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ASSOCIATIONS BETWEEN ESSENTIAL MEDICINE LISTINGS AND HEALTH OUTCOMES FOR CARDIOVASCULAR DISEASE

BY

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Abstract

Context: National essential medicines lists are used to guide medicine selection, appropriate use, medicine reimbursement and public sector medicine procurement for many countries therefore medicine listings may impact health outcomes.

Methods: Countries' national essential medicine lists were scored on whether they listed medicines for ischemic heart disease, cerebrovascular disease and hypertensive heart disease was synthesized. Linear regression was used to measure the association between countries' medicine coverage scores and healthcare access and quality scores.

Results: There was no association between medicine coverage scores and healthcare access and quality scores when country characteristics were accounted for. However, there was an association between health outcome scores and health expenditure for ischemic heart disease, cerebrovascular disease and hypertensive heart disease.

Conclusion: Listing more medicines on national essential medicine lists may not improve health access and quality scores; rather it may only be one factor in reducing mortality from cardiovascular disease.

Keywords: cardiovascular disease, essential medicines, amenable mortality

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List of Abbreviations

ATC- Anatomical Therapeutic Chemical Classification System

CVD- Cardiovascular disease

GBD- Global Burden of Disease

GDP- Gross domestic product

HAQ- Healthcare access and quality

NCD- Non-communicable disease

NEML- National essential medicine list

SDI-Sociodemographic Index

WHO- World Health Organization

WHO Model List- The World Health Organization Model List of Essential Medicines

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Chapter 1. Introduction

Background

Ischemic heart disease and cerebrovascular disease (stroke) are the top two causes of death worldwide and accounted for 15.2 million deaths in 2016; they have been the leading causes of death worldwide for the past 15 years (The World Health Organization, 2018d). According to the Global Burden of Disease (GBD) 2016 data ischemic heart disease accounted for 17.3% of deaths worldwide, cerebrovascular disease accounted for 10.1% of deaths and hypertensive heart disease accounted for 1.6% of deaths ("GBD Compare | IHME Viz Hub," 2018).

Ischemic heart disease, cerebrovascular disease and hypertensive heart disease are all cardiovascular diseases (CVD) under the larger category of non-communicable diseases (NCD). NCD's are diseases not passed from person to person, they have long duration with generally slow progression (The World Health Organization, 2017a) and they are the result of a combination of genetic, physiological, environmental and behaviours factors (The World Health Organization, 2018c). Low- and middle-income countries are particularly vulnerable to NCDs with over three-quarters of heart disease and stroke-related deaths occur in them (The World Health Organization, 2018a). The burden of NCDs will be associated with "productivity loss and catastrophic healthcare costs" (Bazargani, Ugurlu, de Boer, Leufkens, & Mantel-Teeuwisse, 2018) which has the potential to "significantly undermine national macroeconomic development" (Abegunde, 2011). One explanation for increasing disease burden is the increasing urbanization and socio-economic development in low- and middle-income countries which has lead to increased exposure to tobacco smoking, unhealthy diets and reduced physical activity (Bazargani et al., 2018) behaviours which increase risk of developing CVD (The Centers for

Disease Control and Prevention, 2015). Along with an aging population, these changes have lead to an increased rate of CVD and other NCD's (Bazargani et al., 2018). While some medicines to treat chronic conditions are shown to be an effective intervention strategy, they remain largely inaccessible in low- and middle-income countries (Abegunde, 2011; Mahmić-Kaknjo et al., 2018).

This growing burden was recognized by the World Health Organization (WHO) and following a 2011 United Nations meeting, the WHO released a briefing document that stated that the burden of NCD's can not be reduced without access to essential medicines (The World Health Organization, 2011a). The WHO estimated that improving access to existing essential medicines could save 10 million lives per year (The World Health Organization, 2004).

Introduction to Key Terms

Amenable Mortality. Ischemic heart disease, cerebrovascular disease and hypertensive heart disease can be treated through proper medical interventions and therefore considered amendable to healthcare (Fullman et al., 2018). Amenable mortality refers to deaths that should not be fatal in the presence of effective medical care. National levels of personal health-care access and quality can be approximated by amenable mortality (Barber et al., 2017). To decide which conditions are amenable to healthcare, Noltes and McKee (2004) conducted a systematic review of all studies that measured avoidable mortality and created a framework for assessing mortality amendable to personal healthcare. This framework does not include all possible causes of preventable death with adequate healthcare, however it does provide a set of causes for which there is reasonable consensus, within the literature, that personal health care has a major effect (Barber et al., 2017). This framework crested a list of causes of mortality for which there is consensus that healthcare interventions can prevent deaths. The purpose of identifying causes is

to use them as "tracer conditions" whose health outcomes are monitored to study the responses of healthcare systems for causes that should not be fatal when adequate care is received. Tracer conditions can be easily measured over time to determine progress and evaluate health policies. (Nolte & Mckee, 2004)

Amenable mortality is used as a surrogate marker for health access and quality under the assumption that if a healthcare system is easily accessible and properly equipped deaths should not occur. The purpose of measuring amenable mortality is to gain insight into health-system delivery, effectiveness, and performance (16). Measuring healthcare access and quality using amendable mortality is becoming an increasingly popular way to approximate national levels of personal healthcare access and quality (Fullman et al., 2018) because mortality data is measured in many countries and more easily accessed.

Fullman et al., (2018) created a Health Access and Quality (HAQ) Index comprised of 32 causes considered amenable to health care adapted from Nolte and McKee (2004). The study represents a range of health service areas including vaccine-preventable disease; infectious diseases; maternal and child health; non-communicable diseases including cancers, cardiovascular and diabetes; and gastrointestinal conditions from which adequate healthcare can easily avert death (Barber et al., 2017). HAQ score is a measure of amenable mortality and can be used to "benchmark dimensions of health-system performance to identify untapped potential for advancing personal health-care access and quality" (Barber et al., 2017, p. 232). The HAQ score was calculated using data from the Global Burden of Disease (GBD) study, which is a comprehensive worldwide observational epidemiological study that describes morbidity and mortality from major disease, injuries and risk factors to health at national and regional levels (Fullman et al., 2018).

Assigning a HAQ score to a country involved four major steps. The authors mapped the previously identified causes amendable to personal healthcare (Nolte & Mckee, 2004) to a GBD cause list based on corresponding International Classification of Disease (ICD) codes. Some categories from previous research (Nolte & Mckee, 2004) were combined or excluded due to conflict with the GBD cause list, an action supported by GBD (Barber et al., 2017). The variation in death rates among countries could be attributed to differences in behavioural and environmental risk exposure. To mitigate the variation when scoring countries, they risk standardized cause specific mortality rates to remove variations in death rates not easily addressed through personal health care (Barber et al., 2017). To construct the HAQ scores, they computed a summary measure of personal health-care access and quality, on a scale from 0-100, using principal component analysis. To better understand the maximum levels of personal healthcare access and quality achievable, they assessed the highest recorded levels of healthcare access and quality across the development spectrum and produced a frontier analysis model based on the relationship between the HAQ Index and the Socio-Demographic Index (SDI) (Barber et al., 2017). SDI is a summary measure of overall development based on average income per capita, education attainment, and total fertility rates (Fullman et al., 2018).

After the GBD 2016 study results were released, the HAQ Index was updated. Similar data abstraction and analysis procedures were employed, however a few improvements were made since the previous iteration (Fullman et al., 2018). Improvements were possible because researchers were able to access more data, including vital registration data, more cancer registries, risk factors, and cause specific mortality modeling updates (Fullman et al., 2018). Due to the increase in quantity and quality of cancer registries, risk standardization no longer needed to be used and instead mortality to incidence ratios were used, which was found to more strongly

correlate with SDI. (Fullman et al., 2018)

Results show that HAQ scores ranged from more than 97 in Iceland to less than 20 in the Central African Republic and Somalia. Total health spending per capita was strongly positively correlated with HAQ Index performance in 2016 (Fullman et al., 2018); meaning that increases in healthcare spending were associated with higher HAQ Index performance.

Essential Medicines. The WHO defines essential medicines as:

> Medicines that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford. The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility (The World Health Organization, 2004).

Essential medicines lists are a policy tool to provide access to a basic list of medicines aimed at mitigating health inequities, it is well recognized that health and illness are not distributed randomly throughout society (The World Health Organization, n.d.-a). Inequalities in access to essential medicines are part of inequalities in healthcare (Hogerzeil & Mirza, 2011). The social determinants of health are primarily responsible for health inequities between and within countries. (The World Health Organization, n.d.-a) Key social determinants of health include the conditions that people are born into, grow, live, work and age in; the circumstances are shaped by distributions of money, power and resources at multiple levels of governance. (The

World Health Organization, n.d.-a) For example, health systems that rely on medicine supply through out-of-pocket payments unfairly exclude the poor and vulnerable from accessing medicines. (Hogerzeil & Mirza, 2011) Thus, medicines may be available, but access may be limited to varying degrees within or between countries.

The WHO created a Model List of Essential Medicines (WHO Model List) in 1977 and updates every two years based on scientific evidence for the comparative effectiveness, safety and cost–effectiveness of the medicines (The World Health Organization Expert Committee, 2017). The WHO Model List, presents medicines and their common uses, along with an appropriateness recommendation. The core list provides recommendations for minimum medicine needs for a basic health-care system; particularly for priority conditions which are "selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment" (The World Health Organization, 2017d). Essential medicine selection depends on many factors, including the pattern of prevalent diseases, treatment facilities, the training and experience of available personnel, financial resources, and genetic, demographic and environmental factors (The World Health Organization, 2004).

A National Essential Medicines List (NEML) is an essential medicine list specific to a country. NEML's are created to address the health care priorities of individual countries informed by the national burden of disease (Bazargani et al., 2018). "A country's NEML reflects a government's commitment to ensuring that quality health commodities are available and accessible to the population, and can serve an important tool for advocacy."(Rashid, 2016) Particularly in the public sector, essential medicines are more available than other medicines, suggesting that there may be preferential attention from governments given to essential medicines (Bazargani, Ewen, De Boer, Leufkens, & Mantel-Teeuwisse, 2014) therefore adopting

an NEML is the first step in ensuring equitable access to pharmaceutical treatments (Bazargani et al., 2018). As recommended by the WHO, many countries have created or adapted their own essential medicines list to meet the specific priority needs of their country. (The World Health Organization, 2004)

The WHO hosts a repository of all countries' NEML's but not all countries have a NEML. To address this gap, a team of researchers created a Global Essential Medicines (GEM) database of all countries NEML's .(Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019) All medicines, with some exceptions, from countries' NEML's hosted in the WHO's National Essential Medicines Lists Repository were extracted and recorded in an excel database. They identified NEMLs for 137, of 195 countries around the world. They listed 2182 medicines that appeared on at least one countries' NEML, with a mean of 370 ± 175 medicines listed per country. The researchers concluded that country characteristics, including WHO geographic region, population size, life expectancy, infant mortality, per capita gross domestic product and health expenditure, only explained 33% of the differences in NEML's and the substantial NEML variations between countries suggest that it is unlikely that the differences in priority health care needs of the population explain most of the variation (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019).

Research in Context

As previously mentioned, ischemic heart disease and cerebrovascular disease are the two leading causes of death worldwide (The World Health Organization, 2018d). Although it's not one of the leading causes of death, hypertensive heart disease is also a global burden causing

1.6% of deaths worldwide ("GBD Compare | IHME Viz Hub," 2018). Medicine availability and accessibility plays and important role in addressing the burden of NCD's (Abegunde, 2011) like heart disease and hypertension as evident by a reduction in mortality and morbidity in many countries since the implementation of essential medicines (Mahmić-Kaknjo et al., 2018).

Careful selection of essential medicines are thought to be a crucial first step to ensure availability of medicines (The World Health Organization, 2004). Essential medicines listed on countries' NEML's are supposed to be available at all times, in adequate amounts, and at a price people can afford; therefore the coverage of the lists themselves becomes an important indication of a countries' ability to provide pharmaceutical interventions to reduce the burden of disease. With this logic, listing medicines should lead to better health outcomes, particularly for causes of disease and death considered amendable to healthcare.

It is important to evaluate whether NEML's are adequately selected to maximize health access and quality, and reduce the burden of CVD on the country. This study used the previously created GEM database and HAQ scores to determine if listing medicines on a NEML was associated with HAQ scores for ischemic heart disease, cerebrovascular disease and hypertensive heart disease.

Building on Previous Research

There are several previous studies that this research built upon. The first looked at the overlap in medicines between NEML's and the 20th edition of the WHO Model List of Essential Medicines. (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019) This research used their GEM database of NEML's to compare a list of medicines used to manage cardiovascular disease to countries' NEML's.

Previous research assessed countries' NEMLs based on the number of differences from the 20th edition of the WHO Model List of Essential Medicines. The WHO Model List was not expected to be reproduced on countries NEML's, rather due to differing needs, pharmaceutical licensing and policies surrounding the production and sale of pharmaceuticals, it was meant to be used as an evidence based guide to save costs and increase rational medicines' availability and prescribing (Mahmić-Kaknjo et al., 2018). Instead of only using the WHO Model List as the reference, this study will create a list of medicines used to manage ischemic heart disease, cerebrovascular disease and hypertensive heart disease.

This work built upon two previous studies, which looked at the quality of NEMLs by either comparing them to the WHO Model List, or ensuring that they list medicines for all therapeutic groups. The first measured the number and diversity of medicines used to treat CVD, from 34 countries with operational NEML's, across multiple low- and middle-income countries (Bazargani et al., 2018). The researchers found that most medicine groups listed in international guidelines appeared on countries' NEML's, with over 75% of NEML's having adequate treatment for most acute cardiovascular events as well as primary and secondary prevention of CVD (Bazargani et al., 2018). However, they found that the coverage differed significantly across income levels and regions. Because the main classes of medicines used in the treatment of CVD were present, they concluded that selection will not be the limiting step in access to medicines for CVD (Bazargani et al., 2018). Therefore, the study found that the quality of lists assessed was overall adequate for cardiovascular disease. The second similar study compared CVD medicines included in the WHO Model List of Essential Medicines to medicines listed in 19 Eastern Mediterranean countries (Mehrtash, Laing, & Wirtz, 2018). The study compared both medicines listed on NEML's and the dosage forms to the WHO Model List of Essential

Medicines. The researchers concluded that countries should improve their selection of essential medicines for cardiovascular disease because the overall percent of WHO medicines was low in some countries and others did not list medicines in certain therapeutic areas that are needed for the treatment of CVD (Mehrtash et al., 2018). Therefore the study concluded that countries' NEMLs need improvement to meet treatment needs.

