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Societal Economic burden of hypertension at Selected Hospitals in Southern Ethiopia; a patient-level analysis

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I. Abstract

Objectives: There is inadequate information on the economic burden of hypertension treatment in Ethiopia. Therefore, this study was conducted to determine the economic burden of hypertension at Selected Hospitals in Southern Ethiopia.

Methods: Prevalence-based cost of illness (COI) study from a societal perspective was conducted. Disability-adjusted life years (DALYs) were determined by the current world health organization's recommended DALY valuation method. Adjustment for comorbidity and a 3% discount was done for DALYs. The data entry, processing, and analysis were done by using SPSS version 21.0 and Microsoft Excel 2013.

Results: We followed a cohort of 406 adult hypertensive patients retrospectively for 10 years from September 2010 to 2020. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years ranging from 33 to 83 years. Less than 1 in five 71 (18.5%) of patients achieved their blood pressure control target. A total of 13,452,893.15 ETB ($309,261.91) direct cost was incurred due to hypertension. A total of 11,606 years and 579.57 years were lost due to hypertension-related premature mortality and morbidity respectively. Treated and uncontrolled hypertension 44.6% (7826) total years lost due to premature mortality. This equates 845,490.39 ETB ($19,436.56). Treated and uncontrolled hypertension accounted for one-half 2,937.72 (50.84%) of productive life years lost. Total productivity loss due to premature mortality and morbidity was 680,734,561.97 ETB ($15,649,070.39).

Conclusion: Societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Therefore, designing and implanting strategies for the prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels is critical to saving scarce health resources.

Strengths and limitations of this study

- Using the cardiovascular disease policy model adapted to Sub-Saharan African perspective by our research;
- Productivity loss costs associated with hypertension (premature mortality and morbidity) were included,
- All simulation variables and transition probability data obtained were obtained from valid sources (systematic reviews, randomized controlled trials, and prospective cohort studies). However,
- Our study might underestimate the national economic burden of hypertension because of uncertainty in age and sex-specific prevalence of undiagnosed hypertension and retrospective nature of direct cost data and probability of unrecorded procedures and tests.

1. Introduction

Hypertension doubles the risk of death from stroke, heart disease, vascular diseases, diabetes, atherosclerosis, and kidney disease for every increase of 20mmHg in systolic blood pressure (SBP) and/or increase of 10 mmHg in diastolic blood pressure (DBP) (1). According to the national STEPS survey the prevalence of hypertension among adults 15 years and above was 16% in Ethiopia. Only 28.4% of patients were taking antihypertensive medication prescribed by professionals. About 15.6% of individuals with high BP (SBP ≥ 140/90 mmHg) were not currently not on antihypertensive medication (2). According to the International Society of hypertension global hypertension practice guideline 2020, hypertension remains the leading cause of death globally, accounting for 10.4 million deaths per year (3). Similarly, according to a global health estimate in 2016, life years lost directly or indirectly due to hypertension was 42,781,885 in the African region. Regional productive healthy life year lost due to hypertension was estimated to be 19,395,946 (4, 5).

Hypertension is associated with societal and economic consequences particularly in Low and middle-income countries (LMICs). In addition to the direct costs associated with health care utilization for the management of complications, hypertension causes significant productivity loss from disability and premature death (6, 7). WHO report from South East Asian region also indicated huge impact of hypertension in national finances due to premature death, disability, personal and family disruption, loss of income, and healthcare expenditure (8). According to a WHO report in 2017, stroke caused 39,571 deaths or 6.23% of total deaths, coronary heart disease caused 46,943 deaths and hypertension caused 11,050 deaths (i.e. 30 patients per day) in Ethiopia (9).

Cost of illness (COI) study is used to measure the economic burden of disease to individuals, communities, and society as a whole. It can provide information to support the political process and healthcare decision-making if it is conducted from a societal perspective by using an appropriate approach and bottom-up costing strategy (10, 11). There is a consensus agreement for conducting any economic evaluation from a societal perspective. It is critical to include productivity costs into account to present results from this perspective (12). Cost of illness studies follow two different epidemiological approaches, prevalence or incidence approach, and we based prevalence based retrospective bottom-up costing approach in this study (13, 14). The human capital approach for the valuation of costs was used in this study (13, 15-18). In the human capital approach, the productivity losses associated with morbidity and mortality are the 'market value of that individual's future contribution to production in society if s/he had continued to work in full health (15). Despite this huge impact on national economies, the burden of hypertension is not studied in Ethiopia particularly Southern Ethiopia. To fill this evidence gap, this study was conducted to determine the economic burden of hypertension at selected public hospitals in Southern Ethiopia by using the prevalence-based cost-of-illness method from a societal perspective to estimate the direct and indirect costs of hypertension in a given year (2021) in Southern Ethiopia. This study will serve as a baseline study for the country to evaluate the economic burden of hypertension in Ethiopia.

2. Methods and Materials

2.1. Study design, Area and Period

A retrospective cohort study was conducted from September 2010- September 2020 in Southern Ethiopia to evaluate the economic burden of hypertension at selected three selected public hospitals. Prevalence-based retrospective cost of illness study from societal perspective focusing on quantifying direct and indirect costs. The bottom-up approach was used to estimate the economic burden of hypertension in Southern Ethiopia figure 1). The human capital approach was used to calculate indirect costs separately in males and females and also among different age groups. A Prevalence-based COI model was constructed in which hypertensive patients will be simulated from diagnosis through active treatment, palliative care, and death over 15-64 years (i.e. productive age group of Ethiopian population).

Age and sex (in 5-year age groups) cohorts of the Ethiopian population aged 15-64 years were constructed, based on the 2020 Ethiopian population data. Age and sex-specific mortality rates, measures of productivity, and workforce statistics were used to simulate the progression of these cohorts until death or age 64 years. First, the model estimate cumulative years of life and DALYs lived for the working-age population who had hypertension. Then the model re-simulates with the hypothetical assumption that they did not have hypertension, with relevant changes to mortality rates and productivity. Key model parameters include the prevalence of hypertension, mortality rates, and utilization of antihypertensive therapies and other medical care resources, unit costs, workdays missed by patient and caregiver, and wage rates, workforce statistics, and measures of productivity. The differences in total years of life lived, and DALYs between the 2 cohorts reflect the impact of hypertension.

2.2. Study populations

The study populations were selected adult hypertensive patients at three selected public hospitals. According to the world population prospect 2020 estimate, the total population is 114,963, 583. About 43.21% (49,675,764) of the population belongs to age category 0-14 years. While, only 2.97% (3,414,418) were ≥ 65 years (19). In the same year, the Population of the Gamo zone accounted for 1.5% of the total population, Gofa, and South Omo Zone 1.5% of the Total Population. The target population is 3.0% total population of Ethiopia or 20% of the southern Ethiopian population (6,208,034). Based on age distribution: 0-14 years are children, 15-24 years are early working age, 25-54 years are prime working age, 55-64 years are mature working age and ≥ 65 years are elderly (20).

2.3. Inclusion and exclusion criteria

We included all adult hypertensive patients having at least five years of follow-up visits before data collection and receiving care during the study period from selected facilities. However, Patients who are unwilling to participate in this study, patients who have less than five years of follow-up, and incomplete patient records (don't contain follow-up BP records and refill medications, laboratory requests, and results) and illegible were excluded.

2.4. Study Variables

Dependent Variables

- Economic burden of hypertension

Independent variables

- Patient-related (socio-demographic characteristics, heart disease knowledge, healthy lifestyle and heart disease risk perception, presence of comorbidity, type of medications, treatment adherence, shared decision making, health-related quality Life)

Cost related variables

- **Medical costs** (inpatient hospital stay/hospitalization cost, outpatient clinic visit, drug acquisition costs, drug administration cost, laboratory test, and imaging study costs)
- **Non-medical costs** (transportation, meal, patient time cost due to treatment, cost due informal care by family or friends)
- **Indirect costs** (absenteeism, presenteeism, unemployment, early retirement, disability, premature death)

2.5. Sample Size and Sampling Technique

2.5.1. Sample size determination

The sample size was determined by using the single population proportion formula by taking prevalence of patients controlled their BP as 14% from WHO 2016 BP control rate report (21-23) and Z value of 1.96 at 95% confidence interval. We added 10% for non-response rate and two for design effect due to multi-stage sampling technique involvement. Finally, a formula giving a larger sample size was used. Total 407 hypertensive adult patients who are on follow-up care will be included.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2} = 185$$

= 185 + (185 * 10%) = 203.5

= 203.5 *2 = 407

Where: **n** = is the sample size

- **Z^2**= standard normal deviation, set at 1.96, correspond to the 95% confidence interval
- **d** = is the desired level of precision/margin of error (0.05)
- **p**= prevalence of patients taking anti-hypertensive (p=28.4%), and q is 1-p.

2.5.2. Sampling Techniques

A multi-stage simple random sampling technique was used. We randomly selected four zones from a total of 12 zones found in the Southern region. Four general hospitals with experience of providing CVD care for at least five years from selected four zones were included in this study. The total sample size was allocated to these hospitals based on an estimated number of adult hypertensive patients attending respective hospitals (i.e., we included 212 patients from Arba Minch General hospital, 107 patients from Jinka general hospital, and 88 patients from Sawula general hospital). Finally, a consecutive sampling technique was applied in each facility until the desired sample size was achieved.

2.6. Data collection tools and Procedures

Key model inputs variables include; 2020 population of selected Zones, hypertension prevalence by treatment and control status, Transition probabilities to death and healthy state, cost of diagnosis, and management. The data was collected from the National STEPS survey (2), systematic reviews (24-27), and our cohort study. Among those with treated hypertension, treated and controlled hypertension was defined based on BP control target of ISH 2020 guideline (i.e., controlled, if BP < 130/80 mmHg for < 65 years and < 140/90 mmHg for ≥ 65 years and uncontrolled, if BP ≥ 130/80 mmHg for < 65 years and ≥ 140/90 mmHg for ≥ 65 years). Morality rate in 2019 stratified by sex and 5-year age groups in selected zones was used. The demographic profile of the cohort was derived from the estimated resident population of Ethiopia in 2020. The rate of blood pressure control was drawn from the National STEPs 2015 survey (2) and our effectiveness study. Identified rates were applied to projections from 2019 United Nations World Population Prospects (28). Transition probabilities (TP) and relative risk of mortality were taken from the natural history of hypertension studies with good quality (20, 29-33).

We used national STPES risk factor survey data to estimate the prevalence of cardiovascular risk factors (MI, angina, heart failure, stroke, TIA). Incorporating the risk factor prevalence data in the relevant Framingham risk equation, the age and sex-specific probability of CHD and cerebrovascular disease (i.e., stroke and transient ischemic attack) events were estimated. Framingham risk equation was applied only for patients aged 30-79 years with no prior history of coronary heart disease (i.e. will not be used in patients with intermittent claudication or diabetes). The probability of each health state was calculated using the age- and sex-specific CHD and cerebrovascular disease event distributions (2, 34).

To estimate the corresponding probabilities, separate relative risk estimates were used for CHD events (Stable Angina, Unstable Angina, and MI) and cerebrovascular diseases (Stroke and Transient Ischemic Attack), assuming that antihypertensive treatment affects the probability of every disease state similarly across all age and sex groups. Relative risk reductions attributable to antihypertensive treatment were extracted from the peer-reviewed literature (33, 35, 36).

We estimated the probability of death separately for (1) all-cause mortality in absence of hypertension and related complications (general productive age population) and (2) mortality attributable to the included disease states. The first component was estimated using WHO Life Tables, and the second component was calculated based on standardized mortality ratios extracted from the literature. The natural history study conducted in 1974 showed that the mortality rate was 1.85 (3.01 in males and 1.62 in females). The initial height of the diastolic blood pressure was a prognostic factor in the under-sixties. However, there were no increasing mortality rates with rising pressure in the over-sixties (20). Interventional trials suggested that it could be possible to achieve effective BP targets in about 70% of patients by improving adherence and/or intensifying therapy (29).

The 2020 world population prospect estimate was used for the baseline population and number of 33-year-olds projected to enter the model population from 2020-2070 (19). Coronary heart disease and stroke deaths in 2020 were extracted from the national STEPS and WHO STEPS survey, and systematic reviews. Coronary heart disease deaths, stroke deaths, and all other deaths were considered non-CVD deaths. The annual probability of coronary heart disease and stroke was based on national STEPS survey data (2). If country-specific data are not available can be taken from well-accepted international studies like Framingham Heart Study (37) and the Framingham Offspring Study(38), by contextualizing to Ethiopian scenario (Supplementary Table 1).

Incident coronary heart disease events were allocated to angina pectoris, hospitalized myocardial infarction, or cardiac arrest. Prevalence, joint distributions, and means of Ethiopia risk factor values were estimated from the national STEPS survey (2). Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Betas for risk function for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort (38).

Risk factors are assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers are assumed to have a higher relative risk for infarction and arrest (39); and a proportionately lower coefficient for angina. Environmental tobacco exposure is assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with non-exposed non-smokers (40) but not to influence angina. The number of hospitalized MI were obtained from the national STEPS survey (2), and our effectiveness study. Case-fatality rates and rates of MI in subgroups were estimated from national data and other complementary sources. Prehospital arrest deaths and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from our effectiveness study.

Survival after a coronary heart disease event was estimated from national or international data sources (California data on the ratio of in-hospital survival to 30-day survival) (41) and calibrated based on findings of Huffman et al. 2018 (42). Rates of coronary revascularizations was estimated from the National Hospital Discharge Survey, with mortalities estimated from aggregated historical data. Stroke incidence was assumed to be independent of the risk of new-onset coronary heart disease in the same year. The number of hospitalized strokes cases was obtained from national and regional studies. The annual probabilities of stroke after MI (43, 44) and the probability of coronary heart disease in stroke patients were based on natural history studies and systematic reviews of blood pressure control trials (45-50). 30-day heart failure mortality and re-hospitalization data were from the THESEUS-HF registry (51) and Korean Acute Heart Failure Registry (KorAHF)(52, 53) (Supplementary Table 2 and 3).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2020 was estimated from the National Health Survey data (2) and GBD 2017 (54). The background prevalence of prior coronary revascularization was estimated from revascularizations before 2019 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state.

Age and sex-specific health care costs were estimated using national data, and our effectiveness data. Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using WHO Choice (55) inflated to 2021. In addition to this, Outpatient consultations (per visit), and inpatient stay and bed days were also estimated from WHO Choice (55) inflated to 2021. Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis was pooled from the 2015 national STEPS survey. Average annual non-cardiovascular (background) costs were estimated from the national STEPS survey (2), and EDHS 2016 survey (20).

Patient and public involvement

There was no identifiable patient involvement in this research. Patients' demographic characteristics and disease related variables were obtained by using questionnaire based interview after obtaining verbal consent from the patient. No patient identifier information was collected. Finally, most of variables were taken from published national and international literatures, and all relevant sources were acknowledged through citation.

Cost estimation

The overall burden of hypertension was the total of all direct and indirect costs. The outcomes measures are total discounted societal costs, cost/year, and cost/patient-year. This is the amount of health budget that could be saved by effective prevention and control of hypertension. The direct costs were divided into two subcategories: direct medical costs and direct non-medical costs. Direct Medical costs include; inpatient stays, outpatient clinic visits, medical services, drug acquisition, dispensing, administration, monitoring, laboratory test, and imaging study costs. The costs associated with outpatient/inpatient visits were estimated by multiplying the numbers of outpatient visits related to hypertension by the outpatient costs per year (i.e., twelve times WHO cost per outpatient visit for secondary hospitals inflated to 2021) (55).

Data concerning medications prescribed for the management of hypertension, and associated comorbidities, and laboratory tests and imaging studies were done were collected by patient chart abstraction in index year (2020). The cost of medications used for management of hypertension and associated comorbidities was taken from Ethiopian Pharmaceutical supply agency Arba Minch regional hub selling price and retail price of Arba Minch General Hospital in 2020. The retail price of Arba Minch General Hospital was used because of the minimum distance from the Pharmaceutical supply agency hub, which could minimize markup added on retail price due to transportation cost. Costs of laboratory procedures were also taken from Arba Minch Hospital Laboratory's service price list. The prices of relevant laboratory tests and imaging studies were based on the average price of included Hospitals. The salary scale of the health workforce was based on the FMOH of Ethiopia (Supplementary Table 4).

Ongoing program costs for hypertension care (Health Promotion for CVD and diabetes, National Systems Response, and Monitoring and evaluation for CVD and diabetes care) was estimated from WHO tool outputs for CVD and diabetes care and National strategic action plan (NSAP) for prevention & control of non-communicable diseases in Ethiopia 2014-2016 and adjusted for 2021 inflation target population (56). Adjustment for the study population was done by multiplying the national cost by the proportion of the study population (i.e., 3%). National and regional cost estimates were based on the proportion of patients studied (i.e. 3% and 20%). We considered this strategy since the age and sex distribution of hypertension among different regions in the country is did not vary significantly. The collected cost data added up and averaged by using a bottom-up approach. Facility-based or reference costs were used during computing costs. The total medical cost of hypertension treatment was calculated as the sum of the product of medical costs with their respective unit prices. Costs were discounted at an annual rate of 3% and reported in 2021 USD (57, 58).

Direct non-medical costs include transportation costs and patient time costs due to care. The cost of patient time due to care was estimated by using the average daily wage of patients which was calculated from average monthly income (97.00 ETB) 34,931.00 annual income from our treatment effectiveness survey. Transportation cost was determined by using the cost of average traveling distance and local transportation tariff (42.00 ETB) in January

2021. According to EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (20). This proportion was used to determine the patient time cost due to care for employed groups. For the unemployed proportion, the average daily wage of daily laborers workers working 8 hours per day for 6 days per week was used (26.53 ETB) from the monthly wage of 796.00 ETB (420-1172 ETB) (59).

Indirect costs include cost hospitalization, productivity loss due to illness, and cost of death. Cost-of hypertension-related hospitalization was taken from WHO Choice (55), costs per inpatient stay and cost per inpatient bed day times duration of hospitalization inflated for 2021, and professional time (physician, nurse laboratory professional, and pharmacist time). If a patient had multiple admissions during the year, the costs for each admission were aggregated as the total costs (60).

Age and sex-specific mortality rates among the adult general population in Ethiopia were taken from EDHS 2016 survey and extrapolated to selected populations (20). According to EDHS 2016, the probability of dying before age 50 years among adults ≥ 15 years were 10% and 12%, in Women and men respectively (20). Due to the absence of mortality data specific to hypertension treatment and control status in Ethiopia, mortality risk in the general population was attributed to those with and without hypertension using sex-specific estimates of the relative risk (RR) of all-cause mortality associated with hypertension by treatment and control status was derived from a study conducted in India was used (61). A cohort study conducted in India among adults 20 years and above to determine the Rate and Risk of all-cause mortality among people with HTN showed that the incidence of deaths in the study was 4.28% during the follow-up period of 6 years. The relative risk of mortality was 3.13 (CI: 2.91-3.37) and 1.2 in the high BP group and at age of 60 years. The age-adjusted hazard ratio of all-cause mortality for the high BP group was 2.96 (2.56-3.42) (61) (Supplementary Tables 5 and 6).

In 2020 crude death rate of the Ethiopian population-based on global estimates was 6.29 deaths per 1000 population (i.e. 680,032 deaths per 108,113,150) (62). The estimated prevalence of hypertension among adults was calculated from National STEPS Survey 2016, systematic review and meta-analysis, and World health organization report and local studies (19.6%, for 15-30 years, 23% for 30-40 years, 25.9% for 40-49 years and 41.9% for 50 years and above (2, 20, 61, 63-66). Supplementary Table 3). Only 28.4% of patients with the diagnosis are taking antihypertensive medication (2). The mean estimated prevalence of hypertension is 21.39%. The mean relative risk (hazard ratio) of all-cause mortality among the hypertensive population when compared to those without hypertension was 1.39 (0.95 to 1.95) (67).

Years of life lost due to hypertension morbidity was determined by first calculating disability weights for specific ages based on blood pressure control status (X). Then subtract this value (X) from the life expectancy of the Ethiopian population (i.e., 66.7 years for men, and 70.4 years for women) (Y). The productivity loss cost due to hypertension morbidity was calculated by multiplying Y with sex-specific employment rate based on a monthly average income of 2059.078 ETB from the National STEPS survey 2015 adjusted for 2021 inflation

(13,13/9.57=1.372) STEPS Survey, 2015 (2) and EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (20) and for unemployed, 2019 minimum average monthly earnings (ETB) of daily laborers reported by the Ethiopian Ministry of Labor and Social Affairs (MOLSA) 796 ETB (420-1172 ETB) (59). Concerning, cost of productivity lost due to premature mortality: first we calculated potential years of life lost (YLL) by subtracting life expectancy from sex-specific age of death at which the death is recorded (Z). Then Z is multiplied by the number of deaths in each age group (Xi). Finally, we multiplied Xi with sex-specific employment rates like productivity loss due to hypertension-related morbidity above (68). Excess mortality and morbidity due to hypertension to hypertension were determined by subtracting age and sex-specific morbidity and mortality among the general population from the hypertensive cohort. Both were determined by using age, sex, and blood pressure treatment status mortality rate per 1000 person-years (Supplementary Table 6).

2.7. Morbidity adjustment

Patients with hypertension may have more than one disease, the addition of YLDs across causes may result in overestimation of the total loss of health (69). Therefore, it is recommended to estimate comorbidities using the assumption of independence within age-sex groups (4):

$$\mathbf{P_{1+2} = P_1 + P_2 - (P_1 \times P_2) = 1 - (1 - P_1) \times (1 - P_2)}$$

- **Where** P_{1+2} is the prevalence of the two comorbid diseases 1 and 2,
- P_1 is the prevalence of disease 1 and $\mathbf{P_2}$ is the prevalence of disease 2.

The combined disability weight for individuals with multiple conditions is estimated assuming a multiplicative model as follows:

$$\mathbf{DW_{1+2} = 1 - (1 - DW_1) \times (1 - DW_2)}$$

Since prevalence YLDs are calculated for each cause as:

$$\mathbf{YLD_i = DW_i \times P_i}$$

- two preceding equations can be combined into a single calculation resulting in:

$$\mathbf{YLD_{1+2} = 1 - (1\text{-}YLD_1) \times (1 - YLD_2)}$$

2.8. Assumptions and Transition probabilities

The counterfactual comparator (hypothetical cohort of normotensive individuals) with a probability of developing CVD events among the general population. Both in case and comparator cohorts, the probability of non-CV death does not depend on the health state and is similar for both hypertensive and normotensive populations (70) and we chose not to model differential use of antihypertensive medication classes in order not

to bias cost-of-treatment inputs. Antihypertensive dose intensification and frequency of BP monitoring were based on ISH 2020 guidelines for blood pressure control. We did not simulate the effects of any particular medication; instead, we simulated "standard dose" effects and assumed average drug prices across classes (71). The amount of blood pressure change was assumed to be a function of the baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (72). Patients with very high BP (mean SBP of ≥185 mmHg) do not achieve the target of <140 mmHg even with taking four standard dose medications, these patients would on average achieve a BP of about 143 mmHg**.** We also assumed the medication adherence rate as 75% based on clinical trials (72)**.**

Other important assumptions include deaths reported or recorded on hospital registries were considered as hypertension-related unless specified as due to other cases; all disabilities in hypertensive patients were considered as disability due to hypertension except for comorbidities and accidents; cost of illness due to hypertension or associated morbidities were calculated based on the monthly earnings during data collection; all costs incurred before one year were adjusted/accounted to today's value (2021 USD equivalent) and discounted at 3%; years of life lost and years of life lived with disability (YLDs) were not discounted as per the recent WHO recommendations.

2.9. Data Quality control, Processing, and Analysis

Questionnaires are prepared in English and the patient interview part of the questionnaire was translated into Amharic and translated back into English to check its consistency. The Amharic version of the patient interview questionnaire and English version of the health professional interview, data abstraction form, and health system interview questionnaires was used for data collection. The questionnaire was pretested on 30 adult hypertensive patients in Arba Minch General Hospital to ensure that the respondents could understand the questions and to check for consistency and possible amendments were made based on findings. Six professional nurses (BSc.) for data collection and one senior professional working in the respective health facilities for supervision were oriented before data collection about data collection approaches and contents of data collection format for one day by the principal investigator. Continuous follow-up and supervision were made by the principal investigator throughout the data collection period.

The collected data were checked for completeness and consistency by the principal investigator on daily basis at the spot during the data collection time. Then data were transcribed back to English for the patient interview part and entry was made using Epi-data 3.1 software. After data processing, analysis was done by using SPSS version 21.0 and Microsoft excel 2010. A summary of descriptive statistics was computed for most variables such as socio-demographic factors; professional factors structural factors, and health system factors; a bivariate analysis was done to determine the presence of an association between independent variables and hypertension treatment effectiveness.

3. Results

3.1. Description of study participants

In this study, we estimated the regional and national economic burden of hypertension (direct and indirect costs) by using the cardiovascular disease policy model adapted to the Sub-Saharan Africa perspective (73) (Supplementary Figure 1). Total costs of treated hypertension and hypertension-related excess mortality and years of life lost due to hypertension were determined. We followed a cohort of 406 hypertensive patients retrospectively for 10 years from September 2003 to 2013 Ethiopian calendar (September 2010-2020) for baseline assessment and simulated the cost of hypertension for lifelong from a societal perspective. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years ranging from 33 to 83 years. Less than 1 in five 71 (18.5%) of patients achieved their BP control target based on international society of hypertension 2020 guidelines (Table 1).

Table 1: Patient characteristics and Disease related factors among adult hypertensive patients on regular follow-up at selected public hospitals in Southern Ethiopia (n=406)

Sociodemographic factors		Frequency
Sex	Male	156 (38.4%)
	Female	250 (61.6%)
Age in in years	Below 40 years	15 (3.7%)
	40- 65 years	286 (70.4%)
	65 years and above	105 (25.9%)
Religion	Orthodox	215 (53.0%)
	Muslim	37 (9.1%)
	Protestant	144 (35.5%)
	Catholic	10 (2.5%)
Annual gross income before tax (n=406)	Less than 12,000	117 (28.8%)
	12,000- 18,000	89 (21.9%)
	18,000- 23,000	200 (49.2%)
Level of Education	Illiterate	259 (63.8%)
	Grades 1-8	46 (11.3%)
	Grades 9-12	22 (5.4%)
	College and above	73 (18.0%)
	Post-graduate degree	6 (1.5%)
Occupation	Employed	65 (16.0%)
	Merchant	63 (15.5%)
	Farmer	79 (19.5%)
	House wife	149 (36.7%)
Disease related factors		
Duration of hypertension since diagnosis	5 - 9 years	262 (64.5%)
	10 - 14 years	131(32.3%)
	15 and above years	13 (3.2%)
Family history of CVDs	1st degree relative	133 (32.8%)
	Second degree relative	16 (3.9%)
	None	257 (63.3%)
Presence of comorbidities	Yes	310 (76.4%)

(n=406)	No	96 (23.6%)
History of hospitalization	Yes	250 (61.6%)
	No	156 (38.4%)
Duration of hospitalization	Below 5 days	56 (22.4%)
(n=250)	5 to 10 days	112 (44.8%)
	More than 10 days	82 (32.8%)
Target BP achieved based on	Yes	75 (18.5%)
ISH 2020 guideline	No	331 (81.5%)
Antihypertensive regimen	Monotherapy	136 (33.5%)
	Two drug combination	234 (57.6%)
	Three and more drug combination	36 (8.8%)

3.2. Cost of hypertension

3.2.1 Direct (medical and non-medical) costs

Direct medical costs include program costs, cost of drugs for hypertension and comorbidities, laboratory costs, hospitalization costs, annual outpatient visit costs, and costs of medical supplies. A total of 2,820,430.57 ETB ($ 64,837.48 USD) was incurred due to hypertension. Out of this, 80.0% ($51,915.40 USD) was direct medical cost. From direct medical costs, annual outpatient visit cost 33.55% ($17,419.73 USD), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($4,263.29 USD) took the largest share. The regional and national annual estimated direct cost of hypertension were 14,102,151.90 ETB ($324,187.40 USD) and 94,014,346.00 ETB (2,161,249.33 USD) respectively (Table 2). Details of cost estimations and costs were available on online-only supplementary file (Supplementary Table 2 and 3).

Table 2: Direct annual costs of treating hypertension among adults in Southern Ethiopia, January 2021 (n=406)

Cost category	Annual total in ETB Total (mean ± Standard deviation)	Annual cost in July 2021 USD	Estimated national cost USD 2021	Percentage from total direct cost
Direct medical total	**2,258,319.97**	51,915.40	1,730,513.39	80.0%
Program costs	403,275.70 (993.0 ± 0.00)	9,173.40	305,780.00	
Cost of antihypertensives	119,847.64 (295.19 ± 107.78)	2,726.20	90,873.33	
Cost of drugs for comorbidity	598,409.00 (2266.7 ± 1114.52)	13,612.15	453,738.33	
Cost for hospitalization	179,377.03 (3360.76 ± 1594.69)	4,080.33	136,011.00	
Laboratory tests	187,420.00 (461.63 ± 226.98)	4,263.29	142,109.67	
Annual outpatient visit costs	765,795.60 (1886.20 ± 0.00)	17,419.73	580,657.67	
Cost of medical supplies	4,195.00 (85.60 ± 0.00)	95.42	3,180.67	
Professional time total	**128,362.01**	2,950.85	98,361.69	4.6%
Physician time	92,032.08 (226.68 ±0.00)	2,093.47	69,782.33	
Nurse time	2,060.28 (43.84 ± 17.81)	46.87	1,562.33	
Pharmacy time	4,453.01 (10.97 + 0.00)	101.29	3,376.33	
Laboratory time	29,816.64 (73.44 ± 0.00)	678.25	22,608.33	

Direct non-medical costs	**433,748.59** (1068.84 ± 384.78)	9,866.58	328,886.00	**15.37%**
Total direct cost of treated hypertension	2,820,430.57	64,837.48	2,161,249.33	100.00%
1USD= 43.9614 ETB on July 13, 2021				
ETB: Ethiopian Birr; USD: United States Dollar				

3.2.2. Life years lost due to premature mortality and morbidity

We determined the years of life lost due to premature mortality (excess mortality) and years of life lost due to hypertension morbidity for the productive age population (30-64 years) among a cohort of simulated adult hypertensive patients. The excess mortality and years of life lost were different among the hypertensive cohort and simulated population with no hypertension. A total of 11,858 (6,159, men; 5,699 women) years were lost due to hypertension-related premature mortality among 30-64 years old adults with hypertension. This equates 18,660,182.62 ETB (11,748,345.71 ETB, men; 96,911,836.90 ETB, women). The estimated regional life years lost due to premature mortality is 59,290.00. This is equivalent to 93,300,913.01 ETB ($2,144,848.58 USD). Similarly, if the result is extrapolated to national value, the national estimated life years lost due to premature mortality is 395,267 resulting in 622,006,087.33 ETB ($14,298,990.51 USD). From 15,232 years lost due to premature mortality in the hypertension cohort more than one-half of related deaths, 12,656 (83.1%) were due to treated hypertension. Treated and uncontrolled hypertension accounted for more than 6,824 (44.8%) total yeas lost due to premature mortality followed by treated hypertension 5,832 (38.29%) and untreated hypertension 2,575 (16.9%).

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension morbidity. This equates to 845,490.39 ETB ($19,436.56) The estimated regional and national YLL due to hypertension morbidity were 2897.85 equating 4,227,451.95 ETB ($97,182.80 USD) and 19,319, equating 28,183,013.16 ETB ($647,885.36 USD) respectively. More than two-thirds 70.94% (4,099.3) of total life years lost among the hypertension cohort was due to treated hypertension. Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for one-half 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). Details of input variables are available in the online-only supplementary file (Supplementary Table 3, 4, and 5). Treated uncontrolled hypertension contributed to more YLL due to premature mortality in both sexes 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378(50.84%) (Figure 2).

Total productivity loss due to premature mortality and morbidity was 19,505,673.01 ETB ($449,394.69 USD). Overall hypertension related economic burden in the study area was 22,326,103.39 ETB ($513,243.75 USD).

The regional and national estimated total annual economic burden was 111,630,516.95 ETB ($2,566,218.78 USD) and 744,203,446.33 ETB ($17,108,125.203 USD). More than eight out of ten 87.37% dollars were due productivity loss (i.e., premature mortality and morbidity) (Table 3, 4 and 5).

Table 3: Excess deaths among adult hypertensive by treatment and control status over the working lifetime simulated from life table modelling in Southern Ethiopia

Age group	Deaths in hypertension cohort	Deaths in 'hypertension cohort' assuming no hypertension	Excess deaths in those with hypertension	Deaths in those with to hypertension by treatment and control status *		
				Treated and controlled	Treated and uncontrolled	Untreated
Men						
30-34	1,436	448	988	487	654	294
35-39	1,180	381	799	401	537	242
40-44	1,027	428	599	357	479	191
45-49	1,735	224	1,511	1,167	405	162
50-54	989	166	823	370	496	123
55-59	731	123	608	274	367	91
60-64	932	101	831	362	443	127
Total	8,030	1,871	6,159	3,418	3,381	1,230
Women						
30-34	1,401	415	986	434	657	310
35-39	1,187	212	975	368	556	263
40-44	1,019	287	731	324	490	205
45-49	832	279	554	265	400	168
50-54	887	91	796	350	400	137
55-59	805	72	733	277	419	109
60-64	1,071	147	924	396	521	153
Total	7,202	1,503	5,699	2,414	3,443	1,345
Box sex total	15,232	3,374	11,858	5,832	6,824	2,575

* Excess deaths are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension

Table 4: Years of life lost (YLL) by adults with hypertension by treatment and control status over the lifetime simulated from life table modelling in Southern Ethiopia

Age group	Years of life lived in treated hypertension cohort	Years of life lived in 'hypertension cohort' assuming no hypertension	YLL lost to Treated hypertension (excess)	YLL lost due to hypertension by treatment and control status *		Years of life lived in untreated hypertension cohort	YLL lost due to Untreated hypertension
				Treated and controlled	Treated and uncontrolled		
Men							
33-39	199.87	181.2	18.67	141.34	NA	122.67	58.53
40-44	357.48	324.1	33.38	235.09	17.71	219.42	104.68
45-49	587.08	522.5	64.58	NA	418.31	353.73	168.77
50-54	341.9	295.3	46.6	NA	246.52	199.92	95.38
55-59	161.63	140.1	21.53	NA	116.38	94.85	45.25
60-64	129.88	109.4	20.48	NA	94.54	74.06	35.34
Total	1777.84	1572.6	205.24	376.43	893.46	1,064.65	507.95
Women							
33-39	318.33	288.6	29.73	225.11	NA	195.38	93.22
40-44	791.95	718	73.95	560.04	NA	486.09	231.91
45-49	1147.34	1040.2	107.14	NA	811.36	704.22	335.98
50-54	953.59	863.8	89.79	NA	674.58		279.01
55-59	491.71	445.8	45.91	NA	347.72	309.52	143.99
60-64	297.81	270	27.81	NA	210.6	182.79	87.21
Total	4,000.73	3626.4	374.33	785.15	2,044.26	1,878.00	1,171.32
Grand total	5,778.57	5199	579.57	1161.58	2,937.72	2,942.65	1,679.27

NA= No patient is reported in this age group; * YLL=years of life lost by those with hypertension compared to the same cohort assuming no hypertension.

Table 5: Productivity loss associated premature mortality and hypertension morbidity, Southern Ethiopia, January, 2021

Variable	Sex	Excess Years lost	Lost productivity ETB	Lost productivity in 2021 USD
Years lost due to premature morality	Male	6,159	11,748,345.71	$270,699.21
	Female	5,699	6,911,836.90	$159,258.91
	Both	11,858	18,660,182.62	$429,958.12
Years lost due to hypertension morbidity	Male	205.24	391,497.07	$8,999.93
	Female	374.33	453,993.32	$10,436.63
	Both	**579.57**	845,490.39	$19,436.56
	Total productivity loss		19,505,673.01	$449,394.69
1USD=43.5 ETB				

Note: productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB

4. Discussion

In this prevalence-based retrospective cost of illness study from a societal perspective focusing on quantifying direct and indirect costs by the bottom-up approach, we estimated the economic burden of hypertension among

hypertensive productive age (15-64 years) population of Southern Ethiopia. A total of 2,820,430.57 ETB ($ 64,837.48 USD) direct cost were incurred due to hypertension annually. Out of direct costs, 80.0% ($51,915.40 USD) was direct medical cost. Total monthly hypertension treatment cost was 188, 193.33 ETB ($4326.28 USD). From the direct medical costs, annual outpatient visit cost 33.55% ($17,419.73 USD), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($4,263.29 USD) took the largest share. The regional and national annual estimated direct cost of hypertension were 14,102,151.90 ETB ($324,187.40 USD) and 94,014,346.00 ETB (2,161,249.33 USD) respectively. Similarly, a total productivity loss due to premature mortality and morbidity was 19,505,673.01 ETB ($449,394.69).

In our study, the total monthly hypertension treatment cost was 188, 193.33 ETB ($4326.28). This is less than findings from the cost of illness study conducted to determine the economic burden of hypertension among 202 hypertensive patients receiving antihypertensive treatment at Government Hospital in Ghana that showed that the total monthly treatment cost of $6,356.30 (74). Our finding is also less than findings from a study conducted to calculate the healthcare costs attributable to hypertension in the province of Alberta, Canada (>3 million residents) and to project these costs to 2020 showed that hypertension annual individual healthcare cost of which $ 2341 (41% of overall individual healthcare cost) (75). Similarly, a study conducted on the economics of hypertension in the USA showed that relative to individuals without hypertension, individuals with hypertension had $1,920 higher annual adjusted incremental expenditure (76). This variation could be explained by variation in socioeconomic status and population health status, and our findings could underestimate both costs and health-related life loss due to the asymptomatic nature of hypertension (77) and a significant number of undiagnosed hypertension among adults globally and nationally.

Overall hypertension-related annual economic burden in the study area was 22,326,103.39 ETB ($513,243.75 USD). The regional and national estimated total annual economic burden was 111,630,516.95 ETB ($2,566,218.78 USD) and 744,203,446.33 ETB ($17,108,125.203 USD) respectively. To mean that the prevention of hypertension could result in annual $17,108,125.203 national economic savings. Cepheus research team reported that, the Ethiopian parliament approved on July 8, 2019, a federal government budget of Birr 387 billion ETB. Out of this 12.8 billion ETB is allocated for the Health sector (78). Hypertension accounted for 5.8% (744,203,446.33 ETB) of total national health care budget. World health organization estimated the implementation cost of best buys in low-income countries to be about 4% of the national health care budget. This highlights the urgent need of designing and implementing strategies believed to improve blood pressure control and prevention of hypertension.

