figure 5.1: Schematic illustrating the treatment pathways for standard care and earlier initiation of triple therapy in the reference analysis.

COPD incidence, respiratory symptoms, primary care visits, COPD diagnosis, lung function decline, exacerbations, COPD-related and background mortality, medical costs, and QALYs over a lifetime horizon. The rate of exacerbation has been calibrated using reported figures from the Canadian Institute for Health Information [22] and data from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study, a national prospective cohort of patients with COPD that contains patients with diagnosed and undiagnosed COPD [23]. In diagnosed patients, the rate of moderate and severe exacerbations have been validated against major clinical trials (ECLIPSE, MACRO, OPTIMAL, AND STATCOPE) and a meta-analysis [24]. Each component of EPIC has passed rigorous tests of internal and external validation and is available as an open-source R package [25]. EPIC has previously been used in a benefit-harm analysis of long-term therapy with azithromycin [20].

5.2.2 Input values

Model inputs were derived from published studies through a targeted literature search. The selection of studies is described below. Table 5.1 summaries EPIC input values relevant to this analysis.

Treatment effectiveness

Within EPIC, inhaled therapies are assigned to individuals following diagnosis or an exacerbation. Treatment effectiveness is incorporated through the reduction in overall exacerbation rate. Whether a patient experiences an exacerbation is predicted by their age, sex, smoking status, FEV_1, GOLD grade, and medication

Table 5.1: Model parameter values relevant to the evaluation of triple therapy.

Item	**Value**				**References**
Global parameters					
Time horizon	20 years				
Annual discount for QALY	1.5%				[26]
Inhaled therapies					
Exacerbation rate reduction					
LAMA/LABA	0.26				[27]
ICS/LAMA/LABA [a]	0.44				[6]
Medication adherence [b]	0.7				
Pneumonia					
Baseline annual rate	0.0612				[6]
Risk ratio for triple therapy	1.53				[14]
QALY reduction	0.0196				[28]
Health outcomes	*GOLD I*	*GOLD II*	*GOLD III*	*GOLD IV*	
Background utility	0.81	0.72	0.68	0.58	
QALY reduction from mild-moderate [c] exacerbation	0.0225	0.0155	0.0488	0.0488	[29]
QALY reduction from severe-very severe [c] exacerbation	0.0728	0.0683	0.0655	0.0655	

LAMA – long-acting muscarinic antagonists, LABA – long-acting beta-agonists, ICS – inhaled corticosteroids, QALY – quality-adjusted life year.
General EPIC model parameters have been reported previously [18, 19].
[a] Risk ratio for ICS/LAMA/LABA vs placebo calculated as 'risk ratio for ICS/LAMA/LABA vs LAMA/LABA × risk ratio for LAMA/LABA vs placebo' [30].
[b] Medication adherence of 70% means that out of 100 patient-years in which a patient was eligible for a medication, they only took the medication (and therefore received the benefit) in 70 patient-years.
[c] Mild exacerbations are defined as an intensification of symptoms that does not require an encounter with the healthcare system and so are only assigned the cost of increased medication; moderate exacerbations are those in which the patient visits a physician or emergency department but is not hospitalised; severe exacerbations are assumed to result in a hospital admission; and very severe exacerbations in admission to the intensive care unit.

status. The rate of exacerbation and probability of an exacerbation being mild, moderate, severe, or very severe are modelled using separate individualised prediction equations developed through calibration and data from the MACRO trial [24, 31]. The individual-specific rates are modelled across all severities to reflect evidence of an exacerbation susceptibility phenotype independent of exacerbation severity [32]. Further details of EPIC's exacerbation modelling have been provided elsewhere [18].

Our analysis required two treatment effectiveness model inputs. First, the effectiveness of LAMA/LABA compared to placebo was based on the SHINE trial

[27]. Other clinical trials (e.g., AUGMENT and ACLIFORM) have compared LAMA/LABA therapy to placebo, but allowed concomitant ICS therapy, thereby potentially confounding the treatment effectiveness point estimate for exacerbation reduction [33, 34]. To avoid biasing our model, we selected the SHINE trial as it explicitly states that randomisation was stratified by ICS status, such that ICS use was balanced between groups. Second, the additional exacerbation rate reduction associated with triple therapy was based on the risk ratio of ICS/LAMA/LABA compared to LAMA/LABA from the IMPACT trial [6]. However, since EPIC's modelling approach requires treatment effectiveness to be expressed in terms of exacerbation reduction compared to placebo, we converted the risk ratio to a placebo baseline by following the approach adopted in National Institute for Health and Care Excellence's economic report for inhaled triple therapy [30]. Medication adherence was set at 70% and varied in sensitivity analysis.

Pneumonia events

The annual number of pneumonia events was modelled for each patient. Pneumonia can vary significantly in severity, from mild events treated at home with antibiotics, to very severe events requiring admission to the ICU [35]. However, we do not stratify our modelling by pneumonia severity due to a lack of clear criteria for defining episodes in clinical trials that report pneumonia as a secondary endpoint. The baseline rate of pneumonia for COPD patients was taken from the LAMA/LABA arm of the IMPACT trial [6] and the additional risk associated with triple therapy was based on a meta-analysis for triple therapy in the management of COPD [14].

Health state utility values (utilities)

To calculate QALYs, the benefit and harm of triple therapy were captured by health state utility values. Outcomes were discounted at 1.5% per year and varied in sensitivity analysis [26].

EPIC models background utility values for COPD patients by GOLD grade. The QALY reduction associated with exacerbation events, stratified by GOLD grade and exacerbation severity, were determined using EQ-5D health states and are applied at the end of an exacerbation event [29]. The derivation and validation of these values have been described in detail elsewhere [18].

We determined the pneumonia utility value using a study investigating seven different pneumonia scenarios that distinguished between where the event was treated (home/hospital), rate of recovery (progressive/delayed), and whether the patient developed severe complications [28]. We applied the disutility associated with the "uncomplicated hospital" scenario across all pneumonia events in our model. We selected this scenario as an intermediate, average scenario given the lack of detailed reporting on ICS-related pneumonia events in clinical trials. A pneumonia episode is assumed to last 6 weeks, including the event itself and associated recovery to baseline health, translating to an associated QALY reduction of 0.0196 per episode. We consider alternative pneumonia utilities in sensitivity analysis.

5.2.3 Analysis

The primary outcome measure was the benefit-harm metric calculated as net QALY gain from earlier initiation of triple therapy, compared to standard care. Treatment is net beneficial if the value of net QALY is positive. In addition, we report other health outcome results as secondary outcomes, including number of exacerbations, pneumonia events, mortality, and treatment years. All analyses were carried out in R v.4.3.0 and analysis code are available online (`https://github.com/rachaelmountain/Triple-therapy-BHA`).

Subgroup analysis

We performed subgroup analysis to investigate the benefit-harm of earlier initiation of triple therapy among different groups of patients included in the primary target population (GOLD groups C/D, $\geq$2 moderate or $\geq$1 severe exacerbations in the previous 12 months). First, we restricted the target population to patients with a high symptom burden (GOLD group D) [5]. We measured this by functional disability related to dyspnoea (mMRC$\geq$2) since EPIC does not include COPD Assessment Test (CAT) scores. In a separate subgroup analysis, we restricted the target population to patients with moderate to severe airflow limitation (GOLD group C/D and GOLD grades $\geq$2).

Sensitivity analysis

We conducted one-way sensitivity analysis to assess the impact of model assumptions. We evaluated both a higher risk of pneumonia associated with triple therapy (risk ratio 1.87) and a lower risk (risk ratio 1.25) using the 95% confidence interval limits reported in the meta-analysis from which the reference value was derived [14]. The same meta-analysis was used to inform higher and lower triple therapy treatment effectiveness scenarios; the corresponding exacerbation risk reductions are 0.48 and 0.35 respectively. We considered different utility values for a pneumonia episode, including "complicated hospital" and "uncomplicated home" pneumonia treatment scenarios as these respectively produced the highest and lowest QALY reduction (0.12 and 0.0081 respectively) [28]. We also ran separate analyses for: reduced adherence to inhaled therapies of 50% and 30% [36]; using utility discount rates of 3% and 0% [26]; and time horizons of 35 years (lifetime) and 5 years. Since EPIC is a deterministic model, we cannot explore parameter uncertainty via probabilistic sensitivity analysis.

5.3 Results

The study population at baseline was 54.7% female and had mean age 74.0. The distribution between GOLD grades were 19.3% grade I, 48.9% grade II, 27.4% grade III, and 4.5% grade IV. For patients in the primary population (GOLD groups C/D, $\geq$2 moderate or $\geq$1 severe exacerbations in the previous 12 months), earlier initiation of triple therapy resulted in a net QALY gain of 4.8 per 100 COPD patients over a 20-year time horizon. Earlier initiation resulted in 6.8 additional pneumonia events per 100 patients but reduced the number of exacerbations by 36.3. Table 5.2 presents the analysis outcomes standardised to a cohort of 100 COPD patients fulfilling the eligibility criteria.

5.3.1 Subgroup analysis

Figure 5.2 compares the difference (earlier initiation – standard care) in outcome measures between the primary population and subgroups of eligible patients. Both subgroups were associated with a greater net QALY gain compared to the primary analysis group with reduced total exacerbations, severe/very severe exacerbations, and exacerbation-related mortality per 100 patients fulfilling the scenario-specific

Table 5.2: Analysis outcomes over a 20-year time horizon expressed per 100 COPD patients fulfilling the eligibility criteria (GOLD groups C/D).