Between the two similar studies both used different scoring techniques however, there were 4 countries (Afghanistan, Jordan, Morocco, Pakistan) that were included in both studies. Although some of the country level data overlapped between studies, they found mixed results about the quality of NEMLs The discrepancy between studies may lie at a region level because one explored multiple low- and middle- income countries across regions concluding that there are regional differences while the other explored the Eastern Mediterranean only.

Identifying the Gap

No studies were identified that explored if listing CVD medicines, specifically for ischemic heart disease, cerebrovascular disease and hypertensive heart disease, was associated with measures of outcomes amenable to healthcare. We searched medline and embase using "cardiovascular disease" or "ischemic heart disease" or "cerebrovascular disease" or "hypertensive heart disease" (and their unique alternative names identified in the search scope notes) in combination with "essential medicine" (and alternate names identified in the scope notes).

Both the previous studies looking at NEMLs for cardiovascular disease assessed the quality of included NEMLs. In contrast this study looked at the value that medicines add to health outcomes related to cardiovascular disease.

This study built upon previous research studies by using a previously created database to determine if there was a relationship between listing medicines on an NEML and HAQ scores in countries. This study included more countries with a wider range of income then the previous studies (Bazargani et al., 2018; Mehrtash et al., 2018) comparing CVD medicines across countries with an NEML found in the GEM database. This additional country information will allow for broad insight into the ability of countries to provide pharmaceutical interventions; including a larger more diverse sample of countries will also allow us to better determine if relationships exist within the variables.

Research question: Is there a relationship between listing medicines on a countries' national essential medicines list (NEML) and their health access and quality (HAQ) index score for three cardiovascular disease (CVD) causes of morbidity and mortality considered amenable to healthcare.

Chapter 2. Methodology

Study Design

This study is cross sectional observational study that analyzes data at a specific point in time to compare across countries.

Inclusion Criteria

Countries must have a NEML captured in the GEM database and a HAQ score for ischemic heart disease, cerebrovascular disease and hypertensive heart disease.

Exclusion Criteria

Not all countries listed in GEM have an HAQ score, therefore they were excluded.

Defining a List of Medicines

Fullman et al., (2018) used 32 causes of mortality amenable to personal healthcare, that were previously mapped by Barber et al., (2017) to the Nolte and Mckee (2004) cause list. This only examined ischemic heart disease, cerebrovascular disease and hypertensive heart disease, which are 3 of the 32 causes of mortality listed by Fullman et al. (2018). In order to identify which medicines were associated with the three causes, we used the procedure described in the manuscript to create a list of medicines.

Guideline Description

The primary guideline used for creation of a list of medicines was the Technical Package for cardiovascular disease management in primary health care- evidence-based treatment protocols. (The World Health Organization, 2016b) This guideline is put out by the World Health Organization and endorsed by the Pan-American Health Organization, the World Heart Federation, the World Stroke Organization, the International Society for Hypertension, the

World Hypertension League and the Centers for Disease Control and Prevention. (The World Health Organization, 2016b) The package provides recommendations for cardiovascular disease treatment in a primary care setting and is targeted for an international audience while being mindful of fiscal resources. (The World Health Organization, 2016b) This guideline builds on the WHO-PEN guideline with additional tools for CVD management. (The World Health Organization, 2016b)

The second WHO guideline used was: Tackling NCDs: "Best Buys" and other recommended interventions for the prevention and control of non-communicable diseases. (The World Health Organization, 2017b) This guideline makes recommendation for a list of "Best Buys" which are recommended cost effective and feasible interventions. (The World Health Organization, 2017b) This guideline makes recommendations for CVD and other NCDs based on global NCD targets. (The World Health Organization, 2017b) Although the focus of this guideline is broad, including all NCD, there are specific recommendations for CVD.

The last two WHO guidelines are primarily used for diabetes treatment; both Prevention and Control of Non-communicable Diseases: Guidelines for primary health care in low-resource settings (The World Health Organization, 2012) and WHO Package of Essential Non communicable (PEN) Diseases Interventions for Primary Health Care in Low-Resource Settings. (The World Health Organization, 2010) These guidelines are for diabetes and not CVD specifically therefore it may not be a comprehensive list of medicines used to treat CVD; also these guidelines state that they are for low- resource settings therefore some countries may question the applicability. (The World Health Organization, 2012) (The World Health Organization, 2010) However, cardiovascular disease is commonly associated with diabetes therefore we were able to identify some medicines used for CVD treatment from both guidelines.

Additional guidance was sought from the American Heart Association to ensure the list of medicines was comprehensive. The American Heart Association is a not-for-profit association that funds research and educates people about heart disease and stroke, based in the United States of America with some international ties. (American Heart Association, n.d.)

Lastly, the WHO Model List of Essential Medicines was used to create a list of medicines. The WHO Model List is update bi-annually by the WHO Expert Committee on the Selection and Use of Essential Medicines (The World Health Organization, 2017c). The WHO uses the following criteria for selecting essential medicines: medicines must have adequate evidence of efficacy and safety, in a variety of settings, to be selected; relative cost-effectiveness of both the medicines and treatment is considered and compared to efficacy when choosing medicines in the same therapeutic category; In some cases, pharmacokinetic properties or local considerations such as the availability of facilities for manufacture or storage may be considered; medicines must be available in a form in which adequate quality, including bioavailability, can be ensured; essential medicines should be formulated as single compounds, unless "the combination has proven advantage in therapeutic effect, safety, adherence or in decreasing the emergence of drug resistance in malaria, tuberculosis and HIV/AIDS" (The World Health Organization, 2004) (The World Health Organization, 2017c).

Guideline Search Strategy

Identified guidelines and The WHO Model List of Essential Medicines 20th edition were searched by using the ICD-10 diseases, conditions or cause of death and the overall HAQ cause (either ischemic heart disease, cerebrovascular disease or hypertensive heart disease) category to identify relevant medicines. For HAQ causes that were broad we looked at the WHO ICD-10 codes lookup (The World Health Organization, n.d.-b) to identify specific diseases conditions or

causes of death. Identified guidelines and The WHO Model List search was conducted based on listed priority conditions and associated ICD-10 diseases and conditions.

Medicines Abstraction

The procedure for medication abstraction is described in the manuscript in Chapter 3.

Data Management

All data was extracted and stored in excel. There are no privacy concerns because all the information is publicly available.

Data Extraction

For each of the 3 HAQ causes studied (ischemic heart disease, cerebrovascular disease and hypertensive heart disease), all medicines identified were recorded in a table with duplicates removed.

After creating three lists of medicines used to treat each of the HAQ causes, we calculated how many medicines are listed on each countries' NEML, giving each country a medicine coverage score, described in the manuscript and below with additional details. The medicines listed for each HAQ cause were coded into the GEM database, in an excel file. The GEM database has listed medicines in the rows and countries in the columns; presence of a medicine on a list was indicated using a "1" and absence was indicated using a "0". (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrinic, et al., 2019) A formula was inputted under each country that will include presence or absence of a medicine on an NEML multiplied by the presence or absence on our list of medicines. The purpose is to indicating presence of a medicines on both a country in the GEM database and our list of medicines used to treat or

manage diseases. Then the overall number of drugs that overlap on both lists were summed creating a medicine coverage score for each country. The purpose of this score was to determine if countries' NEMLs list medicines that are used to treat or manage ischemic heart disease, cerebrovascular disease and hypertensive heart disease; with higher scores indicating that more medicines are listed on their NEML.

The NEML's were scored in two different ways. The first method listed medicines individually and compare them to medicines listed on countries NEML's creating medicine coverage scores for each country. The second method used the previously created list of medicines, but medicines were grouped by therapeutic class to determine if the NEML included any medicines within the class (Mehrtash et al., 2018). In order to determine which therapeutic class of medicine a drug belongs to we used 2nd level ATC codes provided in the GEM database. ATC codes are an internationally used code to identify active ingredients, they are classified according to the main therapeutic use (WHO Collaborating Centre for Drug Statistics Methodology, n.d.-b). ATC code were used because they are an internationally accepted system of classification and the second level of codes outlines therapeutic subgroups, for the anatomical main group, which in this case is, cardiovascular system. If medicines did not fall under cardiovascular system, they were not included in this analysis. Medicines in a class are therapeutically similar but because of trade deals, price, the political economy and complicated inter country relationships some medicines in a class may be preferred in countries over others therefore this score was included to provide a more fair evaluation of country NEML listings. Further, it is not necessary to list many medicines per class; if they are considered interchangeable, priority healthcare needs can be met without including an excessive number of medicines. We calculated the total number of classes where countries listed at least one medicine

and then divided it by the total number of classes that are appropriately used to treat that condition.

Data Sources

Table 1: Data Sources

Data source	Description	Variables using this source
GEM Database	The GEM Database (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrinic, et al., 2019) is a resource created by researches at St. Michael's Hospital in Toronto, Canada. This resource is an excel database that lists all NEML's from countries' whose NEML is listed in the WHO repository. (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019)	Medicine Coverage Score Class Coverage Score
Health Access and Quality Scores	This score was retrieved from a study by Fullaman et al., (2018). The scores are a measure of amenable mortality, as measured by age standardized mortality rates.	HAQ Score
Global Health Observatory (GHO)	Global Health Observatory is a repository of health statistics data for 194 Member States. The aim is to provide access to country data and statistics and to monitor global regional and country situations and trends (The World Health Organization, 2016c).	Geographic Region Population Size Health Expenditure Life Expectancy
The World Bank	The World Bank connects global financial resources, knowledge, and innovative solutions to meet the needs of developing countries (The World Bank, n.d.). This resource contains information about countries' finances.	Income Level
Global Burden of Disease Study		Prevalence

Variables for Analysis

Table 2: Main Variables

Variable	Independent or	Type	Range	Description	Source	Rationale

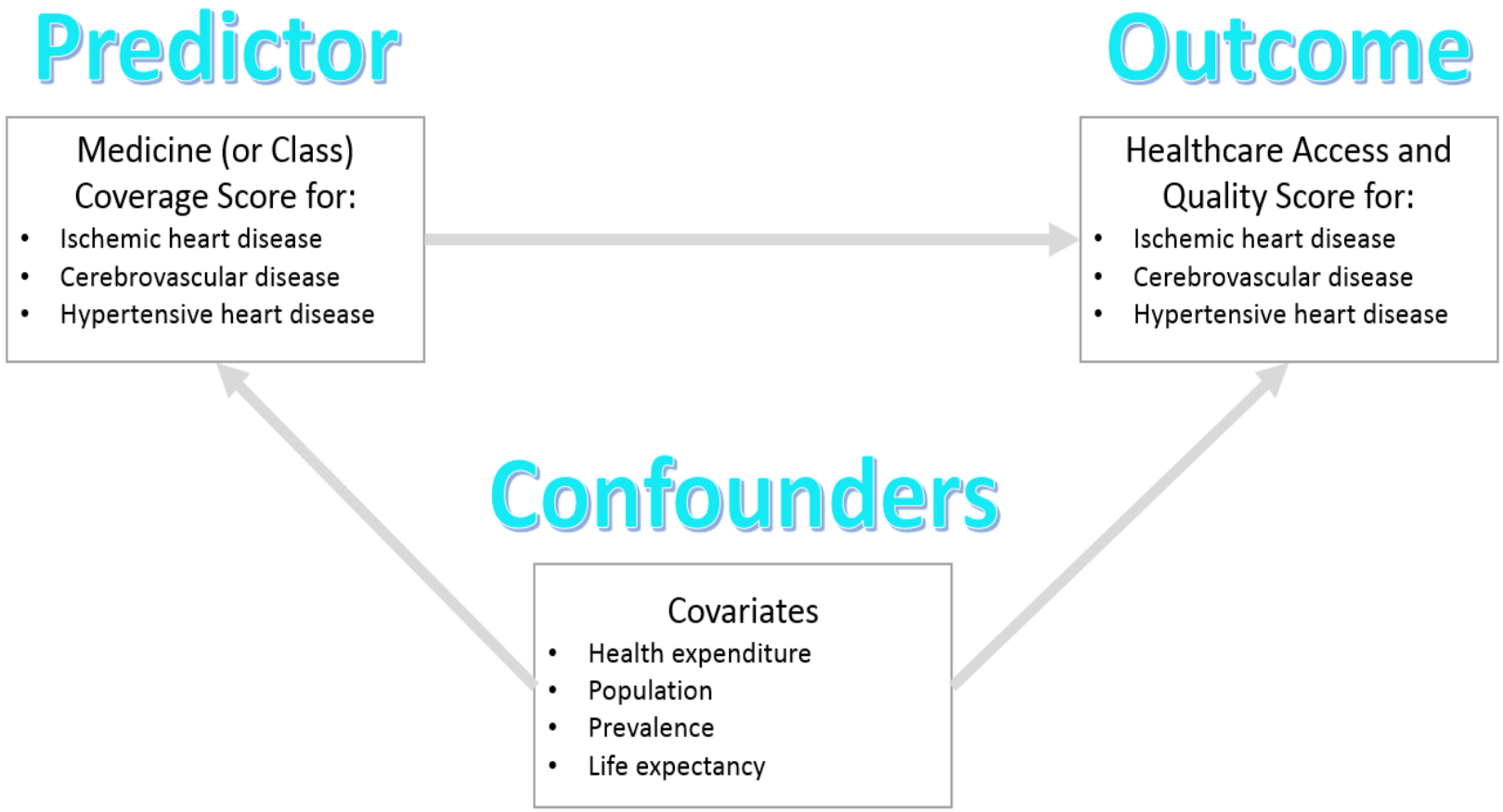
	Dependent					
HAQ Score	Dependent	Continuous	0-100	This is a measure of amenable mortality created using age-standardized death rates.	This score will be pulled directly from Fullman et al. (2018).	This variable represents a score of amenable mortality.
Medicine Coverage Score	Independent	Continuous	>0	This is a medicine coverage score with all medicines separated. See the data extraction section for how the score was calculated.	This score was calculated using the created list of medicines and the GEM database.	The medicine coverage score represents a countries ability to provide pharmaceutical intervention to treat or manage the diseases or conditions
Class Coverage Score	Independent	Continuous	0-10	This is a medicine coverage score with molecules grouped by class of medicine that are considered therapeutically equivalent. See the data extraction section for how the score was calculated.	This score was calculated using the created list of medicines and the GEM database, then grouping them by 2nd level ATC codes.	The class coverage score represents a countries ability to provide pharmaceutical intervention to treat or manage the diseases or conditions. The purpose of grouping medicines is to see if countries have comprehensive medicine coverage.

