UNIVERSAL PRIMARY PREVENTION IMPERATIVE:

The evidence for Primary Prevention worldwide

ACKNOWLEDGEMENTS

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Executive Summary

Background | Primary prevention—the prevention of disease prior to onset—if implemented broadly, has the potential to reap global public health, economic and social benefits.[1-10] Toward this end, conversation about universal health coverage has leaned toward a broader investment in primary prevention as a mainstay of population health improvement. The World Health Organization ("best-buy" package[11]) and the recent global health 2035 Lancet commission report[12] both strongly emphasized the inclusion of population-wide interventions to all universal health coverage plans.

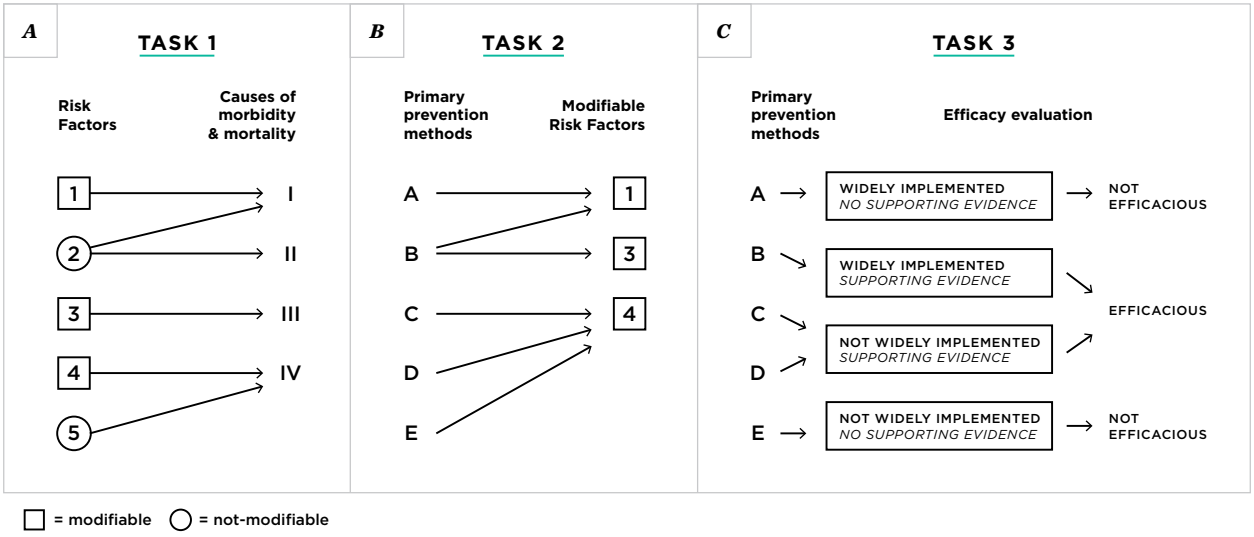
Despite the growing emphasis on primary prevention as an important means of population health improvement in principle, the literature about primary prevention across diseases and contexts remains limited, disparate, and disorganized. For example, there is limited consensus on which population-wide primary prevention services should be included in a baseline level of services in the context of universal health coverage.

There have been several notable efforts to systematically articulate the potential benefits of a broad array of primary prevention approaches including: the Disease Control Priorities in Developing Countries (DCPDC) project[7]; the WHO-CHOosing Interventions that are Cost-Effective (WHO-CHOICE) project[9]; and the Harvard Lifesaving Study.[13] However, these projects have been limited by both poor methodological rigor around estimates of intervention efficacy, and incomplete methodologies.

Here we reviewed the global primary prevention literature to identify evidence-based, efficacious primary prevention packages toward the prevention of top 10 causes of death and their risk factors across each of the World Health Organization's 21 global regions.

We identified the proximal modifiable risk factors; systematically reviewed and evaluated the peer-reviewed scientific literature for efficacious primary prevention interventions; and identified primary prevention packages based on the literature for the top ten causes of death by WHO region. Methods are described in detail in appendix A).

FIGURE 1. Literature review work-plan



The above figure details the overall methods employed in this literature review.

