Enhancing the understanding and application of burden of disease methods

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Abstract

Burden of disease studies can be used to summarise the combined impact that causes of morbidity and mortality have in a defined population in a manner that is consistent and comparable. They have become an increasingly popular means to use in knowledge exchange activities for informing national, and local, policy-making decisions. The Global Burden of Disease (GBD) study provide estimates on the burden of disease for each cause of disease and injury for individual countries, and sub-national areas for selected countries, which are adopted by many researchers and national public health institutes. Alternative national burden of disease studies exist, independent of the GBD study, which utilise country-specific data sources that are representative of the state of health in their country. The co-existence of these studies can potentially be problematic for knowledge exchange activities, particularly when estimates differ and neither party are able to explain why the differences exist. This can often lead to speculation on why the differences occur, and the monopolisation of burden of disease research by the GBD study can often be problematic in ensuring a balanced narrative emerges. Many users often just seek to appraise differences in the input data as they often lack the experience, or will, to understand methodological processes as they are often complex and exhaustive. However, these differences in methods could plausibly play a key contribution in explaining differences in results.

Two such methodological choices are in relation to the choice of severity distribution in assessing the non-fatal burden of disease, and the choice of standard population that is used when estimating standardised rates. These issues are tackled in the first part of this thesis. The impact of these methodological choices were appraised using approaches from the Scottish Burden of Disease study, relative to those of the GBD study. The first aim of this thesis is to establish whether using standard GBD study severity distributions result in major differences, compared to using severity distributions that better reflect the epidemiological situation in Scotland using the example of individual cancer types. The second aim of this thesis is to determine whether using different standard populations to standardise rates leads to major differences in how causes of disease and injury are ranked using disability-adjusted life years (DALYs). The research presented in this thesis gives insights into how impactful seemingly slight methodological choices can result in major differences.

The second subset of research questions relate to establishing methods for COVID-19 burden of disease assessment, and monitoring the burden of COVID-19 using DALYs. The aims of this work presented in this thesis were to:

(i) Assess which European countries were likely to be most vulnerable to severe outcomes from COVID-19;
(ii) Develop an international consensus method for estimating COVID-19 DALYs;
(iii) Estimate COVID-19 DALYs in Scotland during 2020 and contextualise the result compared to the leading pre-pandemic causes of disease;
(iv) Estimate the extent of inequality in COVID-19 DALYs in Scotland during 2020;
(v) Provide an alternative way of assessing the impact of all-cause inequalities by comparing inequality-attributable DALYs to the impact of COVID-19;
(vi) Monitor changes in the fatal COVID-19 burden of disease in 2021, in the context of vaccine availability, compared to 2020.

The research questions posed in this thesis are investigated in the included seven first-author papers. The insights from each of the papers are synthesised in an explanatory essay. This essay attempts to show the impact of each of the individual papers, and how they form a cohesive body of work that enhances the understanding and application of methods for use in burden of disease assessment.

The explanatory essay presents a two-tier approach. The first part considers the impact of: (i) severity distributions; and, (ii) standard populations in age-standardised rate calculations, in burden of disease assessment. The essay discusses the importance of the findings from the included papers. It also highlights their importance for other stakeholders in international burden of disease research networks', given the impact of severity distributions on resulting estimates is now more widely understood.

The second part of the explanatory essay focuses on developing consensus methods to estimate COVID-19 DALYs, and then focuses on their application in monitoring the overall, and inequalities in the, COVID-19 burden of disease in Scotland. The need for a consensus method is justified on the basis of ensuring that the comparative properties of DALYs remain. This work has synergies with the first part of the explanatory essay, as it is important that assessments are reflective of the best available country-specific data inputs.

The significance of this work is discussed through its uptake within the international research community.

The rationale for undertaking burden of disease assessments it to generate comparable estimates for where risk factors, causes of death, disease and injury are causing the largest public health losses. In doing this, it provides compelling evidence to inform resource allocation discussions for tackling population health needs, and the implications for which these needs will have in ensuring care services and workforces are proportionate to the challenge. Through presenting developments and the journey through these seven published works in included in this thesis, I aim to have demonstrated the importance of the work in enhancing the understanding and application of burden of disease assessment methods. It is vital that the methodological context, and any uncertainties for which estimates are produced in, is well understood.

Contents

Dedication

For Anne and Mark Wyper.

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I thank all my co-authors from the published papers included in this thesis, team members from the Scottish Burden of Disease study – past and present – and colleagues from the European Burden of Disease Network. Without your professional support, vital insights, and friendship, this thesis would not have been possible.

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Author's declaration

I, Grant Mark Andrew Wyper declare that, except where explicit reference is made to the contribution of others, that this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Printed name: GRANT MARK ANDREW WYPER

Signed:

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List of published works

Paper I Wyper GMA, Grant I, Fletcher E, McCartney G, Stockton DL. The impact of worldwide, national and sub-national severity distributions in Burden of Disease studies: A case study of cancers in Scotland. *PLoS One*. 2019;14(8):e0221026. doi: 10.1371/journal.pone.0221026.

Paper II Wyper GMA, Grant I, Fletcher E, McCartney G, Fischbacher C, Stockton DL. How do world and European standard populations impact burden of disease studies? A case study of disability-adjusted life years (DALYs) in Scotland. *Archives of Public Health*. 2020;78:1. doi: 10.1186/s13690-019-0383-8.

Paper III Wyper GMA, Assunção R, Cuschieri S, Devleesschauwer B, Fletcher E, Haagsma JA, Hilderink HBM, Idavain J, Lesnik T, von der Lippe E, Majdan M, Milicevic MS, Pallari E, Peñalvo JL, Pires SM, Plaß D, Santos JV, Stockton DL, Thomsen ST, Grant I. Population vulnerability to COVID-19 in Europe: a burden of disease analysis. *Archives of Public Health*. 2020;78:47. doi: 10.1186/s13690-020-00433-y.

Paper IV Wyper GMA, Assunção RMA, Colzani E, Grant I, Haagsma JA, Lagerweij G, von der Lippe E, McDonald SA, Pires SM, Porst M, Speybroeck N, Devleesschauwer B. Burden of disease methods: a guide to calculate COVID-19 disability-adjusted life years. *International Journal of Public Health*. 2021;66:619011. doi: 10.3389/ijph.2021.619011.

Paper V Wyper GMA, Fletcher E, Grant I, McCartney G, Fischbacher C, Harding O, Jones H, de Haro Moro MT, Speybroeck N, Devleesschauwer B, Stockton DL. Measuring disability-adjusted life years (DALYs) due to COVID-19 in Scotland, 2020. *Archives of Public Health*. 2022;80:105. doi: 10.1186/s13690-022-00862-x.

Paper VI Wyper GMA, Fletcher E, Grant I, Harding O, de Haro Moro MT, Stockton DL, McCartney G. Inequalities in population health loss by multiple deprivation: COVID-19 and pre-pandemic all-cause disability-adjusted life

years (DALYs) in Scotland. *International Journal for Equity in Health*. 2021;20:214. doi: 10.1186/s12939-021-01547-7.

Paper VII Wyper GMA, Fletcher E, Grant I, Harding O, de Haro Moro MT, McCartney G, Stockton DL. Widening of inequalities in COVID-19 years of life lost from 2020 to 2021: a Scottish Burden of Disease study. *Journal of Epidemiology and Community Health*. 2022;76:746-749. doi: 10.1136/jech-2022-219090.

Related knowledge exchange activities

Knowledge exchange activities related to the seven published works included in this thesis, are given below.