Table 3: Country Variables

Variable	**Independent or Dependent**	**Type**	**Range**	**Description**	**Source**	**Rationale**
Health Expenditure	Independent	Continuous	>0	Health spending in current PPP per capita (The World Health Organization, 2018e).	The information will be retrieved from the Global Health Observatory created by the WHO, for 2016 (The World Health Organization, 2018e).	Healthcare expenditure may give insight into a country's ability to pay for medicines and other healthcare treatments.

Population Size	Independent	Continuous	>0	The number of people or inhabitants in a region or country (Merriam-Webster, n.d.).	The information will be retrieved from the Global Health Observatory created by the WHO, for 2016 (The World Health Organization, 2018e).	It is important to account for variations in population size to determine if country characteristics impact health outcomes.
Life Expectancy	Independent	Continuous	>0	Average number of years that a newborn is expected to live if current mortality rates continue to apply (The World Health Organization, 2006).	This information will be retrieved from the Global Health Observatory created by the WHO, for 2016 (The World Health Organization, 2016a)	It is important to account for variations in life expectancy because cardiovascular disease is more prevalent in certain age groups (Goff et al., 2014). Also, age is a known risk factor for CVD (Dhingra & Vasan, 2012).
Prevalence	Independent	Continuous	>0	The number of people with the disease (Institute for Health Metrics and Evaluation, 2017) per 100, 000 people	This score will be pulled directly from the Global Health and Data Exchange, for 2017 (Global Health and Data Exchange, 2018)	The addition of prevalence can give insight into quality of care.

Figure 1. Conceptual diagram



Data Analysis

Due to the use of two different scoring techniques, two different analyses were run. Both analyses use HAQ score as the dependent variable and alternated medicine coverage score and class coverage score as the main independent variable. The purpose of including a second analysis was to determine if each country lists at least one medicine for each class of cardiovascular medicines, this information would not be included in the individual medicine analysis. For both analyses the covariates are healthcare expenditure, GDP, life expectancy, prevalence and population.

Data analysis was conducted using the 26th edition of SPSS (Laerd Statistics, 2018), and a p-value ≤ 0.05 was considered significant. However bivariate and multivariate associations and effect sizes were the focus of the analysis. The primary outcome of the analysis was to determine if there is a positive relationship between listing medicines on a countries' NEML and their HAQ score. Assumption of a linear relationship, no significant outliers, independence of observations, homoscedasticity and approximately normally distribution of errors, were checked using the following procedure (Laerd Statistics, 2018).

Frequencies tables were created to examine the range of variables and ensure the data was complete with no errors. Some values were missing however these were determined to be true missing values not found in the data source, particularly health expenditure for some countries.

Assumptions of linearity were checked by producing scatterplots with the independent variable on the x-axis and the dependent variable on the y–axis with a line of best fit (Fields,

2018). We also examined partial plots to examine for any obvious and severe non-linearity. In no case did we find any indications of a violation of the linearity assumption.

The data were checked for outliers. Outliers were detected using z-scores, which were calculated for all data points. The decision criterion level chosen was 0.01, as it is often used (Cousineau & Chartier, 2010). The sample size (number of countries) is approximately 130 therefore the degrees of freedom are approximately 129; after adjusting for the Bonferroni correction to take into account sample size, with the chosen level of 0.01, a z-score of less than -3.891 or greater than 3.891 was considered an outlier (Cousineau & Chartier, 2010).Using the calculated z-score range of less than -3.891 or greater than 3.891, outliers were present particularly for GDP, health expenditure and population. Next outliers were removed from these variables to ensure that they are not to blame for the skewedness; even with outliers removed the skewness pattern persisted. Outliers were kept because removal did not rectify the skewedness and they are true values with no potential to be erroneous; eg: we know that China and India have large populations.

Next we checked assumption of normality using the Shapiro-Wilk test along with histograms with a bell curve added, box plots and Q-Q plots. Most variables were approximately normally distributed with the exception of GDP, health expenditure and population.

To further look at the relationship between the variables, including those that appear to be not normally distributed pairwise correlations were calculated using both the Pearson correlation and Spearman's rho correlation. Based on the histograms the variables were all skewed to the right therefore Log 10 transformations were preformed ("Data transformations - Handbook of

Biological Statistics," n.d.) on GDP, health expenditure and population to make them approximately normally distributed.

Linearity, independence of observations and homoscedasticity were tested by graphing the values of the residuals against the corresponding values of the outcomes predicted by the model in a scatterplot. Visual inspection showed no clear or severe departures from normal distribution and we concluded that the data met these assumptions. (44)

Parametric tests were chosen and two linear regression models were run; the first with the log transformed independent variables for GDP, health expenditure and population, then with the non-log transformed GDP, health expenditure and population. When looking at the R^2 value, the correlation value and the Beta value it appeared that they were similar meaning the log transformation did not appear to affect the model. Therefore, it was decided that the non-transformed variables would be used for the regression to aid in interpretation of the results.

Pearson correlation table suggested that GDP and health expenditure were significantly related to each other and possibly colinear. To explore how this relationship was affecting the model we removed GDP. We decided to remove GDP first because it had a lower Pearson correlation value in relation to the dependent variable. We ran two models removing GDP then added it back into the model; only a small impact to the R^2 value was observed, therefore GDP was not a significant contributor to the model. It was removed because health expenditure is theoretically a more important variable because it is expected to more directly impact mortality outcomes, also there was slightly less missing data.

Chapter 3. Manuscript and Additional Results

Manuscript

The manuscript is a summary of they key findings of this original research.

Approximately 29% of deaths worldwide are from cardiovascular disease specifically, ischemic heart disease, stroke and hypertensive heart disease. ("GBD Compare | IHME Viz Hub," 2018) The burden of these and other non-communicable diseases (NCD) will be associated with productivity loss and catastrophic healthcare costs (Bazargani et al., 2018) which has the potential to significantly undermine national macroeconomic development (Abegunde, 2011). Deaths from cardiovascular disease are amenable to healthcare, meaning adequate healthcare can prevent them (*i.e.* amenable mortality) (Fullman et al., 2018).

Following a 2011 United Nations meeting, the World Health Organization (WHO) released a briefing document which stated that the burden of NCD's cannot be reduced without access to essential medicines. (The World Health Organization, 2011b) Essential medicines are those that satisfy the priority health care needs of the population. (The World Health Organization, 2004) The purpose of an essential medicines list is to ensure quality medicines are available in a functioning health system, in appropriate forms, at affordable prices for both the individual and the community. (The World Health Organization, 2004)The WHO created a Model List of Essential Medicines (WHO Model List) which provides recommendations for minimum medicine needs for a basic health-care system. Many countries have embraced the idea of essential medicines and adapted their own national essential medicines list (NEML) to address their health care priorities informed by their national burden of disease. (Bazargani et al., 2018) NEML's are used to guide appropriate use of medicines, as well as medicine selection, reimbursement and public sector procurement (The World Health Organization, 2016b, 2018b).

In the public sector, essential medicines are more available than other medicines, suggesting that there may be preferential attention from governments given to them, therefore carefully selecting and adopting an NEML is the first step in ensuring equitable access to pharmaceutical treatment (Bazargani et al., 2018).

Medication availability and accessibility plays and important role in addressing the burden of NCD's (Abegunde, 2011) as evident by a reduction in mortality and morbidity in many countries since the implementation of essential medicines (Mahmić-Kaknjo et al., 2018).

The purpose of this study is to determine if there is an association between listing medicines used to treat ischemic heart disease, stroke and hypertensive heart disease and amenable mortality related to these conditions measured by the healthcare access and quality (HAQ) score. (Fullman et al., 2018)

Methods

Dataset sources

All medications, with some exceptions, from countries' NEML's hosted in the WHO's National Essential Medicines Lists Repository were extracted and recorded in an excel database (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019). NEMLs for 137 countries were identified. They listed 2182 medicines that appeared on at least one countries' NEML, with a mean of 370 ± 175 medications listed on NEMLs (Persaud, Jiang, Shaikh, Bali, Oronsaye, Woods, Drozdzal, Rajakulasingam, Maraj, Wadhawan, Umali, Wang, McCall, Aronson, Plüddemann, Moja, Magrini, et al., 2019).

Countries received an amenable mortality score, calculated by measuring age standardized mortality rates, for ischemic heart disease, cerebrovascular disease and hypertensive heart disease. (Fullman et al., 2018) HAQ score was part of a larger study that combined 32 causes to create a composite, HAQ Index for 195 countries.

Inclusion Criteria

Countries were included if they had a NEML captured by GEM database and a HAQ score for ischemic heart disease, cerebrovascular disease and hypertensive heart disease.

Data collection

In order to identify which medications were relevant to the three causes of interest (ischemic heart disease, cerebrovascular disease and hypertensive heart disease), we used the following procedure. Guidelines for ischemic heart disease, cerebrovascular disease and hypertensive heart disease were searched for on the WHO website in June 2019. Four international guidelines distributed by the WHO, an internationally recognized health authority, were selected: Prevention and Control of Non-communicable Diseases: Guidelines for primary health care in low-resource settings (The World Health Organization, 2012), WHO Package of Essential Non communicable (PEN) Diseases Interventions for Primary Health Care in Low-Resource Settings (The World Health Organization, 2010), Technical Package for cardiovascular disease management in primary health care- evidence-based treatment protocols (The World Health Organization, 2016b), Tackling NCDs: “Best Buys” and other recommended interventions for the prevention and control of non-communicable diseases (The World Health Organization, 2017b). Although it is not an internationally recognized guideline, additional guidance from the American Heart Association’s website was used to ensure all relevant medicines were captured (American Heart Association, 2019). These guidelines along with the

WHO Model List of Essential Medicines 20th edition (The World Health Organization, 2017d) were used to identify medicines used for treatment of ischemic heart disease, cerebrovascular disease and hypertensive heart disease. Guidelines were searched using the causes and associated ICD-10 codes provided. (Fullman et al., 2018)

Population size, health expenditure and life expectancy were retrieved from the Global Health Observatory (GHO)(The World Health Organization, 2018e); prevalence for ischemic heart disease, cerebrovascular disease and hypertensive heart disease was retrieved from the Global Burden of Disease Study ("GBD Compare | IHME Viz Hub," 2018). Most data was for the year 2016; if 2016 data was not available, data from the closest year to 2016 was retrieved. Country characteristics can be found in Table 4.

Table 4. Country Characteristics

Country	ISO Code	Geographic Region	Income Group	Health Expenditure for 2015 (per capita in PPP intl$)	Population for 2016 (in thousands)	Life Expectancy for 2016 (in years)	Year of NEML Publication
Afghanistan	AFG	Eastern Mediterranean	Low	183.9	34656	62.7	2014
Albania	ALB	Europe	Upper middle	773.7	2926	76.4	2011
Algeria	DZA	Africa	Upper middle	1031.2	40606	76.4	2016
Angola	AGO	Africa	Lower middle	195.5	28813	62.6	2007
Antigua and Barbuda	ATG	The Americas	High	1105.1	101	75	2008
Argentina	ARG	The Americas	High	1389.8	43847	76.9	2011
Armenia	ARM	Europe	Upper middle	883.2	2925	74.8	2010
Bahrain (Kingdom of)	BHR	Eastern Mediterranean	High	2453.2	1425	79.1	2015
Bangladesh	BGD	South-East Asia	Lower middle	88	162952	72.7	2008
Barbados	BRB	The Americas	High	1233.6	285	75.6	2011
Belarus	BLR	Europe	Upper middle	1084.6	9480	74.2	2012
Belize	BLZ	The Americas	Upper middle	523.7	367	70.5	2008
Bhutan	BTN	South-East Asia	Lower middle	287.1	798	70.6	2016
Bolivia	BOL	The Americas	Lower middle	445.8	10888	71.5	2011
Bosnia and Herzegovina	BIH	Europe	Upper middle	1101.8	3517	77.3	2009
Brazil	BRA	The Americas	Upper middle	1391.5	207653	75.1	2014
Botswana	BWA	Africa	Upper middle	970	2250	66.1	2012
Bulgaria	BGR	Europe	Upper middle	1491.9	7131	74.8	2011
Burkina Faso	BFA	Africa	Low	96.1	18646	60.3	2014
Burundi	BDI	Africa	Low	63.7	10524	60.1	2012
Cabo (Cape) Verde	CPV	Africa	Lower middle	310.4	540	73.2	2009

Cambodia	KHM	South-East Asia	Lower middle	209.6	15762	69.4	2003
Cameroon	CMR	Africa	Lower middle	162.8	23439	58.1	2010
Central African Republic	CAF	Africa	Low	31.9	4595	53	2009
Chad	TCD	Africa	Low	99.8	14453	54.3	2007
Chile	CHL	The Americas	High	1903.1	17910	79.5	2005
China	CHN	Western Pacific	Upper middle	762.2	1411415	76.4	2012
Colombia	COL	The Americas	Upper middle	852.8	48653	75.1	2011
Congo	COG	Africa	Lower middle	202.7	5126	64.3	2013
Costa Rica	CRI	The Americas	Upper middle	1286.5	4857	79.6	2014
Côte d'Ivoire	CIV	Africa	Lower middle	189.6	23696	54.6	2014
Croatia	HRV	Europe	High	1656.4	4213	78.3	2010
Cuba	CUB	The Americas	Upper middle	2478.8	11476	79	2012
Czech Republic	CZE	Europe	High	2469.9	10611	79.2	2012
Democratic Peoples Republic of Korea	PRK	South-East Asia	Low		25369	71.9	2012
Democratic Republic of Congo	COD	Africa	Low	34	78736	60.5	2010
Djibouti	DJI	Eastern Mediterranean	Lower middle	146.7	942	63.8	2007
Dominica	DMA	The Americas	Upper middle	585.7	74		2007
Dominican Republic	DOM	The Americas	Upper middle	873.1	10649	73.5	2015
Ecuador	ECU	The Americas	Upper middle	980.2	16385	76.5	2013
Egypt	EGY	Eastern Mediterranean	Lower middle	495.2	95689	70.5	2012
El Salvador	SLV	The Americas	Lower middle	578.5	6345	73.7	2009
Eritrea	ERI	Africa	Low	56.2	4955	65	2010
Estonia	EST	Europe	High	1886.8	1312	77.8	2012
Ethiopia	ETH	Africa	Low	65.6	102403	65.5	2014
Fiji	FJI	Western Pacific	Upper middle	331.4	899	69.9	2015
Gambia	GMB	Africa	Low	114.1	2039	61.9	2001
Georgia	GEO	Europe	Lower middle	717.7	3925	72.6	2007
Ghana	GHA	Africa	Lower middle	249.3	28207	63.4	2010