Outcome	**Standard care**	**Earlier initiation**	**Difference**
Total exacerbations	1246.9	1210.6	-36.3
Severe/very severe exacerbations	249.7	245.3	-4.4
Pneumonia events	60.7	76.7	6.8
Mortality due to exacerbations	40.1	39.5	-0.6
Dual therapy treatment years	315.6	0	-315.6
Triple therapy treatment years	534.1	855.3	321.2
Life years	870.2	875.8	5.6
Total QALYs	533.6	538.4	4.8

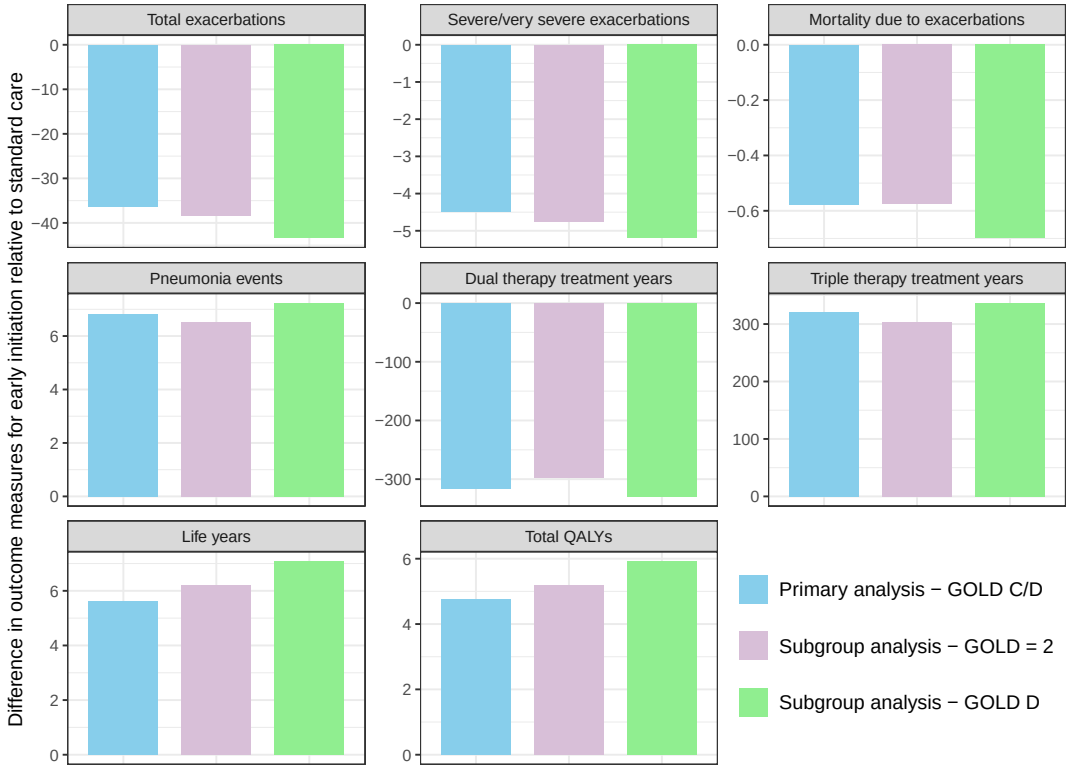

Figure 5.2: Difference in outcome measures for earlier initiation, relative to standard care, compared across primary analysis and subgroup analyses expressed per 100 COPD patients fulfilling the scenario-specific eligibility criteria.

eligibility criteria. Patients with high symptom burden (GOLD group D) derived the most benefit from earlier initiation of triple therapy with a net QALY gain of 5.9 per 100 patients over 20 years, compared to 5.2 for patients with moderate to severe airflow obstruction (GOLD C/D and GOLD $\geq$2).

5.3.2 Sensitivity analysis

Sensitivity analysis showed earlier initiation of triple therapy remained net beneficial under varying model assumptions (Figure 5.3).

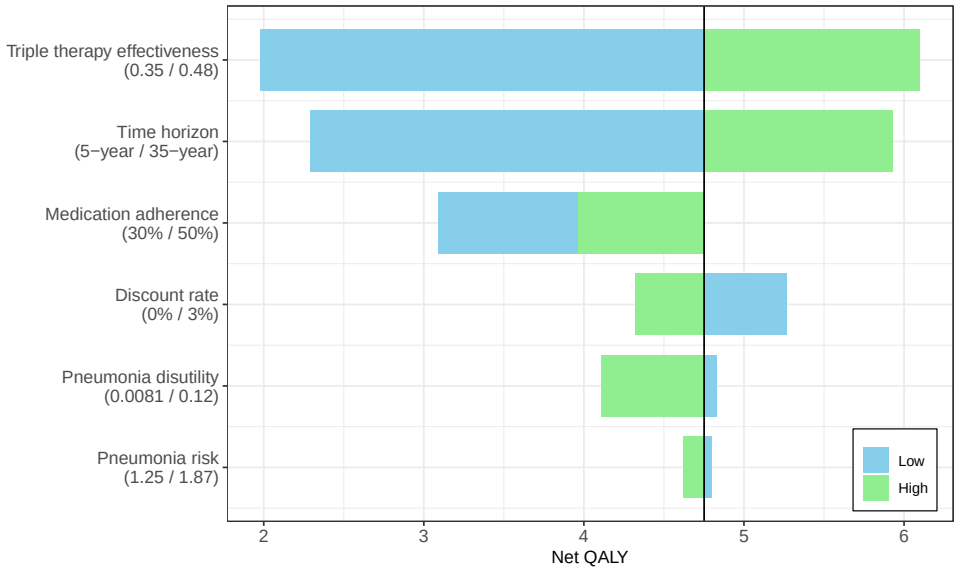

Figure 5.3: One-way sensitivity analysis results for net QALY gain (earlier initiation – standard care) under varying parameter assumptions (low/high values). Black vertical line represents the reference analysis (4.8 net QALYs per 100 patients).

Results were most sensitive to changes in treatment effectiveness, with a difference of 4.1 QALYs between the high and low effectiveness scenarios (rate reductions from triple therapy of 0.48 and 0.35, respectively, compared to 0.44 in the reference analysis). Net benefit decreased in scenarios with lower medication adherence, with a net QALY gain of 3.1 per 100 patients with 30% adherence. Changing the risk of pneumonia associated with triple therapy had the smallest effect on results. A 5-year time horizon had over half the net QALY gain of the reference analysis whereas increasing the time horizon to 35-years only resulted in 1.1 additional QALYs per 100 patients compared to the reference. Hence most benefits accrued before the end of the 20-year time horizon since many severe patients, who will benefit the most

from triple therapy, have died before 20 years.

5.4 Discussion

We used a validated whole disease microsimulation model to evaluate the net benefit of earlier initiation of triple therapy for the prevention of acute exacerbation in patients with COPD. Among patients at high risk of exacerbation, current guidelines recommend triple therapy for patients only as a step-up from dual therapy if exacerbations remain uncontrolled. However, our results indicate that the benefit of earlier initiation of triple therapy for patients at high risk of exacerbations, who are in GOLD groups C/D ($\geq$2 moderate or $\geq$1 severe exacerbation in the previous 12 months), could outweigh the harm incurred through increased risk of pneumonia, with a net QALY gain of 4.8 per 100 patients. The net beneficial finding was robust to all subgroup and sensitivity analyses.

Determining the optimal timing of inhaler escalation has significant implications for patients, the health system, and future guideline development. First, our findings are hypothesis-generating and suggest that additional clinical research should investigate whether our results are robust in real-world clinical settings. If so, earlier initiation of triple therapy could yield important clinical benefits to COPD outcomes at both the patient and population level. Using a recent study from British Columbia, we estimate that 14% of COPD patients, or equivalently, 118,000 Canadians nationwide, would be classified in the primary population cohort of our study and would be affected by a potential change in treatment recommendations [37, 38]. However, potential benefits should be counterbalanced with the risks and costs of triple therapy in individualised, patient-level, shared decision-making, prior to changing recommended clinical practice. Pneumonia was the only adverse event considered in this analysis due to strength of evidence, but our analysis should be updated as additional high-quality data on risks of triple therapy becomes available.

Second, our study highlights the importance of both symptoms and exacerbations in determining therapy step-ups. The current recommendation of LAMA/LABA therapy is based on exacerbation history alone, without accounting for patient symptom severity. Further, the 2023 GOLD report proposes combining groups C and D from the "ABCD" assessment tool into one group "E" to highlight the clinical relevance of exacerbation history [17]. Our results indicate that earlier initiation of

triple therapy would be net beneficial in the GOLD E population. However, studies have shown that greater symptom burden at baseline is associated with a greater rate of exacerbation, and that dyspnoea is a significant predictor of 5-year survival rates [39, 40, 41]. Our subgroup analysis results showed that among patients at high risk of acute exacerbation, symptomatic patients derive the greatest net benefit from earlier initiation of triple therapy (net QALY gain of 5.9 per 100 patients), as these patients have an even greater propensity to exacerbate.

In our sensitivity analysis, the reduced medication adherence (50% and 30%) scenarios, although still net beneficial, resulted in smaller net QALY gains. Medication adherence is a critical component to effective disease management yet adherence to inhaled therapies among COPD patients is notoriously low, with reported values as low as 15% [42]. Our results suggest that the less frequently patients take their medications, the less benefit will result from earlier triple therapy in terms of reduced risk of exacerbation, compared to standard care. This decrease in benefit continues to outweigh the reduced harm from lower pneumonia risk, leading to a reduced, but persistent net QALY gain. Given low inhaler adherence in typical practice, the sensitivity analyses may be more indicative of the effect of early initiation of triple therapy in a real-world setting. Regardless of treatment approach, we would argue that adherence should be optimised prior to stepping-up therapy, since there are additional risks to prescribing intensive and expensive therapy to non-adherent patients, such as harms from abrupt treatment discontinuation and financial harm.

Our study reinforces the importance of disease models, such as EPIC, for evidence generation. Modelling allows researchers to ask important questions about trade-offs in clinical care or population health management and evaluate challenging treatment decisions. For this analysis, EPIC allowed us to study outcome measures over a long-term time horizon. Clinical trials comparing triple and dual therapy are often 6-12 months in length and thus are limited in their ability to consider the long-term benefits and harms of treatment [14]. They also infrequently enrol patients with mild COPD (GOLD 1), and thus fail to consider the benefits of earlier treatment initiation among patients who are frequent exacerbators regardless of disease severity. It is important to note that our analysis did not include the impact of exacerbations on disease progression. Therefore, our results could be considered conservative and a greater net QALY gain would likely be observed if the indirect benefit of preserving

lung function was accounted for as patients would spend greater time in mild disease stages [43, 44].

This study has several limitations. First, we have simplified our modelling of pneumonia. Events are not stratified by severity due to a lack of clear definition and reporting of episodes in clinical trials. In sensitivity analysis our results were not significantly impacted by varying pneumonia risk, but the net benefit of earlier initiation of triple therapy is lower when pneumonia episodes are assumed to have more severe impact on health state (disutility). Second, the reduction in exacerbation rate for LAMA/LABA vs placebo and ICS/LAMA/LABA vs LAMA/LABA are taken from different trials, SHINE and IMPACT respectively. Our modelling approach assumes that the LAMA/LABA populations between the two studies are comparable, yet IMPACT only enrolled patients with $\geq$1 moderate to severe exacerbations in the previous 12 months, compared to SHINE where over 70% of participants had zero exacerbations in the previous 12 months. However, there are no clinical trials comparing triple and dual therapy with a placebo-controlled arm due to the lack of clinical equipoise. To account for this, we varied the treatment effectiveness estimate associated with triple therapy in sensitivity analysis and found that the net benefit was positive at both the high and low plausible limits. Third, our analysis does not consider other indicators for ICS such as asthma-COPD overlap syndrome or blood eosinophil counts as this information is not included within EPIC. Clinical trials (e.g., TRINITY, TRIBUTE, IMPACT) have suggested that eosinophils are a useful biomarker for predicting patients likely to respond to triple therapy and it comprises a key component of GOLD's recommendations for follow-up pharmacological treatment [17]. Future research could consider stratification of patients based on these criteria to further study the benefit-harm in clinically relevant subgroups. Fourth, we did not include costs data in this analysis. The role of a benefit-harm analysis is to assess whether there is a net benefit of treatment, and once established, monetary costs are an important consideration. Economic evaluations, such as cost-effectiveness analyses, will be required to quantify the value of earlier initiation of triple therapy more fully for clinical and policy decision making. Finally, our study did not include the full range of potential harms and benefits of early triple therapy initiation due to limited data availability and data quality. For example, the opportunity cost of patient time associated with taking an additional therapy is not incorporated in our model. There is growing recognition in the health economics community that such factors are important to model, but

require prospective collection and are beyond the scope of this study [45].