Conferences

- **International Conference on Administrative Data Research, Cardiff, United Kingdom, 12/2019**

Related published works: **Paper I**
Presentation title: 'Developing and evaluating national severity distributions for use in Burden of Disease studies: a case study of cancers in Scotland'
Published abstract: https://doi.org/10.23889/ijpds.v4i3.1256

- **European Public Health Conference, virtual conference, 11/2021**

Related published works: **Paper IV**
Presentation title: 'Burden of disease methods: integrating COVID-19 to the cause list'
Published abstract: http://dx.doi.org/10.1093/eurpub/ckab164.621

Related published works: **Papers V and VI**
Presentation title: 'Socioeconomic inequalities in COVID-19 DALYs in Scotland, 2020'
Published abstract: https://doi.org/10.1093/eurpub/ckab164.210

- **UK Public Health Science Conference, virtual conference, 11/2021**

Related published works: **Papers V and VI**
Presentation title: COVID-19 and pre-pandemic all-cause inequalities in disability-adjusted life-years due to multiple deprivation: a Scottish Burden of Disease study
Published abstract: https://doi.org/10.1016/S0140-6736(21)02637-4

- **Faculty of Public Health Scotland, virtual conference, 05/2022**

Related published works: **Papers V, VI and VII**

Presentation title: Monitoring annual changes in COVID-19 disability-adjusted life years (DALYs) in 2020 and 2021: a Scottish Burden of Disease study

Blogs

- **The value of administrative data: DALYs and the Scottish Burden of Disease study**

Related published works: **Papers I and II**
Published by Scottish Centre for Administrative Data Research (SCADR), February 21st, 2020. URL: https://www.scadr.ac.uk/news-and-events/blog-value-administrative-data-dalys-and-scottish-burden-disease-study

- **Years of healthy life lost in Scotland's communities**

Related published works: **Papers V and VI**
Published by Voluntary Health Scotland, September 28th, 2021.URL: https://vhscotland.org.uk/grants-blog-years-of-healthy-life-lost-in-scotlands-communities/

Published by Public Health Scotland, October 11th, 2021.URL: https://publichealthscotland.scot/our-blog/2021/october/years-of-healthy-life-lost-in-scotlands-communities/

Webinars

- **Quantifying COVID-19 disease burden**

Related published works: **Papers III and IV**
European Burden of Disease Network, October 20th, 2020. URL: https://www.burden-eu.net/activities/webinars/194-quantifying-covid-19-disease-burden

- **Burden of disease assessment for COVID-19: initial insights and future perspectives**

Related published works: **Papers IV and V**

European Burden of Disease Network, May 21st, 2021. URL: https://www.burden-eu.net/activities/webinars/318-webinar-burden-of-disease-assessment-for-covid-19-initial-insights-and-future-perspectives

Interviews

- **Identifying Europe's most COVID-vulnerable countries**

Related published works: **Paper III**

Published by European Cooperation in Science and Technology, June 15th, 2020. URL: https://www.cost.eu/identifying-europes-most-covid-vulnerable-countries/

- **The pandemic's true health cost: how much of our lives has COVID stolen?**

Related published works: **Papers IV, V, VI and VII**

Published by Nature, May 18th, 2022. URL: https://doi.org/10.1038/d41586-022-01341-7

List of abbreviations

ASR	Age-standardised rate
ASPHER	Association of Schools of Public Health in the European Region
COVID-19	Coronavirus disease 2019
DALYs	Disability-adjusted life years
ECDC	European Centre for Disease Prevention and Control
ESP	European Standard Population
GBD	Global Burden of Disease
IHME	Institute for Health Metrics and Evaluation
InfAct	Joint Action for Health Information
ISD	Information Services Division
NHS	National Health Service
NSS	National Services Scotland
OHID	Office for Health Improvement and Disparities
PHS	Public Health Scotland
SAGE	Strategic Advisory Group of Experts on Immunization
SBOD	Scottish Burden of Disease
UK	United Kingdom
UKHSA	UK Health Security Agency
WHO	World Health Organization
WSP	World Standard Population
YLD	Years lived with disability
YLL	Years of life lost to premature mortality

Explanatory essay

Introduction

A burden of disease assessment can be used to summarise the combined impact which causes of morbidity and mortality have in a defined population in a manner that is consistent and comparable [1]. To achieve this, the population health impact is framed as a function of time lost due to living with, and dying from, causes of disease and injury. Population health loss due to morbidity is defined as Years Lived with Disability (YLD) which is estimated as the product of the occurrence, duration, and disability of a cause of disease and injury [2]. Years of Life Lost (YLL) estimates reflect estimates of population health loss from premature mortality, which is a function of both the occurrence of death and the age at which death occurs [3]. This reflects the idea that the public health impact of deaths at younger ages is higher than those that occur in older age-groups. Since YLD and YLL are framed using the same unit of time loss, they can be summed to capture the fuller impact of living with, and dying from, causes of disease and injury in a composite measure called disability-adjusted life years (DALYs).

The main benefit of this approach is that DALYs can be used to identify the leading causes of population health loss and provide evidence of potential areas of highest public health gains [4]. This is because comparisons on the proportionate impact of a given disease or injury is not restricted to either the lived experienced, or what kills us. DALYs can be used to make comparisons between: demographic sub-groups; time periods; geographic regions; and fundamentally, with all other causes of disease and injury. However, undertaking a comprehensive burden of disease study across all causes of disease and injury is highly resource intensive. Data inputs and methodological approaches that best reflect the situation of the study under population are required. This thesis explores the potential added value of defining study inputs, and applying methodological approaches, that are most suited to capture the epidemiological situation in Scotland.

The published papers included in this thesis submission are a product of work undertaken in the Scottish Burden of Disease (SBOD) study and, more recently, through membership of the European Burden of Disease Network [5,6]. The research was undertaken working on the SBOD study during my employment at: Information Services Division (ISD) Scotland, National Services Scotland (NSS), National Health Service (NHS) Scotland; NHS Health Scotland; and, Public Health Scotland. Included, are seven papers published

in peer-reviewed scientific journals. All journal papers are first author papers and can be further split into six research-based contributions and one novel methodological contribution. The journal papers were published in the period 2019 to 2022. However, many of the ideas, data retrieval, and analysis that underpins the work presented in this thesis has been ongoing since early in the SBOD study.

This thesis submission comprises of papers that aim to provide a better understanding, and applications, of methods for use in burden of disease assessment. There are direct links between specific papers, with novel insights from subsequent papers that augment prior publications to increase the overall impact of the fuller body of works. The thesis can broadly be split into three sections.

The first part – represented by **Papers I and II** – aims to enhance knowledge over the application of differential burden of disease methods by demonstrating the extent of impact which these methodological choices can have on resulting estimates. The first area is in relation to severity distributions. There is a dearth of information in relation to severity distributions in burden of disease studies. This evidence gap has resulted in the application of identical severity distributions being applied in all countries in the world, across wide study time periods. Whether or not this is appropriate has never been fully tested. The research question answered by **Paper I** is whether this approach leads to major differences, compared to using severity distributions that better reflect the epidemiological situation in Scotland using the example of individual cancer types.

As the GBD study is global in remit, then so too are its methodological choices. One of these choices is in regards to the standard population which is used when calculating standardised rates. Whilst the standard population used in GBD study is relevant for comparisons in a global context, it may not be relevant for all continental, national or local contexts. The standard population from the GBD study has a structure which is vastly different to that of the Scottish population. In Scotland, and other European public health institutes, this approach is therefore at odds with official guidance which specifies the use of different standard population compared to the one used in the GBD study. The difference between the two approaches has never been studied in relation to DALY estimates, therefore an evidence gap existed over whether this approach was potentially misleading. The research question studied in **Paper II** was whether the differences in this

methodological approach resulted in differences in how causes of disease and injury were ranked using DALYs.

In summary, the areas which are presented in the first part of this thesis are on the impact of differences in: (i) severity distribution applications (**Paper I**); and, (ii) standard populations when standardising rates (**Paper II**). As these studies were set up to assess the impact of a particular choice, null findings would also be particularly important as they would help to provide a bridge between differences in estimates from independent national burden of disease studies and that of the GBD study.

The second part of this thesis relates to research undertaken following the emergence of COVID-19 infection. Early in the pandemic the COVID-19 situation in countries such as China and Italy quickly illustrated the substantial impact on health, education, the economy, and social interaction from both the infection itself, and as an adverse consequence of the public health protection measures put in place [7, 8]. As evidence emerged on specific health conditions, and demographics, that were at risk of severe outcomes from COVID-19, there was a gap in relation to how vulnerable the population health of specific countries might be given their current levels of population health. The research question posed in **Paper III** explores what European countries were potentially most vulnerable to severe outcomes from COVID-19.

As COVID-19 was novel there was a methodological gap preventing researchers to estimate its impact on population health using DALYs. **Paper IV** focuses on providing guidance through establishing an international consensus methodology to assist in estimating COVID-19 DALYs. This research was required to undertake the subsequent works presented in **Papers V, VI and VII**. The research question answered by **Paper V** was in relation to quantifying the burden of disease from COVID-19 in Scotland in 2020, and framing this burden against the pre-pandemic leading causes of disease. **Paper VI** advances this by exploring two further research questions. The first is in relation to the extent of inequality in Scottish DALY estimates of COVID-19. Secondly, **Paper VI** seeks to frame the overall annual impact of pre-pandemic health inequalities relative to COVID-19 to present novel insights into how we frame health inequalities.