TABLE 1. Top 10 causes of death by global region, Global Burden of Disease 2013

REGION	CAUSES									
	1	2	3	4	5	6	7	8	9	10
North America, High Income	A	C	E	K	G	F	D	B	H	I
Asia Pacific, High Income	A	F	D	B	E	C	G	I	L	M
Australasia	A	N	C	E	G	K	F	D	B	O
Europe, Central	A	C	D	E	F	K	G	I	N	P
Europe, Western	A	C	E	D	K	F	G	B	I	O
Europe, Eastern	A	C	D	L	E	H	B	K	F	I
Oceania	O	N	B	A	G	C	F	H	E	Q
Asia, East	A	D	E	C	I	F	H	G	B	R
Asia, Central	A	C	D	B	N	F	I	H	E	G
Asia, Southeast	A	B	D	C	G	F	O	H	I	E
Asia, South	B	A	F	C	E	S	D	H	G	J
Latin America, Andean	B	A	N	F	H	G	C	T	D	E
Latin America, Central	A	G	B	C	H	U	F	T	L	D
Latin America, Tropical	A	B	C	G	F	D	H	U	E	L
Latin America, Southern	A	F	C	B	N	G	E	D	H	K
Caribbean	A	B	N	C	G	D	F	H	I	E
North Africa and Middle East	A	B	C	G	D	F	H	E	I	V
Sub-Saharan Africa, Central	B	F	W	A	N	J	Q	S	V	G
Sub-Saharan Africa, Eastern	B	J	A	W	F	S	Q	N	H	X
Sub-Saharan Africa, Southern	B	J	A	N	F	G	D	H	S	X
Sub-Saharan Africa, Western	B	W	S	H	F	J	A	N	V	G
Global	A	B	C	D	E	F	G	H	I	J

A	Cardiovascular Disease
B	Prematurity and low birth weight
C	Ischemic heart disease
D	Cerebrovascular disease
E	Trachea, bronchus, lung cancers
F	Chronic obstructive pulmonary disease
G	Diabetes
H	Road traffic accidents
I	Hypertensive heart disease
J	HIV/AIDS
K	Neurodegenera-tive disorder
L	Self-inflicted injuries
M	Stomach cancer
N	Birth asphyxia and birth trauma
O	Colon and rectum cancers
P	Inflammatory heart disease
Q	Diarrheal diseases
R	Hepatitis
S	Neonatal infections
T	Renal disease
U	Violence
V	Congenital disease
W	Malaria
X	Tuberculosis

Notes. Causes of death are ranked by WHO regional income. Color key: non-communicable diseases in blue, infectious diseases are in red, human-made disease in orange, and maternal and child related in green

After identifying the top ten causes of death per region, risk factors for each of these main twenty-four causes of death were searched and identified from *UpToDate*, a medical information database for clinicians of prevention protocols[16] Twenty-five modifiable proximal risk factors were thus documented.

Interventions were selected for inclusion into packages based on their individual quality scores, effect estimates, and applicability of intervention. Interventions were prioritized as more applicable if they targeted the main cause of death (as opposed to a proximal risk factor), addressed the population at risk for the cause of death, and uniqueness (for implementation methodological breadth, multiple interventions with similar methods were not included in the same package). Table 2 shows a brief description of the interventions included and related citations.