5.5 Conclusion

Among patients at high risk of acute exacerbation, earlier initiation of triple therapy is estimated to be net beneficial, with an even greater benefit to patients with a high symptom burden. Further clinical research is needed to verify these findings from our modelling study.

5.6 References

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Chapter 6

Discussion

The primary aim of this thesis was to investigate chronic respiratory disease care and health service delivery through the use of statistical methodology. Two distinct approaches were used, differing in data source and geographical setting. Firstly, Chapters 2 and 3 used routinely collected health data from the Morecambe Bay CDW to investigate local respiratory care. The findings from these studies provide insight into the impact of the MBRN integrated care initiative and offer contrasting approaches to encountering barriers in research with routine data. Secondly, Chapters 4 and 5 used a discrete event microsimulation model of the development and progression of COPD in the Canadian population to answer questions in the field of health economics and outcomes research. The key discussion points from these studies include recommendations to practice and policy for COPD care that hold relevance to the English healthcare system.

6.1 Chapter overviews

Outpatient services in England are under unprecedented pressure, an issue exacerbated by delayed referrals during the COVID-19 pandemic for routine and chronic care. Integrated care has been argued as the solution for improving the sustainability of the health and social care system, yet there are gaps in the literature for quantitative evidence of the impact of integrated care initiatives on elective care. Chapter 2 of this thesis utilised routinely collected health data from the Morecambe Bay CDW to model space-time patterns in referrals to outpatient respiratory clinics

in the Morecambe Bay area between 2012-2019 and assess the impact of MBRN intervention. The analysis encountered issues with primary care data from the CDW and proposed a novel spatio-temporal methodological solution that could be expanded to other fields using time restricted official statistics. The results estimated areas with full MBRN intervention were associated with a 40% reduction in referral rate by the third year of the initiative. Although the study was limited by a lack of control group, the results showed the potential of integrated care models with enhanced primary care teams to relieve pressure on elective care services and reduce the referral backlog following COVID-19 disruption.

The NHS Long Term Plan has targeted improved diagnostic standards for CRD, yet there is currently no accepted measurement approach for evaluating the diagnostic process. Existing literature recognises the challenge of measuring diagnostic quality and the need for novel sources of data. Chapter 3 discussed the capacity of routinely collected data for measuring diagnostic quality in the formats of a research letter and an extended report to the MBRN. The research encountered limitations associated with relevant data variables extracted from the Morecambe Bay CDW and grouped the issues under thematic headings: data recording, data access, and broader study design considerations. In contrast to the methodological approach taken in Chapter 2, Chapter 3 concluded that the routine data in the CDW was not fit-for-purpose for evaluating the diagnostic process but emphasised the importance of feedback between researchers and clinicians to improve the potential of routine data for research in the future. The extended report included exploratory data results on the impact of the MBRN, exemplifying the potential role of integrated care in improving both diagnostic standard and the capacity of routine data for research purposes. However, findings were limited by lack of control group, disruption of the COVID-19 pandemic, and changes in data recording practices.

Patient outcomes for COPD are considerably improved through optimal preventative and therapeutic management, and yet the disease is notoriously underdiagnosed with consequences for patient long-term outcomes and non-elective admissions. A previous analysis found that a primary care-based case detection programme would likely be cost-effective, but in a time of intense pressure on healthcare budgets, it is important to also consider the affordability. Chapter 4 extended the previous cost-effectiveness analysis by evaluating the budget impact of multiple strategies for primary care-based case detection in the Canadian population using

the EPIC microsimulation model. The most cost-effective strategy, questionnaire-based testing for all patients over the age of 40, was found to be the most expensive and would require prioritisation by budget holders. The analysis highlighted the need for increased diagnostic spirometry capacity, particularly in primary care, which may be the greatest barrier to implementing COPD case detection.

COPD exacerbations represent a major cause of non-elective hospital admissions. Maintenance pharmacotherapy is an important element of managing COPD to reduce the risk of exacerbation and improve patient quality-of-life. Chapter 5 presented a benefit-harm analysis conducted within EPIC to quantify the net benefit for COPD patients of earlier initiation of triple therapy compared to standard timing in current guideline recommendations. Modelling results suggested that the benefit of earlier initiation of triple therapy for patients at high risk of acute exacerbation could outweigh the harm incurred through increased risk of pneumonia adverse events, with an even greater benefit observed for patients with a high symptom burden. Sensitivity analysis suggested the net benefit is smaller at lower assumed medication adherence, reinforcing the importance of effective disease management, including correct medication usage. Further clinical research is needed to verify these findings in empirical studies.

6.2 Implications and future research

6.2.1 Healthcare

Many of the themes encountered in this thesis link to goals from the NHS Long Term Plan for improving respiratory disease care and population health.

First, the Long Term Plan commits to improving earlier detection and diagnosis of respiratory disease, particularly increasing access to spirometry testing in primary care to support the accurate diagnosis of COPD [18]. Chapter 3 results supported existing literature that spirometry is hugely underused, whilst contributing new insight into the impact of the pandemic on diagnostic testing [60]. Chapter 4 considered further consequences of the issue by highlighting the lack of primary care personnel trained in spirometry as a key barrier to implementing case finding programmes to reduce the prevalence of undiagnosed COPD, and its associated significant burden to society and healthcare services [12, 13, 61]. It is clear that

spirometry access must improve. The NHS Spirometry Commissioning Guidance builds upon the initial goals in the Long Term Plan by proposing three service delivery models for primary care-based spirometry testing, namely training GPs, establishing local diagnostic hubs, or a combination [62]. The guidelines emphasise the importance of decision-making at a local-level, to best suit the needs of the local population as well as the importance of integrating services [62, 63]. Chapter 3 provided exploratory evidence of improvements to spirometry completion following MBRN intervention, a local initiative that has trained GPs in the network in spirometry and provides interpretation support from specialists via multi-disciplinary team (MDT) meetings. However, these results faced limitations and additional study is needed of spirometry rates over time and across the country, along with robust evaluation of the the effectiveness of relevant service models in improving diagnostic standards.

Second, the Long Term Plan aims to do more to support those with respiratory disease to receive and use correct medication [18]. Chapter 5 highlighted the importance of research into the optimal timing of initiating or upgrading pharmacotherapy to improve patient quality-of-life and disease management. However, a consequence not discussed in the benefit-harm analysis, is the impact of increased pneumonia events resulting from triple therapy, which may contradict other NHS goals to reduce the burden of community-acquired pneumonia and associated hospital admissions. In order to estimate the impact of earlier initiation of more intensive therapies on acute services, improved definition and recording of adverse event severity is needed in clinical trial data, as outlined in the limitations of the chapter. With regards to medication usage, the sensitivity analyses of both Chapters 4 and 5 showed that at lower medication adherence, treatment effectiveness and the potential for cost-savings decline. Medication adherence is a critical component of effective disease management, yet adherence is estimated at around 50% for patients with chronic illnesses, and as low as 15% for COPD [64, 65]. The factors behind a patient not correctly taking their medication can be complex and varied, including forgetfulness, costs, poor technique, and strong beliefs [65]. NICE guidelines recommend a range of interventions for improving adherence tailored to patients' individual needs, highlighting the importance of a "whole patient" view of care [66]. Medication patterns using routine data was not explored in this thesis, despite the availability of prescription data in the CDW. There is considerable existing literature exploring the relationship between adherence and health outcomes (e.g., [67, 68, 69]), however it

could be of interest to use a linked routine data source to explore how care pathways vary at different adherence levels, for example using state sequence analysis.

Finally, the NHS Long Term Plan advocates integrated care systems to improve efficiency and patient outcomes [18]. Integrated care has been argued as essential for improving the sustainability of the health and social care system, linking to a main theme of this thesis, "healthcare under pressure". Following the 2022 Health and Care Act, integrated care is central to the organisation of the NHS in England [70], yet there is inconclusive evidence for its effectiveness [71, 72, 73]. Existing literature suggests two contributing factors are insufficient data sources and choice of outcome measures [74, 75]. Chapters 2 and 3 provided insight into the impact of the MBRN initiative using a linked cross-tier routine data source. The results showed that a service model with an enhanced primary care team and disease-specific specialist input via MDTs was successful at reducing outpatient service utilisation and increasing recording of key diagnostic markers, such as symptoms and test results, in GP records. It was hoped that this thesis would provide a more thorough and well-rounded evaluation of the MBRN by analysing diverse outcomes. However, potential research questions were limited by data quality, data availability, and the COVID-19 pandemic which disrupted routine care and restricted the time period in which the MBRN operated under regular circumstances. Quantitative evaluation of the MBRN should continue into areas such as symptom control, medication usage, and cost-effectiveness. However, the success of future research will critically depend on access to MDT data, the central component to the MBRN model, and a comparable population elsewhere in the country, particularly if funding for the network is to expand to cover the entirety of the Morecambe Bay area.