Since the 2020 study time period for **Papers V and VI** there has been a mass vaccination campaign which has achieved high levels of vaccine uptake, and has been illustrated to

have averted a high number of deaths [9]. However, in the context of averting deaths has come the relaxation of protection measures and therefore increased case numbers. Finally, the research question explored in **Paper VII** was in relation to how the COVID-19 burden of disease, and inequalities, have changed during these more recent contexts in Scotland in 2021.

The final part concludes the thesis, summarising the individual and collective significance of the seven published papers. I focus on how these papers have furthered not only a Scottish understanding of differential application of burden of disease methods, but how they have had, and continue to have, an impact in international settings. To finish, I offer an afterword to consider the potential unintended opportunities for burden of disease assessment as we emerge from the COVID-19 pandemic.

Burden of disease assessment

Background and historical context

The role of population health metrics is vital to aid our understanding of the health status of a population. Population health metrics are useful because they generate evidence to inform discussions upon where interventions and policies are required to generate health improvements [10]. However, there are different metrics for different occasions which introduces an element of subjectivity when attempting to balance the evidence base.

Using estimates of the occurrence of a cause of death, disease, or injury, for prioritisation decisions can potentially be misleading as the findings can largely be dependent on what indicator is used [11]. If cause of death statistics are used, then those conditions which do not result in death cannot be given prominence. Even within mortality statistics, interpretations of the public health significance of different causes of deaths can be difficult to make due to differences in age-distributions. Opportunities to further understand the proportionate impact of causes of mortality, through YLL estimates, have been around since the 1940s and help guide interpretation of the impact different causes of death have on population health [3,12]. The YLL approach allows researchers to respect that deaths occurring at younger ages have a higher public health impact than deaths at older ages [12]. An example of this is that although deaths due to schizophrenia occur at a relatively low level, they would normally result in a higher estimate of YLL per death,

compared to the most frequent causes of deaths such as heart disease, since schizophrenia deaths would, on average, occur at younger ages.

For the population health impact of morbidity, there are further considerations of the differences in impact at the individual and population levels [13]. At a population level, some causes of disease occur very frequently, such as heart disease, whilst others like schizophrenia occur relatively less frequently. However, at an individual level, the impact of schizophrenia on health-related quality of life is likely to be much more debilitating, compared to living with heart disease [14]. It is therefore clear to comprehend why the selection of a specific metric would influence our perception of what was worse – schizophrenia or heart disease. Although this example is illustrative it gives insights into why individual, and collective experiences at population level, can substantially differ [13].

One of the most common population health metrics is life expectancy. Life expectancy gives important inferences on the theoretical lifespan, based on current age-specific mortality rates [15]. It can be usefully triangulated with cause-specific mortality estimates to give inferences into the contributions of causes of disease and injury in preventing higher estimates of life expectancy being achieved. Alternatively, decomposition methods can be used to illustrate the impact of causes of death on life expectancy between two references, such as time periods or sub-populations [16,17]. However as outlined in the previous examples, estimates of life expectancy do no not reflect the impact of living with health conditions. At a population health level, we need to be able to synthesise the full health impact across the life course to uncover the extent of population health needs in order to effectively tackle them.

In the 1960s and 1970s, research began to incorporate the impact of morbidity and mortality in composite health expectancy measures [11,18]. Metrics such as healthy life expectancy offered a solution to this dilemma through considering the contribution of living in general states of impaired health, to incorporate a health-related quality of life aspect [11]. Estimates of healthy life expectancy augment existing estimates of life expectancy, given that the level of healthy life expectancy changes in relation to the estimate of life expectancy [19]. Although healthy life expectancy allows for an insight into the effects of morbidity, it does not give us a means for decomposing the diseases that are impacting health-related quality of life, particularly in a way which is comparable with causes of death. Solutions to this were developed using health-adjusted life expectancy,

which estimates the impact of health states by using utility weights and health state deletion approaches [20].

Disability-adjusted life years

In the 1990s, a health gap metric that captured the impact of morbidity and mortality called DALYs was included in the World Bank 1993 World Development Report [21]. The DALY metric was developed to estimate the proportionate impact of causes of disease and injury in preventing citizens from achieving aspirational longevity, or living in health states less than ideal. The health gap measure which this thesis is centred on is DALYs, for which the 1994 publication for the technical basis was made by Murray [1]. DALYs comprise of YLD and YLL to incorporate the full impact of disease and injury. They capture three key elements:

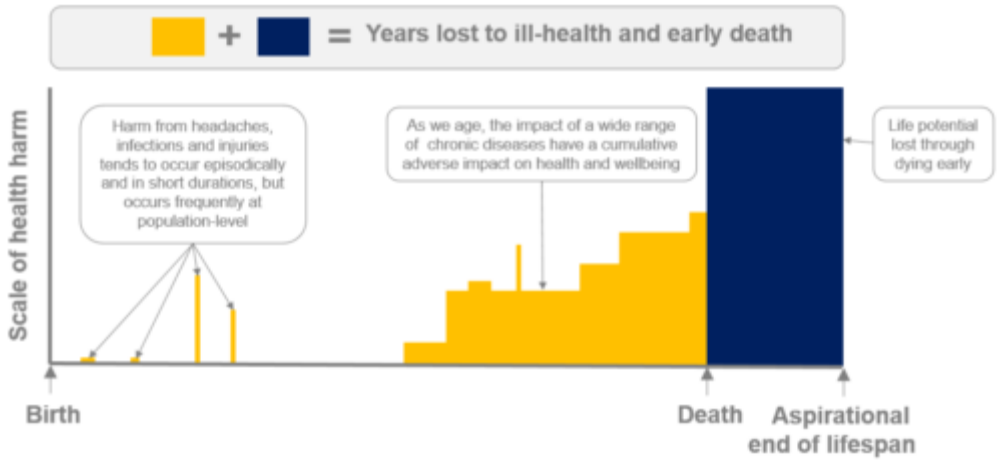
1. How common the occurrence of death, disease, or injury is;
2. How debilitating a cause of disease or injury is, to estimate the extent of loss from living in impaired health states;
3. The age at which death occurs, in order to estimate the extent of loss due to premature mortality.

The elements (2) and (3) allow us to weight the impact of death, disease, and injury in (1) and thus DALYs represent the proportionate impact of death, disease, and injury [22]. For (2), estimates of disability weights are required [14,23]. In burden of disease studies, these are usually derived through pairwise comparisons between two hypothetical individuals with different health states to determine which individual is healthier than the other. Disability weights vary from 0 to 1, with the former being representative of perfect health and 1 being equivalent to death [1]. It has been previously illustrated that there is not only variation between sets of disability weights, but that the methods used to derive them can also vary considerably [23]. Approaches to derive disability weights at national level have started to align more closely with the GBD study since 2010. Despite this, their valuation remains subjective given that values could potentially be influenced by factors such as social and cultural contexts, or differences in levels of health literacy. Notwithstanding these criticisms, it is important that disability weights come from within the same framework meaning that a global use of the same set of disability weights is preferred [24].

In the technical basis for the DALY, the loss function defined in (3) is based on an aspirational standard given that DALYs are a health gap measure [1]. This is a key concept, as it balances the idea that ill-health prevents us from achieving ideal health, and that through dying early, we do not achieve an idealised longevity. Although DALYs solve previous issues related to capturing the fuller impact of morbidity and mortality, as a health metric they cannot always be viewed in isolation. For example, many low-risk common infectious diseases have been illustrated to be highly incident but contribute relative few DALYs. However, these infections can often result in a high healthcare service utilisation which is required in order for individuals to be effectively treated.

Figure 1 outlines a theoretical individual illustration of how a DALY would be estimated. YLD would accumulate for an individual across the life course, and YLL would be conceptually estimated following death.

Figure 1. An individual illustration of health loss during the life course, and conceptual health loss through premature mortality



On average, in the context of Scotland and other high-income countries, we would expect health loss to be relatively low in younger ages. At a population level, the leading health harms would be expected to occur in short durations, or episodically, and generally be as a result of headaches, infections, and injuries. However, as individuals age, the impact of a wide range of non-communicable diseases have a cumulative adverse impact on the health and wellbeing of individuals [25,26]. The health loss observed following death is theoretical, and in the case of DALYs is generally estimated relative to an aspirational life

expectance at a given age. As the residual age-conditional life expectance is usually derived from a life table, each death, including those that occur at very elderly ages, would result in premature loss although the level of age-conditional life expectancy assigned depreciates with age.