In our study, indirect cost accounted for more than three fourth of hypertension-related costs 87.37% ($14,946,875.67) followed by direct medical costs 10.12% ($51,915.40). About a half of the costs associated with cardiovascular disease burden are caused by direct healthcare costs, 26% by work productivity losses, and

21% by informal care. Even though the loss of productivity results in a significant burden for individual CVD patients, their families, caregivers, and society as a whole, it is a relatively underexplored topic (79).

Concerning costs of treatment 80.0% ($51,915.40) of the cost was direct medical. This is similar to findings from a cost of illness study conducted at a Government Hospital in Ghana that direct cost accounting for almost 70% of the total cost of managing hypertension accompanied by a moderate intangible cost as reported by most of the patients (74). Similarly, a study conducted to estimate the economic burden of hypertension in a given year in rural Yunnan Province of China showed that direct costs represented the largest component of the economic cost of hypertension (80).

In addition to this, we found that the societal cost of hypertension is more pronounced than the healthcare costs since more than 8 out of ten dollars were due to productivity loss associated with hypertension. Therefore, it is important to promote existing strategies and develop country-specific strategies for hypertension prevention. Strategies believed to prevent the development of hypertension include; annual screening of the high-risk population, promoting healthy lifestyles (healthy eating, physical activity, weight reduction, psychosocial determinants including stress and anxiety, managing and controlling comorbid illnesses like diabetes, chronic kidney disease, and HIV/AIDS). In our recent scoping review we also identified the reasons for poor blood pressure control in Eastern Sub-Saharan Africa: Looking into 4P's (Primary care, Professional, Patient, and Public health policy) for improving blood pressure control (81). Addressing these multi-sectoral factors to improve the current low-level population awareness about hypertension (< 50% in Sub-Saharan Africa) (82, 83) and setting strategies for screening adults for hypertension to address undiagnosed hypertension and early initiation of treatment to reduce associated complication and comorbidities (84) which were contributing for direct costs significantly by focusing on preventive approach could help to avoid/reduce the economic burden of hypertension Ethiopia. In addition to this improving level of blood pressure control, through care standardization and adherence improving initiatives can also help to reduce hypertension-related complications, since only 18.5% of patients in this study achieved their BP control level. This is supported by evidence from a review and commentary done on the State of hypertension in Sub-Saharan Africa which stated the importance of increasing availability of voluntary blood pressure monitoring with low-cost devices, continued public health initiatives to build and expand patient education on the importance of hypertension management (85). This requires improved commitment from policy level managers which is low in Sub-Saharan Africa (81)

Concerning pre-mature mortality, A total of 11,606 (5,415, men; 6,190 women) years were lost due to hypertension-related premature mortality (917,756) among the regional target population 30-64 years. This equates 23,635,743.87 ETB (14,388,356.78 ETB, men; 9,247,387.08 ETB, women). Concerning health-related life loss, about 26,678 (81.79%) deaths per study population were due to hypertension and related

complications. This is higher than the number of hypertension-related death occurred in 2017, which as 11,050 (9). This could be explained by the increasing trend of hypertension in the country. From 15,232 years lost due to premature death in the hypertension cohort more than one-half of related deaths, 12,656 (83.1%) were due to treated hypertension. Treated and uncontrolled hypertension 6,824 (44.8%) total years lost due to premature mortality followed by treated and controlled hypertension 5,832 (38.3%) and untreated hypertension 2,575 (16.9%). Treated and uncontrolled hypertension contributed to premature mortality 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378(50.84%) in both sexes. This is supported by evidence from other studies that revealed uncontrolled blood pressure cost $370 billion globally in 2001 (i.e. about 10% of the global health expenditure) (86). This is because the relative risk of all-cause mortality is higher among treated and uncontrolled (1.62) than untreated (1.40) and treated controlled (1.12) patients (67).

Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for one-half 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). This is supported by evidence from global health in 2016, productive healthy life year lost due to hypertension was estimated to be 181,813,158 (35.85%). Similarly, in the African region, DALYs attributed to hypertension were 42,781,885 (24.60%) of NCD-related Healthy life years lost. Productive healthy life year lost due to hypertension was estimated to be 19,395,946 (45.8%) (4, 5). A study conducted to estimate the economic burden of hypertension in a given year in rural Yunnan Province of China showed that the overall prevalence of and YLL/1000 population because of hypertension was 24.8% and 1.5 years for the survey population, respectively (80).

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension. The estimated nation life years lost due to hypertension is 19,319. This equates 36,818,990.01 ETB ($846,413.56) (18,178,309.30 ETB men; 18,640,680.71 ETB women). This is supported by evidence from A study conducted among working-age (20 to 69 years) Australians with hypertension showed that hypertension caused the loss of 609, 801 productivity-adjusted life years (2.4%), equating to AUD$ 137.2 billion in the lost gross domestic product over the working lifetime (87). Therefore, prevention of hypertension and improving the rate of blood pressure control is important to reduce hypertension-related complications and productive life-year loss in the region as well as in the country (88). A systematic review conducted to determine productivity losses associated with the cardiovascular disease showed that annual population-level morbidity and mortality-related costs (2015 prices) reported in the studies ranged from US$56.3 billion in the European Union to US$132.3 billion in the USA. A total annual cost has been estimated at US$389.6 billion (2010 prices) globally. These findings suggest that economic evaluations that only consider cardiovascular (CV) deaths and fail to account for reduced productivity among people with CVD who continue working will underestimate the total cost of illness associated with CVD and cost-effectiveness of CVD prevention or treatment (89).

According to the Global Health Estimates technical paper released by WHO in 2018, there were 2,668,475,493 healthy life years were lost globally due to all causes of mortality. From this 1,595,534,582 (60%) deaths were due to NCDs. Healthy life years lost (DALY) directly or indirectly attributed to hypertension were 507,133,202 (31.78%) of NCD-related Healthy life years lost. Productive healthy life year lost due to hypertension is estimated to be 181,813,158 (35.85%). Similarly, there were 173,865,592 healthy life years were lost due to due to NCDs. Healthy life years lost (DALY) directly or indirectly attributed to hypertension were 42,781,885 (24.60%) of NCD-related Healthy life years lost. Productive healthy life year lost due to hypertension was estimated to be 19,395,946 (45.8%) (4, 5).

5. Conclusion

The societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars economic burden. Hypertension accounted for 5.8% of the total national health care budget. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Prevention of hypertension could result in annual $17,108,125.203 national economic savings. Therefore, designing and implanting strategies for prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels (national, regional, zonal, community, and patient-level) is critical to saving scarce health resources.

6. Abbreviations

ACEIs: Angiotensin-Converting Enzyme Inhibitors

BP: Blood Pressure

CPG: Clinical Practice Guideline

CVD: Cardiovascular Diseases

DALY: Disability Adjusted Life Years

DBP: Diastolic Blood Pressure

EDHS: Ethiopia Demographic Health Survey

HDL: High-Density Lipoprotein

ICER: Incremental Cost-Effectiveness Analysis

LDL: Low-Density Lipoprotein

LMICs: Low- and Middle-income Countries

MI: Myocardial Infarction

NCDs: Non-Communicable Diseases

NSAIDs: Non-steroidal Anti-inflammatory Drugs

OSA: Obstructive Sleep Apnea

PACK: Practical Approach to Care Kit

QALY: Quality Adjusted Life Years

SBP: Systolic Blood Pressure

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

YLD: Years Lived with Disability

YLL: Years of Life Lost

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Ethics and Declarations

Ethics approval and consent to participate

The study was approved by Tehran University of medical sciences, Faculty of pharmacy, department of pharmacoeconomics, and pharmaceutical administration ethical review board with Approval ID:

IR.TUMS.MEDICINE.REC.1399.674 and Arba Minch University College of medicine and health sciences Institutional review board with Reference number: *IRB/T10/2012*. After clarifying the study objective and confidentiality of the information; verbal informed consent was obtained from each respective hospital before data collection.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available up on official request of principal investigator upon acceptance of the manuscript

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All Authors read and approved the manuscript. *MM* conceived the research, framed the format design and developed the manuscript for publication; *MD participated in data analysis and reviewed the manuscript and AK* reviewed the manuscript and write-up process; *NS and* TS, participated in literature review and polished the language of the manuscript.

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Legends

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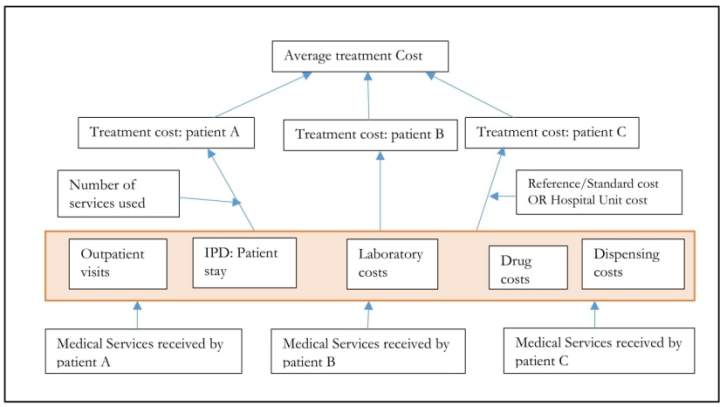

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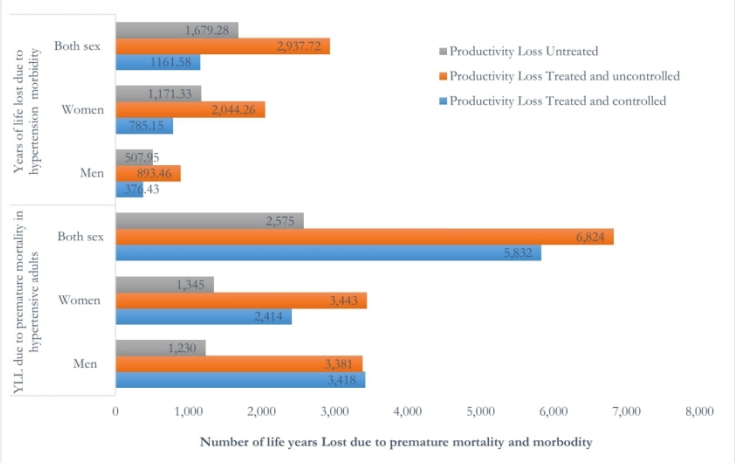

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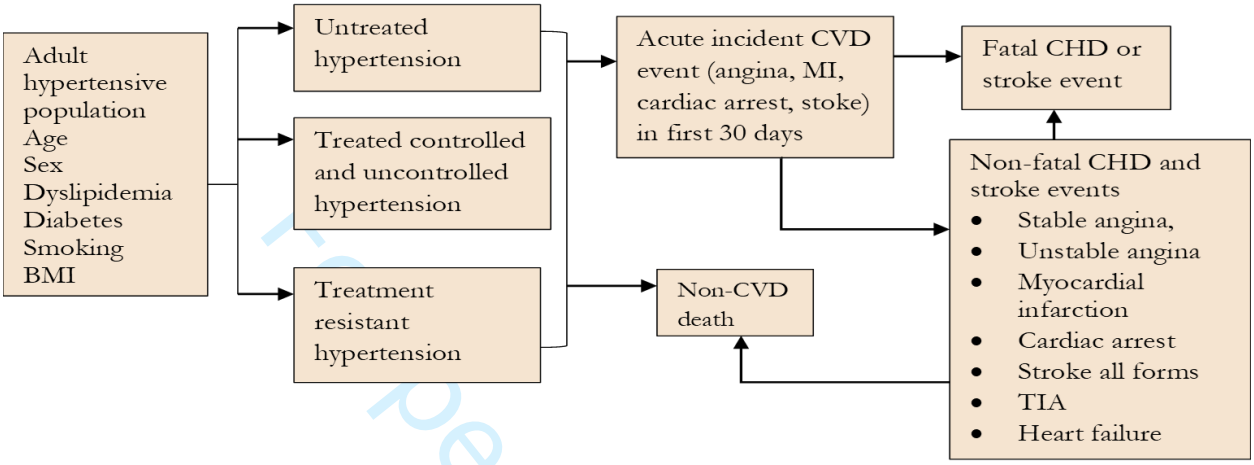
Supplementary materials: Economic burden of hypertension at selected Hospitals in Southern Ethiopia; a patient level analysis

Cardiovascular disease policy model



Supplementary Figure 1: Cardiovascular disease policy model adapted for Sub-Saharan African perspective (1).

Supplementary Table 1: Age and sex specific distribution of Ethiopian population 2020 estimate, prevalence of hypertension and adult mortality rate

Age structure	Male	Female	Total	Estimated prevalence of hypertension	Mortality rate		Data Source
Prevalence of hypertension					Men	Women	(2-8)
0-14 years	21,657,152	21,381,628	43,038,780	NA	-	-	
15-19	5,572,330	5,464,174	11,036,504	19.6	0.00286	0.00222	
20-24	5,930,683	5,816,173	11,746,856	19.6	0.00319	0.00223	
25-29	4,889,739	4,802,450	9,692,189	19.6	0.00293	0.002.32	
30-34	3,761,349	3,757,544	7,518,893	23.0	0.00397	0.003.68	
35-39	3,091,148	3,182,837	6,273,985	23.0	0.00411	0.00222	
40-44	2,445,523	2,488,422	4,933,945	25.9	0.00584	0.00385	
45-49	2,071,480	2,033,228	4,104,708	25.9	0.00360	0.00457	
50-54	1,567,789	1,660,957	3,228,746	41.9	0.00354	0.00274	
55-59	1,159,002	1,316,318	2,475,320	41.9	0.00354	0.00274	
60-64	946,594	1,109,670	2,056,264	41.9	0.00354	0.00274	
≥ 65 years	1,676,478	1,977,857	3,654,335	41.9	0.00354	0.00274	
Total	54,769,267	54,991,258	109,760,525				
				Prevalence of untreated hypertension			
For all ages (15 +)				13.25			(9)

Supplementary Table 2. Model Parameters, Cohort Setting, and Probability of Transition between states and Disability weights for hypertension and related complications the Global Burden of Disease 2013 study and WHO Global Health Estimates

Parameter	Data	Source
Relative risk of hypertension treatment		
Relative risk of CHD event on hypertension treatment	0.683 (95% CI, 0.633–0.717)	(10-13)
Relative risk of a cerebrovascular event on hypertension treatment	0.633 (95% CI, 0.526–0.717)	(14)
Relative risk of CHD event on normotensive men and women	0.49 (95% CI 0.458–0.513) and 0.32 (0.292–0.342)	(15)
Transition probabilities to death		
Health state	**Disability weight Estimate**	**Source**
Hypertension		**(16)**
Treated	0.246	
Untreated	0.323	
Treated and controlled	0.171	
Myocardial Infarction (MI)		(17)
Day 1-2	0·432	
Days 3-28	0·074	
Angina Pectoris		
Mild	0·033	
Moderate	0·080	
Severe	0·167	
Heart failure		
Mild	0·041	
Moderate	0·072	
Diabetes, digestive, and genitourinary disease		
Diabetes	0.015 (0.012 - 0.018)	(18-20)
Treated	0.033	
Untreated	0.012	

Diabetic neuropathy	0.133	
Chronic kidney disease (stage IV)	0.104	
End-stage renal disease: with kidney transplant	0.024	
End-stage renal disease: on dialysis	0.571	
Disutility due to daily medication	0.049 (0.031–0.072)	
Acute Events		
Myocardial Infarction	0.432 (0.288–0.579)	
Stroke	0.570 (0.377–0.707)	
Occurrence of second or later CVD event	0.985 (0.992–0.989)	
Chronic States		
Ischemic Heart Disease	0.08 (0.02–0.24)	
Stroke	0.135 (0.01–0.437)	
Alive post 2+ CVD Events	0.242 (0.11–0.437)	

CHD, coronary heart disease; SMR, standardized mortality ratio. *Age and sex dependent †Applied multiplicatively to general population age- and sex-dependent utilities; CHD= Angina pectoris, coronary insufficiency, myocardial infarction, or coronary death.

Supplementary table 3: Simulation input parameters

Input parameter	Value	Source
Non-CVD death rate	0.005–0.176 (Age- and sex specific)#	Calculated from WHO lifetables and GBD 2017 (21)
Probability of first-time cardiovascular disease (CVD) event	Individual risk characteristic specific	Obtained from the Globorisk Office Calculator standardized for India [25]
Acute CVD events		
MI		
Probability of MI if CVD event occurs	37.6– 66.7% (Age- and sex specific)#	Calculated based on GBD 2017(21)
30-day fatality	0.01–0.13 (Age- and sex–specific)#	Calibrated based on findings of Huffman et al. 2018 (22)
Re-infarction (in 30 days)	0.0120 (0.0099–0·0141)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Acute Stroke (in 30 days)	0.0060 (0.0045–0.0075)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Stroke		
Probability of Stroke if CVD event occurs	33.2–62.3% (Age- and sex specific)#	Calculated based on GBD 2017 (21) And Jushua D. Bundry et al(23)
30-day fatality	0.12, 0.13 (Sex-specific)#	Calibrated based on a multi-site study by Pandian and Sudhan 2013 [30]
Repeat Stroke (in 30 days)	0.15 (0.1–0.2)ψ	Petty et al. 1998 (24)
Sudden cardiac death	0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years	Heart disease and stroke statistics 2021 update
Heart failure		
Probability of AHF		
30-days fatality	0.0945	Obtained from the THESUS-HF registry (25) and Korean Acute Heart Failure Registry (KorAHF)(26, 27)

Re-hospitalization	0.0736	Obtained from the THESUS-HF registry (25)
Chronic events		
Monthly risk of mortality	0.001–0.019 (Age- and sex-specific)#	Calibrated based on GBD 2017 (21)
Reinfarction	0.079 (0.073–0.085)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.014 (0.012–0.016)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20) Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) (29), BP reduction and secondary stroke prevention: systematic review(30)
Stroke		
Monthly risk of mortality	0.001–0.013 (Age- and sex specific)#	Calibrated based on GBD 2017 (21) Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study(31)
Acute MI	0.043 (0.038–0.048)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.037 (0.033–0.041)	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Relative risk of fatality for an individual with two or more CVD events	1.5	Smolina et al. 2012 (32)
Heart failure		
Incidence		Bulter J.et al (33, 34), and Davis BRK. et. al (35)
1 year mortality		
Re-hospitalization		**Moita B.eta al. 2019(36) and (37)**
Effect of antihypertensive medication		
Medication protocol for an individual	Initial SBP-specific#	Based on Ethiopian NCD control guideline
IHD relative risk due to medication	0.32–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009 (38) and Asayam Kei., 2017(39)
Stroke relative risk due to medication	0.20–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009(38)
IHD relative risk if partially adherent	0.66–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009(40)
Stroke relative risk if partially adherent	0.60–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009 (40) and Lisheng Liu, Zengwu Wang. et al(41)

Supplementary Table 4: Price of drugs, medical supplies, procedures and professional time used for management of hypertension in Southern Ethiopia, January, 2021

List of medicines	Unit	Price in 2021 Ethiopian birr		Price USD	Source
		Wholesale price	Retail price	Retail Price in 2021 USD	
Acetylsalicylic Acid - 81mg – Tablet (coated)	10x10	43.72	1.32	1.303	Ethiopian Pharmaceutical supply agency, Arba Minch Hub wholesale price 2021 and Arba Minch General hospital pharmacy retail price 2021
Adrenaline (Epinephrine)-0.1% in 1mL ampoule	Each	36.032	1.09	1.074	
Amiodarone - 100mg – Tablet	10x3	313.34	9.44	9.337	
Amlodipine - 10mg - Tablet	10x10	105.44	3.18	3.142	
Amlodipine - 5mg – Tablet	10x10	75.26	2.27	2.243	
Atenolol - 50mg – Tablet	10x10	58.70	1.77	1.749	
Atorvastatin - 20mg – Tablet	10x10	195.68	5.89	5.831	
Atorvastatin - 40mg – Tablet	10x3	140.76	4.24	4.195	
Beclomethasone Propionate -100mcg/dose – Aerosol	200 MD	131.85	3.97	3.929	
Candesartan - 8mg – Tablet	14x2	152.63	4.60	4.548	
Captopril - 12.5mg – Tablet	10x10	33.54	1.01	1.000	
Captopril - 25mg – Tablet	10x10	26.91	0.81	0.802	
Dexamethasone - 4mg/ml in 1ml Ampoule - Injection	10	3.95	0.12	0.118	
Captopril + HCT (50mg + 25mg)-Tablet	10x10	57.32	1.73	1.708	
Digoxin - 0.25mg – Tablet	10x10	202.18	6.09	6.025	
Enalapril Maleate - 10mg - Tablet	10x10	61.57	1.85	1.835	
Enalapril Maleate - 5mg – Tablet	10x10	63.92	1.93	1.905	
Enalapril Maleate – 2.5mg – Tablet	10x10	19.98	0.60	0.595	
Enalapril Maleate +HCT (10 mg + 25 mg)-tablet	10x10	78.22	2.36	2.331	
Glibenclamide - 5mg – Tablet	10x10	39.09	1.18	1.165	
Glucose 40% in 20 mL – IV infusion	Each	2.54	0.08	0.076	
Glyceryl Trinitrate - 0.4mg – Tablet (Sublingual)	100	487.21	14.67	14.518	
Hydralazine - 20mg/ml in 1ml ampoule - Injection	5	204.01	6.14	6.079	
Hydrochlorothiazide - 25mg – Tablet	25x4	48.05	1.45	1.432	
Insulin Isophane Biphasic (Soluble/Isophane Mixture)-(30 + 70)IU/ml in 10ml Vial -Injection(Suspension)	Each	85.20	2.57	2.539	
Insulin Isophane Human - 100IU/ml in 10ml Vial - Injection(Suspension)	Each	100.28	3.02	2.988	
Insulin Soluble Human - 100IU/ml in 10ml Vial	Each	106.21	3.20	3.165	
Lovastatin - 20mg – Tablet	10x10	84.59	2.55	2.521	
Metformin - 500mg – Tablet	10	27.78	0.84	0.828	
Methyldopa - 250mg – Tablet	100x10	51.75	1.56	1.542	
Metoprolol - 50mg – Tablet	10x10	94.43	2.84	2.814	
Morphine sulphate-30mg-tablet	110	410.71	12.37	12.239	
Nifedipine - 20mg – Tablet	10x10	58.70	1.77	1.749	
Prednisolone - 5 mg – Tablet	100x10	342.23	10.31	10.198	
Propranolol - 40mg – Tablet	10x10	67.54	2.03	2.013	
Propylthiouracil - 100mg - Tablet (Scored)	100	633.87	19.09	18.889	
Salbutamol - 0.1mg/dose - Aerosol (Oral Inhalation)	200 MD	117.20	3.53	3.492	
Spironolactone - 25mg – Tablet	10x10	81.87	2.47	2.440	
Thyroxin Sodium - 0.1mg – Tablet	100	178.49	5.38	5.319	
Valsartan + HCT (80mg +12.5mg)	7*2	38.47	1.16	1.146	
Laboratory and imaging costs		**Price per test ETB**		Price in 2021 USD	
CBC		75.00		1.72	Arba Minch General Hospital Laboratory service price 2021
FBG/RBS		20.00		0.46	
Lipid profile (LDL, HDL, Total cholesterol, Triglyceride)		160.00		3.68	
ECG		120.00		2.76	
ECO		350.00		8.05	
CT-scan		1200		27.59	
RFT (bilirubin, creatinine)		80.00		1.84	
Chest-ray		726		16.69	
Urine analysis		15.00		0.34	
Body fluid analysis		100.00		2.30	
H. pylori		50.00		1.15	

Liver function test (AST, ALT, ALP)	120.00	2.76	
Thyroid function test (T3, T4, TSH)	432.00	9.93	
Hospital bed days			
Primary hospital	52.52	1.21	WHO Choice (42) inflated to 2021
Secondary hospital	54.76	1.26	
Tertiary hospital	70.81	1.63	
Health facility visit		0.00	
Primary hospital	18.58	0.43	
Secondary hospital	21.17	0.49	
Tertiary hospital	22.06	0.51	
Health center visit	23.00	0.53	
PCI intervention	63,000.00	1448.28	
In-patient costs for MI	45240.00	1040.00	
In-patient costs for Stroke	40890.00	940.00	
Outpatient cost for IHD (per annum)	1957.50	45.00	
Outpatient cost for Stroke (per annum)	2914.50	67.00	
Salary scale of human resource		0.00	
Physician	21,100.00	485.06	MOH, Ethiopia 2012/2019
Acute care nurse	7470.00	171.72	
Pharmacy personnel	8047.00	184.99	
Laboratory technician	6460.00	148.51	
Program cost per person per annum	993.29	22.83	(43).
Antihypertensive treatment			
Antihypertensive medication (per individual per annum	Drug costs based on national Drug supply agency wholesale price		
Out-patient consultations (per visit)	$43.36	Annual outpatient visit cost (12*WHO cost per outpatient visit inflated to 2021) WHO Choice (42)	
One-time diagnostic tests		Based on Laboratory procedures and test price of Arba Minch General Hospital, 2021	
In-patient costs for MI	$1040	WHO Choice (42) inflated to 2021	
In-patient costs for Stroke	$940		
Chronic CVD care			
Secondary care medication in public sector (per individual per annum)	$92, $184 (Dosage-specific)§	MSH-2015 International Drug Price Indicator inflated to 2021(25)	
Outpatient cost for IHD (per annum)	$45	WHO Choice (44) inflated to 2021	
Outpatient cost for Stroke (per annum)	$67		
Average inflation rate Ethiopia	16.58%	https://take-profit.org/en/statistics/inflation-rate/ethiopia/	
Average inflation rate foreign	2.02%		
Percentage change	24.6%		
Exchange rate July 2021 (1USD)	43.5 ETB		
1USD = 20.999 ETB in 2016 and 43.5 in 2021; PPP= 12.1/8.1 = 1.5			
MD: metered Dose; MOH: Ministry of Health 1 USD = 43.5 January 2021 **Note**: 30% mark-up at regional EPSA hub, 31% mark-up at Public Hospital level			

Supplementary Table 5: Risk of death across age and gender covariate categories stratified for hypertension

Variables	Categories	Incidence of death (%)		Relative risk in each category (CI)	Source
		High BP group	Normal		
Age	20-29	1.68%	0.54%	3.11 (1.16-8.36)	*(8)*
	30-39	1.71%	0.94%	1.82 (1.04-3.19)	
	40-49	2.43%	1.88%	1.29 (0.91-1.82)	
	50-59	6.30%	4.03%	1.56 (1.28-1.91)	
	60 and above	19.32%	15.9%	1.21 (1.12-1.31)	
Gender	Women	8.71%	1.1%	3.31 (2.98-3.68)	
	Men	15.47%	4.62%	3.34(3.02-3.70)	
Risk of all case mortality					
Gender	Treatment status	< 60 years	> 60 years	HR (95% CI)	(45)
Men	Normal	0.0068	0.0214	1.00 (Reference)	
	Treated controlled	0.0188	0.0305	1.20 (0.92-1.57)	
	Treated uncontrolled	0.0252	0.0372	1.55 (1.19-2.01)	
	Untreated	0.0197	0.0336	1.45 (1.23-1.72)	
Women	Normal	0.00528	0.01870	1.00 (Reference)	
	Treated controlled	0.01675	0.02841	1.11 (0.84-1.47)	
	Treated uncontrolled	0.02533	0.03736	1.63 (1.34-1.99)	
	Untreated	0.02075	0.03471	1.31 (1.06-1.61)	

Supplementary Table 6: Annual mortality rate in the total population, those with hypertension by treatment and control status and those without hypertension in Ethiopia in 2021 by age group and sex based on literature review of systematic reviews and clinical trials

Age group	Mortality rate in the total population	Mortality rate among people without hypertension	Mortality rate among people with treated and controlled hypertension	Mortality rate among people with treated but uncontrolled hypertension	Mortality rate among people with untreated hypertension	References
Women						
15-19	0.00222	0.00222	0.016746	0.025	0.02075	Ko, Min Jung. et al. 2016 (46), Mende Sorato, et al, 2021. (1, 23, 45, 47, 48).
20-24	0.00223	0.00223	0.016746	0.025	0.02075	
25-29	0.00232	0.00232	0.016746	0.025	0.02075	
30-34	0.00368	0.00368	0.016746	0.025	0.02075	
35-39	0.00222	0.00222	0.016746	0.025	0.02075	
40-44	0.00385	0.00385	0.016746	0.025	0.02075	
45-49	0.00457	0.00457	0.016746	0.025	0.02075	
50-54	0.00182	0.00182	0.016746	0.025	0.02075	
55-59	0.00182	0.00182	0.016746	0.025	0.02075	
60 -64	0.00441	0.00441	0.028414	0.037	0.03471	
Men						
15-19	0.00286	0.00286	0.018783	0.025	0.01969	Kuriakose A. et al. 2014. (8), EDHS, 2016 (7, 45, 47-50)
20-24	0.00319	0.00319	0.018783	0.025	0.01969	
25-29	0.00293	0.00293	0.018783	0.025	0.01969	
30-34	0.00397	0.00397	0.018783	0.025	0.01969	
35-39	0.00411	0.00411	0.018783	0.025	0.01969	
40-44	0.00584	0.00584	0.018783	0.025	0.01969	
45-49	0.0036	0.0036	0.018783	0.025	0.01969	
50-54	0.00354	0.00354	0.018783	0.025	0.01969	
55-59	0.00354	0.00354	0.018783	0.025	0.01969	
60-64	0.00354	0.00354	0.030451	0.037	0.03365	

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Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

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	Reporting Item	Page Number
Title		
#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1

Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	1
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	2
Methods			
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	3-10
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	9

Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	10
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	NA
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	4-6
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	NA
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use	NA

		associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	
Methods			
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Supplementary figure 1
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	9

Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-15
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	NA

Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	23

Notes:

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BMJ Open

Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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Keywords:	Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, HEALTH ECONOMICS, Cardiology < INTERNAL MEDICINE, Hypertension < CARDIOLOGY

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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I. Abstract

Objectives: There is inadequate information on the economic burden of hypertension treatment in Ethiopia. Therefore, this study was conducted to determine the societal economic burden of hypertension at Selected Hospitals in Southern Ethiopia.

Methods: Prevalence-based cost of illness (COI) study from a societal perspective was conducted. Disability-adjusted life years (DALYs) were determined by the current world health organization's recommended DALY valuation method. Adjustment for comorbidity and a 3% discount was done for DALYs. The data entry, processing, and analysis were done by using SPSS version 21.0 and Microsoft Excel 2013.

Results: We followed a cohort of 406 adult hypertensive patients retrospectively for 10 years from September 2010 to 2020. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ± 11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their blood pressure control target. A total of 309,261.91 United States Dollar ($US) direct cost was incurred due to hypertension. A total of 11,606 years and 579.57 years were lost due to hypertension-related premature mortality and morbidity respectively. Treated and uncontrolled hypertension 44.8% (6824) total years lost due to premature mortality from total hypertension cohort. Treated and uncontrolled hypertension accounted for one-half 2,937.72 (50.84%) of productive life years lost. Total productivity loss due to premature mortality and morbidity was $US 449,394.69.

Conclusion: Societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Therefore, designing and implanting strategies for the prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels is critical to saving scarce health resources.

Strengths and limitations of this study

- Using the cardiovascular disease policy model adapted to Sub-Saharan African perspective,
- Including productivity loss costs associated with hypertension (premature mortality and morbidity) and
- Obtaining all simulation variables and transition probability data from valid sources (systematic reviews, randomized controlled trials, and prospective cohort studies) were strength of this study
- Uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate which require due consideration during applying the findings of this study were limitations.

1. Introduction

Hypertension doubles the risk of death from stroke, heart disease, vascular diseases, diabetes, atherosclerosis, and kidney disease (1). According to the national STEPS survey, only 28.4% of hypertensive patients were taking antihypertensive medication prescribed by professionals in Ethiopia (2). According to the International Society of hypertension global hypertension practice guideline 2020, hypertension remains the leading cause of death globally, accounting for 10.4 million deaths per year (3).

Hypertension is associated with societal and economic consequences particularly in Low and middle-income countries (LMICs). In addition to the direct costs associated with health care utilization for the management of complications, hypertension causes significant productivity loss from disability and premature death (4, 5). WHO report from South East Asian region also indicated huge impact of hypertension in national finances due to premature death, disability, personal and family disruption, loss of income, and healthcare expenditure (6). According to a WHO report in 2017, stroke, coronary heart disease, and hypertension caused 39,571, 46,943, and 11,050 deaths respectively (i.e. 30 patients per day die due hypertension) in Ethiopia (7).

Cost of illness (COI) study is used to measure the economic burden of disease to individuals, communities, and society as a whole. It can provide information to support the political process and healthcare decision-making if it is conducted from a societal perspective by using an appropriate approach and bottom-up costing strategy (8-10) (11, 12). Despite this huge impact on national economies, the economic burden of hypertension is not studied in Ethiopia particularly Southern Ethiopia. To fill this evidence gap, this study was conducted to determine the economic burden of hypertension at selected public hospitals in Southern Ethiopia by using the prevalence-based cost-of-illness method from a societal perspective to estimate the direct and indirect costs of hypertension in a given year (2021) in Southern Ethiopia.

2. Methods and Materials

2.1. Study design, Area and Period

A prevalence-based retrospective cost of illness study from societal perspective focusing on quantifying direct and indirect costs was conducted from September 2010- September 2020 in at three selected public hospitals Southern Ethiopia. The bottom-up approach was used to estimate the economic burden of hypertension in Southern Ethiopia (figure 1). The human capital approach was used to calculate indirect costs separately in males and females and also among different age groups. A prevalence-based COI model was constructed in which hypertensive patients were simulated from diagnosis through active treatment, palliative care, and death over 15-64 years. Age and sex-specific mortality rates, measures of productivity, and workforce statistics were used to simulate the progression of these cohorts until death or age 64 years. First, the model estimated cumulative years of life and DALYs lived for the working-age population who had hypertension. Then the

model re-simulated with the hypothetical assumption that they did not have hypertension, with relevant changes to mortality rates and productivity. We estimated the probability of death separately for (1) all-cause mortality in absence of hypertension and related complications and (2) mortality attributable to the included disease states. The first component was estimated using WHO Life Tables, and the second component was calculated based on standardized mortality ratios extracted from the literature. The natural history study conducted in 1974 showed that the mortality rate was 1.85 (3.01 in males and 1.62 in females) (13). Interventional trials suggested that it could be possible to achieve effective BP targets in about 70% of patients by improving adherence and/or intensifying therapy (14).

2.2. Study populations

The study populations were selected adult hypertensive patients at three selected public hospitals. According to the world population prospect 2020 estimate (15). In the same year, the population of the Gamo zone accounted for 1.5% of the total population, Gofa, and South Omo Zone 1.5% of the total population. The target population is 3.0% total population of Ethiopia or 20% of the Southern Ethiopian population (6,208,034). Based on age distribution: 0-14 years are children, 15-24 years are early working age, 25-54 years are prime working age, 55-64 years are mature working age and ≥ 65 years are elderly (13).

2.3. Inclusion and exclusion criteria

We included all adult hypertensive patients having at least five years of follow-up visits before data collection and receiving care during the study period from selected facilities. However, patients who are unwilling to participate in this study, patients who have less than five years of follow-up, and incomplete patient records (don't contain follow-up BP records and refill medications, laboratory requests, and results) were excluded.

2.4. Study Variables

Dependent Variables

- Economic burden of hypertension

Independent variables

- Patient-related (socio-demographic characteristics, heart disease knowledge, healthy lifestyle and heart disease risk perception, presence of comorbidity, type of medications, treatment adherence, shared decision making, health-related quality Life)

Cost related variables

- **Medical costs** (inpatient hospital stay/hospitalization cost, outpatient clinic visit, drug acquisition costs, drug administration cost, laboratory test, and imaging study costs)

- **Non-medical costs** (transportation, meal, patient time cost due to treatment, cost due informal care by family or friends)
- **Indirect costs** (absenteeism, presenteeism, unemployment, early retirement, disability, premature death)

2.5. Sample Size and Sampling Technique

2.5.1. Sample size determination

The sample size was determined by using the single population proportion formula by taking prevalence of patients controlled their BP as 14% from WHO 2016 BP control rate report (16-18) and Z value of 1.96 at 95% confidence interval. We added 10% for non-response rate and two for design effect due to multi-stage sampling technique involvement. Finally, a formula giving a larger sample size was used. Total 407 hypertensive adult patients who are on follow-up care will be included.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2} = 185$$

= 185 + (185 * 10%) = 203.5

= 203.5 *2 = 407

Where: **n** = is the sample size

- $\mathbf{Z^2}$= standard normal deviation, set at 1.96, correspond to the 95% confidence interval
- **d** = is the desired level of precision/margin of error (0.05)
- **p**= prevalence of patients taking anti-hypertensive (p=28.4%), and q is 1-p.

2.5.2. Sampling Techniques

A multi-stage simple random sampling technique was used. We randomly selected three zones from a total of 12 zones found in the Southern region. Three general public hospitals with experience of providing CVD care for at least five years from selected four zones were included in this study. The total sample size was allocated to these hospitals based on an estimated number of adult hypertensive patients attending respective hospitals (i.e., we included 212 patients from Arba Minch General Hospital, 107 patients from Jinka General Hospital, and 88 patients from Sawula General Hospital). Finally, a consecutive sampling technique was applied in each facility until the desired sample size was achieved.

2.6. Data collection tools and Procedures

2.6.1. Model input parameters

Key model input variables include; 2020 population of selected zones, hypertension prevalence by treatment and control status, Transition probabilities to death and healthy state, cost of diagnosis, and management. Among those with treated hypertension, treated and controlled hypertension was defined based on BP control target of ISH 2020 guideline (3). We used national STPES survey data to estimate the prevalence of cardiovascular risk factors (MI, angina, heart failure, stroke, TIA). Incorporating the risk factor prevalence data in the relevant Framingham risk equation, the age and sex-specific probability of CHD and cerebrovascular disease (i.e., stroke and transient ischemic attack) events were estimated. The probability of each health state

was calculated using the age- and sex-specific CHD and cerebrovascular disease event distributions (2, 19). To estimate the corresponding probabilities, separate relative risk estimates were used for CHD events (Stable Angina, Unstable Angina, and MI) and cerebrovascular diseases (Stroke and Transient Ischemic Attack), assuming that antihypertensive treatment affects the probability of every disease state similarly across all age and sex groups. Relative risk reductions attributable to antihypertensive treatment were extracted from the peer-reviewed literature (20-22).