6.2.2 Data methods

This thesis has demonstrated the benefits of simulated data for health research, particularly its ability to be applied to a wide range of scenarios. Chapters 4 and 5 used the same simulation model to answer contrasting COPD research questions, with the two studies respectively including short- and long-term time horizons, economic and social outcome measures, service delivery and therapeutic intervention evaluations, as well as focusing on diagnosis and management stages of care. Despite the Canadian setting of the model used, the results hold relevance to the NHS due to the comparability of the populations, healthcare systems, and

healthcare pressures in England and Canada. However, a UK- or England-based microsimulation model for COPD, or even for multiple CRD conditions combined, could still be beneficial. A simulation model similar to EPIC could evaluate different strategies to assist in planning and prioritising health service delivery to achieve the ambitious goals set out in the NHS Long Term Plan [18]. Tan et al. developed a microsimulation model for COPD in Great Britain but the model only comprises of population demographics, smoking prevalence, and lung function decline, and does not model health service interactions. Furthermore, the model uses both outdated and international data sources [76]. Future research could exploit the rich routine data sources in England to construct a CRD microsimulation model. In contrast, EPIC is highly dependent on data from longitudinal cohort studies and clinical trials, thus is arguably limited in its ability to reflect real-world practice [52, 53]. Canadian healthcare is largely managed by province, contributing to a lack of national routine health databases. The Pan-Canadian Health Data Strategy's 2021 report contrasts the Canadian and UK health data systems, and highlights provincial data silos as a major barrier to generating whole health sector intelligence [77]. Although this thesis has recognised potential access barriers to national routine health data for researchers in England, it is not a given that such databases exist in the first place, and represent an invaluable commodity for health research.

Using data generated from patients' routine interactions with the healthcare system holds huge potential to improve services and standard of care. Chapters 2 and 3 of this thesis have demonstrated some of the strengths of using routine data for research, especially the wide range of study variables available within the CDW. Chapter 3 highlighted the importance of access to linked data by constructing patient diagnostic pathways across primary and secondary care. Community care data, although available from the CDW and a novel feature of the database, was not used in this thesis due to inconsistent data quality. More research is needed that utilises community data, in conjunction with primary and secondary data, for studying chronic conditions, particularly those that affect the elderly, as a large proportion of their care is likely to be handled by community services. The use of the CDW additionally exemplified the benefits of access to local health data, which creates potential for more bespoke access arrangements, as well as close collaboration and conversation with local stakeholders. On the other hand, a common limitation between Chapters 2 and 3 was the regional nature of the CDW that prevented a sufficient control group for the MBRN intervention population. This limitation

lends evidence to the need for investment into national or sub-national Secure Data Environments (SDEs) with linked data across healthcare tiers [41]. Future research utilising these new data sources in development present exciting opportunities for insight into health outcomes, interventions, and inequalities that may not be possible with access to only regional or trust level datasets.

A critical topic relating to research with routine data, yet to be addressed in this thesis, are the real concerns from the public surrounding patient privacy. For example, in November 2023, the NHS signed a £330 million contract with Palantir, a US technology company that works closely with intelligence agencies such as the CIA, to develop a "federated data platform", raising patient fears that their personal data would be misused [78]. Public trust is critical to building and promoting safe data platforms, but will also influence how effective the data can be for research. Without sufficient public trust, an increasing number of individuals may opt out of their health data being used for research, if given the choice. This occurred in 2021 following the announcement from the NHS of the General Practice Data for Planning and Research system, where changes to the way general practice data was to be collected was inadequately explained to the public. Although opting out is well within an individual's right, a large opt-out rate increases the risk of reduced data quality [40]. The National Data Guardian's 2021 report "Putting Good Into Practice" found that participants expect more transparency across the entire data life cycle for how their information is used and how decisions are made [79]. The government has recognised the need for improvement in how they communicate and engage with the public surrounding the use of personal data [40].

Synthetic data may hold the solution to stringent data access barriers, privacy concerns, and contribute toward regaining public trust. Synthetic data uses modelling to simulate an artificial copy of a confidential dataset with new data values that mimic the statistical properties of the original data. It could be considered a middle-ground between the two data methods used in this thesis. Since synthetic data does not exactly reproduce patient-level information, it does not require such strict access procedures. There are an increasing number of open-source tools available for synthetic data generation with user-friendly interfaces in R (e.g., SynthPop [80]) and Python (e.g., BIT-ADRUK Synthetic Data Tool [48]), reflecting the growing interest for accessible data [47]. OpenSAFELY, a secure open-source platform for analysis of electronic health records, allows users to build and test their

analysis code with synthetic data prior to submission for execution with real data, removing the need for direct access to patient records [81]. However, compared to other fields such as finance and economics, the use of synthetic clinical and healthcare data is still minimal, in part due to the higher consequences of modelling error [82]. As with all simulated data, the quality of synthetic data is critically dependent on the generating methodology used and may not reflect the true complexity of the real-world setting. A validation study by Chen et al. found that a leading synthetic data generator had limited capability to model deviations from standard care outcomes and practices, which may limit its applications to research questions like those considered in this thesis [83]. Furthermore, synthetic data carries the risk of bias amplification, thus solutions to data quality issues discussed in Chapter 3 remain critical [82]. Additionally, privacy concerns persist, such as duplication of outlying data points in the original data posing a risk of the re-identification of individuals, highlighting the importance of thorough auditing procedures prior to data release [47, 84]. In the future, synthetic data is expected to become more widely used in health research, and research should continue to evaluate synthetic data generation methodology and its application to specific disease areas.

6.3 Conclusion

This thesis has explored chronic respiratory disease care through two contrasting sources of data. Chapters 2 and 3 used routinely collected health data from the Morecambe Bay area to study service utilisation and diagnostic quality, with additional consideration for a local integrated care initiative. Chapters 4 and 5 used a microsimulation model to evaluate the impact of interventions for earlier diagnosis and therapeutic management for COPD patients. The results of the four studies hold great relevance to NHS goals for improving standard of care for respiratory disease, particularly diagnostic standards, correct medication usage, and integrated services. This thesis spotlights the potential role of both routine and simulated data in healthcare research, whilst demonstrating their respective limitations. Synthetic data has been suggested as a middle-ground between the two methods, using simulation to exploit the wealth of information in routine data whilst minimising access barriers and privacy concerns. Future research could further develop synthetic data methodology to enhance the usage of the invaluable routine data commodity available in England for improving health services and population health.

Appendix A

Measuring diagnostic quality using routinely collected data: Supplementary material

A.1 MBRN diagnostic template

Below is a copy of the MBRN diagnostic template provided by Dr Patrick Haslam, GP at Queen Square Medical Practice (Lancaster, UK) and joint clinical lead for the MBRN. Circles indicate fields with a corresponding SNOMED code. Items not circled indicate free text boxes or administrative procedures such as booking next appointment.

Presentation

Current Symptoms

☐ Spirometry screening - Consultation Heading (Spirometry screening)

.....

*** prefix denotes QOF indicator requirements.**
 # prefix denotes QIS indicator requirements.

.....

What are the patient's concerns? (free text):

.....

MRC Dyspnoea Scale (Not disease specific):

Grade	Degree of breathlessness related to activity
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on a level or when walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking 100 yards, or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when dressing/undressing

.....

*MRC score

- ☐ MRC Breathlessness Scale: grade 1
- ☐ MRC Breathlessness Scale: grade 2
- ☐ MRC Breathlessness Scale: grade 3
- ☐ MRC Breathlessness Scale: grade 4

... and 1 more

- ☐ _____

.....

Cough

- ☐ No cough
- ☐ Dry cough
- ☐ Productive cough
- ☐ Blood in sputum - haemoptysis

.....

Wheeze

- ☐ Wheezing
- ☐ Wheeze absent

.....

Sputum production

- ☐ No sputum
- ☐ Moderate sputum

☐ Copious sputum

☐ Mental health review (Mental health review)

☐ Physical activity (Physical activity)

Additional Comments (free text):

Review of Past Year

Any change in weight?
- ☐ Weight steady
- ☐ Intentional weight loss
- ☐ Abnormal weight loss
- ☐ Weight increasing

☐ Number of chest infections in last year (Number of chest infections in last year)

Template Administration

☐ #MBRN Diagnosis Template Monitoring (Initial respiratory assessment)

Background

Relevant PMHx

☐ History of Atopy

☐ No History of Atopy

☐ Patient born prematurely? (Prematurity of fetus)

☐ Patient born at term (H/O: full term delivery)

MBRN Diagnosis Template v8.3x

☐ History of Respiratory disease?

☐ No history of respiratory disease

☐ Pets (current or previous)

☐ Any history of allergies? (H/O: allergies)

Family History

☐ FHx COPD (FH: Bronchitis/COAD)

☐ FHx Asthma (FH: Asthma)

☐ FHx of Lung cancer (Family history of malignant neoplasm of lung)

☐ FHx of Atopy (FH: Atopy)

☐ No FHx of respiratory disease (No family history of respiratory disease)

Additional Details: (free text):

Occupation & Smoking

Patient occupational history (free text):

☐ Patient exposed to asbestos (H/O: asbestos exposure)

*Smoking Status

☐ Current smoker
☐ Ex-smoker

☐ Never smoked tobacco
☐ Declined to give smoking status

.....

QOF update - patients on the Asthma register aged 19 years or under are required to have either smoking status OR exposure to second-hand smoke recorded.

.....

☐ *Passive smoker (Passive smoker)

.....

☐ Smoking Pack Years (Pack years)

.....

Smoking Pack Years Calculator - https://www.smokingpackyears.com/

.....

Spirometry Checklist

Spirometry Safety Checklist

Below are all RELATIVE contraindications to performing spirometry. If in doubt please ask you clinical lead for advice.

Please note that overall studies have shown low incidence of complications from performing spirometry (5 per 10,000 tests in a study of 186,000 tests)

.....

.....

☐ No active bleeding (eg Haemopysis or oral bleeding)

.....

.....

☐ No active respiratory infection (eg TB, COVID19)

.....

.....

☐ No surgical contraindications

.....

Relevant surgery includes:
- Eye, Brain, Thoracic or Abdominal surgery within 4 weeks
- Ear or Sinus surgery within 1 week

.....

.....

☐ No medical contraindications

.....

Relevant medical history includes:

- Current pneumothorax or cerbral aneurysm
- Late-term pregnancy
- MI within the past 1 week
- Unstable hyper/hypotension (>100mmHg or <90mmHg) or pulmonary hypertension
- Uncontrolled angina, cor pulmonale or heart failure
- Untreated PE
- AAA >6cm

.....

--

Adapted from Gram BL *et al.* (2019). Standardisation of Spirometry 2019 Update. An Offical American Thoracic Society and European Respiratory Society Technical Statement

Aligned with UHMB Respiratory Physiology team

.....

Examination

Examination

☐ Weight: (Body weight)

.....

☐ Height: (Standing height)

.....

BMI (erin calculates & codes)

H - Height (m):
W - Weight (kg):
Body Mass Index:

.....

BP: / mmHg

.....

☐ Pulse rate (Pulse rate)

.....

Pulse rhythm

☐ O/E - pulse rhythm regular
☐ O/E - irregular pulse

.....

☐ Oxygen saturation (Peripheral oxygen saturation)

.....

☐ Tick if clinician has listened to patients chest (Auscultation of lower respiratory tract)

.....