Since the first inclusion of DALY estimates in the influential World Bank 1993 World Development Report, the production and use of DALYs has become increasingly popular [21]. Although since that landmark report, their production roots within the World Health Organization moved to the Institute for Health Metrics and Evaluation (IHME), University of Washington, a move largely attributed to the changing key actors within the global health field [27].

The context of this thesis began in the early 2010s, when the global health community were starting to face multiple inconsistencies in global health statistics [27,28]. GBD estimates for countries, and sub-national regions, were increasingly being adopted by national public health institutions to inform strategy discussions [29,30]. Additionally, the use of findings by academic researchers had also become much more widespread by the 2010s, as the number of collaborators within the GBD study grew [31]. However, long-term exceptions to the GBD study existed in the form of independent national burden of disease studies from the Netherlands and Australia [32,33].

The Scottish Burden of Disease study

In the context of Scottish public health intelligence, there was a gap in being able to balance the relative contributions of living with, and dying from, health conditions, in a comparable way. In Scotland, prior to the 2010s, the main all-cause summary measures of population health that were routinely produced were life expectancy, self-assessed health, and healthy life expectancy [34-36]. In 2013, the SBOD study launched and aimed to comprehensively estimate the burden of disease for individual causes of disease and injury using DALYs [5,37]. Since the creation of the SBOD study, there has been a general increase in burden of disease activities that are independent of the GBD study – including comprehensive national studies currently being undertaken in Germany, Belgium, and France [29,30,38-40]. In the context of reports of inconsistent global health statistics, there too must exist the context of inconsistent estimates for member states as the global estimates are a sum of national-level parts [28,41]. One of the most important players in being able to appraise the state of health in any country, are national public health

institutes, and are thus well placed to appraise the impact, and relevance of any consistencies with GBD study estimates. The rationale for the early research papers (**Papers I and II)** presented in this thesis are based on investigating potential reasons for differences between SBOD and GBD study estimates.

The rationale for not adopting the GBD results for Scotland was like that of other independent studies such as those carried out in the Netherlands and Australia [32,33]. The reasons for pursuing the creation of the SBOD study, estimating ground-up DALY estimates, was three-fold:

(i) the GBD study lacked transparency of inputs and in its modelling processes, meaning that there were major uncertainties regarding using findings for knowledge exchange, and translation, purposes [41];
(ii) the GBD study did not estimate the burden of disease for Scottish sub-national areas, so could therefore not detect the impact of health inequalities, which in Scotland are widely understood to be among the widest in Europe [42,43];
(iii) Scotland has many long-standing high-quality routine databases and surveys which could be used to overcome the issues described in (i) and (ii).

The SBOD study was launched as a collaboration between NHS Health Scotland and ISD Scotland, NHS NSS [5]. Initially, several years were spent building up capacity, and understanding, in the application of burden of disease methods in tandem with sourcing relevant input data to complement disease, injury, and health state model definitions. To date, there have been three main iterations of the SBOD study, and the study is now a mainstay as a tool to inform decision making processes nationally, and for decision-makers in local regions of Scotland [37]. The published work presented in this thesis relate to seven journal papers published in the period 2019 to 2022. However, the conceptual ideas, and fundamental generation of YLD, YLL and DALY estimates which underpin the ability to undertake the work in **Papers I and II** has been ongoing since 2013. These ideas have generated the first two research questions answered in this thesis:

(i) Does using country-specific severity distributions lead to differences in estimates of YLD, compared to using standard severity distributions from the GBD study?

(ii) Does the choice of standard population, when standardised rates, impact how causes of disease and injury are ranked using DALYs?

The independent approach in Scotland is not uniform within the UK. Public Health England (now represented by the UK Health Security Agency (UKHSA) and Office for Health Improvement and Disparities (OHID) government agencies) have collaborated closely with the IHME, using the GBD study to undertake UK-wide assessments [44]. This can potentially be problematic for knowledge exchange activities, particularly when estimates differ and neither party are able to explain why the differences exist. This can often lead to speculation on why the differences occur, and the monopolisation of burden of disease research by the GBD study can often be problematic in ensuring balanced discussions over differences [45]. Many users often just seek to appraise differences in the input data as they often lack the experience, or will, to understand methodological processes as they are often complex and exhaustive [46]. In the SBOD study, it was important to seek to find a bridge to GBD estimates, should it exist, as methodological processes could plausibly play a key contribution in explaining any differences between estimates. To share knowledge and experiences, the SBOD study team are members of the European Burden of Disease Network [6]. This is a network which comprises of individuals working on a range of burden of disease related activities. Some of these activities include the secondary use of GBD study findings, to building capacity to perform ground-up independent national studies. Membership of this network is important for all burden of disease researchers, alike, as it allows for evidence-informed debate without being driven by motivations from individual studies.

As the representativeness of data inputs into the SBOD are well understood, I sought to evaluate the impact of concerns raised in (i) and (ii) by carrying out assessments of the impact of methodological choices in burden of disease assessment (**Papers I to II**). In doing this, it has allowed for the development of knowledge of whether efforts to develop burden of disease assessments independent of the GBD study are beneficial, by highlighting the impact that differential methodological choices and data inputs have on end findings.

The impact of different methodological choices in burden of disease studies

Severity distributions

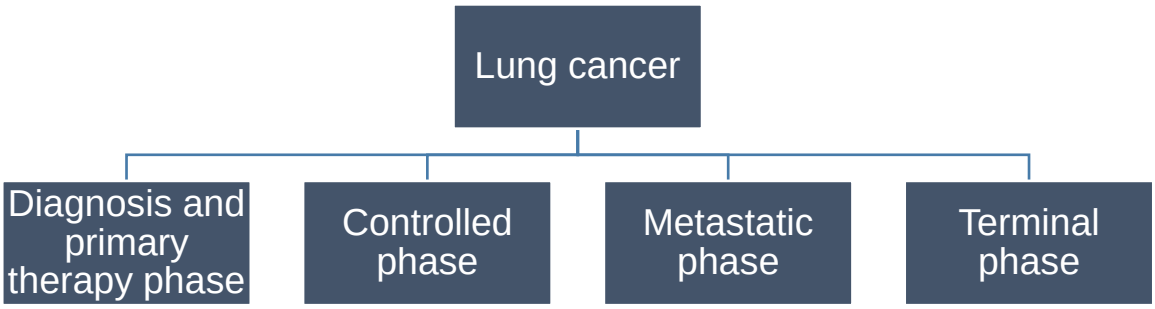
In order to estimate YLD, the occurrence of a disease – measured by incidence or prevalence – is required to map to disability weights to estimate the extent of loss from living with the ill-health consequences of a cause of disease or injury [1]. Disability weights are usually derived from paired comparison surveys whereby respondents consider two hypothetical individuals with different health states and determine which individual they would deem healthier than the other [22,23]. The values of disability weights vary from 0 (no health loss; ideal health) to 1 (health loss equivalent to death). The building blocks of causes of disease and injury are sequelae which are defined at a low granularity, for example many causes of infections share the following sequelae: mild, moderate, and severe acute infection [47].

Given the comprehensive nature of estimating the occurrence of each disease and injury, estimating the occurrence of morbidity at sequelae level presents major challenges. Commonly used data sources such as hospitalisations, medicine prescriptions, community General Practitioner consultations, medical claims data, or surveys, are often unable to present viable solutions as the lowest granularity of disease that can usually be estimated is at the level of the cause of disease or injury itself.

In order to overcome this, the GBD study have developed severity distributions to map the occurrence of diseases and injuries to relevant disability weights [43]. The development of these severity distributions are helpful, however it remains important to be cautious over their application. These severity distributions are derived from three large panel surveys from the United States and Australia, so are unlikely to be the most appropriate for use in other countries [48-50]. However, as there is a lack of more specific alternatives, they are often the only viable option.

Severity distributions can be summarised in terms of the proportional distribution of each sequelae within a cause of disease or injury, as outlined in Figure 2, using the example of lung cancer.