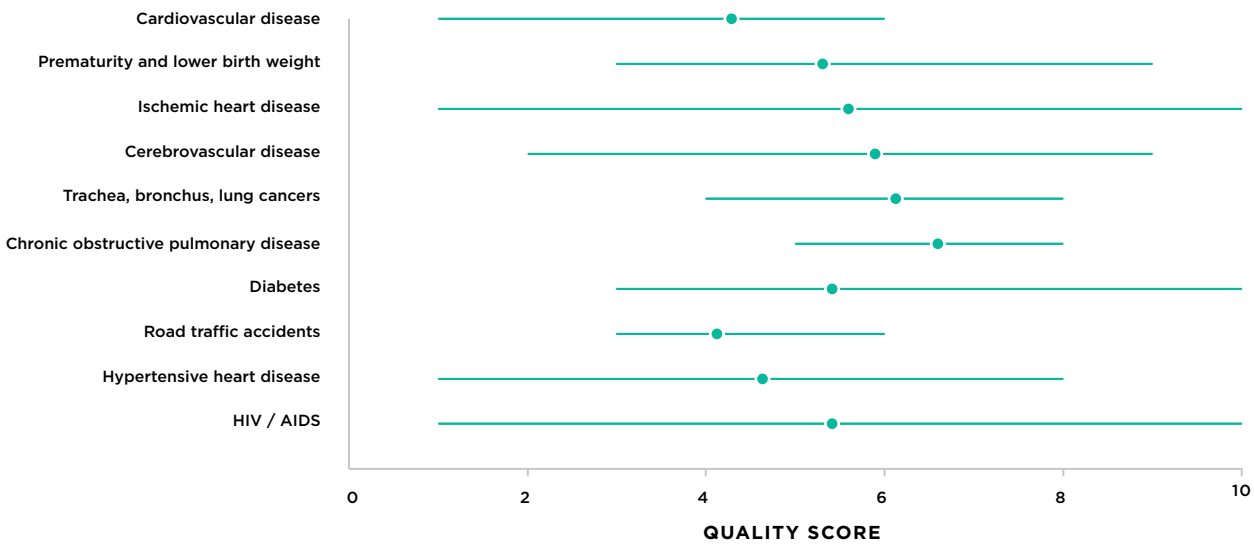


FIGURE 3. Mean intervention quality score for top 10 causes of death, globally

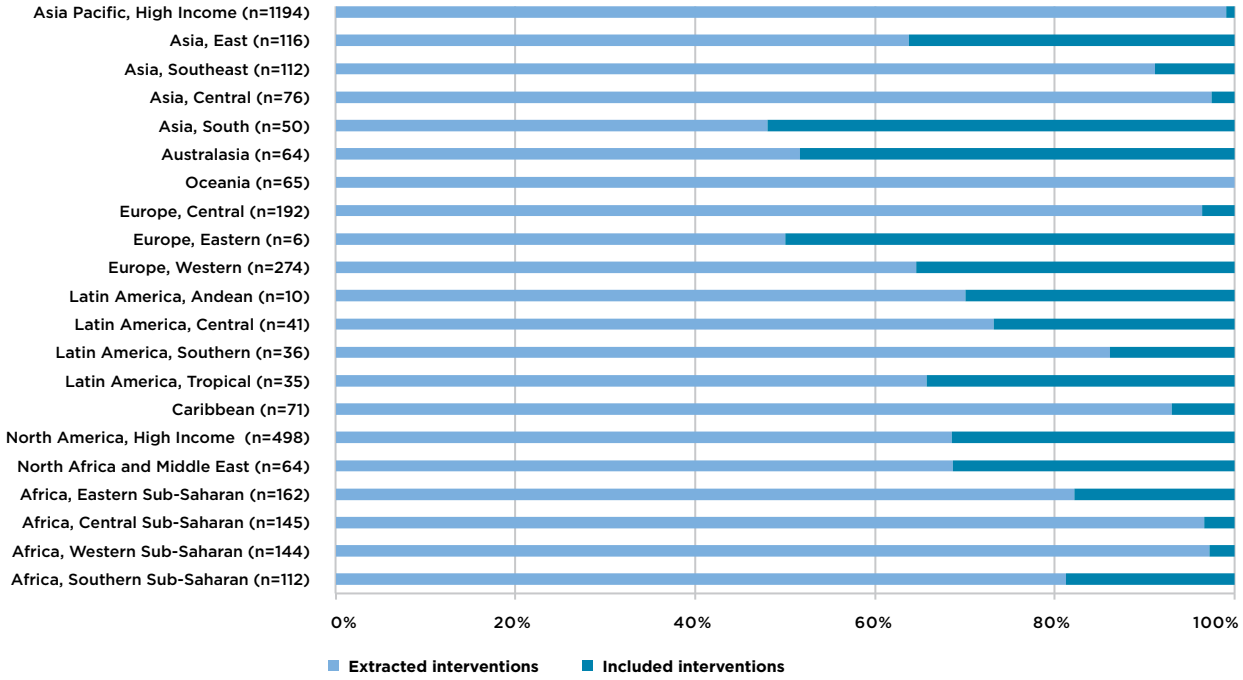
The above figure shows the mean quality score for selected interventions as a dot with the lines representing the range of quality scores included in the prevention packages addressing the top 10 causes of death, globally.