2-Week PEFR Chart - https://baybreathing.com/documents/2-week%20Peak%20Expiratory%20Flow%20Chart.pdf

.....

4-Week Occupational PEFR Chart - https://baybreathing.com/documents/Occupational%20%20PEFR%20Chart%204%20weeks.pdf

.....

.....

Objective Tests

Please use this section to add codes relevant to Asthma and COPD QOF

Please note that Asthma QOF requires TWO objective tests to be recorded

.....

☐ *PEFR (Peak expiratory flow rate)

.....

Predicted peak expiratory flow rate
A - Age (years):
H - Height (cm):
S - Sex (Male/Female/Under 16):
Peak Flow:

.....

☐ Diurnal variation of PEFR (Diurnal variation of peak expiratory flow rate)

.....

Response to treatment (eg ICS)?
☐ Positive reversibility test to salbutamol
☐ Positive reversibility test to corticosteroids

.....

FeNO

☐ QOF (Quality and Outcomes Framework) - FeNO (fractional exhaled nitric oxide) test service not available
☐ Measurement of expired nitric oxide

.....

Pre-Bronchodilator Spirometry

*Spirometry exceptions
☐ Spirometry test declined
☐ Unable to perform spirometry
☐ Spirometry contraindicated

.....

☐ FEV1 before bronchodilation (FEV1 before bronchodilation)
.....

☐ % Predicted FEV1 before bronchodilatation (Percent predicted FEV1)
.....

☐ FVC before Bronchodilatation (Forced vital capacity before bronchodilation)
.....

☐ % Predicted FVC before Bronchodilatation (Percentage of predicted forced vital capacity)
.....

☐ FEV1/FVC ratio before bronchodilatation (FEV1/FVC ratio before bronchodilator)
.....

Post-Bronchodilatation Spirometry

If the FEV1/FVC ratio is <0.7 then perform reversibility testing - 400mcg Salbutamol using MDI and Volumatic Spacer
.....

☐ *Post bronchodilator spirometry completed - QOF requirement (Post bronchodilator spirometry)
.....

☐ FEV1 after bronchodilatation (FEV1 after bronchodilation)
.....

☐ % Predicted FEV1 after bronchodilatation (Percentage predicted forced expiratory volume in 1 second after bronchodilation)
.....

☐ FVC after bronchodilatation (FVC after bronchodilation)

.....

☐ % Predicted FVC after bronchodilatation (Percentage of predicted forced vital capacity after bronchodilation)

.....

☐ *FEV1/FVC ratio after bronchodilatation (FEV1/FVC ratio after bronchodilator)

.....

Variability:

.....

% Variability in FEV1

PostFEV1 - FEV1 after bronchodilation (litre):
PreFEV1 - FEV1 before bronchodilation (litre):
Percentage of FEV1 variability (%): **(PostFEV1-PreFEV1)/PreFEV1*100** =

.....

Change in FEV1 (Litres)

PreFEV1 - FEV1 before bronchodilation (litre):
PostFEV1 - FEV1 after bronchodilation (litre):
Forced expired volume in 1 second reversibility (litre): **(PostFEV1-PreFEV1)** =

.....

Outcome/Plan

Outcome / Plan

Outcome: (free text):

.....

*Smoking Cessation

- ☐ Smoking cessation advice
- ☐ Referral to smoking cessation advisor
- ☐ Seen by smoking cessation advisor
- ☐ Smoking cessation drug therapy declined

.....

Lancashire Quit Squad - http://www.quitsquad.nhs.uk/index.php

.....

Cumbria **Smoking Cessation Advice Number** - 03000 13 3000

.....

*Pulmonary rehabilitation offered

- ☐ Pulmonary rehabilitation offered

☐ COPD patient unsuitable for pulmonary rehabilitation

.....

☐ Follow-up appointment (Spirometry screening)

.....

☐ Medication review (Medication review)

.....

☐ Next medication review due (Medication review)

.....

Any new diagnoses should be followed up within 4 weeks for disease education and initial managment plan

If no clear diagnosis patient should have appointment with inital referrer

.....

If a diagnosis of COPD or Bronchiectasis please request an initial CXR

.....

BLF Asthma Information -
https://cdn.shopify.com/s/files/1/0221/4446/files/FL7_Asthma_v3_2017_PDFdownload.pdf?2973896653491569408&_ga=2.194277037.120268914.1530607868-461513967.1530607868

.....

BLF COPD Information -
https://cdn.shopify.com/s/files/1/0221/4446/files/BK2_Living_with_COPD_v3_2016_PDFdownload.pdf?12345462535456359749&_ga=2.227445533.120268914.1530607868-461513967.1530607868

.....

BLF Bronchiectasis Information -
https://cdn.shopify.com/s/files/1/0221/4446/files/BK33_Bronchiectasis_v1_2017_PDFdownload_cd6eeee6-c54a-4722-aca3-2c1ee1c4cb84.pdf?7633387245447608205&_ga=2.234718750.120268914.1530607868-461513967.1530607868

.....

MBRN Resources

.....

MBRN Diagnostic Pathway -
https://baybreathing.com/documents/MBRN%20Diagnosis%20Pathway%20%20-%20V2%20Final_1.pdf

.....

MBRN Asthma Pathway -

MBRN Diagnosis Template v8.3x

https://baybreathing.com/documents/MBRN%20Asthma%20Pathway%20%20-%20V2%20Final_1.pdf

.....

MBRN Bronchiectasis Pathway - https://baybreathing.com/documents/MBRN%20Bronchiectasis%20Pathway%20%20-%20V2%20Final_1.pdf

.....

MBRN COPD Pathway - https://baybreathing.com/documents/MBRN%20COPD%20Pathway%20%20-%20V2%20Final_1.pdf

.....

MBRN ILD Pathway - https://baybreathing.com/documents/MBRN%20ILD%20Pathway%20%20-%20V2%20Final_1.pdf

.....

.....

A.2 Impact of COVID-19

Many of the data presentations in this report focus on diagnoses made in 2022 to provide a picture of the most up-to-date diagnostic practices since diagnostic technologies and best practice guidelines can change over time. However, the COVID-19 pandemic caused significant disruption to healthcare provision (see Section 3.2.3.7) which may introduce some bias into the exploratory results presented. Here we reproduce certain figures from the report using 2019 data to inspect the impact of COVID-19 on the presented results.

Figure A.1 shows the symptom recording in the six months prior to diagnosis for CRD diagnoses made in 2019, analogous to Figure 3.1. The percentage of diagnoses without any symptom information recorded was 47% in 2019 and 48% in 2022. Further, the percentages for the other symptoms have remained similar, with the exception of a significant increase in recording of wheeze between 2019 and 2022.

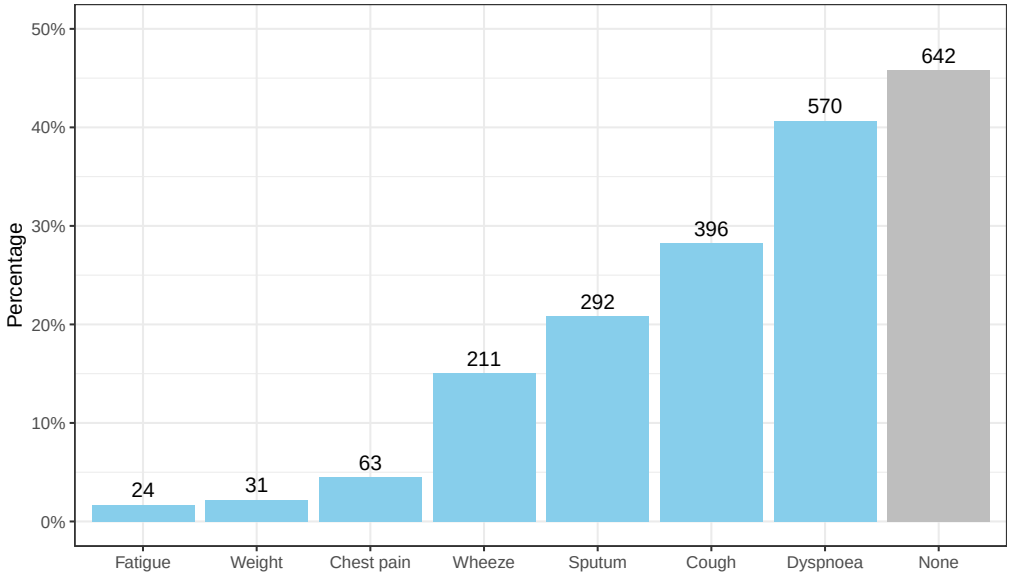


Figure A.1: Analogous to Figure 3.1. Percentage of diagnoses made in 2019 with symptom information recorded in the six months prior to diagnosis. Labels above bars show the frequency.

Figure A.2 in analogous to Figure 3.7 and shows symptom recording by GP in 2019. The two plots are different in terms of order of GPs but this is to be expected given MBRN intervention. However, the plots have similar overall shapes, with GP-level results spread quite evenly between approximately 25% and 80%.

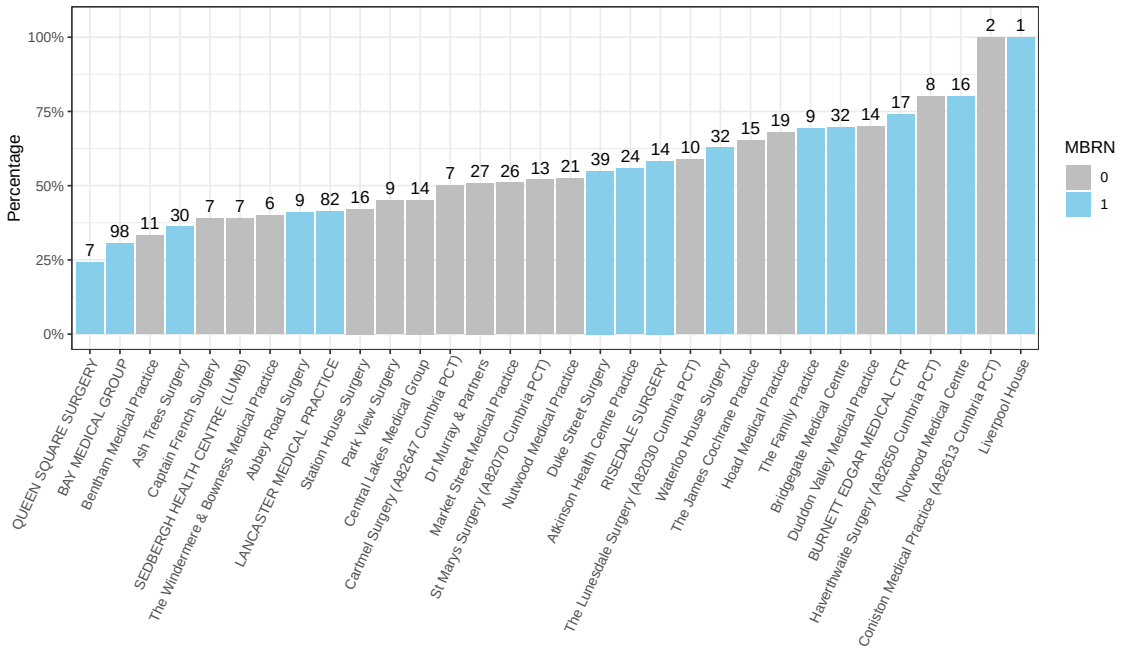


Figure A.2: Analogous to Figure 3.7 Percentage of diagnoses in 2019 with no symptom information recorded in the previous six months by GP. Labels above bars show the frequency.