Figure 2. Hierarchical representation of lung cancer sequelae



As GBD study severity distributions are largely based on data from the United States and Australia, the original GBD research paper notes that there may exist concerns over applying these estimates to the rest of the world [47-50]. These should be seen as a major source of uncertainty in resulting estimates, and therefore be high on the research agenda, but there has been no publication from the GBD study that significantly advances the work from the GBD 2013 study. Pragmatically, they do offer the bridge between health state disability weights and therefore can readily be mapped to disease level prevalence estimates. The major uncertainty that exists is that due to a paucity of data, severity distributions are assumed to be constant over time and location – an assumption unlikely to be true due to differences across countries in factors such as: access to healthcare, availability and affordability of medication, population structures, and wider socioeconomic and environmental mechanisms. Some notable examples, from Australia and Korea, of estimating cause-specific severity distributions, existed prior to those presented in this thesis [51,52]. However, in these examples there were no comparative attempts to deduce to whether country-specific severity distributions yielded any differences compared to using severity distributions derived from the GBD study. Burden of disease studies that estimate alternative severity distributions that map to GBD disability weights should pursue comparative insights with the severity distributions from the GBD study. It will not only provide them with insights into whether their activities are worth continuing resourcing, but it will provide the wider burden of disease research community with evidence in an area which is sparsely researched. In addition, this may help to inform the future research priorities of the GBD study, in relation to severity distributions, and offer a means to improve the interface between the GBD study and independent national burden of disease studies.

Paper I addresses whether the standard approach of applying the same GBD study severity distributions to different countries is appropriate, through developing country-specific severity distributions derived from gold standard Scottish data inputs.

When determining how the occurrence of disease should be estimated in the SBOD study, a range of data and clinical experts were consulted. This was with regards to not only the identification of cases, but also how granular these cases should be defined at e.g. at the disease level, or at the disease sequelae level. In order to pair with disability weights, in a perfect world, data inputs would be defined at the disease sequelae level e.g. mild stroke. However, in most cases the occurrence of disease could only be robustly made at the level of the health condition e.g. stroke. An exception to this was that it was possible to determine national-level severity distributions, and severity distributions for different socioeconomic subgroups, using data from the Scottish Cancer Registry [53,54]. These were possible through using clear definitions on the assumed duration of each sequelae from the GBD study [55]. This allowed for the like-for-like production of GBD style severity distributions for cancer types that utilised more appropriate and representative data inputs. As the methodological approach to defining the severity distributions was consistent, this presented an opportunity to evaluate the impact of being able to adopt country-specific severity distributions relative to those used in the GBD study. At the time of publication of **Paper I**, no comparative assessments of severity distribution ascertainment had been made. Although this study was insightful from a Scottish perspective, it also had important far-reaching implications for both the GBD study and other national burden of disease studies in generating new evidence.

Paper I found that there were major differences between country-specific severity distributions and the standard severity distributions used in the GBD study for cancers. The counterfactual approach of adopting GBD study severity distributions for cancers in the SBOD study would have led to overestimating the non-fatal burden for most cancers. Additionally, it would have led to understating the scale of socioeconomic inequality in the non-fatal burden in Scotland. The findings from **Paper I** were an important development in urging caution, and the need for triangulation with other data sources and disease experts, when adopting GBD study severity distributions. Although this study was intended as a proof-of-concept for Scotland, its methodology has subsequently been used by the Belgian Burden of Disease study to estimate the non-fatal burden of cancer [56].

Despite the findings of **Paper I** being stark in the context of YLD estimates, a limitation was that the YLD component of the overall DALYs estimate for cancer types tends to be very low, as the burden of mortality tends to drive the DALY estimate. The findings initiated further research to understand which health conditions might be at risk of bias due to the assumption of severity distributions being fixed over time and location [57]. This research focused on differencing the highest and lowest disability weight within the severity distribution for each health condition, to gain insights into where the largest spread of potential values might lie. This is important to understand because there is a greater likelihood of variation occurring when the spread of potential values is the largest. This resulted in the identification of areas for prioritisations that were: opioid use disorders, major depressive disorder, ischaemic stroke, musculoskeletal disorders, anxiety, and other mental health disorders. However, most of these health conditions are those which are most difficult to estimate disease prevalence from routine health care data, as there are difficulties over capturing the full spectrum of disease severity. This has highlighted that interrogating routine healthcare datasets and generating proxy definitions is likely not a capture-all solution. This is important to consider when planning the future research agenda on severity distributions. Although in the absence of coordinated approaches to advance the area, further research on severity distributions for health conditions that are not among the priority health conditions can still usefully help to increase the evidence base.

Following this publication of **Paper I**, the GBD study started incorporating the need to improve estimates of severity in their capstone papers published in The Lancet [58]. This focused solely on the leading causes of non-fatal burden and did not consider that larger biases may lie elsewhere, such as through those conditions with the largest range of possible disability weight values. By this point the COVID-19 pandemic had been ongoing for six months, and the pandemic impact had been reported to have caused spikes in the occurrence, and severity, of conditions such as mental health and musculoskeletal disorders [59,60]. In the context of the pandemic shock there was an opportunity to effectively communicate the already published strategy, as early evidence has indicated that some of these health conditions had already been exacerbated. A published commentary used GBD study estimates to display the linear relationships between prevalence and YLD estimates across time [61]. This illustrated that not only were there uncertainties over robustness, but that the pandemic was going to bring further uncertainty. The commentary enlisted cross-country support from over twenty burden of disease

researchers, including key GBD study collaborators and key members of independent national burden of disease studies.

The findings of **Paper I** and two subsequently published commentary articles have provided convincing evidence on the need to improve upon existing efforts regarding disease severity, and where efforts should be focused. Methodologically, as YLD is the product of prevalence multiplied by the disability loss function, it was important to translate to users that ensuring quality inputs for both are vitally important. A ten percent underestimate on the true prevalence is the same as a ten percent reduction in the true severity weighted-average disability weight. Some musculoskeletal clinicians have now started to push for the incorporation of wider data sources within the GBD study, to improve the severity distributions [62,63]. This issue is now high on the European Burden of Disease Networks research agenda, and current collaborative efforts are being discussed – such as the replication of surveys that already capture relevant disease severity data, or through European-wide efforts such as the European Health Information Survey which includes respondents from a subset of individual European countries [64]. Subsequently published research from the German BURDEN 2020 study has cited these included papers. The BURDEN 2020 study carried out a nationally representative survey to estimate the prevalence of headache and low back pain, with severity distributions also being estimated [65,66]. In line with the findings from **Paper I**, the results were vastly different from those used for Germany from the GBD study.

Standard populations

When making comparisons in epidemiological trends, such as between demographic sub-groups or over time, rates per population are a commonly used metric to account for absolute differences in population sizes. However, some of these comparisons may be misleading when the underlying structure of the population of the comparator groups are different [67]. There are several different ways to adjust rates, but the most commonly used method in burden of disease studies is direct age-standardisation.

Direct age-standardisation estimates the age-standardised rate (ASR) by calculating a weighted average of the age-specific rates for each of the comparator population groups [68]. The weighting is set based on a reference standard population. The resulting ASR represents a theoretical rate that reflects the situation of the two comparator groups having

the same underlying age distribution as the standard population, thus facilitating like-for-like comparisons.

National public health, and statistical, institutes in Europe are recommended to standardise rates to the 2013 European Standard Population (ESP), in line with guidelines from the Statistical Office of the European Union (Eurostat) [69]. This recommendation is on the basis that the ESP 2013 represents a suitable consensus standard to reflect the demographic situation within Europe, based on an average of Member States population projections for 2011 to 2030. Previously, the ESP standard was introduced in 1976 and other alternative standard populations exist in other parts of the world, where that standard is deemed to be fit for purpose for a specific number of countries/regions that would seek to compare epidemiological trends [70].

In terms of international health trends, the World Health Organization's (WHO) World Standard Population (WSP) is used to facilitate comparisons across countries of the world, and when reporting global health statistics trends [71]. The GBD study also define a WSP, which has slight differences with the WHO WSP [72]. In terms of difference, the WSPs tend to give higher weights to younger ages, whereas the ESP 2013 gives higher weights to older ages. This is because demographic transition in Europe is such that populations are generally much more elderly.

As the GBD study has become a key tool for use in knowledge exchange activities, for informing national, and local policy-making discussions, the issue exists of whether the use of the GBD WSP when may introduce some difficulties when interpreting findings in certain continental, national and local contexts. This issue is related to the fact that both national, and local area, results are being standardised using a reference population that is not a close reflection of national or local demographic structures. Many supporters of the GBD study cite that their consistency of methods allow for comparisons over time and place, however in relation to this methodological choice, that is only relevant in the context of global and specific international comparisons. On the other hand, many of the comparisons that Scotland and other European countries would seek to make are with the countries that are most similar and at least theoretically, comparisons would be better served by standardising to the ESP 2013.