TABLE 2. Select Interventions per the top 10 causes of death globally

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. **Cardiovascular disease**	Metformin or intensive lifestyle change[14]	Diet program (protein)[15]	Lifestyle counseling[16]
2. **Prematurity and lower birth weight**	Multiple micronutrient supplementation[17]	Micronutrient supplementation, daily in healthy women[18]	Mebendazole[19]
3. **Ischemic heart disease**	Clopidogrel[20]	Exercise promotional campaign[21]	Rehabilitation with family support[22]
4. **Cerebrovascular disease**	Weight-bearing exercise program[23]	Health belief model based motivation[24]	Tailored dietary advice and education[25]
5. **Trachea, bronchus, lung cancers**	Nurse consultation and self-help manual[26]	Motivational interviewing[27]	State cigarette taxes[28]
6. **Chronic obstructive pulmonary disease**	Azithromycin[29]	Tiotropium[30]	Smoking cessation, doctor consultation[31]
7. **Diabetes**	Metformin[32]	Tailored dietary advice and education[33]	Pioglitazone[34]
8. **Road traffic accidents**	Driving education session[35]	Helmet promotion, cyclists[36]	Designated driver program[37]
9. **Hypertensive heart disease**	Familial risk assessment[38]	Nurse care management[39]	Losartan-based hypertensive treatment[40]
10. **HIV/AIDS**	Motivational interviewing[41]	Motivational incentives[42]	Familial HIV risk reduction in adolescents[43]

The above table shows select interventions that were included in prevention packages along with their corresponding original citations. Interventions were selected based on their individual quality score, effect estimate, and applicability of intervention.

FIGURE 4. Interventions included by region



The above figure presents the percentage of interventions included in the final regional prevention protocol packages out of the total interventions, in that region, that were extracted and thoroughly reviewed.

The final primary prevention packages were created, by region, based on published interventions that addressed one of the top ten causes of death in that region. Table 3 presents the percentages of deaths without locally published intervention evidence by WHO region and main cause of death. In the final packages, interventions were included that were not studied within the region, when necessary, giving first priority to high quality interventions that were studied within the same WHO super-region, and if that was not possible, then identifying the most rigorous intervention for that cause of death that has been published, irrespective of the study sample region. Table 3 shows that 100% of the deaths attributed to the top ten causes of death in Central Asia (region 2) and Oceania (region 17) had no locally studied interventions identified in our process. Conversely Western Europe's primary prevention package included at least one intervention studied locally in each of the top ten causes of death except for trachea, bronchus, and lung disease, which accounted for 9% of the top ten causes of death.

TABLE 3. Percentage of deaths without locally published intervention evidence, by WHO region

	WHO REGION																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Birth (newborn)		7%				20%	13%	3%			14%						9%			7%	5%
CVD		32%	28%	19%	23%	25%	23%				15%	18%	24%	24%	26%		3%	7%	7%	9%	5%
Cerebrovascular		10%		6%	12%				13%		5%	5%	8%							3%	
COPD		6%		13%	7%	7%	6%	6%	3%		11%	8%	13%	9%	8%		1%	8%	7%	7%	6%
Colon & rectum					7%	3%											76%				
Congenital															5%			4%			5%
Diabetes		3%				7%	9%	4%			9%	18%	8%	11%			3%	3%		6%	4%
Diarrheal																		7%			
Renal											6%	6%					1%				
Hypertensive heart		5%					4%														
HIV/AIDS																		7%			6%
Ischemic heart		20%			9%		11%	17%	25%		8%						2%				
Malaria																					14%
Neurodegenerative						7%		4%	3%				5%			10%					
Neonatal infections				6%									9%								
Prematurity	10%	9%					16%					12%	5%				5%				
Road accidents		5%	7%	5%			5%		3%		9%	8%		9%			1%			3%	
Self-inflicted									4%			6%		5%							
Stomach cancer	4%																				
Trachea, bronchus, lung	9%	3%			5%	8%	4%	7%	3%	9%	4%		8%	6%	5%		1%				
Total missing	23%	100%	35%	50%	63%	77%	91%	41%	51%	9%	81%	81%	80%	64%	46%	10%	100%	36%	14%	36%	45%

The above table shows the percentage of regional top ten deaths for which no published rigorous interventions were identified and thus included in the primary prevention packages. Specific notes on abbreviations: CVD = cardiovascular disease; COPD = chronic obstructive pulmonary disease; Prematurity includes low birth weight; WHO regional codes 1 = Asia Pacific, High Income; 2 = Asia, Central; 3 = Asia, East; 4 = Asia, South ; 5 = Asia, Southeast ; 6 = Australasia; 7 = Caribbean; 8 = Europe, Central; 9 = Europe, Eastern; 10 = Europe, Western; 11 = Latin America, Andean; 12 = Latin America, Central; 13 = Latin America, Southern; 14 = Latin America, Tropical; 15 = North Africa and Middle East; 16 = North America, High Income; 17 = Oceania; 18 = Sub-Saharan Africa, Central; 19 = Sub-Saharan Africa, Eastern; 20 = Sub-Saharan Africa, Southern; 21 = Sub-Saharan Africa, Western. Many regions were not missing any locally published interventions, for those, there will be a blank, thus each region will not necessarily have 10 entries.