Figure A.3 shows the percentage of diagnoses with each diagnostic test carried out in the six months prior to diagnosis for diagnoses made in 2019, analogous to Figure 3.2. Both plots have blood tests in the top four, ranging between 60% to 67% completion. There are some changes to order in the less frequently used tests, but this is to be expected given low sample sizes. The key difference between the two set of results is the decreased use of pulmonary function tests for diagnoses made in 2022 compared to 2019. Since we consider the six months prior to diagnosis, diagnoses made in 2022 may cover the period of time where pulmonary function testing was limited due to COVID-19 restrictions.

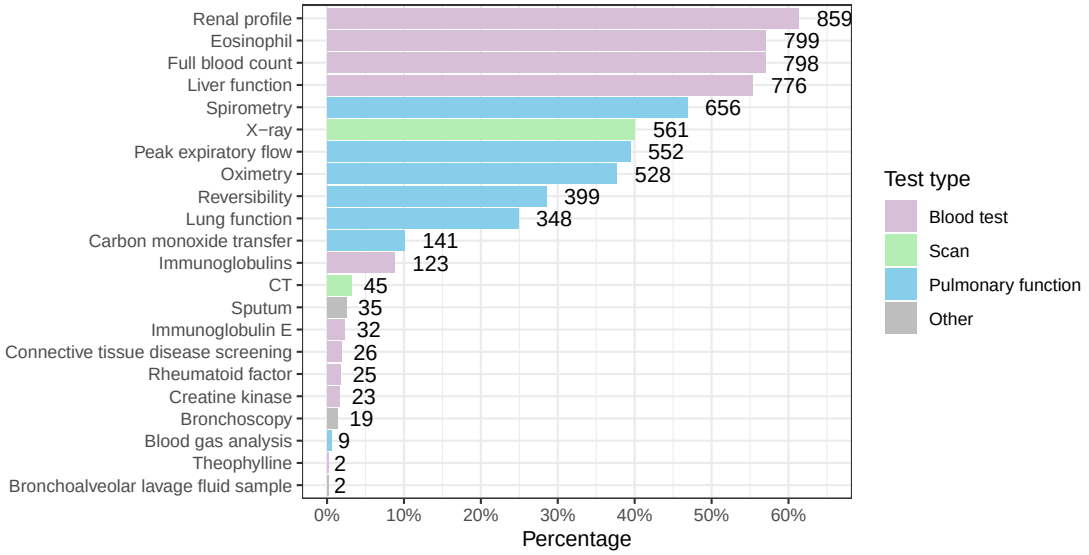


Figure A.3: Analogous to Figure 3.2 Percentage of diagnoses in 2019 with evidence of each diagnostic test in the six months prior to diagnosis. Labels next to bars show the frequency.

Appendix B

Budget impact analysis: Supplementary material

This appendix is the contents of the supplementary material file that was submitted to CMAJ Open and appears online alongside the main article (`https://www.cmajopen.ca/content/suppl/2023/11/07/11.6.E1048.DC1`).

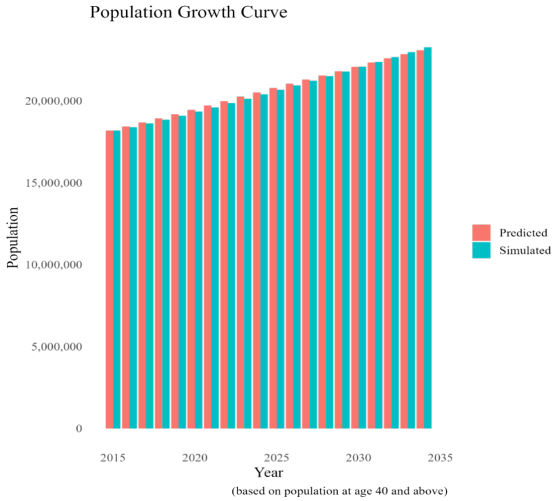
B.1 EPIC validation

The Evaluation Platform in COPD (EPIC) is a previously developed model and has undergone rigorous validation including replicating the rate and severity of exacerbations and COPD-related mortality rate in two external cohort studies. Details have been previously described elsewhere [52, 53]. Below we summarise the key elements relevant to the budget impact analysis.

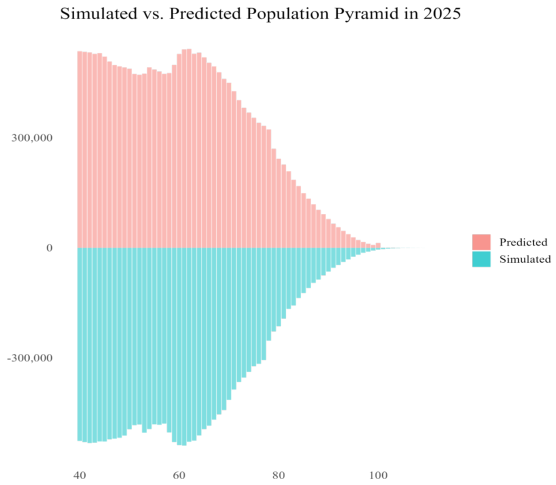
Population size and demographics are based on population projections from Statistics Canada [85]. Figure B.1 shows results of the validation of population size and the population pyramid for 2025 (near the end of the study time horizon).

Within EPIC, patients can be diagnosed with COPD outside of case detection. The diagnosis module uses input data from the Canadian Cohort of Obstructive Lung Disease (CanCOLD) study to model the annual probability of routine diagnosis during primary care visits both among COPD patients and non-COPD patients (overdiagnosis) [53, 86]. Probability of diagnosis is modelled as a function of sex,

symptoms, smoking status, and number of GP visits. The diagnosis module has been calibrated to yield a stable proportion of diagnosed patients among COPD individuals approximately equal to that observed in CanCOLD (29.7%) [87, 86]. Overdiagnosed patients can have their diagnosis reversed annually, the probability for which is calibrated to yield a stable proportion of false positive diagnoses among non-COPD individuals at 3% in accordance with the observed input CanCOLD data source [53] and similar to previous studies [88]. Figure B.2 shows results of the validation for COPD diagnosis and overdiagnosis.

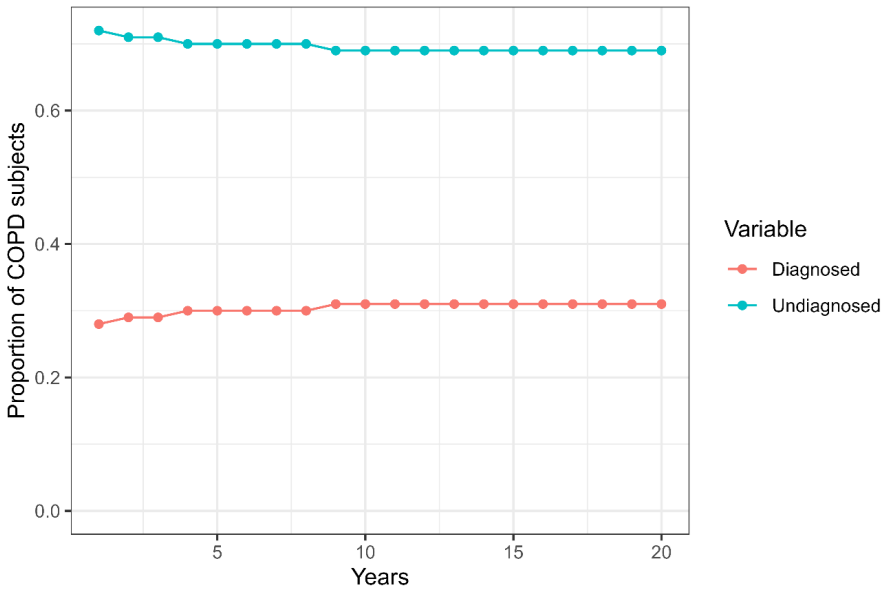


(a) Population growth between 2015-2035.

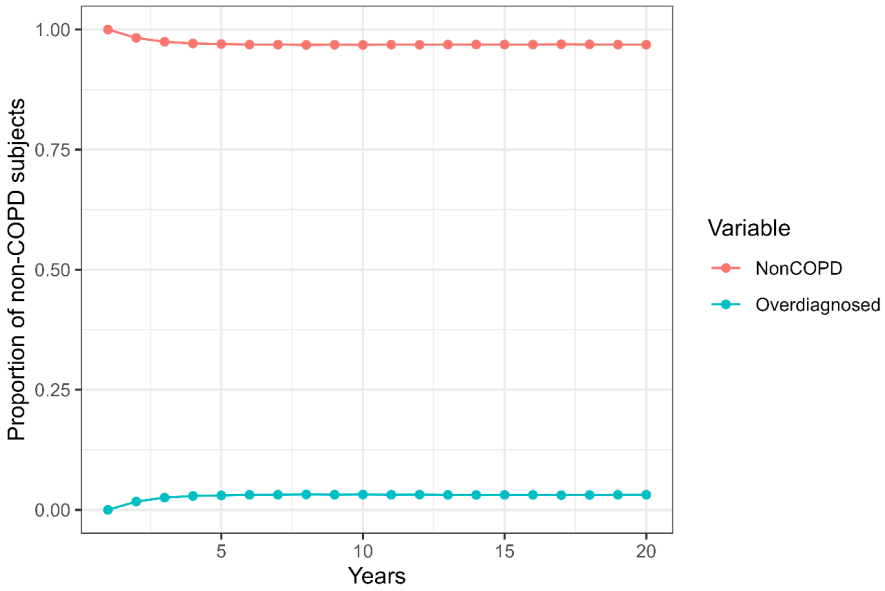


(b) Population pyramid of age in 2025.

Figure B.1: Validation of EPIC population against Statistics Canada projections.



(a) Proportion of COPD patients diagnosed.