Paper II evaluates this theory by assessing differences in ASR for causes of disease and injury from the SBOD study, as a result of using different standard populations. It investigates whether different standard populations result in causes of disease and injury being ranked differently, as well as looking at absolute and relative differences in ASR. Prior to this work, published literature existed on the expected impact of such changes in standard populations in specific country and disease-specific circumstances [73,74]. However, these assessments had never exclusively been made using DALY estimates, in particular between the methods which were being utilised by the GBD study compared to those commonly used across European public health agencies.

Large-scale differences in rates on both the absolute and relative scale, and in the rank order of causes of disease or injury were found depending on the standard population used. The largest absolute differences between approaches were observed in the causes of disease where onset usually occurs at older ages, such as ischaemic heart disease, Alzheimer's disease and other dementias, and cerebrovascular disease. The use of the GBD WSP in ASR calculations generally reduced rates, whereas the use of ESP 2013 resulted in rates which were closely aligned to results of crude rate calculations for Scotland.

Paper II was important in highlighting that the adoption of the GBD study approach to standardising rates is context dependent, and in the context of Scotland, and other European countries, it would be beneficial to align with the already established recommendations of Eurostat [69]. However, the appeal of having readily available estimates of ASR, which can be retrieved within seconds from a query from the GBD Results Tool, may be a barrier to researchers ensuring that their DALY rate estimates are standardised according to the most appropriate standard population for their country under study [75]. This is particularly likely to be true when technical capacity and resource to calculate these ASR is low. However, the ability to readily access estimates does not waive the obligation of researchers and policy makers from understanding how such estimates are arrived at.

Paper II was widely discussed as part of the final workshop of the Joint Action for Health Information (InfAct – https://www.inf-act.eu/), funded by the European Commission [76]. The aim of this programme of work was around the development of burden of disease indicators to monitor the burden of disease in European Member States. The final InfAct workshop included a presentation, and discussion, by Prof. Moshen Naghavi who is

member of the GBD Scientific Council. During the discussion, the issue of age-standardisation was considered with reference to the findings of **Paper II**. It was indicated that the GBD study were considering implementing the possibility for users to choose different standard populations to calculate age-standardised estimates, depending on their national and local needs. To date, this has not yet been implemented in the GBD study, although the COVID-19 pandemic has generally resulted in major delays to further iterations of the GBD study. Since then, several studies have cited **Paper II** in the limitations section of their research studies to indicate that the default ASR estimates might not be the most appropriate to make comparisons. However, fundamentally the studies should seek to correct for the limitation rather than settle for the appeal of using readily available GBD study estimates. This indicates that a systematic change to the GBD Results Tool, and other GBD study interactive data tools, would likely have far reaching benefits for users of national and sub-national GBD estimates.

Burden of disease assessment in times of COVID-19

Contextualising vulnerability to COVID-19 using burden of disease methods

In February 2020, I attended the 1st Working Group Meeting of the European Burden of Disease Network in Copenhagen, Denmark [77]. Around this time, the spread of COVID-19 infection had just started to escalate in Europe. A month later, many people's home had become their place of work, as lockdowns were imposed as protective measures to restrict the spread of the virus. Although this was restrictive in terms of contacting my institutional colleagues, it brought colleagues from Europe closer, as communicating through virtual networking tools became the norm.

As evidence emerged on risk factors and health conditions associated with poor outcomes following COVID-19 infection, it became clear that the burden of COVID-19 was going to affect countries and their sub-populations disproportionately. This was due to inequalities in pre-existing levels of vulnerability, which lead to unequal, and unjust, adverse disease outcomes [8,78,79]. **Paper III** presents an assessment, using demographic and epidemiological indicators, of which countries were likely to be at the highest risk of vulnerability to adverse COVID-19 outcomes. Emerging evidence, at the time, focused on age as the leading risk factor. As other risk factors emerged governments, including the UK, began to publish guidance on the people that were likeliest to be at risk of severe health outcomes from COVID-19. This guidance was largely aimed at the elderly and

people with underlying conditions for which evidence had illustrated an association with adverse outcomes following infections [80].

Synthesising the cumulative vulnerability-level from the published guidance is difficult using traditional epidemiological measures because many health conditions co-exist, meaning research to identify and classify individuals would be highly time consuming. To do this on a continental scale would pose even more difficulties and time restraints. Sourcing estimates from the GBD study allowed for an assessment of how vulnerable individual countries were, based on the population health of their citizens. Undertaking a burden of disease assessment was an ideal way to do this, as this transforms health outcomes into mutually exclusive categories of YLD and captures the cumulative impact of all the individual health conditions and risk factors associated with severe outcomes from COVID-19. This assessment focused on Europe, and was carried out within the remit of the European Burden of Disease Network. At the time, it seemed of particular relevance for European countries as increases in lifespan have resulted in increasingly ageing populations living with effects of non-communicable diseases, multi-morbidity, and frailty [81].

The results indicated that due to pre-existing levels of vulnerability of its citizens health, Scotland was potentially in a relatively vulnerable position compared to other Western European countries. Although this work did not feed into the response for protective measures within Scotland, it was important to understand how different countries have different baseline needs before COVID-19 emerged. Understanding the impact of COVID-19 will need to be assessed relative to the scale of need, to comprehend whether measures to control and prevent infection were successful. Other studies have since undertaken similar assessments and based many of their approaches on **Paper III**. In the two years since publication, **Paper III** has been widely cited. This study has also been featured in the '*What is Inequality? Basic Health Inequality Concepts for Understanding the COVID-19 Pandemic*' guidebook published in 2020 by the Association of Schools of Public Health in the European Region (ASPHER) [82].

Developing methods to estimate the COVID-19 burden of disease

As the COVID-19 pandemic emerged, many burden of disease activities being undertaken were placed on-hold as public health practitioners focused efforts on tackling the challenge from COVID-19. At that point, the IHME were due to release estimates from the GBD

2019 study iteration, which was delayed as the IHME focused efforts on modelling the spread and mortality from COVID-19. In the context of the SBOD study, planned efforts to undertake a study to forecast future scenarios on the burden of disease in Scotland were put on hold, as other study team members were diverted into the pandemic response. Instead, efforts to develop methods to assess DALYs due to COVID-19 commenced.

At this point, the balance of reactiveness between national studies compared to the GBD study had switched. Previously, independent national studies have often lagged behind the GBD study in providing the most up-to-date estimates due to the ongoing nature of depth and capacity required to undertake comprehensive burden of disease studies. However, now national studies were well placed to respond to the need to develop COVID-19 burden of disease studies. As COVID-19 was a novel disease, there was no reliance on the GBD study as a gatekeeper.

As the SBOD study began to contemplate how to estimate the burden of COVID-19, colleagues from the European Burden of Disease Network were faced with similar issues. At this point, there were examples of misuse of methods, and misinformation spread regarding the years of life lost to COVID-19. Many COVID-19 sceptics were misusing life expectancy estimates to illustrate that those that had died from COVID-19 were likely to die very soon, had they not died of COVID-19, to downplay the impact of the virus [83]. This was a clear violation of the burden of disease approach, which looks to treat every cause of disease consistently, and highlighted the clear need for the development of a consensus methodological approach. I joined a wider group within the European Burden of Disease Network to determine how to integrate COVID-19, as a cause of infection, into burden of disease studies. Disease models for causes of disease and injury tend to be developed by the GBD study and map to clearly defined disability weights. However, as COVID-19 was a novel disease, no such disease model existed.

In the months that followed, I developed a disease model in collaboration with experts from seven countries, representing ten different public health institutes including the European Centre for Disease Prevention and Control (ECDC) [84]. **Paper IV** represents a disease model, methodology, and recommendations for data inputs, required for estimating COVID-19 DALYs. This included building upon the evidence base on valuing the YLL due to COVID-19, through being clear about the differences and pitfalls of different approaches to fatal health valuation [85,86]. Taken together, this body of work has been

highly impactful as the work was drawn upon in a policy document from the WHO Strategic Advisory Group of Experts on Immunization (SAGE) [87].

An unintended impact of this work was the clear synergies that it had with the early work which was published in **Paper I**. In terms of COVID-19 cases, the distribution of severity of cases was likely to be driven by the within-country context – from the level of protections put in place, to potentially artefactual differences if hospital care services were unable to meet demand, meaning there would be an unmet need that would not be reflected in published data. **Paper IV** has been highly impactful as many researchers within the European Burden of Disease Network, and some outwith, have been using and citing the approach within their choice of study design when estimating COVID-19 DALYs [88-92]. A key limitation of the work presented is in relation to the concept of long COVID. This was not apparent when the model was initial developed, as long COVID was relatively unknown. Within definitions of long COVID there is a large degree of variability in terms of symptoms, duration, and in terms of how debilitating it is to those that suffer from it. Within the European Burden of Disease Network work is planned to capture different disability weights, to explore differences in the extent of disability suffered through having long COVID i.e. loss of sense of smell would be expected to have a marginal impact on health-related quality of life compared to fatigue.