The 2020 world population prospect estimate was used for the baseline population and number of 33-year-olds projected to enter the model population from 2020-2070 (15). The annual probability of coronary heart disease and stroke was based on national STEPS survey (2), and Framingham Heart Study (23) and the Framingham Offspring Study (24), by contextualizing to Ethiopian scenario. Incident coronary heart disease events were allocated to angina pectoris, myocardial infarction, or cardiac arrest. Prevalence, joint distributions, and means of Ethiopia risk factor values were estimated from the national STEPS survey (2). Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Betas for risk function for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort (24). Risk factors are assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers are assumed to have a higher relative risk for infarction and arrest (25); and a proportionately lower coefficient for angina. Environmental tobacco exposure is assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with non-exposed non-smokers (26) but not to influence angina. The number of hospitalized MI were obtained from the national STEPS survey (2). Case-fatality rates and rates of MI in subgroups were estimated from national data and other complementary sources. Prehospital arrest deaths and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from our effectiveness study (Supplementary Table 1).

Survival after a coronary heart disease event was estimated and calibrated based on national or international data sources (27, 28). Rates of coronary revascularizations was estimated from the National hospital discharge survey, with mortalities estimated from aggregated historical data. Stroke incidence was assumed to be independent of the risk of new-onset coronary heart disease in the same year. The number of hospitalized strokes cases was obtained from national and regional studies. The annual probabilities of stroke after MI (29, 30) and the probability of coronary heart disease in stroke patients were based on natural history studies and systematic reviews of blood pressure control trials (31-36). A 30-day heart failure mortality and re-hospitalization data were from the THESEUS-HF registry (37) and Korean Acute Heart Failure Registry (KorAHF)(38, 39) (Supplementary Table 2 and 3).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2020 was estimated from the National Health Survey data (2) and GBD 2017 (40). The background prevalence of prior coronary revascularization was estimated from revascularizations before 2019 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state. Age and sex-specific health care costs were estimated using national data, and our effectiveness data. Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using WHO Choice (41) inflated to 2021. Outpatient consultations, and inpatient stay and bed days were also estimated from WHO choice (41) inflated to 2021. Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis was pooled from the 2015 national STEPS survey. Average annual non-cardiovascular costs were estimated from the national STEPS survey (2), and EDHS 2016 survey (13).

2.6.2. Cost estimation

The outcomes measures are total discounted societal costs, cost/year, and cost/patient-year. This is the amount of health budget that could be saved by effective prevention and control of hypertension. The direct costs were divided into two subcategories: direct medical costs and direct non-medical costs. Direct medical costs include; inpatient stays, outpatient clinic visits, medical services, drug acquisition, dispensing, administration, monitoring, laboratory test, and imaging study costs. The costs associated with outpatient/inpatient visits were estimated by multiplying the numbers of outpatient visits related to hypertension by the outpatient costs per year (i.e., twelve times WHO cost per outpatient visit for secondary hospitals inflated to 2021) (41).

Data concerning medications prescribed for the management of hypertension, and associated comorbidities, and laboratory tests and imaging studies were done were collected by patient chart abstraction in index year (2020). The cost of medications used for management of hypertension and associated comorbidities was taken from Ethiopian Pharmaceutical supply agency Arba Minch regional hub selling price and retail price of Arba Minch General Hospital in 2020. The retail price of Arba Minch General Hospital was used because of the minimum distance from the Pharmaceutical supply agency hub, which could minimize markup added on retail price due to transportation cost. Costs of laboratory procedures were also taken from Arba Minch Hospital Laboratory's service price list. The prices of relevant laboratory tests and imaging studies were based on the average price of included Hospitals. The salary scale of the health workforce was based on the FMOH of Ethiopia (Supplementary Table 4).

Ongoing program costs for hypertension care was estimated from WHO tool outputs for CVD and diabetes care and National strategic action plan (NSAP) for prevention & control of non-communicable diseases in Ethiopia 2014-2016 and adjusted for 2021 inflation target population (42). Adjustment for the study population was done by multiplying the national cost by the proportion of the study population (i.e., 3%). National and regional cost estimates were based on the proportion of patients studied (i.e. 3% and 20%). We considered this strategy since the

age and sex distribution of hypertension among different regions in the country is did not vary significantly. The collected cost data added up and averaged by using a bottom-up approach. Facility-based or reference costs were used during computing costs. The total medical cost of hypertension treatment was calculated as the sum of the product of medical costs with their respective unit prices. Costs were discounted at an annual rate of 3% and reported in 2021 USD (43, 44).

Direct non-medical costs include transportation costs and patient time costs due to care. The cost of patient time due to care was estimated by using the average daily wage of patients which was calculated from average monthly income (97.00 ETB) 34,931.00 annual income from our treatment effectiveness survey. Transportation cost was determined by using the cost of average traveling distance and local transportation tariff (42.00 ETB) in January 2021. According to EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13). This proportion was used to determine the patient time cost due to care for employed groups. For the unemployed proportion, the average daily wage of daily laborers workers working 8 hours per day for 6 days per week was used (26.53 ETB) from the monthly wage of 796.00 ETB (420-1172 ETB) (45).

Indirect costs include cost hospitalization, productivity loss due to illness, and cost of death. Cost-of hypertension-related hospitalization was taken from WHO Choice (41), costs per inpatient stay and cost per inpatient bed day times duration of hospitalization inflated for 2021, and professional time (physician, nurse laboratory professional, and pharmacist time). If a patient had multiple admissions during the year, the costs for each admission were aggregated as the total costs (46).

2.6.3. Mortality and morbidity estimations

Age and sex-specific mortality rates among the adult general population in Ethiopia were taken from EDHS 2016 survey and extrapolated to selected populations (13). According to EDHS 2016, the probability of dying before age 50 years among adults ≥ 15 years were 10% and 12%, in women and men respectively (13). Due to the absence of mortality data specific to hypertension treatment and control status in Ethiopia, mortality risk in the general population was attributed to those with and without hypertension using sex-specific estimates of the relative risk (RR) of all-cause mortality associated with hypertension by treatment and control status was derived from a study conducted in India was used (47). A cohort study conducted in India among adults 20 years and above to determine the Rate and Risk of all-cause mortality among people with HTN showed that the incidence of deaths in the study was 4.28% during the follow-up period of 6 years. The relative risk of mortality was 3.13 (CI: 2.91-3.37) and 1.2 in the high BP group and at age of 60 years. The age-adjusted hazard ratio of all-cause mortality for the high BP group was 2.96 (2.56-3.42) (47) (Supplementary Tables 5 and 6).

In 2020 crude death rate of the Ethiopian population-based on global estimates was 6.29 deaths per 1000 population (48). The estimated prevalence of hypertension among adults was calculated from National STEPS Survey 2016, systematic review and meta-analysis, and WHO report and local studies and the mean estimated

prevalence of hypertension was 21.39% (2, 13, 47, 49-52). Only 28.4% of patients with hypertension are taking antihypertensive medication (2). The mean relative risk of all-cause mortality among hypertensive population when compared to those without hypertension was 1.39 (0.95 to 1.95) (53) (Supplementary Table 3).

Years of life lost due to hypertension morbidity was determined by first calculating disability weights for specific ages based on blood pressure control status (X). Then subtract this value (X) from the life expectancy of the Ethiopian population (i.e., 66.7 years for men, and 70.4 years for women) (Y). The productivity loss cost due to hypertension morbidity was calculated by multiplying Y with sex-specific employment rate based on a monthly average income of 2059.078 ETB from the National STEPS survey 2015 adjusted for 2021 inflation (13,13/9.57=1.372) STEPS Survey, 2015 (2). The EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13) and for unemployed, 2019 minimum average monthly earnings (ETB) of daily laborers reported by the MOLSA 796 ETB (420-1172 ETB) (45). Concerning, cost of productivity lost due to premature mortality: first we calculated potential years of life lost (YLL) by subtracting life expectancy from sex-specific age of death at which the death is recorded (Z). Then Z is multiplied by the number of deaths in each age group (Xi). Finally, we multiplied Xi with sex-specific employment rates like productivity loss due to hypertension-related morbidity above (54). Excess mortality and morbidity due to hypertension to hypertension were determined by subtracting age and sex-specific morbidity and mortality among the general population from the hypertensive cohort. Both were determined by using age, sex, and blood pressure treatment status mortality rate per 1000 person-years (Supplementary Table 6).

2.6.4 Morbidity adjustment

Patients with hypertension may have more than one disease, the addition of YLDs across causes may result in overestimation of the total loss of health (55). Therefore, it is recommended to estimate comorbidities using the assumption of independence within age-sex groups (56):

$$\mathbf{P_{1+2} = P_1 + P_2 - (P_1 \times P_2) = 1 - (1 - P_1) \times (1 - P_2)}$$

- **Where** P_{1+2} is the prevalence of the two comorbid diseases 1 and 2,
- P_1 is the prevalence of disease 1 and $\mathbf{P_2}$ is the prevalence of disease 2.

The combined disability weight for individuals with multiple conditions is estimated assuming a multiplicative model as follows:

$$\mathbf{DW_{1+2} = 1 - (1 - DW_1) \times (1 - DW_2)}$$

Since prevalence YLDs are calculated for each cause as:

$$\mathbf{YLD_i = DW_i \times P_i}$$

- two preceding equations can be combined into a single calculation resulting in:

$$YLD_{1+2} = 1 - (1-YLD_1) \times (1 - YLD_2)$$

2.6.5 Assumptions and Transition probabilities

The counterfactual comparator (hypothetical cohort of normotensive individuals) with a probability of developing CVD events among the general population. Both in case and comparator cohorts, the probability of non-CV death does not depend on the health state and is similar for both hypertensive and normotensive populations (57) and we chose not to model differential use of antihypertensive medication classes in order not to bias cost-of-treatment. Antihypertensive dose intensification and frequency of BP monitoring were based on ISH 2020 guidelines for blood pressure control. We did not simulate the effects of any particular medication; instead, we simulated "standard dose" effects and assumed average drug prices across classes (58). The amount of blood pressure change was assumed to be a function of the baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (59). We also assumed the medication adherence rate as 75% based on clinical trials (59). Other important assumptions include cost of illness due to hypertension or associated morbidities were calculated based on the monthly earnings during data collection; all costs incurred before one year were adjusted/accounted to today's value (2021 USD equivalent) and discounted at 3%; years of life lost and years of life lived with disability (YLDs) were not discounted as per the recent WHO recommendations.

2.7. Data Quality control, Processing, and Analysis

Questionnaires are prepared in English and the patient interview part of the questionnaire was translated into Amharic and translated back into English to check its consistency. The Amharic version of the patient interview questionnaire and English version of the health professional interview, data abstraction form, and health system interview questionnaires was used for data collection. The questionnaire was pretested on 30 adult hypertensive patients in Arba Minch General Hospital to ensure that the respondents could understand the questions and to check for consistency and possible amendments were made based on findings. Six professional nurses (BSc.) for data collection and one senior professional working in the respective health facilities for supervision were oriented before data collection about data collection approaches and contents of data collection format for one day by the principal investigator. Continuous follow-up and supervision were made by the principal investigator throughout the data collection period. The collected data were checked for completeness and consistency by the principal investigator on daily basis at the spot during the data collection time. Then data were transcribed back to English for the patient interview part and entry was made using Epi-data 3.1 software. After data processing, analysis was done by using SPSS version 21.0 and Microsoft excel 2010. A summary of descriptive statistics was reported for socio-demographic factors; cost of hypertension and life years lost due to hypertension related morbidity and premature mortality and presented in tables and figures.

2.8. Patient and Public involvement

There was no identifiable patient involvement in this research. Patients' demographic characteristics and disease related variables were obtained by using questionnaire based interview after obtaining verbal consent from the patient. No patient identifier information was collected. Finally, most of variables were taken from published national and international literatures, and all relevant sources were acknowledged through citation.

2.9. Statements

Ethics approval and consent to participate

The study was approved by Tehran University of medical sciences, Faculty of pharmacy, department of pharmacoeconomics, and pharmaceutical administration ethical review board with Approval ID: *IR.TUMS.MEDICINE.REC.1399.674* and Arba Minch University College of medicine and health sciences Institutional review board with Reference number: *IRB/T10/2012*. After clarifying the study objective and confidentiality of the information; verbal informed consent was obtained from each respective hospital before data collection.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available up on official request of principal investigator upon acceptance of the manuscript

Competing interests

The authors declare that they have no competing interests.

Funding

There is no funding source for the study.

Authors' contributions

All Authors read and approved the manuscript. *MM* conceived the research, framed the format design and developed the manuscript for publication; *MD participated in data analysis and reviewed the manuscript and AK* reviewed the manuscript and write-up process; *NS* and *TS* participated in literature review and polished the language of the manuscript.

3. Results

3.1. Description of study participants

In this study, we estimated the regional and national economic burden of hypertension (direct and indirect costs) by using the cardiovascular disease policy model adapted to the Sub-Saharan Africa perspective (60) (Supplementary Figure 1). Total costs of treated hypertension and hypertension-related excess mortality and years of life lost due to hypertension were determined. We followed a cohort of 406 hypertensive patients retrospectively for 10 years from September 2003 to 2013 Ethiopian calendar (September 2010-2020) for baseline assessment and simulated the cost of hypertension for lifelong from a societal perspective. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their BP control target based on international society of hypertension 2020 guidelines (Table 1).

Table 1: Patient characteristics and Disease related factors among adult hypertensive patients on regular follow-up at selected public hospitals in Southern Ethiopia, January 2021 (n=406)

Sociodemographic factors		Frequency
Sex	Male	156 (38.4%)
	Female	250 (61.6%)
Age in in years	Below 40 years	15 (3.7%)
	40- 65 years	286 (70.4%)
	65 years and above	105 (25.9%)
Religion	Orthodox	215 (53.0%)
	Muslim	37 (9.1%)
	Protestant	144 (35.5%)
	Catholic	10 (2.5%)
Annual gross income before tax (n=406)	Less than 12,000	117 (28.8%)
	12,000- 18,000	89 (21.9%)
	18,000- 23,000	200 (49.2%)
Level of Education	Illiterate	259 (63.8%)
	Grades 1-8	46 (11.3%)
	Grades 9-12	22 (5.4%)
	College and above	73 (18.0%)
	Post-graduate degree	6 (1.5%)
Occupation	Employed	65 (16.0%)
	Merchant	63 (15.5%)
	Farmer	79 (19.5%)
	House wife	149 (36.7%)
Disease related factors		
Duration of hypertension since diagnosis	5 - 9 years	262 (64.5%)
	10 - 14 years	131 (32.3%)
	15 and above years	13 (3.2%)
Family history of CVDs	1st degree relative	133 (32.7%)
	Second degree relative	16 (3.9%)
	None	257 (63.3%)
Presence of comorbidities (n=406)	Yes	310 (76.4%)
	No	96 (23.6%)
History of hospitalization	Yes	250 (61.6%)

	No	156 (38.4%)
Duration of hospitalization (n=250)	Below 5 days	56 (22.4%)
	5 to 10 days	112 (44.8%)
	More than 10 days	82 (32.8%)
Target BP achieved based on ISH 2020 guideline	Yes	75 (18.5%)
	No	331 (81.5%)
Antihypertensive regimen	Monotherapy	136 (33.5%)
	Two drug combination	234 (57.6%)
	Three and more drug combination	36 (8.8%)

3.2. Cost of hypertension

3.2.1 Direct (medical and non-medical) costs

Direct medical costs include program costs, cost of drugs for hypertension and comorbidities, laboratory costs, hospitalization costs, annual outpatient visit costs, and costs of medical supplies. A total of $US 64,837.48 direct cost was incurred due to hypertension. Out of this, 80.0% ($US 51,915.40) was direct medical cost. From direct medical costs, annual outpatient visit cost 33.55% ($US 17,419.73), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($US 4,263.29) took the largest share. While, total direct non-medical costs of hypertension was $US 9,866.58 (i.e. transportation costs and patient time costs due to care). The regional and national annual estimated direct cost of hypertension were $US 324,187.40 and $US 2,161,249.33 respectively (Table 2).

Table 2: Direct annual costs of treating hypertension among adults in Southern Ethiopia, January 2021 (n=406)

Cost category	Annual total in ETB Total (mean ± Standard deviation)	Annual cost in July 2021 USD	Percentage from total direct cost
Direct medical total	**2,258,319.97**	51,915.40	80.0%
Program costs	403,275.70 (993.0 ± 0.00)	9,173.40	
Cost of antihypertensives	119,847.64 (295.19 ± 107.78)	2,726.20	
Cost of drugs for comorbidity	598,409.00 (2266.7 ± 1114.52)	13,612.15	
Cost for hospitalization	179,377.03 (3360.76 ± 1594.69)	4,080.33	
Laboratory tests	187,420.00 (461.63 ± 226.98)	4,263.29	
Annual outpatient visit costs	765,795.60 (1886.20 ± 0.00)	17,419.73	
Cost of medical supplies	4,195.00 (85.60 ± 0.00)	95.42	
Professional time total	**128,362.01**	2,950.85	4.6%
Physician time	92,032.08 (226.68 ±0.00)	2,093.47	
Nurse time	2,060.28 (43.84 ± 17.81)	46.87	
Pharmacy time	4,453.01 (10.97 + 0.00)	101.29	
Laboratory time	29,816.64 (73.44 ± 0.00)	678.25	
Direct non-medical costs	**433,748.59** (1068.84 ± 384.78)	9,866.58	**15.37%**
Total direct cost of treated hypertension	2,820,430.57	64,837.48	100.00%

1USD= 43.9614 ETB on July 13, 2021

ETB: Ethiopian Birr; USD: United States Dollar

3.2.2. Life years lost due to premature mortality and morbidity

We determined the years of life lost due to premature mortality (excess mortality) and years of life lost due to hypertension morbidity for the productive age population (30-64 years) among a cohort of simulated adult hypertensive patients. Excess mortalities are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension. The excess mortality and years of life lost were different among the hypertensive cohort and simulated population with no hypertension. A total of 11,858 (6,159, men; 5,699 women) life years were lost due to hypertension-related premature mortality among 30-64 years old adults with hypertension. This equates $US 428,969.78 ($US 270,076.91, men; $US 158,892.78). The estimated regional and national life years lost due to premature mortality was 59,290 and 395,267 respectively. This is equivalent to $US 2,144,848.58 and $US 14,298,990.51 respectively. From 15,232 years lost due to premature mortality in the hypertension cohort, treated and uncontrolled hypertension accounted for more than 6,824 (44.8%) total yeas lost due to premature mortality followed by treated controlled hypertension 5,832 (38.29%) and untreated hypertension 2,575 (16.9%) (Table 3 and 4).

Table 3: Excess deaths among adult hypertensive by treatment and control status over the working lifetime simulated from life table modelling in Southern Ethiopia January 2021

Age group	Deaths in hypertension cohort	Deaths in 'hypertension cohort' assuming no hypertension	Excess deaths in those with hypertension	Deaths in those with to hypertension by treatment and control status *		
				Treated and controlled	Treated and uncontrolled	Untreated
Men						
30-34	1,436	448	988	487	654	295
35-39	1,180	381	799	401	537	242
40-44	1,027	428	599	357	479	191
45-49	1,735	224	1,511	1,167	405	163
50-54	989	166	823	370	496	123
55-59	731	123	608	273	367	91
60-64	932	101	831	362	443	127
Total	8,030	1,871	6,159	3,417	3,381	1,232
Women						
30-34	1,401	415	986	434	657	310
35-39	1,187	212	975	368	556	263
40-44	1,019	287	732	324	490	205
45-49	832	279	553	265	400	167
50-54	887	91	796	350	400	137
55-59	805	72	733	277	419	109
60-64	1,071	147	924	396	521	154
Total	7,202	1,503	5,699	2,414	3,443	1,345
Box sex total	15,232	3,374	11,858	5,831	6,824	2,577
* Excess deaths are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension						

Table 4: Years of life lost (YLL) by adults with hypertension by treatment and control status over the lifetime simulated from life table modelling in Southern Ethiopia, January 2021

Age group	Years of life lived in treated hypertension cohort	Years of life lived in 'hypertension cohort' assuming no hypertension	YLL lost to Treated hypertension (excess)	YLL lost due to hypertension by treatment and control status *		Years of life lived in untreated hypertension cohort	YLL lost due to Untreated hypertension
				Treated and controlled	Treated and uncontrolled		
Men							
33-39	199.87	181.2	18.67	141.34	NA	122.67	58.53
40-44	357.48	324.1	33.38	235.09	17.71	219.42	104.68
45-49	587.08	522.5	64.58	NA	418.31	353.73	168.77
50-54	341.9	295.3	46.6	NA	246.52	199.92	95.38
55-59	161.63	140.1	21.53	NA	116.38	94.85	45.25
60-64	129.88	109.4	20.48	NA	94.54	74.06	35.34
Total	1777.84	1572.6	205.24	376.43	893.46	1,064.65	507.95
Women							
33-39	318.33	288.6	29.73	225.11	NA	195.38	93.22
40-44	791.95	718	73.95	560.04	NA	486.09	231.91
45-49	1147.34	1040.2	107.14	NA	811.36	704.22	335.98
50-54	953.59	863.8	89.79	NA	674.58		279.01
55-59	491.71	445.8	45.91	NA	347.72	309.52	143.99
60-64	297.81	270	27.81	NA	210.6	182.79	87.21
Total	4,000.73	3626.4	374.33	785.15	2,044.26	1,878.00	1,171.33
Grand total	5,778.57	5199	579.57	1161.58	2,937.72	2,942.65	1,679.28

NA= No patient is reported in this age group; * YLL=years of life lost by those with hypertension compared to the same cohort assuming no hypertension.

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension morbidity. This equates to $US 19,436.56. A total of 11,858 (6,159 men; 5,699 women) years of life were lost due to hypertension related premature mortality. This equates to $US $429,958.12. Total productivity loss due to premature mortality and morbidity was $US 449,394.68 (Table 5). Treated and uncontrolled hypertension accounted for 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). Treated uncontrolled hypertension contributed to more YLL due to premature mortality in both sexes 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378 (50.84%) (Figure 2).

The overall estimated hypertension related economic burden (direct and indirect cost) was $US 514,232.16 in the study area (Table 2 and Table 5). Since the study population is estimated to be 20% of the Southern region, the estimated economic burden of hypertension in the region is $US 2,571,160.8 in the region. More than eight out of ten 87.37% dollars were due productivity loss. Productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB (Table 5).

Table 5: Mean annual productivity loss associated premature mortality and hypertension morbidity, Southern Ethiopia, January, 2021

Variable	Sex	Excess Years lost	Lost productivity ETB	Lost productivity in 2021 USD
Years lost due to premature morality	Male	6,159	11,748,345.71	$270,699.21
	Female	5,699	6,911,836.90	$159,258.91
	Both	11,858	18,660,182.62	$429,958.12
Years lost due to hypertension morbidity	Male	205.24	391,497.07	$8,999.93
	Female	374.33	453,993.32	$10,436.63
	Both	579.57	845,490.39	$19,436.56
	Total productivity loss		19,505,673.01	$449,394.69
1USD=43.5 ETB				

Note: productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB

4. Discussion

In this prevalence-based retrospective cost of illness study, we estimated the economic burden of hypertension among productive age population from societal perspective. A total direct (medical and non-medical) annual cost incurred due to hypertension in the study population was $US 64,837.48 ($US 13.308 per person per month). Out of direct costs, 80.0% ($US 51,915.40) was direct medical cost. While, the total indirect annual cost incurred due to hypertension was $US 449,394.69 ($US 92.24 per person per month). The total annual economic burden of hypertension was $US 514,232.16 ($ US 105.55 per person per month). This is higher than findings from another institution-based cross-sectional study conducted to evaluate cost of hypertension illness among patients attending hospitals in Southwest Shewa Zone that showed the mean monthly total cost of hypertension illness was US$ 22.3 (95% CI, 21.3–23.3) (61). Findings from an institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that total cost of hypertension was $91.72 ± 78.65 per patient per year (62). The COI study conducted among 202 hypertensive patients in Ghana that showed the total annual treatment cost of hypertension was $US 76,275.60 ($US31.47 per person per month) (63). However, this is less than findings from and a study conducted in Canada also showed that annual individual healthcare cost of hypertension was $ US 2,341 (64), and study conducted in the USA showed that individuals with hypertension had $ US 1,920 higher annual incremental expenditure (65). This variation could be explained by variation in socioeconomic status and population health status, and our findings could underestimate both costs and health-related life loss due to the asymptomatic nature of hypertension (66), a significant number of undiagnosed hypertension among adults, and difference in health care system and level of care.

In this study, indirect cost accounted for more than three fourth of hypertension-related costs 85.6% ($449,394.69 USD). This is against evidence generated by a cross-sectional study conducted to determine the burden of out-of-pocket payments among patients with cardiovascular disease in public and private hospitals in Ibadan, South West, Nigeria showed that across all the hospital facilities, the annual direct and indirect outpatient costs were $1164.2± $2363.8 and $52.87±$148.05 respectively (67). An institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that the direct medical and non-medical cost constituted 60.81% and 12.17% of the total cost of hypertension respectively (62). An institution-based cross-sectional study conducted to evaluate cost of hypertension Illness among Patients Attending Hospitals in Southwest Shewa Zone showed that the mean monthly total cost of hypertension illness was US$ 22.3 (direct cost of US$ 11.39 and indirect cost US$ 10.89) (61). This is also higher than evidence that suggested about a half of the costs associated with CVD burden are caused by direct healthcare costs (68). The findings from a study conducted in Ghana direct cost accounting for almost 70% of the total cost of managing hypertension (63). Similarly, a study conducted in rural Yunnan Province of China showed that direct costs represented the largest component of the economic cost of hypertension (69). The variation could be explained by significant number of productive age populations affected hypertension in the study area and poor blood pressure control. Therefore, it is important to promote existing strategies and develop country/region-specific strategies for hypertension prevention and control (i.e., annual screening of the high-risk population and promoting healthy lifestyles) by all stakeholders could reduce the economic burden of hypertension Ethiopia (70, 71).

Concerning pre-mature mortality, a total of 11,858 (6,159, men; 5,699 women) years were lost due to hypertension-related premature mortality. This equates $US 429,958.12. Concerning health-related life loss, about 26,678 deaths per study population were due to hypertension. This is higher than the number of hypertension-related death occurred in 2017, which as 11,050 (7). This could be explained by the increasing trend of hypertension in the country.

From 15,232 years lost due to premature death in the hypertension cohort. More than two-third of related deaths, 12,656 (83.08%) were due to treated hypertension. Treated and uncontrolled hypertension contributed to premature mortality 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378(50.84%) in both sexes. This is supported by evidence from other studies that revealed uncontrolled blood pressure cost $370 billion globally in 2001 (72). This is because the relative risk of all-cause mortality is higher among treated and uncontrolled (1.62) than untreated (1.40) and treated controlled (1.12) patients (53).

Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for one-half 2,937.72 (50.84%) of productive life years lost. This is higher than findings from a study conducted to estimate the economic burden of hypertension in a given year in rural

Yunnan Province of China showed that the overall prevalence of and YLL/1000 population because of hypertension was 24.8% and 1.5 years for the survey population, respectively (69). A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension. The estimated national life years lost due to hypertension is 19,319 (i.e., $846,413.56 USD). This is supported by evidence from a study conducted Australia that revealed hypertension caused 609, 801 productivity-adjusted life years loss (equating to AUD$ 137.2 billion) over the working lifetime (73). Therefore, prevention of hypertension and improving the rate of blood pressure control is important to reduce hypertension-related complications and productive life-year loss in the region as well as in the country (74).

5. Conclusion

The societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars economic burden. Prevention of hypertension could result in $US 2,571,160.8 annual economic savings in the Southern Region. Therefore, designing and implanting strategies for prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels (national, regional, zonal, community, and patient-level) is critical to saving scarce health resources.

6. Abbreviations

BP: Blood Pressure

CPG: Clinical Practice Guideline

CVD: Cardiovascular Diseases

DALY: Disability Adjusted Life Years

DBP: Diastolic Blood Pressure

EDHS: Ethiopia Demographic Health Survey

HDL: High-Density Lipoprotein

ICER: Incremental Cost-Effectiveness Analysis

LDL: Low-Density Lipoprotein

LMICs: Low- and Middle-income Countries

MI: Myocardial Infarction

QALY: Quality Adjusted Life Years

SBP: Systolic Blood Pressure

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

YLD: Years Lived with Disability

YLL: Years of Life Lost

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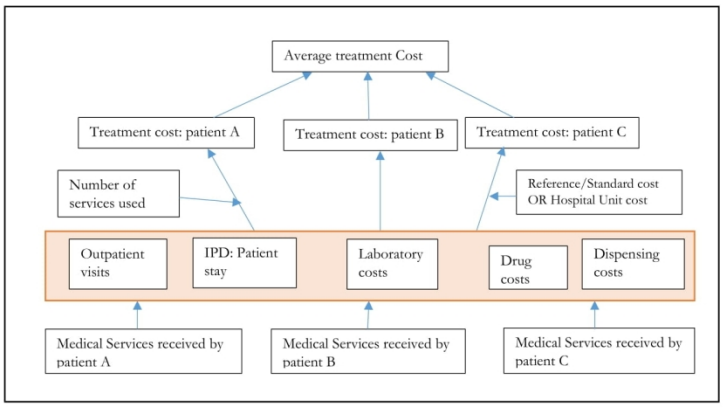
Legends

List of Figures

Figure 1: Micro-costing Bottom-up Approach for Healthcare costs. Adapted from Riewpaiboon A, et al. Cost analysis for efficient management: diabetes treatment at a public district hospital in Thailand.

Figure 2: Number of premature deaths and years of life lost (YLL) due to morbidity among adults with hypertension by sex, treatment and control status over productive life years simulated from life table modelling in Southern Ethiopia



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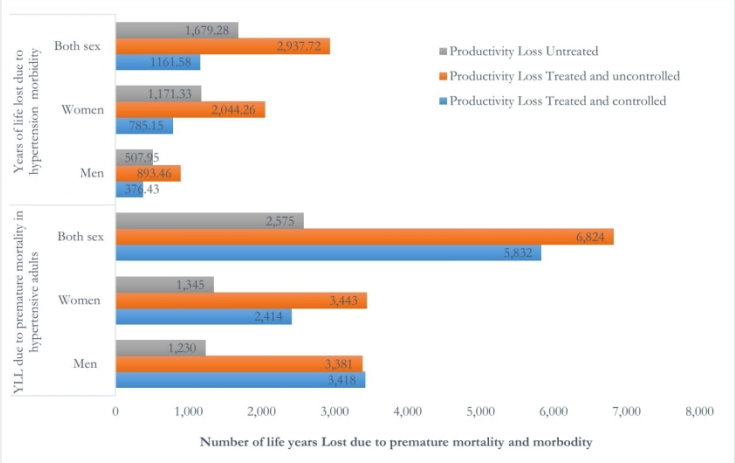

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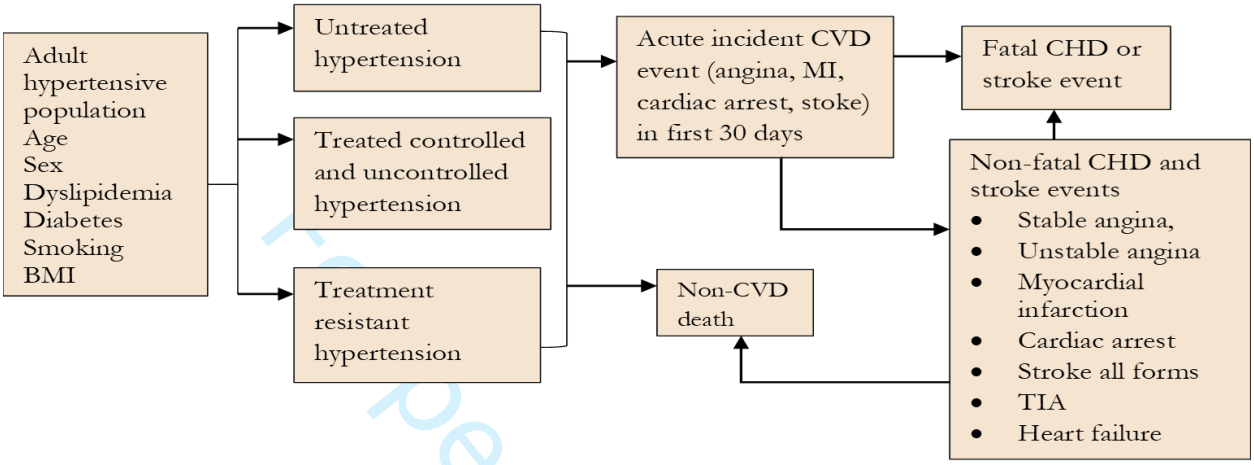
Supplementary materials: Economic burden of hypertension at selected Hospitals in Southern Ethiopia; a patient level analysis

Cardiovascular disease policy model



Supplementary Figure 1: Cardiovascular disease policy model adapted for Sub-Saharan African perspective (1).

Supplementary Table 1: Age and sex specific distribution of Ethiopian population 2020 estimate, prevalence of hypertension and adult mortality rate

Age structure	Male	Female	Total	Estimated prevalence of hypertension	Mortality rate		Data Source
Prevalence of hypertension					Men	Women	(2-8)
0-14 years	21,657,152	21,381,628	43,038,780	NA	-	-	
15-19	5,572,330	5,464,174	11,036,504	19.6	0.00286	0.00222	
20-24	5,930,683	5,816,173	11,746,856	19.6	0.00319	0.00223	
25-29	4,889,739	4,802,450	9,692,189	19.6	0.00293	0.002.32	
30-34	3,761,349	3,757,544	7,518,893	23.0	0.00397	0.003.68	
35-39	3,091,148	3,182,837	6,273,985	23.0	0.00411	0.00222	
40-44	2,445,523	2,488,422	4,933,945	25.9	0.00584	0.00385	
45-49	2,071,480	2,033,228	4,104,708	25.9	0.00360	0.00457	
50-54	1,567,789	1,660,957	3,228,746	41.9	0.00354	0.00274	
55-59	1,159,002	1,316,318	2,475,320	41.9	0.00354	0.00274	
60-64	946,594	1,109,670	2,056,264	41.9	0.00354	0.00274	
≥ 65 years	1,676,478	1,977,857	3,654,335	41.9	0.00354	0.00274	
Total	54,769,267	54,991,258	109,760,525				
				Prevalence of untreated hypertension			
For all ages (15 +)				13.25			(9)

Supplementary Table 2. Model Parameters, Cohort Setting, and Probability of Transition between states and Disability weights for hypertension and related complications the Global Burden of Disease 2013 study and WHO Global Health Estimates

Parameter	Data	Source
Relative risk of hypertension treatment		
Relative risk of CHD event on hypertension treatment	0.683 (95% CI, 0.633–0.717)	(10-13)
Relative risk of a cerebrovascular event on hypertension treatment	0.633 (95% CI, 0.526–0.717)	(14)
Relative risk of CHD event on normotensive men and women	0.49 (95% CI 0.458–0.513) and 0.32 (0.292–0.342)	(15)
Transition probabilities to death		
Health state	**Disability weight Estimate**	**Source**
Hypertension		**(16)**
Treated	0.246	
Untreated	0.323	
Treated and controlled	0.171	
Myocardial Infarction (MI)		(17)
Day 1-2	0·432	
Days 3-28	0·074	
Angina Pectoris		
Mild	0·033	
Moderate	0·080	
Severe	0·167	
Heart failure		
Mild	0·041	
Moderate	0·072	
Diabetes, digestive, and genitourinary disease		
Diabetes	0.015 (0.012 - 0.018)	(18-20)
Treated	0.033	
Untreated	0.012	

Diabetic neuropathy	0.133	
Chronic kidney disease (stage IV)	0.104	
End-stage renal disease: with kidney transplant	0.024	
End-stage renal disease: on dialysis	0.571	
Disutility due to daily medication	0.049 (0.031–0.072)	
Acute Events		
Myocardial Infarction	0.432 (0.288–0.579)	
Stroke	0.570 (0.377–0.707)	
Occurrence of second or later CVD event	0.985 (0.992–0.989)	
Chronic States		
Ischemic Heart Disease	0.08 (0.02–0.24)	
Stroke	0.135 (0.01–0.437)	
Alive post 2+ CVD Events	0.242 (0.11–0.437)	

CHD, coronary heart disease; SMR, standardized mortality ratio. *Age and sex dependent †Applied multiplicatively to general population age- and sex-dependent utilities; CHD= Angina pectoris, coronary insufficiency, myocardial infarction, or coronary death.