Emerging from this work are calls to researchers and policymakers alike. For researchers, there were several important limitations to the primary prevention literature. First, as shown in Table 3, there are many common causes of death for which the research regarding primary prevention is thin. Further, we were unable to identify any interventions against top 10 causes of death in Oceania (651,368) or Central Asia (962,653). Second, the quality of existing prevention science literature is poor. Based on our quality scale rating (with a high score of 17), no identified studies scored higher than 10, meaning that most studies failed to meet even half of the quality benchmarks on which our scores were based. Third, in addition to the poor general quality of the literature, there was substantial heterogeneity in quality across disease and context.

The paucity of research about primary prevention in various contexts and for various causes of disease suggests a potential research equity challenge. The paucity of research in low-income contexts limits our capacity to intervene decisively in these contexts, where disease and death are more prevalent. This suggests that particular attention ought be paid to these contexts in the future. Furthermore, the substantial heterogeneity we observed reflects a poor penetration of rigorous research methods, particularly in low-income contexts. Finally, as prevention science is generally of limited quality, the rigor of prevention policy based thereon is limited. Therefore, prevention scientists would benefit from agreed upon, established, standards of rigor as well as consistent funding to support high quality research in this area.

For policymakers, nevertheless, this work does suggest that, although of limited quality in many contexts, there are important primary prevention interventions that have not penetrated adequately that stand to improve population health tremendously. For example, trachea, bronchus, and lung cancers remain an important cause of death globally, and in most of the WHO regions, specifically. Among the most efficacious interventions we found was a state cigarette tax. However, despite this, achieving cigarette taxes in low- and middle-income countries remains illusive. Hence, the limitations of the literature about primary prevention notwithstanding, there remain tremendous opportunities to reduce morbidity and mortality and to reap the social and economic consequences thereof through investment in efficacious primary prevention.

Digging deeper: A regional perspective | This document is organized by WHO region. Each subsequent chapter presents the specific details of the prevention packages identified for each region, based on their top ten causes of mortality. The chapters start with a brief regional overview identifying the countries within the region, specifies the top ten causes of death (including WHO mortality estimates), lists the top three interventions per cause of death, provides a graphic summary of the quality scores of those included interventions, and provides a succinct narrative description of each of the interventions that was published within the region. To be thorough, interventions without published data are at times presented in the regional package, however the specific descriptions of each intervention will only be detailed in the region for which it was studied.

Asia Pacific, High Income

WHO Region 1, High Income Asia Pacific, is part of the WHO super region High Income and consists of four countries: Brunei Darussalam, Japan, the Republic of Korea, and Singapore. We identified 12 unique efficacious locally-studied interventions in this prevention package, of which seven were conducted in Japan,[44-50] three in Republic of Korea,[51-53] and two were regional interventions.[54; 55] Quality scores ranged from 4 to 8 within this region.

Top 10 causes of death in 2013 (n= deaths)

1. Cardiovascular disease (n= 489,607)
2. Chronic obstructive pulmonary disease (n= 282,716)
3. Cerebrovascular disease (n= 238,605)
4. Prematurity and low birth weight (n= 195,587)
5. Trachea, bronchus, lung cancers (n= 179,057)
6. Ischemic heart disease (n= 159,312)
7. Diabetes (n= 133,934)
8. Hypertensive heart disease (n= 97,205)
9. Self-inflicted injuries (n= 94624)
10. Stomach cancer (n= 81951)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in High Income Asia Pacific

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Lifestyle counseling and modification[44]	Metformin or intensive lifestyle change[14]	Diet program (protein)[15]
2. Chronic obstructive pulmonary disease	Proton pump inhibitor therapy[45]	Azithromycin[56]	Tiotropium[30]
3. Cerebrovascular disease	Lifestyle counseling and modification[46]	Health belief model based motivation[24]	Tailored dietary advice and education[25]
4. Prematurity and low birth weight	Micronutrient supplementation, daily in healthy women[18]	Maternal tailored counseling sessions[57]	Cervical Pessary in short cervix cases [58]
5. Trachea, bronchus, and lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
6. Ischemic heart disease	Cilostazol after DES implantation[51]	Distal protection device[52]	Celecoxib[53]
7. Diabetes	Lifestyle intervention to prevent type II diabetes mellitus[47]	Metformin in obese children[32]	Tailored dietary advice and education[33]
8. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Familial risk assessment[38]
9. Self-inflicted injuries	Health education and depression screening[49]	Postcard message intervention after hospital-treated self-poisoning[60]	Psychotherapy after self-poisoning[61]
10. Stomach Cancer	Early treatment of helicobacter pylori[62]	Counseling and medicinal eradication regimen[63]	Daily alltridum and selenium supplement[64]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; High Income Asia Pacific