Grenada	GRD	The Americas	Upper middle	677.5	107	73.4	2007
Guinea	GIN	Africa	Low	57.2	12396	59.8	2012
Guyana	GUY	The Americas	Upper middle	336.1	773	66.2	2010
Haiti	HTI	The Americas	Low	120.1	10847	63.5	2012
Honduras	HND	The Americas	Lower middle	353.4	9113	75.2	2009
India	IND	South-East Asia	Lower middle	237.7	1324171	68.8	2015
Indonesia	IDN	South-East Asia	Lower middle	369.3	261115	69.3	2011
Iran (Islamic Republic of)	IRN	Eastern Mediterranean	Upper middle	1261.7	80277	75.7	2014
Iraq	IRQ	Eastern Mediterranean	Upper middle	481	37203	69.8	2010
Jamaica	JAM	The Americas	Upper middle	511.4	2881	76	2012
Jordan	JOR	Eastern Mediterranean	Upper middle	568.1	9456	74.3	2011
Kenya	KEN	Africa	Lower middle	157.2	48462	66.7	2016
Kiribati	KIR	Western Pacific	Lower middle	151.8	114	66.1	2009
Kyrgyzstan	KGZ	Europe	Lower middle	286.6	5956	71.4	2009
Latvia	LVA	Europe	High	1429.3	1971	75	2012
Lebanon	LBN	Eastern Mediterranean	Upper middle	1117.3	6007	76.3	2014
Lesotho	LSO	Africa	Lower middle	251.1	2204	52.9	2005
Liberia	LBR	Africa	Low	127.8	4614	62.9	2011
Lithuania	LTU	Europe	High	1874.6	2908	75	2012
Madagascar	MDG	Africa	Low	76.7	24895	66.1	2008
Malawi	MWI	Africa	Low	108.2	18092	64.2	2015
Malaysia	MYS	Western Pacific	Upper middle	1063.9	31187	75.3	2014
Maldives	MDV	South-East Asia	Upper middle	1513.9	428	78.4	2011
Mali	MLI	Africa	Low	118.5	17995	58	2012
Malta	MLT	Europe	High	3470.9	429	81.5	2008
Marshall Islands	MHL	Western Pacific	Upper middle	862.8	53		2007
Mauritania	MRT	Africa	Lower middle	177.1	4301	63.9	2008
Mexico	MEX	The Americas	Upper middle	1008.7	127540	76.6	2011
Mongolia	MNG	South-East Asia	Lower middle	469.6	3027	69.8	2009

Montenegro	MNE	Europe	Upper middle	957	629	76.8	2011
Morocco	MAR	Eastern Mediterranean	Lower middle	435.3	35277	76	2012
Mozambique	MOZ	Africa	Low	63.7	28829	60.1	2016
Myanmar (Burma)	MMR	South-East Asia	Lower middle	267.2	52885	66.8	2010
Namibia	NAM	Africa	Upper middle	942.5	2480	63.7	2016
Nepal	NPL	South-East Asia	Low	150.6	28983	70.2	2011
Nicaragua	NIC	The Americas	Lower middle	406	6150	75.5	2011
Nigeria	NGA	Africa	Lower middle	215.2	185990	55.2	2010
Oman	OMN	Eastern Mediterranean	High	1635.9	4425	77	2009
Pakistan	PAK	Eastern Mediterranean	Lower middle	134.4	193203	66.5	2016
Papua New Guinea	PNG	Western Pacific	Lower middle	98.6	8085	65.9	2012
Paraguay	PRY	The Americas	Upper middle	724.3	6725	74.2	2009
Peru	PER	The Americas	Upper middle	671	31774	75.9	2012
Philippines	PHL	Western Pacific	Lower middle	322.8	103320	69.3	2008
Poland	POL	Europe	High	1704.2	38224	77.8	2017
Portugal	PRT	Europe	High	2661.4	10372	81.5	2011
Republic of Moldova	MDA	Europe	Lower middle	515.3	4060	71.5	2011
Romania	ROU	Europe	Upper middle	1090.4	19778	75.2	2012
Russian Federation	RUS	Europe	Upper middle	1414	143965	71.9	2014
Rwanda	RWA	Africa	Low	143.2	11918	68	2010
Saint Lucia	LCA	The Americas	Upper middle	681.4	178	75.6	2007
Saint Vincent and the Grenadines	VCT	The Americas	Upper middle	469.5	110	72	2010
Senegal	SEN	Africa	Low	97.1	195	75.1	2013
Serbia	SRB	Europe	Upper middle	1323.7	8820	76.3	2010
Seychelles	SYC	Africa	High	867.3	94	73.3	2010
Slovakia	SVK	Europe	High	2062	5444	77.4	2012
Slovenia	SVN	Europe	High	2733.8	2078	80.9	2017
Solomon Islands	SLB	Western Pacific	Lower middle	173	599	71.1	2017

Somalia	SOM	Africa	Low		14318	55.4	2006
South Africa	ZAF	Africa	Upper middle	1086.4	56015	63.6	2014
Sri Lanka	LKA	South-East Asia	Lower middle	353.1	20798	75.3	2013
Sudan	SDN	Africa	Lower middle	277	39579	65.1	2014
Suriname	SUR	The Americas	Upper middle	1016.9	558	71.8	2014
Sweden	SWE	Europe	High	5298.6	9838	82.4	2016
Syrian Arab Republic	SYR	Eastern Mediterranean	Low		18430	63.8	2008
Tajikistan	TJK	Europe	Low	192.7	8735	70.8	2009
Thailand	THA	South-East Asia	Upper middle	610.2	68864	75.5	2013
The former Yugoslav Republic of Macedonia	MKD	Europe	Upper middle	857.1	2081	75.9	2008
Timor-Leste	TLS	South-East Asia	Lower middle	141.3	1269	68.6	2015
Togo	TGO	Africa	Low	95.6	7606	60.6	2012
Tonga	TON	Western Pacific	Upper middle	323.8	107	73.4	2007
Trinidad & Tobago	TTO	The Americas	High	2204.1	1365	71.8	2010
Tunisia	TUN	Eastern Mediterranean	Lower middle	774.1	11403	76	2012
Uganda	UGA	Africa	Low	138.5	41488	62.5	2012
Ukraine	UKR	Europe	Lower middle	469.4	44439	72.5	2009
United Republic of Tanzania	TZA	Africa	Low	96.5	55572	63.9	2013
Uruguay	URY	The Americas	High	1747.8	3444	77.1	2011
Vanuatu	VUT	Western Pacific	Lower middle	106.1	270	72	2006
Venezuela (Bolivarian Republic of)	VEN	The Americas	Upper middle	579.4	31568	74.1	2004
Viet Nam	VNM	Western Pacific	Lower middle	334.3	94569	76.3	2008
Yemen	YEM	Eastern Mediterranean	Low	144.5	27584	65.3	2009
Zambia	ZMB	Africa	Lower middle	203	16591	62.3	2013
Zimbabwe	ZWE	Africa	Low	182.3	16150	61.4	2011

ISO: The International Organization for Standardization

Data extraction

Using the identified guidelines for ischemic heart disease, cerebrovascular disease and hypertensive heart disease, medications used to treat these conditions were abstracted using the following procedure: If a guideline indicated a therapeutic class of medications, that class was fully expanded to include all medicines because medicines within the same chemical subgroup may be considered therapeutically similar. The WHO Model List recognizes interchangeability of certain medicines on their list for others within the same therapeutic class. (The World Health Organization, 2017d) Using this principle, 4th level Anatomical Therapeutic Chemical Classification (ATC) codes (WHO Collaborating Centre for Drug Statistics Methodology, n.d.-a) were used to guide which medicines are in the same therapeutic class. If a therapeutic class was mentioned and specific alternatives were stated, only those medicines were included (no therapeutic class expansion was done).

Medicines listed on the WHO Model List or those from guidelines appearing on the WHO Model List (in a form that is usable for the conditions or cause), with a square box symbol, were fully expanded based on the 4th level, chemical subgroup of the ATC code to include all medicines within that therapeutic class. If the medicine is not denoted with a square box it was not expanded. If specific medicines considered equivalent were stated, only those medicines were included.

An exception to these rules were made for streptokinase, it is not denoted with a square box on the WHO Model List however, it was expanded. Two clinicians (NP, DM) agreed that it was worth expanding because all medicines in the therapeutic class were felt to be equivalent

and widely used. We felt that it would be unfair to exclude streptokinase alternatives because they are equally valid from a clinical perspective.

All medicines identified in the guidelines were combined into one list per HAQ cause, for each list medicines were de-duplicated (Appendix 1). A medicine coverage score was created by summing the number of medicines on a country's NEML that were also listed on our list of medicines used to treat each HAQ cause.

Data analysis

Data was analyzed using IBM SPSS Statistics version 26 (IBM Corp., 2018), and a p-value ≤ 0.05 was considered significant. An ordinary least squares linear regression model was used to test the hypothesis that there would be a positive relationship between listing medicines (medicine coverage score) and HAQ scores. HAQ score was used as the dependent variable and the previously calculated medicine coverage score was used as the independent variable. Linear regression results are reported for both unadjusted and adjusted with health expenditure, population, life expectancy and prevalence as covariates. For the regression, assumptions were checked including assumptions of normality. Two variables (population and healthcare expenditure) were not normally distributed so they were logged; however in the regression little difference was observed between models with logged and not logged variables therefore for interpretation purposes we kept the unlogged variables in the regression.

Results

In total, 131 countries were included in the analysis having both a NEML and HAQ score (Table 4). WHO regions represented by countries were the Eastern Mediterranean (14 countries), Europe (26 countries), Africa (38 countries), the Americas (29 countries), South-East Asia (13

countries) and the Western Pacific (11 countries) (The World Health Organization, 2018e). Using the World Bank categorization, included countries represented a range of income levels with 28 low income countries, 40 lower-middle income countries, 43 upper middle countries and 20 high income countries (The World Bank, n.d.). Three countries (Democratic Peoples Republic of Korea, Somalia and Syrian Arab Republic) were excluded from the regression analysis because they were missing values for healthcare expenditure.

The total number of medicines identified through guideline searches for each cause; 103 medicines for ischemic heart disease, 96 medicines for cerebrovascular disease and 73 medicines for hypertensive heart disease (see appendix for list of medicines).

Ischemic heart disease

For ischemic heart disease, medicine coverage scores ranged from 2 to 73 (median: 28, IQR: 23 to 37). Table 5 reports the results of the unadjusted linear regression model showing that listing ischemic heart disease medicines only explained 0.5% of the variability in the HAQ scores across countries included in the analysis (R^2= 0.005). Figure 2 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. Table 5 reports the results after adjusting for population size, health expenditure, life expectancy and prevalence, which showed that approximately 18% of differences in the HAQ score for ischemic heart disease (R^2= 0.176) were explained by medicine coverage score for ischemic heart disease along with the four covariates; therefore the addition of covariates improved the fit of the model. The small correlation between HAQ and medicine coverage (r= 0.069) confirmed little relationship between these variables for ischemic heart disease, however other variables in the adjusted analysis showed an association with HAQ scores. Health expenditure was associated with a 0.011 point increase in HAQ score for each

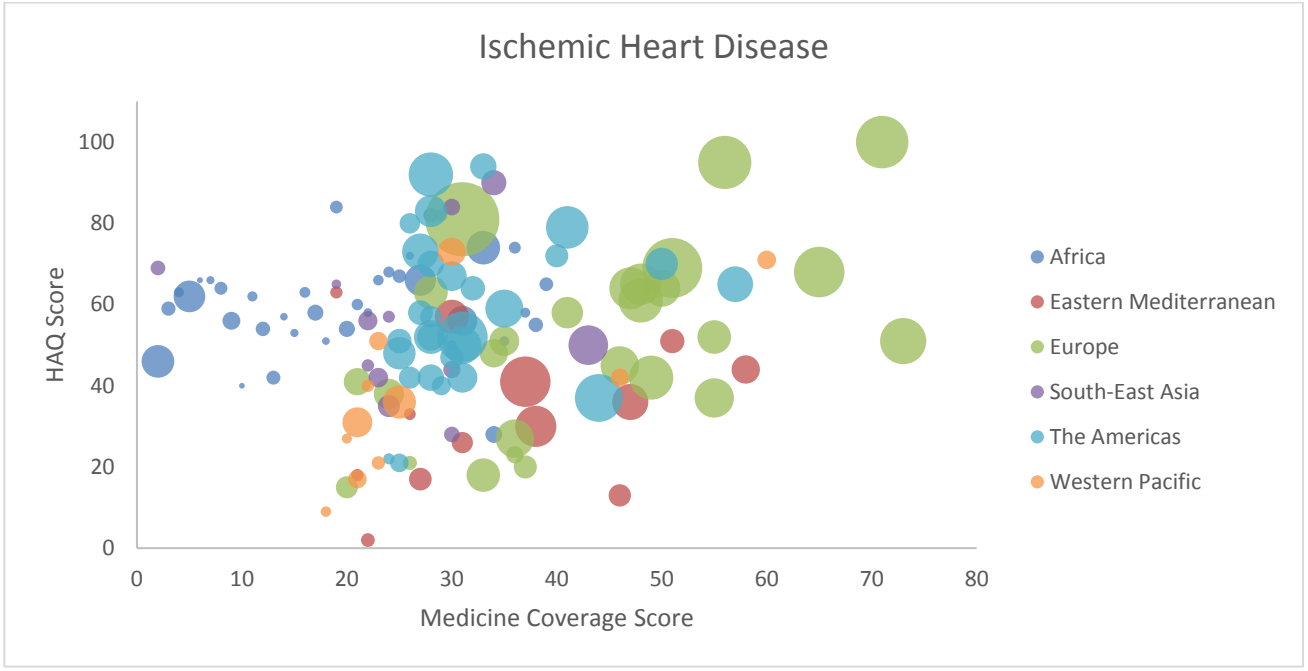
additional per capita dollar ($p<0.001$) and prevalence of ischemic heart disease was associated with a 0.007 point decrease in HAQ score for each additional 100, 000 people diagnosed with ischemic heart disease ($p<0.001$).