Supplementary table 3: Simulation input parameters

Input parameter	Value	Source
Non-CVD death rate	0.005–0.176 (Age- and sex specific)#	Calculated from WHO lifetables and GBD 2017 (21)
Probability of first-time cardiovascular disease (CVD) event	Individual risk characteristic specific	Obtained from the Globorisk Office Calculator standardized for India [25]
Acute CVD events		
MI		
Probability of MI if CVD event occurs	37.6– 66.7% (Age- and sex specific)#	Calculated based on GBD 2017(21)
30-day fatality	0.01–0.13 (Age- and sex–specific)#	Calibrated based on findings of Huffman et al. 2018 (22)
Re-infarction (in 30 days)	0.0120 (0.0099–0·0141)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Acute Stroke (in 30 days)	0.0060 (0.0045–0.0075)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Stroke		
Probability of Stroke if CVD event occurs	33.2–62.3% (Age- and sex specific)#	Calculated based on GBD 2017 (21) And Jushua D. Bundry et al(23)
30-day fatality	0.12, 0.13 (Sex-specific)#	Calibrated based on a multi-site study by Pandian and Sudhan 2013 [30]
Repeat Stroke (in 30 days)	0.15 (0.1–0.2)ψ	Petty et al. 1998 (24)
Sudden cardiac death	0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years	Heart disease and stroke statistics 2021 update
Heart failure		
Probability of AHF		
30-days fatality	0.0945	Obtained from the THESUS-HF registry (25) and Korean Acute Heart Failure Registry (KorAHF)(26, 27)

Re-hospitalization	0.0736	Obtained from the THESUS-HF registry (25)
Chronic events		
Monthly risk of mortality	0.001–0.019 (Age- and sex-specific)#	Calibrated based on GBD 2017 (21)
Reinfarction	0.079 (0.073–0.085)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.014 (0.012–0.016)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20) Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) (29), BP reduction and secondary stroke prevention: systematic review(30)
Stroke		
Monthly risk of mortality	0.001–0.013 (Age- and sex specific)#	Calibrated based on GBD 2017 (21) Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study(31)
Acute MI	0.043 (0.038–0.048)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.037 (0.033–0.041)	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Relative risk of fatality for an individual with two or more CVD events	1.5	Smolina et al. 2012 (32)
Heart failure		
Incidence		Bulter J.et al (33, 34), and Davis BRK. et. al (35)
1 year mortality		
Re-hospitalization		**Moita B.eta al. 2019(36) and (37)**
Effect of antihypertensive medication		
Medication protocol for an individual	Initial SBP-specific#	Based on Ethiopian NCD control guideline
IHD relative risk due to medication	0.32–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009 (38) and Asayam Kei., 2017(39)
Stroke relative risk due to medication	0.20–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009(38)
IHD relative risk if partially adherent	0.66–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009(40)
Stroke relative risk if partially adherent	0.60–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009 (40) and Lisheng Liu, Zengwu Wang. et al(41)

Supplementary Table 4: Price of drugs, medical supplies, procedures and professional time used for management of hypertension in Southern Ethiopia, January, 2021

List of medicines	Unit	Price in 2021 Ethiopian birr		Price USD	Source
		Wholesale price	Retail price	Retail Price in 2021 USD	
Acetylsalicylic Acid - 81mg – Tablet (coated)	10x10	43.72	1.32	1.303	Ethiopian Pharmaceutical supply agency, Arba Minch Hub wholesale price 2021 and Arba Minch General hospital pharmacy retail price 2021
Adrenaline (Epinephrine)-0.1% in 1mL ampoule	Each	36.032	1.09	1.074	
Amiodarone - 100mg – Tablet	10x3	313.34	9.44	9.337	
Amlodipine - 10mg - Tablet	10x10	105.44	3.18	3.142	
Amlodipine - 5mg – Tablet	10x10	75.26	2.27	2.243	
Atenolol - 50mg – Tablet	10x10	58.70	1.77	1.749	
Atorvastatin - 20mg – Tablet	10x10	195.68	5.89	5.831	
Atorvastatin - 40mg – Tablet	10x3	140.76	4.24	4.195	
Beclomethasone Propionate -100mcg/dose – Aerosol	200 MD	131.85	3.97	3.929	
Candesartan - 8mg – Tablet	14x2	152.63	4.60	4.548	
Captopril - 12.5mg – Tablet	10x10	33.54	1.01	1.000	
Captopril - 25mg – Tablet	10x10	26.91	0.81	0.802	
Dexamethasone - 4mg/ml in 1ml Ampoule - Injection	10	3.95	0.12	0.118	
Captopril + HCT (50mg + 25mg)-Tablet	10x10	57.32	1.73	1.708	
Digoxin - 0.25mg – Tablet	10x10	202.18	6.09	6.025	
Enalapril Maleate - 10mg - Tablet	10x10	61.57	1.85	1.835	
Enalapril Maleate - 5mg – Tablet	10x10	63.92	1.93	1.905	
Enalapril Maleate – 2.5mg – Tablet	10x10	19.98	0.60	0.595	
Enalapril Maleate +HCT (10 mg + 25 mg)-tablet	10x10	78.22	2.36	2.331	
Glibenclamide - 5mg – Tablet	10x10	39.09	1.18	1.165	
Glucose 40% in 20 mL – IV infusion	Each	2.54	0.08	0.076	
Glyceryl Trinitrate - 0.4mg – Tablet (Sublingual)	100	487.21	14.67	14.518	
Hydralazine - 20mg/ml in 1ml ampoule - Injection	5	204.01	6.14	6.079	
Hydrochlorothiazide - 25mg – Tablet	25x4	48.05	1.45	1.432	
Insulin Isophane Biphasic (Soluble/Isophane Mixture)-(30 + 70)IU/ml in 10ml Vial -Injection(Suspension)	Each	85.20	2.57	2.539	
Insulin Isophane Human - 100IU/ml in 10ml Vial - Injection(Suspension)	Each	100.28	3.02	2.988	
Insulin Soluble Human - 100IU/ml in 10ml Vial	Each	106.21	3.20	3.165	
Lovastatin - 20mg – Tablet	10x10	84.59	2.55	2.521	
Metformin - 500mg – Tablet	10	27.78	0.84	0.828	
Methyldopa - 250mg – Tablet	100x10	51.75	1.56	1.542	
Metoprolol - 50mg – Tablet	10x10	94.43	2.84	2.814	
Morphine sulphate-30mg-tablet	110	410.71	12.37	12.239	
Nifedipine - 20mg – Tablet	10x10	58.70	1.77	1.749	
Prednisolone - 5 mg – Tablet	100x10	342.23	10.31	10.198	
Propranolol - 40mg – Tablet	10x10	67.54	2.03	2.013	
Propylthiouracil - 100mg - Tablet (Scored)	100	633.87	19.09	18.889	
Salbutamol - 0.1mg/dose - Aerosol (Oral Inhalation)	200 MD	117.20	3.53	3.492	
Spironolactone - 25mg – Tablet	10x10	81.87	2.47	2.440	
Thyroxin Sodium - 0.1mg – Tablet	100	178.49	5.38	5.319	
Valsartan + HCT (80mg +12.5mg)	7*2	38.47	1.16	1.146	
Laboratory and imaging costs		**Price per test ETB**		Price in 2021 USD	
CBC		75.00		1.72	Arba Minch General Hospital Laboratory service price 2021
FBG/RBS		20.00		0.46	
Lipid profile (LDL, HDL, Total cholesterol, Triglyceride)		160.00		3.68	
ECG		120.00		2.76	
ECO		350.00		8.05	
CT-scan		1200		27.59	
RFT (bilirubin, creatinine)		80.00		1.84	
Chest-ray		726		16.69	
Urine analysis		15.00		0.34	
Body fluid analysis		100.00		2.30	
H. pylori		50.00		1.15	

Liver function test (AST, ALT, ALP)	120.00	2.76	
Thyroid function test (T3, T4, TSH)	432.00	9.93	
Hospital bed days			
Primary hospital	52.52	1.21	WHO Choice (42) inflated to 2021
Secondary hospital	54.76	1.26	
Tertiary hospital	70.81	1.63	
Health facility visit		0.00	
Primary hospital	18.58	0.43	
Secondary hospital	21.17	0.49	
Tertiary hospital	22.06	0.51	
Health center visit	23.00	0.53	
PCI intervention	63,000.00	1448.28	
In-patient costs for MI	45240.00	1040.00	
In-patient costs for Stroke	40890.00	940.00	
Outpatient cost for IHD (per annum)	1957.50	45.00	
Outpatient cost for Stroke (per annum)	2914.50	67.00	
Salary scale of human resource		0.00	
Physician	21,100.00	485.06	MOH, Ethiopia 2012/2019
Acute care nurse	7470.00	171.72	
Pharmacy personnel	8047.00	184.99	
Laboratory technician	6460.00	148.51	
Program cost per person per annum	993.29	22.83	(43).
Antihypertensive treatment			
Antihypertensive medication (per individual per annum	Drug costs based on national Drug supply agency wholesale price		
Out-patient consultations (per visit)	$43.36	Annual outpatient visit cost (12*WHO cost per outpatient visit inflated to 2021) WHO Choice (42)	
One-time diagnostic tests		Based on Laboratory procedures and test price of Arba Minch General Hospital, 2021	
In-patient costs for MI	$1040	WHO Choice (42) inflated to 2021	
In-patient costs for Stroke	$940		
Chronic CVD care			
Secondary care medication in public sector (per individual per annum)	$92, $184 (Dosage-specific)§	MSH-2015 International Drug Price Indicator inflated to 2021(25)	
Outpatient cost for IHD (per annum)	$45	WHO Choice (44) inflated to 2021	
Outpatient cost for Stroke (per annum)	$67		
Average inflation rate Ethiopia	16.58%	https://take-profit.org/en/statistics/inflation-rate/ethiopia/	
Average inflation rate foreign	2.02%		
Percentage change	24.6%		
Exchange rate July 2021 (1USD)	43.5 ETB		
1USD = 20.999 ETB in 2016 and 43.5 in 2021; PPP= 12.1/8.1 = 1.5			
MD: metered Dose; MOH: Ministry of Health 1 USD = 43.5 January 2021 **Note**: 30% mark-up at regional EPSA hub, 31% mark-up at Public Hospital level			

Supplementary Table 5: Risk of death across age and gender covariate categories stratified for hypertension

Variables	Categories	Incidence of death (%)		Relative risk in each category (CI)	Source
		High BP group	Normal		
Age	20-29	1.68%	0.54%	3.11 (1.16-8.36)	*(8)*
	30-39	1.71%	0.94%	1.82 (1.04-3.19)	
	40-49	2.43%	1.88%	1.29 (0.91-1.82)	
	50-59	6.30%	4.03%	1.56 (1.28-1.91)	
	60 and above	19.32%	15.9%	1.21 (1.12-1.31)	
Gender	Women	8.71%	1.1%	3.31 (2.98-3.68)	
	Men	15.47%	4.62%	3.34(3.02-3.70)	
Risk of all case mortality					
Gender	Treatment status	< 60 years	> 60 years	HR (95% CI)	(45)
Men	Normal	0.0068	0.0214	1.00 (Reference)	
	Treated controlled	0.0188	0.0305	1.20 (0.92-1.57)	
	Treated uncontrolled	0.0252	0.0372	1.55 (1.19-2.01)	
	Untreated	0.0197	0.0336	1.45 (1.23-1.72)	
Women	Normal	0.00528	0.01870	1.00 (Reference)	
	Treated controlled	0.01675	0.02841	1.11 (0.84-1.47)	
	Treated uncontrolled	0.02533	0.03736	1.63 (1.34-1.99)	
	Untreated	0.02075	0.03471	1.31 (1.06-1.61)	

Supplementary Table 6: Annual mortality rate in the total population, those with hypertension by treatment and control status and those without hypertension in Ethiopia in 2021 by age group and sex based on literature review of systematic reviews and clinical trials

Age group	Mortality rate in the total population	Mortality rate among people without hypertension	Mortality rate among people with treated and controlled hypertension	Mortality rate among people with treated but uncontrolled hypertension	Mortality rate among people with untreated hypertension	References
Women						
15-19	0.00222	0.00222	0.016746	0.025	0.02075	Ko, Min Jung. et al. 2016 (46), Mende Sorato, et al, 2021. (1, 23, 45, 47, 48).
20-24	0.00223	0.00223	0.016746	0.025	0.02075	
25-29	0.00232	0.00232	0.016746	0.025	0.02075	
30-34	0.00368	0.00368	0.016746	0.025	0.02075	
35-39	0.00222	0.00222	0.016746	0.025	0.02075	
40-44	0.00385	0.00385	0.016746	0.025	0.02075	
45-49	0.00457	0.00457	0.016746	0.025	0.02075	
50-54	0.00182	0.00182	0.016746	0.025	0.02075	
55-59	0.00182	0.00182	0.016746	0.025	0.02075	
60 -64	0.00441	0.00441	0.028414	0.037	0.03471	
Men						
15-19	0.00286	0.00286	0.018783	0.025	0.01969	Kuriakose A. et al. 2014. (8), EDHS, 2016 (7, 45, 47-50)
20-24	0.00319	0.00319	0.018783	0.025	0.01969	
25-29	0.00293	0.00293	0.018783	0.025	0.01969	
30-34	0.00397	0.00397	0.018783	0.025	0.01969	
35-39	0.00411	0.00411	0.018783	0.025	0.01969	
40-44	0.00584	0.00584	0.018783	0.025	0.01969	
45-49	0.0036	0.0036	0.018783	0.025	0.01969	
50-54	0.00354	0.00354	0.018783	0.025	0.01969	
55-59	0.00354	0.00354	0.018783	0.025	0.01969	
60-64	0.00354	0.00354	0.030451	0.037	0.03365	

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Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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	Reporting Item	Page Number
Title		
#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1

Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	1
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	2
Methods			
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	3-10
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	9

Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	10
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	NA
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	4-6
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	NA
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use	NA

		associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	
Methods			
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Supplementary figure 1
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	9

Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-15
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	NA

Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	23

Notes:

- 15: Supplementary figure 1 The CHEERS checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 20. August 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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I. Abstract

Objectives: There is inadequate information on the economic burden of hypertension treatment in Ethiopia. Therefore, this study was conducted to determine the societal economic burden of hypertension at Selected Hospitals in Southern Ethiopia.

Methods: Prevalence-based cost of illness (COI) study from a societal perspective was conducted. Disability-adjusted life years (DALYs) were determined by the current world health organization's recommended DALY valuation method. Adjustment for comorbidity and a 3% discount was done for DALYs. The data entry, processing, and analysis were done by using SPSS version 21.0 and Microsoft Excel 2013.

Results: We followed a cohort of 406 adult hypertensive patients retrospectively for 10 years from September 2010 to 2020. Two hundred-fifty (61.6%) of patients were females with a mean age of 55.87 ± 11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their blood pressure control target. A total of 64,837.48 United States Dollar ($US) direct cost was incurred due to hypertension. A total of 11,585 years and 579.57 years were lost due to hypertension-related premature mortality and morbidity respectively. Treated and uncontrolled hypertension accounted for 50.83% (6027) of total years lost due to premature mortality from treated hypertension cohort. Total productivity loss due to premature mortality and morbidity was $US 449,394.69. The overall economic burden of hypertension was $US 514,232.16 ($ US 105.55 per person per month)

Conclusion: Societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Therefore, designing and implanting strategies for the prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels is critical to saving scarce health resources.

Strengths and limitations of this study

- Using the cardiovascular disease policy model adapted to Sub-Saharan African perspective,
- Including productivity loss costs associated with hypertension (premature mortality and morbidity) and
- Obtaining all simulation variables and transition probability data from valid sources (systematic reviews, randomized controlled trials, and prospective cohort studies) were the strengths of this study
- Uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate which require due consideration during applying the findings of this study were limitations.

1. Introduction

Hypertension doubles the risk of death from stroke, heart disease, vascular diseases, diabetes, atherosclerosis, and kidney disease (1). According to the national STEPS survey, only 28.4% of hypertensive patients were taking antihypertensive medication prescribed by professionals in Ethiopia (2). According to the International Society of hypertension global hypertension practice guideline 2020, hypertension remains the leading cause of death globally, accounting for 10.4 million deaths per year (3).

Hypertension is associated with societal and economic consequences particularly in Low and middle-income countries (LMICs). In addition to the direct costs associated with health care utilization for the management of complications, hypertension causes significant productivity loss from disability and premature death (4, 5). WHO report from South East Asian region also indicated huge impact of hypertension in national finances due to premature death, disability, personal and family disruption, loss of income, and healthcare expenditure (6). According to a WHO report in 2017, stroke, coronary heart disease, and hypertension caused 39,571, 46,943, and 11,050 deaths respectively (i.e. 30 patients per day die due hypertension) in Ethiopia (7).

Cost of illness (COI) study is used to measure the economic burden of disease to individuals, communities, and society as a whole. It can provide information to support the political process and healthcare decision-making if it is conducted from a societal perspective by using an appropriate approach and bottom-up costing strategy (8-10) (11, 12). Despite this huge impact on national economies, the economic burden of hypertension is not studied in Ethiopia particularly Southern Ethiopia. To fill this evidence gap, this study was conducted to determine the economic burden of hypertension at selected public hospitals in Southern Ethiopia by using the prevalence-based cost-of-illness method from a societal perspective to estimate the direct and indirect costs of hypertension in a given year (2021) in Southern Ethiopia.

2. Methods and Materials

2.1. Study design, Area and Period

A prevalence-based retrospective cost of illness study from societal perspective focusing on quantifying direct and indirect costs was conducted from September 2010- September 2020 in at three selected public hospitals Southern Ethiopia. The bottom-up approach was used to estimate the economic burden of hypertension in Southern Ethiopia (figure 1). The human capital approach was used to calculate indirect costs separately in males and females and also among different age groups. A prevalence-based COI model was constructed in which hypertensive patients were simulated from diagnosis through active treatment, palliative care, and death over 15-64 years. Age and sex-specific mortality rates, measures of productivity, and workforce statistics were used to simulate the progression of these cohorts until death or age 64 years. First, the model estimated cumulative years of life and DALYs lived for the working-age population who had hypertension. Then the

model re-simulated with the hypothetical assumption that they did not have hypertension, with relevant changes to mortality rates and productivity. We estimated the probability of death separately for (1) all-cause mortality in absence of hypertension and related complications and (2) mortality attributable to the included disease states. The first component was estimated using WHO Life Tables, and the second component was calculated based on standardized mortality ratios extracted from the literature. The natural history study conducted in 1974 showed that the mortality rate was 1.85 (3.01 in males and 1.62 in females) (13). Interventional trials suggested that it could be possible to achieve effective BP targets in about 70% of patients by improving adherence and/or intensifying therapy (14).

2.2. Study populations

The study populations were selected adult hypertensive patients at three selected public hospitals. According to the world population prospect 2020 estimate (15). In the same year, the population of the Gamo zone accounted for 1.5% of the total population, Gofa, and South Omo Zone 1.5% of the total population. The target population is 3.0% total population of Ethiopia or 20% of the Southern Ethiopian population (6,208,034). Based on age distribution: 0-14 years are children, 15-24 years are early working age, 25-54 years are prime working age, 55-64 years are mature working age and ≥ 65 years are elderly (13).

2.3. Inclusion and exclusion criteria

We included all adult hypertensive patients having at least five years of follow-up visits before data collection and receiving care during the study period from selected facilities. However, patients who are unwilling to participate in this study, patients who have less than five years of follow-up, and incomplete patient records (don't contain follow-up BP records and refill medications, laboratory requests, and results) were excluded.

2.4. Study Variables

Dependent Variables

- Economic burden of hypertension

Independent variables

- Patient-related (socio-demographic characteristics, heart disease knowledge, healthy lifestyle and heart disease risk perception, presence of comorbidity, type of medications, treatment adherence, shared decision making, health-related quality Life)

Cost related variables

- **Medical costs** (inpatient hospital stay/hospitalization cost, outpatient clinic visit, drug acquisition costs, drug administration cost, laboratory test, and imaging study costs)

- **Non-medical costs** (transportation, meal, patient time cost due to treatment, cost due informal care by family or friends)
- **Indirect costs** (absenteeism, presenteeism, unemployment, early retirement, disability, premature death)

2.5. Sample Size and Sampling Technique

2.5.1. Sample size determination

The sample size was determined by using the single population proportion formula by taking prevalence of patients controlled their BP as 14% from WHO 2016 BP control rate report (16-18) and Z value of 1.96 at 95% confidence interval. We added 10% for non-response rate and two for design effect due to multi-stage sampling technique involvement. Finally, a formula giving a larger sample size was used. Total 407 hypertensive adult patients who are on follow-up care will be included.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2} = 185$$

= 185 + (185 * 10%) = 203.5

= 203.5 *2 = 407

Where: **n** = is the sample size

- **Z^2**= standard normal deviation, set at 1.96, correspond to the 95% confidence interval
- **d** = is the desired level of precision/margin of error (0.05)
- **p**= prevalence of patients taking anti-hypertensive (p=28.4%), and q is 1-p.

2.5.2. Sampling Techniques

A multi-stage simple random sampling technique was used. We randomly selected three zones from a total of 12 zones found in the Southern region. Three general public hospitals with experience of providing CVD care for at least five years from selected four zones were included in this study. The total sample size was allocated to these hospitals based on an estimated number of adult hypertensive patients attending respective hospitals (i.e., we included 212 patients from Arba Minch General Hospital, 107 patients from Jinka General Hospital, and 88 patients from Sawula General Hospital). Finally, a consecutive sampling technique was applied in each facility until the desired sample size was achieved.

2.6. Data collection tools and Procedures

2.6.1. Model input parameters

Key model input variables include; 2020 population of selected zones, hypertension prevalence by treatment and control status, Transition probabilities to death and healthy state, cost of diagnosis, and management. Among those with treated hypertension, treated and controlled hypertension was defined based on BP control target of ISH 2020 guideline (3). We used national STPES survey data to estimate the prevalence of cardiovascular risk factors (MI, angina, heart failure, stroke, TIA). Incorporating the risk factor prevalence data in the relevant Framingham risk equation, the age and sex-specific probability of CHD and cerebrovascular disease (i.e., stroke and transient ischemic attack) events were estimated. The probability of each health state

was calculated using the age- and sex-specific CHD and cerebrovascular disease event distributions (2, 19). To estimate the corresponding probabilities, separate relative risk estimates were used for CHD events (Stable Angina, Unstable Angina, and MI) and cerebrovascular diseases (Stroke and Transient Ischemic Attack), assuming that antihypertensive treatment affects the probability of every disease state similarly across all age and sex groups. Relative risk reductions attributable to antihypertensive treatment were extracted from the peer-reviewed literature (20-22).

The 2020 world population prospect estimate was used for the baseline population and number of 33-year-olds projected to enter the model population from 2020-2070 (15). The annual probability of coronary heart disease and stroke was based on national STEPS survey (2), and Framingham Heart Study (23) and the Framingham Offspring Study (24), by contextualizing to Ethiopian scenario. Incident coronary heart disease events were allocated to angina pectoris, myocardial infarction, or cardiac arrest. Prevalence, joint distributions, and means of Ethiopia risk factor values were estimated from the national STEPS survey (2). Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Betas for risk function for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort (24). Risk factors are assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers are assumed to have a higher relative risk for infarction and arrest (25); and a proportionately lower coefficient for angina. Environmental tobacco exposure is assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with non-exposed non-smokers (26) but not to influence angina. The number of hospitalized MI were obtained from the national STEPS survey (2). Case-fatality rates and rates of MI in subgroups were estimated from national data and other complementary sources. Prehospital arrest deaths and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from our effectiveness study (Supplementary Table 1).

Survival after a coronary heart disease event was estimated and calibrated based on national or international data sources (27, 28). Rates of coronary revascularizations was estimated from the National hospital discharge survey, with mortalities estimated from aggregated historical data. Stroke incidence was assumed to be independent of the risk of new-onset coronary heart disease in the same year. The number of hospitalized strokes cases was obtained from national and regional studies. The annual probabilities of stroke after MI (29, 30) and the probability of coronary heart disease in stroke patients were based on natural history studies and systematic reviews of blood pressure control trials (31-36). A 30-day heart failure mortality and re-hospitalization data were from the THESEUS-HF registry (37) and Korean Acute Heart Failure Registry (KorAHF)(38, 39) (Supplementary Table 2 and 3).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2020 was estimated from the National Health Survey data (2) and GBD 2017 (40). The background prevalence of prior coronary revascularization was estimated from revascularizations before 2019 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state. Age and sex-specific health care costs were estimated using national data, and our effectiveness data. Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using WHO Choice (41) inflated to 2021. Outpatient consultations, and inpatient stay and bed days were also estimated from WHO choice (41) inflated to 2021. Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis was pooled from the 2015 national STEPS survey. Average annual non-cardiovascular costs were estimated from the national STEPS survey (2), and EDHS 2016 survey (13).

2.6.2. Cost estimation

The outcomes measures are total discounted societal costs, cost/year, and cost/patient-year. This is the amount of health budget that could be saved by effective prevention and control of hypertension. The direct costs were divided into two subcategories: direct medical costs and direct non-medical costs. Direct medical costs include; inpatient stays, outpatient clinic visits, medical services, drug acquisition, dispensing, administration, monitoring, laboratory test, and imaging study costs. The costs associated with outpatient/inpatient visits were estimated by multiplying the numbers of outpatient visits related to hypertension by the outpatient costs per year (i.e., twelve times WHO cost per outpatient visit for secondary hospitals inflated to 2021) (41).

Data concerning medications prescribed for the management of hypertension, and associated comorbidities, and laboratory tests and imaging studies were done were collected by patient chart abstraction in index year (2020). The cost of medications used for management of hypertension and associated comorbidities was taken from Ethiopian Pharmaceutical supply agency Arba Minch regional hub selling price and retail price of Arba Minch General Hospital in 2020. The retail price of Arba Minch General Hospital was used because of the minimum distance from the Pharmaceutical supply agency hub, which could minimize markup added on retail price due to transportation cost. Costs of laboratory procedures were also taken from Arba Minch Hospital Laboratory's service price list. The prices of relevant laboratory tests and imaging studies were based on the average price of included Hospitals. The salary scale of the health workforce was based on the FMOH of Ethiopia (Supplementary Table 4).

Ongoing program costs for hypertension care was estimated from WHO tool outputs for CVD and diabetes care and National strategic action plan (NSAP) for prevention & control of non-communicable diseases in Ethiopia 2014-2016 and adjusted for 2021 inflation target population (42). Adjustment for the study population was done by multiplying the national cost by the proportion of the study population (i.e., 3%). National and regional cost estimates were based on the proportion of patients studied (i.e. 3% and 20%). We considered this strategy since the

age and sex distribution of hypertension among different regions in the country is did not vary significantly. The collected cost data added up and averaged by using a bottom-up approach (Figure 1). Facility-based or reference costs were used during computing costs. The total medical cost of hypertension treatment was calculated as the sum of the product of medical costs with their respective unit prices. Costs were discounted at an annual rate of 3% and reported in 2021 USD (43, 44).

Direct non-medical costs include transportation costs and patient time costs due to care. The cost of patient time due to care was estimated by using the average daily wage of patients (97.00 ETB) which was calculated from 2912 ± 2732.24 average monthly income. Transportation cost was determined by using the cost of average traveling distance and local transportation tariff (42.00 ETB) in January 2021. According to EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13). This proportion was used to determine the patient time cost due to care for employed groups. For the unemployed proportion, the average daily wage of daily laborers workers working 8 hours per day for 6 days per week was used (26.53 ETB) from the monthly wage of 796.00 ETB (420-1172 ETB) (45).

Indirect costs include cost hospitalization, productivity loss due to illness, and cost of death. Cost-of hypertension-related hospitalization was taken from WHO Choice (41), costs per inpatient stay and cost per inpatient bed day times duration of hospitalization inflated for 2021, and professional time (physician, nurse laboratory professional, and pharmacist time). If a patient had multiple admissions during the year, the costs for each admission were aggregated as the total costs (46).

2.6.3. Mortality and morbidity estimations

Age and sex-specific mortality rates among the adult general population in Ethiopia were taken from EDHS 2016 survey and extrapolated to selected populations (13). According to EDHS 2016, the probability of dying before age 50 years among adults ≥ 15 years were 10% and 12%, in women and men respectively (13). Due to the absence of mortality data specific to hypertension treatment and control status in Ethiopia, mortality risk in the general population was attributed to those with and without hypertension using sex-specific estimates of the relative risk (RR) of all-cause mortality associated with hypertension by treatment and control status was derived from a study conducted in India was used (47). A cohort study conducted in India among adults 20 years and above to determine the Rate and Risk of all-cause mortality among people with HTN showed that the incidence of deaths in the study was 4.28% during the follow-up period of 6 years. The relative risk of mortality was 3.13 (CI: 2.91-3.37) and 1.2 in the high BP group and at age of 60 years. The age-adjusted hazard ratio of all-cause mortality for the high BP group was 2.96 (2.56-3.42) (47) (Supplementary Tables 5 and 6).

In 2020 crude death rate of the Ethiopian population-based on global estimates was 6.29 deaths per 1000 population (48). The estimated prevalence of hypertension among adults was calculated from National STEPS Survey 2016, systematic review and meta-analysis, and WHO report and local studies and the mean estimated

prevalence of hypertension was 21.39% (2, 13, 47, 49-52). Only 28.4% of patients with hypertension are taking antihypertensive medication (2). The mean relative risk of all-cause mortality among hypertensive population when compared to those without hypertension was 1.39 (0.95 to 1.95) (53) (Supplementary Table 3).

Years of life lost due to hypertension morbidity was determined by first calculating disability weights for specific ages based on blood pressure control status (X). Then subtract this value (X) from the life expectancy of the Ethiopian population (i.e., 66.7 years for men, and 70.4 years for women) (Y). The productivity loss cost due to hypertension morbidity was calculated by multiplying Y with sex-specific employment rate based on a monthly average income of 2059.078 ETB from the National STEPS survey 2015 adjusted for 2021 inflation (13,13/9.57=1.372) STEPS Survey, 2015 (2). The EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13) and for unemployed, 2019 minimum average monthly earnings (ETB) of daily laborers reported by the MOLSA 796 ETB (420-1172 ETB) (45). Concerning, cost of productivity lost due to premature mortality: first we calculated potential years of life lost (YLL) by subtracting life expectancy from sex-specific age of death at which the death is recorded (Z). Then Z is multiplied by the number of deaths in each age group (Xi). Finally, we multiplied Xi with sex-specific employment rates like productivity loss due to hypertension-related morbidity above (54). Excess mortality and morbidity due to hypertension to hypertension were determined by subtracting age and sex-specific morbidity and mortality among the general population from the hypertensive cohort. Both were determined by using age, sex, and blood pressure treatment status mortality rate per 1000 person-years (Supplementary Table 6).

2.6.4 Morbidity adjustment

Patients with hypertension may have more than one disease, the addition of YLDs across causes may result in overestimation of the total loss of health (55). Therefore, it is recommended to estimate comorbidities using the assumption of independence within age-sex groups (56):

$$\mathbf{P_{1+2} = P_1 + P_2 - (P_1 \times P_2) = 1 - (1 - P_1) \times (1 - P_2)}$$

- **Where** P_{1+2} is the prevalence of the two comorbid diseases 1 and 2,
- P_1 is the prevalence of disease 1 and $\mathbf{P_2}$ is the prevalence of disease 2.

The combined disability weight for individuals with multiple conditions is estimated assuming a multiplicative model as follows:

$$\mathbf{DW_{1+2} = 1 - (1 - DW_1) \times (1 - DW_2)}$$

Since prevalence YLDs are calculated for each cause as:

$$\mathbf{YLD_i = DW_i \times P_i}$$

- two preceding equations can be combined into a single calculation resulting in:

$$YLD_{1+2} = 1 - (1-YLD_1) \times (1 - YLD_2)$$

2.6.5 Assumptions and Transition probabilities

The counterfactual comparator (hypothetical cohort of normotensive individuals) with a probability of developing CVD events among the general population. Both in case and comparator cohorts, the probability of non-CV death does not depend on the health state and is similar for both hypertensive and normotensive populations (57) and we chose not to model differential use of antihypertensive medication classes in order not to bias cost-of-treatment. Antihypertensive dose intensification and frequency of BP monitoring were based on ISH 2020 guidelines for blood pressure control. We did not simulate the effects of any particular medication; instead, we simulated "standard dose" effects and assumed average drug prices across classes (58). The amount of blood pressure change was assumed to be a function of the baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (59). We also assumed the medication adherence rate as 75% based on clinical trials (59). Other important assumptions include cost of illness due to hypertension or associated morbidities were calculated based on the monthly earnings during data collection; all costs incurred before one year were adjusted/accounted to today's value (2021 USD equivalent) and discounted at 3%; years of life lost and years of life lived with disability (YLDs) were not discounted as per the recent WHO recommendations.

2.7. Data Quality control, Processing, and Analysis

Questionnaires are prepared in English and the patient interview part of the questionnaire was translated into Amharic and translated back into English to check its consistency. The Amharic version of the patient interview questionnaire and English version of the health professional interview, data abstraction form, and health system interview questionnaires was used for data collection. The questionnaire was pretested on 30 adult hypertensive patients in Arba Minch General Hospital to ensure that the respondents could understand the questions and to check for consistency and possible amendments were made based on findings. Six professional nurses (BSc.) for data collection and one senior professional working in the respective health facilities for supervision were oriented before data collection about data collection approaches and contents of data collection format for one day by the principal investigator. Continuous follow-up and supervision were made by the principal investigator throughout the data collection period. The collected data were checked for completeness and consistency by the principal investigator on daily basis at the spot during the data collection time. Then data were transcribed back to English for the patient interview part and entry was made using Epi-data 3.1 software. After data processing, analysis was done by using SPSS version 21.0 and Microsoft excel 2010. A summary of descriptive statistics was reported for socio-demographic factors; cost of hypertension and life years lost due to hypertension related morbidity and premature mortality and presented in tables and figures.

2.8. Patient and Public involvement

There was no identifiable patient involvement in this research. Patients' demographic characteristics and disease related variables were obtained by using questionnaire based interview after obtaining verbal consent from the patient. No patient identifier information was collected. Finally, most of variables were taken from published national and international literatures, and all relevant sources were acknowledged through citation.

2.8. Statements

Ethics approval and consent to participate

The study was approved by Tehran University of medical sciences, Faculty of pharmacy, department of pharmacoeconomics, and pharmaceutical administration ethical review board with Approval ID: *IR.TUMS.MEDICINE.REC.1399.674* and Arba Minch University College of medicine and health sciences Institutional review board with Reference number: *IRB/T10/2012*. After clarifying the study objective and confidentiality of the information; verbal informed consent was obtained from each respective hospital before data collection.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available up on official request of principal investigator upon acceptance of the manuscript

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

All Authors read and approved the manuscript. *MM* conceived the research, framed the format design and developed the manuscript for publication; *MD participated in data analysis and reviewed the manuscript and AK* reviewed the manuscript and write-up process; *NS* and *TS* participated in literature review and polished the language of the manuscript.

3. Results

3.1. Description of study participants

In this study, we estimated the regional and national economic burden of hypertension (direct and indirect costs) by using the cardiovascular disease policy model adapted to the Sub-Saharan Africa perspective (60) (Supplementary Figure 1). Total costs of treated hypertension and hypertension-related excess mortality and years of life lost due to hypertension were determined. We followed a cohort of 406 hypertensive patients retrospectively for 10 years from September 2003 to 2013 Ethiopian calendar (September 2010-2020) for baseline assessment and simulated the cost of hypertension for lifelong from a societal perspective. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their BP control target based on international society of hypertension 2020 guidelines (Table 1).

Table 1: Patient characteristics and Disease related factors among adult hypertensive patients on regular follow-up at selected public hospitals in Southern Ethiopia, January 2021 (n=406)

Sociodemographic factors		Frequency
Sex	Male	156 (38.4%)
	Female	250 (61.6%)
Age in in years	Below 40 years	15 (3.7%)
	40- 65 years	286 (70.4%)
	65 years and above	105 (25.9%)
Religion	Orthodox	215 (53.0%)
	Muslim	37 (9.1%)
	Protestant	144 (35.5%)
	Catholic	10 (2.5%)
Annual gross income before tax (n=406)	Less than 12,000	117 (28.8%)
	12,000- 18,000	89 (21.9%)
	18,000- 23,000	200 (49.2%)
Level of Education	Illiterate	259 (63.8%)
	Grades 1-8	46 (11.3%)
	Grades 9-12	22 (5.4%)
	College and above	73 (18.0%)
	Post-graduate degree	6 (1.5%)
Occupation	Employed	65 (16.0%)
	Merchant	63 (15.5%)
	Farmer	79 (19.5%)
	House wife	149 (36.7%)
Disease related factors		
Duration of hypertension since diagnosis	5 - 9 years	262 (64.5%)
	10 - 14 years	131 (32.3%)
	15 and above years	13 (3.2%)
Family history of CVDs	1st degree relative	133 (32.7%)
	Second degree relative	16 (3.9%)
	None	257 (63.3%)
Presence of comorbidities (n=406)	Yes	310 (76.4%)
	No	96 (23.6%)
History of hospitalization	Yes	250 (61.6%)

	No	156 (38.4%)
Duration of hospitalization (n=250)	Below 5 days	56 (22.4%)
	5 to 10 days	112 (44.8%)
	More than 10 days	82 (32.8%)
Target BP achieved based on ISH 2020 guideline	Yes	75 (18.5%)
	No	331 (81.5%)
Antihypertensive regimen	Monotherapy	136 (33.5%)
	Two drug combination	234 (57.6%)
	Three and more drug combination	36 (8.8%)

3.2. Cost of hypertension

3.2.1 Direct (medical and non-medical) costs

Direct medical costs include program costs, cost of drugs for hypertension and comorbidities, laboratory costs, hospitalization costs, annual outpatient visit costs, and costs of medical supplies. A total of $US 64,837.48 direct cost was incurred due to hypertension. Out of this, 80.0% ($US 51,915.40) was direct medical cost. From direct medical costs, annual outpatient visit cost 33.55% ($US 17,419.73), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($US 4,263.29) took the largest share. While, total direct non-medical costs of hypertension was $US 9,866.58 (i.e. transportation costs and patient time costs due to care). The regional and national annual estimated direct cost of hypertension were $US 324,187.40 and $US 2,161,249.33 respectively (Table 2).

Table 2: Direct annual costs of treating hypertension among adults in Southern Ethiopia, January 2021 (n=406)

Cost category	Annual total in ETB Total (mean ± Standard deviation)	Annual cost in July 2021 USD	Percentage from total direct cost
Direct medical total	**2,258,319.97**	51,915.40	80.0%
Program costs	403,275.70 (993.0 ± 0.00)	9,173.40	
Cost of antihypertensives	119,847.64 (295.19 ± 107.78)	2,726.20	
Cost of drugs for comorbidity	598,409.00 (2266.7 ± 1114.52)	13,612.15	
Cost for hospitalization	179,377.03 (3360.76 ± 1594.69)	4,080.33	
Laboratory tests	187,420.00 (461.63 ± 226.98)	4,263.29	
Annual outpatient visit costs	765,795.60 (1886.20 ± 0.00)	17,419.73	
Cost of medical supplies	4,195.00 (85.60 ± 0.00)	95.42	
Professional time total	**128,362.01**	2,950.85	4.6%
Physician time	92,032.08 (226.68 ±0.00)	2,093.47	
Nurse time	2,060.28 (43.84 ± 17.81)	46.87	
Pharmacy time	4,453.01 (10.97 + 0.00)	101.29	
Laboratory time	29,816.64 (73.44 ± 0.00)	678.25	
Direct non-medical costs	**433,748.59** (1068.84 ± 384.78)	9,866.58	**15.37%**
Total direct cost of treated hypertension	2,820,430.57	64,837.48	100.00%

1USD= 43.9614 ETB on July 13, 2021

ETB: Ethiopian Birr; USD: United States Dollar

3.2.2. Life years lost due to premature mortality and morbidity

We determined the years of life lost due to premature mortality (excess mortality) and years of life lost due to hypertension morbidity for the productive age population (30-64 years) among a cohort of simulated adult hypertensive patients. Excess mortalities are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension. The excess mortality and years of life lost were different among the hypertensive cohort and simulated population with no hypertension. A total of 11,858 (6,159, men; 5,699 women) life years were lost due to hypertension-related premature mortality among 30-64 years old adults with hypertension. This equates $US 428,969.78 ($US 270,076.91, men; $US 158,892.78). The estimated regional and national life years lost due to premature mortality was 59,290 and 395,267 respectively. This is equivalent to $US 2,144,848.58 and $US 14,298,990.51 respectively. From 15,232 years lost due to premature mortality in the hypertension cohort, treated and uncontrolled hypertension accounted for more than 6,824 (44.8%) total yeas lost due to premature mortality followed by treated controlled hypertension 5,832 (38.29%) and untreated hypertension 2,575 (16.9%) (Table 3 and 4).

