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Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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UNIVERSITY OF BERGEN

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Scientific environment

This research project was undertaken at the Global Health Priorities research group at Department of Global Public Health and Primary Care, University of Bergen. Professor Kjell Arne Johansson served as the main supervisor. Professor Ole Frithjof Norheim (Adjunct professor, Department of Global Health and Population, Harvard T.H. Chan School of Public Health) and Professor Stéphane Verguet (Department of Global Health and Population, Harvard T.H. Chan School of Public Health) were the co-supervisors.

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Abstracts (English, Amharic, and Norwegian)

English summary

Introduction: The burden from cardiovascular disease (CVD) and its risk factors is growing in Ethiopia, especially in urban areas. Yet, the coverage of effective strategies towards its successful control is low. In the absence of universal coverage, affected households are forced to cover the cost of needed health care through direct out-of-pocket (OOP) payments upon use of services. OOP payments could be prohibitive to health care access and often entail trading-off other essential consumptions, especially among the poor. Therefore, protecting households from such unprecedented financial consequences is one of the key health systems objectives. Nevertheless, Ethiopia is faced with extreme resource scarcity. Therefore, priorities need to be carefully evaluated and systematically identified among competing alternatives. This thesis aims to generate policy-relevant evidence on health outcomes, costs, and financial risk protection of CVD interventions so as to inform priority setting decisions in Ethiopia.

Methods: To meet these aims, we conducted three studies using distinct methods. First, to assess the financial risk related to seeking CVD care, we conducted a cross-sectional cohort study among individuals who sought prevention and treatment services for CVD in selected hospitals in Addis Ababa, Ethiopia. In study II, a cost-effectiveness analysis (CEA) of a broad range of prevention and treatment services for CVD was performed in an Ethiopian setting so as to identify cost-effective alternatives for a potential scale-up in Ethiopia. In study III, extended cost-effectiveness analysis was used to estimate the distribution (across income quintiles) of health benefits (disability-adjusted life years (DALYs) averted) and financial risk protection (cases of catastrophic health expenditure averted (CHE)) from universal public finance (UPF) of primary prevention of CVD with a multidrug therapy (aspirin, antihypertensives, and statins) for individuals with increased absolute risk of CVD. CHE is here defined as annual OOP expenditure on CVD care 10% or more of households' annual income.

Results: Overall, 27% [95% CI (23.1, 30.6)] of the households faced CHE. About 28% among the poorest quintile, in contrast to 14% among the richest quintile faced CHE. This financial risk affected mainly the poor, those who have had stroke, those who have been hospitalized, and those who travelled to Addis Ababa from outside the city to seek CVD care. Moreover, the households that faced CHE among the poorest quintile spent 34% of their annual income on CVD care per year compared with a 15% average among the richest quintile. This shows that the poorest households suffered a more severe intensity of financial risk among than the richest quintile.

We found that primary prevention of CVD with the multidrug therapy is cost-effective in an Ethiopian setting with an estimated cost of US$ 67 per DALY averted at > 35% absolute risk of developing a CVD event over the next 10 years. The incremental cost per an additional DALY averted increased moderately at lower risk levels and reached US$ 340 per DALY averted at > 5% risk level. A package of aspirin, ACE-inhibitor, beta-blocker, and streptokinase for acute myocardial infarction (with an estimated cost of US$ 1,000 per DALY averted); a package of aspirin, ACE-inhibitor, beta-blocker, and statin for secondary prevention of ischemic heart disease (with an estimated cost of US$ 1,850 per DALY averted); and a package of aspirin, ACE-inhibitor and statin for secondary prevention of stroke (with an estimated cost of US$ 1,060 per DALY averted), although they dominated the comparators within their respective clusters, they were deemed less cost-effective than primary prevention.

Furthermore, we estimated that substantial health and financial risk protection gains can be expected from UPF of the multidrug therapy for primary prevention of CVD. In total, the policy averted about 5,800 DALYs and 850 cases of CHE per year at an estimated annual cost of US$ 1.9 million. Disaggregated by risk level, the DALYs averted ranged from 1,180 (at > 25%) to 2,240 (at > 15%), whereas the cases of CHE averted ranged from 96 (at > 35%) to 394 (at > 5%). The DALYs averted were distributed across income quintiles (Q1—the poorest to Q5—the richest) as: 22% (Q1), 18% (Q2), 24% (Q3), 26% (Q4), and 10% (Q5); while CHE averted were

distributed as: 23% (Q1), 20% (Q2), 21% (Q3), 23% (Q4), and 13% (Q5). These distributional patterns were maintained at all CVD risk levels.

Conclusions: Seeking prevention and treatment of CVD represents a significant financial risk to households, with a disproportionate impact on the poorest, those who have had stroke, and those who reside outside Addis Ababa. Primary prevention of CVD with multidrug therapy to individuals with increased absolute risk of CVD is a cost-effective strategy that Ethiopia could consider for successful control of CVD. Public finance of this intervention would generate a sizeable financial risk protection gains in addition to the health benefits. Both the health gain and financial risk protection gains favor the poorer households—qualifying the strategy as a pro-poor with respect to both outcomes. Primary prevention of cardiovascular disease saves more than lives in Ethiopia.

Keywords: cost-effectiveness, extended cost-effectiveness analysis, financial risk protection, equity, poverty, Ethiopia, cardiovascular disease, prevention, treatment.

Amharic summary

መግቢያ: የልብ ስትሮክ እና ተያያዥ በሽታዎች በኢትዮጲያ በተለይም በከተሞች አካባቢ እየጨመረ ይገኛል ሆኖም በሽታውን ለመቆጣጠር የሚስችሉ የጠፋ አገልግሎቶች ሽፋን አናሳ ነው። የጠፋ መድህን ሽፋን በበቂ ሁኔታ በሚኖርበት ጊዜ በበሽታው የተጎዱ ቤተሰቦች አስፈላጊውን የጠፋ አገልግሎት ለማገኘት ከራሳቸው ኪስ በቀጥታ ለመክፈል ይገደዳሉ። እንዲህ ያሉ ከጠፋ አገልግሎት ጋር የተያያዙ ቀጥተኛ ወጪዎች ደግሞ በአንድ በኩል ህብረተሰቡ አጥጋቢ በሆነ መልኩ የጠፋ አገልግሎት እንዳያገኝ እክል ሲፈጥሩ በሌላ በኩል ደግሞ ቤተሰቦችን ለድህነት አዘቅት አደጋ ያጋልጣቸዋል። ስለዚህም ቤተሰቦች የሚስፈልጋቸውን የጠፋ አገልግሎት ለማገኘት ከሚወጡት ቀጥተኛ ወጪ ጋር ተያይዞ ከሚጣጣቸው ኢኮኖሚያዊ አደጋ ማጠቀ የጠፋ ስርዓቶች ዋነኛ አላማዎች አንዱ ነው። ሆኖም ኢትዮጲያ ከፍተኛ የፋይናንስ እጥረት አለባት። ስለሆነም ቅድሚያ አግኝተው ሽፋን ሊሰጣቸው የሚቡ የጠፋ አገልግሎቶችን ለይቶ ማወቅ ይገባል። የዚህ ጥናት አላማ የልብ ስትሮክ እና ተያያዥ በሽታዎችን ለመቆጣጠር የሚስፈልጉ የጠፋ አገልግሎቶች ለቤተሰቦች የሚስገኙትን ጥቅም ከጠፋ እና ከኢኮኖሚያዊ የመድን ዋስትና አንፃር እንዲሁም አስፈላጊ ወጪዎችን በተመለከተ የጠፋ ፖሊሲ ለመቅረፅ ግብዓት የሚሆኑ መረጃዎችን ማመላከት ነው።

ዘዴዎች: እነዚህን አላማዎች ለማከናት ልዩ ልዩ ዘዴዎችን በማጠቃለም ሶስት ጥናቶችን ተግባራዊ አድርገናል። በመጀመሪያው ጥናት ለተጠቀሱት ለልብ እና ተያያዥ በሽታዎች የጠፋ አገልግሎት ለማገኘት በሚፈጉ ቀጥተኛ የኪስ ወጪዎች በቤተሰቦች ላይ የሚስከትሉትን ኢኮኖሚያዊ ስጋቶች ለመገምገም በኢትዮጲያ ዋና ከተማ በአዲስ አበባ በሚገኙ ሆስፒታሎች ወስጥ አገልግሎቱን ለማገኘት በማጡ ግለሰቦች ላይ ነው። ሁለተኛው ጥናት ደግሞ በኢትዮጲያ እነዚህን በሽታዎች ለመቆጣጠር የሚስችሉ አዋጪ የጠፋ አገልግሎቶችን ለመለየት የተደረገ ጥናት ሲሆን በሶስተኛው ጥናት ደግሞ በሁለተኛው ጥናት አዋጪ ሆኖ የተገኘውን የጠፋ አገልግሎት የኢትዮጲያ መንግስት መሉ በመሉ ቀጥተኛ ወጪውን ቢሸፍን ለቤተሰቦች የሚስገኘው ጥቅም ከጠፋ (በዳሊ አቨርትድ) እና ከኢኮኖሚያዊ የመድን ዋስትና (በካታስትሮፊክ የጠፋ ወጪዎች አቨርትድ) አንፃር እንዲሁም አስፈላጊ ወጪዎችን ግምት መገምገም ነው።

ካታስትሮፊክ የጠፋ ወጪ ብለን የምንጠራው አንድ ቤተሰብ በዓመት ወስጥ ለልብ እና ተያያዥ በሽታዎች አገልግሎት ለማገኘት ቀጥተኛ የኪስ ወጪ ከአጠቃላይ የቤተሰቡ አመታዊ ገቢ አስር በመቶ እና ከዚያ በላይ የሚሆን ከሆነ ነው።

ዳሊ መድህኒቶቹ የሚስገኙትን የጠፋ ጥቅም ለመለካት የተጠቀመው መለኪያ ሲሆን በሽታዎች የሚስከትሉትን ሞትና አካል ጉዳት ያካተተ የጠፋ ደረጃ መለኪያ ነው።

ውጤት: በአጠቃላይ ከ27 በመቶ የሚሆኑ ቤተሰቦች (27% [23.1, 30.6]) ለካታስትሮፊክ የጠፋ ወጪ የተዳረጉ ሲሆን ይህ ችግር በተለይም በዝቅተኛ የኑሮ ደረጃ ላይ በሚገኙ ቤተሰቦች ላይ ጎልቶ

የሚከተለው ነው፡ እንደ ኢኮኖሚያዊ ደረጃቸው ቤተሰቦችን በአምስት ብንከፍላቸው በጣም ደሀ ከሆኑት የመጀመሪያዎቹ 20 በመቶ መካል 28 በመቶ የሚሆኑት ካታስትሮፊክ የጠፋ ወጪ ሲያጋጥማቸው በአንፃሩ ደግሞ በጣም ሀብታም ከሆኑት 20 በመቶዎቹ ደግሞ 14 በመቶ የሚሆኑት ለተመሳሳይ ኢኮኖሚያዊ ቀውስ ተዳርገዋል፡፡ ይህ ኢኮኖሚያዊ ችግር በተለይም በዝቅተኞቹ 20 በመቶዎች ላይ እንዲሁም በስትሮክ በሽታ በተጋለጡ ላይ እና የጠፋ አገልግሎቱን ለማገኘት ከተለያዩ ከተሞች ወደ አዲስ አበባ በማኩ ቤተሰቦች ላይ ነው፡ በተጨማሪም በጣም ደሀ የሆኑት (የመጀመሪያው 20 በመቶ) ቤተሰቦች በአማካኝ 34 በመቶ የቤተሰቡ አማካዊ ገቢ ቀጥተኛ የኪስ ወጪ ሲጋለጡ በአንፃሩ ደግሞ በጣም ሀብታም የሆኑት (አምስተኛው 20 በመቶ) ለ15 በመቶ ወጪ ተጋልጠዋል፡፡ይህ የሚያመለክተው ከልብ እና ተያያዥ በሽታዎች ጋር በተያያዘ ደሀ ቤተሰቦች ከፍተኛ ለሆነ ኢኮኖሚያዊ አደጋ እንደሚጋለጡ ነው፡፡

በተጨማሪም በ10 አመታት ወስጥ ከ35 በመቶ በላይ የልብ በሽታ ለመከሰት አደጋ ያላቸው ግለሰቦች ላይ ያተኮረ የቅድመ መከላከል ጥቅል ህክምና (አስፕሪን፣ ኤሲኢ ኢንሂቢተር፣ ቤታ፣ ብሎከር እና ስታቲን) በአመት $67 በዳሊ አቨርትድ ይፈጃል፡፡ ይህ የቅድመ መከላከል ጥቅል መድሀኒት ከ 5 በመቶ በላይ አደጋ ላላቸው ግለሰቦች ቢሰጥ በአመክኝ $340 በ ዳሊ አቨርትድ ይፈጃል፡፡ ይህ የሚያሳየው የቅድመ መከላከል ጥቅል ህክምና ዋጋ የግለሰቦቹ አደጋ ተጋላጭነት ሲቀንስ በማኩ ይጨምራል፡፡ በተጨማሪም አስፕሪን ፣ ኤሲኢ ኢንሂቢተር፣ ቤታ ብሎከር እና እስትሪፕቶካይኒዝ ለአስቸኳይ የልብ ደካም ህክምና $1000 በዳሊ አቨርትድ ሲፈጅ ፤ ዳግም የልብ በሽታ መከላከል ጥቅል (አስፕሪን ኤሲኢ ኢንሂቢተር፣ ቤታ ብሎከር እና ስታቲን) $1850 በዳሊ አቨርትድ ይፈጃል፡፡በተጨማሪም ዳግም ስትሮክን ለመከላከል (አስፕሪን ፣ ኤሲኢ ኢንሂቢተር እና ስታቲን) $1060 በዳሊ አቨርትድ ይፈጃል፡፡በመሆኑም እነዚህ መድሀኒቶች ከለሎቹ አስቸኳይ ህክምናና ዳግም ህክምና አንፃር የተሻሉ ቢሆኑም ከቅድመ መከላከል ህክምና አንፃር አዋጪ አይደሉም፡

እንዲሁም መንግስት አዋጪ የሆነውን የቅድመ መከላከል ጥቅል ህክምና (አስፕሪን ፣ ኤሲኢ ኢንሂቢተር፣ ቤታ ብሎከር እና ስታቲን) ሙሉ በሙሉ የቀጥተኛ ወጪውን ከ20 በመቶ ለሚሆኑ ለአደጋው ተጋላጭ ግለሰቦች ሽፋን ፖሊሲ ተግባራዊ ቢያደርግ በአጠቃላይ 5800 ዳሊዎች እንዲሁም 850 የሚሀሉ የካታስትሮፊክ የጠፋ ወጪዎችን መግታት ይቻላል፡፡ ይህም ፖሊሲ በአመት $1.9 ሚሊዮን አሜሪካን ዶላር የሚሆን ወጪ መንግስት ላይ ያስከትላል፡፡ እንደ የልብ በሽታ መከሰት አደጋ ተጋላጭነት ደረጃቸው ተጠቂ ግለሰቦችን ብንከፋፍል ደግሞ 25% አደጋ ባላቸው ላይ 1180 ዳሊ አቨርትድ እስከ 15% አደጋ ባላቸው ላይ 2240 ዳሊ አቨርትድ ይደርሳሉ፡፡ እንዲሁም ከ35% በላይ የልብ በሽታ መከሰት አደጋ ባላቸው ቤተሰቦች ላይ 96 ካታስትሮፊክ የጠፋ ወጪዎች እስከ ከ5% በላይ የልብ በሽታ መከሰት አደጋ ባላቸው ቤተሰቦች ላይ ደግሞ 394 ይደርሳሉ፡፡የተገቱት ዳሊዎች ከፍፍል ደግሞ 22% (የመጀመሪያ 20 በመቶዎቹን) ተጠቃሚ ሲያደርጋቸው 18% (ሁለተኛ 20 በመቶ)፣ 24% (ሶስተኛ 20 በመቶ)፣ 26% (አራተኛ 20 በመቶ) እና 10% (አምስተኛ 20 በመቶዎቹን) ተጠቃሚ አድርጓል፡፡ በተመሳሳይ በፖሊሲው የተገቱት የካታስትሮፊክ የጠፋ ወጪዎች 23% (በመጀመሪያ

20 በመቶ)፣ 20% (ሀለተኛ 20 በመቶ)፣ 21% (ሶስተኛ 20 በመቶ)፣ 23% (አራተኛ 20 በመቶ) እንዲሁም የተቀረው 13% (አምስተኛ 20 በመቶ) ተጠቃሚ አድርጓል፡፡

ማጠቃለያ

የልብ እና ተያያዥ በሽታዎችን ለመከላከል እና ለመቆጣጠር የሚያስፈልጉ የጠፍ አገልግሎቶችን ለማግኘት የሚረጉ ቀጥተኛ የኪስ ወጪዎች በቤተሰቦች ላይ ከፍተኛ ኢኮኖሚያዊ ጫ የሚያሳድሩ ሲሆን ይህም ተፅዕኖ በተለይም በኑሮ ደረጃቸው ዝቅተኛ የሆኑ ቤተሰቦችን በስትሮክ የተጎዱ ቤተሰቦችን እንዲሁም ከአዲስ አበባ ወጪ የሚኖሩ ቤተሰቦችን በተለየ መልኩ ተጎጂ ያደረገ ነው፡፡ የዚህ በሽታ ቅድመ መከላከያ ጥቅል አገልግሎት ለአደጋው ተጋላጭ ለሆኑ ግለሰቦች ቢሰጥ አዋጪ ሲሆን መንግስት ይህንን ህክምና አገልግሎት ሽፋን ቢያደርግ ጉልህ የሚል የጠፍ እና ኢኮኖሚያዊ ጥቅሞች ለቤተሰቦች የሚስገኝ ነው፡፡ በተጨማሪም የሚኙት የጠፍ እና ኢኮኖሚያዊ ጥቅሞች በተለይም ደሀ ቤተሰቦችን ተጠቃሚ ስለሚደርጉ ይህ የቅድመ መከላከያ ጥቅል ህክምና አገልግሎት ድሆችን ያማከለ ተብሎ ለፈረጅ ይችላል፡፡ በመሆኑም አገልግሎቱ በኢትዮጲያ ከህይወት መታደግ ያለፈ ጥቅም ይሰጣል፡፡

Norwegian summary

Introduksjon: Sykdomsbyrden fra hjerte- og kar lidelser (CVD) øker i Etiopia, spesielt i byområder. Det er også en økning i forekomst av CVD risikofaktorer. Dekningen av effektiv behandling og forebygging er ekstremt lav. I mangel på helsehjelp, er de berørte pasientene og familiene tvunget til å dekke kostnadene for behandling og forebygging ved direkte egenbetaling. Disse kostnadene kan være svært høye og katastrofale, særlig for de fattige. Derfor er beskyttelse fra slike uforutsette helseutgifter en av de viktigste målene til helsevesenet. I tillegg står Etiopia overfor ekstrem ressursskarphet. Derfor er det viktig å systematisk identifisere konkurrerende alternative helsetjenester og prioritere de mest kostnadseffektive tjenestene som også vektlegger rettferdig fordeling og finansiell risikobeskyttelse. Denne oppgaven tar sikte på å generere policy relevant evidens på helseutfall, kostnader og finansiell risikobeskyttelse av CVD-intervensjoner for å informere prioriteringsbeslutninger i Etiopia.

Metode: For å nå disse målene har vi gjennomført tre studier med tre ulike metoder. For det første, for å vurdere den eksisterende økonomiske risikoen knyttet til å søke CVD-omsorg, gjennomførte vi en tverrsnittstudie blant personer som søkte forebygging og behandling for CVD på utvalgte sykehus i Addis Ababa, Etiopia. I studie II gjorde vi en helseøkonomisk evaluering av flere ulike typer forebygging og behandling for hjerteinfarkt og slag i et etiopisk helsevesen for å identifisere de mest kostnadseffektive alternativene for en potensiell oppskalering i Etiopia. I studie III utvidet vi den helseøkonomiske evalueringen for å estimere den forventede fordelingen (mellom inntektsgrupper) av helsegevinsten (sykdomsjusterte leveår (DALYs) unngått) og finansiell risikobeskyttelse (tilfeller av katastrofale helseutgifter avverget ved hjelp av universell offentlig finansiering av primær forebygging av CVD med tre ulike medikament (aspirin, antihypertensiva og statiner) for personer med økt absolutt risiko for CVD. Katastrofale helseutgifter er definert som at de årlige egenbetalingene til CVD omsorg overstiger 10% av husholdningenes årlige inntekt.

Resultat: Samlet sett hadde 27% [95% CI (23,1, 30,6)] av husstandene katastrofale helseutgifter. Om lag 28% blant den fattigste kvintilen, i motsetning til 14% blant den rikeste kvintilen, opplevde katastrofale helseutgifter. Denne økonomiske risikoen påvirket i hovedsak de fattige, de som har hatt slag, og de som reiste til Addis Ababa fra utenfor byen for å søke CVD-omsorg. Videre brukte husholdningene blant den fattigste kvintilene som opplevde katastrofale helseutgifter 24% av sin årlige inntekt på CVD omsorg per år sammenlignet med et gjennomsnitt på 5% blant de rikeste kvintilene. Dette viser en mer alvorlig intensitet av finansiell risiko blant de fattigste kvintilene sammenlignet med de rikeste.

Vi fant at primær forebygging av CVD er et kostnadseffektivt tiltak i en etiopisk kontekst med en estimert kostnad på USD 67 per DALY unngått ved >35% absolutt risiko for å utvikle en CVD-hendelse de neste 10 årene. Inkrementell kostnad-nytte rate økte moderat ved de lavere risikonivåene og nådde USD 340 per DALY unngått på > 5% risikonivået. En pakke med acetylsalisylsyre, ACE-hemmer, beta-blokkere og streptokinase for akutt hjerteinfarkt (med en estimert kostnad på USD 1.000 per DALY unngått); en pakke med acetylsalisylsyre, ACE-hemmer, beta-blokkere og statiner for sekundær forebygging av iskemisk hjertesykdom (med en estimert kostnad på USD 1,850 per DALY unngått); og en pakke med acetylsalisylsyre, ACE-hemmer og statiner for sekundær forebygging av slag (med en estimert kostnad på USD 1 060 per DALY avverget), selv om de dominerte komparatorene i sine respektive klynger, ble de ansett for å være mindre kostnadseffektive enn primærforebygging.

Videre anslår vi at det kan forventes betydelige gevinster i form av forbedret helse og finansiell risikobeskyttelse fra universell offentlig finansiering av de de tre medikamentene som primær forebygging av hjerte-kar lidelser. Samlet sett hindret primærforebygging ca. 5.800 DALY og 850 tilfeller av katastrofale helseutgifter per år til en estimert årlig kostnad på USD 1,9 millioner. Disaggregert i forhold til risikonivået, varierte DALY gevinstene fra 1,180 (ved> 25 %) til 2,240 (ved> 15%), mens katastrofale helseutgifttilfellene avverget varierte fra 96 (ved> 35%) til 394 (ved> 5%). DALY unngått ble fordelt relativt over inntektskvintilene (Q1-de fattigste

til Q5-de rikeste) som: 22% (Q1), 18% (Q2), 24% (Q3), 26% (Q4) og 10%); mens katastrofale helseutgifter avverget ble fordelt som 23% (Q1), 20% (Q2), 21% (Q3), 23% (Q4) og 13% (Q5). Dette distribusjonsmønsteret ble opprettholdt på alle hjerte-kar risikonivåer.

Konklusjon: Å oppsøke forebygging og behandling av hjerte-kar lidelser representerer en betydelig finansiell risiko for husholdninger, med en uforholdsmessig påvirkning på de aller fattigste, de som har hatt slag, og de som bor utenfor Addis Ababa. Primær forebygging av hjerte-kar lidelser med til personer med forhøyet absolutt risiko for en kardiovaskulær hendelse er en kostnadseffektiv strategi som Etiopia bør vurdere for å lykkes med å kontrollere hjerte-kar lidelser nå og i fremtiden. Offentlig finansiering av dette tiltaket vil gi store finansiell risikobeskyttelse i tillegg til helsemessige fordeler. Både helsegevinsten og den finansielle risikobeskyttelsen favoriserer de fattigste husholdningene – som gjør at strategien kvalifiserer som pro-fattig med hensyn til begge utfall. Primær forebygging av kardiovaskulær sykdom sparer mer enn liv i Etiopia.

List of publications

1. Tolla MT, Norheim OF, Verguet S, Bekele A, Amenu K, Abdisa SG, Johansson KJ. **Out-of-pocket expenditures for prevention and treatment of cardiovascular disease in general and specialized cardiac hospitals in Addis Ababa, Ethiopia: a cross-sectional cohort study.** BMJ Global Health 2017, 2:11.

2. Tolla MT, Norheim OF, Memirie ST, Abdisa SG, Ababulgu A, Jerene D, Bertram M, Strand K, Verguet S, Johansson KJ. **Prevention and treatment of cardiovascular disease: a cost-effectiveness analysis.** Cost-Effectiveness and Resource Allocation 2016, 14:10.

3. Tolla MT, Habtemariam MK, Haaland ØA, Økland JM, Norheim OF, Johansson KJ. **Health benefits and financial risk protection from primary prevention of cardiovascular disease in Addis Ababa, Ethiopia: an extended cost-effectiveness analysis.** (submitted)

Abbreviations

CEA	Cost-effectiveness analysis
CHE	Catastrophic health expenditure
CI	Confidence interval
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DCEA	Distributional cost-effectiveness analysis
DCP	Disease control priorities
ECEA	Extended cost-effectiveness analysis
EPHI	Ethiopian public health institute
FMOH	Federal ministry of health
FRP	Financial risk protection
GBD	Global burden of disease
GCEA	Generalized cost-effectiveness analysis
GDP	Gross domestic product
GTP	Growth and transformation plan
HSDP	Health sector development program
HSTP	Health sector transformation program
ICER	Incremental cost-effectiveness analysis
IHD	Ischemic heart disease
NCD	Non-communicable disease
NCDI	Non-communicable disease and injuries
OOP	Out-of-pocket
PCI	Percutaneous coronary intervention
SDG	Sustainable development goals

STEPS	Step-wise approach to NCD risk factor surveillance
UHC	Universal health coverage
US	United states
UPF	Universal public finance
WHO	World health organization
WHO-CHOICE	WHO-Choosing interventions that are cost-effective
YLD	Years lived with disability
YLL	Years of life lost

Figures and tables

Contents

1. Introduction

Ethiopia is a low-income country with about 100 million people characterized by high disease burden and as a result, high demand for health care. The burden of cardiovascular disease and its risk factors is rising, especially in urban areas. This development constrains the already strained Ethiopian health system. Besides, since Ethiopia lacks universal health coverage, the effect extends to households in the form of financial distress and lack of access to health care. Therefore, there is an acute need for evidence to inform priority setting decisions to allocate public funds among several competing alternatives. In this thesis, I intend to generate evidence to facilitate better informed resource allocation decisions, specifically addressing three main policy relevant questions focusing on cardiovascular disease, as an entry point to this crucial endeavor. The first question was: is seeking CVD services a financial risk to households in Ethiopia? If so, who are affected the most? Or what are the factors associated with it? The second question was, are there cost-effective prevention and treatment strategies for CVD that Ethiopia could consider for a potential scale-up? Finally, I examined the expected costs, gains (in terms of health and financial risk protection (FRP) benefits), and the expected distributional consequences of public finance of the most cost-effective strategy that we identified when addressing the second question.

This thesis is organized in eight sections. Section 1 introduces the topics of this thesis: universal health coverage (section 1.1), priority setting for health care (section 1.2), Ethiopian context (section 1.3) that covers the health system context and epidemiology of CVD in Ethiopia—among others, and justification of the study (section 1.4). Study objectives are presented in section 2, while section 3 describes the study setting (section 3.1), discussion of the methodological considerations (section 3.2, where I discuss the rationale behind the choice of analytical approaches and outcome measures), and a summary of the specific methods employed in each paper (section 3.3). The results section follows in section 4, providing a summary of the key findings from the three studies that we conducted and in section 5, I discuss

these results in view of the secondary objectives and existing literature (section 5.2) and highlighted the main methodological strengths and limitations (section 5.3). Finally, key conclusions from the study are presented in section 6, followed by implications for future practice (section 7.1) and recommendations for future research (section 7.2), and the last section (section 8) offers the references I used.

1.1 Universal Health Coverage

UHC is defined as all people receiving quality health services that meet their needs without being exposed to financial hardship in paying for the services (1, 2). It covers promotive, preventive, curative, and rehabilitation services that respond to the needs of populations. Given its prominent role to development, UHC is set as one of the key sub-targets of the Sustainable Development Goal 3 (3). The motivation behind pursuing UHC finds its main root at the society's moral obligation to protect its members against the consequences of poor health in all its forms. This relates to a large extent to the inherent value of health for one's well-being and consequently its role in determining individuals' fate of reaching maximum potential in life, their livelihood, and enjoyment in life (4). An equally appealing pro-UHC cause, however, is the enormous economic dividend that follows investments on health (5). It is estimated that a 10% increase in life expectancy translates to an economic growth of 0.4% per year of a country's gross domestic product (GDP) (6). *The Lancet* Commission Global Health 2035 estimated that nearly 24% of the increase in full income in low-and middle-income countries, between 2000 and 2011, was the consequence of reductions in mortality, improvements in health, and enhanced economic productivity (5). The commission also forecasted that per $ invested, health services could generate a 9-20 fold higher economic return—positioning UHC as an essential prerequisite for a sound social and economic development (5, 7).

Commitment to UHC implies making continual progress on three fronts: expanding the package of essential health services covered, scale-up coverage of beneficiaries, and increasingly raise the share of health care costs financed through pooled pre-payment arrangements (1, 2). Nevertheless, the progress towards UHC is faced with

steeply increasing health care costs related to continued advancements in health care technologies, changing demography and epidemiologic patterns resulting in change in health needs, and rising public expectations (8). Therefore, countries are required to carefully define a comprehensive package of essential services that they can effectively deliver within their local constraints. Among other things, these constraints include resource scarcity, other social goals such as improving access to education or roads, adequacy of available health service delivery infrastructure, human resources for health, and the political economy (9-11). Consequently, countries face a perpetual challenge of defining the best route to move toward the UHC goal, in particular: which services to cover first, whom to cover first, and how to switch from out-of-pocket (OOP) payments to prepayment mechanisms (12).

In 2005, Ethiopia identified a prioritized Essential Health Services Package (EHSP) that the country can afford to offer to its citizens at the primary health care level (13). The services offered include a list of promotive, preventive, basic curative, and rehabilitation services that target major causes of disease burden that are subject to three distinct cost-sharing arrangements based on the level of priority. First, *exempted services* are those that are provided *free of charge (no cost sharing) to all* and typically constitute immunization, TB, HIV, family planning, and child delivery at primary health care facilities. The second group constitutes the services that are offered on *a cost-sharing* basis that individuals have to pay directly to providers upon use of the services (13). The subsidy could reach 60-70% for some services (14). These include curative services for common infectious diseases and selected primary prevention interventions for some NCDs such as hypertension and diabetes mellitus (14). The third group constitutes services that are delivered on a high (full) *cost recovery* basis, and include all services that are not in the prioritized package (13). Based on the EHSP, it seems that primary prevention of CVD falls under the second group (subsidized service), while treatment of acute conditions and secondary prevention seem to fall under the third payment arrangement (high or full cost recovery). Health insurance coverage is still very low in Ethiopia—although it increased from 1% in 2011 to 7% in 2016 (15, 16). Additionally, with the main aim

of enhancing equitable access to health care, the *fee-waiver* scheme reached out to nearly 1.5 million poor individuals (about 1.5% of total population) with free access to health care of all kinds—with an estimated annual average spending of less than US$ 2 per capita in 2015/2016 (17). Although encouraging, this is far from meeting the high demand for health care in Ethiopia.

Nevertheless, UHC is not an unpredictable journey to a promised land even in resource-limited settings. With the right-mix of policy choices and unwavering commitment, countries such as Rwanda, Ghana, and Thailand have demonstrated that a remarkable progress can be made towards UHC even in low- and middle-income settings (1). Countries are free to define pathways that better suit their local context (1, 18). However, there are broadly accepted guiding ethical principles that countries ought to comply with to accelerate progress towards UHC in a fair manner (2). At any given level of available resources, it is a "moral imperative" (19) to maximize the total health benefits for the whole population while ensuring a fair distribution of the benefits between sub-populations—especially the poor (2, 20, 21). In so doing, countries need to protect citizens from an unacceptable financial risk households face due to illness in general, but at least due to payments for needed health care (2, 22). These are key principles and are further discussed in subsequent sections.