Table 5. Ischemic Heart Disease: Medicine Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Medicine Coverage Score	0.109	-0.164	0.382	0.69	0.43	0.069
Adjusted	Medicine Coverage Score	0.194	-0.14	0.528	0.123	0.252	0.108
	Health Expenditure	0.011	0.005	0.017	0.467	<0.001	0.232
	Population	-1.056E-7	0	0	0.001	0.991	-0.008
	Life Expectancy	0.058	-0.636	0.752	0.02	0.869	0.093
	Prevalence	-0.007	-0.01	-0.004	-0.49	<0.001	-0.108

Note: $R^2_{unadjussted} = 0.005$ ($F = 0.626$, (df: 130), $p = 0.43$). $R^2_{adjussted} = 0.176$ ($F = 5.131$, (df: 125), $p < 0.001$)

Figure 2. Ischemic Heart Disease: Medicine Coverage Score



Cerebrovascular disease

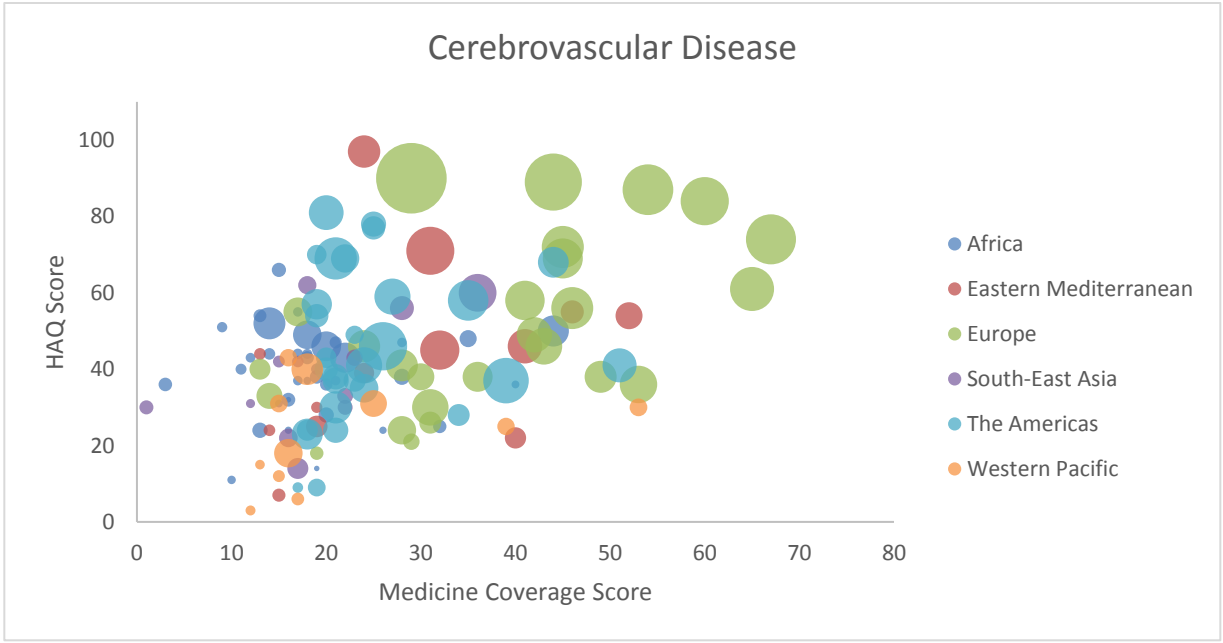
For cerebrovascular disease, medicine coverage scores ranged from 1 to 67 (median: 21, IQR: 17 to 31). Table 6 reports the results of the unadjusted linear regression model showing that listing cerebrovascular disease medicines explained approximately 15% of the variation in the HAQ scores (R^2= 0.153). Figure 3 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. Table 6 reports the results of the adjusted analysis, which showed that approximately 44% of differences in the HAQ score for cerebrovascular disease (R^2= 0.443) were explained by medicine coverage score for cerebrovascular disease along with the four covariates, again the addition of covariates improved the fit of the model. The correlation (r=0.391) confirms an association between medicine coverage score and HAQ score for cerebrovascular disease however the multivariate relationship was not present when covariates were included. Similar to ischemic heart disease, other variables in the adjusted analysis showed a significant association with HAQ scores. Health expenditure was associated with a 0.014 point increase in HAQ score for each additional per capita dollar (p<0.001), life expectancy was associated with a 0.557 point increase with each additional year of life (p=0.042) and prevalence of cerebrovascular disease was associated with a 0.008 point decrease in HAQ score for each additional 100, 000 people diagnosed with cerebrovascular disease (p=0.001).

Table 6. Cerebrovascular Disease: Medicine Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Medicine Coverage Score	0.565	0.333	0.796	0.391	<0.001	0.391
Adjusted	Medicine Coverage Score	0.173	-0.089	0.435	0.117	0.194	0.393
	Health Expenditure	0.014	0.009	0.018	0.587	<0.001	0.609
	Population	-3.977E-06	0	0	-0.037	0.596	-0.092
	Life Expectancy	0.557	0.1	1.095	0.2	0.042	0.476
	Prevalence	-0.008	-0.013	-0.004	-0.319	0.001	0.185

Note: $R^2_{unadjussted} = 0.153$ (F = 23.225, (df: 130), p <0.001). $R^2_{adjussted} = 0.443$ (F = 19.071, (df: 125), p <0.001)

Figure 3. Cerebrovascular Disease: Medicine Coverage Score



Hypertensive heart disease

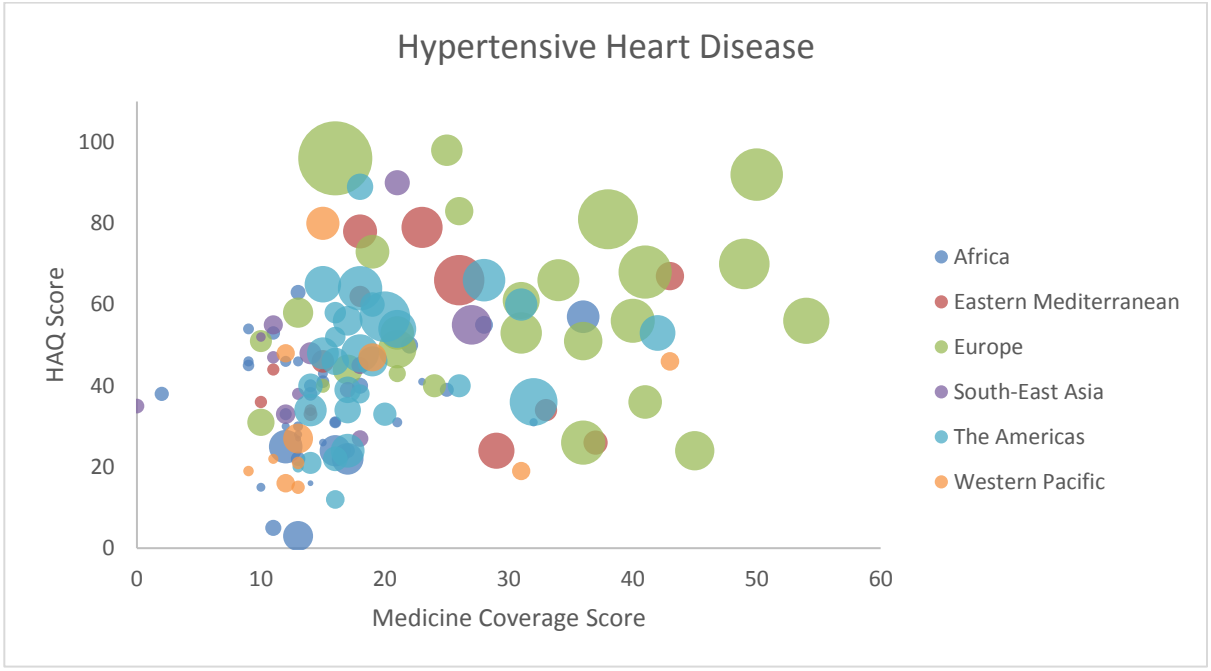
For hypertensive heart disease, medication coverage scores ranged from 0 to 54 (median: 17, IQR 13 to 25). Table 7 reports the results of the unadjusted linear regression model showing that listing hypertensive heart disease medicines explained approximately 11% of the variation in the HAQ score (R^2= 0.109). Figure 4 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. Table 7 reports the results of the adjusted analysis, which showed that approximately 45% of differences in the HAQ score for hypertensive heart disease (R^2= 0.454) were explained by listing medicines for hypertensive heart disease along with the four covariates. Similar to cerebrovascular disease, the correlation (r= 0.331) confirms the association between medicine coverage score and the HAQ score for hypertensive heart disease, however the multivariate relationship was not present when covariates were included. Other variables in the adjusted analysis showed a significant association with HAQ scores. Health expenditure was associated with a 0.008 point increase in HAQ score for each additional per capita dollar (p<0.001), life expectancy was associated with a 1.371 point increase with each additional year of life (p<0.001) and prevalence of hypertensive heart disease was associated with a 0.044 point decrease in HAQ score for each additional 100, 000 people diagnosed with hypertensive heart disease (p<0.001).

Table 7. Hypertensive Heart Disease: Medicine Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Medicine Coverage Score	0.621	0.312	0.929	0.331	<0.001	0.331
Adjusted	Medicine Coverage Score	0.204	-0.116	0.524	0.11	0.209	0.324
	Health Expenditure	0.008	0.004	0.013	0.346	<0.001	0.533
	Population	2.073E-06	0	0	0.019	0.782	-0.009
	Life Expectancy	1.371	0.829	1.913	0.484	<0.001	0.554
	Prevalence	-0.044	-0.063	-0.026	-0.402	<0.001	0.084

Note: $R^2_{unadjussted} = 0.109$ ($F = 15.846$, (df: 130), $p < 0.001$). $R^2_{adjussted} = 0.454$ ($F = 19.963$, (df: 125), $p < 0.001$)

Figure 4. Hypertensive Heart Disease: Medicine Coverage Score



Discussion

The number of medications used to treat ischemic heart disease, cerebrovascular disease and hypertensive heart disease included in national essential medicines lists was associated with amenable mortality but the association was not present when country characteristics such as health spending were accounted for.

Our research suggests that increases in a country's health expenditure may improve HAQ scores for cardiovascular disease. Fullman et al., (2018) found that health spending per capita was strongly correlated with HAQ Index performance, however there was a large variation in score within similar levels of spending (Fullman et al., 2018). Government spending as a fraction of total health spending was also positively correlated with HAQ Index performance (Fullman et al., 2018). Per-capita health expenditure is inadequate to pay for basic healthcare interventions in some low-income countries (Backman et al., 2008; Mendis & Banerjee, 2010). For the countries included in this study, 62 countries' (of the 131 total countries; one country had no data) per-capita government expenditure on health was less than the minimum required for basic effective public-health system (Backman et al., 2008). A modest increase in public spending, efficient resource use and an investment in prevention programs is necessary for addressing inequity in healthcare (Mendis & Banerjee, 2010). It is also possible that higher healthcare spending would allow countries to purchase a better selection of medicines which may, in turn, lead to better health outcomes.

We found that prevalence of cardiovascular disease was significantly associated with HAQ score in all of the adjusted regression models. This finding indicates that higher prevalence of cardiovascular disease was associated with a lower HAQ score for each cause. Life expectancy was also significantly associated with HAQ score for cerebrovascular disease and

hypertensive heart disease in the multivariate regression models. Life expectancy and prevalence have similar individual and societal level risk factors underpinning them, including the social determinants of health. The social determinants of health can impact both prevalence and life expectancy but they may also be independently related to HAQ score, however we were unable to find a measure of the social determinants of health that could be tested in the regression.

Many studies have linked cardiovascular disease to the social determinants of health (Havranek et al., 2015; Jeemon & Reddy, 2010; Martínez-García et al., 2018; Mendis & Banerjee, 2010). An individual's social status including income, education and literacy, housing and living conditions, employment, social exclusion and access to other health care services can influence behavioural risk factors for the development of cardiovascular disease and subsequent outcomes related to cardiovascular disease (Mendis & Banerjee, 2010). We suspect that barriers within the healthcare system, driven by the social determinants of health, are particularly important for cardiovascular health. For example, inequity exist within the implementation of cost-effective interventions and the provision of care for cardiovascular disease predominantly in low-income countries where health systems are may not be adequately equipped for providing chronic disease care (Mendis & Banerjee, 2010).

Other factors, such as quality of care, may impact mortality from cardiovascular disease. A study of 137 low- and middle-income countries found that amenable mortality outcomes were predominantly due to poor quality healthcare (84% of cardiovascular deaths amenable to healthcare), while the remaining 16% was due to non-utilization of healthcare (Kruk et al., 2018). This study shows that cardiovascular deaths for people entering the healthcare system are predominantly driven by poor quality of care. Therefore, quality of care, may account for some

of the observed differences in amendable mortality and this would attenuate any real relationship between medicine selection and health outcomes.

Strengths and Limitations

This was the first study we are aware of to compare NEML medications listings for cardiovascular diseases on a large scale.

As a cross-sectional associational study, it would inappropriate to draw causal conclusions about a relationship between medicine coverage scores and HAQ scores. Studying these associations over time may help solidify the conclusions drawn in this cross-sectional study.