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Chronic obstructive pulmonary disease							✓			
Cerebrovascular Disease							✓	✓		
Prematurity and low birth weight										
Trachea, bronchus, and lung cancers										
Ischemic Heart Disease						✓	✓			
Diabetes				✓						
Hypertensive Heart Disease				✓	✓					
Self-Inflicted Injuries					✓					
Stomach cancer										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cardiovascular disease | One local protocol was effective at improving cardiovascular disease outcomes. It aimed to prevent new vascular events using a lifestyle intervention in patients with noncardioembolic mild ischemic stroke.[44] The intervention group increased physical activity ($p<0.001$), decreased systolic blood pressure ($p<0.001$), and decreased salt intake ($p = 0.018$) by significantly more than the control group.[44]

Chronic obstructive pulmonary disease | One protocol was effective in improving COPD related outcomes.[45] In this randomized controlled trial, the intervention of proton pump inhibitor therapy in addition to conventional therapies among older, ex-smoker patients with COPD resulted in lower number of COPD exacerbations 0.34 ± 0.72, compared to control group, 1.18 ± 1.40 ($p<0.001$) and the adjusted odds ratio (aOR) for having greater than or equal to one exacerbation a year in the PPI group was 0.23 ($p = 0.004$) compared to the control group.[45]

Cerebrovascular disease | One protocol focused on the prevention of cerebrovascular disease through an educational and lifestyle intervention on physical activity.[46] Physical activity after 5 years of intervention was significantly higher in the intervention group than in the control group ($p = 0.028$), and the intervention group was associated with an approximately 40% significant risk reduction for stroke when adjusting for significant univariate correlates ($p = 0.04$).[46]

Ischemic heart disease | Three protocols were found efficacious in ischemic heart disease outcomes.[51-53] They assessed triple (aspirin, clopidogrel, and cilostazol) or dual (aspirin and clopidogrel) antiplatelet therapy in patients undergoing successful drug-eluting stent implantation,[51] primary angioplasty with distal protection (DP) group or angioplasty alone in acute myocardial infarction patients,[52] and celecoxib regimen with paclitaxel-eluting stent intervention in patients with angina pectoris or positive stress test and native coronary artery lesions.[53] Studies found 12 month myocardial infarction (hazard ratio (HR): 0.233, $p = 0.0097$) and stent thrombosis (HR = 0.136, $p = 0.0036$) significantly lower in triple therapy group,[51] after-angioplasty achievement of final thrombolysis in mycoardial infarction (TIMI) grade 3 and TIMI myocardial perfusion Grade 3 more frequent in DP group ($p = 0.016$), baseline and hyperemic average peak velocities significantly higher ($p = 0.029$ and $p = 0.014$) and hyperemic microvascular resistance indices significantly lower ($p = 0.036$) in DP group, and patients in DP group with more favorable phasic flow pattern ($p = 0.035$),[52] and mean in-stent late luminal loss lower in celecoxib group (0.26 mm, 95% confident interval (CI): 0.12-0.40) and frequency of secondary outcomes lower at 6 months in celecoxib group.[53]

Diabetes | One efficacious protocol focused on alleviating the onset of diabetes through a lifestyle intervention among individuals in Japan with impaired glucose tolerance.[47] The study found that the incidence of the development of type II diabetes mellitus was significantly lower in the intervention group that in the usual care group ($p = 0.04$).[47]

Hypertensive heart disease | One protocol was effective in reducing risk of hypertensive heart disease.[55] This randomized trial included an intervention that was a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients. At week 52, mean absolute Framingham 10-year coronary heart disease risk was 12.5% in PMI group and 16.3% in the usual care group (p<0.001). Compared to the usual care group, the PMI group had greater change from baseline at week 52 for systolic blood pressure (-10% vs. -19.8%; p<0.001), diastolic blood pressure (-5.3% vs. -10.5%; p<0.001), total cholesterol (0.7% vs. -17.4%; p<0.001), and LDL cholesterol (2.7% vs. -25.6%; p<0.001). A sub-analysis of this protocol showed that PMI was more effective in reducing calculated coronary heart disease risk compared with usual care in individuals living in both Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001).[54]

Self-inflicted injuries | One protocol was efficacious in preventing suicide amongst a population of elderly in rural Japan through depression screening, follow-up and health education.[49] The intervention reduced the female risk of completing suicide by 70% (0.14-0.67; p = 0.003) with no change in risk for males.[49]

Prematurity and low birth weight, trachea, bronchus, and lung cancers, and stomach cancer had no rigorous and effective interventions published within this region.