1.2 Priority setting for health care

In as much as the global community is convinced about the importance of pursuing UHC, the prevailing resource scarcity proves an important rate-limiting factor towards achieving that goal (23). Countries cannot cater to all health needs of their populations in the face of immense resource scarcity, growing demand for health care, and ever improving health technology development (24). In such situations, decision makers are forced to take the tough job of choosing between alternative services for prioritized financing (25). Needless to say, it is not an easy task to make those trade-offs, since such decisions may mean denying potentially beneficial interventions for some who could have benefited from the same resources (8, 25, 26). Typically, priority setting decisions are taken by "agents" on behalf of others and the

consequences of their decisions might equate allowing some to enjoy a better quality or longer life at the expense of others who are destined to have less health because the available resources are allocated to the needs of others. Hence, systematic priority setting becomes not just an unavoidable route, but a pragmatic means to a desired end. Ad-hoc approaches to priority setting could leave out important interventions that deserve higher priority, may risk leaving behind disadvantaged sub-populations, or cause inefficiency—resulting in a huge opportunity cost in healthy life years lost (8, 10, 19, 24, 26). Therefore, explicit priority setting grounded on legitimate evidence and agreed upon criteria helps to optimize the gains from the available resources in a fair manner (8, 10).

Varying descriptions have been used to define the concept of priority setting for health care. In this thesis, I use rank-ordering of health interventions for prioritized public financing as the definition of priority setting (24). According to this definition, interventions are ranked based on agreed upon set of criteria for a fair priority setting so that the available resources can be allocated first to high-ranking interventions while setting aside low-ranking ones until sufficient resources become available for all. Although many concur this approach broadly, its practical application entails critical value judgments and making explicit trade-offs between alternative choices. In addition, the priority setting approach has been debated and scrutinized from ethical, philosophical and political perspectives (8, 10). Therefore, one needs to actively engage all relevant stakeholders including the public to get their buy-in on the relevance of the criteria chosen and the decisions made with appropriate mechanisms in place to allow incorporation of possible suggested changes as well as enforcement mechanisms to follow through agreed proceedings (27).

Unfortunately, priority setting is not always undertaken in a systematic and explicit manner, especially in low-income settings (10, 25, 28, 29). Factors such as historical trends in financing, past experience, political interest, and pressure from various interest groups such as donors, the private sector, and patient groups could influence resource allocation decisions more than the rational principles (10, 28).

Given the background discussed so far and in the subsequent health financing section, it is obvious that severe resource scarcity remains an ongoing challenge for health care financing in Ethiopia. One alternative to deal with this challenge is to increase the allocation of funds to health care (30). An equally important and more realistic response in the short term, however, is to improve efficiency in the use of existing resources (1, 30, 31). In this thesis, I aim to generate policy-relevant evidence to inform macro-level priority setting decisions for health care within a "fixed" budget constraint that is expected to grow continually as the government intends to revise the EHSP.

Due to its complexity, multiple criteria are deemed necessary and have typically been used to guide priority setting for health care (32-34). Examples include disease burden, age, need for health care, poverty, equity, and severity of disease—with a predominant representation of benefit maximization criteria across settings (8, 10, 32-36). The ultimate goal is to maximize health and ensure its fair distribution while protecting people from financial risk or medical impoverishment (37, 38). A critical first step is then to agree on the criteria that should dictate the decision-making process. Through careful review of the global experiences, recommendations from the literature, and extensive consultation with relevant stakeholders, WHO's Consultative group on equity and UHC proposed three criteria to guide prioritized resource allocation decisions on a fair path to UHC. These are: priority to *cost-effective interventions*, priority to interventions that generate greater benefits to the *worse-off*, and priority to interventions that promote *FRP*. I discuss these criteria in subsequent sections.

1.2.1 Priority to intervention that maximize health benefits

The prime aim of health systems is to improve the health of populations (2). Health systems strive to achieve this goal within a given budget limits. Cost-effectiveness analysis (CEA) compares the value of the outcome generated by an intervention with those that could have been achieved with an alternative use of the same resources (39, 40). Hence, it helps policy makers to choose interventions that maximize total health

benefits for the population within a given budget limit. Cost-effectiveness of interventions is judged by their incremental cost-effectiveness ratio (ICER) which is given as the ratio of the incremental cost of the intervention to its incremental health gain relative to a comparator. The ratio, reported as cost expressed in monetary units per health gain (e.g., cost in US$ per disability-adjusted life year (DALY) averted, DALY is a health metric that combines the health lost due to premature death and life years lived with disability—discussed in the methods section), informs us of how much additional cost the intervention under consideration requires for a unit increase in health benefits over its comparator. Therefore, the lower the ratio, the more cost-effective the intervention is (21). To inform priority setting decision, ICERs can be used in two ways (30). ICERs can be compared with a certain fixed cost-effectiveness threshold signifying the opportunity cost for a unit health gain. I will return to cost-effectiveness threshold in the discussion section. Alternatively, interventions can be ranked in increasing order of their ICERs; followed by selection of interventions based on their rank-order for prioritized financing until the available budget is exhausted (21). Allocating resources in such a way helps to arrive at a list of interventions that maximize health within the available budget. It is often considered unethical not aim to achieve the maximum attainable benefit for a given resource (24) due to the subsequent huge opportunity cost in life years lost (19). Nevertheless, this criterion is not universally favored by all, such as in the US and Germany (24, 41).

One challenge is that CEA is resource- (skilled manpower) and- data-intensive—for which low-income settings like Ethiopia have limited capacity and preparedness (30, 42). In order to fill this gap, the *Disease Control Priorities project* (DCP, started in 1993) and the *World Health Organization's "Choosing Interventions that are Cost-Effective"* (WHO-CHOICE, started in 1998) pioneered cost-effectiveness analysis of a wide range of interventions and programs for most regions globally (43-45). The WHO-CHOICE (tasked to provide information of cost-effectiveness, costs, and strategic planning to policy makers) and the *DCP project* (an ongoing project tasked to systematically assess the cost-effectiveness of interventions that address major causes of disease burden and specific service delivery platforms in low-and middle-

income countries) have laid the foundation for the introduction of CEA considerations in resource allocation decisions at the national levels.

However, direct transferability and applicability of cost-effectiveness analysis results from one setting to another is restricted due to several methodological and practical constraints (10, 42, 46). Differences in the analytic approach (the perspective for the analysis, choice of comparator, target population, diverging ways valuing costs and health benefits), uncertainties in input parameters as well as differences in context specific factors (such as epidemiology, demography, relative price of inputs, and the institutional make-up of health systems) contribute to the limited transferability of results from one setting to another (10, 42). Therefore, building a local capacity to undertake the needed economic evaluation evidence is urgently needed in low-income settings to fill the evidence gap in a timely manner so as to facilitate evidence-based decision making based on contextualized CEAs (42).

Furthermore, benefit maximization does not sufficiently address all societal concerns. The society also cares about ensuring a fair distribution of the health benefits between sub-populations, even at the expense of a certain level of benefits foregone on an aggregate level (47). Mostly, the services that are preferred on the basis of the benefit maximization principle also address distributional concerns. However, on some occasions, adherence to distributional concerns may require extra costs—and hence, diverge from the prior principle. Therefore, exclusively relying on the benefit maximization principle may not always align with other relevant ethical concerns (2, 32). Particularly, standard cost-effectiveness analysis lack sensitivity to the distributional concerns as it gives equal weight to all benefits regardless of who gains them (32). Moreover, FRP considerations are not captured in standard cost-effectiveness analysis. Therefore, the method needs to be complemented with other methods that allow incorporation of relevant distributional concerns as well as concerns for FRP. In the next sections I discuss the rationale behind these two criteria and how they can be applied into priority setting decisions with emphasis on the latter.

1.2.2 Priority to interventions that benefit the worse-off

The priority to the worse-off principle prescribes giving higher priority to services that preferentially benefit those worse-off as it would help to narrow the gap in the distribution of health benefits across sub-populations. Meaning, a unit of health benefit to the worse-off has greater value than the same unit of health among the better-off.

To understand the implication of the principle, one needs to operationalize worse-off-ness as it may mean different things in different contexts (10). Worse-off-ness can be defined in several ways: in terms of *need or overall health* (e.g. those with lower life time health without the intervention, or those having conditions with the lowest healthy life expectancy), or alternatively, it may mean those *disadvantaged with respect to other relevant parameters such as socio-economic status and geography* (e.g., the poor and residents in rural areas that often have weak infrastructure development entailing poor access to health care, poor health outcomes, or poor access to other basic services) (2, 10, 39, 48). Giving priority to the worse-off often has a dual effect—it may improve total health (because of the substantial "catch up" health gain among the worse-off) and promotes equalization of health (2). In most cases, what is preferred from a benefit maximization perspective is also beneficial to those worse-off. However, this may not be universally true, requiring careful assessment and incorporation of trade-offs between health maximization and concern to the worse-off into the decision equation.

Several methods have been proposed to incorporate the concern to the worse-off into standard economic evaluation methods. To mention some: equity impact analysis (disaggregating the impact of alternative courses of action by certain equity-relevant variable) (39); equity constraint analysis (assessment of opportunity cost of equity promoting option compared to equity-neutral option, which is estimated as the difference in total health between the two alternatives) (49); and equity-weighting analysis (a method of applying varying equity weights—reflecting the concern for

equity—to health benefits to people that vary with respect to certain equity relevant characteristics) (49, 50). However, I will not go into these details in this thesis.

1.2.3 Priority to interventions that promote financial risk protection

Out-of-pocket (OOP) payments for health care can be a substantial financial risk to households in most low-income settings that lack universal coverage. I will return to the problems with direct OOP payments in health care financing section subsequently. FRP can defined as protecting households from incurring high medical expenses or the risk of impoverishment (51). Alternatively, FRP has been defined as "the absence of a risk of financial hardship" (52). The FRP criterion is especially relevant in settings where direct OOP payments constitute a major part of the health financing mechanism—putting households at an increased risk of medical impoverishment and making them unprotected from income loss due to illness (51). FRP is considered as one of the core elements of UHC with an intent to reduce the burden on households of high OOP payments for health services and it is therefore incorporated as part of the global monitoring framework for UHC (53, 54).

Generally, public finance of health services improves health care access while conferring FRP to individuals in multiple ways (2): 1) it protects households from high health care expenditures; 2) preventive services can also protect households from potential future expenditures by preventing occurrence of diseases (e.g., primary prevention of CVD could prevent the occurrence of acute myocardial infarction or stroke and hence, saves households from incurring a potentially substantial spending on costly acute care for these conditions), and 3) by improving individuals health status, it protects households from potential income loss due to lost productivity. However, the expected FRP gains from the coverage of health services can vary depending on several factors: epidemiology of the condition targeted, health service utilization, service availability, the magnitude of OOP payments, and the cost of services (2, 5).

The FRP criterion justifies additional priority to health services that promote high FRP even if they are less cost-effective (2, 24). It is often assumed that public

finance of costly services would confer high FRP gains (55). However, in settings where OOP payments are present even for basic services, public finance of low-cost essential services (hence, very cost-effective) could generate high FRP gains at the aggregate level (2, 5, 56-58). Under such conditions, these low-cost services could be considered good both from the health and FRP perspectives. The challenge is when the service under consideration have different impact with respect the two criteria. I use the matrix below (Figure 1) to illustrate the possible performance of services with respect to health and FRP (I will further return to this matrix in the discussion section). If the service under consideration falls in the "*High FRP and low health benefits*" quadrant and "*High health benefits and low FRP*" quadrant, trade-offs would have to be made—for which there could be reasonable disagreements. In addition, the weight of the FRP criteria relative to health is another area amenable for discussion.

High FRP Low health benefits	**High FRP** **High health benefits**
Low Health Benefits Low FRP	**High health benefits** Low FRP

Figure 1: Cost-effectiveness versus financial risk protection (FRP) matrix for an intervention compared to an alternative, reproduced from Verguet et al., (56).

The next question is how do we explicitly incorporate the concern for FRP into economic evaluation of health services to facilitate priority ranking of health services? Recently, a methodology called extended cost-effectiveness analysis (ECEA) was developed under the auspices of the *DCP*, 3rd edition (www.dcp-3.org) (59). Building on standard CEA, ECEA allows examination of the impact of health policies with respect to health and FRP gains (e.g., cases of catastrophic health

expenditures (CHE) averted—a measure of financial risk discussed in the methods section) as well as the cost to the government of such policies. Therefore, ECEA helps policymakers to quantify the efficiency in purchasing FRP by investing public funds on alternative health services (56). Furthermore, ECEA quantifies the health and FRP gains disaggregated by relevant sub-population groups (e.g., per income quintile, or geographical setting)—allowing possible examination of distributional concerns (56, 58). In addition, as indicated earlier, when interventions of interest perform differentially with respect to the health and FRP perspective—trade-offs may arise. The ECEA provides for a quantitative examination of such trade-offs between health and FRP. I provide further details about the ECEA approach in the methods section of this dissertation.

A specific framework for incorporating the concern for FRP is the one suggested by WHO's consultative group on equity and a fair path to UHC (2). The commission suggested a three-step approach to ranking of services. After identifying all potential services that could be considered for public finance: first, one needs to classify the services into high, medium, and low priority classes based on relevant cost-effectiveness thresholds. Subsequently, some services may fall on a clearly demarcated priority classes, but some others might fall in an overlapping region between two priority classes. This is where the Consultative group suggested to introduce the other two criteria, priority to the worse-off and financial risk protection, as a differentiation mechanism (2). Services that clearly fall in one category maintain their priority class. However, for those services that lie in an over-lapping region, further comparison needs to be made based on the priority to the *worse-off* and *FRP* criteria.

1.3 Ethiopian context

1.3.1 Geographic, socio-demographic, and economic background

Ethiopia is a federal democratic state located in the Horn of Africa. It shares boarders with Kenya in the south, Eritrea in the north, Sudan and South Sudan in the west, and

Djibouti and Somalia in the east and hence, it is a land-locked country (Figure 2). Spread over a land area of 1.1 million square kilometers, it stands as one of the least urbanized countries globally, where more than 80% of its population reside in rural area (60). The country exhibits a unique terrain with an altitude that ranges from 110 meters below the sea level in Afar to 4,620 meters above sea level in Ras Dashen Mountain. Ancient civilization and glorious history are among the key identities of Ethiopia that served a home to human origin and pledges several United Nations Educational, Scientific and Cultural Organization World heritage sites including the Rock-Hewn Churches of Lalibela and Aksum obelisk (61)

Figure 2: Map of Ethiopia (62).

The country has the second largest population in Africa, projected at 99.4 million as of 2016 (60, 63).The population pyramid is still characterized by a young population, with a nearly even male to female ratio (Figure 3). With respect to the age structure: 40% of the total population is younger than 15 years, while those older than 65 years constitute about 3% of the share (63, 64). However, as shown in Figure 3, the

Ethiopian population is projected to grow older in the next 30 years (64), which have important implications to shifting the epidemiology towards a non-communicable disease (NCD) dominated pattern. The total fertility rate declined significantly to 4.6 in 2016 from 5.5 in 2000 (65), and consequently roughly about 2.3 million children are born annually. Ethiopia is a diverse country with more than 80 ethnic tribes having different languages and socio-cultural background. Oromo constituted 34.5% of the total population, followed by Amhara (26.9%), and Somali (6.2%). Orthodox Christian, Islam, and Protestant Christian were the three leading religious denominations that 34.5%, 26.9%, and 18.6 % of the population were affiliated with in 2007, respectively (66).

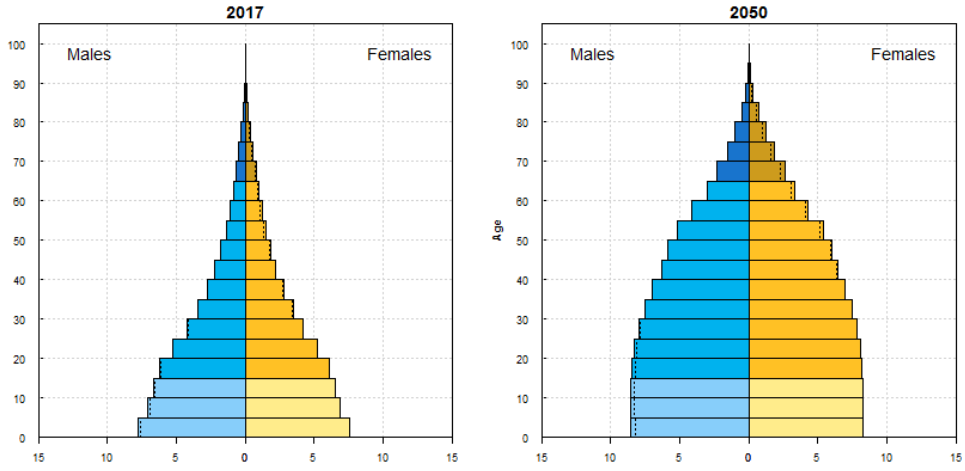

Figure 3: Ethiopia population pyramid 2017 and 2050 (64).

As a federal state, the country follows a decentralized administration system that is composed of nine regions, two city administrations, close to 1,000 districts (woredas), and about 15,000 kebeles—representing the smallest administrative unit under districts and sub-cities (67-69). Power is fully devolved to regional governments (states) and city administrations, which in turn empower the district and sub-city authorities. The administration at the district and sub-city level is composed of elected council members and represents a critical decision making structure in the governance system including decision on fiscal allocations to specific sectors (67-69).

Due to their autonomy, it is not uncommon to see variation in sectoral allocation patterns across regions according to the perceived local priorities. In the health care financing section further below, I have provided concrete examples of variation in government's allocation to the health sector across the different regions.

Ethiopians witnessed tremendous economic and human development gains over the past 15 years. The economy registered a steady GDP growth at an average rate of about 10% per year since 2004—with a slight deceleration to 9.6% in 2015. As a result, the proportion of the poor population (those below the international poverty line, purchasing power parity (PPP) $ 1.25) declined to 31% in 2011 from 56% in 2000 (70). The average life expectancy at birth increased to 64 years in 2015 from 52 years in 2000 (60). About two-thirds (65%) of Ethiopian school children were attending primary school in 2016. Infant mortality and under-five mortality rates were reduced by 50 to 60% between 2000 and 2016 to reach 48 and 67 per 1,000 live births, respectively (71). In addition, a substantial infrastructure expansion was also undertaken during this period. As a result, 65% of Ethiopian households drink water from improved sources (includes tap water and protected well or spring), 68% of kebeles are connected by all-weather roads and the number of mobile phone subscribers reached 28 million in 2014 (69).

Building on the successes thus far, the country sets an ambitious goal to become a middle-income country by 2035. The Growth and Transformation Plan (GTP) II (2015/2016 - 2019/2020) directs the remaining journey to the envisioned macro-economic development (69, 72). Nevertheless, the vision is confronted with real challenges demanding unyielding efforts before realization. The gross national income (GNI) stood at US$ 590 per capita in 2015 compared to a minimum of US$ 4,036 baseline for an upper-middle income country (73). The economy is still largely dependent on subsistent agriculture that comprised 40% of the GDP in 2015, while tax revenue and manufacturing industry constituted 12.7% and 4.4% of the economy, respectively (69). In addition, access to basic services such as secondary education, electricity, water, sanitation facilities are still far from optimal, which is further compounded by wide urban-rural and socio-economic disparity (Table 1). In the next

section, I have described the Ethiopian health system context with emphasis on services delivery platforms and the successes and challenges for the health sector so far.

	National	Urban	Rural	Poorest quintile	Richest quintile	Addis Ababa
Skilled birth attendance	28	80	21	13	67	97
Modern contraceptive use	35	45	32	22	46	50
Ante-natal care 4+ visits	32	63	27	38	77	89
Pentavalent 3 vaccine	53	80	50	38	77	96
Stunting in under-5	38	25	40	42	27	15
Some secondary education	6	18	4	2	17	19
Access to improved source of water	57	65	97			
Access to improved toilet facilities	4	6	16			

Table 1: Distribution of access to basic services in 2016 (in percentages), Ethiopia (65).

1.3.2 Health system context

The Ethiopian health care delivery system is organized as a three-tier system, firmly founded on primary health care (68, 74). The primary health care unit forms the base of the health system and it is composed of five health posts, a health center, and a primary hospital. Health posts serve as the first contact point to the formal health care system for the rural majority in Ethiopia (68, 74). Staffed with two health extension workers: health posts serve as the main delivery platform for Ethiopia's flagship health extension program providing preventive, promotive, and very limited curative

services to about 3,000 to 5,000 people. Whereas, health centers provide preventive, promotive, and curative services including limited inpatient care (five beds) to about 25,000 people per a health center. Primary hospitals (20 to 50 beds) serve as a referral station for lower level units and provide a broader range of curative services including emergency surgery. The second-tier is composed of general hospitals that serve about one and half a million people. Whereas, tertiary level specialized hospitals provide a highly specialized services to nearly five million people on a referral basis from lower levels (68).

The previous 20-year health sector development programs (HSDP I-IV ((1994/1995 to 2014/2015)) mainly focused on expanding the health infrastructure among other things. In 2014, the number of fully functional health facilities reached: about 16,000 health posts, 3,101 health centers, 27 primary hospitals, 48 general hospitals, and 19 referral hospitals (75, 76). The public health care delivery system is significantly complemented by the private sector—more so for inpatient care. In a nationwide survey, 20% of households that sought outpatient care for a reported illness visited private facilities whereas 30% of those that sought inpatient care received care from private facilities in 2011 (15).

Moreover, along with the infrastructure expansion, the human resource for health has increased both in number and diversity. The number of mid-to-high level health cadres in the system has increased exponentially by a factor of 3 to 15 folds. For example, between 2005 and 2015, the number of newly graduated medical doctors increased from 309 to 948, pharmacists from 70 to 379, midwives from 43 to 548, and more than 36,000 health extension workers have been trained and deployed (76, 77). Led by a strong government commitment, remarkable progress has been made in reducing morbidity and mortality from major communicable diseases, childhood and maternal conditions, and in improving access to basic health services in Ethiopia. Morbidity and mortality from TB, HIV, and malaria were cut by more than half over the past decade (17, 78). The health sector transformation plan I (HSTP I) 2015/2016 - 2019/2020 outlines the sector's key strategic directions and forms the first part of the next 20 years health sector envisioning document and a core element of the GTP-

II (68). The development process involves a mix of bottom-up and top-down approach that engage relevant stakeholders at the national and sub-national level including development partners, health professionals, and civil society organizations (68).

In spite of the remarkable progress, Ethiopia still lags behind in ensuring universal access to basic health services (71). Only 28% of the deliveries were attained by skilled providers; coverage of antenatal care stood at 32% (for four visits); while only 53% of eligible children received Pentavalent-3 vaccine in 2016 (71). The low coverage of services is compounded by persistent socio-economic and geographic disparity (e.g., 50% of children in rural areas received pentavalent-3 compared to 80% in urban areas and only 22% women in the poorest quintile used modern contraceptive methods compared to 46% among the richest group). Furthermore, the emerging burden from NCDs presents an ongoing challenge to the sector in the years to come. The growing NCD burden and its implication are discussed in the next section with emphasis on cardiovascular disease.

1.3.3 Cardiovascular disease (CVD) in Ethiopia and what is being done?

Worldwide, the total burden from NCDs is rising steadily. In 2013, about 60% of total DALYs were attributed to NCDs compared to about 50 % in 2005. Of the NCDs, CVD is the leading cause of disease burden. From CVD, ischemic heart disease (IHD) and stroke represent the first two major causes of DALYs lost globally. In 2015, these two conditions accounted for nearly 80% of all DALYs lost due to CVD (79). In terms of mortality, more than 14,000 lives (nearly 27% of all deaths) were lost due to the two conditions globally in 2015. Sub-Saharan Africa is one of the regions that has seen an increasing NCD burden—a further increase predicted in the coming decades with the total DALYs lost from CVD projected at 36% of total DALYs by 2030 that increased from 25% in 2010 (80, 81). In 2015, nearly 10% of all deaths were attributed to IHD and stroke, although the conditions contribute to relatively small share of total DALYs lost in the region (3.4%) (79).

CVD is emerging as an important public health challenge to Ethiopia. According to the global burden of disease (GBD) study, nearly 15% all deaths in Ethiopia in 2015 were caused by CVD. IHD and stroke together contributed to 5.4% of total DALYs lost and ranked third among the leading causes of disease burden following lower respiratory tract diseases and diarrhea in Ethiopia (79). Local studies also affirmed an emerging epidemiologic shift towards NCD dominated pattern especially in urban areas in Ethiopia (82-85). In Ethiopia's capital Addis Ababa, Misganaw et al., estimated using verbal autopsy methods that about 24% all deaths between 2006 and 2009 were due to CVD (Figure 4) (86). The same group reported that 11% of all hospital deaths in Addis Ababa between 2002 and 2012 were due to CVD (86, 87).

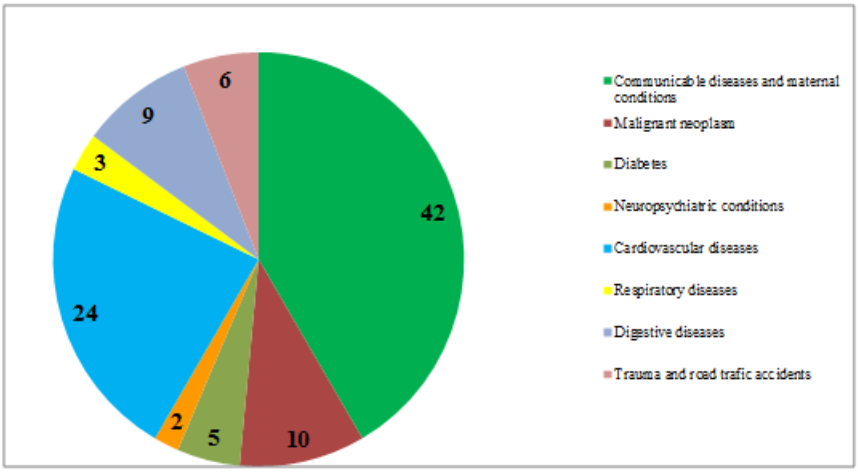

Figure 4: Mortality burden by condition in Addis Ababa between 2006-2009, reproduced from Misganaw et al., (86).

Apart from the health loss, CVD has a multi-dimensional impact on countries' economy (88, 89). In Bloom's words, the World Economic Forum identified NCDs as "one of the leading threats to global economic growth" (90). Observational studies revealed that CVD occurs 10 to 15 years earlier in low-income settings as compared to high-income settings (6). Hence, CVD may deplete economic systems off otherwise productive human capital. Therefore, it greatly compromises countries'

macro-economic potential due to premature loss of life and long-term disability of working age adults associated with the disease.

Moreover, acute IHD and stroke are costly to treat to health systems in low-income settings that already suffer from severe resource scarcity and have weak human resource and infrastructure capacity. Therefore, the best possible CVD treatment and prevention services are not widely available to patients, e.g., percutaneous coronary intervention (PCI) for treatment of acute myocardial infarction and long-term rehabilitation care for patients who suffered stroke (91, 92).

At the micro-level, CVD affects household's economy in several ways (88, 93-96): 1) high OOP spending on health care. This is especially relevant in settings like Ethiopia that lack UHC. Given its relevance to my research question, I have explained below the problems with OOP payments when used as a major source of health care financing, 2) lost household income due to loss of life or disability of families' bread winner(s) or change in the work schedule of other family members as a result of the sick family members, and 3) it may also lead to compromise on other essential consumptions such as food or education—which have potential impact in determining one's future economic potential (88, 93-96).

Nevertheless, opportunities are available for successful prevention and control of CVD. Evidence showed that CVD is to a large extent caused by potentially modifiable risk factors; the most common ones being hypertension, high cholesterol, and high body mass index (97). According to the 2015 *Stepwise approach to NCD risk factors surveillance* (STEPS) survey, 94% of Ethiopians between the age of 15-69 years were found to have at least one or more of the well-known risk factors for CVD (98). 15.6% had raised blood pressure (having systolic blood pressure of > = 140 mmHg or diastolic blood pressure of > = 90mmHg). However, 97% of the hypertensive individuals were not on treatment. 7.9% were either obese or overweight, 5.6% had raised total cholesterol, 4.2% were current smokers, and inadequate intake of fruit and vegetables was a nearly universal problem. Most of risk factors were more prevalent among urban residents compared to rural (98). Based on

these risk factor profile, the Ethiopian Public Health Institute (EPHI) estimated that, about 4.7% of adults aged 40-69 years (4.5% in rural and 5.3% in urban) have more than 30% risk of developing CVD events over the next 10 years including those with established CVD events.

Generally, CVD and its risk factors disproportionately affect the socioeconomically disadvantaged groups. According to the World Health Survey (2003), most CVD risk factors were more prevalent among the socio-economically disadvantaged groups. Smoking, alcohol intake, inadequate intake of fruits and vegetables, and inadequate physical activity were about 1.5 times more prevalent among the poorest quintile compared to the richest quintile. In addition, it is well-known that the poorest households have poorer access to health care compared to the richest (99, 100).

With the appropriate measures to address these modifiable risk factors in place, Ethiopia can contain the increasing CVD burden. On the one hand, sustained life-style modification can help prevent a substantial share of the CVD burden (97, 101). On the other hand, there are population-wide and individual based primary prevention strategies that are of proven effectiveness and cost-effectiveness in many low-income settings (92, 102, 103).

So far, the Ethiopian health sector has paid little attention to NCDs, CVD included (78, 91). The coverage of low-cost preventive interventions is low in Ethiopia (85). The Ethiopian STEPS survey reported that only 11.5% of individuals with an established CVD event or those that have > 30% risk of developing CVD events over the next 10 years were taking statins to prevent stroke and myocardial infarction in 2015 (98).

In spite of this, the policy environment for NCD control is changing favorably as demonstrated by some new initiatives towards that goal. In 2013, a NCD case team was established under the disease prevention and control directorate of the Federal Ministry of Health (FMOH) with a responsibility to coordinate NCD programs (91). In 2014, a national strategic action plan was formulated to stimulate the implementation of sectoral and cross-sectoral strategies targeting the four major

NCDs, of which CVD is a core component (104). The first comprehensive national guideline for clinical and programmatic management of major NCD was launched in 2016 (105). Moreover, Ethiopia is one of the target countries for *The Lancet* non-communicable diseases and injuries (NCDI) poverty commission that aims to facilitate redefining the NCDI agenda nationally and at the global level (http://www.ncdipoverty.org/). Nevertheless, although improvements have been witnessed in recognizing the growing NCD problem in Ethiopia, translating this ultimately to ensure that the people in need of these services have actually received them is a question of resources availability and or the political will to commit resources, among other things.

1.3.4 Health care financing

The Ethiopian health sector remains severely under-financed with a need for improvement in government's allocation for health (60, 106). According to the World Bank's estimates, the health sector took 5% of Ethiopia's GDP in 2015 (60). In 2015/2016, the Ethiopian Ministry of Finance and Economic Development (MOFED) reported that 7% of the federal level budget was allocated to health sector compared to 25% allocation for education and road sector each and 7% allocation to agriculture (107).

In terms of total government budget at regional level, about 12.5% was spent on health in 2015/2016 with wide variation in commitment across regions (76). In relative terms, Addis Ababa city administration allocated the lowest amount to health as share of government's budget at 6.4% whereas, Gambella region allocated more than a-quarter (28.5%) of the total government budget in 2015/2016. In absolute terms, Somali region spent the least amount (US$ 6 per capita) compared to US$ 64 per capita in Gambella (76).

According to the six National Health Accounts (NHA), Ethiopia spent about US$ 29 in 2014 in per capita terms—a significant growth from about US$ 6 in 2000 (60, 106, 108). Still, the country's spending falls short of the average for sub-Saharan Africa (US$ 98) and the recent resource requirement estimates by Stenberg et al., to meet the

SDG goals by 2030 —US$ 112 for low-income settings and US$ 146 for low middle-income countries (which Ethiopia envisions to become by 2025) (109). Furthermore, the growth in Ethiopia's health spending came largely at the expense of high OOP payments by households and support from international donors, respective contribution from each amounted to 34% and 50% of the total share in 2011 (Figure 5) (106). However, government's contribution to total health spending grew substantially in absolute and relative terms (from 16% of total spending in 2011 to 30% in 2014). Nevertheless, the relative share of OOP payments by households grew in absolute terms and remained the same in relative terms, while development partner's contribution remained the same in absolute terms and declined in relative terms (from 50% of total spending in 2011 to 36% in 2014) (Figure 5) (106, 108).