Applying a global medicine coverage score calculation represents a number of challenges. The score does not account for medications that are therapeutically interchangeable within a class; therefore, only one medication in the class needs to be present for treatment, and the others are redundant. In the medicine coverage score calculations we did not take into account equivalence therefore countries that listed multiple equivalent medicines in a class would have received additional points for each drug listed. However, listing more than one medicine in a class can be beneficial in certain circumstances, for example in the case of drug recalls or shortages. In addition, there are no guidelines for the number of medicines needed in a class for proper coverage so we opted to include any that were listed in the country score. Although there are limitations to creating a medicine coverage score, this approach allowed for an overall score that could be compared across many countries.

For the HAQ Index it is possible that misclassifications of disease codes and causes of death occurred. Also the database does not capture substantial inequalities in personal healthcare

access and quality across geographic regions or socioeconomic status. Further details about limitations for the HAQ score calculations can be found in the article by Fullman et al., (2018). The GEM database captured the most recent NEMLs in the WHO repository however, it is possible that a more recent NEML existed, and data extraction was liable to errors; further details can be found in the article by Persaud et al., (2019).

Future research

Future research could study the associations over time to better quantify the association between tested variables. In addition, future research may also consider how the social determinants of health perpetuate cycles of inequity within the health system and better measure them.

Conclusion

The number of medicines relevant to cardiovascular disease included in NEMLs is associated with amenable cardiovascular mortality but this association is not present when accounting for country attributes such as national healthcare spending. Other country attributes appear to be more related to cardiovascular deaths amenable to healthcare.

Chapter 4. Additional Analysis

Additional Results

In addition to the results in the manuscript, a medicine class score was calculated for the thesis to determine if countries listed at least one medication per therapeutic class. Medicines from several therapeutic classes were present in the list of medicines used to treat ischemic heart disease, cerebrovascular disease and hypertensive heart disease. For all causes, therapeutic classes present were: cardiac therapy, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system and lipid modifying agents. For ischemic heart there was one additional class: vasoprotectives. Three countries (Democratic Peoples Republic of Korea, Somalia and Syrian Arab Republic) were excluded from the regression analysis because they were missing values for healthcare expenditure.

Ischemic Heart Disease.

Medicine class analysis. For ischemic heart disease, class coverage scores ranged from 12.5% to 100%. Table 8 reports the results of the unadjusted linear regression model showing that listing therapeutic classes for ischemic heart disease only explained 0.1% of the variation in the HAQ score (R^2= 0.001). Figure 5 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. An adjusted linear regression model showed that approximately 17% of differences in the HAQ score for ischemic heart disease (R^2= 0.173) were explained by listing therapeutic classes for ischemic heart disease along with the four covariates (Table 8). The small correlation between HAQ score and class coverage score (r= -0.032) confirms little relationship between these variables for ischemic heart disease, however other variables in the adjusted analysis showed an association with HAQ scores. Other variables in the adjusted analysis showed a significant association with

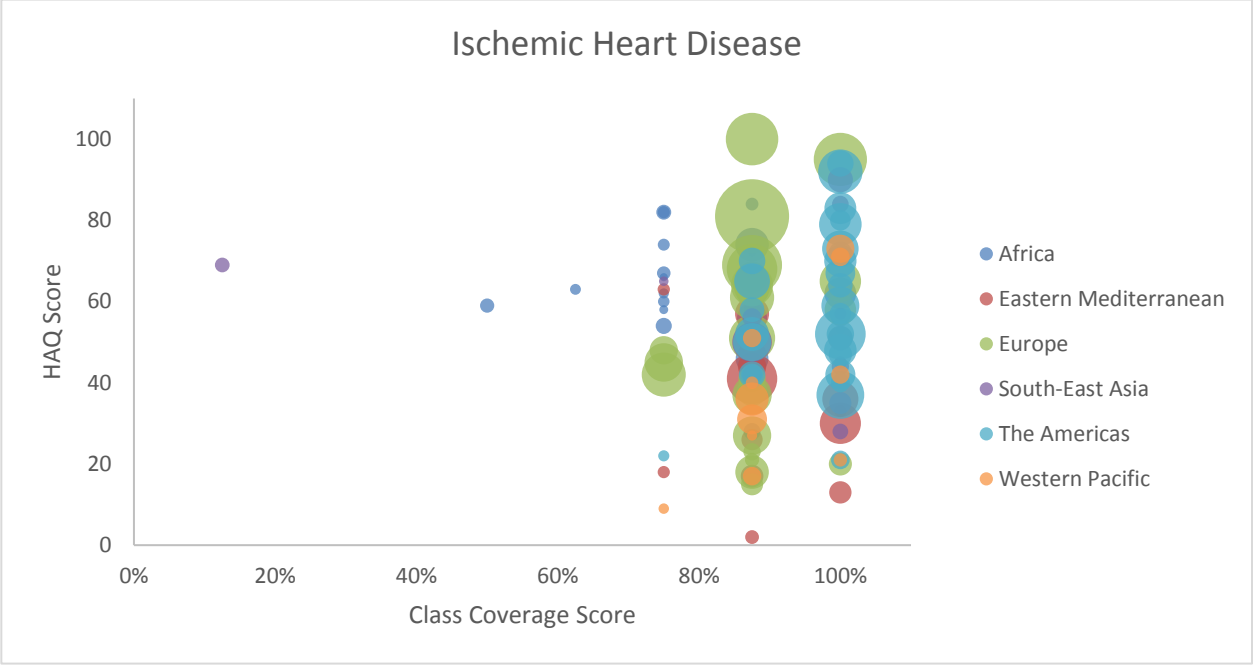
HAQ scores. Health expenditure was associated with a 0.012 point increase in HAQ score for each additional per capita dollar ($p<0.001$) and prevalence of ischemic heart disease was associated with a 0.007 point decrease in HAQ score for each additional 100, 000 people diagnosed with ischemic heart disease ($p<0.001$).

Table 8. Ischemic Heart Disease: Class Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Class Coverage Score	-5.328	-34.614	23.958	-0.032	0.719	-0.032
Adjusted	Class Coverage Score	-13.843	-44.150	16.464	-0.081	0.368	-0.016
	Health Expenditure	0.012	0.006	0.018	0.493	<0.001	0.232
	Population	1.211E-06	0	0	0.011	0.9	-0.008
	Life Expectancy	0.226	-0.498	0.95	0.077	0.537	0.093
	Prevalence	-0.007	-0.01	-0.003	-0.464	<0.001	-0.108

Note: $R^2_{unadjussted}$ = 0.001 (F = 0.130, (df: 130), p =0.719). $R^2_{adjussted}$ = 0.173 (F = 5.009, (df: 125), p <0.001)

Figure 5. Ischemic Heart Disease: Class Coverage Score



Cerebrovascular Disease.

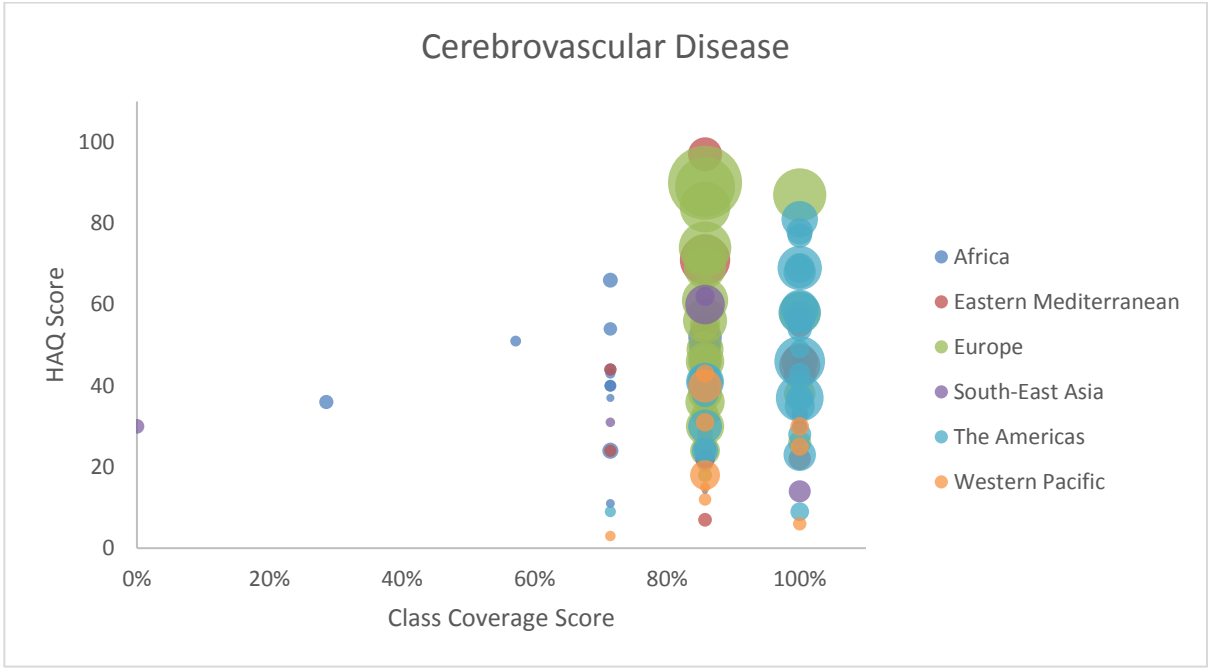
Medicine class analysis. For cerebrovascular disease, class coverage scores ranged from 0% to 100%. Table 9 reports the results of the unadjusted linear regression model showing that listing therapeutic classes for cerebrovascular disease explained approximately 2% of the variation in the HAQ score (R^2= 0.023). Figure 6 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. An adjusted linear regression model showed that approximately 44% of differences in the HAQ score for cerebrovascular disease (R^2= 0.435) were explained by listing therapeutic classes for cerebrovascular disease along with the four covariates (Table 9). The small correlation (*r*= 0.152) between HAQ score and class coverage score confirms little relationship between these variables for cerebrovascular disease, however other variables in the adjusted analysis showed a significant association with HAQ scores. Health expenditure was associated with a 0.015 point increase in HAQ score for each additional per capita dollar (p<0.001), life expectancy was associated with a 0.64 point increase with each additional year of life (p=0.026) and prevalence of cerebrovascular disease was associated with a 0.008 point decrease in HAQ score for each additional 100, 000 people diagnosed with cerebrovascular disease (p=0.001).

Table 9. Cerebrovascular Disease: Class Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Class Coverage Score	20.692	-2.671	44.055	0.152	0.082	0.152
Adjusted	Class Coverage Score	-2.051	-23.162	18.16	-0.018	0.811	0.141
	Health Expenditure	0.015	0.01	0.019	0.622	<0.001	0.609
	Population	-4.017E-06	0	0	-0.037	0.597	-0.092
	Life Expectancy	0.64	0.079	1.201	0.229	0.026	0.476
	Prevalence	-0.008	-0.012	-0.003	-0.29	0.001	0.185

Note: $R^2_{unadjussted}$ = 0.023 (F = 3.071, (df: 130), p =0.082). $R^2_{adjussted}$ = 0.435 (F = 18.487, (df: 125), p <0.001)

Figure 6. Cerebrovascular Disease: Class Coverage Score



Hypertensive Heart Disease

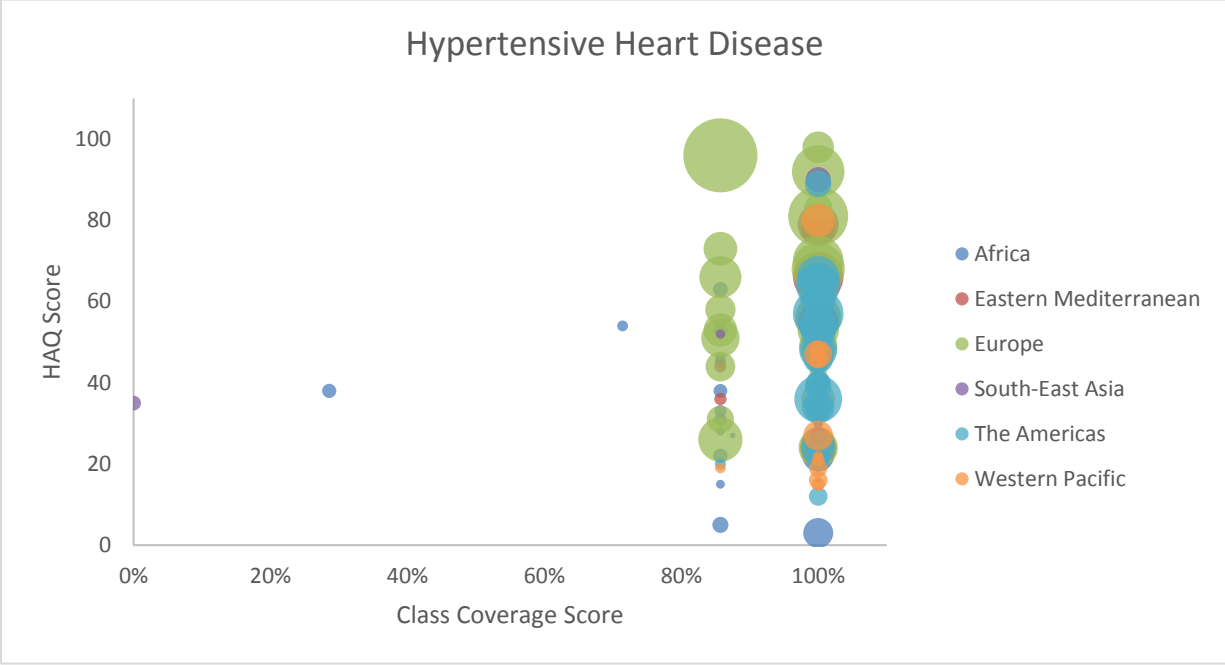
Medicine class analysis. For hypertensive heart disease, medicine coverage scores ranged from 0% to 100%. Table 10 reports the results of the unadjusted linear regression model showing that listing therapeutic classes for hypertensive heart disease explained approximately 0.7% of the variation in the HAQ score (R^2= 0.007). Figure 7 shows the unadjusted relationship between variables by regions, with the size of the bubbles representing per capita health expenditure. The results of the adjusted analysis showed that approximately 45% of differences in the HAQ score for hypertensive heart disease (R^2= 0.44.8) were explained by listing therapeutic classes for hypertensive heart disease along with the four covariates (Table 10). The small correlation between HAQ score and class coverage score (r = 0.084) confirms little relationship between these variables for hypertensive heart disease, however other variables in the adjusted analysis showed a significant association with HAQ scores. Health expenditure was associated with a 0.009 point increase in HAQ score for each additional per capita dollar ($p<0.001$), life expectancy was associated with a 1.429 point increase with each additional year of life ($p<0.001$) and prevalence of hypertensive heart disease was associated with a 0.041 point decrease in HAQ score for each additional 100, 000 people diagnosed with hypertensive heart disease ($p<0.001$).