One further potential future synergy related to **Paper II** is regarding the use of standard population in ASR calculations. Due to the nature of it being a global pandemic, there is a strong justification to stick to the WSP when using the ASR to make comparisons. However, since the COVID-19 burden largely occurs in the elderly, there may strong justification to use the 2013 ESP if comparisons are between European, or other high income, countries, or for within country comparisons across their local regions.

COVID-19 burden of disease in Scotland

Following establishing an international consensus model and methods to estimate COVID-19 DALYs, as outlined in **Paper IV**, the SBOD study used these to carry out a COVID-19 burden of disease assessment. The aims were not to provide a near real-time assessment of the COVID-19 burden, but instead to make use of the comparative benefits of DALYs. The rationale for this was that DALYs represent the case, as is, and do not reflect the counterfactual that could have happened had preventative measures to restrict the spread and severity of COVID-19 not occurred. From early in the pandemic published statistics

have enabled us to understand the extent of the COVID-19 death toll [93]. The aim of **Paper V** was to enhance the comparability of these types of statistics, through estimating COVID-19 DALYs. This then allowed for its impact on population health to be framed comparatively with the leading causes of pre-pandemic health loss.

Paper V found that COVID-19, emerging from a single case in early March, was a leading cause of DALYs in 2020, likely second only to heart disease. This study was useful in communicating the impact of COVID-19 on population health in a manner that is consistent and comparable. Furthermore, it provides a useful yardstick for future international comparisons. This publication was discussed and cited in the Nature feature that was comparing ways in which researchers have been trying to understand the impact of COVID-19 on population health [94].

The same published statistics on the COVID-19 death toll were not only stark at the overall level, but highlighted that Scotland's most deprived areas had higher rates of COVID-19 mortality [95,96]. These statistics were persisting in the context of the Scottish Government's shielding guidance, which was designed to protect those that were likely at greatest risk of COVID-19 infection and mortality [80]. The shielding guidelines included a list of underlying health conditions, which would be expected to give rise to more people shielding that were from areas experiencing the highest levels of deprivation, given that the gradient in the occurrence of these health conditions were socially patterned [97]. At this time, commentators were pointing out that there was a 'syndemic' in play, which was due to the interaction of the pandemic threat alongside long legacies of systemic inequalities [78].

Paper VI explored the extent to which the 2020 estimate of COVID-19 DALYs was attributable to inequalities in area deprivation, defined by the Scottish Index of Multiple Deprivation (SIMD) [98]. SIMD uses seven domains to examine the extent of area deprivation: income; employment; education; health; access to services; crime; and, housing. **Paper VI** found that there were marked inequalities in the extent of inequality in COVID-19 DALYs, with 40% being attributable to inequalities in area-based deprivation. This is now widely understood and confirms the idea that the existing mechanisms which shape health inequalities have resulted in COVID-19 outcomes following this same, familiar, pattern [99].

Through using DALYs, it also allowed comparisons with pre-pandemic causes of disease, and the fuller toll of health inequalities. This allowed for the scale of impact of health inequalities to be communicated against the impact of COVID-19, representing a novel and refreshed way of communicating the overall impact of health inequalities. This may be an effective means to retain, and improve, public and policy empathy and engagement over tackling inequality, given the well-understood impact of COVID-19. To date this work has been well received and represents the only inequalities COVID-19 DALYs study to date. The findings from this study were presented at the UK Public Health Science and European Public Health conferences to wider national and international public health audiences. Furthermore, the study findings featured in the February 2022 update of Scotland's Strategic Framework which provide a framework for decision making regarding the harms from the COVID-19 pandemic [100].

Since the publication of **Papers V and VI**, several COVID-19 DALY studies have been published from other countries, highlighting the continual impact of the methods **Paper IV**. Routine knowledge exchange activities within the European Burden of Disease Network, such as sharing the approaches and findings from **Papers V and VI**, are having a positive impact for capacity building to undertake COVID-19 burden of disease assessments. At the time of submission of this thesis, published papers from other countries using this the methods and models in **Paper V** have emerged from: Australia; Denmark; Germany; Ireland; Malta; and, the Netherlands [101]. Ongoing studies which are utilising these models are taking place in: Belgium; Cyprus; France; and Sweden. To capture the intellectual significance of the work presented in the '*Burden of disease assessment in times of COVID-19'* section of this thesis, a review paper outlining the significance of the success of collaboration in helping to build capacity has been published by members of the European Burden of Disease Network COVID-19 Task Force [102].

Following the works from **Papers V and VI,** the main limitation was with regards to the estimation of long COVID. When the initial disease model was developed, the concept of long COVID was relatively unknown. There is a now a much larger degree of variability contained within the scope of the definition of long COVID in terms of represented symptoms. Extending this, difficulties exist regarding extracting the duration of individual, and similarly grouped symptoms. From a modelling perspective, the original published model in **Paper V** needs to be extended to capture a broader range of potential disability weights. Within the SBOD study, we therefore opted to monitor the population health

impact of COVID-19 using YLL in 2021, until appropriate disability weights can be characterised.

Paper VII aims to assess how the fatal population health impact of COVID-19 has changed from 2020 and 2021. Although the success of averting deaths from vaccination is well understood, it is important to consider how this success can be interpreted using summary measures of population health, reflecting the more recent situation of vastly increased case numbers. The findings were that the fatal burden of disease from COVID-19 was smaller in 2021 compared with 2020, measured by the death and YLL rate. However, YLL rate reductions were smaller than those observed for deaths which indicate that deaths were occurring at younger ages in 2021. Despite these reductions, both absolute and relative inequalities were further exacerbated in 2021. This was driven by two factors: (i) unequal improvements in mortality from COVID-19; and, (ii) a disproportionately higher number of deaths from younger ages in deprived areas. Since publication, this study has featured in the Scottish Parliament's inquiry into health inequalities in Scotland [103]. Furthermore, it gives an early expectation into one of the main factors likely to influence the forthcoming publication of inequalities in life expectancy, and healthy life expectancy, estimates for 2022.

Conclusion

This thesis includes seven peer-reviewed journal articles, and this explanatory essay on the need, development, and intellectual significance of each published work. These papers have originated through the development of the SBOD study and represent a body of significant evidence, insights, and novel methods for application in burden of disease assessment.

Structurally, the explanatory essay presents a three-tier approach, with the first part considering the impact of severity distributions, and standard populations in age-standardised rate calculations, in burden of disease assessment. The findings from this research have strong implications for those that use burden of disease estimates at national and local levels; methodological choices can have a vast impact on results.

Prior to the COVID-19 pandemic, the GBD outlined a willingness to make the choice of standard population used in standardised rate calculations a modifiable choice for users when they are generating estimates through data visualisations and results tools. This

would be an important step for users of continental, national and local estimates to choose the context which best reflects the comparisons that they are seeking to make. The capacity to integrate this has likely been impacted by the pandemic, so further work will be required to put these findings into action. Whilst the findings are definitive in the case of research into the impact of standard populations, efforts to push the research agenda forward on severity distributions is still relatively undeveloped. However, given there was a dearth of evidence in relation to the impact of the issue, the work presented within this thesis represents a forward step to move the conversation from talking about the problem, to quantifying the potential size of the issue. Further research efforts have given insights into where the best approaches for improvements would lie, and in doing so, has set a collective research direction for both independent burden of disease studies, and the GBD study. The incorporation of these works into key recommendation, and methodological burden of disease research papers, are a key milestone in allowing the work to have visibility and longevity in message, for future research activities [104,105].

Although these papers sit within the first part of this thesis, their significance within the second part, relating to COVID-19, are clear. Diseases rarely differentiate when it comes to methods choices, with the differential impact of the severity of COVID-19 within, and across, countries, providing further evidence. As we emerge from the pandemic, the monitoring of disease severity will have a key role to play as we consider the pandemic impacts on non-COVID-19 health conditions, such as through latent demand for care services. Historically unmet demand in the care system has been thought to have had an impact on our ability to identify people with conditions. Due to the shock to the care system, as a result of the COVID pandemic, this has been exacerbated and not only are we more uncertain of how many people may have health issues, but we are also struggling to identify where cases have become more severe, as a high proportion of individuals have opted to avoid care services [106]. These factors should potentially fast-track better, and more creative, ways to estimate changes in disease severity.