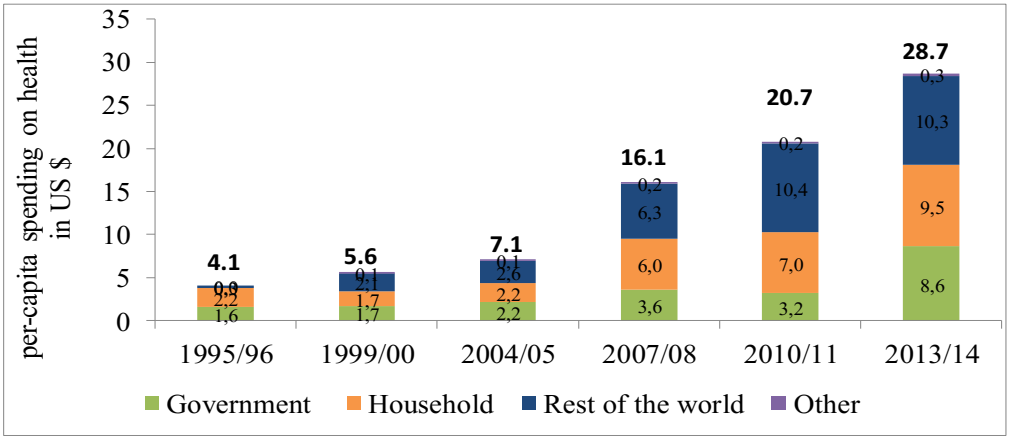

Figure 5 Trend in per capita annual spending health care in Ethiopia by source of finance (106, 108).

The health sector receives its financing through multiple channels (74, 110). The *first channel* draws on block grants from the treasury that are allocated to regional states and city administrations by the MOFED (74, 110). The finance offices at the regional state level in turn distribute the allocations to districts and sub-city councils within their catchment. The districts have the full autonomy to make allocation decisions based on the perceived priority needs of the population. Subsequently, district and sub-city authorities decide on sectoral allocations and transfer the health sector's share to respective district health bureaus, which in turn make in-kind or in-cash

transfers to health facilities. The *second channel* represents funding that flows from international partners to the FMOH as ear-marked funding for specific programs or in the form of flexible funding channeled through the pooled SDG performance fund which is used to cover under-funded priority programs in HSTP. The *third channel* constitutes direct transfer from development partners to implementing institutions and health facilities (74, 110).

Additionally, user-fees represent another source of revenue to health facilities. The Ethiopian health care financing strategy allows health facilities to collect, retain, and use the revenues that health facilities collect—to improve the quality of services delivered (74, 111-113). The revenue collected at the health facility level is supposed to be additional to the regular budget. In 2015/2016, 225 hospitals and 3,192 health centers retained internally generated revenues mainly from user-fees and used them to purchase drugs, laboratory supplies, medical equipment, facility renovation and staff motivation activities among other things (17).

The way health systems are financed has substantial impact on health service utilization and hence, the health of the population (1, 114-117). With this regard, overreliance on direct OOP payments is prohibitive to health care access and exposes households to financial risks (117). This is because OOP payments are often unpredictable and regressive in nature (1, 114-116). More explicitly, such financing arrangements attach payments to demand for health care instead of ability to pay. As a consequence, the sick with the most need for health care and the poor with lower ability to pay are disproportionately burdened (1, 117, 118). OOP payments could take the form of expenditures on consultation fees, drugs, hospital bed days, laboratory investigation, transportation to and from health facilities and informal payments to providers (22, 119).

In addition to their impact on health service utilization, expenditures on health care have long been identified among the main causes of deprivation and poverty globally, more so in Asia and Africa (22, 52, 120-124). Financial risk is said to occur when payments on health care are high relative to one's ability to pay forcing households to

compromise on other essential consumptions (22, 125). In other words, it is a measure of the impact of health systems on non-health aspects of well-being (52). Therefore, progressively shifting to prepayment arrangements where the contribution to health system is determined based on ability to pay and not linked with health status or use of health services is vital to protect households from such financial risk and it allows risk-pooling between the poor and the rich as well as the sick and the healthy (1, 2, 115, 124). Measurement of financial risk and its protection are further discussed in the methods section.

In Ethiopia, although households are still required to pay out of their pocket for most of the health services, progress has been made in shifting towards prepayment financing mechanisms. In 2008, the country launched a community-based health insurance (CBHI) scheme on a pilot basis in 12 districts in Amhara, Oromia, Southern Nations Nationalities and People, and Tigray regions. This voluntary scheme targets the informal sector and has been expanded to 191 districts in 2015/2016 (17). Overall, only 15% of the eligible households (81% are in the informal sector in Ethiopia) were covered by the scheme to date. Moreover, the average enrolment rate stalls at 36% in 2015/2016, with the highest enrolment rate of 50% in Tigray region and a minimum rate of 26% in Oromia region (17). In addition to this, preparations are under way to launch social health insurance scheme for the formal sector employees in the years to come (68, 113).

Besides the challenge of low total health spending and high OOP payments I have discussed so far, the allocation between the different program areas seems to be another area for improvement in Ethiopia. In spite of the increasing burden, programs that target NCDs still receive very little resources (68, 74). The next five-year health sector strategy ,HSTP I, is estimated to cost about US$ 16 billion, with a 21% funding gap (68). Of this, close to 2% of total budget (US$ 300 million) is allocated to prevention and control NCDs (that contributes to more than one-third of the disease burden) compared to a ten-fold higher (21%) allocation to TB, HIV, malaria, maternal, new-born, child health, and nutritional conditions (68). Yet, Ethiopia is committed to ensure UHC that requires health system to provide health services that

responds to the needs of population (68). Therefore, generating relevant evidence is a necessary first step towards explicit priority setting for health care in Ethiopia. In the next section, I describe the justification for this study and the knowledge gaps that we intend to fill with this PhD dissertation.

1.4 Justification of the study

Health care resource allocation decisions have profound impact on the health status of the population at the aggregate level and how such benefits are distributed between important population subgroups. In Ethiopia, faced with an acute resource scarcity along with an increasing burden from NCDs, a more systematic approach to priority setting is needed more than ever to respond to the needs of the population in an efficient and fair manner. Economic evaluation is the cornerstone of priority setting decisions for health care resources, as misallocation of resources imply a huge opportunity cost in terms of healthy life year lost. However, such evidence is lacking in Ethiopia for most of the health conditions.

Ethiopia spends very little on health (108). The financing is hugely dependent on direct OOP payments and the coverage of prepaid risk pooling mechanisms is very low (15, 16). The EHSP provides a basic minimum package of services free of charge at primary care level such as for immunization and child delivery (13). Households that seek care for NCDs such as CVD typically receive care upon direct payment to providers in public and private settings.

Previous studies have investigated OOP spending for various health services in Ethiopia (126, 127). Substantial financial risks have been reported even for highly subsidized services and prioritized services e.g. child delivery care and treatment of pneumonia and diarrhea (126, 127). With the lower priority given to NCDs, it is expected that households with CVD could be suffering a greater financial risk for receiving needed health care. This is especially relevant in places like Addis Ababa where the burden from CVD and its risk factors is high (82, 83, 86, 87, 128). However, none to our knowledge have investigated financial risk related to accessing

CVD care in Ethiopia. Although FRP has been identified as one of the key health policy concerns in Ethiopia (68, 129), the recent Plos Medicine's case study on Monitoring and Evaluation of progress towards UHC in Ethiopia by Alebachew et al., reported that none of the "direct" measures of FRP (the typically used parameters such as CHE) were routinely (regularly) measured and monitored in Ethiopia in 2015 (130).

With regards to cost-effectiveness of CVD interventions, WHO-CHOICE and the *DCP*, 2nd edition (www.dcp-2.org) have evaluated cost-effectiveness of several population-wide and individual-based CVD interventions at regional level for East Africa and other regions (43, 131). However, direct transferability of such evidence to local decision making is limited due to differences in several parameters such as differences in health system organization and price of inputs (10, 42). In addition, several ECEA have been undertaken in Ethiopia to quantify the expected health and FRP gains from investing on a broad range of interventions including childhood immunization, caesarean section, and mental health conditions (57, 132-136). However, there is no systematic cost-effectiveness and extended cost-effectiveness analysis of a broad range of CVD interventions in Ethiopia.

In this thesis, we intend to fill these knowledge gaps by taking Addis Ababa as an example due to the high burden of CVD and a greater concentration of specialized cardiac centers in the city.

2. OBJECTIVES

This thesis aims to generate policy-relevant evidence on health outcomes, costs, and financial risk protection of cardiovascular disease interventions so as to inform priority setting decisions in Ethiopia.

Secondary objectives are:

1) to estimate the magnitude and intensity of catastrophic health expenditure and factors associated with catastrophic health expenditure for prevention and treatment of cardiovascular disease in a hospital-based cross-sectional cohort study in Addis Ababa.

2) to undertake a cost-effectiveness analysis of primary prevention, acute treatment, and secondary prevention of ischemic heart disease and stroke in an Ethiopian setting.

3) to evaluate the expected health benefits, financial risk protection, and provider cost of the universal public finance (UPF) of primary prevention (disaggregated by income quintile) among individuals at an increased risk of cardiovascular disease in Addis Ababa, Ethiopia.

3. Methods

Three studies with three distinct methods were conducted to address the thesis' objectives. First, a hospital-based cross-sectional cohort study was conducted to assess the magnitude of financial risk that households face when seeking prevention and treatment of CVD. Second, a CEA of a broad range of prevention and treatment interventions for CVD was performed to assess which services offer the best value for money in a potential scale-up in Ethiopia. Third, after establishing the magnitude of financial risk related to seeking CVD care and identifying the most cost-effective CVD intervention in Ethiopia, we performed an ECEA to further examine what the Ethiopian government could expect to gain (in terms of health and FRP) along with the expected cost, if decision is made to publicly finance the cost-effective intervention of choice. The details on the methods used in each paper have been published in respective papers. In the following sub-sections I give a description of the study setting (3.1); provide an account of the rationale behind the choice of analytic approaches and the outcome measures used in specific studies (3.2); and I end the section with a brief description of the specific methods used in study I-III (3.3).

3.1 Study setting

Study I and study III were sub-national studies, while study II was a national level model-based study (CEA). The Ethiopian setting has been extensively covered in the introduction section. Here, I shall provide a short summary about Addis Ababa and its population mainly focusing of data that were not covered in the introduction section.

Addis Ababa is the capital city of Ethiopia. A fully urban locality, the city had an estimated population of 3.3 million as June 2015 with a male to female ratio of 47 to 53 (137). In contrast with the total national population, more adults and fewer under 5 children live in the capital—with a population dependency ratio of 38 compared to national average of 93 in 2015 (76). As expected, the city performs by far better than

the national average with respect to many of the key health and human development indicators as shown in Table 1. For example, in 2016, close to 90% of the pregnant women in Addis Ababa had four or more antenatal care visits compared to 32% at the national level (71). In a similar manner, close to 96% of children between the age of 12 to 23 months have received Pentavalent-3 vaccine in Addis Ababa in contrast with a 53% coverage at the national level (71). The population also has a better health seeking behavior with an annual per capita outpatient care attendance of 1.7 compared to a national average of 0.7 (17).

3.2 Methodological considerations

In this section, I give a short overview of the analytic approaches and the outcome measures (health and non-health outcomes) that we used together with the rationale behind our choice. I then provide more details on the choice of methods for each paper (I-III).

3.2.1 Catastrophic health expenditures (averted)

FRP is a way of measuring health system's impact on individuals' wellbeing above and beyond health per se (52). The root cause for incorporating FRP as one of the key health system objectives as well as stating it as a core element of UHC is that it is believed that health systems should not strive to achieve better health at the expense of essential consumptions that are key to the attainment of social goals other than health (52). Therefore, FRP is concerned with the *economic impact* of paying for health care as well as the *risk protection* aspect of health systems (22, 52).

Broadly, measures of financial risk have taken four forms in the literature. 1) Using parameters that describe the financial burden in terms of "*OOP payments as a function of some measure of subjects' ability to pay*". Two of the commonly used threshold based metrics fall under this category—CHE and medical impoverishment. CHE is defined as OOP expenditure on health care exceeding a given proportion of *resources available* to households (52, 118). Resources available to households can be expressed in terms of total consumption expenditures or households income less of

expenditures on essential consumptions such as food (22). Medical impoverishment occurs when an individual who was originally above the poverty line drops below the poverty line after the OOP expenditures (52). These two measures are complemented by two other parameters that measure the intensity of financial risk referred to as mean positive overshoot (that describes the OOP payments as a share of households' income or total expenditures above the chosen threshold for CHE) and poverty gap (a measure that intends to capture the worsening (if any) on living condition among the originally poor individuals due to OOP expenditures by quantifying how much further these households have gone below the poverty line due the payments for health care (22). 2) Measured as insurance value of protection against financial risk (money-metric value of insurance) which is quantified using risk averse individuals' willingness to pay to avoid the risk of financial risk (59). 3) Expressed in relation to prevalence of distress financing—a parameter that intends to capture the use of coping mechanism to smoothen potential fluctuations in essential consumption due to OOP payments (122, 138). (4) Financial risk has also been expressed in terms of absolute $ spent on health care. For example, Waters et al., defined financial catastrophe as OOP spending of more than US$ 2,000 per capita per year in the US (119). This approach is less commonly used and it is also not preferable as it lacks sensitivity to individuals' ability to pay.

To mention some of the limitations of the commonly used financial risk measures (CHE and medical impoverishment): 1) these parameters do not capture the lack of FRP which may manifest as non-use (under-use) of health services due to financial barriers; 2) the "risky" nature (aspect) of direct OOP payments is not so well captured in these measures (52); and 3) these parameters have limitations that emanate from their threshold-based nature. The thresholds are meant to represent the level of OOP expenditure (relative to income or consumption expenditures) that is adequate to result in a compromise on other essential consumptions (22). However, there is no consensus about what might be the appropriate cut-off points for the thresholds (22). Typically, lower thresholds (e.g., 5%-10%) are used when income or total consumption is used in the denominator compared to capacity to pay measures that

consider expenditures net of spending on essential consumptions (e.g., 25%-40%) (123, 124). However, more problematic than the lack of consensus on the cut-off points is, by nature thresholds are not concerned about those who are just below the given cut-off point. For example, at 10% household income threshold level, a household that spent 9.9% of household income is identified as "okay"—which may be considered unreasonable. In the literature, some have used scenario analysis at different threshold levels (22), but this would not solve the problem as at any given threshold level the problem persists.

In our study, we used CHE as a financial risk measure in study I and CHE cases averted as a measure of FRP in study III because CHE as this is a commonly used measure in the literature (88) and that it is advantageous because it does not discriminate between different population sub-groups (e.g., a single threshold can be applied to people with different socio-economic status—the poor and the rich) (52, 88). We defined CHE as annual OOP expenditures on CVD care of 10% or more of households' annual income.

3.2.2 Generalized cost-effectiveness analysis (GCEA)

CEAs are performed to inform allocation decisions about alternative courses of actions (21, 40). To the extent possible, all relevant alternatives should be evaluated with respect to their cost and consequences to avoid risk of erroneous misallocation. "Current practice" is a commonly used comparator. CEAs that evaluate new intervention(s) compared to the current practice are known as intervention mix constrained CEAs. (42, 139). Therefore, their application is very narrow. Besides, outcomes of such analysis could be misleading if the existing practice is not efficient. Hence, the validity of the results is highly contingent on how cost-effective the "current practice" is (140).

Generalized CEA (GCEA) examines cost-effectiveness of an intervention(s) compared to the counterfactual of a "no intervention" scenario—that designates what would happen to the study population in the absence of the intervention under consideration (139). In so doing, GCEA expands applicability of CEA results for

decision making in two critical ways:1) it removes the narrow “current practice” constraint from the decision equation so that interventions can be assessed independent of the “goodness” or “badness” of the existing practice; 2) it allows examination of the any potential inefficiency in the “current practice”. The implicit assumption is that if the current practice is found less cost-effective compared to the newly proposed, re-allocation decisions towards a more efficient use of the resources (better value for money) is possible. Therefore, GCEA allows comparison of a broader range of interventions so as to select the intervention mix that gives an optimal benefit to the society within the resource limit—a sectoral perspective (139). Ultimately, it helps in improving the overall allocation efficiency of the health sector by promoting consistent decision making across program areas. As my aim in this thesis is to inform macro-level priority setting decisions at the sectoral level—GCEA is better suited for that purpose. The GCEA approach is further discussed in the discussion section.

In addition, the availability of a validated model developed by WHO-CHOICE was a unique opportunity to generate CEAs on a broad range on interventions e.g., interventions targeting maternal and child health and mental conditions. This study is part of a country contextualization effort with an overarching aim of informing sectoral level priority setting in Ethiopia.

3.2.3 Extended cost-effectiveness analysis (ECEA)

ECEA is one key methodological developments in health care priority setting that allows for evaluation of health policies with respect to multiple dimensions. Specifically, ECEA, is “conceived for health policy assessment to evaluate the health and financial consequences of health policies in four domains: (1) the health gains; (2) the FRP benefits; (3) the total costs of the policy to the decision makers; and (4) the distributional consequences” (56). As shown in the ECEA analytic framework presented below in Figure 6, ECEA examines health policies with respect to health benefits, financial risk protection gains (e.g. CHE cases averted), and the distribution of these benefits across sub-populations of interest (e.g., income quintiles) as well as

the cost to the government of these gains (56). In other words, it quantifies the investment return from health policies in terms of health, financial risk protection, and equity gains (56). The unique addition of FRP in this analytic framework makes the tool suitable for assessing health policies' impact in reducing financial hardship for households. The tool is especially suitable in low- and middle-income settings that lack effective health insurance mechanisms where OOP expenditures for health care and illness-related productivity loss expose many to catastrophic expenditure and medical impoverishment (56, 58). In Ethiopia, OOP payments represent a substantial burden to households. Therefore, FRP is one of the important dimensions for health policy considerations. In addition, since ECEA provides for an assessment of the distributional consequences of health policies, it offers a good framework to study the impact of conditions that disproportionately affect different sub-populations (2, 58). In Ethiopia, CVD risk factors and utilization of health services have gradients across income groups (e.g., 10% of individuals with reported angina sought care among the poorest quintile compared with a share of 26% among the richest quintile in 2003) (98, 100). These features make the ECEA a suitable analytic tool for our study. Therefore, ECEAs help policy makers to account for health, FRP, and equity considerations when allocating the limited resources in a way that meets the priority policy objectives.

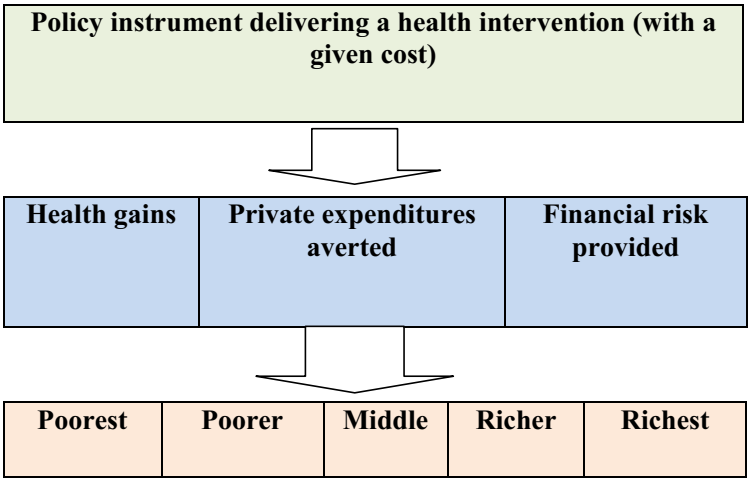

Figure 6: Conceptual framework for ECEA, reproduced from Verguet et al., (56).

3.2.4 Disability-adjusted life years (DALYs)

DALY is a composite measure that quantifies the aggregate "health lost" in the form years of life lost due to premature death (YLL) and years of life lived with disability (YLD). Typically used for two main purposes: 1) to estimate the global burden of disease, 2) DALYs averted is used as one of the key outcome measures in CEAs—especially in low-income settings (141). DALY is a health gap measure. It is something that one wants to avoid and hence, it is typically expressed as—DALYs averted—when used as an outcome measure in economic evaluations. Typically, different conditions affect distinct aspects of health: namely, length and quality of life. Therefore, health outcome measures using natural units such as cases of CVD events prevented has limited relevance for comparison across different groups. With this regard, DALY is advantageous in that it allows comparison between services that affect different aspects of health (142). For example, when we compare the health gains from highly fatal myocardial infraction with non-fatal depression. This makes the DALY powerful measure to inform resource allocation decisions across program areas.

DALY is calculated as:

$$\mathbf{DALY = YLL + YLD}$$

The YLL is straight forward, provided data on the life expectancy of a reference population and life expectancy of the population with the disease is available. YLL represents the life years lost because the person dies earlier (at age X, life expectancy of people with the condition at a given age) instead what could have been achieved without the condition (age Y, life expectancy for the reference population without the condition at a given age) (142). The YLL is then given by Y minus X.

The YLD component represents the "health loss" due to the years lived with disability due to the condition. Each year is adjusted for quality of life measure that reflects the value of a year being in that state. Each health state is assigned a value (disability weight) on a scale of 0 (perfect health) to 1 (equivalent to death) based on

individuals' preferences. Therefore, the YLD is calculated as the disability weight multiplied by the difference between the age of onset of the condition and age at death with the condition (age X). In the global burden of disease study (2013) (141), the health state valuation was elicited using paired comparison questions for which respondents were asked which of the two hypothetical individuals with different health states they considered worse than the comparator. The responses were modeled to derive the disability weights for more than 200 health states (141).

Several criticisms have been forwarded to the DALY measure, one of them being health state valuation with regards to its approach to preference elicitation, choice of the informant, and whose preference should be used to derive the disability weights? Yet, the DALY measure remains an important health outcome measure in low-income settings. We chose to use DALY as a heath outcome measure in study II and study III because: 1) it allows accounting for improvements in the length as well as quality of life which is appropriate for the interventions that we evaluated (e.g., non-fatal stroke may result in long-term disability), and 2) it allows comparison across wide range of disease programs—thereby, expands the usability of the evidence we generated to sectoral level decision making.

3.3 Methods used in specific papers

3.3.1 Cross-sectional cohort study of financial risk of cardiovascular disease care (Paper I)

Study population and design

This is a hospital-based cross-sectional cohort study. Data for this study was collected from individuals that sought prevention and treatment services for CVD in Ethiopia's capital Addis Ababa. In consultation with local experts, we selected eight hospitals in Addis Ababa where the study population was expected to concentrate. Overall, four public and four private hospitals consisting of four general and four specialized cardiac hospitals were selected for the study. Although primary prevention of CVD is provided at lower level health facilities (e.g., health centers or clinics), we focused on

the hospitals because chronic disease follow-up at lower level is less organized—making the data collection process practically challenging. Therefore, we opted to purposively select hospitals with expected high case load and organized service provision for CVD prevention and treatment.

The inclusion criteria were all adults having a diagnosis of IHD, stroke, hypertension or dyslipidemia, both on outpatient and inpatient basis with at least one prior outpatient follow up visit. We excluded those on their first outpatient visit. In each hospital, nurses recruited all eligible adults based on the diagnoses recorded on individuals' medical charts. With the assumption that the public and private sector have equal role in CVD service provision in Addis Ababa, the total sample was distributed 50-50 between public and private hospitals. Generally, the public sector is the major provider of health care even in urban settings (nearly 60-40 distribution) (143).

Data collection

Data was collected through an exit interview using a structured questionnaire which was adapted from a tool that was used in a similar previous study in Tanzania and other low-income settings (94). The questionnaire was developed in English and subsequently translated to Amharic (the Ethiopian national language) for ease of administration. However, to ensure consistency, it was back-translated to English and pilot-tested in one public and one private hospital before the actual data collection began. The data collection was completed over eight weeks during February to March 2015.

Among other things, we collected data on participants' socio-demographic characteristics, previous follow-up visits for the conditions of our interest, OOP expenditures on outpatient and inpatient care, source(s) of financing households used to cover OOP expenses, and households' income. OOP payments constitute direct medical costs such as fees for consultation, hospital bed-days, drugs, and laboratory tests as well as direct non-medical costs such as expenses on transportation, food, and accommodation for patients and accompanying care-givers to and from the hospitals.

Households' income was defined as the average reported monthly earnings of all economically active members of the household net of tax through formal employment, self-employment, in exchange of goods or services as well as cash transfers from any sources including family and friends.

Given the chronic nature of CVD, a 12-month recall period was chosen to be able to capture non-uniform expenditure pattern over the long term. Therefore, we gathered expenses on outpatient and inpatient care received at the time of data collection as well as for the CVD care received prior to the day of data collection at multiple data points.

All monetary data were collected in Ethiopian birr (ETB) and subsequently they were converted to 2015 US$ using the prevailing official exchange rate that applies to the study period (1 US dollar = ETB 20.33) (144). An exchange rate of 4.92 ETB per unit $ PPP in 2011 was used for the poverty analysis.

A total of 625 subjects were recruited for the study and 94% of them responded; five of them refused to participate and 31 subjects were excluded due to missing data on OOP payments and or households' income. The excluded subjects were more likely to be from the private hospitals, otherwise they were reasonably comparable with the subjects included in the final analysis, e.g. with respect to residence and sex.

Households were used as the unit of analysis. We used STATA version 14 for data analyses. Descriptive statistics was used to quantify the magnitude and intensity of CHE base on previously published methods (22). The magnitude of CHE was estimated as the percentage of households with annual OOP expenditure that amount to 10% or more of households' annual income. Annual OOP payments on CVD care were estimated as the sum of estimated annual outpatient care expenditures and inpatient care expenditures, as appropriate.

Whereas the intensity of financial risk among those that suffered CHE was assessed using a commonly cited parameter called mean positive overshoot. Mean positive overshoot quantifies how much more households spend (in % terms relative to

households' annual income) on CVD care in a year above the 10% annual income thresholds that we used to define CHE. To allow subgroup analysis, households were divided into quintiles based on households' income and were designated as Q1 (the poorest) to Q5 (the richest). T-test was used to assess the significance of the differences in the proportion of households that faced CHE across income groups.

Factors associated with CHE were examined using logistic regression models. We selected potential covariates mainly based on the existing body of literature (94, 122, 145). Variables were solely assessed in bivariate models for potential association, followed by a multivariate analysis. We examined several variables; income level (as categorical variable in quintiles), residence, type of hospital visited, hospitalization, presence of established CVD event, patient's age, patient's occupation, and household size were included in the final model. These were chosen from bivariate models because they were significantly associated with CHE at p-value of 0.1 (146). P-values of less than or equal to 0.05 and 95% confidence intervals (CIs) were used as cut-off points to classify respective odds ratios (ORs) as statistically significant.

In this study, I focus on a relative measure of financial burden to take into account households' ability to pay as it better informs about the economic consequences of OOP expenditures at the household level.

3.3.2 Cost-effectiveness analysis of prevention and treatment of cardiovascular disease (Paper II)

Cost-effectiveness analysis is a key tool that helps decision makers to select interventions or programs, among competing alternatives, that maximize the total health benefits for a given resources available (147). This is particularly relevant in resource constrained settings like Ethiopia, where the opportunity cost of investing in less-efficient alternatives could translate to huge life years lost. Here, we performed a GCEA of selected interventions for primary prevention, acute treatment, and secondary prevention of IHD and stroke in an Ethiopian setting.

We used WHO-CHOICE's CVD model for East Africa: a multi-stage population model that builds on the life-table approach to estimate health benefits in terms of

DALYs averted (148). The model has been validated as evidenced by the several regional level CEAs and country contextualization efforts in low-income settings (92, 102, 149, 150). In this study, the regional model was populated with best available recent local data to the extent possible complemented by other sources when local evidence was lacking. A summary of the updates incorporated in the regional model is presented in subsequent sections.

31 interventions (including 15 single and 16 integrated packages of interventions) were selected for the analysis guided by local experts' recommendation and WHO's guidelines. Detailed description of all the interventions is provided in Table 1 of paper II. To give a brief account here, primary prevention interventions constitute basic drug regimens to be delivered on an outpatient basis at primary health care level. This includes: (a) a beta-blocker and a thiazide diuretic at systolic blood pressure of > 140 mmHg or > 160 mmHg; (b) statin at serum total cholesterol level of > 5.7 mmol/l or > 6.2 mmol/l; (c) combination of aspirin, beta-blocker, thiazide diuretic, and statin at > 5%, > 15%, > 25%, and > 35% absolute risk of developing a CVD over the next 10-year period.

For acute myocardial infarction, inpatient care at tertiary level with a basic pharmaceutical regimen consisting of aspirin, streptokinase, clopidogrel, beta-blocker and ACE-inhibitor and a highly skilled surgical revascularization with percutaneous coronary intervention (PCI) were assessed solely or in combination. Secondary prevention interventions constitute treatment with aspirin, beta-blocker, ACE-inhibitor, and statin on outpatient basis at primary health care level to individuals with a history of established CVD events.

Health benefits

In order to estimate the net health gains from the interventions, subjects in the model were followed with and without respective interventions over a life time of 100 years. The model assumes that interventions are implemented only during the first 10 years of the follow up period. Health benefits were estimated in terms of DALYs averted. In the absence of local evidence, the efficacy estimates for the interventions were

drawn from published evidence from elsewhere. Given the current sub-optimal coverage of interventions (5% based on expert opinion), scaling up the proposed interventions to a 20% target coverage level was assessed. However, the model provides for eliminating the benefits from current coverage of interventions and adjusts the epidemiologic parameters accordingly—to create a hypothetical reference case of the "null scenario" which designates a simulation of what would happen to the study population in the absence of the interventions under consideration. Further details on the model design and the assumptions and inputs used are discussed at length in the methods section of study II.

Costs

As we aimed to inform health policy makers on resource allocation decisions in Ethiopia, we adopted a health care provider perspective to estimate the costs. Therefore, direct non-medical costs (such as transportation expenses) and indirect costs to households (such as productivity loss) were not accounted for in the analysis. We included program costs needed to administer the intervention as well as direct medical costs incurred at the point of service delivery including drug costs, hospital bed days and laboratory tests. An ingredient costing approach was used, where the quantity and respective unit prices of resources required to deliver the interventions were measured separately. The quantity of the resources consumed was largely determined based on WHO-CHOICE's assumptions (43). Equipment and material prices were drawn from WHO price estimates for Ethiopia (151). The salary scale for the health workforce was updated based on data from the FMOH, while the price of relevant laboratory tests and imaging was informed by data from two public hospitals in Addis Ababa. The lowest 'supplier' price from the international drug price indicator guide was used to estimate unit cost of drugs (152).

Cost-effectiveness

Interventions were assessed in five mutually exclusive clusters within the groups described earlier. In each cluster, interventions were first compared with a 'no intervention' scenario. This was followed by incremental analysis within each

category to assess the relative cost-effectiveness of interventions starting from the one with the lowest effectiveness—as recommended by economic evaluation text books (40). Subsequently, we ranked the non-dominated interventions based on their cluster specific ICER—so that interventions can be prioritized for public financing in a step-wise manner based on their rank order until the available resources are exhausted—the league table approach.

Therefore, the incremental costs for moving from an intervention to the next more effective intervention were divided by the incremental effects to compute respective incremental cost-effectiveness ratios (ICERs). Interventions that were more costly and less effective than their comparators or those that had higher ICER than their more effective comparators within mutually exclusive clusters were excluded from the analysis as they were dominated. The average cost-effectiveness ratios presented in Table 4 of study II represent the ICERs compared with a 'no intervention' scenario. And, what was reported as ICER represents results from incremental analysis within respective mutually exclusive categories. As recommended by WHO-CHOICE both health benefits and costs were discounted at 3% rate annually. ICERs are reported as cost in 2012 US$ per DALY averted.

In addition, we assessed the impact of uncertainties surrounding input parameter estimates on our final results in two ways. A probabilistic uncertainty analysis was undertaken using Monte Carlo simulations to assess the combined effect of uncertainty pertaining to the costs and effectiveness estimates. In addition, one way sensitivity analysis was performed to assess which one of the parameters impact the results the most; where we applied the lowest boundary for efficacy estimates, 50% of point estimates for efficacy, doubled the estimated unit price of drugs and laboratory tests, and a zero discount rate both for health benefits and costs.