Table 3: Excess deaths among adult hypertensive by treatment and control status over the working lifetime simulated from life table modelling in Southern Ethiopia January 2021

Age group	Deaths in Treated hypertension cohort	Deaths in 'hypertension cohort' assuming no hypertension	Excess deaths in those with treated hypertension	Deaths in those with hypertension by treatment and control status *		
				Treated and controlled	Treated and uncontrolled	Untreated
Men						
30-34	1,436	448	988	487	501	295
35-39	1,180	381	799	401	398	242
40-44	1,027	428	599	357	242	191
45-49	1,735	224	1,511	1,167	344	163
50-54	989	166	823	370	453	123
55-59	731	123	608	273	335	91
60-64	932	101	831	362	469	127
Total	8,030	1,871	6,159	3,417	2742	1,232
Women						
30-34	1,401	415	986	434	552	310
35-39	1,187	212	975	368	607	263
40-44	1,019	287	732	324	408	205
45-49	832	279	553	265	288	167
50-54	887	91	796	350	446	137
55-59	805	72	733	277	456	109
60-64	1,071	147	924	396	528	154
Total	7,202	1,503	5,699	2,414	3285	1,345
Box sex total	15,232	3,374	11,858	5,831	6027	2,577
* Excess deaths are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension						

Table 4: Years of life lost (YLL) by adults with hypertension by treatment and control status over the lifetime simulated from life table modelling in Southern Ethiopia, January 2021

Age group	Years of life lived in treated hypertension cohort	Years of life lived in 'hypertension cohort' assuming no hypertension	YLL lost to Treated hypertension (excess)	YLL lost due to hypertension by treatment and control status *		Years of life lived in untreated hypertension cohort	YLL lost due to Untreated hypertension
				Treated and controlled	Treated and uncontrolled		
Men							
33-39	199.87	181.2	18.67	18.67	NA	122.67	58.53
40-44	357.48	324.1	33.38	16.67	17.71	219.42	104.68
45-49	587.08	522.5	64.58	NA	64.58	353.73	168.77
50-54	341.9	295.3	46.6	NA	46.6	199.92	95.38
55-59	161.63	140.1	21.53	NA	21.53	94.85	45.25
60-64	129.88	109.4	20.48	NA	20.48	74.06	35.34
Total	1777.84	1572.6	205.24	35.34	169.9	1,064.65	507.95
Women							
33-39	318.33	288.6	29.73	29.73	NA	195.38	93.22
40-44	791.95	718	73.95	73.95	NA	486.09	231.91
45-49	1147.34	1040.2	107.14	NA	107.14	704.22	335.98
50-54	953.59	863.8	89.79	NA	89.79		279.01
55-59	491.71	445.8	45.91	NA	45.91	309.52	143.99
60-64	297.81	270	27.81	NA	27.81	182.79	87.21
Total	4,000.73	3626.4	374.33	103.68	270.65	1,878.00	1,171.33
Grand total	5,778.57	5199	579.57	139.02	440.55	2,942.65	**1,679.28**

NA= No patient is reported in this age group; * YLL=years of life lost by those with hypertension compared to the same cohort assuming no hypertension.

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension morbidity. This equates to $US 19,436.56. A total of 11,858 (6,159 men; 5,699 women) years of life were lost due to hypertension related premature mortality. This equates to $US $429,958.12. Total productivity loss due to premature mortality and morbidity was $US 449,394.68 (Table 5). Treated and uncontrolled hypertension accounted for 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). Treated uncontrolled hypertension contributed to more YLL due to premature mortality in both sexes 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378 (50.84%) (Figure 2).

The overall estimated hypertension related economic burden (direct and indirect cost) was $US 514,232.16 in the study area (Table 2 and Table 5). Since the study population is estimated to be 20% of the Southern region, the estimated economic burden of hypertension in the region is $US 2,571,160.8 in the region. More than eight out of ten 87.37% dollars were due productivity loss. Productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB (Table 5).

Table 5: Mean annual productivity loss associated premature mortality and hypertension morbidity, Southern Ethiopia, January, 2021

Variable	Sex	Excess Years lost	Lost productivity ETB	Lost productivity in 2021 USD
Years lost due to premature morality	Male	6,159	11,748,345.71	$270,699.21
	Female	5,699	6,911,836.90	$159,258.91
	Both	11,858	18,660,182.62	$429,958.12
Years lost due to hypertension morbidity	Male	205.24	391,497.07	$8,999.93
	Female	374.33	453,993.32	$10,436.63
	Both	579.57	845,490.39	$19,436.56
	Total productivity loss		19,505,673.01	$449,394.69
1USD=43.5 ETB				

Note: productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB

4. Discussion

In this prevalence-based retrospective cost of illness study, we estimated the economic burden of hypertension among productive age population from societal perspective. A total direct (medical and non-medical) annual cost incurred due to hypertension in the study population was $US 64,837.48 ($US 13.308 per person per month). Out of direct costs, 80.0% ($US 51,915.40) was direct medical cost. While, the total indirect annual cost incurred due to hypertension was $US 449,394.69 ($US 92.24 per person per month). The total annual economic burden of hypertension was $US 514,232.16 ($ US 1266.58 per person per year). This is higher than findings from another institution-based cross-sectional study conducted to evaluate cost of hypertension illness among patients attending hospitals in Southwest Shewa Zone that showed the mean monthly total cost of hypertension illness was US$ 22.3 (95% CI, 21.3–23.3) (61). Findings from an institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that total cost of hypertension was $91.72 ± 78.65 per patient per year (62). The COI study conducted among 202 hypertensive patients in Ghana that showed the total annual treatment cost of hypertension was $US 76,275.60 ($US31.47 per person per month) (63). However, this is less than findings from and a study conducted in Canada also showed that annual individual healthcare cost of hypertension was $ US 2,341 (64), and study conducted in the USA showed that individuals with hypertension had $ US 1,920 higher annual incremental expenditure (65). This variation could be explained by variation in socioeconomic status and population health status, and our findings could underestimate both costs and health-related life loss due to the asymptomatic nature of hypertension (66), a significant number of undiagnosed hypertension among adults, and difference in health care system and level of care.

In this study, indirect cost accounted for more than three fourth of hypertension-related costs 85.6% ($449,394.69 USD). This is against evidence generated by a cross-sectional study conducted to determine the

burden of out-of-pocket payments among patients with cardiovascular disease in public and private hospitals in Ibadan, South West, Nigeria showed that across all the hospital facilities, the annual direct and indirect outpatient costs were $1164.2± $2363.8 and $52.87±$148.05 respectively (67). An institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that the direct medical and non-medical cost constituted 60.81% and 12.17% of the total cost of hypertension respectively (62). An institution-based cross-sectional study conducted to evaluate cost of hypertension Illness among Patients Attending Hospitals in Southwest Shewa Zone showed that the mean monthly total cost of hypertension illness was US$ 22.3 (direct cost of US$ 11.39 and indirect cost US$ 10.89) (61). This is also higher than evidence that suggested about a half of the costs associated with CVD burden are caused by direct healthcare costs (68). The findings from a study conducted in Ghana direct cost accounting for almost 70% of the total cost of managing hypertension (63). Similarly, a study conducted in rural Yunnan Province of China showed that direct costs represented the largest component of the economic cost of hypertension (69). The variation could be explained by significant number of productive age populations affected hypertension in the study area and poor blood pressure control. Therefore, it is important to promote existing strategies and develop country/region-specific strategies for hypertension prevention and control (i.e., annual screening of the high-risk population and promoting healthy lifestyles) by all stakeholders could reduce the economic burden of hypertension Ethiopia (70, 71).

Concerning pre-mature mortality, a total of 11,858 (6,159, men; 5,699 women) years were lost due to hypertension-related premature mortality. This equates $US 429,958.12. Concerning health-related life loss, about 26,678 deaths per study population were due to hypertension. This is higher than the number of hypertension-related death occurred in 2017, which as 11,050 (7). This could be explained by the increasing trend of hypertension in the country.

From 11,585 years lost due to premature death in the treated hypertension cohort. More than one-half of related deaths, 6027 (50.83%) were due to treated uncontrolled hypertension. This is supported by evidence from other studies that revealed uncontrolled blood pressure cost $370 billion globally in 2001 (72). This is because the relative risk of all-cause mortality is higher among treated and uncontrolled (1.62) than untreated (1.40) and treated controlled (1.12) patients (53).

Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for 440.55 (76.01%) of productive life years lost from treated hypertension cohort. This is higher than findings from a study conducted to estimate the economic burden of hypertension in a given year in rural Yunnan Province of China showed that the overall prevalence of and YLL/1000 population because of hypertension was 24.8% and 1.5 years for the survey population, respectively (69). A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to treated hypertension. The

estimated national life years lost due to hypertension is 19,319 (i.e., $US 846,413.56). This is supported by evidence from a study conducted Australia that revealed hypertension caused 609, 801 productivity-adjusted life years loss (equating to AUD$ 137.2 billion) over the working lifetime (73). Therefore, prevention of hypertension and improving the rate of blood pressure control is important to reduce hypertension-related complications and productive life-year loss in the region as well as in the country (74).

5. Conclusion

The societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars economic burden. Prevention of hypertension could result in $US 2,571,160.8 annual economic savings in the Southern Region. Therefore, designing and implanting strategies for prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels (national, regional, zonal, community, and patient-level) is critical to saving scarce health resources.

6. Abbreviations

BP: Blood Pressure

CPG: Clinical Practice Guideline

CVD: Cardiovascular Diseases

DALY: Disability Adjusted Life Years

DBP: Diastolic Blood Pressure

EDHS: Ethiopia Demographic Health Survey

HDL: High-Density Lipoprotein

ICER: Incremental Cost-Effectiveness Analysis

LDL: Low-Density Lipoprotein

LMICs: Low- and Middle-income Countries

MI: Myocardial Infarction

QALY: Quality Adjusted Life Years

SBP: Systolic Blood Pressure

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

YLD: Years Lived with Disability

YLL: Years of Life Lost

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Legends

List of Figures

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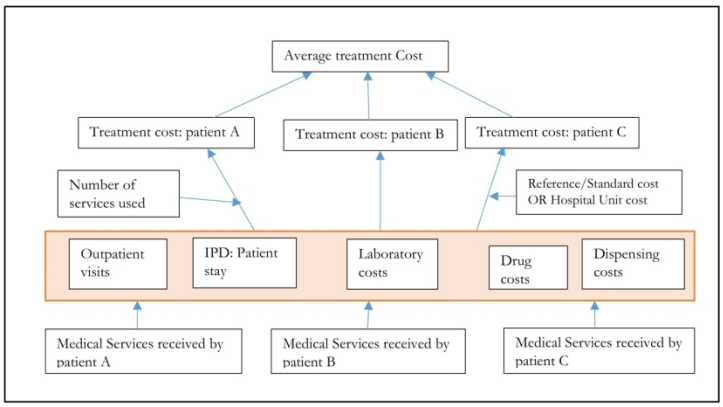
Figure 2: Number of premature deaths and years of life lost (YLL) due to morbidity among adults with hypertension by sex, treatment and control status over productive life years simulated from life table modelling in Southern Ethiopia



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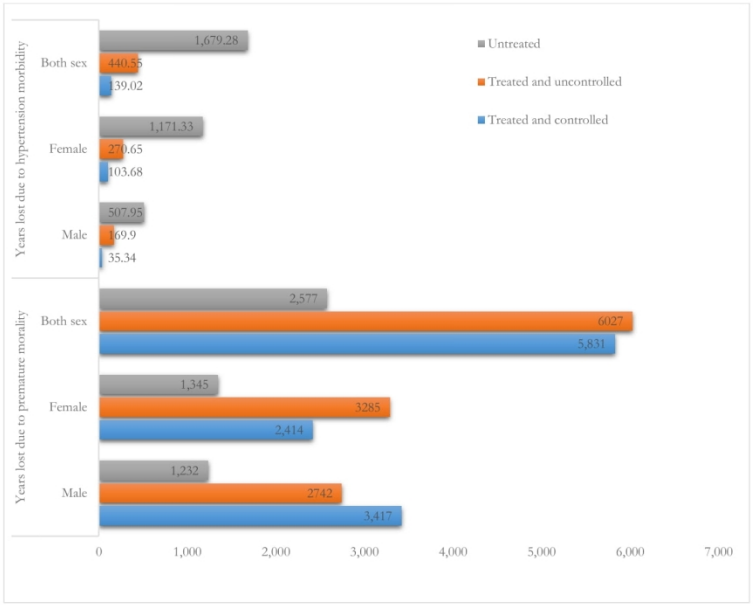

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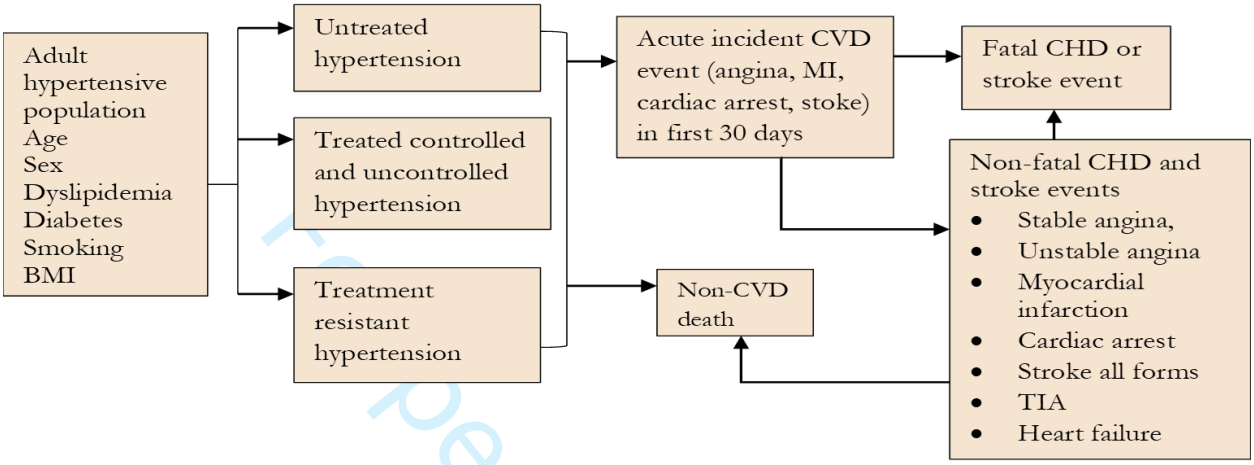
Supplementary materials: Economic burden of hypertension at selected Hospitals in Southern Ethiopia; a patient level analysis

Cardiovascular disease policy model



Supplementary Figure 1: Cardiovascular disease policy model adapted for Sub-Saharan African perspective (1).

Supplementary Table 1: Age and sex specific distribution of Ethiopian population 2020 estimate, prevalence of hypertension and adult mortality rate

Age structure	Male	Female	Total	Estimated prevalence of hypertension	Mortality rate		Data Source
Prevalence of hypertension					Men	Women	(2-8)
0-14 years	21,657,152	21,381,628	43,038,780	NA	-	-	
15-19	5,572,330	5,464,174	11,036,504	19.6	0.00286	0.00222	
20-24	5,930,683	5,816,173	11,746,856	19.6	0.00319	0.00223	
25-29	4,889,739	4,802,450	9,692,189	19.6	0.00293	0.002.32	
30-34	3,761,349	3,757,544	7,518,893	23.0	0.00397	0.003.68	
35-39	3,091,148	3,182,837	6,273,985	23.0	0.00411	0.00222	
40-44	2,445,523	2,488,422	4,933,945	25.9	0.00584	0.00385	
45-49	2,071,480	2,033,228	4,104,708	25.9	0.00360	0.00457	
50-54	1,567,789	1,660,957	3,228,746	41.9	0.00354	0.00274	
55-59	1,159,002	1,316,318	2,475,320	41.9	0.00354	0.00274	
60-64	946,594	1,109,670	2,056,264	41.9	0.00354	0.00274	
≥ 65 years	1,676,478	1,977,857	3,654,335	41.9	0.00354	0.00274	
Total	54,769,267	54,991,258	109,760,525				
				Prevalence of untreated hypertension			
For all ages (15 +)				13.25			(9)

Supplementary Table 2. Model Parameters, Cohort Setting, and Probability of Transition between states and Disability weights for hypertension and related complications the Global Burden of Disease 2013 study and WHO Global Health Estimates

Parameter	Data	Source
Relative risk of hypertension treatment		
Relative risk of CHD event on hypertension treatment	0.683 (95% CI, 0.633–0.717)	(10-13)
Relative risk of a cerebrovascular event on hypertension treatment	0.633 (95% CI, 0.526–0.717)	(14)
Relative risk of CHD event on normotensive men and women	0.49 (95% CI 0.458–0.513) and 0.32 (0.292–0.342)	(15)
Transition probabilities to death		
Health state	**Disability weight Estimate**	**Source**
Hypertension		**(16)**
Treated	0.246	
Untreated	0.323	
Treated and controlled	0.171	
Myocardial Infarction (MI)		(17)
Day 1-2	0·432	
Days 3-28	0·074	
Angina Pectoris		
Mild	0·033	
Moderate	0·080	
Severe	0·167	
Heart failure		
Mild	0·041	
Moderate	0·072	
Diabetes, digestive, and genitourinary disease		
Diabetes	0.015 (0.012 - 0.018)	(18-20)
Treated	0.033	
Untreated	0.012	

Diabetic neuropathy	0.133	
Chronic kidney disease (stage IV)	0.104	
End-stage renal disease: with kidney transplant	0.024	
End-stage renal disease: on dialysis	0.571	
Disutility due to daily medication	0.049 (0.031–0.072)	
Acute Events		
Myocardial Infarction	0.432 (0.288–0.579)	
Stroke	0.570 (0.377–0.707)	
Occurrence of second or later CVD event	0.985 (0.992–0.989)	
Chronic States		
Ischemic Heart Disease	0.08 (0.02–0.24)	
Stroke	0.135 (0.01–0.437)	
Alive post 2+ CVD Events	0.242 (0.11–0.437)	

CHD, coronary heart disease; SMR, standardized mortality ratio. *Age and sex dependent †Applied multiplicatively to general population age- and sex-dependent utilities; CHD= Angina pectoris, coronary insufficiency, myocardial infarction, or coronary death.

Supplementary table 3: Simulation input parameters

Input parameter	Value	Source
Non-CVD death rate	0.005–0.176 (Age- and sex specific)#	Calculated from WHO lifetables and GBD 2017 (21)
Probability of first-time cardiovascular disease (CVD) event	Individual risk characteristic specific	Obtained from the Globorisk Office Calculator standardized for India [25]
Acute CVD events		
MI		
Probability of MI if CVD event occurs	37.6– 66.7% (Age- and sex specific)#	Calculated based on GBD 2017(21)
30-day fatality	0.01–0.13 (Age- and sex–specific)#	Calibrated based on findings of Huffman et al. 2018 (22)
Re-infarction (in 30 days)	0.0120 (0.0099–0·0141)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Acute Stroke (in 30 days)	0.0060 (0.0045–0.0075)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Stroke		
Probability of Stroke if CVD event occurs	33.2–62.3% (Age- and sex specific)#	Calculated based on GBD 2017 (21) And Jushua D. Bundry et al(23)
30-day fatality	0.12, 0.13 (Sex-specific)#	Calibrated based on a multi-site study by Pandian and Sudhan 2013 [30]
Repeat Stroke (in 30 days)	0.15 (0.1–0.2)ψ	Petty et al. 1998 (24)
Sudden cardiac death	0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years	Heart disease and stroke statistics 2021 update
Heart failure		
Probability of AHF		
30-days fatality	0.0945	Obtained from the THESUS-HF registry (25) and Korean Acute Heart Failure Registry (KorAHF)(26, 27)

Re-hospitalization	0.0736	Obtained from the THESUS-HF registry (25)
Chronic events		
Monthly risk of mortality	0.001–0.019 (Age- and sex-specific)#	Calibrated based on GBD 2017 (21)
Reinfarction	0.079 (0.073–0.085)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.014 (0.012–0.016)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20) Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) (29), BP reduction and secondary stroke prevention: systematic review(30)
Stroke		
Monthly risk of mortality	0.001–0.013 (Age- and sex specific)#	Calibrated based on GBD 2017 (21) Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study(31)
Acute MI	0.043 (0.038–0.048)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.037 (0.033–0.041)	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Relative risk of fatality for an individual with two or more CVD events	1.5	Smolina et al. 2012 (32)
Heart failure		
Incidence		Bulter J.et al (33, 34), and Davis BRK. et. al (35)
1 year mortality		
Re-hospitalization		**Moita B.eta al. 2019(36) and (37)**
Effect of antihypertensive medication		
Medication protocol for an individual	Initial SBP-specific#	Based on Ethiopian NCD control guideline
IHD relative risk due to medication	0.32–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009 (38) and Asayam Kei., 2017(39)
Stroke relative risk due to medication	0.20–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009(38)
IHD relative risk if partially adherent	0.66–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009(40)
Stroke relative risk if partially adherent	0.60–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009 (40) and Lisheng Liu, Zengwu Wang. et al(41)

Supplementary Table 4: Price of drugs, medical supplies, procedures and professional time used for management of hypertension in Southern Ethiopia, January, 2021

List of medicines	Unit	Price in 2021 Ethiopian birr		Price USD	Source
		Wholesale price	Retail price	Retail Price in 2021 USD	
Acetylsalicylic Acid - 81mg – Tablet (coated)	10x10	43.72	1.32	1.303	Ethiopian Pharmaceutical supply agency, Arba Minch Hub wholesale price 2021 and Arba Minch General hospital pharmacy retail price 2021
Adrenaline (Epinephrine)-0.1% in 1mL ampoule	Each	36.032	1.09	1.074	
Amiodarone - 100mg – Tablet	10x3	313.34	9.44	9.337	
Amlodipine - 10mg - Tablet	10x10	105.44	3.18	3.142	
Amlodipine - 5mg – Tablet	10x10	75.26	2.27	2.243	
Atenolol - 50mg – Tablet	10x10	58.70	1.77	1.749	
Atorvastatin - 20mg – Tablet	10x10	195.68	5.89	5.831	
Atorvastatin - 40mg – Tablet	10x3	140.76	4.24	4.195	
Beclomethasone Propionate -100mcg/dose – Aerosol	200 MD	131.85	3.97	3.929	
Candesartan - 8mg – Tablet	14x2	152.63	4.60	4.548	
Captopril - 12.5mg – Tablet	10x10	33.54	1.01	1.000	
Captopril - 25mg – Tablet	10x10	26.91	0.81	0.802	
Dexamethasone - 4mg/ml in 1ml Ampoule - Injection	10	3.95	0.12	0.118	
Captopril + HCT (50mg + 25mg)-Tablet	10x10	57.32	1.73	1.708	
Digoxin - 0.25mg – Tablet	10x10	202.18	6.09	6.025	
Enalapril Maleate - 10mg - Tablet	10x10	61.57	1.85	1.835	
Enalapril Maleate - 5mg – Tablet	10x10	63.92	1.93	1.905	
Enalapril Maleate – 2.5mg – Tablet	10x10	19.98	0.60	0.595	
Enalapril Maleate +HCT (10 mg + 25 mg)-tablet	10x10	78.22	2.36	2.331	
Glibenclamide - 5mg – Tablet	10x10	39.09	1.18	1.165	
Glucose 40% in 20 mL – IV infusion	Each	2.54	0.08	0.076	
Glyceryl Trinitrate - 0.4mg – Tablet (Sublingual)	100	487.21	14.67	14.518	
Hydralazine - 20mg/ml in 1ml ampoule - Injection	5	204.01	6.14	6.079	
Hydrochlorothiazide - 25mg – Tablet	25x4	48.05	1.45	1.432	
Insulin Isophane Biphasic (Soluble/Isophane Mixture)-(30 + 70)IU/ml in 10ml Vial -Injection(Suspension)	Each	85.20	2.57	2.539	
Insulin Isophane Human - 100IU/ml in 10ml Vial - Injection(Suspension)	Each	100.28	3.02	2.988	
Insulin Soluble Human - 100IU/ml in 10ml Vial	Each	106.21	3.20	3.165	
Lovastatin - 20mg – Tablet	10x10	84.59	2.55	2.521	
Metformin - 500mg – Tablet	10	27.78	0.84	0.828	
Methyldopa - 250mg – Tablet	100x10	51.75	1.56	1.542	
Metoprolol - 50mg – Tablet	10x10	94.43	2.84	2.814	
Morphine sulphate-30mg-tablet	110	410.71	12.37	12.239	
Nifedipine - 20mg – Tablet	10x10	58.70	1.77	1.749	
Prednisolone - 5 mg – Tablet	100x10	342.23	10.31	10.198	
Propranolol - 40mg – Tablet	10x10	67.54	2.03	2.013	
Propylthiouracil - 100mg - Tablet (Scored)	100	633.87	19.09	18.889	
Salbutamol - 0.1mg/dose - Aerosol (Oral Inhalation)	200 MD	117.20	3.53	3.492	
Spironolactone - 25mg – Tablet	10x10	81.87	2.47	2.440	
Thyroxin Sodium - 0.1mg – Tablet	100	178.49	5.38	5.319	
Valsartan + HCT (80mg +12.5mg)	7*2	38.47	1.16	1.146	
Laboratory and imaging costs		**Price per test ETB**		Price in 2021 USD	
CBC		75.00		1.72	Arba Minch General Hospital Laboratory service price 2021
FBG/RBS		20.00		0.46	
Lipid profile (LDL, HDL, Total cholesterol, Triglyceride)		160.00		3.68	
ECG		120.00		2.76	
ECO		350.00		8.05	
CT-scan		1200		27.59	
RFT (bilirubin, creatinine)		80.00		1.84	
Chest-ray		726		16.69	
Urine analysis		15.00		0.34	
Body fluid analysis		100.00		2.30	
H. pylori		50.00		1.15	

Liver function test (AST, ALT, ALP)	120.00	2.76	
Thyroid function test (T3, T4, TSH)	432.00	9.93	
Hospital bed days			
Primary hospital	52.52	1.21	WHO Choice (42) inflated to 2021
Secondary hospital	54.76	1.26	
Tertiary hospital	70.81	1.63	
Health facility visit		0.00	
Primary hospital	18.58	0.43	
Secondary hospital	21.17	0.49	
Tertiary hospital	22.06	0.51	
Health center visit	23.00	0.53	
PCI intervention	63,000.00	1448.28	
In-patient costs for MI	45240.00	1040.00	
In-patient costs for Stroke	40890.00	940.00	
Outpatient cost for IHD (per annum)	1957.50	45.00	
Outpatient cost for Stroke (per annum)	2914.50	67.00	
Salary scale of human resource		0.00	
Physician	21,100.00	485.06	MOH, Ethiopia 2012/2019
Acute care nurse	7470.00	171.72	
Pharmacy personnel	8047.00	184.99	
Laboratory technician	6460.00	148.51	
Program cost per person per annum	993.29	22.83	(43).
Antihypertensive treatment			
Antihypertensive medication (per individual per annum	Drug costs based on national Drug supply agency wholesale price		
Out-patient consultations (per visit)	$43.36	Annual outpatient visit cost (12*WHO cost per outpatient visit inflated to 2021) WHO Choice (42)	
One-time diagnostic tests		Based on Laboratory procedures and test price of Arba Minch General Hospital, 2021	
In-patient costs for MI	$1040	WHO Choice (42) inflated to 2021	
In-patient costs for Stroke	$940		
Chronic CVD care			
Secondary care medication in public sector (per individual per annum)	$92, $184 (Dosage-specific)§	MSH-2015 International Drug Price Indicator inflated to 2021(25)	
Outpatient cost for IHD (per annum)	$45	WHO Choice (44) inflated to 2021	
Outpatient cost for Stroke (per annum)	$67		
Average inflation rate Ethiopia	16.58%	https://take-profit.org/en/statistics/inflation-rate/ethiopia/	
Average inflation rate foreign	2.02%		
Percentage change	24.6%		
Exchange rate July 2021 (1USD)	43.5 ETB		
1USD = 20.999 ETB in 2016 and 43.5 in 2021; PPP= 12.1/8.1 = 1.5			
MD: metered Dose; MOH: Ministry of Health 1 USD = 43.5 January 2021 **Note**: 30% mark-up at regional EPSA hub, 31% mark-up at Public Hospital level			

Supplementary Table 5: Risk of death across age and gender covariate categories stratified for hypertension

Variables	Categories	Incidence of death (%)		Relative risk in each category (CI)	Source
		High BP group	Normal		
Age	20-29	1.68%	0.54%	3.11 (1.16-8.36)	*(8)*
	30-39	1.71%	0.94%	1.82 (1.04-3.19)	
	40-49	2.43%	1.88%	1.29 (0.91-1.82)	
	50-59	6.30%	4.03%	1.56 (1.28-1.91)	
	60 and above	19.32%	15.9%	1.21 (1.12-1.31)	
Gender	Women	8.71%	1.1%	3.31 (2.98-3.68)	
	Men	15.47%	4.62%	3.34(3.02-3.70)	
Risk of all case mortality					
Gender	Treatment status	< 60 years	> 60 years	HR (95% CI)	(45)
Men	Normal	0.0068	0.0214	1.00 (Reference)	
	Treated controlled	0.0188	0.0305	1.20 (0.92-1.57)	
	Treated uncontrolled	0.0252	0.0372	1.55 (1.19-2.01)	
	Untreated	0.0197	0.0336	1.45 (1.23-1.72)	
Women	Normal	0.00528	0.01870	1.00 (Reference)	
	Treated controlled	0.01675	0.02841	1.11 (0.84-1.47)	
	Treated uncontrolled	0.02533	0.03736	1.63 (1.34-1.99)	
	Untreated	0.02075	0.03471	1.31 (1.06-1.61)	

Supplementary Table 6: Annual mortality rate in the total population, those with hypertension by treatment and control status and those without hypertension in Ethiopia in 2021 by age group and sex based on literature review of systematic reviews and clinical trials

Age group	Mortality rate in the total population	Mortality rate among people without hypertension	Mortality rate among people with treated and controlled hypertension	Mortality rate among people with treated but uncontrolled hypertension	Mortality rate among people with untreated hypertension	References
Women						
15-19	0.00222	0.00222	0.016746	0.025	0.02075	Ko, Min Jung. et al. 2016 (46), Mende Sorato, et al, 2021. (1, 23, 45, 47, 48).
20-24	0.00223	0.00223	0.016746	0.025	0.02075	
25-29	0.00232	0.00232	0.016746	0.025	0.02075	
30-34	0.00368	0.00368	0.016746	0.025	0.02075	
35-39	0.00222	0.00222	0.016746	0.025	0.02075	
40-44	0.00385	0.00385	0.016746	0.025	0.02075	
45-49	0.00457	0.00457	0.016746	0.025	0.02075	
50-54	0.00182	0.00182	0.016746	0.025	0.02075	
55-59	0.00182	0.00182	0.016746	0.025	0.02075	
60 -64	0.00441	0.00441	0.028414	0.037	0.03471	
Men						
15-19	0.00286	0.00286	0.018783	0.025	0.01969	Kuriakose A. et al. 2014. (8), EDHS, 2016 (7, 45, 47-50)
20-24	0.00319	0.00319	0.018783	0.025	0.01969	
25-29	0.00293	0.00293	0.018783	0.025	0.01969	
30-34	0.00397	0.00397	0.018783	0.025	0.01969	
35-39	0.00411	0.00411	0.018783	0.025	0.01969	
40-44	0.00584	0.00584	0.018783	0.025	0.01969	
45-49	0.0036	0.0036	0.018783	0.025	0.01969	
50-54	0.00354	0.00354	0.018783	0.025	0.01969	
55-59	0.00354	0.00354	0.018783	0.025	0.01969	
60-64	0.00354	0.00354	0.030451	0.037	0.03365	

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Reporting checklist for economic evaluation of health interventions.

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	Reporting Item	Page Number
Title		
#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1

Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	1
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	2
Methods			
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	3-10
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	9

Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	10
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	NA
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	4-6
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	NA
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use	NA

		associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	
Methods			
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Supplementary figure 1
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	9

Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-15
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	NA

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Notes:

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BMJ Open

Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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I. Abstract

Objectives: There is inadequate information on the economic burden of hypertension treatment in Ethiopia. Therefore, this study was conducted to determine the societal economic burden of hypertension at Selected Hospitals in Southern Ethiopia.

Methods: Prevalence-based cost of illness (COI) study from a societal perspective was conducted. Disability-adjusted life years (DALYs) were determined by the current world health organization's recommended DALY valuation method. Adjustment for comorbidity and a 3% discount was done for DALYs. The data entry, processing, and analysis were done by using SPSS version 21.0 and Microsoft Excel 2013.

Results: We followed a cohort of 406 adult hypertensive patients retrospectively for 10 years from September 2010 to 2020. Two hundred-fifty (61.6%) of patients were females with a mean age of 55.87 ± 11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their blood pressure control target. A total of 64,837.48 United States Dollar ($US) direct cost was incurred due to hypertension. A total of 11,585 years and 579.57 years were lost due to hypertension-related premature mortality and morbidity respectively. Treated and uncontrolled hypertension accounted for 50.83% (6027) of total years lost due to premature mortality from treated hypertension cohort. Total productivity loss due to premature mortality and morbidity was $US 449,394.69. The overall economic burden of hypertension was $US 514,232.16 ($ US 105.55 per person per month)

Conclusion: Societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Therefore, designing and implanting strategies for the prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels is critical to saving scarce health resources.

Strengths and limitations of this study

- Using the cardiovascular disease policy model adapted to Sub-Saharan African perspective,
- Including productivity loss costs associated with hypertension (premature mortality and morbidity) and
- Obtaining all simulation variables and transition probability data from valid sources (systematic reviews, randomized controlled trials, and prospective cohort studies) were the strengths of this study
- Uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate which require due consideration during applying the findings of this study were limitations.

1. Introduction

Hypertension doubles the risk of death from stroke, heart disease, vascular diseases, diabetes, atherosclerosis, and kidney disease (1). According to the national STEPS survey, only 28.4% of hypertensive patients were taking antihypertensive medication prescribed by professionals in Ethiopia (2). According to the International Society of hypertension global hypertension practice guideline 2020, hypertension remains the leading cause of death globally, accounting for 10.4 million deaths per year (3).

Hypertension is associated with societal and economic consequences particularly in Low and middle-income countries (LMICs). In addition to the direct costs associated with health care utilization for the management of complications, hypertension causes significant productivity loss from disability and premature death (4, 5). WHO report from South East Asian region also indicated huge impact of hypertension in national finances due to premature death, disability, personal and family disruption, loss of income, and healthcare expenditure (6). According to a WHO report in 2017, stroke, coronary heart disease, and hypertension caused 39,571, 46,943, and 11,050 deaths respectively (i.e. 30 patients per day die due hypertension) in Ethiopia (7).

Cost of illness (COI) study is used to measure the economic burden of disease to individuals, communities, and society as a whole. It can provide information to support the political process and healthcare decision-making if it is conducted from a societal perspective by using an appropriate approach and bottom-up costing strategy (8-10) (11, 12). Despite this huge impact on national economies, the economic burden of hypertension is not studied in Ethiopia particularly Southern Ethiopia. To fill this evidence gap, this study was conducted to determine the economic burden of hypertension at selected public hospitals in Southern Ethiopia by using the prevalence-based cost-of-illness method from a societal perspective to estimate the direct and indirect costs of hypertension in a given year (2021) in Southern Ethiopia.

2. Methods and Materials

2.1. Study design, Area and Period

A prevalence-based retrospective cost of illness study from societal perspective focusing on quantifying direct and indirect costs was conducted from September 2010- September 2020 in at three selected public hospitals Southern Ethiopia. The bottom-up approach was used to estimate the economic burden of hypertension in Southern Ethiopia (figure 1). The human capital approach was used to calculate indirect costs separately in males and females and also among different age groups. A prevalence-based COI model was constructed in which hypertensive patients were simulated from diagnosis through active treatment, palliative care, and death over 15-64 years. Age and sex-specific mortality rates, measures of productivity, and workforce statistics were used to simulate the progression of these cohorts until death or age 64 years. First, the model estimated cumulative years of life and DALYs lived for the working-age population who had hypertension. Then the

model re-simulated with the hypothetical assumption that they did not have hypertension, with relevant changes to mortality rates and productivity. We estimated the probability of death separately for (1) all-cause mortality in absence of hypertension and related complications and (2) mortality attributable to the included disease states. The first component was estimated using WHO Life Tables, and the second component was calculated based on standardized mortality ratios extracted from the literature. The natural history study conducted in 1974 showed that the mortality rate was 1.85 (3.01 in males and 1.62 in females) (13). Interventional trials suggested that it could be possible to achieve effective BP targets in about 70% of patients by improving adherence and/or intensifying therapy (14).

2.2. Study populations

The study populations were selected adult hypertensive patients at three selected public hospitals. According to the world population prospect 2020 estimate (15). In the same year, the population of the Gamo zone accounted for 1.5% of the total population, Gofa, and South Omo Zone 1.5% of the total population. The target population is 3.0% total population of Ethiopia or 20% of the Southern Ethiopian population (6,208,034). Based on age distribution: 0-14 years are children, 15-24 years are early working age, 25-54 years are prime working age, 55-64 years are mature working age and ≥ 65 years are elderly (13).

2.3. Inclusion and exclusion criteria

We included all adult hypertensive patients having at least five years of follow-up visits before data collection and receiving care during the study period from selected facilities. However, patients who are unwilling to participate in this study, patients who have less than five years of follow-up, and incomplete patient records (don't contain follow-up BP records and refill medications, laboratory requests, and results) were excluded.

2.4. Study Variables

Dependent Variables

- Economic burden of hypertension

Independent variables

- Patient-related (socio-demographic characteristics, heart disease knowledge, healthy lifestyle and heart disease risk perception, presence of comorbidity, type of medications, treatment adherence, shared decision making, health-related quality Life)

Cost related variables

- **Medical costs** (inpatient hospital stay/hospitalization cost, outpatient clinic visit, drug acquisition costs, drug administration cost, laboratory test, and imaging study costs)

- **Non-medical costs** (transportation, meal, patient time cost due to treatment, cost due informal care by family or friends)
- **Indirect costs** (absenteeism, presenteeism, unemployment, early retirement, disability, premature death)

2.5. Sample Size and Sampling Technique

2.5.1. Sample size determination

The sample size was determined by using the single population proportion formula by taking prevalence of patients controlled their BP as 14% from WHO 2016 BP control rate report (16-18) and Z value of 1.96 at 95% confidence interval. We added 10% for non-response rate and two for design effect due to multi-stage sampling technique involvement. Finally, a formula giving a larger sample size was used. Total 407 hypertensive adult patients who are on follow-up care will be included.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2} = 185$$

= 185 + (185 * 10%) = 203.5

= 203.5 *2 = 407

Where: **n** = is the sample size

- $\mathbf{Z^2}$= standard normal deviation, set at 1.96, correspond to the 95% confidence interval
- **d** = is the desired level of precision/margin of error (0.05)
- **p**= prevalence of patients taking anti-hypertensive (p=28.4%), and q is 1-p.