Table 10. Hypertensive Heart Disease: Class Coverage Score

	Variable	B	95% CI lower bound	95% CI upper bound	Beta	P-value	Pearson correlation
Unadjusted	Class Coverage Score	13.277	-14.112	40.667	0.084	0.339	0.084
Adjusted	Class Coverage Score	-4.736	-26.334	16.862	-0.03	0.665	0.077
	Health Expenditure	0.009	0.005	0.013	0.378	<0.001	0.535
	Population	1.965E-06	0	0	0.018	0.795	-0.01
	Life Expectancy	1.429	0.881	1.977	0.505	<0.001	0.548
	Prevalence	-0.041	-0.058	-0.023	-0.367	<0.001	0.071

Note: $R^2_{unadjussted}$ = 0.007 (F = 0.92, (df: 130), p =0.339). $R^2_{adjussted}$ = 0.448 (F = 19.455, (df: 125), p <0.001)

Figure 7. Hypertensive Heart Disease: Class Coverage Score



Changes from Proposal

In the original proposal, three databases were used to derive the list of medicines used to treat ischemic heart disease, cerebrovascular disease and hypertensive heart disease. However we were unable to find internationally recognized guidelines that dictate which medicines should be used for these conditions; it was felt that guidelines endorsed by the WHO (Prevention and Control of Non-communicable Diseases: Guidelines for primary health care in low-resource settings, WHO Package of Essential Non communicable (PEN) Diseases Interventions for Primary Health Care in Low-Resource Settings, Technical Package for cardiovascular disease management in primary health care- evidence-based treatment protocols and Tackling NCDs: "Best Buys" and other recommended interventions for the prevention and control of non-communicable diseases) were a more reliable and rigorously composed source of information, so they were used instead.

Some covariates were added or removed from the original proposal. The original proposal included NEML year, geographic region, SDI, GDP, health expenditure, population size, age distribution, sex distribution, and life expectancy. Prevalence, separated by cause (ischemic heart disease, cerebrovascular disease and hypertensive heart disease), per 100,000 was added as a covariate to the final regression because prevalence is a measure of disease burden and it was felt that prevalence may give us an idea of availability and quality of cardiovascular care in a country.

Age and sex distribution were removed because the data was grouped and we were unable to separate it for the analysis. NEML year was removed because countries are responsible for updating their NEML on a regular basis therefore, they should be held to the standard of the

most recent guidelines for treatment of cardiovascular disease. SDI and GDP both measured income; SDI was chosen for removal because it also measured education and infant mortality, which were not likely related to cardiovascular disease outcomes. GDP and healthcare expenditure were also highly correlated; we could not include both for fear that the colinearity may influence the regression model. We ran both GDP and healthcare expenditure in the regression model and there was not much difference between them; following the lead of Fullman et al., (2018) we chose to include health expenditure.

Chapter 5. Discussion, Limitations and Conclusion

Discussion

Summary of Findings. In the unadjusted analysis listing medicines used to treat cerebrovascular disease and hypertensive heart disease was associated with HAQ scores. In the adjusted analysis, listing medicines used to treat ischemic heart disease, cerebrovascular disease and hypertensive heart disease was not associated with HAQ scores when accounting for country characteristics. Disease prevalence and health expenditure were significantly associated with HAQ scores for all causes (ischemic heart disease, cerebrovascular disease and hypertensive heart disease). In the medicine class analysis most countries listed medicines in each of the researched medicine classes. In the adjusted analysis we were able to explain 45% at most of the dependent variable, HAQ score, therefore variables such as the social determinants of health likely contribute to amenable mortality outcomes.

Social Determinants of Health. Many studies have linked cardiovascular disease to the social determinants of health (Havranek et al., 2015; Jeemon & Reddy, 2010; Martínez-García et al., 2018; Mendis & Banerjee, 2010). Risk factors for cardiovascular disease are tobacco consumption, high blood pressure, high cholesterol and diabetes (Mendis & Banerjee, 2010; Yusuf, Reddy, Ôunpuu, & Anand, 2001), yet other factors can increase the risk of cardiovascular disease including, low socioeconomic status, diet, physical inactivity, obesity, age, sex, family history and insulin resistance. (Mendis & Banerjee, 2010) An individual's social status including income, education and literacy, housing and living conditions, employment, social exclusion and other health care services can influence behavioural risk factors, the development of cardiovascular disease and subsequent outcomes, including mortality, related to cardiovascular disease (Mendis & Banerjee, 2010). The social determinants of health can impact cardiovascular

mortality based on both individual and societal factors; these factors can also impact life expectancy and the prevalence of cardiovascular disease.

Socioeconomic status. Socioeconomic status encompasses wealth and income, education, employment and other factors. (Havranek et al., 2015) Like many other diseases, there is a social gradient for cardiovascular disease with people who are of low socioeconomic status experiencing more incidence and mortality of cardiovascular disease particularly in high income countries. (Mendis & Banerjee, 2010) They also experience worse health outcomes after cardiovascular events such as stroke or myocardial infarction (Kapral, Wang, Mamdani, & Tu, 2002; Salomaa et al., 2001). Having a stroke or myocardial infarction leads to a diagnosis of cerebrovascular disease or ischemic heart disease.

There are several interconnected reasons people of low socioeconomic status experience worse health outcomes. Education is one of the most important predictors of cardiovascular disease outcomes (Rosengren et al., 2019; Winkleby, Jatulis, Frank, & Fortmann, 1992). People who are less educated are more likely to exhibit negative health behaviors like smoking, which accounted for the widening of an existing social difference in cardiovascular risk (Osler et al., 2000). It is important that people are in a position to receive preventative advice, understand it and act upon it; this can be accomplished when people receive at least a primary education (Mendis & Banerjee, 2010). Education is interconnected with other factors of socioeconomic status, for example education can lead to better employment and thus more financial stability (Hahn & Truman, 2015) There are many different factors acting on individual's ability to achieve greater education, for example government policies about the provision of education, or ability to pay.

Employment is an important contributor to cardiovascular health, however it can contribute both positively and negatively depending on the type of employment. Employment can lead to higher income which leads to better health (The World Health Organization, n.d.-a) because income provides access to resources such as healthier foods, safe environments and healthcare. (Hahn & Truman, 2015) Unemployment can contribute to poor health by increasing risk profiles for cardiovascular disease (P. Zagozdzon, Parszuto, Wrotkowska, & Dydjow-Bendek, 2014); it was also found to double the risk of cardiovascular mortality (Pawel Zagozdzon, Zaborski, & Ejsmont, 2009). Employment can also be a source of stress, which is associated with cardiovascular disease (Kivimäki & Kawachi, 2015). In addition, physically hazardous working conditions along with low job control were the driving factors behind an association between occupational class and less than good perceived general health. (Schrijvers, Dike Van De Mheen, Stronks, & Mackenbach, 1998)

Income level is important for health both directly through being able to afford shelter and healthy food, and indirectly by reducing stress etc. Specifically, cost of care can prevent people of low socioeconomic status from accessing healthcare (Kapral et al., 2002; Kristiansson et al., 2009). In 2015, 1.4 billion people incurred catastrophic health spending, which is defined as out-of-pocket spending that exceeds 10% of the household budget, which pushed 371.7 million people below the poverty line. (The World Health Organization & The World Bank, 2019) Out of pocket spending is a source of socioeconomic inequality because healthcare spending leads to service delivery only if the individual can pay. (The World Health Organization & The World Bank, 2019) Research shows that wealthier populations are more likely to seek healthcare when they need it (Makinen et al., 2000); inability to seek care can lead to worse health outcomes. Poor health outcomes can perpetuate the cycle of poverty because paying medical bills can

increase the risk of impoverishment and illness may result in productivity loss and loss of income (Mendis & Banerjee, 2010; The World Health Organization & The World Bank, 2019).

We know that socioeconomic status can impact health outcomes between and within countries. Areas where there are many people of low socioeconomic status may experience worse health outcomes for the reasons listed above. Socioeconomic status may act as a confounder that neither the HAQ score or our regression model was able to account for due to the lack of a standardized measure for included countries.

Health system barriers. Equity gaps exist within the implementation of cost-effective interventions and the provision of care for cardiovascular disease. They are particularly relevant for low-income countries where health systems are improperly equipped for providing chronic disease care. (Mendis & Banerjee, 2010) A study of 137 low- and middle-income countries and classified cardiovascular deaths amenable to healthcare into two categories, deaths due to poor quality of care and those related to non-utilization of healthcare. (Kruk et al., 2018) To differentiate poor quality care they assumed that once users seek care correct management and retention in care is the system's responsibility. They found that amenable mortality outcomes were predominantly due to poor quality healthcare. Specifically, for cardiovascular disease, 84% of mortality was due to poor quality care, while the remaining 16% of amenable deaths was due to non-utilization of healthcare, (Kruk et al., 2018) suggesting that quality of care is the biggest driver of mortality for causes amenable to healthcare. For example in Kenya, cardiovascular medicines can only be prescribed by physicians, (Vedanthan et al., 2016) however it can be difficult for patients to access physicians due to a lack of effective referral networks (Mercer et al., 2019) and a shortage of physicians making it difficult to contend with the disease burden.

(Vedanthan et al., 2016) Therefore, patients may be entering the healthcare system but not receiving proper cardiovascular care.

In many countries the per-capita expenditure is inadequate to pay for basic healthcare interventions; the poor suffer the most from the high cost of diagnostics, drugs and inaccessibility of healthcare and thus have worse health outcomes. (Mendis & Banerjee, 2010) For the countries included in this study 60 countries' (one country had no data) per capita government expenditure on health was less than the minimum required for basic effective public-health system. (Backman et al., 2008) In our research, we found that health expenditure was related to cardiovascular deaths that are amenable to healthcare. Possible explanations for this observation are healthcare spending may directly relate to medicine listing because medicines can be costly, particularly newer and patented medicines, therefore countries that spend more money on medicines may list more medicines and higher cost medicines; or perhaps this trend is explained by countries inability to spend on other basic healthcare interventions. Fullman et al., (2018) also found that for the overall HAQ Index score, encompassing all 32 causes of amenable mortality, healthcare expenditure was related to better performance. Our research suggests that increases in a country's health expenditure may improve healthcare access and quality scores for cardiovascular disease, which is consistent with the previous research (Fullman et al., 2018; Mendis & Banerjee, 2010)

In order to address equity gaps in low income countries, a modest increase in public spending, efficient resource use and an investment in prevention programs is necessary. (Mendis & Banerjee, 2010) Increasing health expenditure is not necessarily feasible because resources are finite. In our statistical analysis, health expenditure and GDP were associated with each other, so much so that GDP had to be removed from the regression. This relationship shows that a

country's ability to spend on healthcare is related to their overall country income. However, this is a general trend, and HAQ index performance showed a large variation in score within similar levels of spending (Fullman et al., 2018). Perhaps variations within similar levels of spending are caused by the implementation of cost-effective interventions and although countries can not increase spending they could organize healthcare more efficiently. Healthcare dollars spent in areas other than medicine provision may be more important investments for preventing cardiovascular deaths considering the relationship between health expenditure and HAQ score.

Medicine access. From previous research findings, medicine access is effected by both the quality of healthcare and non-utilization of healthcare. (Kruk et al., 2018) People may not receive prescription medicine as required due to either not being appropriately prescribed or not being able to access medicines because of cost or other systematic barriers. A previous study echoed this sentiment with their finding that medicine selection was not the limiting step in access because most countries listed medicines in each therapeutic categories. (Bazargani et al., 2018)

The purpose of listing medicines on NEMLs is to ensure the population it serves has reasonable access to listed medicines and although countries may have adequate coverage of cardiovascular medicines on their NEML, listing medicines does not necessarily guarantee access. Research found that essential medicines remain largely inaccessible particularly in low- and middle-income countries (Abegunde, 2011; Vialle-Valentin, Serumaga, Wagner, & Ross-Degnan, 2015). Access to essential medicines has been recognized by many as part of the right to health, and it has been added as an indicator to measure the "progress in progressive realization of the right to health". (Hogerzeil & Mirza, 2011) The concept underpinning essential medicines of equity, solidarity and social justice are in line with the principles of human rights (Hogerzeil

& Mirza, 2011). However, NEMLs are not necessarily enforceable in court, meaning there is not necessarily a legal right to access NEML listed medicines; there is a move towards making them enforceable in order to guarantee people access to the listed medicines (Hogerzeil & Mirza, 2011). Unfortunately, we were unable to find a reliable measure of medicine access measured globally that we could test in our regression analysis, we had to assume that if a medicine was listed on an NEML, people were able to access them as per the definition of an essential medicine (The World Health Organization, 2004).

From our results, we believe that simply having access to medicines may not be enough to overcome the negative impact of the social determinants of health on cardiovascular outcomes. Our research findings are consistent with health expenditure (and related social spending) both directly affecting medicine listing and cardiovascular outcomes; and indirectly affecting cardiovascular outcomes via the social determinants of health. We were unable to include the social determinants of health as a covariate because the data is not available for a large number of countries. Health expenditure and the size of the economy (measured by GDP) could also similarly indirectly affect amenable mortality through other factors.

Results in Context

This was the first study we could find to compare NEML medicines listings for cardiovascular diseases on a large scale. Previous research focused on the content of the lists to determine if included NEMLs met minimum standards for treatment of cardiovascular disease using both the WHO Model List and international guidelines (Bazargani et al., 2018; Mehrtash et al., 2018). The authors found mixed results; the first study found that countries' NEML met coverage standards for cardiovascular disease treatment (Bazargani et al., 2018) and the other found that they did not. (Mehrtash et al., 2018) These studies looked at different groupings of

countries and used different benchmarks for coverage standards therefore mixed results can be explained.