3.3.3 Extended cost-effectiveness analysis of medical primary prevention of cardiovascular disease (Paper III)

Study population, health policy, and estimation of the health benefits

In this study, building on the previous two studies, we modelled UPF of a multidrug therapy for primary prevention of CVD with aspirin, statin, and anti-hypertensives to individuals with an increased absolute risk of CVD events over the next 10-years period according to four risk thresholds: > 5%, > 15%, > 25%, or > 35%. We assumed the current coverage of this multidrug therapy to be 5% and hence, we set a modest incremental coverage of 20% for the base-case analysis and performed scenario analysis for a 50% and 90% incremental coverage.

The model was developed in two steps. In step 1, we calculated the number of people at each CVD risk level disaggregated by age and sex in Addis Ababa following the approach of study II (43, 153). To estimate the CVD risk profile of respective age–sex groups, we updated the WHO-CHOICE CVD model for East Africa (study II) with the demographic data as well as the age- and sex-distribution of mean systolic blood pressure, mean total cholesterol level, body mass index, and prevalence of smoking for Addis Ababa population (85). In step 2, we estimated the number of CVD events prevented by the UPF policy. To do this, first, the annual number of CVD events without the intervention was estimated by multiplying the annual risk of developing acute myocardial infarction and stroke at various risk levels (154) with the number of individuals at each risk level calculated in step 1. This was followed by estimation of the expected number of CVD events averted by the intervention—calculated by multiplying the number of CVD events without interventions by the intervention's efficacy (0.54 for IHD and 0.64 for stroke) (155, 156) on annual basis considering the incremental coverage. All the input parameters that we used are presented in Tables 1 and 2 of paper III. The unit cost to the government of the multidrug therapy, mean OOP expenditures, and probability to CHE by income quintile were drawn from paper I.

Subsequently, the number of CVD events prevented was converted to DALYs averted by using the standard health economic methods: see supplementary annex of study III for the details. In the absence of local data on the distribution of CVD incidence, we disaggregated the health gains into income quintiles from Q1 (poorest 20%) to Q5 (richest 20%) based on a study from India (157).

Provider costs

Under the proposed UPF policy, the government covered the direct medical costs related to the multidrug therapy at primary health care level. Therefore, the analysis did not take into account direct non-medical costs and potential income loss resulting from the illness. The unit cost per treated person per year was assumed to be US$ 25 per year (153). We estimated the total costs by multiplying the number of individuals treated with this preventive policy by the unit cost for the respective incremental coverage levels. All future costs and health benefits were discounted at a rate of 3% per year. All monetary values were reported in US$ 2015.

Household out-of-pocket expenditure averted

The UPF policy is expected to protect households from incurring OOP payments in two ways: 1) OOP expenditures for primary prevention—estimated by multiplying the mean OOP payments for primary prevention in each quintile (presented in Table 2 of paper III) by the number of individuals expected to receive the preventive intervention at the current coverage level (5%), 2) potential OOP payments for the CVD events prevented—estimated as the product of the mean OOP payments for the treatment and secondary prevention of CVD events in each quintile by the number of CVD events prevented for the incremental coverage (20%). The sum of these two estimates gave the total OOP expenditures averted by the UPF policy.

Catastrophic health expenditures averted

In a similar manner, we estimated the total number of CHE cases averted by the UPF policy as the sum of the CHE cases averted when seeking primary prevention before the policy and the CHE cases averted because of the CVD events prevented by the

policy. The prior was estimated as a product of the number of individuals expected to receive the preventive intervention at the current coverage level (5%) by the probability of CHE conditional on seeking care. Whereas, the latter was estimated by multiplying the number of CVD events prevented by the policy for the chosen incremental coverage (20%) by the probability of CHE for CVD treatment and secondary prevention based on data extracted from study I (Table 2 of study III). The product was subsequently multiplied by the probability of seeking health care conditional of having the CVD events (Table 2 of study III).

These steps for estimation of the health benefits, OOP expenditures, CHE cases averted, and costs were repeated four times for all the risk thresholds to estimate the gains disaggregated at the four risk levels. Subsequently, these estimates were summed up to get the total benefits and costs of the UPF policy. Moreover, although a 10-year time horizon was used for the analysis; all outcomes were reported on an annual basis.

3.4 Ethical approval

The whole project has been reviewed and exempted by the Norwegian Regional Research Ethics Committee as it was beyond their scope. Study I was approved by the Scientific Ethical Review Committee of the Ethiopian Public Health Institute (EPHI) with a reference number: 005-02-2015/EPHI 6.13/65. We also obtained informed consent from study participants before commencing the interviews for the data collection. In addition, data was stored and used in de-identifiable form to ensure confidentiality. Study III is the extension of study I and benefited from the same primary data used in study I. Study II is a modelling exercise that fully used publicly available data.

4. Results

In this section I present the results from the three studies that this thesis was founded on. In study I, we estimated the financial risk households faced related to seeking prevention and treatment of CVD in Addis Ababa. Study II explored cost-effectiveness of a broad range of CVD interventions that the Ethiopian government could consider for a potential scale-up to successfully control the growing CVD burden. In study III, we estimated the expected investment return that the government can anticipate to gain from scaling-up the most cost-effective strategy that we identified in Study II with respect to health and FRP gains and assessed the distribution of these benefits across income quintiles of the at-risk population. The results are presented below under each sub-section.

4.1 Synopsis of paper I:

Financial risk of cardiovascular disease care.

A total of 589 subjects were included in the final analysis. Of them, close to 85% were 45 years old or above and about half of them were engaged in an economically productive job during the survey (see Table 2). The majority of the participants (80%) were residents of Addis Ababa, while the remaining travelled from outside the city to seek CVD care. About 54% had established CVD events, including the 6% that were hospitalized for it during the survey period; the rest were on primary prevention regimen. Further details on the socio-economic characteristics of the study population are presented in Table 2.

Table 2 Socio-demographic characteristics of study participants.

		N=589	(%)
Age(in years)	25-44	88	**(15)**
	45-64	281	**(48)**
	65-79	192	**(32)**
	> = 80	28	**(5)**
Gender	Female	298	**(51)**
	Male	291	**(49)**
Marital status	Single	51	**(9)**
	Married	428	**(73)**
	Divorced	26	**(4)**
	Widowed	84	**(14)**
Residence	Addis Ababa	470	**(80)**
	Outside Addis	119	**(20)**
Education	No formal education	115	**(20)**
	Grade 8 or less	163	**(28)**
	Grade 9-12	146	**(25)**
	Diploma	85	**(14)**
	Bachelor degree+	80	**(13)**
Occupation	Government employee	119	**(20)**
	Private employee	38	**(6)**
	Private business	109	**(19)**
	Stay home mum	162	**(28)**
	Retired	135	**(23)**
	Other	26	**(4)**
Diagnosis	Ischemic heart disease	233	**(40)**
	Stroke	83	**(14)**
	Hypertension	235	**(40)**
	Dyslipidemia	38	**(6)**
Number of hospital admission(s) over the last 12 months	0	489	**(83)**
	1	90	**(15)**
	2	10	**(2)**
Type of hospital visited	Public	306	**(52)**
	Private	283	**(48)**

In total, about 27% (CI [21.1, 30.6]) of the study subjects faced financial catastrophe—having an annual spending on CVD care that exceeds 10% of household annual income. The financial risk was unevenly distributed across income

quintiles, although it seems to be non-monotonic. Notably, 28% (CI [20.0, 37.3]) of the poorest quintile had CHE compared to 14% (CI [7.9, 23.1]) among the richest—which was statistically significant (p-value comparing the two proportion was 0.02) (see Table 3 below).

Table 3 Proportion of households that faced catastrophic out-of-pocket payments for prevention and treatment of cardiovascular disease in general and specialized hospitals in Addis Ababa, Ethiopia, 2015.

	Percentage (%)	**Standard error***	**[95% CI] †**	
Total	26.7	1.9	23.1	30.6
Q1	27.9	4.4	20.0	37.3
Q2	28.5	3.8	21.7	36.6
Q3	32.2	5.0	23.3	42.6
Q4	28.3	4.1	21.0	37.0
Q5	13.9	3.8	7.9	23.1

*standard error of the mean, †95% confidence interval, p-value comparing Q1 and Q5 = 0.015.

The results from the logistic regression analysis are presented in Table 4 below. Several factors were found to be significantly associated with CHE. To give examples, hospitalization for CVD events increased the odds of CHE by about eight-fold (OR = 8.4 [4.2, 16.6])—stroke being the strongest predictor (OR = 4.1 [1.8, 9.2]). Likewise, households that travelled to Addis Ababa to seek CVD care faced a greater financial risk compared to Addis Ababa residents (OR = 3.3 [1.8, 5.9]), as was the case for those that sought CVD care in private hospitals (OR = 20.7 [20.2, 42.1]). More importantly, CHE was found to have a strong negative association with income group. The odds of CHE among the poorest quintile was significantly higher than that of the richest quintile (OR = 58.6 [16.5, 208.0]). The ORs decline steadily as the income group increases, although the CIs were wide (Table 4).

Table 4 Multiple logistic regression analysis of factors associated with catastrophic out-of-pocket payments for prevention and treatment of cardiovascular diseases in general and specialized hospitals in Addis Ababa, Ethiopia 2015.

Covariates		OR	[95%CI]	p-value
Income quintiles	Q1	**58.6**	[16.52, 208.0]	0.00
	Q2	**39.0**	[11.87, 128.24]	0.00
	Q3	**20.9**	[6.97, 62.92]	0.00
	Q4	**6.9**	[2.4, 19.99]	0.00
	Q5	1		
Residence	Addis Ababa	1		
	Outside Addis	**3.25**	[1.79, 5.90]	0.00
Type of hospital visited	Public	1		
	Private	**20.71**	[10.21, 42.05]	0.00
Received in-patient care for CVD over the past 12 month	No	1		
	Yes	**8.39**	[4.24, 16.59]	0.00
Diagnosis*	IHD	1.15	[0.65, 2.06]	0.63
	Stroke	**4.10**	[1.82, 9.18]	0.01
	Hypertension or Dyslipidemia	1		
Household size	Household size	**1.20**	[1.06, 1.36]	0.04
Age of participants	Patient's age	**1.00**	[0.98, 1.02]	0.02
Duration since diagnosed	Duration since diagnosed	**0.99**	[0.98, 0.99]	0.05
Occupation of participants	Employed†	**1.07**	[0.44, 2.58]	0.88
	Private business	**0.91**	[0.38, 2.17]	0.84
	Housewife/husbandman	**1.34**	[0.67, 2.65]	0.41
	Retired	**1**		
	Others	**1.23**	[0.36, 4.14]	0.73

***** IHD stands for ischemic heart disease, Q1 stands for poorest quintile and Q5 stands for richest quintile. **†**includes government and private employees

In addition, we found that the bottom two quintiles spent about 24% more of households' annual income on CVD care, while the richest quintile had only 5% extra spending (Table 4 of paper I). This indicates a more severe financial risk among the poorest.

As expected, households used various coping mechanisms to cover OOP expenditures—more so for inpatient care than for outpatient care. As shown in Table 5 of study I, family support was the predominant means. About 40% of households

fully covered inpatient care expenditures through family support, while another 30% tapped into this source to cover outpatient expenditures. A smaller proportion of households (5% for outpatient and 15% for inpatient care) used their savings (see Table 5 of study I). Dependence on family support tends to be common among the poorer households compared to the better-off (result not shown).

We now know that households in Addis Ababa faced a sizeable financial risk when seeking prevention and treatment services for CVD and that this financial risk unevenly affected the poor and those with established CVD events among others.

4.2 Synopsis of paper II:

Cost-effectiveness of prevention and treatment of cardiovascular disease.

Of the 31 interventions we assessed, combination drug treatment with anti-hypertensives, aspirin, and statin based on individuals' absolute risk was found to be the most cost-effective (see Table 5 below). The ICER for this package was US$ 67 per DALY averted, if initiated at the highest risk threshold level (> 35%). The incremental cost per an additional DALY averted increased moderately at lower risk levels— and reached US$ 340 at the lowest risk (> 5%) (Table 5). The absolute risk based approach dominated the alternatives that targeted high blood pressure and high total serum cholesterol level in isolation (Table 4 of study II).

Table 5 Annual cost, annual health benefits and cost-effectiveness ratio and ICER ranking of non-dominated CVD interventions in Ethiopia.

	Annual cost in US$	Annual DALYs averted	ACER	ICER
Combination drug treatment for absolute risk of CVD > 35%	7.18	107,687	67	67
Combination drug treatment for absolute risk of CVD > 25%	9.83	127,712	77	131
Combination drug treatment for absolute risk of CVD > 15%	14.41	153,877	94	177
Combination drug treatment for absolute risk of CVD > 5%	26.85	190,391	141	341
Acute IHD: ASA+streptokinase +ACE-inhibitor+beta-blocker	2.92	2919	999	999
Sec. prev. stroke: ASA+ statin + ACE-inhibitor	3.48	3,284	1,061	1,061
Sec.prev IHD: ASA + beta-blocker + statin + ACE-inhibitor	2.88	1,557	1,849	1,849
Acute IHD: ASA+ clopidogrel + PCI	8.50	4,015	2,115	5,087

ACER stands for ICER compared to null scenario, ICER stands for cluster specific ICER, IHD stands for ischemic heart disease, PCI stands for percutaneous coronary intervention

Generally, treatment and secondary prevention of CVD was relatively less cost-effective than primary prevention. Among the alternatives for treatment of acute myocardial infarction, an integrated package of aspirin, ACE-inhibitor, beta-blocker, and streptokinase generated the most value for money within its cluster (ICER = US$ 1,000 per DALY averted). Notably, the incremental cost for an additional DALY averted escalated by a factor of five when moving from this basic integrated package to a package that consisted of PCI, aspirin, and clopidogrel (ICER = US$ 5,100 per DALY averted) (Table 5).

Provision of interventions in packages improved interventions' cost-effectiveness. Accordingly, for secondary prevention of IHD, a package of aspirin, beta-blocker, ACE-inhibitor, and statin (costing US$ 1,850 per DALY averted) was relatively more cost-effective than its comparators, as was a package of aspirin, ACE-inhibitor and

statin (for costing US$ 1,060 per DALY averted) for secondary prevention of stroke within its respective cluster (Table 5).

However, the results from the probabilistic sensitivity analysis presented in Figure 1 of paper II revealed substantial uncertainty surrounding the costs and effectiveness estimates of the interventions. The level of willingness to pay was shown to have a meaningful impact on the probability of a given interventions being cost-effective. On the other hand, the results from the one-way sensitivity analysis demonstrated that halving the effectiveness assumption had modest effect on the ICER estimates, while other changes (e.g., unit costs) had little or no effect (Table 5 of paper II). However, the outcomes from these scenarios did not change the conclusions about the results of the paper.

4.3 Synopsis of paper III

Health benefits and financial risk protection from cardiovascular disease prevention.

This study estimated the costs and the expected health and FRP gains from UPF of multidrug therapy for primary prevention of CVD in Addis Ababa—the most cost-effective intervention among those assessed in study II. Overall, the UPF policy afforded significant health and FRP gains that preferentially benefited the poorer households.

For a 20% incremental coverage, the UPF policy would avert about 5,800 DALYs per year in total. The largest health gain—2,240 DALYs averted per year—would be attained at > 15% risk level, while 1,240 (at > 35%), 1,180 (at > 25%), and 1,200 (at > 5%) DALYs would be averted (at respective risk levels). The DALYs averted were distributed across income as: 22% (Q1), 18% (Q2), 24% (Q3), 26% (Q4), and 10% (Q5)—a pattern consistent regardless of risk level chosen (Table 6).

Table 6 Annual health benefits, financial risk protection and costs of 20% increased coverage of

universal public finance of primary cardiovascular disease prevention in Addis Ababa, Ethiopia, 2015.

	Income quintile					
	1	**2**	**3**	**4**	**5**	**Total**
Total DALYs averted (discounted)						
Absolute risk>35%	270	230	290	320	130	1 240
Absolute risk>25%	260	220	270	310	120	1 180
Absolute risk>15%	490	410	530	580	230	2 240
Absolute risk>5%	260	220	290	310	120	1 200
Total	1,280	1,080	1,380	1,520	600	5,860
Number of catastrophic health expenditure cases averted						
Absolute risk>35%	22	18	21	23	12	96
Absolute risk>25%	28	23	26	23	16	116
Absolute risk>15%	55	47	51	58	31	242
Absolute risk>5%	91	78	79	93	52	394
Total	196	166	177	197	111	848
Total household out-of-pocket expenditures averted (in 2015 US$, discounted)						
Absolute risk>35%	18,600	24,900	22,500	31,500	31,200	128,700
Absolute risk>25%	24,000	31,700	28,700	38,700	37,600	160,700
Absolute risk>15%	48,100	63,800	55,900	75,000	74,200	317,000
Absolute risk>5%	80,100	106,400	88,200	115,400	116,800	506,900
Total	170,800	226,000	195,300	260,000	259,800	1,113,300
Total cost of UPF of primary prevention to government (in 2015 US$, discounted)[b]						
Absolute risk>35%	39,300	39,300	39,300	39,300	39,300	196,500
Absolute risk>25%	50,800	50,800	50,800	50,800	50,800	254,000
Absolute risk>15%	104,000	104,000	104,000	104,000	104,000	520,000
Absolute risk>5%	192,000	192,000	192,000	192,000	192,000	960,000
Total	386,100	386,100	386,100	386,100	386,100	1,930,500

In addition, the policy would avert about 850 cases of CHE at the aggregate level. The FRP gain was progressive across risk levels, where 96 cases of CHE would be averted at > 35% risk level: while respective figures were estimated to be 116 (at > 25%), 242 (at > 15%), and 394 (at > 5%) risk levels. About 87% of the cases of CHE averted would benefit the four bottom quintiles: 23% (Q1), 20% (Q2), 21% (Q3), 23% (Q4), and 13% (Q5) (Table 6). There was no remarkable difference in the distributional pattern across risk levels.

We estimated that the policy would avert more than US$ 1.1 million per year overall (Table 6). The OOP expenditures averted increased steadily across risk levels: in US$, 129,000 (at > 35%); 160,000 (at > 25%); 317,000 (at > 15%); and 507,000 (at > 5%) would be averted annually at each risk level (Table 6). About 85% of the OOP expenditures averted would benefit the upper four quintiles: 15% (Q1), 20% (Q2), 18% (Q3), 23% (Q4), and 23% (Q5) (Table 6). This holds true regardless of the risk level chosen.

The UPF policy procured these benefits with a total annual cost of US$ 1.9 million per year. When disaggregated by risk level, the costs translated to US$190,000 at > 35% risk level and increased steadily at lower risk levels to reach 960,000 at > 5% risk level (Table 6).

The results from the scenario analysis with a 50% and 90% incremental coverage predicted a substantial growth in the expected health and FRP gains in absolute terms (Tables A.3 and A.4 in supplementary annex of paper III). At 50% incremental coverage: 14,500 DALYs; 2,050 cases of CHE; and US$ 2,800,000 on private OOP expenditure would be averted per year with a total annual cost of US$ 4,800,000. Whereas, for 90% incremental coverage: 25,700 DALYs; 3,640 cases of CHE; and US$ 4,900,000 on private OOP expenditure would be averted per year with a total annual cost of US$ 9,200,000. However, in relative terms, the returns per US$ invested were marginally lower at higher coverage level compared to the base-case scenario (20% incremental coverage) (Tables A.5 and Tables A.6 in supplementary annex of paper III). The distribution of the benefits across income quintiles at 50% and 90% coverage levels were similar to the pattern for the 20% incremental coverage.

5. Discussion

This thesis was set out to generate policy-relevant evidence on health outcomes, costs, and FRP of CVD interventions in Ethiopia. In the subsequent section, I discuss the main findings in view of the secondary objectives and provide interpretations of the results followed by a brief discussion of the key strengths and limitations of the methodological approaches that we used in the three papers.

5.1 Main findings

In study I, we found that more than a quarter (27%) of the households that sought prevention and treatment of CVD in hospitals in Addis Ababa faced CHE. Low income was a strong predictor of a higher magnitude and severe intensity of financial catastrophe. The households that faced CHE among the bottom quintile spent about 24% of households' annual income over the CHE threshold compared to a 5% excess among the top quintile. Hospitalization, established history of CVD events especially stroke, seeking CVD care in private hospitals, larger family size, and residence outside Addis Ababa were among the key determinants of higher likelihood of CHE.

Study II revealed that primary prevention of CVD with a multidrug regimen composed of aspirin, antihypertensives, and statins to individuals at increased CVD risk generated the most value for money of all the interventions that we assessed. This preventive package was estimated to cost about US$ 67 per DALY averted at > 35% absolute risk level with a modest increase in the ICER at lower risk levels. Within the acute myocardial infarction category, a package of aspirin, streptokinase, ACE-inhibitor, and beta-blocker dominated its comparators and costed about US$ 1,000 per DALY. However, when one moves from this basic pharmaceutical package to package that contained aspirin, clopidogrel, and PCI—the ICER escalated to US$ 5,100 per an extra DALY averted. The secondary prevention packages consisting of aspirin, ACE-inhibitor, beta-blocker, and statins for IHD (ICER = US$ 1,850 per DALY averted) and stroke (ICER = US$ 1,060 per DALY averted) were found to be less cost-effective than medical primary prevention.

Study III estimated that, in total, the UPF of medical prevention of CVD would avert 5,860 DALYs, 850 cases of CHE, and US$ 1.1 million on private OOP expenditure per year at an annual cost of US$ 1.9 million for a 20% incremental coverage. When disaggregated by risk level, the DALYs averted ranged from 1,180 (at > 25%) to 2,200 (at > 15%); the number of CHE averted ranged from 96 (at > 35%) to 394 (at > 5%); OOP payments averted ranged from US$ 129,000 (at > 35%) to US$ 510,000 (at > 5%); the costs to the government ranged from US$ 196,000 (at > 35%) to 960,000 (at > 5%). Both health and FRP gains would disproportionately benefit the poorer households.

5.2 Interpretation and comparison of results

5.2.1 Financial risk of cardiovascular disease care (Paper I)

This study is the first to examine financial risk related to seeking CVD care in Ethiopia. Consistent with the existing body of literature from several low- and middle-income countries (94, 125, 158-160), our findings uncovered the existence of sizeable financial risk that households faced when seeking prevention and treatment of CVD in hospitals in Addis Ababa (161).

Generally speaking, the magnitude of CHE that we found (27%) was relatively lower in contrast with a range of 55%-85% reported by others from Tanzania, India, and China (94, 125). We have given a detailed account the possible explanations for this seemingly low magnitude of CHE in the discussion section of study I. Of the possible explanations provided, under-utilization of CVD services is among the most relevant. According to the recent STEPS survey, only about 12% of the individuals aged 40-69 years with established CVD events or having 30% or more risk of developing CVD in the next 10-years were taking statins and counseling for prevention of heart attack or stroke, while 97% of the hypertensive individuals reported not taking any medication for it (98). Financial reasons are among the major barriers to access health services in Ethiopia, especially among the poor (15, 16). In 2015/16, 48% among the poorest quintile reported lack of money or high cost of health care as the main reasons for not

seeking health care for reported illnesses compared to a rate of 12% among the richest quintile (16).

As discussed in the methods section, parameters such as CHE do not capture the prohibitive impact of OOP expenditures on health service utilization that often manifest as non-use or under-utilization of services due to financial reasons (22, 52). As a consequence, such parameters could seem low (erroneously indicating a good FRP) when service utilization is far from optimal (52). In response to this methodological deficit, the WHO and World Bank group suggested these parameters should be evaluated together with service coverage indicators so as to get a fuller picture of the FRP situation (53).

Moreover, we found that the poorest quintile faced a greater magnitude and intensity of financial risk compared to the richest quintile. These findings are in line with several previous studies (93, 94, 125, 158-160). For example, in a recent assessment of progress towards UHC in Bangladesh, Islam et al., reported higher financial risk among the poor, those that received inpatient care, and households with a member affected by chronic diseases (162). The higher magnitude of CHE among the poor in the Ethiopian setting is further compounded by higher prevalence of CVD risk factors and poorer access to health care among this sub-group compared with the richer sub-populations (100).

Health financing systems that overly rely on OOP payments expose households to substantial financial risk (1, 117). The principle of *fairness in contribution* —one of the key considerations for a fair progress towards UHC—requires dissociating use of and payment for health services and that it dictates contribution to health financing systems be determined based on individuals' ability to pay regardless of their health status or demand for care (2, 12). OOP payments violate this principle in two ways. Typically, individuals pay a flat rate when receiving services regardless of their ability to pay (1). As a consequence, the poor and the sick are taxed more with such payment arrangements—which is considered unfair (1). The resultant effect of this could be far reaching—to the extent of denying access to needed health care, cause

financial hardship, and related medical impoverishment (117). Therefore, reducing OOP payments especially for high priority services and progressively shifting to prepayment mechanisms is key to protect households from such unwanted consequences (1, 2). Well-regulated prepayment and risk pooling arrangements have been shown to be effective in reducing financial risk and in promoting equitable access to health care (1, 2, 163).

The challenge now is how to progressively shift to prepayment arrangements and how to prioritize services for coverage. The Making fair choices on the path to UHC report stressed the need to begin with the high priority services and reduce or eliminate OOP payments for such services first (2). In addition, Gwatkin and Ergo—in what they termed progressive universalism—argued that unless countries put an intentional effort not to leave the poor behind (20), the movement towards UHC might have an unprecedented negative effect on the poor. Three pathways have been proposed to ensure inclusion of the poor in this endeavor: 1) to provide a package for all that consists mainly of services addressing the needs of the poor, 2) to have a broader package of services for all and exempt the poor from the required financial contributions (5), and 3) start with high priority services and exempt either selectively the poorer households or all depending on the feasibility of employing effective mechanisms to mobilize the "lost" revenue for the health system in question (2, 164).

So far, Ethiopia has offered a very basic list of services to all citizens based on an essential package defined more than a decade ago (13). Furthermore, the fee-waiver scheme—targeted at the poorest of the poor individuals—extended access to health care to about 1.5 million people in 2015 (17) (which is less than 2% of the total population in a country where more than 30% of the population lives under the poverty line). In addition to its sub-optimal coverage, the effectiveness of the fee-waiver scheme was compromised by its less-effective targeting, where the beneficiaries were nearly evenly distributed across the bottom four quintiles (15).

In addition, under the CBHI scheme that reached out to the informal sector in over 190 districts, the federal government pays 25% of the premium for all beneficiaries

while, the local governments subsidize the poorest households within their catchment. However, although the CBHI scheme showed a positive trend in improving health service utilization and protecting beneficiaries from financial risk associated with health service utilization (111, 165), the scheme enrolled only 15% of "the potential beneficiaries" in 2015 (17).

When such formal mechanisms fail to provide the much needed protection against financial risk, households are forced to resort to several coping mechanisms (e.g., borrowing, asset sale, and support from family and friends) (117)—as was the case in our study. Several studies have also showed high prevalence of such coping mechanisms in many low-income settings (122, 138). We found a huge reliance particularly on support from family in our study—more so for inpatient care and among the poorest households. It is generally believed that these coping mechanisms would help households to smoothen the potential fluctuations in essential consumptions due to the "unexpected" OOP expenditures (22, 122, 166). However, I argue that the naïve assumption that such mechanisms have only positive impact could be misleading. In our study, it was the poorest households who were more dependent on such mechanism—support was mainly sought from their adult off-springs who are more likely to be poor as well, while the richest households were tapped more into their income and savings—indicating a potential trans-generational effect of lack of FRP.

Finally, due to the emerging changes in epidemiologic and demographic patterns (see Figure 2) and a positive economic prospect, there is a need for the revision of the EHSP to accommodate the evolving health needs of the Ethiopian population. As it is now, the EHSP to a large extent excludes even the "best-buy" NCD services (103)—CVD included (13). Given the resource scarcity, the revision requires due attention to relevant evidence and transparent processes to ensure efficiency in the use and fairness in the allocation of the limited available resources—to which we hope to contribute through this thesis.

As expected, having established CVD events, especially stroke was associated with higher financial risk. This can confirm the expectation of the potential of scaling-up primary prevention of CVD in conferring FRP to households through averting possible future expenditures by reducing incidence of CVD events. Therefore, evidence on the relative cost-effectiveness of alternative strategies is crucial to identify the CVD interventions that deserve high priority in a potential scale-up. This is what we did in study II and the results are discussed in the next section.

5.2.2 Cost-effectiveness of prevention and treatment of cardiovascular disease (Paper II*)*

In study II, we performed a GCEA where we evaluated five sets of mutually exclusive intervention clusters for prevention and treatment of IHD and stroke, followed by ICER ranking across clusters. Accordingly, primary prevention with combination of aspirin, antihypertensive, and statin to individuals with an increased absolute CVD risk was more cost-effective than the single risk factor based approaches for primary prevention as well as the treatment and secondary prevention measures that we assessed. These findings are in harmony with others' findings in sub-Saharan Africa and other low-income settings (92, 131, 167). The ICERs we estimated for specific interventions were also within a close margin with the results of previous studies from sub-Saharan Africa by Ortegon et al., and the *DCP*, 2nd edition (92, 131). For example, at > 35% risk threshold, we estimated the ICER for medical primary prevention to be US$ 67 per DALY averted compared to $ 104 per DALY averted estimated by Ortegon et al., in sub-Saharan Africa (92). In a similar manner, the ICER estimates for acute myocardial infarction and secondary prevention packages were within a close range with the *DCP*, 2nd edition estimates for the same region (131). For example, the *DCP*, 2nd edition estimated an ICER of $ 1,955 per DALY averted for a secondary prevention package of IHD consisting aspirin, statin and beta-blocker compared to our estimate of $ 1,850 per DALY averted for the same package.

Although the aim of study II was to explore cost-effective CVD strategies that Ethiopia could consider for a potential scale-up to halt the growing CVD burden in its

narrower version; this aim is embedded in an overarching goal of informing macro level priority setting decisions for health care in Ethiopia—for which GCEA is better suited especially when evidence is available on cost-effectiveness of a broad range of services from the same setting (30, 139). With this broader aim in mind, when we compare our results with results of Strand et al., (149), the CEA of mental health services in Ethiopia, except for the acute myocardial infarction package that contained aspirin, clopideogrel, and PCI (with an ICER of 5,200 per DALY), most of the CVD interventions that we assessed fared either favorably (e.g., primary prevention with a multidrug therapy) or fairly equivalently (e.g., secondary prevention packages for IHD and stroke (ICER = US$ 1,000 to US$ 1,850 per DALY averted) compared with new anti-depressants with psychotherapy (ICER = 1,026 per DALY averted, lithium combined with psychosocial treatment for bipolar disorder (ICER = 1,807 per DALY averted).

In contrast with the maternal and neonatal health services that were evaluated by Memirie et al., (168), the multidrug therapy based on the absolute CVD risk still compared well with most interventions except for a few interventions with very low ICER such as the Kangaroo mother care (ICER = US$ 9 per DALY averted). Therefore, we can conclude that medical primary prevention is as cost-effective as well recognized high priority services with respect to cost-effectiveness e.g., safe abortion care (ICER = US$ 198 per DALY averted) or tetanus toxoid for pregnant women (ICER = US$ 59 per DALY averted). Our findings come against the general expectation that NCD interventions are too costly to be considered for scale-up in low-income settings such as Ethiopia.

An advantage of the GCEA is that it obviates the very context-specific “current practice” constraint from the ICER calculations of particular interventions, as comparison is made between the intervention of interest and the “null scenario” within the GCEA framework (139). Hence, our ICER estimates were not affected by the “cost-ineffective comparator” or “incomparable comparator” problem that league table approaches are criticized for (140). Furthermore, the comparison of these three GCEAs from Ethiopia was deemed reasonable. This is because the commonly cited

differences between CEAs—with respect of certain methodological considerations—were fairly similar across these three studies (149, 153, 168). Some of these methodological considerations include the year of origin, choice of comparator, the health system context, choice of the perspective for the analysis, costing assumptions, discount rate, source of disability weight (169). Hence, the comparisons could be considered reasonable.

In CEAs, when the intervention under consideration generates additional health benefits with an extra cost requirement, one needs to examine the value of what is likely to be given up by not investing these same resources (required for the intervention under consideration) in the next best alternative use—to be able to judge whether the additional costs required is justifiable (40). This is what economists call—the opportunity cost. With a fixed health budget assumption, choosing to finance an intervention automatically translate to less resources available for the next best alternative within the health sector. The opportunity cost, then, represents what is likely to be given up, in terms of health foregone, as a result of the allocation decision (40). This benchmark is typically expressed as a cost-effectiveness threshold in the economic evaluation literature and is defined by Woods et al., as "*the amount of money that, if removed from the health care system, would result in one less unit of health being generated, or equivalently, the cost of generating an extra unit of health in the present health system*" (170). In other words, the threshold is the marginal cost of producing an incremental unit of health within the existing health care system. Therefore, interventions that consume less than this cost-effectiveness threshold to produce an additional unit of health benefit are considered cost-effective, while those that require more than this amount are deem cost-ineffective because the resources they consume would generate greater health benefits if used to fund other high priority services within the existing system.