Asia, Central

WHO Region 2, Central Asia, is part of the WHO super region Eastern Europe and Central Asia and consists of nine countries: Albania, Armenia, Azerbaijan, Georgia, Kyrgyzstan, Mongolia, Tajikistan, Turkmenistan, and Uzbekistan. There were no rigorous and effective interventions published within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 310,827)
2. Ischemic heart disease (n= 187,984)
3. Cerebrovascular disease (n= 97,435)
4. Prematurity and low birth weight (n= 84,669)
5. Birth asphyxia and birth trauma (n= 64,432)
6. Chronic obstructive pulmonary disease (n= 59,391)
7. Hypertensive heart disease (n= 50,354)
8. Road traffic accidents (n= 43,460)
9. Trachea, bronchus, lung cancers (n= 32,325)
10. Diabetes (n= 31,776)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Central Asia

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Ischemic heart disease	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]	Rehabilitation with family support[22]
3. Cerebrovascular disease	Exercise to Enhance Mobility Post-stroke[23]	Health Belief Model Telephonic Intervention[24]	Tailored dietary advice and education[25]
4. Prematurity and low birth weight	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation, daily for healthy women[18]	Mebendazole supplementation[19]
5. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
6. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
7. Hypertensive heart disease	Family Healthware web-based tool[38]	Nurse care management[39]	Losartan[40]
8. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
9. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
10. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

There were no rigorous and effective interventions published within this region.

Asia, East

WHO Region 3, East Asia, is part of the WHO super region East Asia and Pacific and consists of the following countries: China (including Taiwan) and Democratic People's Republic of Korea. There were 17 locally studied efficacious interventions included in our package, of which nine were conducted in China,[31; 68; 70-76 77; 78] two were conducted in Taiwan,[79; 80] two were conducted in multiple countries in the region.[54; 55] Quality scores ranged from 4 to 7 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 3,853,266)
2. Cerebrovascular disease (n= 1,979,965)
3. Trachea, bronchus, lung cancers (n= 1,524,945)
4. Ischemic heart disease (n= 1,442,662)
5. Hypertensive heart disease (n= 1,267,557)
6. Chronic obstructive pulmonary disease (n= 1,127,733)
7. Road traffic accidents (n= 925,426)
8. Diabetes (n= 539,603)
9. Prematurity and low birth weight (n= 534,959)
10. Hepatitis (n= 492,521)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in East Asia

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups [16]
2. Cerebrovascular disease	Cardiac Rehabilitation Program[72]	Remote Ischemic Post-conditioning[73]	Pharmacist Drug education[74]
3. Trachea, bronchus, lung cancers	Smoking behavior intervention[31]	Motivational interviewing[27]	Communities That Care program[59]
4. Ischemic heart disease	Xuezhikang[79]	Pharmacist Drug education[74]	Tranexamic Acid on Clopidogrel[68]
5. Hypertensive heart disease	Electronic follow-up system[75]	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]
6. Chronic obstructive pulmonary disease	Practitioner education and smoking behavior[31]	Integrated education, treatment and rehabilitation[76]	Azithromycin[56]
7. Road traffic accidents	Road safety and helmet promotion[81]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
8. Diabetes	Diabetic smoking cessation program[70]	Integrated community management of diabetes[77]	Metformin in obese children[32]
9. Prematurity and low birth weight	In-hospital developmental care[80]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation[18]
10. Hepatitis	Intravenous HBIG administration[78]	Hepatitis B vaccination[71]	Protein supplementation in Hepatitis-C patients[82]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; East Asia

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Cerebrovascular disease					✓		✓✓			
Trachea, bronchus, lung cancers						✓				
Ischemic heart disease				✓			✓✓			
Hypertensive heart disease				✓	✓✓					
Chronic obstructive pulmonary disease							✓✓			
Road traffic accidents										
Diabetes					✓		✓			
Prematurity and low birth weight						✓				
Hepatitis				✓	✓					
Coronary Heart Disease					✓					