2.5.2. Sampling Techniques

A multi-stage simple random sampling technique was used. We randomly selected three zones from a total of 12 zones found in the Southern region. Three general public hospitals with experience of providing CVD care for at least five years from selected four zones were included in this study. The total sample size was allocated to these hospitals based on an estimated number of adult hypertensive patients attending respective hospitals (i.e., we included 212 patients from Arba Minch General Hospital, 107 patients from Jinka General Hospital, and 88 patients from Sawula General Hospital). Finally, a consecutive sampling technique was applied in each facility until the desired sample size was achieved.

2.6. Data collection tools and Procedures

2.6.1. Model input parameters

Key model input variables include; 2020 population of selected zones, hypertension prevalence by treatment and control status, Transition probabilities to death and healthy state, cost of diagnosis, and management. Among those with treated hypertension, treated and controlled hypertension was defined based on BP control target of ISH 2020 guideline (3). We used national STPES survey data to estimate the prevalence of cardiovascular risk factors (MI, angina, heart failure, stroke, TIA). Incorporating the risk factor prevalence data in the relevant Framingham risk equation, the age and sex-specific probability of CHD and cerebrovascular disease (i.e., stroke and transient ischemic attack) events were estimated. The probability of each health state

was calculated using the age- and sex-specific CHD and cerebrovascular disease event distributions (2, 19). To estimate the corresponding probabilities, separate relative risk estimates were used for CHD events (Stable Angina, Unstable Angina, and MI) and cerebrovascular diseases (Stroke and Transient Ischemic Attack), assuming that antihypertensive treatment affects the probability of every disease state similarly across all age and sex groups. Relative risk reductions attributable to antihypertensive treatment were extracted from the peer-reviewed literature (20-22).

The 2020 world population prospect estimate was used for the baseline population and number of 33-year-olds projected to enter the model population from 2020-2070 (15). The annual probability of coronary heart disease and stroke was based on national STEPS survey (2), and Framingham Heart Study (23) and the Framingham Offspring Study (24), by contextualizing to Ethiopian scenario. Incident coronary heart disease events were allocated to angina pectoris, myocardial infarction, or cardiac arrest. Prevalence, joint distributions, and means of Ethiopia risk factor values were estimated from the national STEPS survey (2). Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Betas for risk function for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort (24). Risk factors are assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers are assumed to have a higher relative risk for infarction and arrest (25); and a proportionately lower coefficient for angina. Environmental tobacco exposure is assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with non-exposed non-smokers (26) but not to influence angina. The number of hospitalized MI were obtained from the national STEPS survey (2). Case-fatality rates and rates of MI in subgroups were estimated from national data and other complementary sources. Prehospital arrest deaths and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from our effectiveness study (Supplementary Table 1).

Survival after a coronary heart disease event was estimated and calibrated based on national or international data sources (27, 28). Rates of coronary revascularizations was estimated from the National hospital discharge survey, with mortalities estimated from aggregated historical data. Stroke incidence was assumed to be independent of the risk of new-onset coronary heart disease in the same year. The number of hospitalized strokes cases was obtained from national and regional studies. The annual probabilities of stroke after MI (29, 30) and the probability of coronary heart disease in stroke patients were based on natural history studies and systematic reviews of blood pressure control trials (31-36). A 30-day heart failure mortality and re-hospitalization data were from the THESEUS-HF registry (37) and Korean Acute Heart Failure Registry (KorAHF)(38, 39) (Supplementary Table 2 and 3).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2020 was estimated from the National Health Survey data (2) and GBD 2017 (40). The background prevalence of prior coronary revascularization was estimated from revascularizations before 2019 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state. Age and sex-specific health care costs were estimated using national data, and our effectiveness data. Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using WHO Choice (41) inflated to 2021. Outpatient consultations, and inpatient stay and bed days were also estimated from WHO choice (41) inflated to 2021. Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis was pooled from the 2015 national STEPS survey. Average annual non-cardiovascular costs were estimated from the national STEPS survey (2), and EDHS 2016 survey (13).

2.6.2. Cost estimation

The outcomes measures are total discounted societal costs, cost/year, and cost/patient-year. This is the amount of health budget that could be saved by effective prevention and control of hypertension. The direct costs were divided into two subcategories: direct medical costs and direct non-medical costs. Direct medical costs include; inpatient stays, outpatient clinic visits, medical services, drug acquisition, dispensing, administration, monitoring, laboratory test, and imaging study costs. The costs associated with outpatient/inpatient visits were estimated by multiplying the numbers of outpatient visits related to hypertension by the outpatient costs per year (i.e., twelve times WHO cost per outpatient visit for secondary hospitals inflated to 2021) (41).

Data concerning medications prescribed for the management of hypertension, and associated comorbidities, and laboratory tests and imaging studies were done were collected by patient chart abstraction in index year (2020). The cost of medications used for management of hypertension and associated comorbidities was taken from Ethiopian Pharmaceutical supply agency Arba Minch regional hub selling price and retail price of Arba Minch General Hospital in 2020. The retail price of Arba Minch General Hospital was used because of the minimum distance from the Pharmaceutical supply agency hub, which could minimize markup added on retail price due to transportation cost. Costs of laboratory procedures were also taken from Arba Minch Hospital Laboratory's service price list. The prices of relevant laboratory tests and imaging studies were based on the average price of included Hospitals. The salary scale of the health workforce was based on the FMOH of Ethiopia (Supplementary Table 4).

Ongoing program costs for hypertension care was estimated from WHO tool outputs for CVD and diabetes care and National strategic action plan (NSAP) for prevention & control of non-communicable diseases in Ethiopia 2014-2016 and adjusted for 2021 inflation target population (42). Adjustment for the study population was done by multiplying the national cost by the proportion of the study population (i.e., 3%). National and regional cost estimates were based on the proportion of patients studied (i.e. 3% and 20%). We considered this strategy since the

age and sex distribution of hypertension among different regions in the country is did not vary significantly. The collected cost data added up and averaged by using a bottom-up approach (Figure 1). Facility-based or reference costs were used during computing costs. The total medical cost of hypertension treatment was calculated as the sum of the product of medical costs with their respective unit prices. Costs were discounted at an annual rate of 3% and reported in 2021 USD (43, 44).

Direct non-medical costs include transportation costs and patient time costs due to care. The cost of patient time due to care was estimated by using the average daily wage of patients (97.00 ETB) which was calculated from 2912 ± 2732.24 average monthly income. Transportation cost was determined by using the cost of average traveling distance and local transportation tariff (42.00 ETB) in January 2021. According to EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13). This proportion was used to determine the patient time cost due to care for employed groups. For the unemployed proportion, the average daily wage of daily laborers workers working 8 hours per day for 6 days per week was used (26.53 ETB) from the monthly wage of 796.00 ETB (420-1172 ETB) (45).

Indirect costs include cost hospitalization, productivity loss due to illness, and cost of death. Cost-of hypertension-related hospitalization was taken from WHO Choice (41), costs per inpatient stay and cost per inpatient bed day times duration of hospitalization inflated for 2021, and professional time (physician, nurse laboratory professional, and pharmacist time). If a patient had multiple admissions during the year, the costs for each admission were aggregated as the total costs (46).

2.6.3. Mortality and morbidity estimations

Age and sex-specific mortality rates among the adult general population in Ethiopia were taken from EDHS 2016 survey and extrapolated to selected populations (13). According to EDHS 2016, the probability of dying before age 50 years among adults ≥ 15 years were 10% and 12%, in women and men respectively (13). Due to the absence of mortality data specific to hypertension treatment and control status in Ethiopia, mortality risk in the general population was attributed to those with and without hypertension using sex-specific estimates of the relative risk (RR) of all-cause mortality associated with hypertension by treatment and control status was derived from a study conducted in India was used (47). A cohort study conducted in India among adults 20 years and above to determine the Rate and Risk of all-cause mortality among people with HTN showed that the incidence of deaths in the study was 4.28% during the follow-up period of 6 years. The relative risk of mortality was 3.13 (CI: 2.91-3.37) and 1.2 in the high BP group and at age of 60 years. The age-adjusted hazard ratio of all-cause mortality for the high BP group was 2.96 (2.56-3.42) (47) (Supplementary Tables 5 and 6).

In 2020 crude death rate of the Ethiopian population-based on global estimates was 6.29 deaths per 1000 population (48). The estimated prevalence of hypertension among adults was calculated from National STEPS Survey 2016, systematic review and meta-analysis, and WHO report and local studies and the mean estimated

prevalence of hypertension was 21.39% (2, 13, 47, 49-52). Only 28.4% of patients with hypertension are taking antihypertensive medication (2). The mean relative risk of all-cause mortality among hypertensive population when compared to those without hypertension was 1.39 (0.95 to 1.95) (53) (Supplementary Table 3).

Years of life lost due to hypertension morbidity was determined by first calculating disability weights for specific ages based on blood pressure control status (X). Then subtract this value (X) from the life expectancy of the Ethiopian population (i.e., 66.7 years for men, and 70.4 years for women) (Y). The productivity loss cost due to hypertension morbidity was calculated by multiplying Y with sex-specific employment rate based on a monthly average income of 2059.078 ETB from the National STEPS survey 2015 adjusted for 2021 inflation (13,13/9.57=1.372) STEPS Survey, 2015 (2). The EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13) and for unemployed, 2019 minimum average monthly earnings (ETB) of daily laborers reported by the MOLSA 796 ETB (420-1172 ETB) (45). Concerning, cost of productivity lost due to premature mortality: first we calculated potential years of life lost (YLL) by subtracting life expectancy from sex-specific age of death at which the death is recorded (Z). Then Z is multiplied by the number of deaths in each age group (Xi). Finally, we multiplied Xi with sex-specific employment rates like productivity loss due to hypertension-related morbidity above (54). Excess mortality and morbidity due to hypertension to hypertension were determined by subtracting age and sex-specific morbidity and mortality among the general population from the hypertensive cohort. Both were determined by using age, sex, and blood pressure treatment status mortality rate per 1000 person-years (Supplementary Table 6).

2.6.4 Morbidity adjustment

Patients with hypertension may have more than one disease, the addition of YLDs across causes may result in overestimation of the total loss of health (55). Therefore, it is recommended to estimate comorbidities using the assumption of independence within age-sex groups (56):

$$\mathbf{P_{1+2} = P_1 + P_2 - (P_1 \times P_2) = 1 - (1 - P_1) \times (1 - P_2)}$$

- **Where** P_{1+2} is the prevalence of the two comorbid diseases 1 and 2,
- P_1 is the prevalence of disease 1 and $\mathbf{P_2}$ is the prevalence of disease 2.

The combined disability weight for individuals with multiple conditions is estimated assuming a multiplicative model as follows:

$$\mathbf{DW_{1+2} = 1 - (1 - DW_1) \times (1 - DW_2)}$$

Since prevalence YLDs are calculated for each cause as:

$$\mathbf{YLD_i = DW_i \times P_i}$$

- two preceding equations can be combined into a single calculation resulting in:

$$YLD_{1+2} = 1 - (1-YLD_1) \times (1 - YLD_2)$$

2.6.5 Assumptions and Transition probabilities

The counterfactual comparator (hypothetical cohort of normotensive individuals) with a probability of developing CVD events among the general population. Both in case and comparator cohorts, the probability of non-CV death does not depend on the health state and is similar for both hypertensive and normotensive populations (57) and we chose not to model differential use of antihypertensive medication classes in order not to bias cost-of-treatment. Antihypertensive dose intensification and frequency of BP monitoring were based on ISH 2020 guidelines for blood pressure control. We did not simulate the effects of any particular medication; instead, we simulated "standard dose" effects and assumed average drug prices across classes (58). The amount of blood pressure change was assumed to be a function of the baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (59). We also assumed the medication adherence rate as 75% based on clinical trials (59). Other important assumptions include cost of illness due to hypertension or associated morbidities were calculated based on the monthly earnings during data collection; all costs incurred before one year were adjusted/accounted to today's value (2021 USD equivalent) and discounted at 3%; years of life lost and years of life lived with disability (YLDs) were not discounted as per the recent WHO recommendations.

2.7. Data Quality control, Processing, and Analysis

Questionnaires are prepared in English and the patient interview part of the questionnaire was translated into Amharic and translated back into English to check its consistency. The Amharic version of the patient interview questionnaire and English version of the health professional interview, data abstraction form, and health system interview questionnaires was used for data collection. The questionnaire was pretested on 30 adult hypertensive patients in Arba Minch General Hospital to ensure that the respondents could understand the questions and to check for consistency and possible amendments were made based on findings. Six professional nurses (BSc.) for data collection and one senior professional working in the respective health facilities for supervision were oriented before data collection about data collection approaches and contents of data collection format for one day by the principal investigator. Continuous follow-up and supervision were made by the principal investigator throughout the data collection period. The collected data were checked for completeness and consistency by the principal investigator on daily basis at the spot during the data collection time. Then data were transcribed back to English for the patient interview part and entry was made using Epi-data 3.1 software. After data processing, analysis was done by using SPSS version 21.0 and Microsoft excel 2010. A summary of descriptive statistics was reported for socio-demographic factors; cost of hypertension and life years lost due to hypertension related morbidity and premature mortality and presented in tables and figures.

2.8. Patient and Public involvement

There was no identifiable patient involvement in this research. Patients' demographic characteristics and disease related variables were obtained by using questionnaire based interview after obtaining verbal consent from the patient. No patient identifier information was collected. Finally, most of variables were taken from published national and international literatures, and all relevant sources were acknowledged through citation.

2.8. Statements

Ethics approval and consent to participate

The study was approved by Tehran University of medical sciences, Faculty of pharmacy, department of pharmacoeconomics, and pharmaceutical administration ethical review board with Approval ID: *IR.TUMS.MEDICINE.REC.1399.674* and Arba Minch University College of medicine and health sciences Institutional review board with Reference number: *IRB/T10/2012*. After clarifying the study objective and confidentiality of the information; verbal informed consent was obtained from each respective hospital before data collection.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available up on official request of principal investigator upon acceptance of the manuscript

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

All Authors read and approved the manuscript. *MM* conceived the research, framed the format design and developed the manuscript for publication; *MD participated in data analysis and reviewed the manuscript and AK* reviewed the manuscript and write-up process; *NS* and *TS* participated in literature review and polished the language of the manuscript.

3. Results

3.1. Description of study participants

In this study, we estimated the regional and national economic burden of hypertension (direct and indirect costs) by using the cardiovascular disease policy model adapted to the Sub-Saharan Africa perspective (60) (Supplementary Figure 1). Total costs of treated hypertension and hypertension-related excess mortality and years of life lost due to hypertension were determined. We followed a cohort of 406 hypertensive patients retrospectively for 10 years from September 2003 to 2013 Ethiopian calendar (September 2010-2020) for baseline assessment and simulated the cost of hypertension for lifelong from a societal perspective. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their BP control target based on international society of hypertension 2020 guidelines (Table 1).

Table 1: Patient characteristics and Disease related factors among adult hypertensive patients on regular follow-up at selected public hospitals in Southern Ethiopia, January 2021 (n=406)

Sociodemographic factors		Frequency
Sex	Male	156 (38.4%)
	Female	250 (61.6%)
Age in in years	Below 40 years	15 (3.7%)
	40- 65 years	286 (70.4%)
	65 years and above	105 (25.9%)
Religion	Orthodox	215 (53.0%)
	Muslim	37 (9.1%)
	Protestant	144 (35.5%)
	Catholic	10 (2.5%)
Annual gross income before tax (n=406)	Less than 12,000	117 (28.8%)
	12,000- 18,000	89 (21.9%)
	18,000- 23,000	200 (49.2%)
Level of Education	Illiterate	259 (63.8%)
	Grades 1-8	46 (11.3%)
	Grades 9-12	22 (5.4%)
	College and above	73 (18.0%)
	Post-graduate degree	6 (1.5%)
Occupation	Employed	65 (16.0%)
	Merchant	63 (15.5%)
	Farmer	79 (19.5%)
	House wife	149 (36.7%)
Disease related factors		
Duration of hypertension since diagnosis	5 - 9 years	262 (64.5%)
	10 - 14 years	131 (32.3%)
	15 and above years	13 (3.2%)
Family history of CVDs	1st degree relative	133 (32.7%)
	Second degree relative	16 (3.9%)
	None	257 (63.3%)
Presence of comorbidities (n=406)	Yes	310 (76.4%)
	No	96 (23.6%)
History of hospitalization	Yes	250 (61.6%)

	No	156 (38.4%)
Duration of hospitalization (n=250)	Below 5 days	56 (22.4%)
	5 to 10 days	112 (44.8%)
	More than 10 days	82 (32.8%)
Target BP achieved based on ISH 2020 guideline	Yes	75 (18.5%)
	No	331 (81.5%)
Antihypertensive regimen	Monotherapy	136 (33.5%)
	Two drug combination	234 (57.6%)
	Three and more drug combination	36 (8.8%)

3.2. Cost of hypertension

3.2.1 Direct (medical and non-medical) costs

Direct medical costs include program costs, cost of drugs for hypertension and comorbidities, laboratory costs, hospitalization costs, annual outpatient visit costs, and costs of medical supplies. A total of $US 64,837.48 direct cost was incurred due to hypertension. Out of this, 80.0% ($US 51,915.40) was direct medical cost. From direct medical costs, annual outpatient visit cost 33.55% ($US 17,419.73), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($US 4,263.29) took the largest share. While, total direct non-medical costs of hypertension was $US 9,866.58 (i.e. transportation costs and patient time costs due to care). The regional and national annual estimated direct cost of hypertension were $US 324,187.40 and $US 2,161,249.33 respectively (Table 2).

Table 2: Direct annual costs of treating hypertension among adults in Southern Ethiopia, January 2021 (n=406)

Cost category	Annual total in ETB Total (mean ± Standard deviation)	Annual cost in July 2021 USD	Percentage from total direct cost
Direct medical total	**2,258,319.97**	51,915.40	80.0%
Program costs	403,275.70 (993.0 ± 0.00)	9,173.40	
Cost of antihypertensives	119,847.64 (295.19 ± 107.78)	2,726.20	
Cost of drugs for comorbidity	598,409.00 (2266.7 ± 1114.52)	13,612.15	
Cost for hospitalization	179,377.03 (3360.76 ± 1594.69)	4,080.33	
Laboratory tests	187,420.00 (461.63 ± 226.98)	4,263.29	
Annual outpatient visit costs	765,795.60 (1886.20 ± 0.00)	17,419.73	
Cost of medical supplies	4,195.00 (85.60 ± 0.00)	95.42	
Professional time total	**128,362.01**	2,950.85	4.6%
Physician time	92,032.08 (226.68 ±0.00)	2,093.47	
Nurse time	2,060.28 (43.84 ± 17.81)	46.87	
Pharmacy time	4,453.01 (10.97 + 0.00)	101.29	
Laboratory time	29,816.64 (73.44 ± 0.00)	678.25	
Direct non-medical costs	**433,748.59** (1068.84 ± 384.78)	9,866.58	**15.37%**
Total direct cost of treated hypertension	2,820,430.57	64,837.48	100.00%

1USD= 43.9614 ETB on July 13, 2021

ETB: Ethiopian Birr; USD: United States Dollar

3.2.2. Life years lost due to premature mortality and morbidity

We determined the years of life lost due to premature mortality (excess mortality) and years of life lost due to hypertension morbidity for the productive age population (30-64 years) among a cohort of simulated adult hypertensive patients. Excess mortalities are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension. The excess mortality and years of life lost were different among the hypertensive cohort and simulated population with no hypertension. A total of 11,858 (6,159, men; 5,699 women) life years were lost due to hypertension-related premature mortality among 30-64 years old adults with hypertension. This equates $US 428,969.78 ($US 270,076.91, men; $US 158,892.78). The estimated regional and national life years lost due to premature mortality was 59,290 and 395,267 respectively. This is equivalent to $US 2,144,848.58 and $US 14,298,990.51 respectively. From 15,232 years lost due to premature mortality in the hypertension cohort, treated and uncontrolled hypertension accounted for more than 6,824 (44.8%) total yeas lost due to premature mortality followed by treated controlled hypertension 5,832 (38.29%) and untreated hypertension 2,575 (16.9%) (Table 3 and 4).

Table 3: Excess deaths among adult hypertensive by treatment and control status over the working lifetime simulated from life table modelling in Southern Ethiopia January 2021

Age group	Deaths in Treated hypertension cohort	Deaths in 'hypertension cohort' assuming no hypertension	Excess deaths in those with treated hypertension	Deaths in those with hypertension by treatment and control status *		
				Treated and controlled	Treated and uncontrolled	Untreated
Men						
30-34	1,436	448	988	487	501	295
35-39	1,180	381	799	401	398	242
40-44	1,027	428	599	357	242	191
45-49	1,735	224	1,511	1,167	344	163
50-54	989	166	823	370	453	123
55-59	731	123	608	273	335	91
60-64	932	101	831	362	469	127
Total	8,030	1,871	6,159	3,417	2742	1,232
Women						
30-34	1,401	415	986	434	552	310
35-39	1,187	212	975	368	607	263
40-44	1,019	287	732	324	408	205
45-49	832	279	553	265	288	167
50-54	887	91	796	350	446	137
55-59	805	72	733	277	456	109
60-64	1,071	147	924	396	528	154
Total	7,202	1,503	5,699	2,414	3285	1,345
Box sex total	15,232	3,374	11,858	5,831	6027	2,577
* Excess deaths are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension						

Table 4: Years of life lost (YLL) by adults with hypertension by treatment and control status over the lifetime simulated from life table modelling in Southern Ethiopia, January 2021

Age group	Years of life lived in treated hypertension cohort	Years of life lived in 'hypertension cohort' assuming no hypertension	YLL lost to Treated hypertension (excess)	YLL lost due to hypertension by treatment and control status *		Years of life lived in untreated hypertension cohort	YLL lost due to Untreated hypertension
				Treated and controlled	Treated and uncontrolled		
Men							
33-39	199.87	181.2	18.67	18.67	NA	122.67	58.53
40-44	357.48	324.1	33.38	16.67	17.71	219.42	104.68
45-49	587.08	522.5	64.58	NA	64.58	353.73	168.77
50-54	341.9	295.3	46.6	NA	46.6	199.92	95.38
55-59	161.63	140.1	21.53	NA	21.53	94.85	45.25
60-64	129.88	109.4	20.48	NA	20.48	74.06	35.34
Total	1777.84	1572.6	205.24	35.34	169.9	1,064.65	507.95
Women							
33-39	318.33	288.6	29.73	29.73	NA	195.38	93.22
40-44	791.95	718	73.95	73.95	NA	486.09	231.91
45-49	1147.34	1040.2	107.14	NA	107.14	704.22	335.98
50-54	953.59	863.8	89.79	NA	89.79		279.01
55-59	491.71	445.8	45.91	NA	45.91	309.52	143.99
60-64	297.81	270	27.81	NA	27.81	182.79	87.21
Total	4,000.73	3626.4	374.33	103.68	270.65	1,878.00	1,171.33
Grand total	5,778.57	5199	579.57	139.02	440.55	2,942.65	**1,679.28**

NA= No patient is reported in this age group; * YLL=years of life lost by those with hypertension compared to the same cohort assuming no hypertension.

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension morbidity. This equates to $US 19,436.56. A total of 11,858 (6,159 men; 5,699 women) years of life were lost due to hypertension related premature mortality. This equates to $US $429,958.12. Total productivity loss due to premature mortality and morbidity was $US 449,394.68 (Table 5). Treated and uncontrolled hypertension accounted for 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). Treated uncontrolled hypertension contributed to more YLL due to premature mortality in both sexes 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378 (50.84%) (Figure 2).

The overall estimated hypertension related economic burden (direct and indirect cost) was $US 514,232.16 in the study area (Table 2 and Table 5). Since the study population is estimated to be 20% of the Southern region, the estimated economic burden of hypertension in the region is $US 2,571,160.8 in the region. More than eight out of ten 87.37% dollars were due productivity loss. Productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB (Table 5).

Table 5: Mean annual productivity loss associated premature mortality and hypertension morbidity, Southern Ethiopia, January, 2021

Variable	Sex	Excess Years lost	Lost productivity ETB	Lost productivity in 2021 USD
Years lost due to premature morality	Male	6,159	11,748,345.71	$270,699.21
	Female	5,699	6,911,836.90	$159,258.91
	Both	11,858	18,660,182.62	$429,958.12
Years lost due to hypertension morbidity	Male	205.24	391,497.07	$8,999.93
	Female	374.33	453,993.32	$10,436.63
	Both	579.57	845,490.39	$19,436.56
	Total productivity loss		19,505,673.01	$449,394.69
1USD=43.5 ETB				

Note: productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB

4. Discussion

In this prevalence-based retrospective cost of illness study, we estimated the economic burden of hypertension among productive age population from societal perspective. A total direct (medical and non-medical) annual cost incurred due to hypertension in the study population was $US 64,837.48 ($US 13.308 per person per month). Out of direct costs, 80.0% ($US 51,915.40) was direct medical cost. While, the total indirect annual cost incurred due to hypertension was $US 449,394.69 ($US 92.24 per person per month). The total annual economic burden of hypertension was $US 514,232.16 ($ US 1266.58 per person per year). This is higher than findings from another institution-based cross-sectional study conducted to evaluate cost of hypertension illness among patients attending hospitals in Southwest Shewa Zone that showed the mean monthly total cost of hypertension illness was US$ 22.3 (95% CI, 21.3–23.3) (61). Findings from an institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that total cost of hypertension was $91.72 ± 78.65 per patient per year (62). The COI study conducted among 202 hypertensive patients in Ghana that showed the total annual treatment cost of hypertension was $US 76,275.60 ($US31.47 per person per month) (63). This variation could be explained by some uncertainties in our estimation (i.e. uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate).

However, this is less than findings from and a study conducted in Canada also showed that annual individual healthcare cost of hypertension was $ US 2,341 (64), and study conducted in the USA showed that individuals with hypertension had $ US 1,920 higher annual incremental expenditure (65). This variation could be explained by variation in socioeconomic and population health status, and asymptomatic nature of hypertension (66), a significant number of undiagnosed hypertension among adults, and difference in health care system and level of care.

In this study, indirect cost accounted for more than three fourth of hypertension-related costs 85.6% ($449,394.69 USD). This is against evidence generated by a cross-sectional study conducted to determine the burden of out-of-pocket payments among patients with cardiovascular disease in public and private hospitals in Ibadan, South West, Nigeria showed that across all the hospital facilities, the annual direct and indirect outpatient costs were $1164.2± $2363.8 and $52.87±$148.05 respectively (67). An institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that the direct medical and non-medical cost constituted 60.81% and 12.17% of the total cost of hypertension respectively (62). An institution-based cross-sectional study conducted to evaluate cost of hypertension Illness among Patients Attending Hospitals in Southwest Shewa Zone showed that the mean monthly total cost of hypertension illness was US$ 22.3 (direct cost of US$ 11.39 and indirect cost US$ 10.89) (61). This is also higher than evidence that suggested about a half of the costs associated with CVD burden are caused by direct healthcare costs (68). The findings from a study conducted in Ghana direct cost accounting for almost 70% of the total cost of managing hypertension (63). Similarly, a study conducted in rural Yunnan Province of China showed that direct costs represented the largest component of the economic cost of hypertension (69). The variation could be explained by significant number of productive age populations affected hypertension in the study area and poor blood pressure control. Therefore, it is important to promote existing strategies and develop country/region-specific strategies for hypertension prevention and control (i.e., annual screening of the high-risk population and promoting healthy lifestyles) by all stakeholders could reduce the economic burden of hypertension Ethiopia (70, 71).

Concerning pre-mature mortality, a total of 11,858 (6,159, men; 5,699 women) years were lost due to hypertension-related premature mortality. This equates $US 429,958.12. Concerning health-related life loss, about 26,678 deaths per study population were due to hypertension. This is higher than the number of hypertension-related death occurred in 2017, which as 11,050 (7). This could be explained by the increasing trend of hypertension in the country.

From 11,585 years lost due to premature death in the treated hypertension cohort. More than one-half of related deaths, 6027 (50.83%) were due to treated uncontrolled hypertension. This is supported by evidence from other studies that revealed uncontrolled blood pressure cost $370 billion globally in 2001 (72). This is because the relative risk of all-cause mortality is higher among treated and uncontrolled (1.62) than untreated (1.40) and treated controlled (1.12) patients (53).

Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for 440.55 (76.01%) of productive life years lost from treated hypertension cohort. This is higher than findings from a study conducted to estimate the economic burden of hypertension in a given year in rural Yunnan Province of China showed that the overall prevalence of and

YLL/1000 population because of hypertension was 24.8% and 1.5 years for the survey population, respectively (69). A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to treated hypertension. The estimated national life years lost due to hypertension is 19,319 (i.e., $US 846,413.56). This is supported by evidence from a study conducted Australia that revealed hypertension caused 609, 801 productivity-adjusted life years loss (equating to AUD$ 137.2 billion) over the working lifetime (73). Therefore, prevention of hypertension and improving the rate of blood pressure control is important to reduce hypertension-related complications and productive life-year loss in the region as well as in the country (74).

5. Conclusion

The societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars economic burden. Prevention of hypertension could result in $US 2,571,160.8 annual economic savings in the Southern Region. Therefore, designing and implanting strategies for prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels (national, regional, zonal, community, and patient-level) is critical to saving scarce health resources.

6. Abbreviations

BP: Blood Pressure

CPG: Clinical Practice Guideline

CVD: Cardiovascular Diseases

DALY: Disability Adjusted Life Years

DBP: Diastolic Blood Pressure

EDHS: Ethiopia Demographic Health Survey

HDL: High-Density Lipoprotein

ICER: Incremental Cost-Effectiveness Analysis

LDL: Low-Density Lipoprotein

LMICs: Low- and Middle-income Countries

MI: Myocardial Infarction

QALY: Quality Adjusted Life Years

SBP: Systolic Blood Pressure

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

YLD: Years Lived with Disability

YLL: Years of Life Lost

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Legends

List of Figures

Figure 1: Micro-costing Bottom-up Approach for Healthcare costs. Adapted from Riewpaiboon A, et al. Cost analysis for efficient management: diabetes treatment at a public district hospital in Thailand.

Figure 2: Number of premature deaths and years of life lost (YLL) due to morbidity among adults with hypertension by sex, treatment and control status over productive life years simulated from life table modelling in Southern Ethiopia

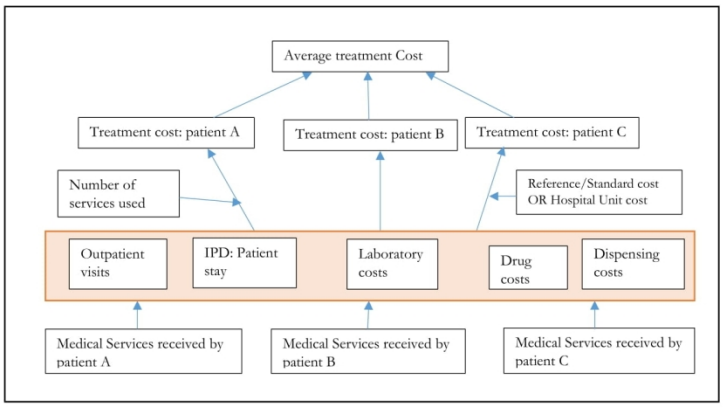

Figure 1: Micro-costing Bottom-up Approach for Healthcare costs. Adapted from Riewpaiboon A, et al. Cost analysis for efficient management: diabetes treatment at a public district hospital in Thailand.

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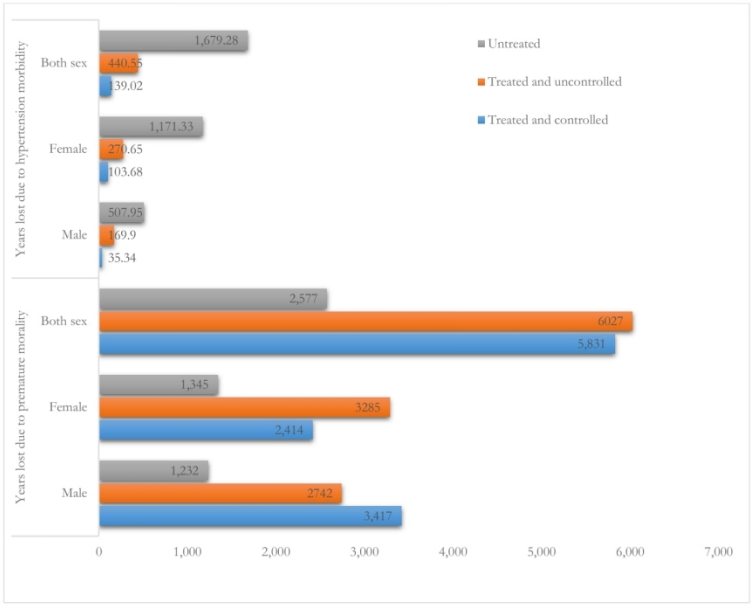

Figure 2: Number of premature deaths and years of life lost (YLL) due to morbidity among adults with hypertension by sex, treatment and control status over productive life years simulated from life table modelling in Southern Ethiopia

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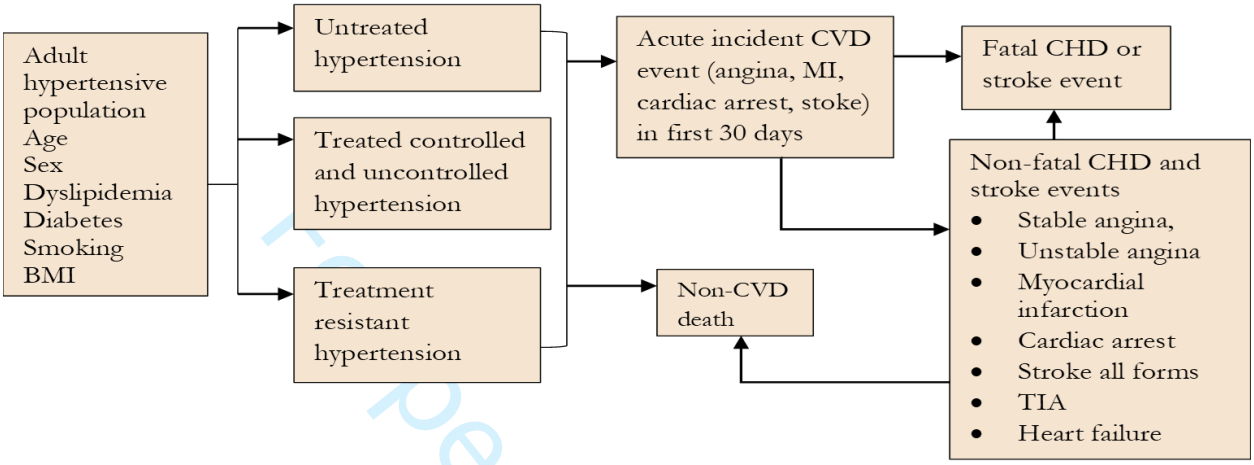
Supplementary materials: Economic burden of hypertension at selected Hospitals in Southern Ethiopia; a patient level analysis

Cardiovascular disease policy model



Supplementary Figure 1: Cardiovascular disease policy model adapted for Sub-Saharan African perspective (1).

Supplementary Table 1: Age and sex specific distribution of Ethiopian population 2020 estimate, prevalence of hypertension and adult mortality rate

Age structure	Male	Female	Total	Estimated prevalence of hypertension	Mortality rate		Data Source
Prevalence of hypertension					Men	Women	(2-8)
0-14 years	21,657,152	21,381,628	43,038,780	NA	-	-	
15-19	5,572,330	5,464,174	11,036,504	19.6	0.00286	0.00222	
20-24	5,930,683	5,816,173	11,746,856	19.6	0.00319	0.00223	
25-29	4,889,739	4,802,450	9,692,189	19.6	0.00293	0.002.32	
30-34	3,761,349	3,757,544	7,518,893	23.0	0.00397	0.003.68	
35-39	3,091,148	3,182,837	6,273,985	23.0	0.00411	0.00222	
40-44	2,445,523	2,488,422	4,933,945	25.9	0.00584	0.00385	
45-49	2,071,480	2,033,228	4,104,708	25.9	0.00360	0.00457	
50-54	1,567,789	1,660,957	3,228,746	41.9	0.00354	0.00274	
55-59	1,159,002	1,316,318	2,475,320	41.9	0.00354	0.00274	
60-64	946,594	1,109,670	2,056,264	41.9	0.00354	0.00274	
≥ 65 years	1,676,478	1,977,857	3,654,335	41.9	0.00354	0.00274	
Total	54,769,267	54,991,258	109,760,525				
				Prevalence of untreated hypertension			
For all ages (15 +)				13.25			(9)

Supplementary Table 2. Model Parameters, Cohort Setting, and Probability of Transition between states and Disability weights for hypertension and related complications the Global Burden of Disease 2013 study and WHO Global Health Estimates

Parameter	Data	Source
Relative risk of hypertension treatment		
Relative risk of CHD event on hypertension treatment	0.683 (95% CI, 0.633–0.717)	(10-13)
Relative risk of a cerebrovascular event on hypertension treatment	0.633 (95% CI, 0.526–0.717)	(14)
Relative risk of CHD event on normotensive men and women	0.49 (95% CI 0.458–0.513) and 0.32 (0.292–0.342)	(15)
Transition probabilities to death		
Health state	**Disability weight Estimate**	**Source**
Hypertension		**(16)**
Treated	0.246	
Untreated	0.323	
Treated and controlled	0.171	
Myocardial Infarction (MI)		(17)
Day 1-2	0·432	
Days 3-28	0·074	
Angina Pectoris		
Mild	0·033	
Moderate	0·080	
Severe	0·167	
Heart failure		
Mild	0·041	
Moderate	0·072	
Diabetes, digestive, and genitourinary disease		
Diabetes	0.015 (0.012 - 0.018)	(18-20)
Treated	0.033	
Untreated	0.012	

Diabetic neuropathy	0.133	
Chronic kidney disease (stage IV)	0.104	
End-stage renal disease: with kidney transplant	0.024	
End-stage renal disease: on dialysis	0.571	
Disutility due to daily medication	0.049 (0.031–0.072)	
Acute Events		
Myocardial Infarction	0.432 (0.288–0.579)	
Stroke	0.570 (0.377–0.707)	
Occurrence of second or later CVD event	0.985 (0.992–0.989)	
Chronic States		
Ischemic Heart Disease	0.08 (0.02–0.24)	
Stroke	0.135 (0.01–0.437)	
Alive post 2+ CVD Events	0.242 (0.11–0.437)	

CHD, coronary heart disease; SMR, standardized mortality ratio. *Age and sex dependent †Applied multiplicatively to general population age- and sex-dependent utilities; CHD= Angina pectoris, coronary insufficiency, myocardial infarction, or coronary death.