The long standing threshold recommended by WHO as a multiple of national GDP per capita (one to three times) was in use widely to guide resource allocation decisions since its introduction in 2001 (43). Recently, however, Revill et al., criticized this threshold for its lack of empirical foundation and warned that the

continued naïve use of the threshold might result in unprecedented loss of lives and worsen health inequality (171). For example, some services might have a favorable ICER based on the three times GDP threshold, but it might be that the resources required to fund the newly accepted service might displace more cost-effective options or crowd-out resources that could have been made available for services that are relatively more cost-effective (172). In addition, by simply accepting services for financing on the grounds of such thresholds, one might overlook the notion of affordability, feasibility, and the required implementation costs—resulting in an unprecedented escalation of health care expenditures (30, 140, 172-174).

Based on an empirical assessment of the opportunity cost, Revill et al., recommended a range of 1-51% of national GDP per capita as a reasonable cost-effectiveness threshold for low-income settings such as Ethiopia (171). Informed by their recommendation, I used a 51% GDP per capita threshold to represent a reasonable (efficient) use of health care resources in Ethiopia: which translates to US$ 315 per DALY averted in 2015 US$. This is not, however, to suggest that we should use the proposed threshold in isolation; even if it was informed by some empirical analysis, other relevant considerations remain crucial to priority setting decisions e.g., the feasibility of implementation and implementation costs of the services under consideration (172).

According to the proposed cost-effectiveness threshold (US$ 315 per DALY averted), we can conclude that except the multidrug regimen for primary prevention of CVD, the packages for treatment and secondary prevention of CVD are not cost-effective in the current Ethiopian setting. Given this background, if for example, the Ethiopian government choses to invest in the acute myocardial infarction package that contain PCI, aspirin, and clopideogrel (ICER = US$ 5,100 per DALY). This means that the Ethiopian population would have gotten about 17 times (ICER of the package / cost-effectiveness threshold) more health if these same resources were used for other higher priority interventions. Alternatively, if the same resources were used to scale up medical prevention at > 35% risk level—about 77 times more DALYs would have been averted. Therefore, choosing cost-ineffective services could be very

unfortunate and has a magnificent negative impact on the total health of Ethiopian population. This is what WHO's consultative group on equity and UHC refer to as "unacceptable trade-off # I"—expanding coverage of medium low priority services before a near-universal coverage is achieved for high priority services (2, 175).

On a related note, Birch and colleagues challenged the theoretical assumptions underlying the application of the league table approach in informing priority setting decisions with a limited budget context in real world case (140, 174). The league table approach has two fundamental assumptions—a perfect divisibility of services and constant rate of return for a proportional investment (21, 176). However, these two assumptions may not always hold true in reality (140, 174) e.g., these principles may be violated for practical (when it is not possible to implement a "portion" of the next eligible service on the list with the budget left) or ethical reasons (for mutually exclusive interventions, one can be ethically challenged for giving a "better" alternative for those that receive services later than earlier). In such situations, the suggested alternatives include the use of computer programs to arrive at alternative combinations of services that maximize total benefit within the budget limits (176).

When planning for expanding the coverage of services in the absence of adequate additional resources that match the extra resource requirements—an inevitable consequence is disinvestment. According to Williams et al., disinvestments can take the form of retraction ("investing in less of an intervention'), restriction ('withdraw an intervention from certain groups'), or substitution ('replacing an intervention with one deemed more efficient') (30). In Ethiopia, displacement is an inevitable consequence of any decision to expand the publicly financed basket of health services as evidenced by the trend in health care financing in Ethiopia (discussed in the introduction section) (106, 108). Particularly, given the lower attention paid to NCDs so far, decisions to cover cost-effective services targeting common NCDs in the essential health services package (e.g., multidrug therapy for primary prevention of CVD) may entail hard investment choices and trade-offs to be made. However, I do not anticipate this to be realized in the form of substituting other basic high priority cost-effective services (e.g., treatment of childhood diarrhea) if there is openness to

carefully appraise current investment choices in Ethiopia's health sector beyond the essential package.

In recent years, it is not uncommon to see public funds being allocated for expansion of costly services such as dialysis for end-stage renal disease and high tech radiotherapy machines in public tertiary hospitals, while the country still lags behind in full coverage of high priority basic services. The net effect of public finance of such costly services on the health of the Ethiopian population, although could be beneficial to the families affected by these conditions, would be negative. Therefore, in the face of extreme resource scarcity, investment choices should be subject to open scrutiny against an agreed set of criteria or guiding principles when selecting interventions for prioritized public financing so as to avoid the potential huge opportunity costs. I will illustrate this point using the following example.

Studies in Malaysia and Thailand estimated that haemodialysis for end-stage renal failure costs roughly about US$ 10,000–US$ 15,000 per healthy life year saved (177, 178). Let us simplify this and assume that haemodialysis costs US$ 10,000 per DALY averted in Ethiopia, without forgetting issues with transferability of CEA results from one setting to another (46). This means that by choosing to invest a dollar on dialysis, one is letting go a potential health gain of about 150 times more (ICER of dialysis/ICER of medical primary prevention = US$ 10, 000 per DALY averted / US$ 67 per DALY averted) that the Ethiopian population could have achieved if the same resources were used to scale-up medical primary prevention of CVD at > 35% risk level instead of the dialysis. This is the rationale behind the strong recommendation of *The Lancet* Commission on investing in health that stated that low-income countries should first aim for universal coverage of what the WHO called the "best-buy NCD interventions" during the initial phase of the fight against the rising NCD burden in those settings (5, 103). The "best-buys"— which include most of the interventions that we assessed except the packages that contain PCI for acute myocardial infarction—were shown to be highly effective, highly cost-effective, and feasible to be implemented within the existing health infrastructures in

low-income settings without the need for complex and highly skilled delivery platforms (5, 103).

Having said this, I acknowledge that cost-effectiveness is not the sole criterion to be considered in resource allocation decisions and hence, results from CEAs are not to be used in a formulaic manner. Typically, priority setting decisions are informed by other criteria regarded as valuable by the society. Some services that ranked lower on the basis of CEA might assume higher priority when other criteria are taken into account. In the next section, I discuss the results from study III, where we examined the expected FRP gains—one of the key additional criteria for priority setting decisions—of publicly financing multidrug therapy for primary prevention of CVD to individuals with an increased absolute risk of developing CVD events.

5.2.3 Health benefits and financial risk protection from cardiovascular disease prevention (Paper III)

Building on study I and II, in study III, we estimated the expected health and FRP gains from UPF of medical prevention of CVD and showed that significant health and FRP gains favoring the poorer households could be achieved from the policy. Our findings confirm the existing knowledge that the ECEA methods provides a useful tool to assess the impact of policies targeting conditions with a gradient across population sub-groups (as is the case with CVD risks in Ethiopia) and that it is more applicable for health policy analysis in health financing systems where OOP payments have a significant role (1, 5, 22, 49, 56, 179).

This study is one of the few but growing body of ECEAs in Ethiopia (57, 132-136) and the first for CVD strategies that was largely based on primary data collected from a local setting. Ideally, evidence on a broad range of interventions would be needed to make sensible priority setting decisions. We have provided a detailed discussion of how our results compare with existing ECEAs from Ethiopia and elsewhere in paper III (179).

To give a brief account here, the health and FRP gains in our study are larger and more pro-poor that what Watkins et.al., estimated from UPF of a salt policy among a cohort of one million South Africans (179). We standardized our study population to 1 million to ensure comparability with Watkins' et al., and estimated that for a 90% incremental coverage, about 2,860 cases of IHD and stroke (compared to 720) and 1,980 cases of CHE (compared to 75) would be averted in our study population compared to what Watkins et al., estimated (179). Respective estimates for a 20% incremental coverage were 650 cases of IHD and stroke in addition to 460 cases of CHE averted. We estimated that about 23% of the CHE averted concentrated among the bottom income quintile, while only 13% of the share concentrated among the top quintile: compared with a distribution of 3% (among the bottom quintile) and 46% (among the richest) in South Africa (179).

This difference between the two studies can possibly be due to differences in the way CVD care is financed between the two settings. In Ethiopia, CVD care is largely financed by households through OOP payments. Therefore, in settings like Ethiopia, where OOP payments constitute a great share of health financing, UPF would have a key role in protecting the poorest households from financial risk. By contrast, in South Africa, CVD care is offered for free or at a highly subsidized rate for the poorest households (179). Therefore, the better-off benefited the most from the UPF policy because they tend to incur high OOP payments as a result of their greater demand for health care and their preference for costly private care settings (179). Moreover, the socio-economic gradient in CVD incidence, health service utilization, and probability of CHE drive the distribution of the expected FRP gains from the policy in our study (94, 100, 145, 161).

Verguet et al., estimated that for a 20% incremental coverage substantial FRP gains from UPF could be attained for selected interventions in Ethiopia: antihypertensive treatment (1,200 cases of poverty averted per US$ 2 million invested, US$ 1,700 per poverty case); malaria treatment (460 cases of poverty averted per US$ 1.1 million invested, US$ 2,200 per poverty case); diarrhea treatment in under-5 children (40,000 cases of poverty averted per US$ 75 million invested, US$ 1,875 per poverty case);

pneumonia treatment in under-5 children (23,000 cases of poverty averted per US$ 47 million invested, US$ 2,000 per poverty case); caesarian section (410 cases of poverty averted per US$ 570,000 invested, US$ 1,400 per poverty case); and TB treatment (6,700 cases of poverty averted per US$ 9.5 million invested, US$ 1,400 per poverty case). Although direct comparison is not possible, UPF of medical primary prevention of CVD seemed to be as efficient as anti-malaria treatment and pneumonia treatment in purchasing FRP benefits, while the other interventions seemed to be more efficient in purchasing FRP gains than the CVD policy that we evaluated. Partly, this could be due the higher utilization assumptions that Verguet et al., used in their models compared to ours (57). Johansson et al., reported very low FRP gains from a UPF policy on mental health interventions in Ethiopia because of low service availability and utilization (133).

"Equity-efficiency" and "FRP-efficiency" trade-offs, when they arise, are difficult questions to address for resource allocation. For example, a s briefly highlighted in the introduction (section 1.2.3), the intervention under consideration for expanded coverage could fare favorably both from health and FRP perspectives or alternatively, it could have a diverging performance with respect to the two concerns—potentially requiring trade-offs to be made in the final decisions. Here, I use Figure 1 presented earlier (see section 1.2.3) to examine possible trade-offs and discuss some suggested decision rules to handle the trade-offs in the literature.

"High health benefits and high FRP" quadrant: the intervention under consideration performs well with respect to both health-maximization and FRP perspectives. This is a win-win situation where there is no trade-off to be made. A typical example is a situation where OOP payments exist even for basic high priority low cost services in low-income settings. Improved coverage such services through UPF will improve both health and FRP benefits significantly (2). Among the interventions that we assessed, medical primary prevention of CVD seems to fall under this category to a great extent.

"*High health benefits and low FRP*" quadrant: represents a scenario where the intervention considered does well with respect to health benefit maximization, but less so from FRP perspective. In this scenario, diverging recommendations have been forwarded by experts. The WHO's commission of equity and UHC recommended that interventions such as this deserve may deserve higher priority on the grounds that health ought to have higher weight than FRP as a priority ranking criteria of health services. The Commission forwarded two key arguments in support of their recommendation: 1) on the basis of the intrinsic value of health for one's wellbeing, they hypothesized that it is better for someone to be impoverished (used as a measure of FRP) than to die (as a measure of health); and 2) being healthy provides FRP indirectly—by protecting the individual from potential future expenditures on health care if one gets sick and by improving individuals productivity and income-earning potential (2).

"*Low health benefits and low FRP*" quadrant: in this scenario, the intervention can be ignored safely with no trade-off required.

"*High FRP and low health benefits*" quadrant: in this scenario, the intervention under consideration confers high FRP benefits coupled with low return from the benefit maximization perspective. This is the commonly thought of scenario when FRP is discussed and it is generally favored by pro-FRP groups. Generally, there is no clear cut direction on how to handle such trade-offs. WHO's Commission warned that such choices might result in an unprecedented loss in total health and choices such as this are inconsistent with the fairness principle categorized their report titled " Making a fair choice on the path to UHC" as the "unacceptable trade-off # 2"—"to give high priority to very costly services whose coverage will provide substantial FRP when the health benefits are small compared to the alternative less costly services" (2). Michael Hoel suggested to give higher priority to the alternative, with a rationale that costly services with high FRP impact should be prioritized over low-cost services for public financing in the absence of universal coverage (180). An example of this scenario from our study could be the public finance of PCI for acute myocardial infarction which is costly and hence, is expected to have high FRP impact at the individual

level. In a related scenario, where interventions have comparable cost-effectiveness but differ with respect to FRP, Peter Smith suggested the one that generates better FRP gain should be given higher priority (55).

So far I have discussed the findings of the three studies in comparison with the literature, where we showed that seeking CVD care is a financial risk to households in Addis Ababa (study I), and that there is a cost-effective CVD prevention strategy that Ethiopia could consider for a potential scale-up (study II), and that this cost-effective intervention could also procure substantial health and FRP gains that would preferentially benefit the poor at a modest budget requirement (study III). To reflect on priority setting in Ethiopia more generally, the health care financing trend indicates a continuing challenge of resource scarcity in the years to come; total spending on health grew from US$ 4 (in 1996) to US$ 29 (in 2014) in per capita terms (106, 108). Besides, the emerging demographic and epidemiologic transitions call for an appropriate response. Therefore, choosing an optimal mix of interventions that respond to the needs of the population is crucial to maximize the population health within the available budget. However, the response to the evolving health needs has to be done in a fair manner taking into account the multiple concerns relevant for the Ethiopian context including those discussed in this thesis but not limited to them. Among other things, actual priority setting decisions are shaped by the institutional capacity of the health system to accommodate the proposed intervention, the transaction cost associated with adopting the proposed intervention, and feasibility of scale-up (10, 172). In view of this, the multidrug regimen for primary prevention of CVD could be scaled-up relatively easily through the existing solid primary health care infrastructure.

5.3 Strengths and limitations

In the methods section, I have provided a short account of the background and the rationale behind our choice of the analytic approaches and the outcome parameters that we used to measure health and FRP gains. In addition, methodological issues were discussed in detail in each specific paper. Here, I mainly focus on the key

methodological strengths and weaknesses that were not well covered previously and highlight the most important ones.

5.3.1 Data availability

One of the strengths of this dissertation is that the three studies we conducted to a large extent benefited from primary data collected from a local setting (e.g., data on OOP expenditure that we used in study I and study III, cost of laboratory tests and salary for human resource in study II). However, to meet the huge data requirement of economic evaluations, we had to complement the primary sources with data from multiple sources including assumptions based on expert opinion (e.g., coverage of CVD care), data from other settings, or old data from local sources. This may have important implications for the robustness of our results. For example, estimates of efficacy of interventions used in study II and III were drawn mostly from meta-analysis of randomized control trials in developed settings; epidemiology of CVD risk factors in study III was drawn from an old study conducted in 2006; CVD care utilization gradient across income quintiles in study III was drawn from a national level data from 2003; unit cost of drugs in study II from international drug price data.

In order to examine the robustness of our results in the face of these limitations, we did sensitivity analysis and characterized the potential impact of such uncertainties on our findings. In study II and III, we did one-way sensitivity analysis varying the values of each selected parameter (e.g., efficacy of intervention, unit cost assumptions, or coverage level) at a time to estimate their expected impact on the results. Whereas, probabilistic sensitivity analysis was undertaken in study II to assess the combined effect of multiple parameters (e.g., costs and effects) simultaneously (40). However, this weakness is inevitable and can only be improved by doing more research to improve availability of locally relevant data (e.g., on efficacy of interventions, health service utilization, and epidemiology of CVD and risk factors) in a timely manner. For example, the EPHI completed a national STEPS survey in 2015. However, the raw data was not yet made available at the time we did the analysis for the papers.

5.3.2 Study design issues

In order to trace the impact of OOP expenditures for CVD care on household economy, it would have been better to adopt a longitudinal study design and follow households over a reasonable period of time. However, this was not possible for practical reasons. Instead, we conducted a cross-sectional cohort study where we asked households to report expenditures on the day of data collection as well as retrospectively over a 12-month recall period with a detailed breakdown of cost items—this can be considered a strength given the study design.

The choice of the recall-period and number of cost-items (expenditure breakdown) have important implications to the validity and reliability of OOP expenditure estimates (181). There is no gold standard framework for such design issues (182). However, more breakdowns and shorter recall periods tend to lead to higher estimates for OOP expenditures (181, 182)—although validating whether higher OOP estimates mean closer to the truth ("true expenditures") or not remains to be a methodological challenge (181). Generally, shorter recall periods are assumed be better to memorize previous expenditures (183), while a more detailed cost breakdown has a prompting effect on respondents that reduces the risk of misunderstanding and improves reporting accuracy (182). Whereas with longer recall periods, one would be able to capture more information, especially if non-uniform expenditure patterns are expected (a typical scenario with chronic diseases such as CVD). Some have shown that the longer the period between the event (the expenditure) and interview date is—there is higher tendency to omit details and misreport information (183). However, Clarke et al., argues that shorter recall period does not necessary mean good. It depends on the outcome we are interested in and the policy relevant (meaningful) period, among other things. As a consequence, trade-offs have to be made to balance precision (which is assumed to be better with short recall period) and the potential information loss (which improves with longer recall periods) (184). Therefore, innovative solutions are much needed (181) to help guide with the decision about these trade-offs. In our case, given the chronic nature of CVD, we used a 12-month

recall-period with an 8-item breakdown of expenditures to mitigate some of these study design issues.

Another limitation that emanates from the specific study design pertains to the "hospital-based cross-sectional cohort" nature of study I from which estimates of OOP expenditure and probability of CHE were drawn for of study I and III. As discussed in the methods section, hospital-based studies have inherent limitation to fully capture the financial burden that households face due to the prohibitive impact of direct OOP payments. This is because reported OOP payments tend to be presumably low when households do not use health services—which translate to low magnitude of financial risk as measured by parameters such as CHE. As a results we might have under-estimated the magnitude of financial risk in study I and the potential FRP gains in study III. We acknowledge this as one important inherent limitation of the study design which we cannot avoid fully.

5.3.3 Internal validity

Internal validity of the study is concerned with the extent to which the study measures what it intends to measure—can one make sensible conclusions about the study population (185)? The way we selected the study population and collected the information have important implication to the validity our findings (particularly for study I and III). Details about the selection procedure, the rationale for our choice, and the possible implications of factors related selection have been discussed at length in paper I. Here, I focus on a couple of issues related to measurement.

With regards to the measurement of households' living standards (in papers I and III), although consumption expenditures are generally assumed to better reflect individuals' or households' living standards in low-income settings, we used reported income instead. This is because half of the study participants were men (less informed than women about consumption expenditures in the Ethiopian setting) and were working in the formal sector. Therefore, reporting income was relatively easier for them compared to consumption expenditures. However, in settings where households rely to a greater extent on the informal economy, reported income is

considered a less reliable measure of living standards (22). Moreover, in settings where home-grown products represents a huge part of household consumption, reported income under-represents living standards. Therefore, consumptions are assumed to reflect household economic conditions better. Another advantage of consumption is that, households use several coping mechanisms (e.g., use of savings) to smoothen potential fluctuations in the face shocks (health or income)—which is less well reflected in pure income measurement (22). In order to mitigate some of these methodological challenges with reported income, we collected data on the coping mechanisms that households used to finance OOP payments for CVD care and explored its impact on financial risk as discussed in previous sections and in paper I.

Furthermore, in order to assess factors associated with CHE, we used widely applied logistic regression models. However, odds ratios do not predict "risk" well when the outcome of interest is common—which is often defined as prevalence of the attribute of interest more than 10% (146). In our case, 27% of households had CHE. Therefore, care should be taken not to make firm conclusions about the estimates of the strength of association between the dependent variable (CHE) and the covariates.

5.3.4 External validity

External validity refers to the generalizability of the findings of the study beyond the population studied (185). Generalizability of our findings to other relevant populations (e.g., rural population in Ethiopia or populations in other low-income settings) depends to a large extent on how similar (representative) the population we studied is with those broader populations that we intend to extrapolate or apply our findings to. Therefore, one needs to compare the population we studied with the broader population with respect to factors that have important implication to the outcome of interest (e.g., demography, CVD and risk factor epidemiology, health service utilization, and cost of services). Study I and III are sub-national studies from Addis Ababa largely based on hospital-based survey data, while study II is a modeling exercise (CEA) at the national level. Therefore, the generalizability of our finding to the broader Ethiopian population may be deemed limited given the

important differences between the population in Addis Ababa and the rest of the country which is largely rural and have limited access to CVD care. Some of the differences include higher prevalence of CVD and its risk factors, better educated largely adult population, better access to CVD care (availability), better health service utilization, and higher cost of health care in Addis Ababa than the rest of the country (16, 65, 86). However, given the fact that 20% of the study population were from different parts of the country outside the capital, our findings could still be considered relevant to the national level priority setting decisions. In addition, our finding may to a certain extent apply to populations in the capitals of other low-income settings that have similar epidemiological and health service availability and utilization pattern as in Addis Ababa.

6. Conclusions

In this thesis, we sought to assess the health outcomes, costs, and FRP of CVD interventions so as to inform priority setting decisions for health care in Ethiopia.

This study uncovered the existence of substantial financial risk that households face when seeking prevention and treatment of CVD in hospitals in Addis Ababa—where more than a-quarter (27%) of the households suffered financial catastrophe with an annual OOP spending on CVD care of more than a-tenth of households' annual income. The poorest, those with an established CVD event especially stroke, those that were hospitalized, and households that travelled to Addis Ababa to seek CVD care were among the most affected.

Moreover, the study showed that primary prevention of CVD with a basic multidrug regimen consisting of aspirin, antihypertensive, and statins to be the most cost-effective intervention (at all risk levels) compared with treatment and secondary prevention interventions for CVD that we assessed. Respective ICERs for this preventive package ranged from US$ 67 per DALY averted (at > 35%) to US$ 340 per DALY averted (at > 5%) absolute risk levels.

Lastly, we demonstrated that UPF of primary prevention of CVD with a basic multidrug regimen could lead to more than just efficient purchase of health. In total, the UPF policy would avert about 850 cases of CHE per year, in addition to averting 5,800 DALYs at an estimated annual cost of US$ 1.9 million. The distribution of both the health and FRP gains would favor the poorer households, where nearly 90% of these gains accrued to the bottom four quintiles in general, and about 20% of the total gains benefited the poorest quintile compared with roughly 10% of the share among the richest quintile at all risk levels. Therefore, the UPF of medical primary prevention is an attractive strategy worth considering for public financing in Ethiopia as it addresses key health system concerns, such as FRP and distributional concerns, in addition to its cost-effectiveness. I, therefore, conclude that primary prevention of CVD saves more than lives in Ethiopia.

7. Implications

7.1 Implications for future practice

Many ethicists agree that it is unethical to ignore the need for a systematic priority setting of scarce health care resources (8, 24). Priority setting, in turn, requires a set of widely agreed criteria that guide such decisions informed by a solid evidence base and through transparent processes (8). Evidence on economic evaluation of health interventions is at the heart of priority setting decisions. In this thesis, I discussed economic evidence that we generated pertaining to CVD care in a low-income country where there is a growing but still limited local capacity to undertake economic evaluations. Such evidence was lacking in Ethiopia and needs to be filled to improve health care resource allocation decisions. Our findings would help to better understand the financial risk related to seeking CVD care and the expected investment return from scaling-up selected CVD interventions with respect of health, FRP, and distributional consequences—which in turn facilitate the explicit examination of the trade-offs between multiple health policy objectives in Ethiopia.

However, the continuous and evolving nature of priority setting decisions with changes in the disease epidemiology, demography, coverage of services, costs, and availability of resources requires ensuring a sustained availability of good quality evidence reflecting those developments (10). With this regard, I see two broader challenges that need to be dealt with in Ethiopia. First, the issue of local capacity to generate evidence relevant for policy and priority setting—this includes but not limited to economic evaluations (e.g., data on epidemiology, unit costs, service utilization etc.). Furthermore, in as much as striving to generate local evidence by conducting new studies or surveys, timely data sharing practice is also important to optimally utilize the existing resources.

Second, in addition to generating evidence, translating the evidence in to practice is needed. Therefore, the process of evidence generation needs to be followed up with the appropriate next steps to for optimal use of the evidence produced. To this end, a

10-step framework has been proposed for a sound priority setting steps to define and implement a prioritized health benefit package (186). A key requirement is therefore institutionalizing priority setting through mechanisms such as the UK's National Institute for Health and Care and Care Excellence. Recently, the FMOH has established a Health Economics and Financing Analysis case team which may assume a leading role in the institutionalization the priority setting functions for the health sector in Ethiopia.

In a related matter, studies including from developed settings have shown the limited role of economic evaluations in informing actual priority setting decisions (10, 187). Several reasons were cited for this gap including the lack of timeliness of CEAs, lack of sensitivity of CEAs to the decision context, and methodological limitations. However, economists strongly concur that the use of CEAs with all its imperfections is by far better than implicit priority setting decisions (21).

7.2 Recommendations for future research

Given the challenges to memorize OOP expenditures over the long term, the uncertainty surrounding what might be an ideal recall-period, and the desirable level of detail of cost items reporting, I believe that randomized controlled trials of mobile phone based data collection systems could help answer some of these question and lead to a potential revolution in OOP expenditure data collection.

In addition, more research is needed to further develop mechanisms that would help incorporate FRP in priority ranking of health services. Although a potential application of indifference curves to explore possible trade-offs between health maximization and FRP gains have been suggested (57), further research is highly needed to inform decision makers about the decision rules when faced with such difficult trade-offs.

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9. Appendix 1: Papers I-III

Research

BMJ Global Health

Out-of-pocket expenditures for prevention and treatment of cardiovascular disease in general and specialised cardiac hospitals in Addis Ababa, Ethiopia: a cross-sectional cohort study

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ABSTRACT

Background Cardiovascular disease poses a great financial risk on households in countries without universal health coverage like Ethiopia. This paper aims to estimate the magnitude and intensity of catastrophic health expenditure and factors associated with catastrophic health expenditure for prevention and treatment of cardiovascular disease in general and specialised cardiac hospitals in Addis Ababa.

Methods and findings We conducted a cross-sectional cohort study among individuals who sought cardiovascular disease care in selected hospitals in Addis Ababa during February to March 2015 (n=589, response rate 94%). Out-of-pocket payments on direct medical costs and direct non-medical costs were accounted for. Descriptive statistics was used to estimate the magnitude and intensity of catastrophic health expenditure within households, while logistic regression models were used to assess the factors associated with it. About 27% (26 .7;95% CI 23.1 to 30.6) of the households experienced catastrophic health expenditure, defined as annual out-of-pocket payments above 10% of a household's annual income. Family support was the the most common coping mechanism. Low income, residence outside Addis Ababa and hospitalisation increased the likelihood of experiencing catastrophic health expenditure. The bottom income quintile was about 60 times more likely to suffer catastrophic health expenditure compared with the top quintile (adjusted OR=58.6 (16.5–208.0), p value=0.00). Of those that experienced catastrophic health expenditure, the poorest and richest quintiles spent on average 34% and 15% of households' annual income, respectively. Drug costs constitute about 50% of the outpatient care cost.

Conclusions Seeking prevention and treatment services for cardiovascular disease in Addis Ababa poses substantial financial burden on households, affecting the poorest and those who reside outside Addis Ababa more. Economic and geographical inequalities should also be considered when setting priorities for expanding coverage of these services. Expanded coverage has to go hand-in-hand with implementation of sound prepayment and risk pooling arrangements to ensure financial risk protection to the most needy.

Key questions

What is already known about this topic?

- Out-of-pocket payments for healthcare impose catastrophic financial burden on households especially affecting those with chronic conditions such as cardiovascular disease.
- In Ethiopia, out-of-pocket payments constitute about one-third of the total health spending.
- No evidence exists on the magnitude of financial burden related to accessing cardiovascular disease care in Addis Ababa, Ethiopia.

What are the new findings?

- Seeking care for cardiovascular disease presents substantial financial burden on households in Addis Ababa, Ethiopia.
- Poorer households face a multifold higher financial risk compared with the richer.
- Hospitalisation and seeking care in private facilities were among the factors that increased the likelihood of catastrophic health expenditure.
- Households largely depended on support from family members to cope with high out-of-pocket payments.

Recommendations for policy

- Drug costs constitute about half of out-of-pocket payments. This might encourage practitioners to increasingly prescribe generic drugs.
- Additionally, findings could inform the design of benefit packages for health insurance mechanisms.

INTRODUCTION

Universal health coverage (UHC) calls for ensuring that all people receive quality health

services they need without exposing them to financial hardship.[1–3] Countries that overly rely on out-of-pocket (OOP) payments to finance their health system pose a huge financial burden on households,[4] forcing them to receive healthcare at the expense of other essential needs such as food and education.[1] In addition, OOP payments at the point of service delivery may force households to delay or abandon some or all health services that people need.[2 5]

Major sources of financial burden include spending on direct medical costs (eg, consultation fees, drugs, laboratory and hospital bed days), direct non-medical costs (eg, transportation) and indirect costs (eg, lost income due to lost productivity by patients and their attendants).[5 6] Households resort to various coping strategies to ensure other essential needs in the face of high OOP payments. Commonly used mechanisms include use of personal savings, borrowing, seeking support from family or friends and asset sale.[5 7 8] At times, household members may be forced to adjust work schedule, downgrade living conditions and disrupt children's schooling.[5–12] Low socioeconomic status, rural residence, not having health insurance, long inpatient days and having a chronic disease were associated with increased risk of catastrophic health expenditure (CHE) in Asia and Africa.[4 6 11 13]

Globally, millions bear catastrophic financial burden due to OOP payments related to seeking healthcare.[3 14] Patients with chronic diseases such as cardiovascular disease (CVD) face higher financial risk due to the need for long-term treatment and care, loss of productivity as a result of long-term illness and disability, and high costs when acute episodes occur.[15–18] In a large study from India, households with a member suffering from CVD spent 17% more of the total households' expenditure for healthcare compared to households without CVD.[6] High rates of CHE related to CVD have also been reported in various low-income and middle-income countries. Among patients with a recent history (15 months) of hospitalisation for CVD, 80% in Tanzania, 55% in China[13 19] and up to 84% in India[11 13] experienced CHE. In another study from seven Asian countries, 66% of patients with a history of admission for acute coronary syndrome experienced CHE.[20]

Addis Ababa, being the capital city and a home to about a quarter of the urban population in Ethiopia, is heavily affected by CVD and its risk factors.[21–25] During the period 2002–2010, CVD was among the leading causes of mortality accounted for 11%–24% of all deaths in Addis Ababa.[22 23] A significant reduction in financial burden related to CVD care could be attained through scale-up of cost-effective prevention and treatment strategies[26–28] through prepayment financing arrangements.[1 5] However, coverage of such interventions is low in Addis Ababa.[21 29] The Ethiopian health system is severely underfinanced (US$27 per capita in 2015) and highly dependent on OOP payments by households.[30 31] The coverage of health insurance is very low (about 1% in 2012), although plans are underway for expansion.[32] As a result, 59% and 88% of those who sought outpatient and inpatient care covered cost of care fully through OOP payments, respectively.[32]

In 2005, the government identified a prioritised list of basic Essential Health Services Package (EHSP) that the country can afford to offer its citizens at public primary care settings.[33] The EHSP offers only a basic package of services free of charge to all, such as immunisation, child delivery and tuberculosis/HIV treatment . Except for treatment of hypertension, which is subsidised, CVD care is largely offered on the basis of high (full) cost recovery, even in public facilities that households pay on use of services.[33] With the aim of protecting the poorest households from financial risk related to seeking healthcare, the fee-waiver scheme reached out to nearly 1.5 million people (1.5% of the Ethiopian population) with free healthcare access at an average spending of less than US$2 per capita in 2015/2016.[34] In addition to its suboptimal coverage, less effective targeting further compromises the effectiveness of the scheme.[32]

According to the World Health Survey (2003), 27% of households in Ethiopia faced financial catastrophe—defined as OOP payments of more than 10% of household's consumption expenditure.[35 36] Little is known about CVD-related CHE in Ethiopia. Given the high and increasing burden of CVD and its risk factors in Addis Ababa[21–24] and the fact that OOP payments by households contribute to about 34% of the total health expenditure in Ethiopia,[32] it is crucial to document the magnitude of financial burden households face related to seeking prevention and treatment services for CVD in Addis Ababa. Lack of such information has been identified as one of the gaps that needs to be addressed for better monitoring of the progress towards UHC in Ethiopia.[37]

The objective of this paper is to estimate the magnitude and intensity of CHE and factors associated with CHE for prevention and treatment of CVD in general and specialised cardiac hospitals in Addis Ababa.