Our research built upon this work by assessing the value of listing cardiovascular diseases medicines on amenable mortality outcomes. Our research found an association between listing cardiovascular disease medicines and HAQ scores (measure of amenable mortality) in an unadjusted linear regression model however we did not find an association when covariates were added to the regression model. However we did find a relationship between healthcare expenditure and HAQ scores for cardiovascular disease, therefore the association is likely more complicated.

Limitations

Underlying Data. The study has several limitations particularly due to the source of information gathered. The HAQ Index score as a measure of amenable mortality was subject to several key limitations. First, the risk-standardization procedure may not represent all possible risk-outcome pairs, for example, they did not look at determinants of neonatal disorders. Second, there are limitations within the GBD cause of death estimation, which is used to calculate HAQ scores. However GBD updates their data annually and aims to improve their comparative risk assessment, which will then improve future HAQ score calculations. Third, the HAQ score does not directly capture causes amenable to healthcare without substantial mortality rates (eg: depression); therefore the measure could be improved by calculating the effects of healthcare access and quality for non-fatal health outcomes. Fourth, it is possible that misclassifications of disease codes and causes of death occurred; this can affect the results because it may influence the total number of deaths that are included for each cause of death. Lastly, the database does not capture substantial inequalities in personal healthcare access and quality across geographic

regions or socioeconomic status. Despite the limitations the Fullman et al., (2018) have stated that the HAQ scores are a more robust indicator of overall healthcare access and quality than previous measures. Previous research in this area focused on specific countries or regions therefore their research was able to provide a comparison between countries on a much larger scale, which can help countries prioritize healthcare reform and monitor overall progress. With each iteration the measure is updated and methods are improved and although the HAQ score is not a perfect measure, it provides a basis for comparison between countries and over time.

The second data set used was the GEM Database, which contains NEMLs that were found in the WHO essential medicine list repository. The authors used the most up to date NEML's listed in the WHO repository at the time of extraction (2017), but it is possible that the NEML lists in the repository were not the most recent NEML for a country because it is the country's responsibility to update the repository. Finally, the database was liable to errors because country documents were extracted by hand, documents in the repository had to be translated, medicine names were not standardized, and judgments had to be made in ambiguous cases. To attempt to mitigate as many errors as possible, data was abstracted by two individuals to reduce the likelihood of errors. Now that the database is publically available, future updated can be carried out be countries themselves to reduce potential errors.

Methodology. In the process of HAQ score creation, researchers risk and age standardized death rates (Fullman et al., 2018). It is possible that population and prevalence are related to the dependent variable because they were factored into the HAQ calculation; however the equation standardized these variables, therefore we added them back in as covariates to see if difference in these variables were associated with HAQ score performance.

The WHO states that an essential medicine list should consist of a limited number of medicines. (The World Health Organization, 2004) The purpose of this recommendation is to ensure that countries have enough medicines to meet their national priority conditions, while not including an excessive number of medicines, to ensure reasonable supply and access to listed medicines. We did not consider the length of the NEMLs in the analysis; the first analysis calculated a medicine coverage score based on the number of medicines listed on a countries' NEML. If the total number of medicines on the list was included in the medicine coverage score calculations, we could take into account the WHO recommendations of limited number of medicines and reward countries, within the scoring technique, for maintaining a limited list length.

Another critique of the scoring calculation used, is that it does not account for medicines that are therapeutically interchangeable within a class; therefore, only one medicine in the class needs to be present for treatment, and the others are redundant. This idea was taken from the WHO Model List where only one drug in a class was listed and they stated that other in the class can be used alternatively, therefore countries may only need to list one medicine in a class for sufficient coverage. In the medicine coverage score calculations we did not take into account equivalence therefore countries that listed multiple equivalent medicines in a class would have received additional points for each drug listed. We tried to counteract this limitation by calculating a class coverage score to determine if countries listed at least one medicine per class. Although it is important to consider overall number of medicines listed on NEMLs, there is no recommended number of medicines that should be listed, therefore we could not compare countries by this metric. Future work may improve these methods by collapsing medicine classes only when indicated as therapeutically equivalent by a guideline (the current method grouped them by ATC code), where countries would receive a point for listing one of the medicines.

Conclusion

Listing more medicines was associated with HAQ score in a univariate linear regression however the relationship was no longer significant after accounting for country attributes such as healthcare expenditure. However, some country attributes were significantly related to HAQ score. Approximately half of the variation in HAQ score was explained by the tested variables therefore, there are other drivers of cardiovascular deaths amenable to healthcare that we were unable to explore because they are unknown or not currently measured globally.

Future Research

This research was based on the assumption that listing cardiovascular medicines meant that the medicine was available in the listing country, however we know that this is not always the case, therefore more robust measures of essential medicine access should be measured globally. Also, cardiovascular disease mortality rates were used as a surrogate marker for healthcare access and quality; future research could measure healthcare access or quality using other metrics such as affordability of care or treatment follow-up in order to better determine targets for health system improvements. Finally, future research may also consider how the social determinants of health perpetuate cycles of inequity within the health system.

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Ethics

Ethics approval was not needed for this project because the information is publically available.

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Appendix A: Medicines for Cardiovascular Disease

Table 11. Medicines for Ischemic heart Disease

Medicine Name	Primary ATC Code
Acebutolol	C07AB04
Acenocoumarol	B01AA07
Acetylsalicylic acid	B01AC06
Alteplase	B01AD02
Amiodarone	C01BD01
Amlodipine	C08CA01
Atenolol	C07AB03
Atorvastatin	C10AA05
Benazepril	C09AA07
Bendrofluazide (Bendroflumethiazide)	C03AA01
Betaxolol	C07AB05
Bevantolol	C07AB06
Bisoprolol	C07AB07
Bumetanide	C03CA02
Candesartan	C09CA06
Captopril	C09AA01
Carvedilol	C07AG02
Celiprolol	C07AB08
Chlorothiazide	C03AA04
Chlortalidone (Chlorthalidone)	C03BA04
Cilazapril	C09AA08
Cilnidipine	C08CA14
Clopidogrel	B01AC04
Cyclopenthiazide	C03AA07
Dalteparin	B01AB04
Delapril	C09AA12
Digoxin	C01AA05
Dopamine	C01CA04
Drotrecogin alfa	B01AD10
Enalapril	C09AA02
Enoxaparin	B01AB05
Epanolol	C07AB10
Epinephrine (Adrenaline)	C01CA24
Eplerenone	C03DA04
Eprosartan	C09CA02
Esmolol	C07AB09

Ethyl biscoumacetate	B01AA08
Felodipine	C08CA02
Fibrinolysin	B01AD05
Fluindione	B01AA12
Fluvastatin	C10AA04
Fosinopril	C09AA09
Furosemide	C03CA01
Heparin	B01AB01
Hydrochlorothiazide	C03AA03
Hydromorphone	N02AA03
Imidapril	C09AA16
Indapamide	C03BA11
Irbesartan	C09CA04
Isosorbide	C01DA
Isosorbide dinitrate	C01DA08
Isosorbide mononitrate	C01DA14
Isradipine	C08CA03
Lacidipine	C08CA09
Landiolol	C07AB14
Lercanidipine	C08CA13
Lidocaine (Lignocaine, Xylocaine)	C05AD01
Lisinopril	C09AA03
Losartan	C09CA01
Lovastatin	C10AA02
Manidipine	C08CA11
Methylchlorothiazide	C03AA
Metoprolol	C07AB02
Moexipril	C09AA13
Morphine	N02AA01
Nadroparin	B01AB06
Nebivolol	C07AB12
Nicardipine	C08CA04
Nifedipine	C08CA05
Nilvadipine	C08CA10
Nimodipine	C08CA06
Nisoldipine	C08CA07
Nitrendipine	C08CA08
Nitroglycerin (Glyceryl trinitrate)	C01DA02
Nitroprusside	C02DD01
Olmesartan	C09CA
Oxygen	V03AN01
Pentaerythritol tetranitrate	C01DA05
Perindopril	C09AA04

Phenprocoumon	B01AA04
Plasminogen activator	B01AD
Polythiazide	C03AA05
Practolol	C07AB01
Pravastatin	C10AA03
Prourokinase	B01AD
Quinapril	C09AA06
Ramipril	C09AA05
Reteplase	B01AD07
Rosuvastatin	C10AA07
Simvastatin	C10AA01
Spirapril	C09AA11
Spironolactone	C03DA01
Streptokinase	B01AD01
Talinolol	C07AB13
Telmisartan	C09CA07
Tenecteplase	B01AD11
Torsemide	C03CA04
Trandolapril	C09AA10
Urokinase	B01AD04
Valsartan	C09CA03
Verapamil	C08DA01
Warfarin	B01AA03
Zofenopril	C09AA15

Table 12. Medicines for Cerebrovascular Disease

Medicine Name	Primary ATC Code
Acebutolol	C07AB04
Acenocoumarol	B01AA07
Acetylsalicylic acid	B01AC06
Alteplase	B01AD02
Amiodarone	C01BD01
Amlodipine	C08CA01
Apixaban	B01AF02
Atenolol	C07AB03
Atorvastatin	C10AA05
Benazepril	C09AA07
Bendrofluazide (Bendroflumethiazide)	C03AA01
Betaxolol	C07AB05
Bevantolol	C07AB06
Bisoprolol	C07AB07
Bumetanide	C03CA02
Candesartan	C09CA06
Captopril	C09AA01
Carvedilol	C07AG02
Celiprolol	C07AB08
Chlorothiazide	C03AA04
Chlortalidone (Chlorthalidone)	C03BA04
Cilazapril	C09AA08
Cilnidipine	C08CA14
Clopidogrel	B01AC04
Cyclopenthiazide	C03AA07
Dabigatran	B01AE07
Dalteparin	B01AB04
Delapril	C09AA12
Digoxin	C01AA05
Dipyridamole	B01AC07
Drotrecogin alfa	B01AD10
Enalapril	C09AA02
Enoxaparin	B01AB05
Epanolol	C07AB10
Eplerenone	C03DA04
Eprosartan	C09CA02
Esmolol	C07AB09
Ethyl biscoumacetate	B01AA08

Felodipine	C08CA02
Fibrinolysin	B01AD05
Fluindione	B01AA12
Fluvastatin	C10AA04
Fosinopril	C09AA09
Furosemide	C03CA01
Heparin	B01AB01
Hydrochlorothiazide	C03AA03
Imidapril	C09AA16
Indapamide	C03BA11
Irbesartan	C09CA04
Isradipine	C08CA03
Lacidipine	C08CA09
Landiolol	C07AB14
Lercanidipine	C08CA13
Lisinopril	C09AA03
Losartan	C09CA01
Lovastatin	C10AA02
Manidipine	C08CA11
Methylchlorothiazide	C03AA
Metoprolol	C07AB02
Moexipril	C09AA13
Nadroparin	B01AB06
Nebivolol	C07AB12
Nicardipine	C08CA04
Nifedipine	C08CA05
Nilvadipine	C08CA10
Nimodipine	C08CA06
Nisoldipine	C08CA07
Nitrendipine	C08CA08
Nitroprusside	C02DD01
Olmesartan	C09CA
Perindopril	C09AA04
Phenprocoumon	B01AA04
Plasminogen activator	B01AD
Polythiazide	C03AA05
Practolol	C07AB01
Pravastatin	C10AA03
Prourokinase	B01AD
Quinapril	C09AA06
Ramipril	C09AA05
Reteplase	B01AD07
Rivaroxaban	B01AF01

Rosuvastatin	C10AA07
Simvastatin	C10AA01
Spirapril	C09AA11
Spironolactone	C03DA01
Streptokinase	B01AD01
Talinolol	C07AB13
Telmisartan	C09CA07
Tenecteplase	B01AD11
Torsemide	C03CA04
Trandolapril	C09AA10
Urokinase	B01AD04
Valsartan	C09CA03
Verapamil	C08DA01
Warfarin	B01AA03
Zofenopril	C09AA15

Table 13. Medicines for Hypertensive Heart Disease

Medicine Name	Primary ATC Code
Acebutolol	C07AB04
Amlodipine	C08CA01
Atenolol	C07AB03
Atorvastatin	C10AA05
Benazepril	C09AA07
Bendrofluazide (Bendroflumethiazide)	C03AA01
Betaxolol	C07AB05
Bevantolol	C07AB06
Bisoprolol	C07AB07
Bumetanide	C03CA02
Candesartan	C09CA06
Captopril	C09AA01
Carvedilol	C07AG02
Celiprolol	C07AB08
Chlorothiazide	C03AA04
Chlortalidone (Chlorthalidone)	C03BA04
Cilazapril	C09AA08
Cilnidipine	C08CA14
Cyclopenthiazide	C03AA07
Delapril	C09AA12
Digoxin	C01AA05
Dopamine	C01CA04
Enalapril	C09AA02
Epanolol	C07AB10
Eplerenone	C03DA04
Eprosartan	C09CA02
Esmolol	C07AB09
Felodipine	C08CA02
Fluvastatin	C10AA04
Fosinopril	C09AA09
Furosemide	C03CA01
Hydralazine	C02DB02
Hydrochlorothiazide	C03AA03
Imidapril	C09AA16
Indapamide	C03BA11
Irbesartan	C09CA04
Isradipine	C08CA03
Lacidipine	C08CA09
Landiolol	C07AB14
Lercanidipine	C08CA13

Lisinopril	C09AA03
Losartan	C09CA01
Lovastatin	C10AA02
Manidipine	C08CA11
Methylchlorothiazide	C03AA
Methyldopa	C02AB
Metoprolol	C07AB02
Moexipril	C09AA13
Nebivolol	C07AB12
Nicardipine	C08CA04
Nifedipine	C08CA05
Nilvadipine	C08CA10
Nimodipine	C08CA06
Nisoldipine	C08CA07
Nitrendipine	C08CA08
Nitroprusside	C02DD01
Olmesartan	C09CA
Perindopril	C09AA04
Polythiazide	C03AA05
Practolol	C07AB01
Pravastatin	C10AA03
Quinapril	C09AA06
Ramipril	C09AA05
Rosuvastatin	C10AA07
Simvastatin	C10AA01
Spirapril	C09AA11
Spironolactone	C03DA01
Talinolol	C07AB13
Telmisartan	C09CA07
Torsemide	C03CA04
Trandolapril	C09AA10
Valsartan	C09CA03
Zofenopril	C09AA15