Supplementary table 3: Simulation input parameters

Input parameter	Value	Source
Non-CVD death rate	0.005–0.176 (Age- and sex specific)#	Calculated from WHO lifetables and GBD 2017 (21)
Probability of first-time cardiovascular disease (CVD) event	Individual risk characteristic specific	Obtained from the Globorisk Office Calculator standardized for India [25]
Acute CVD events		
MI		
Probability of MI if CVD event occurs	37.6– 66.7% (Age- and sex specific)#	Calculated based on GBD 2017(21)
30-day fatality	0.01–0.13 (Age- and sex–specific)#	Calibrated based on findings of Huffman et al. 2018 (22)
Re-infarction (in 30 days)	0.0120 (0.0099–0·0141)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Acute Stroke (in 30 days)	0.0060 (0.0045–0.0075)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Stroke		
Probability of Stroke if CVD event occurs	33.2–62.3% (Age- and sex specific)#	Calculated based on GBD 2017 (21) And Jushua D. Bundry et al(23)
30-day fatality	0.12, 0.13 (Sex-specific)#	Calibrated based on a multi-site study by Pandian and Sudhan 2013 [30]
Repeat Stroke (in 30 days)	0.15 (0.1–0.2)ψ	Petty et al. 1998 (24)
Sudden cardiac death	0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years	Heart disease and stroke statistics 2021 update
Heart failure		
Probability of AHF		
30-days fatality	0.0945	Obtained from the THESUS-HF registry (25) and Korean Acute Heart Failure Registry (KorAHF)(26, 27)

Re-hospitalization	0.0736	Obtained from the THESUS-HF registry (25)
Chronic events		
Monthly risk of mortality	0.001–0.019 (Age- and sex-specific)#	Calibrated based on GBD 2017 (21)
Reinfarction	0.079 (0.073–0.085)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.014 (0.012–0.016)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20) Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) (29), BP reduction and secondary stroke prevention: systematic review(30)
Stroke		
Monthly risk of mortality	0.001–0.013 (Age- and sex specific)#	Calibrated based on GBD 2017 (21) Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study(31)
Acute MI	0.043 (0.038–0.048)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.037 (0.033–0.041)	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Relative risk of fatality for an individual with two or more CVD events	1.5	Smolina et al. 2012 (32)
Heart failure		
Incidence		Bulter J.et al (33, 34), and Davis BRK. et. al (35)
1 year mortality		
Re-hospitalization		**Moita B.eta al. 2019(36) and (37)**
Effect of antihypertensive medication		
Medication protocol for an individual	Initial SBP-specific#	Based on Ethiopian NCD control guideline
IHD relative risk due to medication	0.32–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009 (38) and Asayam Kei., 2017(39)
Stroke relative risk due to medication	0.20–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009(38)
IHD relative risk if partially adherent	0.66–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009(40)
Stroke relative risk if partially adherent	0.60–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009 (40) and Lisheng Liu, Zengwu Wang. et al(41)

Supplementary Table 4: Price of drugs, medical supplies, procedures and professional time used for management of hypertension in Southern Ethiopia, January, 2021

List of medicines	Unit	Price in 2021 Ethiopian birr		Price USD	Source
		Wholesale price	Retail price	Retail Price in 2021 USD	
Acetylsalicylic Acid - 81mg – Tablet (coated)	10x10	43.72	1.32	1.303	Ethiopian Pharmaceutical supply agency, Arba Minch Hub wholesale price 2021 and Arba Minch General hospital pharmacy retail price 2021
Adrenaline (Epinephrine)-0.1% in 1mL ampoule	Each	36.032	1.09	1.074	
Amiodarone - 100mg – Tablet	10x3	313.34	9.44	9.337	
Amlodipine - 10mg - Tablet	10x10	105.44	3.18	3.142	
Amlodipine - 5mg – Tablet	10x10	75.26	2.27	2.243	
Atenolol - 50mg – Tablet	10x10	58.70	1.77	1.749	
Atorvastatin - 20mg – Tablet	10x10	195.68	5.89	5.831	
Atorvastatin - 40mg – Tablet	10x3	140.76	4.24	4.195	
Beclomethasone Propionate -100mcg/dose – Aerosol	200 MD	131.85	3.97	3.929	
Candesartan - 8mg – Tablet	14x2	152.63	4.60	4.548	
Captopril - 12.5mg – Tablet	10x10	33.54	1.01	1.000	
Captopril - 25mg – Tablet	10x10	26.91	0.81	0.802	
Dexamethasone - 4mg/ml in 1ml Ampoule - Injection	10	3.95	0.12	0.118	
Captopril + HCT (50mg + 25mg)-Tablet	10x10	57.32	1.73	1.708	
Digoxin - 0.25mg – Tablet	10x10	202.18	6.09	6.025	
Enalapril Maleate - 10mg - Tablet	10x10	61.57	1.85	1.835	
Enalapril Maleate - 5mg – Tablet	10x10	63.92	1.93	1.905	
Enalapril Maleate – 2.5mg – Tablet	10x10	19.98	0.60	0.595	
Enalapril Maleate +HCT (10 mg + 25 mg)-tablet	10x10	78.22	2.36	2.331	
Glibenclamide - 5mg – Tablet	10x10	39.09	1.18	1.165	
Glucose 40% in 20 mL – IV infusion	Each	2.54	0.08	0.076	
Glyceryl Trinitrate - 0.4mg – Tablet (Sublingual)	100	487.21	14.67	14.518	
Hydralazine - 20mg/ml in 1ml ampoule - Injection	5	204.01	6.14	6.079	
Hydrochlorothiazide - 25mg – Tablet	25x4	48.05	1.45	1.432	
Insulin Isophane Biphasic (Soluble/Isophane Mixture)-(30 + 70)IU/ml in 10ml Vial -Injection(Suspension)	Each	85.20	2.57	2.539	
Insulin Isophane Human - 100IU/ml in 10ml Vial - Injection(Suspension)	Each	100.28	3.02	2.988	
Insulin Soluble Human - 100IU/ml in 10ml Vial	Each	106.21	3.20	3.165	
Lovastatin - 20mg – Tablet	10x10	84.59	2.55	2.521	
Metformin - 500mg – Tablet	10	27.78	0.84	0.828	
Methyldopa - 250mg – Tablet	100x10	51.75	1.56	1.542	
Metoprolol - 50mg – Tablet	10x10	94.43	2.84	2.814	
Morphine sulphate-30mg-tablet	110	410.71	12.37	12.239	
Nifedipine - 20mg – Tablet	10x10	58.70	1.77	1.749	
Prednisolone - 5 mg – Tablet	100x10	342.23	10.31	10.198	
Propranolol - 40mg – Tablet	10x10	67.54	2.03	2.013	
Propylthiouracil - 100mg - Tablet (Scored)	100	633.87	19.09	18.889	
Salbutamol - 0.1mg/dose - Aerosol (Oral Inhalation)	200 MD	117.20	3.53	3.492	
Spironolactone - 25mg – Tablet	10x10	81.87	2.47	2.440	
Thyroxin Sodium - 0.1mg – Tablet	100	178.49	5.38	5.319	
Valsartan + HCT (80mg +12.5mg)	7*2	38.47	1.16	1.146	
Laboratory and imaging costs		**Price per test ETB**		Price in 2021 USD	
CBC		75.00		1.72	Arba Minch General Hospital Laboratory service price 2021
FBG/RBS		20.00		0.46	
Lipid profile (LDL, HDL, Total cholesterol, Triglyceride)		160.00		3.68	
ECG		120.00		2.76	
ECO		350.00		8.05	
CT-scan		1200		27.59	
RFT (bilirubin, creatinine)		80.00		1.84	
Chest-ray		726		16.69	
Urine analysis		15.00		0.34	
Body fluid analysis		100.00		2.30	
H. pylori		50.00		1.15	

Liver function test (AST, ALT, ALP)	120.00	2.76	
Thyroid function test (T3, T4, TSH)	432.00	9.93	
Hospital bed days			
Primary hospital	52.52	1.21	WHO Choice (42) inflated to 2021
Secondary hospital	54.76	1.26	
Tertiary hospital	70.81	1.63	
Health facility visit		0.00	
Primary hospital	18.58	0.43	
Secondary hospital	21.17	0.49	
Tertiary hospital	22.06	0.51	
Health center visit	23.00	0.53	
PCI intervention	63,000.00	1448.28	
In-patient costs for MI	45240.00	1040.00	
In-patient costs for Stroke	40890.00	940.00	
Outpatient cost for IHD (per annum)	1957.50	45.00	
Outpatient cost for Stroke (per annum)	2914.50	67.00	
Salary scale of human resource		0.00	
Physician	21,100.00	485.06	MOH, Ethiopia 2012/2019
Acute care nurse	7470.00	171.72	
Pharmacy personnel	8047.00	184.99	
Laboratory technician	6460.00	148.51	
Program cost per person per annum	993.29	22.83	(43).
Antihypertensive treatment			
Antihypertensive medication (per individual per annum	Drug costs based on national Drug supply agency wholesale price		
Out-patient consultations (per visit)	$43.36	Annual outpatient visit cost (12*WHO cost per outpatient visit inflated to 2021) WHO Choice (42)	
One-time diagnostic tests		Based on Laboratory procedures and test price of Arba Minch General Hospital, 2021	
In-patient costs for MI	$1040	WHO Choice (42) inflated to 2021	
In-patient costs for Stroke	$940		
Chronic CVD care			
Secondary care medication in public sector (per individual per annum)	$92, $184 (Dosage-specific)§	MSH-2015 International Drug Price Indicator inflated to 2021(25)	
Outpatient cost for IHD (per annum)	$45	WHO Choice (44) inflated to 2021	
Outpatient cost for Stroke (per annum)	$67		
Average inflation rate Ethiopia	16.58%	https://take-profit.org/en/statistics/inflation-rate/ethiopia/	
Average inflation rate foreign	2.02%		
Percentage change	24.6%		
Exchange rate July 2021 (1USD)	43.5 ETB		
1USD = 20.999 ETB in 2016 and 43.5 in 2021; PPP= 12.1/8.1 = 1.5			
MD: metered Dose; MOH: Ministry of Health 1 USD = 43.5 January 2021 **Note**: 30% mark-up at regional EPSA hub, 31% mark-up at Public Hospital level			

Supplementary Table 5: Risk of death across age and gender covariate categories stratified for hypertension

Variables	Categories	Incidence of death (%)		Relative risk in each category (CI)	Source
		High BP group	Normal		
Age	20-29	1.68%	0.54%	3.11 (1.16-8.36)	*(8)*
	30-39	1.71%	0.94%	1.82 (1.04-3.19)	
	40-49	2.43%	1.88%	1.29 (0.91-1.82)	
	50-59	6.30%	4.03%	1.56 (1.28-1.91)	
	60 and above	19.32%	15.9%	1.21 (1.12-1.31)	
Gender	Women	8.71%	1.1%	3.31 (2.98-3.68)	
	Men	15.47%	4.62%	3.34(3.02-3.70)	
Risk of all case mortality					
Gender	Treatment status	< 60 years	> 60 years	HR (95% CI)	(45)
Men	Normal	0.0068	0.0214	1.00 (Reference)	
	Treated controlled	0.0188	0.0305	1.20 (0.92-1.57)	
	Treated uncontrolled	0.0252	0.0372	1.55 (1.19-2.01)	
	Untreated	0.0197	0.0336	1.45 (1.23-1.72)	
Women	Normal	0.00528	0.01870	1.00 (Reference)	
	Treated controlled	0.01675	0.02841	1.11 (0.84-1.47)	
	Treated uncontrolled	0.02533	0.03736	1.63 (1.34-1.99)	
	Untreated	0.02075	0.03471	1.31 (1.06-1.61)	

Supplementary Table 6: Annual mortality rate in the total population, those with hypertension by treatment and control status and those without hypertension in Ethiopia in 2021 by age group and sex based on literature review of systematic reviews and clinical trials

Age group	Mortality rate in the total population	Mortality rate among people without hypertension	Mortality rate among people with treated and controlled hypertension	Mortality rate among people with treated but uncontrolled hypertension	Mortality rate among people with untreated hypertension	References
Women						
15-19	0.00222	0.00222	0.016746	0.025	0.02075	Ko, Min Jung. et al. 2016 (46), Mende Sorato, et al, 2021. (1, 23, 45, 47, 48).
20-24	0.00223	0.00223	0.016746	0.025	0.02075	
25-29	0.00232	0.00232	0.016746	0.025	0.02075	
30-34	0.00368	0.00368	0.016746	0.025	0.02075	
35-39	0.00222	0.00222	0.016746	0.025	0.02075	
40-44	0.00385	0.00385	0.016746	0.025	0.02075	
45-49	0.00457	0.00457	0.016746	0.025	0.02075	
50-54	0.00182	0.00182	0.016746	0.025	0.02075	
55-59	0.00182	0.00182	0.016746	0.025	0.02075	
60 -64	0.00441	0.00441	0.028414	0.037	0.03471	
Men						
15-19	0.00286	0.00286	0.018783	0.025	0.01969	Kuriakose A. et al. 2014. (8), EDHS, 2016 (7, 45, 47-50)
20-24	0.00319	0.00319	0.018783	0.025	0.01969	
25-29	0.00293	0.00293	0.018783	0.025	0.01969	
30-34	0.00397	0.00397	0.018783	0.025	0.01969	
35-39	0.00411	0.00411	0.018783	0.025	0.01969	
40-44	0.00584	0.00584	0.018783	0.025	0.01969	
45-49	0.0036	0.0036	0.018783	0.025	0.01969	
50-54	0.00354	0.00354	0.018783	0.025	0.01969	
55-59	0.00354	0.00354	0.018783	0.025	0.01969	
60-64	0.00354	0.00354	0.030451	0.037	0.03365	

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Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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	Reporting Item	Page Number
Title		
#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1

Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	1
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	2
Methods			
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	3-10
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	9

Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	10
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	NA
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	4-6
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	NA
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use	NA

		associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	
Methods			
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Supplementary figure 1
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	9

Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-15
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	NA

Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	23

Notes:

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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Societal economic burden of hypertension at selected hospitals in southern Ethiopia; a patient-level analysis

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I. Abstract

Objectives: There is inadequate information on the economic burden of hypertension treatment in Ethiopia. Therefore, this study was conducted to determine the societal economic burden of hypertension at Selected Hospitals in Southern Ethiopia.

Methods: Prevalence-based cost of illness (COI) study from a societal perspective was conducted. Disability-adjusted life years (DALYs) were determined by the current world health organization's recommended DALY valuation method. Adjustment for comorbidity and a 3% discount was done for DALYs. The data entry, processing, and analysis were done by using SPSS version 21.0 and Microsoft Excel 2013.

Results: We followed a cohort of 406 adult hypertensive patients retrospectively for 10 years from September 2010 to 2020. Two hundred-fifty (61.6%) of patients were females with a mean age of 55.87 ± 11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their blood pressure control target. A total of 64,837.48 United States Dollar ($US) direct cost was incurred due to hypertension. A total of 11,585 years and 579.57 years were lost due to hypertension-related premature mortality and morbidity respectively. Treated and uncontrolled hypertension accounted for 50.83% (6027) of total years lost due to premature mortality from treated hypertension cohort. Total productivity loss due to premature mortality and morbidity was $US 449,394.69. The overall economic burden of hypertension was $US 514,232.16 ($ US 105.55 per person per month).

Conclusion: Societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars. Treated and uncontrolled hypertension took the lion's share of economic cost and productivity loss due to premature mortality and morbidity. Therefore, designing and implanting strategies for the prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels is critical to saving scarce health resources.

Strengths and limitations of this study

- Using the cardiovascular disease policy model adapted to Sub-Saharan African perspective,
- Including productivity loss costs associated with hypertension (premature mortality and morbidity) and
- Obtaining all simulation variables and transition probability data from valid sources (systematic reviews, randomized controlled trials, and prospective cohort studies) were the strengths of this study
- Uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate which require due consideration during applying the findings of this study were limitations.

1. Introduction

Hypertension doubles the risk of death from stroke, heart disease, vascular diseases, diabetes, atherosclerosis, and kidney disease (1). According to the national STEPS survey, only 28.4% of hypertensive patients were taking antihypertensive medication prescribed by professionals in Ethiopia (2). According to the International Society of hypertension global hypertension practice guideline 2020, hypertension remains the leading cause of death globally, accounting for 10.4 million deaths per year (3).

Hypertension is associated with societal and economic consequences particularly in Low and middle-income countries (LMICs). In addition to the direct costs associated with health care utilization for the management of complications, hypertension causes significant productivity loss from disability and premature death (4, 5). WHO report from South East Asian region also indicated huge impact of hypertension in national finances due to premature death, disability, personal and family disruption, loss of income, and healthcare expenditure (6). According to a WHO report in 2017, stroke, coronary heart disease, and hypertension caused 39,571, 46,943, and 11,050 deaths respectively (i.e. 30 patients per day die due hypertension) in Ethiopia (7).

Cost of illness (COI) study is used to measure the economic burden of disease to individuals, communities, and society as a whole. It can provide information to support the political process and healthcare decision-making if it is conducted from a societal perspective by using an appropriate approach and bottom-up costing strategy (8-10) (11, 12). Despite this huge impact on national economies, the economic burden of hypertension is not studied in Ethiopia particularly Southern Ethiopia. To fill this evidence gap, this study was conducted to determine the economic burden of hypertension at selected public hospitals in Southern Ethiopia by using the prevalence-based cost-of-illness method from a societal perspective to estimate the direct and indirect costs of hypertension in a given year (2021) in Southern Ethiopia.

2. Methods and Materials

2.1. Study design, Area and Period

A prevalence-based retrospective cost of illness study from societal perspective focusing on quantifying direct and indirect costs was conducted from September 2010- September 2020 in at three selected public hospitals Southern Ethiopia. The bottom-up approach was used to estimate the economic burden of hypertension in Southern Ethiopia (figure 1). The human capital approach was used to calculate indirect costs separately in males and females and also among different age groups. A prevalence-based COI model was constructed in which hypertensive patients were simulated from diagnosis through active treatment, palliative care, and death over 15-64 years. Age and sex-specific mortality rates, measures of productivity, and workforce statistics were used to simulate the progression of these cohorts until death or age 64 years. First, the model estimated cumulative years of life and DALYs lived for the working-age population who had hypertension. Then the

model re-simulated with the hypothetical assumption that they did not have hypertension, with relevant changes to mortality rates and productivity. We estimated the probability of death separately for (1) all-cause mortality in absence of hypertension and related complications and (2) mortality attributable to the included disease states. The first component was estimated using WHO Life Tables, and the second component was calculated based on standardized mortality ratios extracted from the literature. The natural history study conducted in 1974 showed that the mortality rate was 1.85 (3.01 in males and 1.62 in females) (13). Interventional trials suggested that it could be possible to achieve effective BP targets in about 70% of patients by improving adherence and/or intensifying therapy (14).

2.2. Study populations

The study populations were selected adult hypertensive patients at three selected public hospitals. According to the world population prospect 2020 estimate (15). In the same year, the population of the Gamo zone accounted for 1.5% of the total population, Gofa, and South Omo Zone 1.5% of the total population. The target population is 3.0% total population of Ethiopia or 20% of the Southern Ethiopian population (6,208,034). Based on age distribution: 0-14 years are children, 15-24 years are early working age, 25-54 years are prime working age, 55-64 years are mature working age and ≥ 65 years are elderly (13).

2.3. Inclusion and exclusion criteria

We included all adult hypertensive patients having at least five years of follow-up visits before data collection and receiving care during the study period from selected facilities. However, patients who are unwilling to participate in this study, patients who have less than five years of follow-up, and incomplete patient records (don't contain follow-up BP records and refill medications, laboratory requests, and results) were excluded.

2.4. Study Variables

Dependent Variables

- Economic burden of hypertension

Independent variables

- Patient-related (socio-demographic characteristics, heart disease knowledge, healthy lifestyle and heart disease risk perception, presence of comorbidity, type of medications, treatment adherence, shared decision making, health-related quality Life)

Cost related variables

- **Medical costs** (inpatient hospital stay/hospitalization cost, outpatient clinic visit, drug acquisition costs, drug administration cost, laboratory test, and imaging study costs)

- **Non-medical costs** (transportation, meal, patient time cost due to treatment, cost due informal care by family or friends)
- **Indirect costs** (absenteeism, presenteeism, unemployment, early retirement, disability, premature death)

2.5. Sample Size and Sampling Technique

2.5.1. Sample size determination

The sample size was determined by using the single population proportion formula by taking prevalence of patients controlled their BP as 14% from WHO 2016 BP control rate report (16-18) and Z value of 1.96 at 95% confidence interval. We added 10% for non-response rate and two for design effect due to multi-stage sampling technique involvement. Finally, a formula giving a larger sample size was used. Total 407 hypertensive adult patients who are on follow-up care will be included.

$$n = \frac{(Z\alpha/2)^2 P(1-P)}{d^2} = 185$$

= 185 + (185 * 10%) = 203.5

= 203.5 *2 = 407

Where: **n** = is the sample size

- $\mathbf{Z^2}$= standard normal deviation, set at 1.96, correspond to the 95% confidence interval
- **d** = is the desired level of precision/margin of error (0.05)
- **p**= prevalence of patients taking anti-hypertensive (p=28.4%), and q is 1-p.

2.5.2. Sampling Techniques

A multi-stage simple random sampling technique was used. We randomly selected three zones from a total of 12 zones found in the Southern region. Three general public hospitals with experience of providing CVD care for at least five years from selected four zones were included in this study. The total sample size was allocated to these hospitals based on an estimated number of adult hypertensive patients attending respective hospitals (i.e., we included 212 patients from Arba Minch General Hospital, 107 patients from Jinka General Hospital, and 88 patients from Sawula General Hospital). Finally, a consecutive sampling technique was applied in each facility until the desired sample size was achieved.

2.6. Data collection tools and Procedures

2.6.1. Model input parameters

Key model input variables include; 2020 population of selected zones, hypertension prevalence by treatment and control status, Transition probabilities to death and healthy state, cost of diagnosis, and management. Among those with treated hypertension, treated and controlled hypertension was defined based on BP control target of ISH 2020 guideline (3). We used national STPES survey data to estimate the prevalence of cardiovascular risk factors (MI, angina, heart failure, stroke, TIA). Incorporating the risk factor prevalence data in the relevant Framingham risk equation, the age and sex-specific probability of CHD and cerebrovascular disease (i.e., stroke and transient ischemic attack) events were estimated. The probability of each health state

was calculated using the age- and sex-specific CHD and cerebrovascular disease event distributions (2, 19). To estimate the corresponding probabilities, separate relative risk estimates were used for CHD events (Stable Angina, Unstable Angina, and MI) and cerebrovascular diseases (Stroke and Transient Ischemic Attack), assuming that antihypertensive treatment affects the probability of every disease state similarly across all age and sex groups. Relative risk reductions attributable to antihypertensive treatment were extracted from the peer-reviewed literature (20-22).

The 2020 world population prospect estimate was used for the baseline population and number of 33-year-olds projected to enter the model population from 2020-2070 (15). The annual probability of coronary heart disease and stroke was based on national STEPS survey (2), and Framingham Heart Study (23) and the Framingham Offspring Study (24), by contextualizing to Ethiopian scenario. Incident coronary heart disease events were allocated to angina pectoris, myocardial infarction, or cardiac arrest. Prevalence, joint distributions, and means of Ethiopia risk factor values were estimated from the national STEPS survey (2). Annual transition rates between risk factor levels were calculated to preserve age-range trends over time. Betas for risk function for non-blood pressure risk factors were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort (24). Risk factors are assumed to affect the incidence of MI, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers are assumed to have a higher relative risk for infarction and arrest (25); and a proportionately lower coefficient for angina. Environmental tobacco exposure is assumed to carry a relative risk of 1.26 for MI and cardiac arrest compared with non-exposed non-smokers (26) but not to influence angina. The number of hospitalized MI were obtained from the national STEPS survey (2). Case-fatality rates and rates of MI in subgroups were estimated from national data and other complementary sources. Prehospital arrest deaths and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from our effectiveness study (Supplementary Table 1).

Survival after a coronary heart disease event was estimated and calibrated based on national or international data sources (27, 28). Rates of coronary revascularizations was estimated from the National hospital discharge survey, with mortalities estimated from aggregated historical data. Stroke incidence was assumed to be independent of the risk of new-onset coronary heart disease in the same year. The number of hospitalized strokes cases was obtained from national and regional studies. The annual probabilities of stroke after MI (29, 30) and the probability of coronary heart disease in stroke patients were based on natural history studies and systematic reviews of blood pressure control trials (31-36). A 30-day heart failure mortality and re-hospitalization data were from the THESEUS-HF registry (37) and Korean Acute Heart Failure Registry (KorAHF)(38, 39) (Supplementary Table 2 and 3).

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2020 was estimated from the National Health Survey data (2) and GBD 2017 (40). The background prevalence of prior coronary revascularization was estimated from revascularizations before 2019 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state. Age and sex-specific health care costs were estimated using national data, and our effectiveness data. Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using WHO Choice (41) inflated to 2021. Outpatient consultations, and inpatient stay and bed days were also estimated from WHO choice (41) inflated to 2021. Chronic outpatient CVD costs additional to average background health care costs for the first year after the event and subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis was pooled from the 2015 national STEPS survey. Average annual non-cardiovascular costs were estimated from the national STEPS survey (2), and EDHS 2016 survey (13).

2.6.2. Cost estimation

The outcomes measures are total discounted societal costs, cost/year, and cost/patient-year. This is the amount of health budget that could be saved by effective prevention and control of hypertension. The direct costs were divided into two subcategories: direct medical costs and direct non-medical costs. Direct medical costs include; inpatient stays, outpatient clinic visits, medical services, drug acquisition, dispensing, administration, monitoring, laboratory test, and imaging study costs. The costs associated with outpatient/inpatient visits were estimated by multiplying the numbers of outpatient visits related to hypertension by the outpatient costs per year (i.e., twelve times WHO cost per outpatient visit for secondary hospitals inflated to 2021) (41).

Data concerning medications prescribed for the management of hypertension, and associated comorbidities, and laboratory tests and imaging studies were done were collected by patient chart abstraction in index year (2020). The cost of medications used for management of hypertension and associated comorbidities was taken from Ethiopian Pharmaceutical supply agency Arba Minch regional hub selling price and retail price of Arba Minch General Hospital in 2020. The retail price of Arba Minch General Hospital was used because of the minimum distance from the Pharmaceutical supply agency hub, which could minimize markup added on retail price due to transportation cost. Costs of laboratory procedures were also taken from Arba Minch Hospital Laboratory's service price list. The prices of relevant laboratory tests and imaging studies were based on the average price of included Hospitals. The salary scale of the health workforce was based on the FMOH of Ethiopia (Supplementary Table 4).

Ongoing program costs for hypertension care was estimated from WHO tool outputs for CVD and diabetes care and National strategic action plan (NSAP) for prevention & control of non-communicable diseases in Ethiopia 2014-2016 and adjusted for 2021 inflation target population (42). Adjustment for the study population was done by multiplying the national cost by the proportion of the study population (i.e., 3%). National and regional cost estimates were based on the proportion of patients studied (i.e. 3% and 20%). We considered this strategy since the

age and sex distribution of hypertension among different regions in the country is did not vary significantly. The collected cost data added up and averaged by using a bottom-up approach (Figure 1). Facility-based or reference costs were used during computing costs. The total medical cost of hypertension treatment was calculated as the sum of the product of medical costs with their respective unit prices. Costs were discounted at an annual rate of 3% and reported in 2021 USD (43, 44).

Direct non-medical costs include transportation costs and patient time costs due to care. The cost of patient time due to care was estimated by using the average daily wage of patients (97.00 ETB) which was calculated from 2912 ± 2732.24 average monthly income. Transportation cost was determined by using the cost of average traveling distance and local transportation tariff (42.00 ETB) in January 2021. According to EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13). This proportion was used to determine the patient time cost due to care for employed groups. For the unemployed proportion, the average daily wage of daily laborers workers working 8 hours per day for 6 days per week was used (26.53 ETB) from the monthly wage of 796.00 ETB (420-1172 ETB) (45).

Indirect costs include cost hospitalization, productivity loss due to illness, and cost of death. Cost-of hypertension-related hospitalization was taken from WHO Choice (41), costs per inpatient stay and cost per inpatient bed day times duration of hospitalization inflated for 2021, and professional time (physician, nurse laboratory professional, and pharmacist time). If a patient had multiple admissions during the year, the costs for each admission were aggregated as the total costs (46).

2.6.3. Mortality and morbidity estimations

Age and sex-specific mortality rates among the adult general population in Ethiopia were taken from EDHS 2016 survey and extrapolated to selected populations (13). According to EDHS 2016, the probability of dying before age 50 years among adults ≥ 15 years were 10% and 12%, in women and men respectively (13). Due to the absence of mortality data specific to hypertension treatment and control status in Ethiopia, mortality risk in the general population was attributed to those with and without hypertension using sex-specific estimates of the relative risk (RR) of all-cause mortality associated with hypertension by treatment and control status was derived from a study conducted in India was used (47). A cohort study conducted in India among adults 20 years and above to determine the Rate and Risk of all-cause mortality among people with HTN showed that the incidence of deaths in the study was 4.28% during the follow-up period of 6 years. The relative risk of mortality was 3.13 (CI: 2.91-3.37) and 1.2 in the high BP group and at age of 60 years. The age-adjusted hazard ratio of all-cause mortality for the high BP group was 2.96 (2.56-3.42) (47) (Supplementary Tables 5 and 6).

In 2020 crude death rate of the Ethiopian population-based on global estimates was 6.29 deaths per 1000 population (48). The estimated prevalence of hypertension among adults was calculated from National STEPS Survey 2016, systematic review and meta-analysis, and WHO report and local studies and the mean estimated

prevalence of hypertension was 21.39% (2, 13, 47, 49-52). Only 28.4% of patients with hypertension are taking antihypertensive medication (2). The mean relative risk of all-cause mortality among hypertensive population when compared to those without hypertension was 1.39 (0.95 to 1.95) (53) (Supplementary Table 3).

Years of life lost due to hypertension morbidity was determined by first calculating disability weights for specific ages based on blood pressure control status (X). Then subtract this value (X) from the life expectancy of the Ethiopian population (i.e., 66.7 years for men, and 70.4 years for women) (Y). The productivity loss cost due to hypertension morbidity was calculated by multiplying Y with sex-specific employment rate based on a monthly average income of 2059.078 ETB from the National STEPS survey 2015 adjusted for 2021 inflation (13,13/9.57=1.372) STEPS Survey, 2015 (2). The EDHS 2016 survey showed that 33% of women and 88% of men are currently employed (13) and for unemployed, 2019 minimum average monthly earnings (ETB) of daily laborers reported by the MOLSA 796 ETB (420-1172 ETB) (45). Concerning, cost of productivity lost due to premature mortality: first we calculated potential years of life lost (YLL) by subtracting life expectancy from sex-specific age of death at which the death is recorded (Z). Then Z is multiplied by the number of deaths in each age group (Xi). Finally, we multiplied Xi with sex-specific employment rates like productivity loss due to hypertension-related morbidity above (54). Excess mortality and morbidity due to hypertension to hypertension were determined by subtracting age and sex-specific morbidity and mortality among the general population from the hypertensive cohort. Both were determined by using age, sex, and blood pressure treatment status mortality rate per 1000 person-years (Supplementary Table 6).

2.6.4 Morbidity adjustment

Patients with hypertension may have more than one disease, the addition of YLDs across causes may result in overestimation of the total loss of health (55). Therefore, it is recommended to estimate comorbidities using the assumption of independence within age-sex groups (56):

$$\mathbf{P_{1+2} = P_1 + P_2 - (P_1 \times P_2) = 1 - (1 - P_1) \times (1 - P_2)}$$

- **Where** P_{1+2} is the prevalence of the two comorbid diseases 1 and 2,
- P_1 is the prevalence of disease 1 and $\mathbf{P_2}$ is the prevalence of disease 2.

The combined disability weight for individuals with multiple conditions is estimated assuming a multiplicative model as follows:

$$\mathbf{DW_{1+2} = 1 - (1 - DW_1) \times (1 - DW_2)}$$

Since prevalence YLDs are calculated for each cause as:

$$\mathbf{YLD_i = DW_i \times P_i}$$

- two preceding equations can be combined into a single calculation resulting in:

$$YLD_{1+2} = 1 - (1-YLD_1) \times (1 - YLD_2)$$

2.6.5 Assumptions and Transition probabilities

The counterfactual comparator (hypothetical cohort of normotensive individuals) with a probability of developing CVD events among the general population. Both in case and comparator cohorts, the probability of non-CV death does not depend on the health state and is similar for both hypertensive and normotensive populations (57) and we chose not to model differential use of antihypertensive medication classes in order not to bias cost-of-treatment. Antihypertensive dose intensification and frequency of BP monitoring were based on ISH 2020 guidelines for blood pressure control. We did not simulate the effects of any particular medication; instead, we simulated "standard dose" effects and assumed average drug prices across classes (58). The amount of blood pressure change was assumed to be a function of the baseline BP and the effect of a standard-dose antihypertensive agent at that pre-treatment level (59). We also assumed the medication adherence rate as 75% based on clinical trials (59). Other important assumptions include cost of illness due to hypertension or associated morbidities were calculated based on the monthly earnings during data collection; all costs incurred before one year were adjusted/accounted to today's value (2021 USD equivalent) and discounted at 3%; years of life lost and years of life lived with disability (YLDs) were not discounted as per the recent WHO recommendations.

2.7. Data Quality control, Processing, and Analysis

Questionnaires are prepared in English and the patient interview part of the questionnaire was translated into Amharic and translated back into English to check its consistency. The Amharic version of the patient interview questionnaire and English version of the health professional interview, data abstraction form, and health system interview questionnaires was used for data collection. The questionnaire was pretested on 30 adult hypertensive patients in Arba Minch General Hospital to ensure that the respondents could understand the questions and to check for consistency and possible amendments were made based on findings. Six professional nurses (BSc.) for data collection and one senior professional working in the respective health facilities for supervision were oriented before data collection about data collection approaches and contents of data collection format for one day by the principal investigator. Continuous follow-up and supervision were made by the principal investigator throughout the data collection period. The collected data were checked for completeness and consistency by the principal investigator on daily basis at the spot during the data collection time. Then data were transcribed back to English for the patient interview part and entry was made using Epi-data 3.1 software. After data processing, analysis was done by using SPSS version 21.0 and Microsoft excel 2010. A summary of descriptive statistics was reported for socio-demographic factors; cost of hypertension and life years lost due to hypertension related morbidity and premature mortality and presented in tables and figures.

2.8. Patient and Public involvement

There was no identifiable patient involvement in this research. Patients' demographic characteristics and disease related variables were obtained by using questionnaire based interview after obtaining verbal consent from the patient. No patient identifier information was collected. Finally, most of variables were taken from published national and international literatures, and all relevant sources were acknowledged through citation.

2.8. Statements

Ethics approval and consent to participate

The study was approved by Tehran University of medical sciences, Faculty of pharmacy, department of pharmacoeconomics, and pharmaceutical administration ethical review board with Approval ID: *IR.TUMS.MEDICINE.REC.1399.674* and Arba Minch University College of medicine and health sciences Institutional review board with Reference number: *IRB/T10/2012*. After clarifying the study objective and confidentiality of the information; verbal informed consent was obtained from each respective hospital before data collection.

Consent for publication

All authors read the full version of this manuscript and agreed to publish

Availability of data and materials

All the data reported in the manuscript are publicly available up on official request of principal investigator upon acceptance of the manuscript

Competing interests

The authors declare that they have no competing interests.

Funding

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Authors' contributions

All Authors read and approved the manuscript. *MM* conceived the research, framed the format design and developed the manuscript for publication; *MD participated in data analysis and reviewed the manuscript and AK* reviewed the manuscript and write-up process; *NS* and *TS* participated in literature review and polished the language of the manuscript.

3. Results

3.1. Description of study participants

In this study, we estimated the regional and national economic burden of hypertension (direct and indirect costs) by using the cardiovascular disease policy model adapted to the Sub-Saharan Africa perspective (60) (Supplementary Figure 1). Total costs of treated hypertension and hypertension-related excess mortality and years of life lost due to hypertension were determined. We followed a cohort of 406 hypertensive patients retrospectively for 10 years from September 2003 to 2013 Ethiopian calendar (September 2010-2020) for baseline assessment and simulated the cost of hypertension for lifelong from a societal perspective. About two-thirds, 250 (61.6%) of patients were females with a mean age of 55.87 ±11.03 years. Less than 1 in five 75 (18.5%) of patients achieved their BP control target based on international society of hypertension 2020 guidelines (Table 1).

Table 1: Patient characteristics and Disease related factors among adult hypertensive patients on regular follow-up at selected public hospitals in Southern Ethiopia, January 2021 (n=406)

Sociodemographic factors		Frequency
Sex	Male	156 (38.4%)
	Female	250 (61.6%)
Age in in years	Below 40 years	15 (3.7%)
	40- 65 years	286 (70.4%)
	65 years and above	105 (25.9%)
Religion	Orthodox	215 (53.0%)
	Muslim	37 (9.1%)
	Protestant	144 (35.5%)
	Catholic	10 (2.5%)
Annual gross income before tax (n=406)	Less than 12,000	117 (28.8%)
	12,000- 18,000	89 (21.9%)
	18,000- 23,000	200 (49.2%)
Level of Education	Illiterate	259 (63.8%)
	Grades 1-8	46 (11.3%)
	Grades 9-12	22 (5.4%)
	College and above	73 (18.0%)
	Post-graduate degree	6 (1.5%)
Occupation	Employed	65 (16.0%)
	Merchant	63 (15.5%)
	Farmer	79 (19.5%)
	House wife	149 (36.7%)
Disease related factors		
Duration of hypertension since diagnosis	5 - 9 years	262 (64.5%)
	10 - 14 years	131 (32.3%)
	15 and above years	13 (3.2%)
Family history of CVDs	1st degree relative	133 (32.7%)
	Second degree relative	16 (3.9%)
	None	257 (63.3%)
Presence of comorbidities (n=406)	Yes	310 (76.4%)
	No	96 (23.6%)
History of hospitalization	Yes	250 (61.6%)

	No	156 (38.4%)
Duration of hospitalization (n=250)	Below 5 days	56 (22.4%)
	5 to 10 days	112 (44.8%)
	More than 10 days	82 (32.8%)
Target BP achieved based on ISH 2020 guideline	Yes	75 (18.5%)
	No	331 (81.5%)
Antihypertensive regimen	Monotherapy	136 (33.5%)
	Two drug combination	234 (57.6%)
	Three and more drug combination	36 (8.8%)

3.2. Cost of hypertension

3.2.1 Direct (medical and non-medical) costs

Direct medical costs include program costs, cost of drugs for hypertension and comorbidities, laboratory costs, hospitalization costs, annual outpatient visit costs, and costs of medical supplies. A total of $US 64,837.48 direct cost was incurred due to hypertension. Out of this, 80.0% ($US 51,915.40) was direct medical cost. From direct medical costs, annual outpatient visit cost 33.55% ($US 17,419.73), cost of comorbidity 26.21% ($13,612.15 USD), and laboratory test costs 8.17% ($US 4,263.29) took the largest share. While, total direct non-medical costs of hypertension was $US 9,866.58 (i.e. transportation costs and patient time costs due to care). The regional and national annual estimated direct cost of hypertension were $US 324,187.40 and $US 2,161,249.33 respectively (Table 2).