MATERIALS AND METHODS

Study design and population

We conducted a cross-sectional cohort study among individuals who sought prevention and treatment care for CVD in a sample of general and specialised cardiac hospitals in Addis Ababa, Ethiopia. All adults with a diagnosis of ischaemic heart disease (IHD), stroke, hypertension and dyslipidaemia were included in the study. Newly diagnosed patients who were on their first outpatient visit were excluded.

Study site and sample selection

We estimated a sample size of 625, assuming 27% CHE among the richest quartile (Q4),[35 36] 15% point difference with the poorest (Q1) and 1.5% non-response rate using the formula[38]:

$n = (Z\alpha/2+Z\beta)^2 * (p1\ (1-p1)+p2\ (1-p2))\ /\ (p1-p2)^2$, where n is the sample size required in each quartile, p1 and p2 are the expected sample proportions of any two quartiles, $Z\alpha/2$ is the critical value of the normal distribution at $\alpha/2$ for a confidence level of 95%, α is 0.05, Z is 1.96, $Z\beta$ is the critical value of the normal distribution at β for a power of 80%, β is 0.2 and the critical value is 0.84.

There were 11 public and 38 private hospitals in Addis Ababa at the time of the data collection, including one public and three private specialised cardiac hospitals.[39] In general, public facilities are major providers of outpatient and inpatient care in urban settings in Ethiopia.[32] We anticipated public and private facilities to have an equal role in the provision of CVD care, given the large number of private facilities in Addis Ababa. Therefore, we used a purposive sampling technique to select eight hospitals—in consultation with experts—where individuals having the diagnoses of interest were expected to concentrate. Four specialised cardiac hospitals (one public and three private) and four general hospitals (three public and one private) were selected.

To ensure representativeness at a hospital level, we used a stratified sampling technique and distributed the sample quota equally between public and private facilities overall and allocated 70% of the sample for the specialised cardiac centres taking one-third of this share from the only public cardiac centre. To adjust for this sampling variation, each observation was weighted according to the inverse of its probability of being selected.

In each hospital, all eligible individuals were sequentially recruited from cardiac or chronic disease outpatient follow-up clinics and inpatient wards by hospital nurses based on the diagnosis on respective medical charts until the sample quota for that particular facility was met.

Data collection

The data collection period ran from February to March 2015 with a range of 4–8 weeks, depending on the time needed to recruit the allocated sample quota in specific hospitals. Data were collected through face-to-face interviews by trained enumerators using a structured questionnaire (see online supplementary annex 1). The questionnaire was developed building on an instrument used in a study on 'microeconomic impact of CVD hospitalisation in four low- and middle-income countries' including Tanzania.[13] The questionnaire was prepared in English and then translated to Amharic (national language) for ease of administration and then back translated to English to ensure consistency. It was pilot-tested in one public hospital and one private hospital in Addis Ababa prior to the actual data collection. Strong data quality assurance measures were employed including, random on-site visits during the interviews, random verification checks using hospital records, and random phone calls to patients for data validation.

Outpatients were interviewed on exit from the follow-up visits, while interviews with inpatients were completed on discharge from the hospitals so as to fully capture the expenditures during the data collection period. The interviews were conducted in nurses' rooms or other dedicated rooms and were to a large extent (82%) informed by the care-seekers themselves, followed by accompanying relatives attending to 15% of the interviews. On average, respondents took 24 min to complete the interviews with a range of 14–52 min and SD of 7 min.

Among others, data on participants' sociodemographic characteristics, medical history, households' income and OOP payments for outpatient and inpatient care and the number of outpatient follow-up visits were collected. Households' income was defined as the average reported monthly earnings of all economically active household members' net of tax through formal employment, self-employment, in exchange of goods or services as well as cash transfers from any sources including family and friends. OOP payments constitute fees for consultations, drugs, laboratory tests, imaging and hospital bed days as well as direct non-medical expenses on transportation, accommodation and food for patients and accompanying caregivers. We found no report of informal payments to service providers. We also collected information on sources of financing that households used to cope with OOP payments.

For each individual, OOP payments for CVD care was estimated over a 12-month reference period retrospectively from the day of data collection. Outpatient care expenditures were reported at two data points: for outpatient care received at the day of data collection and for the outpatient visit prior to the day of data collection. The time elapsed between these two visits ranged from 1 to 6 months for 95% of the participants with a range of 2 weeks to 12 months. Whereas, inpatient care expenditures were reported separately for each hospitalisation over the same reference period. OOP payments and income data were measured in Ethiopian birr (ETB) and then converted to 2015 US$ using the prevailing official exchange rate for the study period (1 US$ = ETB 20.33).[40] An exchange rate of 4.92 ETB per unit $ purchasing power parity (PPP)) in 2011 was used for the poverty analysis.[30]

Six hundred and twenty-five individuals were recruited for the study. Of them, five refused to participate and 31 were excluded due to missing data on OOP payments and or household's income, as these participants did not report such data or inconsistent diagnosis with the inclusion criteria. In the end, 589 were included in the final analysis, making the response rate 94%. Of these 589, 69% (n=406) and 52% (306) were recruited from specialised centres and from public facilities, respectively. Whereas 94% (n=553) were recruited from outpatient units, 6% (n=36) were hospitalised on emergency basis at the time of the survey, 65% of which in private facilities.

The subjects that were excluded due to poor data quality were fairly comparable with the remaining study subjects with respect to place of residence and gender. However, excluded subjects tend to be younger and more in the private hospitals (data not shown). The potential

impact of this exclusion on our results is minimal given their small number.

Analysis

Data were cleaned and processed using Stata V.14. Households were used as the unit of analysis. As CVD is a chronic condition, estimation of annual OOP payments was needed to allow a reasonable assessment of the financial burden on households. Accordingly, annual OOP payments were estimated as the sum of annual OOP payments for outpatient care and annual OOP payments for inpatient care for those who received inpatient care. Annual outpatient care expenditures were estimated as a product of the mean OOP payments per outpatient visit and the number of outpatient follow-up visits over the 12-month period. Mean OOP payments per visit, in turn, were estimated from OOP payments for outpatient care received at the day of data collection and the outpatient follow-up visit prior to that date. For individuals that received inpatient care, annual inpatient care expenditures were derived as the sum of OOP payments for each hospitalisation over the same reference period. Although only 6% of the study participants were hospitalised at the time of the survey, another 11% had received inpatient care historically.A smaller proportion (2% of all subjects) that had two hospitalisations. Accordingly, all these expenditures were taken into account in estimating annual OOP payments. On a related note, only OOP payments directly related to prevention and treatment of CVD were included in our analysis. Nearly 10% of study participants had diabetes as comorbidity. However, participants were asked to exclusively report on OOP payments pertaining to CVD care and hence only such reported expenditures were included in the analysis.

Descriptive statistics was used to quantify the magnitude and intensity of CHE based on previously published methods (details are provided in online supplementary annex 2.1).[5 41] We used a 10% threshold to define CHE: a given household is said to have experienced CHE when the estimated annual OOP payments exceed 10% of the household's annual income. The magnitude of CHE is then given by the proportion of households that experienced CHE. Households used various means other than current income to cover OOP payments. We therefore explored the impact of using these coping mechanisms on CHE by deducting OOP payments financed through such means from the total OOP payments as recommended by Leive and others[7 9] and presented respective results for comparison. To assess the intensity of CHE among households that faced CHE, we estimated the average amount by which such households exceeded the 10% income threshold. This is known as mean positive overshoot, and it is expressed in percentage relative to household's' income over the given CHE threshold.[5 41] In order to assess the distribution and intensity of CHE across income quintiles, households were divided into quintiles based on households' income and were designated as Q1 (the poorest) to Q5 (the richest). We used t-test to assess the significance of the differences in the magnitude of CHE across income groups. Given the nature of the study population (secondary and tertiary hospital-level study in the capital), the income level of households in our study is higher compared with the national figure.[30] Only 11% of households in our study were below the poverty line of $1.9 per day (in 2011 PPP) compared with 33% for the whole country in 2011 and 36% for Addis Ababa in 2000.[30 42]

Logistic regression models were used to examine factors associated with CHE. Potential covariates were chosen mainly guided by existing literature and scientific relevance[7 13 18] and include income level, residence, type of hospital, hospitalisation for CVD over the past 12 months, having developed a CVD event (stroke or IHD), age of patient, time elapsed since diagnosed, occupation and household size. Each covariate was first assessed in bivariate models, followed by a multivariate analysis controlling for all covariates that were significantly associated with CHE at p value of less than or equal to 0.1 in bivariate models taking Q5 (the richest) as the reference group. p -Values of less than or equal to 0.05 and 95% CIs were used as cut-off points to classify respective ORs as statistically significant.

Ethical considerations

The research protocol was reviewed and approved by the Scientific Ethical Review Committee of the Ethiopian Public Health Institute (005-02-2015/EPHI 6.13/65) and exempted by the Norwegian Regional Research Ethics Committee. We acquired written informed consent from the study participants before administering the questionnaire. The consent form was translated to Amharic (local language) before use.

Sociodemographic characteristics of study participants

With a mean age of 58 years, about half (48%) of the study subjects were engaged in an economically productive job at the time of data collection. One-in-five resides outside of Addis Ababa (table 1), with an average distance of 254 km (range: 10–1000 km) from the respective hospitals (data not shown).

Fifty-four per cent of the participants had developed a CVD event (IHD and stroke), and the rest were still on primary prevention. Although only 6% of the participants were hospitalised during the data collection period, 17% in total have received inpatient care for CVD during the 12-month reference period (table 1).

RESULTS

Magnitude of catastrophic household OOP payments

The magnitude and distribution of CHE across income quintiles is presented in table 2. Overall, about 27% of the households experienced CHE. Regarding the distribution of CHE, 28% was among the poorest quintile (Q1) compared with 14% among the richest quintile (Q5) (table 2). p Value from t-test comparing the two proportions was found to be 0.02, indicating a statistically significant

Table 1 Sociodemographic characteristics

Characteristics		n=589	%
Age (in years)	25–44	88	15
	45–64	281	48
	65–79	192	32
	>=80	28	5
Gender	Female	298	51
	Male	291	49
Marital status	Single	51	9
	Married	428	73
	Divorced	26	4
	Widowed	84	14
Residence	Addis Ababa	470	80
	Outside Addis Ababa	119	20
Education	No formal education	115	20
	Grade 8 or less	163	28
	Grade 9–12	146	25
	Diploma	85	14
	Bachelor degree+	80	13
Occupation	Government employee	119	20
	Private employee	38	6
	Private business	109	19
	Stay home mum	162	28
	Retired	135	23
	Other	26	4
Diagnosis	Ischaemic heart disease	233	40
	Stroke	83	14
	Hypertension	235	40
	Dyslipidaemia	38	6
Number of hospital admission(s) over the last 12 months	0	489	83
	1	90	15
	2	10	2
Type of hospital visited	Public	306	52
	Private	283	48

higher magnitude of CHE among the poorest households. However, the increase in the magnitude of CHE across income quintiles was not monotonic. The magnitude of CHE dropped to about 8% when OOP payments financed through sources other than households' current income were deducted from the total OOP payments. Absolute amount of OOP payments across quintiles is presented in figure 1, showing steady increase in the mean annual OOP payments with increasing income level. Further details regarding absolute OOP payments are provided in table A.2.2.1 in online supplementary annex 2. Here we focus on relative measure of financial burden—CHE.

Factors explaining catastrophic OOP payments

Results from multiple logistic regression model are shown in table 3. After adjustment for available covariates, the odds of facing CHE among hospitalised subjects was about eight times that of the non-hospitalised subjects (OR=8.39, 95% CI (4.24, 16.59) p value<0.001). Seeking care in private hospitals increased the odds of CHE by 20 fold (OR=20.7, 95% CI (10.2, 42.04) p value<0.001) compared with public hospitals. Moreover, travelling to Addis Ababa for CVD care and having developed stroke substantially increased the likelihood of facing CHE. In contrast, the odds of facing CHE went down the longer the duration since diagnosed (table 3). Age and occupation were not significantly associated with CHE.

Income level was strongly negatively associated with CHE. The odds of facing CHE among the poorest quintile was about 60 times that of the richest (OR=58.62, 95% CI (16.2, 208.0) p value<0.00). ORs increase steadily going down the income strata (table 3).

Intensity of catastrophic OOP payment

Households in lower economic strata experienced higher magnitude of CHE and suffered a more intense degree of CHE. The share of OOP payments relative to households' income increased as we go down income strata. Among households that faced CHE, the bottom two quintiles overshoot the CHE threshold on average by 24% of households' income compared with an overshoot of only 5% for the richest quintile (table 4). In other words, households that experienced CHE in Q1 spent 34% of households' income on average for CVD care compared with a share of 15% among those in Q5. This indicates a more intense financial risk among the economically disadvantaged groups.

Cost items

About 80% (n=475) of the participants were able to report outpatient care expenditures disaggregated by cost items. Accordingly, direct medical costs constitute 65%–83% of OOP payments, while direct non-medical costs, mainly transport, contribute to 16%–34% of outpatient care cost. Drug costs were the major cost drivers comprising about 50% of outpatient care costs (figure 2). Disaggregating inpatient care expenditures was challenging to respondents and hence data are not presented.

Sources of financing

Households resort to various coping mechanisms to deal with high OOP payments for CVD care. The commonly used coping strategies other than current income were support from family members and savings (table 5). Dependence on coping strategies was more pronounced for inpatient care compared with outpatient care. We found that 39% fully financed inpatient care through support from family members compared with 27% for outpatient care. A percentage of 11–27 tapped into their savings and another 2%–8% had to borrow to cover part or all of outpatient and inpatient care costs (table 5).

Table 2 Proportion of households that faced catastrophic out-of-pocket (OOP) payments for prevention and treatment of cardiovascular disease in general and specialised cardiac hospitals in Addis Ababa, Ethiopia, 2015.

	Without adjustment			Adjusted*		
	Proportion (%)	SE†	95% CI‡	Proportion (%)	SE†	95% CI‡
Total	26.7	1.9	23.1 to 30.6	7.9	1.2	5.8 to 10.5
Q1	27.9	4.4	20.0 to 37.3	8.0	2.7	4.1 to 15.1
Q2	28.5	3.8	21.7 to 36.6	7.1	2.2	3.8 to 13.0
Q3	32.2	5.0	23.3 to 42.6	9.3	3.1	4.7 to 17.3
Q4	28.3	4.1	21.0 to 37.0	7.7	2.4	4.1 to 14.0
Q5	13.9	3.8	7.9 to 23.1	7.7	3.0	3.5 to 15.9

*The amount of OOP payments financed through means other than current income is deducted from the total OOP payment, p value comparing proportion without adjustment among Q1 an Q5 =0.015.
SE is standard error of the mean.
‡95% CI for the proportion.

DISCUSSION

This is the first study to quantify the magnitude and intensity of CHE related to seeking CVD care in Ethiopia. Our analysis revealed seeking CVD care at hospitals in Addis Ababa exposes households to substantial financial risk, with about 27% of those that do so face CHE. Low economic status, residence outside Addis Ababa, hospitalisation and seeking care in private hospitals were among factors that increased likelihood of CHE. Poorest households suffered greater intensity of CHE compared with the richest. The magnitude of CHE in our study was lower than what others reported in various low-income and middle-income settings,[6 11 13 18] although direct comparison is not straightforward due to differences in study populations and criteria for CHE. For example, Huffman *et al* reported CHE that ranges from 55% in China to 80% in Tanzania.[13] Nevertheless, 27% is still much higher than what Memirie *et al* reported (about 11%) among households that sought inpatient care for severe pneumonia and diarrhoea among children under 5 years in Ethiopia.[43]

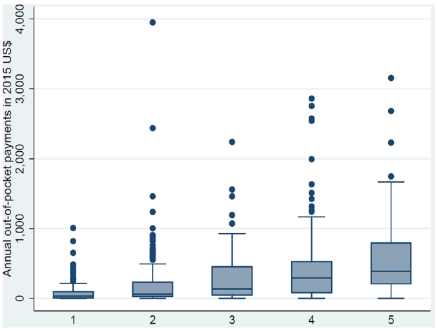

Figure 1 Annual out-of-pocket payments across income quintile for prevention and treatment of cardiovascular disease in general and specialised cardiac hospitals in Addis Ababa, Ethiopia in 2015 US$.

Several factors could have contributed to the seemingly lower magnitude of CHE in Addis Ababa. First, poorest households that are more prone to CHE were under-represented in our study resulting in possible underestimation of CHE. This is because direct OOP payments at the point of care are well-established barriers to access healthcare, disproportionately affecting poorer households.[1 32] This could have been further exacerbated by a low utilisation of CVD care in Ethiopia (approximately 12% according to the latest STEPwise approach to NCD risk factor surveillance (STEPS))[24 29 44] and the fact that hospitals are more accessible to richer people compared with poorer.[36 42 45] This is one of the limitations of hospital-based cross-sectional cohort study designs, warranting cautious interpretation of our results. Due to the deceptive nature of parameters such as CHE, the WHO and World Bank recommended their use along with coverage indicators to get a fuller picture.[46]

However, differences in composition of study subjects could also offer a partial explanation. Only 14% of our study participants were hospitalised for an acute CVD event, while 46% were still on primary prevention whereas the other studies were largely based on data from recently hospitalised patients for acute CVD events that are costlier (eg, percutaneous coronary intervention) than basic pharmaceutical prevention and treatment packages available in Ethiopia.[11 13 47] Still, on a subgroup analysis of our data, we found higher CHE especially among those that developed stroke (close to 50%). We did not present those results as our study was not powered to allow detailed analysis by specific diagnostic categories.

CHE was shown to be inversely related with income level. Nevertheless, the increase in magnitude was not monotonic going down income strata (table 3). This is possibly due to suboptimal utilisation of needed services among the poorest, for example, skipping some of prescribed drugs or tests due to inability to pay, though we do not have data to validate this. Consequently,

Table 3 Logistic regression analysis of factors associated with catastrophic out-of-pocket payments for prevention and treatment of cardiovascular diseases in general and specialised cardiac hospitals in Addis Ababa, Ethiopia, 2015

Covariates		OR	95% CI	p Value
Income quintiles	Q1	**58.6**	16.52 to 208.0	0.00
	Q2	**39.0**	11.87 to 128.24	0.00
	Q3	**20.9**	6.97 to 62.92	0.00
	Q4	**6.9**	2.4 to 19.99	0.00
	Q5	1		
Residence	Addis Ababa	1		
	Outside Addis Ababa	**3.25**	1.79 to 5.90	0.00
Type of hospital visited	Public	1		
	Private	**20.71**	10.21 to 42.05	0.00
Received inpatient care for CVD over the past 12 months	No	1		
	Yes	**8.39**	4.24 to 16.59	0.00
Diagnosis*	IHD	1.15	0.65 to 2.06	0.63
	Stroke	**4.10**	1.82 to 9.18	0.01
	Hypertension or Dyslipidaemia	1		
Household size	Household size	**1.20**	1.06 to 1.36	0.04
Age of participants	Patient's age	1.00	0.98 to 1.02	0.02
Duration since diagnosed	Duration since diagnosed	**0.99**	0.98 to 0.99	0.05
Occupation of participants	Employed†	1.07	0.44 to 2.58	0.88
	Private business	0.91	0.38 to 2.17	0.84
	Housewife/househusband	1.34	0.67 to 2.65	0.41
	Retired	1		
	Others	1.23	0.36 to 4.14	0.73

*IHD stands for ischaemic heart disease, Q1 for poorest quintile and Q5 stands for richest quintile. †Includes government and private employees.
CVD, cardiovascular disease.

poorest households might have incurred lower expenditures resulting in a relatively lower magnitude of CHE. Although with wide 95% CI due to smaller sample (169 developed CHE), results from multiple logistic regression models also confirmed this linear inverse relationship consistent with Huffman *et al*'s finding in Tanzania.[13] As

Table 4 Intensity of catastrophic out-of-pocket payments for prevention and treatment of cardiovascular disease across income group in general and specialised cardiac hospitals in Addis Ababa, Ethiopia, 2015.

	Mean positive overshoot over the 10% income threshold (%)					
	Baseline			Adjusted*		
Income group	Mean†	SE‡	95% CI§	Mean	SE‡	95% CI§
Total	17.6	2.2	13.1 to 22.1	12.9	3.3	6.3 to 19.5
Q1	23.6	5.2	13.4 to 33.9	14.5	5.9	2.6 to 26.4
Q2	23.9	6.7	10.6 to 37.1	25.2	11.8	1.5 to 48.9
Q3	14.0	2.6	8.8 to 19.2	9.3	3.0	3.3 to 15.3
Q4	12.9	2.4	8.2 to 17.6	9.3	3.8	1.7 to 16.9
Q5	4.8	1.2	2.4 to 7.1	3.0	1.0	0.9 to 5.1

*Amount of OOP payments financed through means other than current income is deducted from the total OOP payment.
†The average amount by which households that experienced catastrophic OOP payments within the total population, Q1, Q2, Q3, Q4 and Q5 exceeded the 10% household income threshold expressed as in % as a share of household income.
‡SE of the mean.
§95% CI for the mean.
OOP, out-of-pocket.

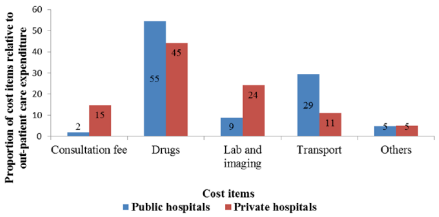

Figure 2 Contribution of cost items as a share of total outpatient expenditure for prevention and treatment of cardiovascular disease in general and specialised cardiac hospitals in Addis Ababa, Ethiopia, 2015.

might be expected, hospitalisation, patients who travel to Addis Ababa to receive CVD care and those who visited private settings experienced greater financial risk. This is due to the additional cost related to travel and higher prices of services in private settings. The significance of direct non-medical costs to CHE have also been identified by others.[41]

It is, however, worrisome that the poorest households who by large sought care in public hospitals (more than 80% of bottom 40%, Table A.2.2.2 in online supplementary annex 2) where services are offered at subsidised rate suffered a greater financial risk even after controlling relevant covariates.[48] This is possibly indicative of suboptimal implementation of ongoing healthcare financing reforms.[49] For example, even though drugs could have been purchased at a subsidised price in public facilities, promised benefits may not be realised unless sustained availability and use of generic drugs is ensured.[50] We found drug costs to be major drivers in outpatient care costs—a finding also reported elsewhere.[6 42] Therefore, ensuring effective implementation of ongoing reforms would be vital to attain the desired financial risk protection benefits. Conversely, poorest households' limited capacity to cope with an even small amount of OOP payments could also partly explain the greater financial risk among this subgroup.[5]

Table 5 Proportion of out-of-pocket payments financed through various sources by type of care for prevention and treatment of cardiovascular disease in general and specialized cardiac hospitals in Addis Ababa, Ethiopia.

		Type of care	
Sources of finance	**Proportion***	**Outpatient**	**Inpatient**
Current income	None	36.7	71.0
	100%	48.0	20.0
Saving	None	89.1	73.0
	100%	5.6	14.0
Family support	None	59.7	45.0
	100%	27.1	39.0
Borrowing	None	98.6	92.0
	100%	0.4	5.0
Asset sale	None	99.3	97.0
	100%	0.2	2.0
Insurance	None	90.5	98.0
	100%	0.2	0

*Proportion of out-of-pocket payment financed from each source.

The magnitude of CHE dropped remarkably on adjustment of OOP payments covered through sources of financing other than households' current income. Reliance on such coping mechanisms was higher among the poorest households as is the case elsewhere.[7 8 13] Though this might signal that households were able to temporarily cope with high OOP demand, it largely came at the expense of support from family members. The long-term impact of such expenditures on economic situation of the supporting families is questionable and worth further investigation.[9]

Now that the health infrastructure and human resource situation have greatly improved in Ethiopia,[51] expansion of health insurance and health services is a natural next step that could address part of the problem. Effective mechanisms need to be put in place to confine the unwanted financial consequences seeking CVD care for affected households and their families. To this end, the Ethiopian national health policy (draft, 2015/2016) identified financial risk protection as one of its main goals.[52] Accordingly, the draft national Health Care Financing strategy (2015–2035) proposed four reforms: (A) scale-up of community based health insurance for those in the informal sector (about 89% of the population), (B) launching of social health insurance for formal sector employees, (C) expanding the fee waiver system to the poorest households and (D) maintaining the general subsidy at public health facilities.[49 53–55]

Our results should be interpreted with caution in view of the study limitations. The study does not capture the prohibitive impact of OOP payments on utilisation of CVD care. Not capturing non-use and underutilisation of health services due to financial barriers is one of the major limitations of facility-based cross-sectional cohort studies—a limitation that has also been previously identified.[56] Another limitation is that we relied on self-reported data on OOP payments and household income with significant risk of reporting error.

Given the 12-month reference period used to measure OOP payments, respondents might not remember all expenditures correctly. To a large extent, this could have resulted in an under-reporting of OOP payments although one cannot rule out the possibility of over-reporting.[57]

In contrast, though shorter recall periods may help in minimising memory loss, one might fail to capture possible non-uniform expenditure patterns evident over longer time span.[57] Therefore, it is important to find the right balance between the appropriate recall period and risk of recall problem especially for chronic conditions such as CVD. Related to this, OOP payments were

captured with a detailed breakdown of cost–items such as drugs, bed days and so on. Though these could be cited among the strengths of our study,[57 58] it was not always easy for respondents to provide all the details. In the future, alternative ways of real-time data collection mechanisms, for example, prospective mobile phone-based data collection systems could be explored. Additionally, we did not capture OOP payments for traditional treatment of CVD, if any. However, OOP payments to traditional providers constituted only to 2% of household OOP expenditures in Ethiopia in 2012.[32]

Although consumption expenditures are preferred measures of living standards especially in low-income settings, we used reported income. Nearly half of the study participants were in the formal sector and were men. Therefore, reporting income was relatively easier for them compared with consumption expenditures. However, we did not account for possible in-kind transfers to households. Given that Addis Ababa is a large urban centre, we do not anticipate this to introduce major bias. Moreover, as our main focus was assessing the impact of OOP payments, we did not include lost income in our analysis, but we have provided results on time lost in Table A.2.2.3 in online supplementary annex 2.

Though primary prevention services for CVD are available at health centres and clinics, the service provision for chronic conditions is not so organised in those settings making data collection a bit more challenging. Therefore, we excluded those facilities from our sample. In view of this, generalisability of our findings beyond hospital settings is deemed limited.

Moreover, although households were used as the unit of analysis in our study, we did not collect data regarding possible OOP payments on CVD care for household member(s) other than the primary participants. Though relevant, we do not anticipate this to have a major impact on the final results given the low prevalence of family history of CVD in our study (4.8% reported having a first degree relative with a history of CVD). Additionally, even though we have explored a number of potential predictors of CHE available in our data, problems of endogeneity and identification are always an issue when fitting logistic regression to cross-sectional cohort data. Our model might therefore be lacking other unobserved covariates relevant to the independent variables as well as CHE. However, the goodness-of-fit of the model was reasonably good based on Hosmer-Lemeshow test (p-value=0.3).

Finally, we limited the scope of the study to Addis Ababa due to high burden of CVD and the higher concentration of CVD specialised centers in the city compared with other regions in Ethiopia. Still about 20% of our study subjects travelled from outside Addis Ababa.

CONCLUSION

Seeking prevention and treatment services for CVD in Addis Ababa poses substantial financial risk on households, affecting the poorest and those who reside outside Addis Ababa more. Drug costs constitute about half of the outpatient care expenditures. Economic and geographical inequalities should also be considered when setting priorities for expanding coverage for these services. Expanded coverage has to go hand-in-hand with implementation of sound prepayment and risk pooling arrangements to ensure financial risk protection to the most needy.

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Correction notice This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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Annex 2.1: Estimation of the magnitude and intensity of catastrophic health expenditure (CHE)

The magnitude and intensity of CHE was estimated based on previously published methods as follows [1, 2]:

A household ´i´ is said to have faced CHE if:

$$T_i/X_i > Z \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where T_i is the total out-of-pocket (OOP) payments for prevention and treatment of CVD household 'i' spent, X_i is the respective total household income and Z is the threshold chosen for CHE. In our analysis, the threshold for CHE is set at > 10% of household income.

The catastrophic headcount (*H*) for the sample, the proportion of households that faced CHE, is given by:

$$H=1/N \Sigma_{i=1}^{N} E_i,$$

$$E_i=1 \text{ if } T_i/X_i > Z \text{ and otherwise zero} \ldots\ldots (2),$$

where *N* is the sample size.

Households use various coping mechanisms other than current income to meet the OOP payments, we therefore deducted the amount of OOP payments financed through sources other than current income to estimate the adjusted CHE rate as recommended by others [3, 4].

The mean positive overshoot, the average amount by which households that suffered CHE exceeded the 10% household income threshold, was used to estimate the intensity of financial catastrophe households faced. We first assessed the catastrophic overshoot (O) defined as:

Overshoot (O) for household 'i' is given by:

$$O_i = E_i((T_i/X_i) - Z) \ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Overshoot for the sample:

$$O = 1/N \Sigma_{i=1}^{N} O_i \ldots\ldots\ldots\ldots\ldots\ldots\ldots (4)$$

Mean Positive Overshoot (MPO) = O/H..... (2 & 4)

Annex 2.2: ***Household out-of-pocket expenditure***

Table A.2.2.1. Annual out-of-pocket payment for prevention and treatment of cardiovascular disease in general and specialized hospitals in Addis Ababa, Ethiopia in 2015 US$.

	OOP payment*	Mean	(SD)**	Median	(iqr)***	N
Public hospitals	total	**96.6**	(172.9)	**45.4**	(68.8)	306
	out-patient	**70.5**	(123.2)	**41.0**	(60.5)	294
	in-patient	**246.1**	(239.5)	**195.1**	(234.1)	40
Private hospitals	total	**582.5**	(600.4)	**390.2**	(514.4)	283
	out-patient	**447.0**	(448.1)	**340.6**	(371.0)	273
	in-patient	**722.4**	(577.5)	**570.7**	(535.7)	60
Ischemic heart disease	total	**403.4**	(519.2)	**239.0**	(452.4)	233
	out-patient	**308.3**	(366.9)	**183.4**	(355.6)	225
	in-patient	**666.6**	(502.0)	**590.2**	(402.0)	41
Stroke	total	**451.0**	(585.1)	**243.9**	(511.0)	83
	out-patient	**229.9**	(318.9)	**78.0**	(307.3)	71
	in-patient	**511.8**	(569.3)	**378.0**	(341.5)	39
Hypertension	total	**229.4**	(444.2)	**60.6**	(249.9)	235
	out-patient	**203.4**	(398.6)	**58.5**	(219.8)	233
	in-patient	**367.5**	(517.1)	**243.9**	(248.8)	18
Dyslipidemia	total	**217.8**	(337.5)	**84.1**	(244.4)	38
	out-patient	**198.9**	(311.3)	**78.3**	(178.5)	38
	in-patient	**291.9**	(59.9)	**329.3**	(85.4)	2
Reside in Addis	total	**296.7**	(478.8)	**103.2**	(339.0)	470
	out-patient	**223.9**	(351.8)	**79.0**	(281.0)	452
	in-patient	**534.2**	(546.0)	**378.0**	(494.3)	76
Reside outside Addis	total	**464.6**	(549.0)	**271.0**	(570.3)	119
	out-patient	**363.8**	(435.9)	**219.5**	(429.3)	115
	in-patient	**580.2**	(494.7)	**465.9**	(824.4)	24
Income quintiles ****	Q1	**102.1**	(170.7)	**35.9**	(91.2)	121
	Q2	**219.5**	(465.6)	**59.1**	(203.4)	157
	Q3	**318.2**	(403.2)	**136.1**	(405.9)	96
	Q4	**464.1**	(571.9)	**293.2**	(443.7)	128
	Q5	**617.1**	(606.9)	**390.2**	(584.1)	87

* out-of-pocket payment **standard deviation *** interquartile range **** total annual out-of-pocket payment both for out-patient and in-patient care disaggregated by income quintiles

Table A.2.2.2. Distribution of the study population by the type of hospital visited

	Public hospitals		Private hospitals	
	Percent (%)	**[95 % CI]†**	**Percent**	**[95 % CI]†**
Total	**51.8**	[47.5 56.1]	**48.2**	[43.9 52.5]
Q1	**86.5**	[78.0 93.0]	**13.5**	[7.0 20.0]
Q2	**76.6**	[69.4 93.8]	**23.4**	[16.1 30.6]
Q3	**46.0**	[35.3 56.6]	**54.0**	[43.4 64.7]
Q4	**30.3**	[21.6 38.9]	**69.7**	[61.1 78.4]
Q5	**6.3**	[0.3 12.3]	**93.7**	[87.7 99.7]

† 95% confidence interval for the mean

Table A.2.2.3 Time lost by patients due to illness related to cardiovascular disease or while seeking care for cardiovascular disease in Addis Ababa over one and twelve months period.