In the second part of the thesis, the initial collection of published work focuses on developing and underpinning consensus methods for application in COVID-19 DALY studies. At time of submission of this thesis, the GBD study has not yet publicly published DALY estimates for COVID-19. There was a mixed narrative on the methods which researchers should adopt for COVID-19, which was largely based upon the valuation of age-conditional YLL. This is important because adopting different COVID-19-specific

approaches would result in the comparative properties of DALYs (and YLL) being lost. The methodological work presented in this thesis makes clear that although COVID-19 is novel, the methodological situation is not and therefore the technical basis has not changed. From the perspective of researchers looking to carry out COVID-19 burden of disease assessments or integrate COVID-19 into their already established national studies, a shared consensus and way forward is important. To date the method paper included in this thesis has been well cited, and more specifically used within numerous studies that have either been completed, or are still being carried out, by members of the European Burden of Disease Network. Additional countries outside the network have also been adopting these methods, understanding the importance of international comparisons in the context of a global pandemic. Importantly, the methodological approaches have been recognised by the ECDC and the WHO, with the WHO highlighting the importance of being able to interpret levels of inequality, and disadvantage, from resulting estimates.

In the final part of the thesis, published works are presented related to COVID-19 burden of disease assessment for Scotland. Within Scotland, we have a comprehensive, and now well-developed SBOD study. The Scottish study has made important contributions to knowledge, in the framing of the overall, and disproportionate socioeconomic impact of COVID-19 on population health. Not only that, but by levering on the comparative properties of DALYs, it has also helped to provide novel insights into the extent of health inequalities in a comprehensive manner. Finally, the published works have indicated that COVID-19 mortality inequalities have been exacerbated in the times of high overall vaccine uptake. It remains important to consider how we can not only reduce inequalities in vaccine uptake, but how we can tackle the fundamental causes of inequality which lead to disproportionate levels of vulnerability.

These results are an important marker and could potentially integrate into future research to describe the population-level success of mitigation and prevention efforts, in the context of changing societal and economic circumstances. As the situation in Scotland has recently moved to an endemic phrase, communicating the population health impact of COVID-19 clearly, and relative to the disease burden due to other health conditions, is a valuable tool to scale the size of challenges faced by the public health, and health and social care, systems in Scotland. Furthermore, these insights are important to unravel the fuller impacts of the pandemic; through direct (e.g., COVID-19) and indirect mechanisms (e.g., latent demand due to barriers, and individual reluctance, in accessing care services) [8,106].

DALYs are well suited as they allow direct and indirect impacts to be additive, due to them measuring the impacts consistent across morbidity and mortality. It is important to consider that these types of assessments might take time due to their complexity, and for data collections and systems to regulate following the pandemic shock. At present, comprehensive burden of disease assessments may have a large degree of confounding from competing mortality hazards. From a morbidity perspective, the reliance on routine data sources and medical claims data will be very difficult to interpret due to the recent barriers and individual reluctance in accessing care services. Additionally, there are novel ways in which people are now increasingly accessing services, such as through tele-consultations.

The rationale for undertaking burden of disease assessments is to generate comparable estimates to identify what risk factors, causes of death, disease and injury are causing the largest public health losses. Findings can be helpful to inform discussions over resource allocation to ensure that care services and workforces are proportionate to the population health needs of a region. Through presenting the developments and wider intellectual significance of the seven published works included in this thesis, I have hopefully demonstrated their importance in enhancing the understanding and application of burden of disease methods. It is vital that the methodological context, and any uncertainties for which estimates are produced in, is well understood.

Afterword

When choosing the thesis title '*Enhancing the understanding and application of burden of disease methods*' I have been considering the relevance of this research as we move to an endemic phase of the pandemic within Scotland. The published works reflect the journey of my intellectual inputs, and evolutions, in the research field, which are largely based around methods. When it comes to application, using research to help inform policy action remains difficult [107]. The belief amongst burden of disease researchers is that additional barriers exist due to the seemingly technical nature in how burden of disease research is presented [108]. However, the pandemic has covered many basic epidemiological concepts, which when considered in tandem, signify the steps which we take when trying to estimate DALYs.

Firstly, the response to the COVID-19 pandemic has instigated major debate, given the pandemic has impacted everyone worldwide; either directly, or indirectly. Whilst many

people have generally supported cautious, evidence-guided, public health responses, others have sought to promote specific metrics that confirm less cautious opposing *a priori* stances. This links back to the first ideas presented, and the very basis for the justification of the DALY metric; the choice of metric highly influences the result [1]. Fundamental to this is the differentiation between individual and population health, which can often be widely misunderstood [13].

Since early in the pandemic, people have tried to make sense of the situation by comparing the impact of COVID-19 to things that they are more familiar with, such as other causes of death. These approaches aid our understanding of the scale of challenge faced. However, as information arose that deaths were mostly occurring in the elderly, some researchers attempted to move the debate to estimate the YLL of COVID-19 deaths, as a means for progressing comparisons of mortality that were based only on death counts or rates. This advanced the discussion somewhat, as it made the impact of age inherent in resulting estimates. It highlighted the importance of framing health issues comparatively, in a like-for-like manner. This again, is a key basis for the computation of DALYs; we can compare the population health impact of causes of disease and injury against each other in a consistent, and comparable, way.

Gathering, triangulating, and interpreting population health data to help inform responses is not a straightforward process, and there are uncertainties related to every metric. This was heightened in the face of the pandemic but is also true when trying to derive strategies to tackle other common health issues that existed pre-pandemic, and still exist today. Some health conditions are highly fatal, such as heart disease, whereas some common health conditions rarely, or never, directly result in death, such as the common cold or anxiety. Within those non-fatal health conditions, there are also major differences. Some occur frequently like the common cold, or relatively less frequently like rheumatoid arthritis. However rheumatoid arthritis is much more debilitating that the common cold. It is easy to see how the choice of metric, can easily skew the narrative, and how it can therefore be difficult for people to understand the fuller impact of living with, and dying from, causes of disease and injury. In the case of COVID-19, there has also been increased and widespread public and policy interest in case numbers, particularly as vaccination became available, and offered a potential solution to the relaxing of some protective measures [109,110]. Interpreting the severity of cases, defined as those requiring hospital care, with or without intensive care, has been vital in guiding the response. Case numbers, and

severity, have been extensively evidenced when considerations for restrictive measures have been discussed during the latest omicron wave. However, responses have had to consider whether increased transmission, would negate the benefit of decreased severity.

A solution to capturing the widespread disease impacts was through using a composite index of morbidity in mortality. In the early 1990s, this gave rise to DALYs which incorporated the comprehensive impact of living with, and dying from, disease and injury. This allowed the relative public health impact of diseases and injuries to be framed in a comparable manner. In the case of COVID-19, DALYs on their own would not have provided definitive answers to inform the entire public health response. As like with all infectious disease – heightened in the case of COVID-19 due to its rapid transmission – there would likely be major differences between different counterfactual scenarios, due to the differences in opportunity costs between alternative strategies. However, it is clear that DALYs are certainly a useful tool when discussions involve comparing the population health impact of COVID-19 with other diseases and injuries.

There remains much work to be done to integrate DALYs into discussions over informing population health related decision making. However, what is clear is that both the policy and public levels of interest have heightened in the face of the pandemic. Both groups have been attempting to make sense of the impact of COVID-19 on morbidity and mortality estimates on a daily basis. In particular, the omicron wave has reiterated the simple maths lesson that a small percentage of a large number can still result in a large number, due to the considerations of trying to interpret the end impact of increased transmissibility in the context of decreased severity [111]. Combining all these factors epitomise the concept of burden of disease assessment. These factors are widely understood by epidemiologists, and other related professions, but often face barriers when looking to use knowledge to inform action. The combined public and policy engagement to understanding data and metrics has never been as high as it has been during the pandemic [112]. There are major opportunities to use this as a bridge to understanding measures such as DALYs, to advise that how we recover from the pandemic is proportionate to where the largest population health losses are occurring.

References

References related to the published works included in this PhD thesis are denoted by emboldened Roman numerals e.g. **Paper VII**. References related to published literature cited in the explanatory essay are denoted using Arabic numerals in square brackets within the thesis text e.g. [7].

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