(b) Proportion of non-COPD patients overdiagnosed.

Figure B.2: Validation of EPIC COPD diagnosis module against CanCOLD data over 20-year time horizon for 150,000 simulated individuals.

B.2 Recalibrating the cost-effectiveness plane

The cost-effectiveness plane used by Johnson et al. (2021) was recalibrated at lower willingness-to-pay (WTP) thresholds [53]. The preferred case detection strategy using the efficiency frontier approach with a WTP threshold of $25,000/QALY gained was S3b (questionnaire-based screening for adults aged ≥50 years with a smoking history) (Figure B.3).

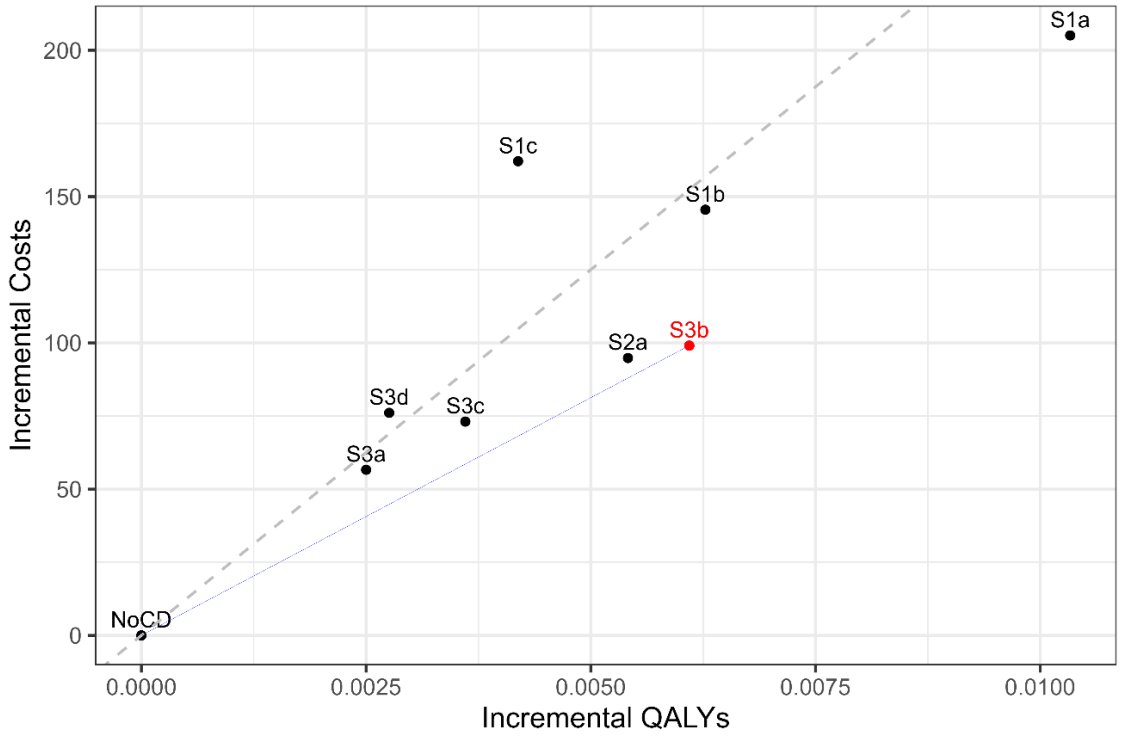


Figure B.3: Cost-effectiveness plane for case detection scenarios. Solid blue line indicates the efficiency frontier, and the grey dashed line indicated the WTP threshold ($25,000/QALY gained). The highest value scenario is highlighted in red.

B.3 Budget impact results tables

Tables B.1-B.8 show the extended annual budget impact results for each strategy compared to a baseline scenario of no case detection.

Table B.1: Annual budget impact results for case detection strategy S1a.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	8,426,599	16,512,477	23,225,846	27,980,080	30,417,175
CD: use cost	0	23,182,793	45,379,385	63,882,768	76,851,041	83,544,168
Treatment	393,530,276	418,197,267	442,737,753	470,714,863	500,838,467	532,892,687
Hospitalisation	857,500,298	886,324,440	914,199,119	948,754,968	990,866,199	1,032,316,209
Outpatient	1,382,501,810	1,426,806,092	1,472,958,585	1,524,109,881	1,578,888,806	1,634,717,281
Total	2,633,532,385	2,762,937,191	2,891,787,318	3,030,688,325	3,175,424,593	3,313,887,519
Budget impact						
CD: time	0	-8,426,599	16,512,477	-23,225,846	-27,980,080	-30,417,175
CD: use cost	0	-23,182,793	-45,379,385	-63,882,768	-76,851,041	-83,544,168
Treatment	0	-683,530	-3,874,643	-10,107,817	-19,572,258	-31,040,917
Hospitalisation	0	319,343	1,126,259	2,588,389	3,494,020	5,937,109
Outpatient	0	716,593	2,326,169	5,353,374	8,445,205	11,744,518
Total	0	-31,256,986	-62,314,077	-89,274,668	-112,464,154	-127,320,633

Table B.2: Annual budget impact results for case detection strategy S1b.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	8,426,599	16,512,477	23,225,846	27,980,080	30,417,175
CD: use cost	0	18,095,941	35,403,697	49,809,695	59,924,520	65,138,034
Treatment	393,530,276	417,502,295	439,839,584	464,000,396	488,865,354	514,550,406
Hospitalisation	857,500,298	886,488,161	915,155,450	949,922,059	992,470,688	1,035,052,965
Outpatient	1,382,501,810	1,427,128,994	1,473,885,031	1,526,189,614	1,582,014,503	1,639,472,537
Total	2,633,532,385	2,757,641,990	2,880,796,239	3,013,147,609	3,151,255,145	3,284,631,118
Budget impact						
CD: time	0	-8,426,599	-16,512,477	-23,225,846	-27,980,080	-30,417,175
CD: use cost	0	-18,095,941	-35,403,697	-49,809,695	-59,924,520	65,138,034
Treatment	0	11,442	-976,475	-3,393,350	-7,599,146	-12,698,637
Hospitalisation	0	155,621	169,929	1,421,298	1,889,531	3,200,353
Outpatient	0	393,691	1,399,723	3,273,642	5,319,508	6,989,261
Total	0	-25,961,786	-51,322,997	-71,733,952	-88,294,706	-98,064,232

Table B.3: Annual budget impact results for case detection strategy S1c.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	8,426,599	16,512,477	23,225,846	27,980,080	30,417,175
CD: use cost	0	24,838,754	48,648,753	68,439,896	82,366,712	89,561,692
Treatment	393,530,276	417,277,873	438,904,708	461,889,458	485,073,969	508,838,130
Hospitalisation	857,500,298	886,545,719	915,165,446	950,042,531	992,523,607	1,035,330,430
Outpatient	1,382,501,810	1,427,235,127	1,474,200,864	1,526,918,210	1,583,028,815	1,641,116,604
Total	2,633,532,385	2,764,324,071	2,893,432,247	3,030,515,942	3,170,973,183	3,305,264,032
Budget impact						
CD: time	0	-8,426,599	-16,512,477	-23,225,846	-27,980,080	-30,417,175
CD: use cost	0	-24,838,754	-48,648,753	-68,439,896	-82,366,712	-89,561,692
Treatment	0	235,864	-41,599	-1,282,412	-3,807,760	-6,986,361
Hospitalisation	0	98,063	159,933	1,300,825	1,836,612	2,922,888
Outpatient	0	287,558	1,083,890	2,545,045	4,305,196	5,345,195
Total	0	-32,643,867	-63,959,006	-89,102,284	-108,012,744	-118,697,145

Table B.4: Annual budget impact results for case detection strategy S2a.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	5,004,082	9,995,920	14,512,228	18,294,522	21,179,422
CD: use cost	0	11,288,986	22,462,791	32,590,260	41,111,291	47,541,278
Treatment	393,530,276	417,643,275	440,194,486	464,888,659	490,426,731	516,246,279
Hospitalisation	857,500,298	886,890,213	917,303,826	950,967,898	991,630,518	1,031,811,258
Outpatient	1,382,501,810	1,427,009,214	1,473,636,753	1,526,851,278	1,581,440,262	1,639,090,025
Total	2,633,532,385	2,747,835,770	2,863,593,776	2,989,810,322	3,122,903,323	3,255,868,263
Budget impact						
CD: time	0	-5,004,082	-9,995,920	-14,512,228	-18,294,522	-21,179,422
CD: use cost	0	-11,288,986	-22,462,791	-32,590,260	-41,111,291	-47,541,278
Treatment	0	-129,538	-1,331,377	-4,281,613	-9,160,522	-14,394,510
Hospitalisation	0	-246,431	-1,978,448	375,459	2,729,702	6,442,060
Outpatient	0	513,471	1,648,001	2,611,978	5,893,749	7,371,774
Total	0	-16,155,566	-34,120,535	-48,396,664	-59,942,884	-69,301,376

Table B.5: Annual budget impact results for case detection strategy S3a.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	3,614,923	6,996,089	9,691,191	11,515,588	12,319,716
CD: use cost	0	7,321,358	14,133,386	19,504,765	23,177,778	24,826,494
Treatment	393,530,276	417,315,771	438,732,867	461,384,970	483,317,058	505,457,281
Hospitalisation	857,500,298	888,080,237	915,186,809	951,013,298	993,184,504	1,033,515,705
Outpatient	1,382,501,810	1,427,151,698	1,474,621,789	1,528,567,283	1,585,023,474	1,644,148,744
Total	2,633,532,385	2,743,483,986	2,849,670,940	2,970,161,507	3,096,218,403	3,220,267,939
Budget impact						
CD: time	0	-3,614,923	-6,996,089	-9,691,191	-11,515,588	-12,319,716
CD: use cost	0	-7,321,358	-14,133,386	-19,504,765	-23,177,778	-24,826,494
Treatment	0	197,966	130,243	-777,924	-2,050,849	-3,605,511
Hospitalisation	0	-1,436,454	138,570	330,059	1,175,715	4,737,614
Outpatient	0	370,987	662,965	895,972	2,310,537	2,313,055
Total	0	-11,803,782	-20,197,698	-28,747,849	-33,257,963	-33,701,053