Time lost in number days			
Time lost over 1 month	**Percent(%)**	**Time lost over 12 months**	**Percent(%)**
<=1	73.7	<= 7	68.4
2 - 7	17.7	8 -14	11.9
> 7	8.6	> 14	19.7

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Cost Effectiveness and Resource Allocation

RESEARCH Open Access

Prevention and treatment of cardiovascular disease in Ethiopia: a cost-effectiveness analysis

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Abstract

Background: The coverage of prevention and treatment strategies for ischemic heart disease and stroke is very low in Ethiopia. In view of Ethiopia's meager healthcare budget, it is important to identify the most cost-effective interventions for further scale-up. This paper's objective is to assess cost-effectiveness of prevention and treatment of ischemic heart disease (IHD) and stroke in an Ethiopian setting.

Methods: Fifteen single interventions and sixteen intervention packages were assessed from a healthcare provider perspective. The World Health Organization's Choosing Interventions that are Cost-Effective model for cardiovascular disease was updated with available country-specific inputs, including demography, mortality and price of traded and non-traded goods. Costs and health benefits were discounted at 3 % per year. Incremental cost-effectiveness ratios are reported in US$ per disability adjusted life year (DALY) averted. Sensitivity analysis was undertaken to assess robustness of our results.

Results: Combination drug treatment for individuals having >35 % absolute risk of a CVD event in the next 10 years is the most cost-effective intervention. This intervention costs US$67 per DALY averted and about US$7 million annually. Treatment of acute myocardial infarction (AMI) (costing US$1000–US$7530 per DALY averted) and secondary prevention of IHD and stroke (costing US$1060–US$10,340 per DALY averted) become more efficient when delivered in integrated packages. At an annual willingness-to-pay (WTP) level of about US$3 million, a package consisting of aspirin, streptokinase, ACE-inhibitor and beta-blocker for AMI has the highest probability of being most cost-effective, whereas as WTP increases to > US$7 million, combination drug treatment to individuals having >35 % absolute risk stands out as the most cost-effective strategy. Cost-effectiveness ratios were relatively more sensitive to halving the effectiveness estimates as compared with doubling the price of drugs and laboratory tests.

Conclusions: In Ethiopia, the escalating burden of CVD and its risk factors warrants timely action. We have demonstrated that selected CVD intervention packages could be scaled up at a modest budget increase. The level of willingness-to-pay has important implications for interventions' probability of being cost-effective. The study provides valuable evidence for setting priorities in an essential healthcare package for CVD in Ethiopia.

Keywords: Cost-effectiveness analysis, Cardiovascular disease, Ischemic heart disease, Stroke, Prevention, Treatment, Ethiopia

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Background

Cardiovascular disease (CVD) is the leading cause of mortality globally. The Global Burden of Disease study estimated that about 32 % of all deaths worldwide in 2013 were caused by CVD [1], with about 80 % of these deaths occurring in low-and middle-income countries (LMIC) [1, 2].

Approximately 9 % of all deaths in Ethiopia in 2012 were caused by CVD according to World Health Organization (WHO) estimates [3]. Small-scale local studies also reported an increasing burden from CVD and its risk factors, especially in urban settings in Ethiopia [4–15]. In a systematic review of studies conducted in Ethiopia between 1960 and 2011, CVD was reported to be among: (a) the prevalent causes of morbidity (range 4–24 %); (b) the main causes of hospital admission, especially among those older than 60 years (range 3–31 %); (c) the leading causes of medical intensive care unit admission (range 8.9–9.8 %); and (d) among the major causes of mortality (range 6.5–24 %) [15]. In Ethiopia's capital, Addis Ababa, an estimated 25 % of all household deaths between 2006 and 2009 and 11 % of all hospital deaths between 2002 and 2010 were attributed to CVD [7, 8]. Myocardial infarction, stroke and hypertensive heart disease accounted for about 75 % of CVD deaths [7, 8]. Modifiable risk factors like smoking, high cholesterol and high blood pressure explain the major share of the CVD burden [16, 17]. The prevalence of hypertension in Ethiopia is estimated to range from 16 to 30 % [5, 6, 13, 14].

WHO recommends a combination of population-wide and individual-based prevention and basic treatment strategies for successful control of CVD [18, 19]. Current coverage of such interventions is low in Ethiopia. Only about a quarter of the patients diagnosed with CVD at two referral hospitals in Ethiopia were found to be on medication [6, 9].

Cognizant of the increasing burden from non-communicable diseases (NCDs), the Federal Ministry of Health of Ethiopia (FMOH) has launched a National Strategic Action Plan (NSAP) for Prevention and Control of NCDs, envisioning the scale-up of an essential package of NCD interventions targeting the four major NCDs, including CVD [20]. With Ethiopia's meager health spending of only about US$ 21 per capita per year in 2011 [21], it is imperative to identify the most efficient strategies for further scale-up.

Cost-effectiveness analysis is a key tool to assist policy makers in selecting the most efficient strategy among competing alternatives. WHO-CHOICE (Choosing Interventions that are Cost-Effective) has undertaken cost-effectiveness analysis of CVD interventions for the major regions in low- and middle-income countries [22–24]. Regional estimates have limited relevance to country-level decision making due to variation in key parameters. Parameters such as demography, epidemiology, costs and coverage of interventions vary widely across countries within the same regions, warranting the need for local evidence for better decision-making [23, 25–27]. To our knowledge there is no local evidence on cost-effectiveness of CVD interventions in Ethiopia. We therefore intend to fill this knowledge gap and inform the process of evidence-based resource allocation and priority setting for essential package for CVD interventions in Ethiopia.

This paper's objective is to undertake a cost-effectiveness analysis of primary prevention, acute treatment and secondary prevention of ischemic heart disease (IHD) and stroke in an Ethiopian setting.

Methods

We performed a generalized cost-effectiveness analysis of prevention and treatment strategies for CVD in an Ethiopian setting based on the WHO-CHOICE approach whereby, cost-effectiveness of each intervention is assessed compared with a 'no intervention' scenario [28]. Box 1 below depicts key socio-demographic and economic indicators for Ethiopia. A brief description of the interventions assessed, the modeling approach and the country-specific revisions are outlined below.

Box 1 Key socio-demographic and economic parameters for Ethiopia, 2013/14

Parameter	Level	Source
Total population	96.96 million	
Life expectancy at birth	64 years	[29]
GDP per capita	US$505	
Currency exchange rate to US$	17.7	
PPP exchange rate	7.08	
Total health expenditure (annual)	US$1.6 billion	
Per capita spending on health (annual)	US$21	[21]
Number of health facilities		[30]
Hospital	189	
Health center	3547	
Health post	16,251	

Interventions

Fifteen single interventions and sixteen integrated intervention packages were assessed. Interventions target individuals without a history of established CVD but at risk of developing a CVD event; those with an acute CVD event; and those with a history of established CVD event. Interventions were selected based on the recommendations of WHO and local experts and scientific evidence of effectiveness. Full description of the interventions is outlined in Table 1.

Table 1 Description of interventions assessed

Intervention	Description	Health facility stay	Laboratory/imaging
Acute myocardial infarction		9 hospital bed days at tertiary level	CBC, blood glucose, PT, INR, aPTT and serum lipid profile (3 times) plus ECG and RFT twice
Aspirin	Aspirin 325 mg po daily 30 days		
ACE-inhibitor	Enalapril 20 mg po daily for 30 days		
Beta-blocker	Atenolol 50 mg po daily for 28 days		
Aspirin + clopidogrel	Aspirin 325 mg + clopidogrel 300 mg 30 days		
Thrombolytic	Streptokinase 1.5 million i-u		
Primary PCI	Insertion of ballon-tipped catheter with stent into blocked area	6 hospital bed days at tertiary level	
Post-acute myocardial infarction			
Aspirin	ASA 100 mg po daily	4 hospital visit per year (year 1–3) 3 hospital visit per year (year 4–10) at primary hospital	CBC, LFT, RFT, serum lipid profile, serum electrolyte
ACE-inhibitor	Enalapril 20 mg po daily		
Beta-blocker	Atenolol 50 mg po daily		
Statin	Simvastatin 40 mg po daily		
Acute stroke			
Aspirin	Aspirin 160 mg po daily for 1 month	30 hospital bed days at level 3	CBC,PT, INR, aPTT, serum glucose, serum lipid profile, RFT,LFT and serum electrolyte plus brain CT,ECG &CXR once
Post-acute stroke			
Aspirin	Aspirin 100 mg po daily	4 hospital visit per year (year 1–3) 3 hospital visit per year (year 4–10) at primary hospital	CBC, RFT, LFT, serum lipid profile, serum electrolyte
ACE-inhibitor	Enalapril 20 mg po daily		
Statin	Simvastatin 40 mg po daily		
Primary prevention of IHD and stroke			
Anti-hypertensive treatment for SBP (>140 or >160 mmHg)	HCT 25 mg + Atenolol 50 mg po daily	4 visit to a health center for the first year followed by 3 visits per year for the remaining 9 years. Additionally, 20 % will have 1.5 visit per year at primary hospital	RFT, serum lipid, blood glucose, U/A
Cholesterol lowering treatment for total cholesterol (>5.7 or >6.2 mmol/l)	Simvastatin 40 mg po daily		LFT, serum lipid, blood glucose, U/A
Combination drug treatment for absolute CVD risk (>5, >15, >25, >35 %)	ASA 100 mg + Hydrochlorothiazide 25 mg + Atenolol 50 mg + Simvastatin 20 mg		RFT, LFT, serum lipid, blood glucose

The intervention packages for 'acute MI,' 'post-acute MI,' and 'post-acute stroke' were formed as combinations of the drugs under the single interventions during the same health facility stay and the same laboratory investigation requirements as the respective single interventions. A complete list of all the interventions is provided in Table 4

MI myocardial infarction; *IHD* ischemic heart disease; *SBP* systolic blood pressure; *CBC* complete blood count; *PT* prothrombin time; *ECG* electrocardiogram; *RFT* renal function test; *LFT* liver function test; *U/A* urinalysis

For primary prevention, individual-based drug regimens based on either the level of systolic blood pressure (SBP), the level of total serum cholesterol or the absolute risk of developing a CVD event over the next 10 years were assessed. Absolute risk is determined based on well-known CVD risk factors (age, gender, SBP, smoking status, body mass index and total serum cholesterol level) [18, 19]. The distribution of mean risk factor levels and smoking status in the population was stratified by age and gender based on the estimates from WHO's Comparative Risk Assessment project for East Africa region. Estimates of relative risk of developing a CVD event per unit increase in the level of risk factors was then applied to estimate the individual level relative risk of developing a CVD event which is then used to extrapolate the absolute risk of CVD event at population level [19, 31]. The drug regimens are to be delivered on an outpatient basis at health centers and constitute: (a) a beta-blocker and a diuretic at SBP of >140 mmHg or >160 mmHg; (b) statin treatment at serum cholesterol level of >5.7 mmol/l or >6.2 mmol/l; and (c) a combination of aspirin, beta-blocker, diuretic and statin-based on the absolute risk of a CVD event for four thresholds (>5, >15, >25 or >35 %) respectively.

Interventions for acute myocardial infarction (AMI) constitute treatment with aspirin, streptokinase, clopidogrel, beta-blocker, ACE-inhibitor and surgical revascularization with percutaneous coronary intervention (PCI) on an inpatient basis. Aspirin is used for acute treatment of ischemic stroke; and beta-blocker, aspirin, ACE-inhibitor and statin for secondary prevention of IHD and stroke. Interventions were first assessed individually; clinically relevant packages were then formed, building on the intervention with the lowest cost-effectiveness ratio.

Given the current low coverage of interventions—less than 5 %, based on experts' recommendations—we set modest target coverage of 20 % for all of the interventions.

In the absence of local evidence, efficacy estimates were drawn from previous randomized controlled trials and meta-analyses performed elsewhere (Table 2) [32–46]. Efficacy estimates were adjusted by target coverage and patient adherence level [47–49].

Modeling approach

The WHO-CHOICE's CVD model for East Africa was used to undertake the analysis [50]. The model was updated with age and sex distribution, birth rate and background mortality rate for Ethiopia [51–53]. In the absence of national data on the current level of incidence, prevalence and mortality rates of IHD and stroke and the distribution of CVD risk factors, the analysis used respective estimates for the East Africa region [22, 23, 31, 50, 52].

The effect of primary prevention interventions is modeled through their impact on the level of risk factors, which is used to recalculate the expected incidence rate for IHD and stroke after implementing the specific intervention. The new incidence rate is applied to estimate the reduction in mortality from the respective diseases. Interventions targeting AMI and acute stroke were modeled through the interventions' impact on 28-day case fatality rate, while secondary prevention interventions were modeled through their impact on post–acute case fatality rate. The effect of interventions was assumed to be the same across sub-groups.

We used PopMod, a multi-state population model, to estimate the health benefits in disability adjusted life years (DALYs) averted for the Ethiopian population resulting from changes in CVD risk due to specific interventions.

The population in the model is divided into age–sex categories of one-year intervals which are further stratified into four health states: (a) those having IHD; (b) those having stroke; (c) those having both; and (d) those without any of the conditions. Transition between states is dictated by the respective incidence, case fatality and mortality rates. Disability weights for the health states were drawn from the Global Burden of Disease Study 2010 [54]. PopMod traces the changes in population size in each age–sex category over a lifetime of 100 years by standard life table methods with and without specific interventions ('no intervention' scenario). Interventions are implemented for 10 years, after which the epidemiologic rates are taken back to the 'no intervention' level. Births and background mortality are taken into account [31, 55]. The expected health benefits of the current coverage level of interventions are eliminated to create a hypothetical reference case of null scenario. The model provides removal of the benefits of current coverage of interventions, thereby allowing recalculation of the incidence, prevalence and case fatality rates for MI and stroke, assuming a scenario where the currently implemented interventions are stopped. The health benefits are reported in terms of DALYs averted, discounted at 3 % per year without age weighting. The model has been used to undertake CEAs of various interventions in multiple settings [22]; and details have been published elsewhere [23, 24, 55].

Costs

A healthcare provider perspective was used for analysis and hence only program costs, training costs and patient-related costs to the provider were taken into account. Program costs constitute the cost of development and

Table 2 Effectiveness assumption used in the model expressed in percentage reduction in the outcome of interest

Intervention	Outcome affected	Efficacy in %	Source
Acute myocardial infarction			
Aspirin	28 day mortality	22 (15, 29)	[31, 36]
ACE-inhibitor	28 day mortality	7 (2, 11)	[37, 40]
Beta-blocker	28 day mortality	13 (2, 23)	[37, 40]
Streptokinase	28 day mortality	26 (17, 31)	[36]
ASA + clopidogrel	28 day mortality	32 (17, 47)	[31, 34]
PCI	28 day mortality	61 (38, 75)	[33, 36, 41]
Post-acute myocardial infarction			
Aspirin	Case fatality rate	13 (2, 22)	[31, 66]
ACE-inhibitor	Case fatality rate	23 (14, 30)	[42]
Beta-blocker	Case fatality rate	23 (16, 30)	[43]
Statin	Case fatality rate	19 (15, 24)	[44, 67]
Acute ischemic stroke			
Aspirin	28 day case fatality rate	5 (1, 9)	[31]
Post-acute stroke			
Aspirin	Case fatality rate	16 (2, 29)	[31]
ACE-inhibitor	Case fatality rate	16 (12, 30)	[45]
Statin	Case fatality rate	24 (16, 37)	[35]
Primary prevention of IHD and stroke			
Anti-hypertensive treatment for systolic blood pressure (>140 or >160 mmHg)	Difference between actual systolic blood pressure and 115 mmHg	33 (31, 44)	[40, 46, 68]
Cholesterol lowering treatment for total cholesterol (>5.7 or >6.2 mmol/l)	Serum level of total cholesterol	20 (17, 23)	[27, 44]
Combination drug treatment for absolute risk of CVD (>5, >15, >25, >35 %)	Effect on the level of systolic blood pressure plus serum cholesterol plus aspirin	(33) + (20) + (18)	[27, 40, 44, 46, 66, 68]

administration of an intervention at national and sub-national levels. This includes cost of administration and planning, media and communication, law enforcement, training, monitoring and evaluation. Patient-related costs consist only of direct medical costs incurred by the provider at the point of service delivery, including hospital bed days, outpatient visits, drugs and laboratory [28]. The analysis did not include direct non-medical costs such as transportation and indirect costs to patients and care givers such as lost productivity. The ingredients costing approach was employed whereby the quantities of resources required to deliver the interventions and respective unit prices were accounted for separately (Table 3). The quantities of resources used were largely determined based on WHO-CHOICE assumptions. We updated the prices of relevant laboratory tests and imaging using pricing from two public hospitals in Addis Ababa (Tikur Anbessa teaching hospital and Zewditu hospital). Salary scale of the health workforce was based on the FMOH of Ethiopia. Equipment and material prices were based on WHO price estimates for Ethiopia for the year 2012/13 [56] and drug prices were based on the lowest supplier prices for 2012, as noted in the International Drug Price Indicator Guide [57]. WHO-CHOICE's transport multiplier factor was applied to the drug prices. The total cost of an intervention was then calculated as the sum of the product of the quantities of resources with their respective unit prices. As recommended by WHO-CHOICE costs were discounted at an annual rate of 3 % [28] and reported in 2012 US$.

Cost-effectiveness

All interventions were assessed compared to 'no intervention' scenario first, followed by incremental analysis between mutually exclusive interventions. Average cost-effectiveness ratios (ACERs) were estimated dividing the incremental cost by incremental effects of each intervention compared with a 'no intervention' scenario. In order to assess the relative cost-effectiveness of mutually exclusive interventions, incremental cost-effectiveness ratios (ICERs) were estimated as the ratio of the incremental cost to incremental effects for moving from one intervention to the next more effective intervention, starting from the null scenario. Interventions that are more costly and less effective than their comparators or those having higher ICER than their more effective comparator are designated as dominated. ACERs and ICERs are reported in US$ per DALY averted for the year 2012.

Table 3 Price of intervention inputs applied in the model in Ethiopian birr 2012

	Unit price		Unit price
Salary scale for human resource			
Medical specialist	112,781	Director of public health	51,293
Medical officer	76,723	Public health specialist	94,712
Nursing director/manager	64,728	Public health assistant	28,339
Registered nurse	28,339	Health educator/trainer	28,339
Health worker	51,293	Social/welfare worker	28,339
Source: Federal Ministry of Health, Ethiopia 2012			
Health facility visit/stay			
Hospital bed days		Health facility visit	
Primary hospital	52.52	Primary hospital visit	18.58
Secondary hospital	54.76	Secondary hospital visit	21.17
Tertiary hospital	70.81	Tertiary hospital visit	22.06
Percutaneous coronary intervention[a] 63,000		Health center visit	23.00
Source: WHO_CHOICE [69]			
Laboratory and imaging			
Complete blood count	20	Blood glucose	10
Prothrombin time (INR)	15	Urinalysis	5
aPTT	15	Liver function test	30
Serum electrolytes	45	Total cholesterol	7
Renal function test	20	Serum lipids	42
Blood glucose	10	CT scan	600
Echocardiography	150	Endoscopy	400
Source: Tikur Anbesa teaching hospital and Zewditu memorial hospital			
Drugs			
ASA 100 mg	0.08	Simvastatin 20 mg	0.25
Enalapril 10 mg	0.05	Streptokinase 1.5 iu	601.8
Atenolol 50 mg	0.06	Clopidogrel 75 mg	0.55
		Hydrochlorothiazide 25 mg	0.08
Source: International drug price indicator [57]			

[a] Unit price per procedure. The program cost was assumed to be double the program cost required for other acute myocardial infarction interventions

Uncertainty analysis

A probabilistic sensitivity analysis was conducted using Monte Carlo League (MCLeague) software to assess the effect of uncertainty surrounding the costs and effectiveness estimates [58]. A truncated normal distribution was used to execute 1000 simulation runs with 15 and 25 % coefficient of variation for costs and effectiveness estimates, respectively. We assessed interventions that were not dominated by respective comparators in each intervention category. In addition, one-way sensitivity analysis was undertaken, applying the lower boundary of the effectiveness range; doubling the price of drugs, procedures and laboratory tests; a zero discounting rate to health benefits; and applying 50 % of the effectiveness point estimates (Tables 1, 2).

Results

Treatment of acute myocardial infarction with ACE-inhibitor costs the least at US$2.4 million annually. Combination drug treatment to individuals having >5 % absolute risk of developing a CVD event incurs the highest annual cost US$26.9 million— and generates the highest annual health benefit of 190,000 DALYs averted. Treatment of acute stroke with aspirin generates the smallest annual health benefit. The estimated annual costs, health benefits, ACER and ICERs for all interventions are presented in Table 4 below.

The absolute risk-based approach turns out to be the most cost-effective strategy of all the interventions. Combination drug treatment to individuals having an absolute risk >35 % yields the most value for money with an ICER of US$67 per DALY averted, with ICER reaching US$340 per DALY averted when the risk threshold is lowered to >5 %. When compared with the single risk–factor based approach, the absolute risk-based approach is the most cost-effective option. Notably, initiating treatment at higher CVD risk threshold generates better efficiency gain compared to lower risk thresholds regardless of the approach chosen. This means, for example, that initiating anti-hypertensive drug treatment at SBP of >160 mmHg is more efficient than treatment at >140 mmHg. Of all the interventions for AMI, an integrated package of aspirin, ACE-inhibitors, beta-blockers and streptokinase has the lowest ICER (i.e., US$999 per DALY averted). Provision of interventions in an integrated package generates better efficiency gain and dominates all the single interventions, as shown in Table 4. Moving from the most cost-effective pharmaceutical package to an integrated package that includes the highly skilled intervention PCI, aspirin and clopidogrel raised the ICER substantially—to US$5087 per one additional DALY averted.

Treatment of acute ischemic stroke with aspirin costs US$40,000 per DALY averted. Single drug interventions for secondary prevention of IHD and stroke cost between US$2400 and US$10,300 per DALY averted respectively. Interventions become more efficient when delivered in an integrated package. A package consisting of aspirin, beta-blocker ACE-inhibitor and statin for secondary prevention of IHD costs US$1850 per DALY averted, while a package consisting of aspirin, ACE-inhibitor and statins for secondary prevention of stroke costs US$1060 per DALY averted.

Table 4 Annual cost, annual health benefits and cost-effectiveness ratio of selected CVD interventions in Ethiopia

Intervention description	Annual cost in million US$	Annual DALYs averted (discounted)	Annual DALYs averted (undiscounted)	ACER	ICER
Acute myocardial infarction					
ACE-inhibitor	2.37	316	422	7531	Dominated
Beta-blocker	2.38	586	784	4057	Dominated
ASA	2.38	990	1325	2200	Dominated
Streptokinase	2.82	1170	1566	2408	Dominated
ASA + clopidogrel	2.38	1441	1927	1556	Dominated
ASA + streptokinase	2.84	2110	2822	1295	Dominated
ASA + streptokinase + ACE-inhibitor	2.85	2396	3205	1149	Dominated
Primary PCI	8.29	2747	3675	3013	Dominated
ASA + streptokinase + ACE-inhibitor + beta-blocker	2.92	2919	3905	999	999
ASA + clopidogrel + PCI	8.5	4015	5370	2115	5087
Acute stroke					
ASA	2.53	63	80	39,892	39,892
Post-acute IHD					
ASA	2.54	245	330	10,345	Dominated
Statin	2.74	310	417	8822	Dominated
Beta-blocker	2.53	488	657	5177	Dominated
ACE-inhibitor	2.55	524	705	4857	Dominated
ASA + beta-blocker	2.57	732	985	3511	Dominated
ASA + beta-blocker + statin	2.82	1038	1397	2717	Dominated
ASA + beta-blocker + statin + ACE-inhibitor	2.88	1557	2096	1849	1849
Post-acute stroke					
ACE-inhibitor	2.87	912	1200	3153	Dominated
ASA	2.86	1013	1348	2821	Dominated
Statin	3.30	1375	1813	2396	Dominated
ASA + statin	3.40	2382	3150	1428	Dominated
ASA + statin + ACE-inhibitor	3.48	3284	4337	1061	1061
Primary prevention of IHD and stroke					
Cholesterol lowering treatment for total chol. >6.2 mmol/l	4.67	8768	15,913	532	Dominated
Cholesterol lowering treatment for total chol. >5.7 mmol/l	10.62	19,073	34,143	557	Dominated
Anti-hypertension treatment for SBP >160 mmHg	7.33	98,880	172,868	74	Dominated
Combination drug treatment for absolute risk of CVD >35 %	7.18	107,687	185,249	67	67
Anti-hypertension treatment for SBP >140 mmHg	19.42	125,712	220,992	154	Dominated
Combination drug treatment for absolute risk of CVD >25 %	9.83	127,957	219,230	77	131
Combination drug treatment for absolute risk of CVD >15 %	14.41	153,877	263,747	94	177
Combination drug treatment for absolute risk of CVD >5 %	26.85	190,391	329,117	141	341

In order to facilitate step-wise selection of the most cost-effective interventions, interventions that dominate their comparators in each category were ranked according to their category-specific ICER. Accordingly, combination drug treatment to individuals having >35 % absolute risk of developing a CVD event is the first intervention to be selected, followed by the same intervention at lower risk thresholds (>25, >15 and >5 %, respectively). A basic integrated package of aspirin, ACE-inhibitor, beta-blocker and streptokinase for AMI and a package of aspirin, statin and ACE-inhibitor for secondary prevention of stroke are the next two interventions that could be selected when more resources become available. Scale-up of combination drug treatment at an absolute risk >35 % to a coverage level of 20 % costs about US$7 million per year and averts 107,000 DALYs annually.

Table 5 presents the results from the one-way sensitivity analysis. At the lower boundary of the effectiveness range, all interventions become less cost-effective. The ACERs increased by a factor of 1.5-to sixfold for AMI and secondary prevention interventions. Primary prevention interventions were less sensitive. Halving the point estimates for effectiveness has a relatively larger impact on the primary prevention interventions, with respective ACERs increasing by a factor of 1.4–1.8. However, even at half point estimate of effectiveness, combination drug treatment to individuals having >35 % CVD risk costs US$94 per DALY averted. Doubling the price of drugs and laboratory tests increases ACERs minimally compared with halving or applying lower limit of effectiveness estimates. All the interventions become more cost-effective at a zero discounting rate for the health benefits (Table 5).

The probabilistic sensitivity analysis illustrates the serious uncertainty surrounding our results, with wide and overlapping uncertainty ranges for cost and effectiveness estimates (Fig. 1). Budget size has considerable impact on the probability of interventions being cost-effective. At an annual budget of US$3–US$4 million, an integrated package consisting of ASA, streptokinase, ACE-inhibitor and beta-blocker for AMI has the highest probability (0.50) of being the most cost-effective approach. Between US$4 and US$7 million, the probability curve for a secondary prevention package for stroke consisting of aspirin, ACE-inhibitor and statin overlaps on the basic AMI package, making the choice less straight forward. As the budget increases to more than US$7 million per year, combination drug treatment to individuals having more than 35 % absolute risk of CVD stands out as the most cost-effective intervention. However, even at this budget level, the other interventions have less but meaningful probability of being cost-effective (Fig. 2).

Discussion

Our analysis illustrates that primary prevention of ischemic heart disease and stroke is a more efficient strategy for maximizing population-level health benefits compared with acute treatment and secondary prevention. All primary prevention interventions cost less than US$ 560 per DALY averted. The absolute risk-based approach is more cost-effective than the single risk-factor approaches for primary prevention of CVD. This corresponds with the findings of similar studies for the sub-Saharan Africa region and other regions [23, 24]. The superiority of the absolute risk-based approach is primarily explained by: (a) the linear nature of the correlation between blood pressure and cholesterol level with the risk of CVD event and (b) the tendency for co-existence and interaction between CVD risk factors [19, 59, 60]. The modest 'efficiency loss' related to lowering the risk thresholds is due to the larger number of eligible individuals significantly increasing the cost for a relatively modest additional health benefits. It is therefore worthwhile to set the CVD risk threshold at >35 % initially; this can be lowered when more resources become available. The proposed risk threshold of >35 % accords with WHO's recommendation for resource-limited settings like Ethiopia [18].

All the single pharmacologic interventions for treatment of AMI were dominated by the integrated package consisting of aspirin, ACE-inhibitor, beta-blocker and streptokinase. Delivering interventions in integrated packages yields significant efficiency gain due to savings from program costs and patient costs [23]. This is comparable with the results from the Disease Control Priorities project 2nd edition [61]. Interestingly, the ICER escalates by about six fold if one moves from this basic pharmaceutical package to a highly skilled intervention consisting of PCI, aspirin, and clopidogrel. Although PCI is the treatment of choice for AMI in ideal settings [41, 62], our results indicate the need to prioritize the scale-up of basic pharmacologic regimens for AMI treatment in resource-constrained settings like Ethiopia rather than investing the limited resources on high-standard interventions.