Table 2: Direct annual costs of treating hypertension among adults in Southern Ethiopia, January 2021 (n=406)

Cost category	Annual total in ETB Total (mean ± Standard deviation)	Annual cost in July 2021 USD	Percentage from total direct cost
Direct medical total	**2,258,319.97**	51,915.40	80.0%
Program costs	403,275.70 (993.0 ± 0.00)	9,173.40	
Cost of antihypertensives	119,847.64 (295.19 ± 107.78)	2,726.20	
Cost of drugs for comorbidity	598,409.00 (2266.7 ± 1114.52)	13,612.15	
Cost for hospitalization	179,377.03 (3360.76 ± 1594.69)	4,080.33	
Laboratory tests	187,420.00 (461.63 ± 226.98)	4,263.29	
Annual outpatient visit costs	765,795.60 (1886.20 ± 0.00)	17,419.73	
Cost of medical supplies	4,195.00 (85.60 ± 0.00)	95.42	
Professional time total	**128,362.01**	2,950.85	4.6%
Physician time	92,032.08 (226.68 ±0.00)	2,093.47	
Nurse time	2,060.28 (43.84 ± 17.81)	46.87	
Pharmacy time	4,453.01 (10.97 + 0.00)	101.29	
Laboratory time	29,816.64 (73.44 ± 0.00)	678.25	
Direct non-medical costs	**433,748.59** (1068.84 ± 384.78)	9,866.58	**15.37%**
Total direct cost of treated hypertension	2,820,430.57	64,837.48	100.00%

1USD= 43.9614 ETB on July 13, 2021

ETB: Ethiopian Birr; USD: United States Dollar

3.2.2. Life years lost due to premature mortality and morbidity

We determined the years of life lost due to premature mortality (excess mortality) and years of life lost due to hypertension morbidity for the productive age population (30-64 years) among a cohort of simulated adult hypertensive patients. Excess mortalities are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension. The excess mortality and years of life lost were different among the hypertensive cohort and simulated population with no hypertension. A total of 11,858 (6,159, men; 5,699 women) life years were lost due to hypertension-related premature mortality among 30-64 years old adults with hypertension. This equates $US 428,969.78 ($US 270,076.91, men; $US 158,892.78). The estimated regional and national life years lost due to premature mortality was 59,290 and 395,267 respectively. This is equivalent to $US 2,144,848.58 and $US 14,298,990.51 respectively. From 15,232 years lost due to premature mortality in the hypertension cohort, treated and uncontrolled hypertension accounted for more than 6,824 (44.8%) total yeas lost due to premature mortality followed by treated controlled hypertension 5,832 (38.29%) and untreated hypertension 2,575 (16.9%) (Table 3 and 4).

Table 3: Excess deaths among adult hypertensive by treatment and control status over the working lifetime simulated from life table modelling in Southern Ethiopia January 2021

Age group	Deaths in Treated hypertension cohort	Deaths in 'hypertension cohort' assuming no hypertension	Excess deaths in those with treated hypertension	Deaths in those with hypertension by treatment and control status *		
				Treated and controlled	Treated and uncontrolled	Untreated
Men						
30-34	1,436	448	988	487	501	295
35-39	1,180	381	799	401	398	242
40-44	1,027	428	599	357	242	191
45-49	1,735	224	1,511	1,167	344	163
50-54	989	166	823	370	453	123
55-59	731	123	608	273	335	91
60-64	932	101	831	362	469	127
Total	8,030	1,871	6,159	3,417	2742	1,232
Women						
30-34	1,401	415	986	434	552	310
35-39	1,187	212	975	368	607	263
40-44	1,019	287	732	324	408	205
45-49	832	279	553	265	288	167
50-54	887	91	796	350	446	137
55-59	805	72	733	277	456	109
60-64	1,071	147	924	396	528	154
Total	7,202	1,503	5,699	2,414	3285	1,345
Box sex total	15,232	3,374	11,858	5,831	6027	2,577
* Excess deaths are all-cause deaths observed in those with hypertension compared to the same cohort assuming no hypertension						

Table 4: Years of life lost (YLL) by adults with hypertension by treatment and control status over the lifetime simulated from life table modelling in Southern Ethiopia, January 2021

Age group	Years of life lived in treated hypertension cohort	Years of life lived in 'hypertension cohort' assuming no hypertension	YLL lost to Treated hypertension (excess)	YLL lost due to hypertension by treatment and control status *		Years of life lived in untreated hypertension cohort	YLL lost due to Untreated hypertension
				Treated and controlled	Treated and uncontrolled		
Men							
33-39	199.87	181.2	18.67	18.67	NA	122.67	58.53
40-44	357.48	324.1	33.38	16.67	17.71	219.42	104.68
45-49	587.08	522.5	64.58	NA	64.58	353.73	168.77
50-54	341.9	295.3	46.6	NA	46.6	199.92	95.38
55-59	161.63	140.1	21.53	NA	21.53	94.85	45.25
60-64	129.88	109.4	20.48	NA	20.48	74.06	35.34
Total	1777.84	1572.6	205.24	35.34	169.9	1,064.65	507.95
Women							
33-39	318.33	288.6	29.73	29.73	NA	195.38	93.22
40-44	791.95	718	73.95	73.95	NA	486.09	231.91
45-49	1147.34	1040.2	107.14	NA	107.14	704.22	335.98
50-54	953.59	863.8	89.79	NA	89.79		279.01
55-59	491.71	445.8	45.91	NA	45.91	309.52	143.99
60-64	297.81	270	27.81	NA	27.81	182.79	87.21
Total	4,000.73	3626.4	374.33	103.68	270.65	1,878.00	1,171.33
Grand total	5,778.57	5199	579.57	139.02	440.55	2,942.65	**1,679.28**

NA= No patient is reported in this age group; * YLL=years of life lost by those with hypertension compared to the same cohort assuming no hypertension.

A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to hypertension morbidity. This equates to $US 19,436.56. A total of 11,858 (6,159 men; 5,699 women) years of life were lost due to hypertension related premature mortality. This equates to $US $429,958.12. Total productivity loss due to premature mortality and morbidity was $US 449,394.68 (Table 5). Treated and uncontrolled hypertension accounted for 2,937.72 (50.84%) of productive life years lost, followed by untreated hypertension 1,679.28 (29.06%). Treated uncontrolled hypertension contributed to more YLL due to premature mortality in both sexes 6,824 (44.8%), and life years lost due to hypertension morbidity 2, 9378 (50.84%) (Figure 2).

The overall estimated hypertension related economic burden (direct and indirect cost) was $US 514,232.16 in the study area (Table 2 and Table 5). Since the study population is estimated to be 20% of the Southern region, the estimated economic burden of hypertension in the region is $US 2,571,160.8 in the region. More than eight out of ten 87.37% dollars were due productivity loss. Productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB (Table 5).

Table 5: Mean annual productivity loss associated premature mortality and hypertension morbidity, Southern Ethiopia, January, 2021

Variable	Sex	Excess Years lost	Lost productivity ETB	Lost productivity in 2021 USD
Years lost due to premature morality	Male	6,159	11,748,345.71	$270,699.21
	Female	5,699	6,911,836.90	$159,258.91
	Both	11,858	18,660,182.62	$429,958.12
Years lost due to hypertension morbidity	Male	205.24	391,497.07	$8,999.93
	Female	374.33	453,993.32	$10,436.63
	Both	579.57	845,490.39	$19,436.56
	Total productivity loss		19,505,673.01	$449,394.69
1USD=43.5 ETB				

Note: productivity loss is calculated by taking 88% employment rate for men, 33% employment rate for women. Monthly wage of employed 2059.078 from EDHS 2016 and National STEPS survey 2015 which is adjusted for current inflation (1.3689). Unemployment/unpaid monthly wage of 796 ETB

4. Discussion

In this prevalence-based retrospective cost of illness study, we estimated the economic burden of hypertension among productive age population from societal perspective. A total direct (medical and non-medical) annual cost incurred due to hypertension in the study population was $US 64,837.48 ($US 13.308 per person per month). Out of direct costs, 80.0% ($US 51,915.40) was direct medical cost. While, the total indirect annual cost incurred due to hypertension was $US 449,394.69 ($US 92.24 per person per month). The total annual economic burden of hypertension was $US 514,232.16 ($ US 1266.58 per person per year). This is higher than findings from another institution-based cross-sectional study conducted to evaluate cost of hypertension illness among patients attending hospitals in Southwest Shewa Zone that showed the mean monthly total cost of hypertension illness was US$ 22.3 (95% CI, 21.3–23.3) (61). Findings from an institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that total cost of hypertension was $91.72 ± 78.65 per patient per year (62). The COI study conducted among 202 hypertensive patients in Ghana that showed the total annual treatment cost of hypertension was $US 76,275.60 ($US31.47 per person per month) (63). This variation could be explained by some uncertainties in our estimation (i.e. uncertainty in age and sex-specific prevalence of undiagnosed hypertension and variability in employment rate). Consideration of fixed employment rate according to EDHS 2016 survey (i.e., 33% of women and 88% of men) could contribute to the relatively higher annual economic burden of hypertension in our study area (13).

However, this is less than findings from and a study conducted in Canada also showed that annual individual healthcare cost of hypertension was $ US 2,341 (64), and study conducted in the USA showed that individuals with hypertension had $ US 1,920 higher annual incremental expenditure (65). This variation could be explained by variation in socioeconomic and population health status, and asymptomatic nature of hypertension (66), a

significant number of undiagnosed hypertension among adults, and difference in health care system and level of care.

In this study, indirect cost accounted for more than three fourth of hypertension-related costs 85.6% ($449,394.69 USD). This is against evidence generated by a cross-sectional study conducted to determine the burden of out-of-pocket payments among patients with cardiovascular disease in public and private hospitals in Ibadan, South West, Nigeria showed that across all the hospital facilities, the annual direct and indirect outpatient costs were $1164.2± $2363.8 and $52.87±$148.05 respectively (67). An institution-based cross-sectional study conducted to estimate the direct and indirect costs of hypertension at Gondar Specialized Hospital showed that the direct medical and non-medical cost constituted 60.81% and 12.17% of the total cost of hypertension respectively (62). An institution-based cross-sectional study conducted to evaluate cost of hypertension Illness among Patients Attending Hospitals in Southwest Shewa Zone showed that the mean monthly total cost of hypertension illness was US$ 22.3 (direct cost of US$ 11.39 and indirect cost US$ 10.89) (61). This is also higher than evidence that suggested about a half of the costs associated with CVD burden are caused by direct healthcare costs (68). The findings from a study conducted in Ghana direct cost accounting for almost 70% of the total cost of managing hypertension (63). Similarly, a study conducted in rural Yunnan Province of China showed that direct costs represented the largest component of the economic cost of hypertension (69). The variation could be explained by significant number of productive age populations affected hypertension in the study area and poor blood pressure control. Therefore, it is important to promote existing strategies and develop country/region-specific strategies for hypertension prevention and control (i.e., annual screening of the high-risk population and promoting healthy lifestyles) by all stakeholders could reduce the economic burden of hypertension Ethiopia (70, 71).

Concerning pre-mature mortality, a total of 11,858 (6,159, men; 5,699 women) years were lost due to hypertension-related premature mortality. This equates $US 429,958.12. Concerning health-related life loss, about 26,678 deaths per study population were due to hypertension. This is higher than the number of hypertension-related death occurred in 2017, which as 11,050 (7). This could be explained by the increasing trend of hypertension in the country.

From 11,585 years lost due to premature death in the treated hypertension cohort. More than one-half of related deaths, 6027 (50.83%) were due to treated uncontrolled hypertension. This is supported by evidence from other studies that revealed uncontrolled blood pressure cost $370 billion globally in 2001 (72). This is because the relative risk of all-cause mortality is higher among treated and uncontrolled (1.62) than untreated (1.40) and treated controlled (1.12) patients (53).

Untreated hypertension accounted for 1,679.28 (507.95 men, 1171.33 women) years of life lost. Treated and uncontrolled hypertension accounted for 440.55 (76.01%) of productive life years lost from treated

hypertension cohort. This is higher than findings from a study conducted to estimate the economic burden of hypertension in a given year in rural Yunnan Province of China showed that the overall prevalence of and YLL/1000 population because of hypertension was 24.8% and 1.5 years for the survey population, respectively (69). A total of 579.57 (205.24 men; 374.33 women) years of life were lost due to treated hypertension. The estimated national life years lost due to hypertension is 19,319 (i.e., $US 846,413.56). This is supported by evidence from a study conducted Australia that revealed hypertension caused 609, 801 productivity-adjusted life years loss (equating to AUD$ 137.2 billion) over the working lifetime (73). Therefore, prevention of hypertension and improving the rate of blood pressure control is important to reduce hypertension-related complications and productive life-year loss in the region as well as in the country (74).

5. Conclusion

The societal economic burden of hypertension in Southern Ethiopia was substantial. Indirect costs accounted for more than eight out of 10 dollars economic burden. Prevention of hypertension could result in $US 2,571,160.8 annual economic savings in the Southern Region. Therefore, designing and implanting strategies for prevention of hypertension, early screening, and detection, and improving the rate of blood pressure control by involving all relevant stakeholders at all levels (national, regional, zonal, community, and patient-level) is critical to saving scarce health resources.

6. Abbreviations

BP: Blood Pressure

CPG: Clinical Practice Guideline

CVD: Cardiovascular Diseases

DALY: Disability Adjusted Life Years

DBP: Diastolic Blood Pressure

EDHS: Ethiopia Demographic Health Survey

HDL: High-Density Lipoprotein

ICER: Incremental Cost-Effectiveness Analysis

LDL: Low-Density Lipoprotein

LMICs: Low- and Middle-income Countries

MI: Myocardial Infarction

QALY: Quality Adjusted Life Years

SBP: Systolic Blood Pressure

VLDL: Very Low-Density Lipoprotein

WHO: World Health Organization

YLD: Years Lived with Disability

YLL: Years of Life Lost

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Legends

List of Figures

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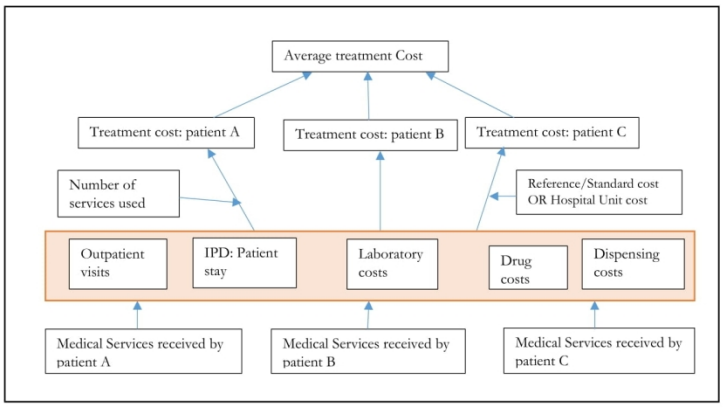
Figure 2: Number of premature deaths and years of life lost (YLL) due to morbidity among adults with hypertension by sex, treatment and control status over productive life years simulated from life table modelling in Southern Ethiopia



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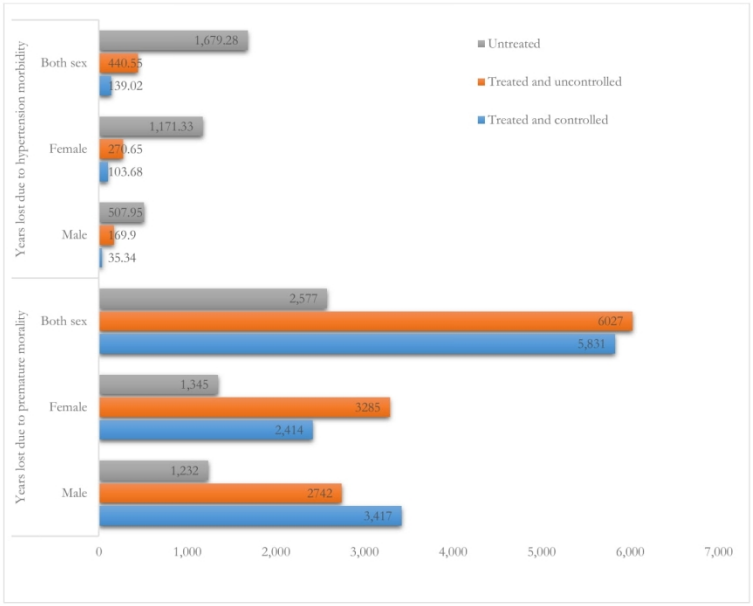

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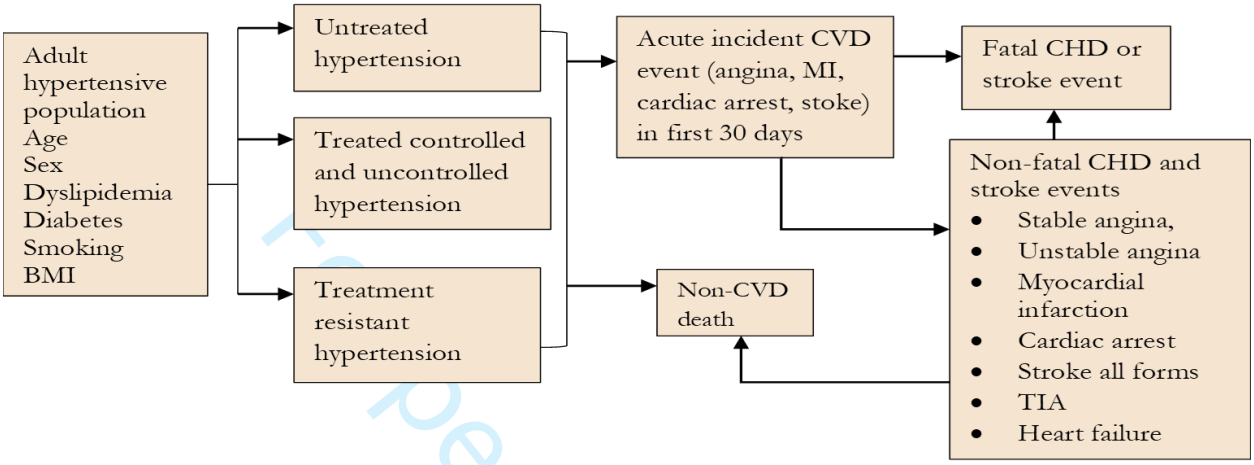
Supplementary materials: Economic burden of hypertension at selected Hospitals in Southern Ethiopia; a patient level analysis

Cardiovascular disease policy model



Supplementary Figure 1: Cardiovascular disease policy model adapted for Sub-Saharan African perspective (1).

Supplementary Table 1: Age and sex specific distribution of Ethiopian population 2020 estimate, prevalence of hypertension and adult mortality rate

Age structure	Male	Female	Total	Estimated prevalence of hypertension	Mortality rate		Data Source
Prevalence of hypertension					Men	Women	(2-8)
0-14 years	21,657,152	21,381,628	43,038,780	NA	-	-	
15-19	5,572,330	5,464,174	11,036,504	19.6	0.00286	0.00222	
20-24	5,930,683	5,816,173	11,746,856	19.6	0.00319	0.00223	
25-29	4,889,739	4,802,450	9,692,189	19.6	0.00293	0.002.32	
30-34	3,761,349	3,757,544	7,518,893	23.0	0.00397	0.003.68	
35-39	3,091,148	3,182,837	6,273,985	23.0	0.00411	0.00222	
40-44	2,445,523	2,488,422	4,933,945	25.9	0.00584	0.00385	
45-49	2,071,480	2,033,228	4,104,708	25.9	0.00360	0.00457	
50-54	1,567,789	1,660,957	3,228,746	41.9	0.00354	0.00274	
55-59	1,159,002	1,316,318	2,475,320	41.9	0.00354	0.00274	
60-64	946,594	1,109,670	2,056,264	41.9	0.00354	0.00274	
≥ 65 years	1,676,478	1,977,857	3,654,335	41.9	0.00354	0.00274	
Total	54,769,267	54,991,258	109,760,525				
				Prevalence of untreated hypertension			
For all ages (15 +)				13.25			(9)

Supplementary Table 2. Model Parameters, Cohort Setting, and Probability of Transition between states and Disability weights for hypertension and related complications the Global Burden of Disease 2013 study and WHO Global Health Estimates

Parameter	Data	Source
Relative risk of hypertension treatment		
Relative risk of CHD event on hypertension treatment	0.683 (95% CI, 0.633–0.717)	(10-13)
Relative risk of a cerebrovascular event on hypertension treatment	0.633 (95% CI, 0.526–0.717)	(14)
Relative risk of CHD event on normotensive men and women	0.49 (95% CI 0.458–0.513) and 0.32 (0.292–0.342)	(15)
Transition probabilities to death		
Health state	**Disability weight Estimate**	**Source**
Hypertension		**(16)**
Treated	0.246	
Untreated	0.323	
Treated and controlled	0.171	
Myocardial Infarction (MI)		(17)
Day 1-2	0·432	
Days 3-28	0·074	
Angina Pectoris		
Mild	0·033	
Moderate	0·080	
Severe	0·167	
Heart failure		
Mild	0·041	
Moderate	0·072	
Diabetes, digestive, and genitourinary disease		
Diabetes	0.015 (0.012 - 0.018)	(18-20)
Treated	0.033	
Untreated	0.012	

Diabetic neuropathy	0.133	
Chronic kidney disease (stage IV)	0.104	
End-stage renal disease: with kidney transplant	0.024	
End-stage renal disease: on dialysis	0.571	
Disutility due to daily medication	0.049 (0.031–0.072)	
Acute Events		
Myocardial Infarction	0.432 (0.288–0.579)	
Stroke	0.570 (0.377–0.707)	
Occurrence of second or later CVD event	0.985 (0.992–0.989)	
Chronic States		
Ischemic Heart Disease	0.08 (0.02–0.24)	
Stroke	0.135 (0.01–0.437)	
Alive post 2+ CVD Events	0.242 (0.11–0.437)	

CHD, coronary heart disease; SMR, standardized mortality ratio. *Age and sex dependent †Applied multiplicatively to general population age- and sex-dependent utilities; CHD= Angina pectoris, coronary insufficiency, myocardial infarction, or coronary death.

Supplementary table 3: Simulation input parameters

Input parameter	Value	Source
Non-CVD death rate	0.005–0.176 (Age- and sex specific)#	Calculated from WHO lifetables and GBD 2017 (21)
Probability of first-time cardiovascular disease (CVD) event	Individual risk characteristic specific	Obtained from the Globorisk Office Calculator standardized for India [25]
Acute CVD events		
MI		
Probability of MI if CVD event occurs	37.6– 66.7% (Age- and sex specific)#	Calculated based on GBD 2017(21)
30-day fatality	0.01–0.13 (Age- and sex–specific)#	Calibrated based on findings of Huffman et al. 2018 (22)
Re-infarction (in 30 days)	0.0120 (0.0099–0·0141)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Acute Stroke (in 30 days)	0.0060 (0.0045–0.0075)ψ	ACS QUIK Study by Huffman et al. 2018 (22)
Stroke		
Probability of Stroke if CVD event occurs	33.2–62.3% (Age- and sex specific)#	Calculated based on GBD 2017 (21) And Jushua D. Bundry et al(23)
30-day fatality	0.12, 0.13 (Sex-specific)#	Calibrated based on a multi-site study by Pandian and Sudhan 2013 [30]
Repeat Stroke (in 30 days)	0.15 (0.1–0.2)ψ	Petty et al. 1998 (24)
Sudden cardiac death	0.10 per 100 patient-years (95% CI, 0.07–0.14) in a cohort of 33 of 3242 untreated hypertensive patients without evidence of coronary or cerebrovascular HD at entry and followed up for an average of 10.3 years	Heart disease and stroke statistics 2021 update
Heart failure		
Probability of AHF		
30-days fatality	0.0945	Obtained from the THESUS-HF registry (25) and Korean Acute Heart Failure Registry (KorAHF)(26, 27)

Re-hospitalization	0.0736	Obtained from the THESUS-HF registry (25)
Chronic events		
Monthly risk of mortality	0.001–0.019 (Age- and sex-specific)#	Calibrated based on GBD 2017 (21)
Reinfarction	0.079 (0.073–0.085)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.014 (0.012–0.016)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20) Continue Or Stop post-Stroke Antihypertensives Collaborative Study (COSSACS) (29), BP reduction and secondary stroke prevention: systematic review(30)
Stroke		
Monthly risk of mortality	0.001–0.013 (Age- and sex specific)#	Calibrated based on GBD 2017 (21) Stroke Risk in Treated Hypertension Based on Home Blood Pressure: the Ohasama Study(31)
Acute MI	0.043 (0.038–0.048)ψ	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Acute Stroke	0.037 (0.033–0.041)	Based on Steg et al. 2007 (28) and derived by Lin et al. 2019 (20)
Relative risk of fatality for an individual with two or more CVD events	1.5	Smolina et al. 2012 (32)
Heart failure		
Incidence		Bulter J.et al (33, 34), and Davis BRK. et. al (35)
1 year mortality		
Re-hospitalization		**Moita B.eta al. 2019(36) and (37)**
Effect of antihypertensive medication		
Medication protocol for an individual	Initial SBP-specific#	Based on Ethiopian NCD control guideline
IHD relative risk due to medication	0.32–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009 (38) and Asayam Kei., 2017(39)
Stroke relative risk due to medication	0.20–0.89 (Age- and initial SBP-specific)#	Based on findings by Law et al. 2009(38)
IHD relative risk if partially adherent	0.66–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009(40)
Stroke relative risk if partially adherent	0.60–0.95 (Age- and initial SBP-specific)	Calculated based on a linear relationship between adherence and efficacy as considered by Cherry et al. 2009 (40) and Lisheng Liu, Zengwu Wang. et al(41)

Supplementary Table 4: Price of drugs, medical supplies, procedures and professional time used for management of hypertension in Southern Ethiopia, January, 2021

List of medicines	Unit	Price in 2021 Ethiopian birr		Price USD	Source
		Wholesale price	Retail price	Retail Price in 2021 USD	
Acetylsalicylic Acid - 81mg – Tablet (coated)	10x10	43.72	1.32	1.303	Ethiopian Pharmaceutical supply agency, Arba Minch Hub wholesale price 2021 and Arba Minch General hospital pharmacy retail price 2021
Adrenaline (Epinephrine)-0.1% in 1mL ampoule	Each	36.032	1.09	1.074	
Amiodarone - 100mg – Tablet	10x3	313.34	9.44	9.337	
Amlodipine - 10mg - Tablet	10x10	105.44	3.18	3.142	
Amlodipine - 5mg – Tablet	10x10	75.26	2.27	2.243	
Atenolol - 50mg – Tablet	10x10	58.70	1.77	1.749	
Atorvastatin - 20mg – Tablet	10x10	195.68	5.89	5.831	
Atorvastatin - 40mg – Tablet	10x3	140.76	4.24	4.195	
Beclomethasone Propionate -100mcg/dose – Aerosol	200 MD	131.85	3.97	3.929	
Candesartan - 8mg – Tablet	14x2	152.63	4.60	4.548	
Captopril - 12.5mg – Tablet	10x10	33.54	1.01	1.000	
Captopril - 25mg – Tablet	10x10	26.91	0.81	0.802	
Dexamethasone - 4mg/ml in 1ml Ampoule - Injection	10	3.95	0.12	0.118	
Captopril + HCT (50mg + 25mg)-Tablet	10x10	57.32	1.73	1.708	
Digoxin - 0.25mg – Tablet	10x10	202.18	6.09	6.025	
Enalapril Maleate - 10mg - Tablet	10x10	61.57	1.85	1.835	
Enalapril Maleate - 5mg – Tablet	10x10	63.92	1.93	1.905	
Enalapril Maleate – 2.5mg – Tablet	10x10	19.98	0.60	0.595	
Enalapril Maleate +HCT (10 mg + 25 mg)-tablet	10x10	78.22	2.36	2.331	
Glibenclamide - 5mg – Tablet	10x10	39.09	1.18	1.165	
Glucose 40% in 20 mL – IV infusion	Each	2.54	0.08	0.076	
Glyceryl Trinitrate - 0.4mg – Tablet (Sublingual)	100	487.21	14.67	14.518	
Hydralazine - 20mg/ml in 1ml ampoule - Injection	5	204.01	6.14	6.079	
Hydrochlorothiazide - 25mg – Tablet	25x4	48.05	1.45	1.432	
Insulin Isophane Biphasic (Soluble/Isophane Mixture)-(30 + 70)IU/ml in 10ml Vial -Injection(Suspension)	Each	85.20	2.57	2.539	
Insulin Isophane Human - 100IU/ml in 10ml Vial - Injection(Suspension)	Each	100.28	3.02	2.988	
Insulin Soluble Human - 100IU/ml in 10ml Vial	Each	106.21	3.20	3.165	
Lovastatin - 20mg – Tablet	10x10	84.59	2.55	2.521	
Metformin - 500mg – Tablet	10	27.78	0.84	0.828	
Methyldopa - 250mg – Tablet	100x10	51.75	1.56	1.542	
Metoprolol - 50mg – Tablet	10x10	94.43	2.84	2.814	
Morphine sulphate-30mg-tablet	110	410.71	12.37	12.239	
Nifedipine - 20mg – Tablet	10x10	58.70	1.77	1.749	
Prednisolone - 5 mg – Tablet	100x10	342.23	10.31	10.198	
Propranolol - 40mg – Tablet	10x10	67.54	2.03	2.013	
Propylthiouracil - 100mg - Tablet (Scored)	100	633.87	19.09	18.889	
Salbutamol - 0.1mg/dose - Aerosol (Oral Inhalation)	200 MD	117.20	3.53	3.492	
Spironolactone - 25mg – Tablet	10x10	81.87	2.47	2.440	
Thyroxin Sodium - 0.1mg – Tablet	100	178.49	5.38	5.319	
Valsartan + HCT (80mg +12.5mg)	7*2	38.47	1.16	1.146	
Laboratory and imaging costs		**Price per test ETB**		Price in 2021 USD	
CBC		75.00		1.72	Arba Minch General Hospital Laboratory service price 2021
FBG/RBS		20.00		0.46	
Lipid profile (LDL, HDL, Total cholesterol, Triglyceride)		160.00		3.68	
ECG		120.00		2.76	
ECO		350.00		8.05	
CT-scan		1200		27.59	
RFT (bilirubin, creatinine)		80.00		1.84	
Chest-ray		726		16.69	
Urine analysis		15.00		0.34	
Body fluid analysis		100.00		2.30	
H. pylori		50.00		1.15	

Liver function test (AST, ALT, ALP)	120.00	2.76	
Thyroid function test (T3, T4, TSH)	432.00	9.93	
Hospital bed days			
Primary hospital	52.52	1.21	WHO Choice (42) inflated to 2021
Secondary hospital	54.76	1.26	
Tertiary hospital	70.81	1.63	
Health facility visit		0.00	
Primary hospital	18.58	0.43	
Secondary hospital	21.17	0.49	
Tertiary hospital	22.06	0.51	
Health center visit	23.00	0.53	
PCI intervention	63,000.00	1448.28	
In-patient costs for MI	45240.00	1040.00	
In-patient costs for Stroke	40890.00	940.00	
Outpatient cost for IHD (per annum)	1957.50	45.00	
Outpatient cost for Stroke (per annum)	2914.50	67.00	
Salary scale of human resource		0.00	
Physician	21,100.00	485.06	MOH, Ethiopia 2012/2019
Acute care nurse	7470.00	171.72	
Pharmacy personnel	8047.00	184.99	
Laboratory technician	6460.00	148.51	
Program cost per person per annum	993.29	22.83	(43).
Antihypertensive treatment			
Antihypertensive medication (per individual per annum	Drug costs based on national Drug supply agency wholesale price		
Out-patient consultations (per visit)	$43.36	Annual outpatient visit cost (12*WHO cost per outpatient visit inflated to 2021) WHO Choice (42)	
One-time diagnostic tests		Based on Laboratory procedures and test price of Arba Minch General Hospital, 2021	
In-patient costs for MI	$1040	WHO Choice (42) inflated to 2021	
In-patient costs for Stroke	$940		
Chronic CVD care			
Secondary care medication in public sector (per individual per annum)	$92, $184 (Dosage-specific)§	MSH-2015 International Drug Price Indicator inflated to 2021(25)	
Outpatient cost for IHD (per annum)	$45	WHO Choice (44) inflated to 2021	
Outpatient cost for Stroke (per annum)	$67		
Average inflation rate Ethiopia	16.58%	https://take-profit.org/en/statistics/inflation-rate/ethiopia/	
Average inflation rate foreign	2.02%		
Percentage change	24.6%		
Exchange rate July 2021 (1USD)	43.5 ETB		
1USD = 20.999 ETB in 2016 and 43.5 in 2021; PPP= 12.1/8.1 = 1.5			
MD: metered Dose; MOH: Ministry of Health 1 USD = 43.5 January 2021 **Note**: 30% mark-up at regional EPSA hub, 31% mark-up at Public Hospital level			

Supplementary Table 5: Risk of death across age and gender covariate categories stratified for hypertension

Variables	Categories	Incidence of death (%)		Relative risk in each category (CI)	Source
		High BP group	Normal		
Age	20-29	1.68%	0.54%	3.11 (1.16-8.36)	*(8)*
	30-39	1.71%	0.94%	1.82 (1.04-3.19)	
	40-49	2.43%	1.88%	1.29 (0.91-1.82)	
	50-59	6.30%	4.03%	1.56 (1.28-1.91)	
	60 and above	19.32%	15.9%	1.21 (1.12-1.31)	
Gender	Women	8.71%	1.1%	3.31 (2.98-3.68)	
	Men	15.47%	4.62%	3.34(3.02-3.70)	
Risk of all case mortality					
Gender	Treatment status	< 60 years	> 60 years	HR (95% CI)	(45)
Men	Normal	0.0068	0.0214	1.00 (Reference)	
	Treated controlled	0.0188	0.0305	1.20 (0.92-1.57)	
	Treated uncontrolled	0.0252	0.0372	1.55 (1.19-2.01)	
	Untreated	0.0197	0.0336	1.45 (1.23-1.72)	
Women	Normal	0.00528	0.01870	1.00 (Reference)	
	Treated controlled	0.01675	0.02841	1.11 (0.84-1.47)	
	Treated uncontrolled	0.02533	0.03736	1.63 (1.34-1.99)	
	Untreated	0.02075	0.03471	1.31 (1.06-1.61)	

Supplementary Table 6: Annual mortality rate in the total population, those with hypertension by treatment and control status and those without hypertension in Ethiopia in 2021 by age group and sex based on literature review of systematic reviews and clinical trials

Age group	Mortality rate in the total population	Mortality rate among people without hypertension	Mortality rate among people with treated and controlled hypertension	Mortality rate among people with treated but uncontrolled hypertension	Mortality rate among people with untreated hypertension	References
Women						
15-19	0.00222	0.00222	0.016746	0.025	0.02075	Ko, Min Jung. et al. 2016 (46), Mende Sorato, et al, 2021. (1, 23, 45, 47, 48).
20-24	0.00223	0.00223	0.016746	0.025	0.02075	
25-29	0.00232	0.00232	0.016746	0.025	0.02075	
30-34	0.00368	0.00368	0.016746	0.025	0.02075	
35-39	0.00222	0.00222	0.016746	0.025	0.02075	
40-44	0.00385	0.00385	0.016746	0.025	0.02075	
45-49	0.00457	0.00457	0.016746	0.025	0.02075	
50-54	0.00182	0.00182	0.016746	0.025	0.02075	
55-59	0.00182	0.00182	0.016746	0.025	0.02075	
60 -64	0.00441	0.00441	0.028414	0.037	0.03471	
Men						
15-19	0.00286	0.00286	0.018783	0.025	0.01969	Kuriakose A. et al. 2014. (8), EDHS, 2016 (7, 45, 47-50)
20-24	0.00319	0.00319	0.018783	0.025	0.01969	
25-29	0.00293	0.00293	0.018783	0.025	0.01969	
30-34	0.00397	0.00397	0.018783	0.025	0.01969	
35-39	0.00411	0.00411	0.018783	0.025	0.01969	
40-44	0.00584	0.00584	0.018783	0.025	0.01969	
45-49	0.0036	0.0036	0.018783	0.025	0.01969	
50-54	0.00354	0.00354	0.018783	0.025	0.01969	
55-59	0.00354	0.00354	0.018783	0.025	0.01969	
60-64	0.00354	0.00354	0.030451	0.037	0.03365	

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Reporting checklist for economic evaluation of health interventions.

Based on the CHEERS guidelines.

Instructions to authors

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	Reporting Item	Page Number
Title		
#1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	1

Abstract			
	#2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	1
Introduction			
Background and objectives	#3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	2
Methods			
Target population and subgroups	#4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	3
Setting and location	#5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	3
Study perspective	#6	Describe the perspective of the study and relate this to the costs being evaluated.	3-10
Comparators	#7	Describe the interventions or strategies being compared and state why they were chosen.	9

Time horizon	#8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	2
Discount rate	#9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	10
Choice of health outcomes	#10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	NA
Meaurement of effectiveness	#11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	4-6
Measurement of effectiveness	#11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	NA
Measurement and valuation of preference based outcomes	#12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
**Estimating resources and costs **			
	#13a	Single study-based economic evaluation: Describe approaches used to estimate resource use	NA

		associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	
Methods			
Estimating resources and costs	#13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	6-9
Currency, price date, and conversion	#14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	9
Choice of model	#15	Describe and give reasons for the specific type of decision analytical model used. Providing a figure to show model structure is strongly recommended.	Supplementary figure 1
Assumptions	#16	Describe all structural or other assumptions underpinning the decision-analytical model.	9

Analytical methods	#17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	9
Results			
Study parameters	#18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	11
Incremental costs and outcomes	#19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	11
Characterising uncertainty	#20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
Characterising uncertainty	#20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	11-12
Characterising heterogeneity	#21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	#22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-15
Other			
Source of funding	#23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	NA

Conflict of interest	#24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	23

Notes:

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