Table B.6: Annual budget impact results for case detection strategy S3b.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	3,614,923	6,996,089	9,691,191	11,515,588	12,319,716
CD: use cost	0	11,419,437	22,042,829	30,502,949	36,241,553	38,805,529
Treatment	393,530,276	417,904,014	441,044,569	466,551,891	492,458,299	519,274,253
Hospitalisation	857,500,298	887,932,717	915,133,889	950,001,828	992,166,827	1,031,847,452
Outpatient	1,382,501,810	1,426,894,720	1,473,704,146	1,526,774,157	1,582,156,778	1,639,691,744
Total	2,633,532,385	2,747,765,811	2,858,921,522	2,983,522,015	3,114,539,046	3,241,938,693
Budget impact						
CD: time	0	-3,614,923	-6,996,089	-9,691,191	-11,515,588	-12,319,716
CD: use cost	0	-11,419,437	-22,042,829	-30,502,949	-36,241,553	-38,805,529
Treatment	0	-354,498	-1,879,732	-5,565,440	-10,484,144	-17,249,349
Hospitalisation	0	2,086,309	-1,918,798	3,748,029	2,246,765	3,386,751
Outpatient	0	-219,296	1,065,053	1,551,379	4,970,980	5,143,954
Total	0	-13,636,897	-31,901,672	-40,800,360	-51,418,050	-60,300,220

Table B.7: Annual budget impact results for case detection strategy S3c.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	3,614,923	6,996,089	9,691,191	11,515,588	12,319,716
CD: use cost	0	8,168,405	15,777,432	21,830,947	25,972,872	27,740,809
Treatment	393,530,276	417,595,501	439,815,630	463,797,758	487,644,177	511,947,716
Hospitalisation	857,500,298	888,032,675	915,174,395	950,639,141	992,516,680	1,032,900,277
Outpatient	1,382,501,810	1,427,012,736	1,474,176,971	1,527,669,771	1,583,628,648	1,641,959,473
Total	2,633,532,385	2,744,424,241	2,851,940,517	2,973,628,809	3,101,277,965	3,226,867,991
Budget impact						
CD: time	0	-3,614,923	-6,996,089	-9,691,191	-11,515,588	-12,319,716
CD: use cost	0	-8,168,405	-15,777,432	-21,830,947	-25,972,872	-27,740,809
Treatment	0	-81,764	-952,520	-3,190,712	-6,377,968	-10,095,946
Hospitalisation	0	-1,388,893	150,983	704,216	1,843,539	5,353,041
Outpatient	0	509,949	1,107,783	1,793,484	3,705,364	4,502,325
Total	0	-12,744,036	-22,467,275	-32,215,151	-38,317,526	-40,301,105

Table B.8: Annual budget impact results for case detection strategy S3d.

Outcome	**2021 (Baseline)**	**2022**	**2023**	**2024**	**2025**	**2026**
No case detection strategy costs						
CD: time	0	0	0	0	0	0
CD: use cost	0	0	0	0	0	0
Treatment	393,530,276	417,513,737	438,863,110	460,607,046	481,266,209	501,851,770
Hospitalisation	857,500,298	886,643,782	915,325,378	951,343,357	994,360,219	1,038,253,318
Outpatient	1,382,501,810	1,427,522,685	1,475,284,754	1,529,463,255	1,587,334,011	1,646,461,799
Total	2,633,532,385	2,731,680,204	2,829,473,242	2,941,413,658	3,062,960,439	3,186,566,886
Case detection strategy costs						
CD: time	0	3,614,923	6,996,089	9,691,191	11,515,588	12,319,716
CD: use cost	0	10,821,693	20,929,498	29,003,098	34,429,943	36,828,162
Treatment	393,530,276	417,463,330	439,317,841	462,665,119	485,642,400	508,979,062
Hospitalisation	857,500,298	888,060,245	915,246,260	950,806,652	992,681,448	1,033,176,370
Outpatient	1,382,501,810	1,427,097,525	1,474,411,581	1,528,047,035	1,584,247,905	1,642,978,516
Total	2,633,532,385	2,747,057,717	2,856,901,270	2,980,213,095	3,108,517,284	3,234,281,826
Budget impact						
CD: time	0	-3,614,923	-6,996,089	-9,691,191	-11,515,588	-12,319,716
CD: use cost	0	-10,821,693	-20,929,498	-29,003,098	-34,429,943	-36,828,162
Treatment	0	50,407	-454,732	-2,058,073	-4,376,191	-7,127,292
Hospitalisation	0	-1,416,463	79,118	536,705	1,678,771	5,076,948
Outpatient	0	425,160	873,173	1,416,220	3,086,106	3,483,283
Total	0	-15,377,513	-27,428,028	-38,799,437	-45,556,845	-47,714,940

B.4 Overdiagnosis results

At baseline the prevalence of overdiagnosed COPD among non-COPD Canadians aged ≥40 years was 3.0%, which reflects the prevalence observed in the CanCOLD study [53]. Within EPIC, diagnosis and case detection are modelled as annual events and a patient cannot be overdiagnosed with COPD in the same year that they receive case detection. Figure B.4 shows prevalence of overdiagnosis among non-COPD patients over the time horizon. Overdiagnosis results are equivalent within eligibility criteria groups since each group selects the same cohort of patients for case detection. Compared to the baseline scenario (S0 – current practice) all case detection strategies result in a reduction in overdiagnosis prevalence. Strategies with eligibility criteria based on patients' smoking history (S3 group) observes the smallest reduction since the S3 group has the strictest eligibility criteria thus is administering case detection to the smallest number of patients. The difference between the S1 (all patients) and S2 (symptomatic patients) group is minimal despite significant differences in the number of patients administered case detection (Table 4.3 of the main article). Symptoms are a significant risk factor for overdiagnosis so the S2 group is more targeted at patients who would typically be at greater risk of overdiagnosis.

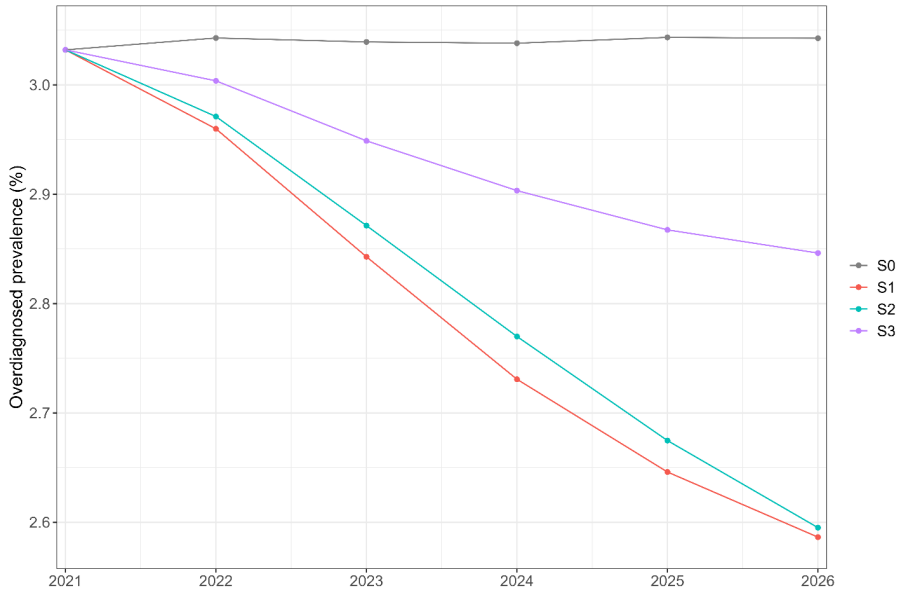


Figure B.4: Prevalence of overdiagnosed COPD among non-COPD patients over the time horizon by eligibility criteria group. S0 - baseline (no case detection); S1 - all patients; S2 - symptomatic patients; S3 - patients with a smoking history.

B.5 Additional sensitivity analysis results

Figure B.5 shows sensitivity analysis results for an upper age limit ≤75 years for considering patients for case detection. The overall budget expansion decreases on average by 22.5% with an upper age limit as fewer individuals would be administered case detection, and consequently, diagnosed. For S1a, the number of individuals administered case detection over 5 years reduces by 1.5 million (from 8.9 million under the reference case to 7.4 million) and the budget expansion reduces by $72 million (from $423 million to $351 million). By 2026, the diagnosed prevalence reaches 35.7% with an upper age limit compared to 37.8% under the reference case.

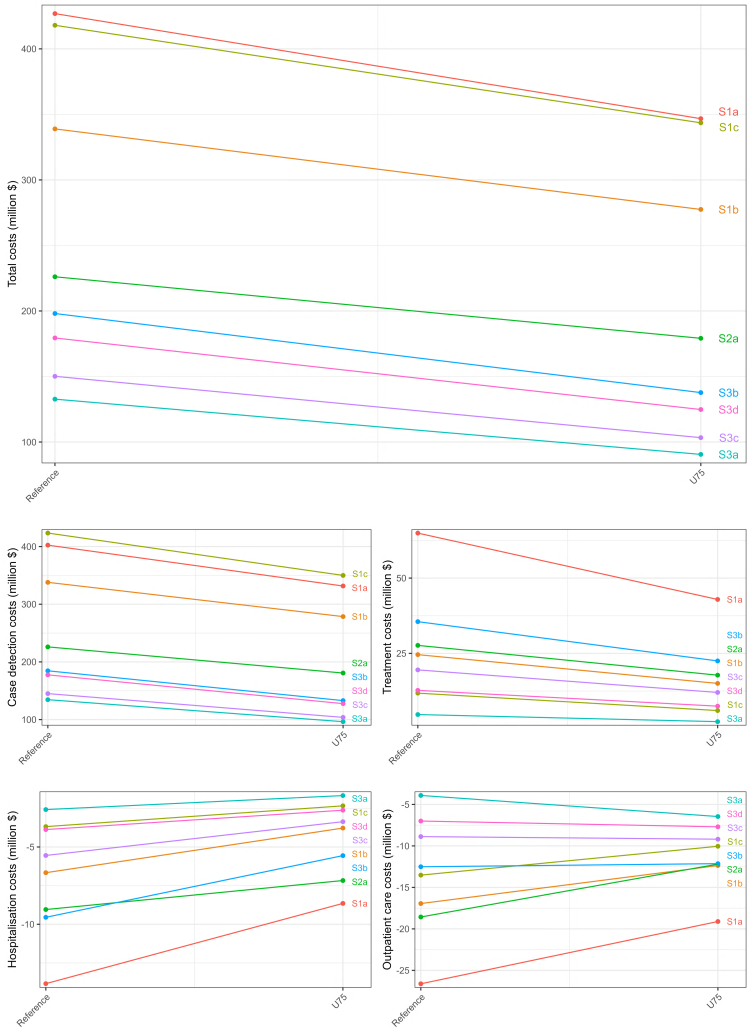


Figure B.5: Sensitivity analysis of total additional costs of case detection strategies compared to no case detection. Negative additional costs indicate cost savings. U75 – additional eligibility criteria ≤75 years.

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