An integrated package of aspirin, beta-blocker, ACE-inhibitor and statin for secondary prevention of IHD and a package of aspirin, ACE-inhibitor and statin for secondary prevention of stroke appears to be the preferred options within their categories. This is in line with the findings of Ortegon et al. for the sub-Saharan Africa region [23]. On the grounds of cost-effectiveness, secondary prevention interventions are ranked lower than primary prevention interventions. This is partly because primary prevention interventions generate a larger population-level aggregate health benefit with relatively lower unit delivery costs [23]. In addition, the need for

Table 5 Average cost-effectiveness ratios for cardiovascular disease interventions under multiple scenarios

Intervention description	Base-case	Undiscounted health benefits[a]	10 % coverage[b]	Double cost[c]	Lower effect[d]	50 % effect[e]
Acute myocardial infarction						
ACE-inhibitor	7526	5626	14,718	7777	26,556	15,172
Beta-blocker	4054	3031	7926	4191	26,556	8171
ASA	2398	1792	4685	2480	3545	4831
Streptokinase	2407	1799	4343	2855	3714	4850
ASA + clopidogrel	1652	1235	3225	1712	2958	3327
ASA + streptokinase	1345	1006	2419	1603	2015	2669
ASA + streptokinase + ACE-inhibitor	1188	888	2133	1411	1903	2342
Primary PCI	3013	2252	4560	4460	4833	5983
ASA + streptokinase + ACE-inhibitor + beta-blocker	998	746	1774	1210	1839	1950
ASA + clopidogrel + PCI	2112	1579	3171	2240	3410	4062
Acute stroke						
ASA	39,896	31,586	75,658	42,135	99,269	79,449
Post-acute myocardial infarction						
ASA	10,345	7701	19,853	11,173	50,593	19,029
Statin	8822	6552	16,139	10,119	10,659	11,594
Beta-blocker	5177	3844	9823	5575	7386	10,296
ACE-inhibitor	4856	3612	9182	5264	6092	6771
ASA + beta-blocker	3512	2610	6612	3835	6556	6793
ASA + beta-blocker + statin	2717	2018	4904	3182	4351	4597
ASA + beta-blocker + statin + ACE-inhibitor	1849	1373	3349	2197	2704	2908
Post-acute stroke						
ACE-inhibitor	3152	2394	5642	3663	3153	3153
ASA	2822	2121	5065	3264	9996	4833
Statin	2397	1820	4046	3042	3427	4355
ASA + statin	1429	1080	2382	1844	2730	2528
ASA + statin + ACE-inhibitor	1061	803	1751	1386	1616	1545
Primary prevention of IHD and stroke						
Cholesterol lowering treatment for total chol. >6.2 mmol/l	532	293	791	738	605	941
Cholesterol lowering treatment for total chol. >5.7 mmol/l	557	311	676	888	636	1002
Anti-hypertension treatment for SBP >160 mmHg	74	42	97	102	77	124
Combination drug treatment for absolute risk of CVD >35 %	67	39	88	103	69	94
Anti-hypertension treatment for SBP >140 mmHg	154	88	172	234	161	263
Combination drug treatment for absolute risk of CVD >25 %	77	45	95	124	80	108
Combination drug treatment for absolute risk of CVD >15 %	94	55	108	157	98	132
Combination drug treatment for absolute risk of CVD >5 %	141	82	153	245	148	199

[a] Undiscounted health benefits

[b] 10 % target coverage

[c] Double price for drugs, procedures and laboratory test

[d] Lower boundary of effectiveness estimate

[e] 50 % of point estimate of effectiveness

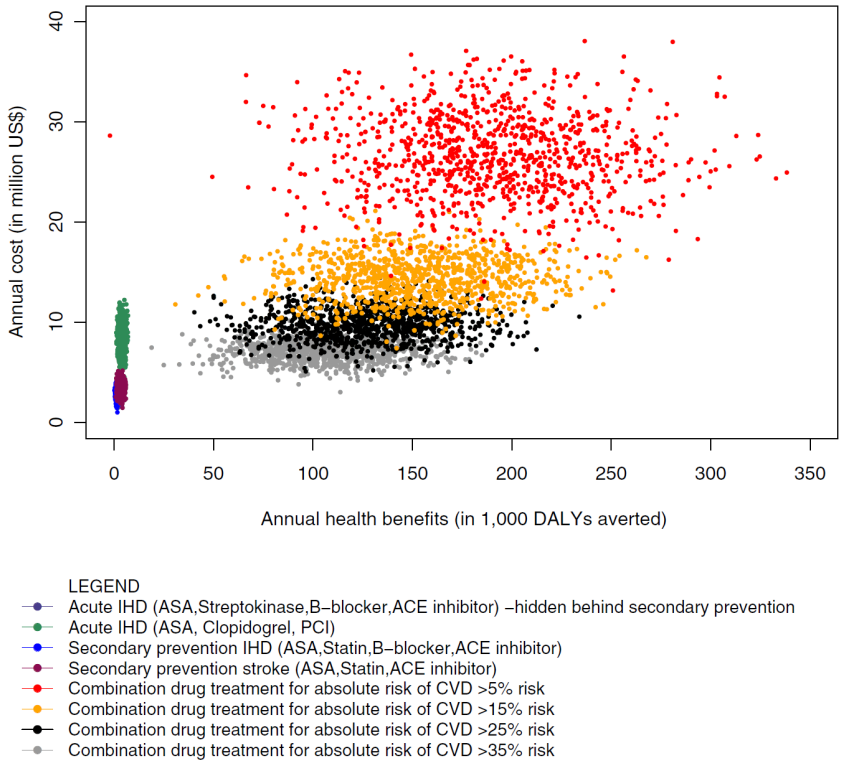

Fig. 1 Probabilistic sensitivity analysis of non-dominated CVD interventions in Ethiopia

relatively more frequent follow-up visits at primary hospital level for secondary prevention interventions partly explains higher cost-effectiveness ratios as compared with primary prevention interventions.

Continuing controversy about appropriate thresholds for cost-effectiveness ratios highlights the need for more empirical work in that area [50, 63, 64]. Woods et al. suggested a very low CER threshold of about 50 % of GDP per capita compared with WHO's recommendation of 1–3 times GDP per capita, which translates to US$505–US$1515 for the year 2013 [50, 63, 64]. Determining the appropriate cost-effectiveness ratio threshold level is beyond the scope of this paper, we therefore discuss the implications of scaling-up the intervention with the lowest ICER and leave the decision to policymakers to further select interventions that best fit the local budget constraint. Accordingly, combination drug treatment to individuals having more than 35 % absolute risk of CVD event is a reasonable starting point. Scale-up of this intervention to a coverage level of 20 % averts 107,000 DALYs annually at a cost of about US$ 7 million per year. This is equivalent to 0.4 % of the 2010/11 annual total health expenditure for Ethiopia [21]. In terms of GDP per capita, the ICER is about 13 % of GDP per capita for 2013.

With the evident escalating burden from CVD and its risk factors [5, 7, 11, 12], investing in primary prevention early on could help Ethiopia partially reduce the need to invest in more costly acute care and secondary prevention measures in the long term. Notably, the most cost-effective combination drug treatment based on an absolute risk approach could be scaled up at the primary health care level, for which Ethiopia has already

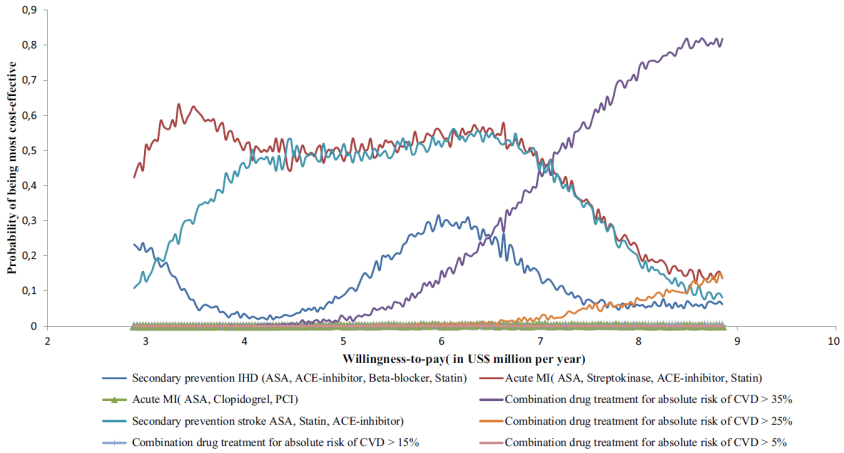

Fig. 2 Probabilistic sensitivity analysis of non-dominated CVD interventions in Ethiopia

established a solid foundation [30]. This could facilitate scaling up of the proposed primary prevention interventions at a more modest additional resource requirement than originally estimated. The actual budget implication, however, needs to be assessed separately using appropriate tools.

However, based on the probabilistic sensitivity analysis, the choice of intervention depends on the level of willingness-to-pay. When resources are scarce (<US$7 million annually), a package consisting of aspirin, streptokinase, ACE-inhibitor and beta-blocker for AMI is a preferred option over combination drug treatment for an absolute risk of CVD >35 %, although it ranked lower based on the ICER. It is also worth noting that CEA results are only one of the key parameters to be considered in priority setting. Policy makers need to take into account other important parameters for fair resource allocation, such as severity of disease, equity and financial risk protection [65].

Our study has a number of limitations. We have not included all possible sets of CVD interventions in our analysis. In the absence of country-level data on epidemiology of ischemic heart disease, stroke and the risk factors (incidence, prevalence, and case fatality rate), such estimates were drawn from estimates for the East Africa region. For the same reason, the effectiveness estimates for interventions were drawn from studies in developed settings. This may introduce bias into our cost-effectiveness ratio estimates, as it may be unrealistic to attain the same health benefit level from interventions in an Ethiopian setting; reasons for this may include differences in quality of health services, availability of resources and skilled human resources.

Interventions' effect is assumed to be uniform across sub-groups with varying risk level. This may have resulted in an overestimation of the potential impact of interventions in individuals with relatively lower risk and underestimation of the potential impact in high risk group. Therefore, detection of the direction of the bias on the final results is not straight forward; our intuition is that the net effect on the final results is very minimal.

PopMod estimates interventions' health benefits by tracing what would happen to the population with and without the interventions over a lifetime of 100 years. The interventions are assumed to be implemented only for the first 10-year period; the epidemiologic rates are subsequently returned to the 'no intervention' level. This only partially captures intervention health benefits; possible extended benefits from interventions on the outcome of interest are missed, resulting in possible underestimation of interventions' relative cost-effectiveness. Intervention period of more than 10 years involves a high degree of uncertainty and it is difficult to predict how CVD interventions may look like after 10 years from now.

Given the healthcare provider perspective we adopted for the analyses, we have not considered patient and caregiver costs such as transportation and cost of time lost while seeking healthcare. In addition, out-of-pocket expenditure by households constitutes one-third of total

health spending in Ethiopia [21]. Such factors might influence households' decision to access especially prevention strategies that entail repeated visits to health facilities and this aspect requires further exploration.

For primary prevention interventions, we did not consider the cost of screening all eligible individuals to identify 'at risk' sub-population groups. Scaling up screening programs could be very costly in low-income settings like Ethiopia [19]; therefore we included the cost of a health center visit and laboratory test only for those identified as 'at risk' through opportunistic screening. This would underestimate the potentially huge cost screening could entail at population level.

In addition to the proposed interventions, the potential benefit from sustained life style modification among the public cannot be over-stated for successful prevention and control of CVD in Ethiopia [19].

Conclusions

In Ethiopia, the escalating burden from CVD and its risk factors warrants timely action. We have demonstrated that selected packages CVD interventions could be scaled up in Ethiopia at a modest budget increase and that combination drug treatment to individuals having more than 35 % absolute risk of CVD event is the most cost-effective intervention. However, the level of willingness-to-pay has important implications for interventions' probability of being most cost-effective. The study provides valuable evidence for setting priorities in an essential health care package for cardiovascular diseases in Ethiopia.

Abbrevations

ACE-inhibitor: angiotensin converting enzyme inhibitors; ACER: average cost-effectiveness ratio; AMI: acute myocardial infarction; CBC: complete blood count; CEA: cost-effectiveness analysis; CHOICE: choosing inteventions that are cost-effective; CVD: cardiovascular disease; DALYs: disability-adjusted life years; ECG: electrocardiogram; FMOH: Federal Ministry of Health; GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; IHD: ischemic heart disease; INR: international normalized ratio; LFT: liver function test; LMIC: low- and middle-income countries; NCD: non-communicable disease; NSAP: national strategic action plan; PCI: percutaneous coronary intervention; PT: prothrombin time; RFT: renal function test; SBP: systolic blood pressure; SSA: sub-Saharan Africa; US: United States; WHO: World Health Organization.

Authors' contributions

MT, KAJ and KPS led the design of the study. MT and KAJ performed the analysis. KPS, STM and MB helped in the analysis. MT coordinated the overall research and was responsible for writing of the manuscript and incorporating feedbacks. AA and DJ contributed in collecting local data on the price of non-traded goods. DJ, SGA, AA, STM, KPS, OLF, SV and KAJ reviewed the manuscript and provided feedback. MT is responsible for finalization and submission of the final manuscript for publication. All authors read and approved the final manuscript.

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Competing interests

The funding agents had no role in the design, analysis and write-up of the manuscript, and the views expressed in the manuscript reflect only the authors' view and not that of any organization. The authors declare that they have no competing interests.

Availability of data and materials

The dataset supporting the conclusions in this article could be made available up on request. However, it is worth noting that the analysis is done based on a publicly available cardiovascular disease model for Africa region East (AfrE) developed by WHO-CHOICE. All updates made as part of the contextualization have been described in the text, and the assumptions that went into the model have been provided in Tables 1, 2 and 3.

Ethics approval and consent to participate

Ethical approval was not required for this study as it is entirely based on publicly available data. The study didn't involve individual-persons' level data.

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Annex 1: Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

Section	Item no.	Recommendation	Reported on page no./line no.
Title and abstract			
Title	**1**	Identify the study as an economic evaluation or use more specific terms such as " cost-effectiveness analysis" and describe the interventions compared	Line 1-2
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	Line 43-73
Introduction			
Background and objective	**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	Line 87-129
Methods			
Target population and subgroups	**4**	Describe characteristics of the base-case population and sub-groups analyzed including why they were chosen	Line 136-142
Setting and location	**5**	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	Line 106-115, Line 131-137
Study perspectives	**6**	Describe the perspective of the study and relate this to the costs being evaluated	Line 208-216
Comparators	**7**	Describe the interventions or strategies being compared and state why they were chosen	Line 139-164
Time horizon	**8**	State the time horizon(s) over which the costs and consequences are being evaluated and say why appropriate	Line 194-198
Discount rate	**9**	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	Line 203-204, Line 227-228

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	Line 203-204
Measurment 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	Not applicable
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	Line 170-172
Measurement and valuation of preference-based outcomes	**12**	If applicable, describe the population and methods used to elicit preferences for outcomes	Line 193-194
Estimating resources and costs	**13a**	Single study-based economic evaluation: describe approaches used to estimate resource use associated with 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.	Not applicable

	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.	Line 216-227
Currency, price date, and conversion	**14**	Report the dates of the estimated resource quantities and unit cost. Describe the 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.	Line 221-228, Line 239-240
Choice of model	**15**	Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show the model structure is strongly recommended	Line 175, Line 187-203
Assumptions	**16**	Describe all structural or other assumptions underpinning the decision analytic model	Line 187-203
Analytic methods	**17**	Describe all the analytic methods for 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(e.g half-cycle corrections) to a model ; methods for handling population heterogeneity and uncertainty	Line 242-250

3

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 uncertainity where appropirate. Providing a table to show input values is strongly recommended	Tables 2 and 3
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 the incremental cost-effectiveness ratios.	Table 4
Characterizing uncertainity	**20a**	Single study-based economic evaluation : Describe the effects of sampling uncertainty for the estimated incremental cost, incremental effectiveness and incremental cost-effectiveness, together with the impact of methodological assumptions(such as discount rate, study perspective)	
	20b	Model-based economic evaluation: Describe the effects on the result of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	Line 302-313
Characterizing heterogeity	**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	Line 186, Line 388-392

4

Discussion			
Study findings, limitations, generalizability, and current knowledge	**22**	Summarize key study findings and describe how they support the conclusion reached. Discuss limitations and generalizability of the findings and how the findings fit with current knowledge	Line 316-415
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	Line 442-445
conflict of interest	**24**	Describe any potential for conflict of interest among 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	Line 438-440

10. Appendix 2: Ethical approval

Mieraf Taddesse Tolla
University of Bergen
Kalfarveien 31
5018 Bergen

2014/1978 Etiske og økonomiske aspekter ved kardiovaskulære sykdommer i Etiopia

Institution responsible for the research: University of Bergen
Chief Investigator: Mieraf Taddesse Tolla

Project description
Cardiovascular diseases (CVD) are becoming an emerging challenge to health systems in Ethiopia, especially in urban areas. Much of the burden could be averted through modification of risk factors and scale-up of proven prevention and treatment strategies.However, coverage of prevention and treatment strategies for CVD is low and mainly provided in private settings,putting households at a huge financial risk.We aim to fill the information gap on cost-effective prevention and treatment of CVD in an Ethiopian context, estimate of extent of financial risk households are facing related to CVD care and the potential financial risk protection and health benefit that could be generated through universal public finance anti-hypertensive treatment. We plan to use a number of data sources including primary and secondary data sources. We plan to collect primary data mainly on household expenditures made to receive CVD care through patient interview using a cross-sectional survey in Addis Ababa.

We hereby confirm that the Regional Committee for Medical and Health Research Ethics, section South-East D, Norway has received the project "The Ethics and Economics of cardiovascular disease in Ethiopia" for review. The project was discussed on the 26th of November 2014.

The ethics committee system consists of seven independent regional committees, with authority to either approve or disapprove medical research studies conducted within Norway, or by Norwegian institutions, in accordance with ACT 2008-06-20 no. 44: Act on medical and health research (the Health Research Act).

For the purposes of The Act, the following definition applies for medical and health research: activity conducted using scientific methods to generate new knowledge about health and disease, cf. § 4 of The Act.

The committee considers the purpose of this project to be to explore the ethics and economics of cardiovascular disease. The project will not generate new knowledge about health and disease. The above mentioned study therefore is considered to be outside of the remits of The Act, and is exempt from review in Norway, cf. §§ 2 and 4 of The Act. The project can be implemented without the approval by the Regional Committee for Medical Research Ethics.

Please do not hesitate to contact the Regional Committee for Medical and Health Research Ethics, section South-East D (REK Sør-Øst D) if further information is required.

Besøksadresse:
Gullhaugveien 1-3, 0484 Oslo

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All post og e-post som inngår i saksbehandlingen, bes adressert til REK sør-øst og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK sør-øst, not to individual staff

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Ref. No
ቀን 05/02/2015
Date

Dr. Miraf Tadesse Tolla
University of Bergen
Norway

Subject:- **Approval of project proposal**

I would like to congratulate you and your group that your Research proposal entitled **«Financial catastrophe and medical implement related to accessing health care for cardiovascular diseases (CVD)»** has been examined and approved for its scientific and ethical merits by our Scientific and Ethical Review Committee.

Looking forward to seeing the best outcome of this work as a contribution to solving the health problem of our country. I wish you a successful implementation.

Sincerely yours,

Yibeltal Assefa (MD,MSc,PHD)
Deputy Director General

CC:-
- General Directer Office
- SERO
EPHI

11. Appendix 3: Questionnaire

Economic impact of accessing prevention and treatment services for cardiovascular disease in Addis Ababa, Ethiopia-2015.

I. IDENTIFICATION	
Name of the health facility _____ Sub-city……. District…….	Diagnosis of the patient (please write all that is in the patient's record):
Interviewer's name and signature: _____ Date of the interview:	Day Month Year ☐☐ ☐☐ ☐☐☐☐ Time at the start of the interview……a.m/p.m

Consent

Hello! My name is _____. I am representing the Ethiopian Public Health Institute and University of Bergen. We are conducting a survey regarding the economic impact of accessing prevention and treatment services for cardiovascular diseases in Addis Ababa, Ethiopia. As you might be aware, cardiovascular diseases are becoming an increasing burden to the Ethiopian health system, particularly in urban areas. We therefore intend to study the financial risk households face related to accessing health services for prevention and treatment of cardiovascular disease. The evidence generated will inform the process of priority setting for cardiovascular disease care and facilitate formulation of policy that will address financial risk protection challenges faced by households. For this purpose, we would like to collect information on the direct and indirect out-of-pocket payments patients (households) make to access health services for cardiovascular diseases in Addis Ababa. We are conducting this survey in a sample of public and private hospitals providing cardiovascular disease care in Addis Ababa. The information you provide in this study will only be used for the purpose stated above.
The interview will take about 30 minutes. We would appreciate to get your consent to be part of this study. We reassure you that the information you provide will be handled anonymously and only for the purpose of the study. Do you agree to be part of this study?
Agree…….. Disagree…….

Thank you for agreeing to be part of this study. If you have any question or if there is anything unclear or if you would like to stop the interview at any point during the course of the interview, please feel free to do so at any time.

Should you have any question about the study please contact Dr.Mieraf Taddesse on +251912603313

I. Socio-demographic characteristics of the patient

No.	Question	Response	Remark
1	What is the patient's date of birth?	……/……../…… If date is not known, age in years….	
2	What is the patient's sex?	Female……..1 Male.....2	
3	What is the patient's highest educational attainment?	less than 8……...1 9-12…….2 Diploma…….3 Bsc/BA…….4 Msc/MA……5 PhD……6 No formal education.....8 Other(describe)……..9	
4	What is the patient's marital status?	Never married .....1 Married .....2 Divorced .....3 Widow.....4 Other (Specify) _____ 5	
5	What is the patient's current occupation?	Government employee…1 Private employee...2 Self-employed.3 Business man/women…4 Housewife/husehusband……5 Retired…….....6 Student…….....7 Farmer.....8 Other (specify)……9	Ask what is his/her specialty?
6	Where does the patient live?	Addis Ababa…….1 Outside Addis (specify)……2	
6a	What is the size of the household? (How many people live in the same housing unit as you and share food together)		

II. Patient medical history

7	When was the first time you ('you' refers to the patient hereafter) were diagnosed as having this heart/stroke /hypertension problem?	……../……../…….	
8	Are you currently taking any medication? (List all if yes, check medical record if patients couldn't provide the information)	Yes.....1..... No.....0	
9	Do you have a regular follow up outpatient visit with your doctor for the heart/stroke problem?	Yes……1 No…....0	If no to Q9, go toQ12
10	If yes to Q 09, how often?	Monthly……...1 Quarterly…….....2 Others (specify)……3	
11	How many outpatient visits did you have over the past 12 months?	……..regular follow up ……emergency visit ……other(specify)	
12	If no to Q 09, why not?	not prescribed…1 Other(specify).....3 Can't afford ……2	
13	Were you able to take all the care prescribed by your physician over the past 12months (treatments, investigations and procedures)?	Yes…….1 No……..0 (If no explain, which services you skipped? Why?)	If response is NO, ask why

	III. Out-patient care expenditure		
14	During the current out-patient department (OPD) follow-up visit, how much did you spend on the following items (in Ethiopian birr, ETB)? Read through all the items,	Total..... Drugs……... Laboratory /imaging……... Physiotherapy ……..... Physician (consultation) fee…… Transportation (to and from hospital)……. Attendant related expenses……... Other (describe)……...	
15	How did you cover the expense for these services? Multiple answers are possible. Provoke by asking what other source of finance the patient or house used to cover expenses	Current income of household(amount)……1 Own savings (amount).....2 Received support from family or friends other than household members(amount)…….....3 Borrowed (amount)……..4 Sold items (amount)……..5 Insurance (amount)……...6 Equb/Idir(amount)…….....7 Other (specify.....) (amount).....8	
16	If answer to Q15 includes borrowed, ask: a) how long the repay schedule is? b) if any interest rate applied to it?	a) Repay schedule…… b) Interest rate……..	
17	When did you have your last out-patient follow up visit (the one prior to the current)?	Date..... If date not known, report in months or weeks.....	
18	During this last out-patient follow up visit (reported in Q17) how much did you spend on the following (in ETB)? Read through all the items	Total..... Drugs……... Laboratory /imaging…… Physiotherapy ……..... Physician (consultation) fee…….. Transportation (to and from hospital)…… Attendant related expense……... Others (describe)……	

19	How did you cover the expense for these services? Multiple answers are possible. Provoke by asking what other source of finance the patient or house used to cover expenses	Current income of the household(amount)…….1 Own savings (amount)…….2 Received support from family or friends other than household members(amount)…….3 Borrowed (amount)……..4 Sold items (amount)…….5 Insurance (amount)……..6 Equb/Idir(amount)……..7 Other (specify) (amount)…….8	
20	If answer to Q19 includes borrowed, ask: a) how long the repay schedule is? b) if any interest rate applied to it?	a) Repay schedule…… b) Interest rate……..	
21	Over the past 12months including the data collection period, how much did you spend on out-patient follow-up visit related to your heart/stroke/hypertension in total?	Total spending over the past 12months…….	
22	How did you cover the expense for these services? Multiple answers are possible. Provoke by asking what other source of finance the patient or house used to cover expenses	Current income of the household (amount)…….1 Own savings (amount)…….2 Received support from family or friends other than household members (amount).....3 Borrowed (amount)……4 Sold items (amount)……..5 Insurance (amount)……...6 Equb/Idir(amount)…….....7 Other (specify) (amount amount).....8 If sold items, ask what item?	
23	If answer to Q22 includes borrowed, ask: a) how long the repay schedule is? b) if any interest rate applied to it?	a) Repay schedule…… b) Interest rate……..	
24	Where do you go for your last out-patient follow up visit?	Government hospital……..1 Private hospital……..2 Private cardiac center……3	
25	How far is the hospital that you go to receive out-patient follow-up visit from your residence (home)?	…….in km …….hour drive …….hour(minute) walk	
	IV. In-patient care expenditure		

26	Over the past 12months, how many times have you been hospitalized related to your heart/stroke/hypertension problem?		.....in number	
27	When were you hospitalized for the heart/stroke/hypertension problem?	(start with the most recent) from...../…/…. to…/…./…..	2nd most recent from...../…/…….. to……/…/…….	3rd most recent from…../.../……... to……. /…./…….
28	Where were you hospitalized?	Government…1 Private……..2 NGO hospital…3 Other…....4(specify)	Government…1 Private…2 NGO hospital…3 Other…....4(specify)	Government…1 Private…2 NGO hospital…3 Other…....4(specify)
29	What was your admission diagnosis?	Acute coronary syndrome….1 Stroke……...2 Heart failure...3 Hypertension….4 Other(specify)…… …….5	Acute coronary syndrome….1 Stroke……...2 Heart failure...3 Hypertension…..4 Other(specify)…… …….5	Acute coronary syndrome….1 Stroke……...2 Heart failure...3 Hypertension….4 Other(specify)…… …….5
30	What type of transport did you use to reach to the hospital?	Ambulance…..1 Own car……...2 Got a ride…….3 Taxi or rented car……4 Walking…..5 Local transport means such as cart ……..6 Other(Specify).....7	Ambulance…..1 Own car……...2 Got a ride…….3 Taxi or rented car……4 Walking…..5 Local transport means such as cart ……..6 Other(Specify).....7	Ambulance…..1 Own car……...2 Got a ride…….3 Taxi or rented car……4 Walking…..5 Local transport means such as cart……..6 Other(Specify).....7
31	During each hospitalization, how much did you spend on the below items?(in ETB)	Total expense	Total expense	Total expense .....
31.1	Hospital bed days			
31.2	Drugs			
31.3	Investigations/imaging			
31.4	Procedures			
31.5	Food			

31.6	Physiotherapy			
31.7	Transportation to and from the hospital			
31.8	Attendant related expenses(transportation, food..etc)			
31.9	Other(specify)			
32	How did you cover the cost? Multiple answers are possible. Provoke by asking what other source of finance the patient or house used to cover expenses	Current income of the household(amount)…1 Own savings (amount).....2 Received support from family or friends other than household members(amount)...3 Borrowed(amount)….4 Sold items(amount)…5 Insurance(amount)….6 Equb/idir(amount)…7 Other(specify) amount)...8 If sold items, ask what item?	Current income of the household (amount)…1Own savings (amount)..2 Received support family or friends other than household members (amount)...3 Borrowed(amount)….4 Sold items(amount)…5 Insurance(amount)…….6 Equb/idir(amount)…….7 Other(specify) amount)...8 If sold items, ask what item?	Current income of the household(amount)…1 Own savings (amount).....2 Received support from family or friends other than household members (amount)...3 Borrowed(amount)….4 Sold items(amount)…5 Insurance(amount)…… .6 Equb/idir(amount)……. 7 Other(specify)amount).. .8 If sold items, ask what item?
33	If answer to Q32 includes borrowed, ask: a) how long the repay schedule is? b) if any interest rate applied to it?	a) Repay schedule…… b) Interest rate……..	a) Repay schedule…… b) Interest rate……..	a) Repay schedule…… b) Interest rate……..

	V. Consequences	
34	Over the past one month, how much time did you spend or miss from your regular work due to your heart/stroke /hypertension problem or seeking health care for the illness? (Ask the patient even if they are not formally employed)	……hours ……days ……weeks
34.1	Over the past twelve month, how much time did you spend or miss from your regular work due to your heart/stroke/hypertension problem or seeking health care for the illness? (Ask the patient even if they are not formally employed)	……day ……weeks ……Months
35	(ask only for those employed) Do you get paid for the period you missed from work due to illness related to your heart/stroke/hypertension problem or while seeking care?	Yes, fully……1 Yes, partially…..2 No……...0
36	How many care givers do you have who attend to you on a regular basis?	.....in number
37	Over the past one month, how much time did your attendant(s) spend related to your heart/stroke/hypertension problem?	……hours ……day ……weeks
37.1	Over the past twelve month, how much time did your attendant(s) spend related to your heart/stroke/hypertension?	……day ……weeks ……Months
38	Did your or family member's work schedule affected due to your heart /stroke/hypertension problem? (multiple answer is possible)	Yes, I work less…..1 Yes, family members work more……..2 Yes, family members work less……..3 Yes, I work more…..4 No……0
39	Has your households' income changed due to your heart/stroke/hypertension problem?	Yes, it has decreased…...1 Yes, it has increased……..2 No, it hasn't change…….3
40	Does the out-of-pocket expenses made for you to receive health care for your heart/stroke/hypertension problem affect the household's other essential consumption? (such as food, education and other essential consumptions)	Yes.....1 No.....2
41	If answer to Q40 is yes, please describe the change?	Food quantity or amount has reduced …..1 Children's/family member's education has been disrupted....2 Other(describe)…….3

42	If you did not have to come to the hospital to seek care for your heart/stroke/hypertension problem, how would you have used this time? What would you have done? Read out options, multiple answers are possible	Regular work….1 Leisure……..2 School……3 Spend time with family/friends….4 Other(describe).....5
43	If you did not have to pay for your medical expenses out-of –pocket, how would you have used the money you spend to cover the costs for receiving the medical care for your heart/stroke/hypertension problem?	Save it……1 Buy more food…2 Pay for education/school….3 Other(describe)……...4
44	If there was a complete cure to your heart/stroke/hypertension problem, how much would you be willing to pay for it?	
	VI-Risk factors for CVD	
47	Did you ever smoke?	Yes, ……1 No……..0
48	If yes to Q47, ask for how long?	
49	Do you smoke currently?	Yes, regularly…1 Yes, occasionally…2 No……..0
50	If yes to Q49, ask how many cigarettes?	……..(amount)per day ……..(amount)per week ……..(amount)per month
51	Do you do regular physical exercise? (120 minutes of moderate exercise per week)	Yes…...1 No……0
52	Do you eat adequate fruits and vegetables in your daily meals? (5 portions or about 400gm every day)	Yes…...1 No……0
53	Do you have history of heart disease or history of premature death (at age younger than 65years) among your first degree relative?	1…Yes, a first degree relative has CVD 2…..Yes a first degree relative died of CVD 0….No, no one in my family has history of CVD
54.1	How much is the current weight of the patient?	Weight…….kg
54.2	What is the height of the patient?	Height……meter
54.3	What is the patient's blood pressure? (check chart)	Blood pressure(before treatment)…...…(s/d)mmHg Current blood pressure(after treatment)…...…(s/d)mmHg

54.4	What is the patient's lipid profile?	Total cholesterol……. Serum HDL…….. Serum LDL.....	
VII-Essential consumptions for patient's household			
55. On average how much does your household spend on the following essential consumptions in ETB?.....ETB in total per month			
55.1	Food/food items	…….per month	…….per year
55.2	Utilities (electricity, water , telephone)		
55.3	Education (School for children or self)		
55.4	House rent		
55.5	Health care (total for the household)		
55.6	Other(describe)		
56.1	Goods (properties) and utensils for the household use		
56.2	Clothes		
56.3	Maintenance of properties		
56.4	Reimbursement of loan (describe, if it is related to health spending)		
56.5	Others (describe)		
57	Estimated total annual household expenditure in ETB?		.....ETB
58	How much is the patient's current monthly net income in ETB?		.....per month
59	How much is the household's total monthly net income in ETB?		Monthly…… Annual……
	VIII-Household amenities		
60	Does the household own a house?	Yes……1 No…….0	

61	Do you live in your own house?	Yes….1 No…..0
62	If you live in a rental house, how much do you pay per month?	…….ETB
63	How many rooms does the house you live in have?	
64	How many of these goods does the household own?	Bicycle? ……..(number) Motor cycle?…….(number) Bajaj……(number) Car?……..(number)
65	What is the main source of drinking water for the household?	Pipe within the house….1 Public tap……2 Well in the house…3 Public well……4 Other.(describe)…..5
66	What source of energy does your household use for cooking?	Gas……..1 Electricity…...2 Kerosene…….3 Wood……4 Coal……..5 Other……6
67	What kind of toilet facility does your household use?	Private flush……..1 Public flush……...2 Private pit toilet….3 Public pit toilet…..4 Other……..5
68	How many of the following animals does the household own?	Cattle…… Milk cows…… Horses, donkey….. Goats…….. Sheep…… Chickens….. Others(describe)
69	Does the household have electricity?	Yes…..1 No…….0
70	Does the household own refrigerator?	Yes…..1 No…….0
71	Does the household own telephone/mobile phone?	Yes…..1 No……0
72	Does the household own television?	Yes…..1 No……0
73	Does the household own radio?	Yes…..1 No……0

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74	Does the household own a computer (desktop/laptop)?	Yes(how many)……..1 No…….0
75	Does the household own land for farming?	.....in hectar

Who was the respondent…….patient
……..family member (relationship to the patient)

Thank you very much for your participation, we would appreciate if you would be willing to give us your name and contact details. This is optional and the information will be used only to contact you again if we need to clarify something regarding the data collected. Please provide any final remark if you have any……

Name of the patient (only if respondent(s) are willing)……..
Contact address (tele-phone or e-mail only if respondents are willing)…….

Time at the end of the interview……a.m/p.m