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cerebrovascular disease | Three protocols focused on the prevention of cerebrovascular disease through improvement of risk factors such as blood pressure and serum lipids.[72-74] The first protocol examined the effect of a nurse-led cardiac rehabilitation program on health behaviors and cardiac physiological risk parameters and found that compared to the control group, the intervention group performed significantly better in walking (p<0.001), step II diet adherence (p<0.001), and medication adherence (p = 0.029); experienced a greater reduction in serum lipids including triglyceride (p = 0.008), total cholesterol (p<0.001), and low-density lipoprotein (p<0.001); and had significantly better control of systolic (p = 0.021) and diastolic blood pressure (p = 0.030) at three months, with the majority of these impacts maintained at 6 months.[72] A second protocol determined the cardio-protective effect of remote ischemic post-conditioning on children undergoing cardiac surgery.[73] Compared with the control group, the postoperative levels of cTnI (p = 0.037) and CK-MB (p = 0.046) were significantly reduced in the intervention group.[73] The MAP was higher (p = 0.008) and intensive care unit stay (36.87 hours vs. 60.57 hours, p = 0.006) and postoperative hospital stay (8.56 days vs. 10.06 days, p = 0.048) were significantly shorter in the intervention group than in the control group.[73] The third protocol examined the effect of a pharmacist intervention on the control of modifiable risk factors in ischemic stroke outpatients.[74] At baseline, 43% of the control group and 40% of the intervention group had adequate blood pressure control (p = 0.64), 27% and 13% respectively had adequate lipid control (p = 0.09), and 36% and 21% respectively had adequate glucose control (p = 0.15).[74] Post-intervention, the corresponding proportions were for BP 43% vs. 83% (P < 0.001), lipid 27% vs. 40% (p = 0.16) and glucose 46% vs. 35% (p = 0.40).[74]

Trachea, bronchus, lung cancers | One intervention efficaciously reduced smoking prevalence in order to prevent trachea, bronchus, and lung cancers.[31] This protocol focused on behavioral smoking-cessation counseling.[31] Study participants were Chinese COPD patients who identified as smokers during the start of the study period.[31] This protocol was a randomized control trial with one group receiving a behavioral intervention and another group receiving usual care.[31] Self-reported smoking abstinence prevalence was significantly higher from 24 to 30 months of study follow-up in the intervention group as compared to the control group (p<0.001).[31]

Ischemic heart disease | Three protocols were found efficacious in ischemic heart disease related outcomes.[68; 74; 79] Studies examined lipid-lowering therapy with xuezhikang in patients with coronary heart disease aged 65 and older through randomized, double-blind, placebo-controlled trial,[79] management of modifiable risk factors in a group of ischemic stroke outpatients in a randomized controlled study,[74] and clopidogrel bisulfate and tranexamic acid in patients

receiving coronary artery bypass grafting (CABG) especially exposed to antiplatelet agents in a multicenter randomized and blinded trial.[68] Results found xuezhikang therapy reduced incidence of coronary events 36.9% (p = 0.001), death from coronary heart disease 31.0% (p = 0.04), all-cause mortality 31.9% (p =0.01), stroke 44.1% (p = 0.04) and need for percutaneous coronary intervention or coronary artery bypass graft 48.6% (p = 0.07) and malignancies (p = 0.03)[79], increased proportion of adequate control of BP (p = 0.00), lipid (p = 0.16) and flucose (p = 0.40)[74], and transexamic acid to reduce blood loss (-278 mL, 95% CI: -380 to -176; p<0.001), major bleeding (RD=-19.5, 95% CI: -27.7 to -11.4; p<0.001), volume of red blood cells transfused (mean difference (MD) = -2.58 U, 95% CI: -3.61 to -1.55; p<0.001) and red blood cell transfusion exposure (risk difference (RD) = -18.9, 95% CI: -26.4 to -11.4; p<0.001).[68]

Hypertensive heart disease | Three randomized trial protocols were effective in reducing risk of hypertensive heart disease.[54; 55; 75] Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients[54; 55] and an electronic follow-up system to promote secondary prevention of coronary heart disease among individuals who underwent percutaneous coronary intervention.[75] Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55] greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001),[55] and the intervention group fairing better than the control group in total cholesterol levels (3.76 vs. 3.99; p = 0.002),[75] systolic blood pressure (135.71 vs. 142.41; p = 0.0001),[75] and low-density lipoprotein cholesterol (2.42 vs. 2.72; p = 0.0001) at 1 year of follow-up.[75]

Chronic obstructive pulmonary disease (COPD) | Two protocols, both randomized controlled trials, were effective in improving COPD related outcomes.[31;76] Interventions included a behavioral intervention in which general practitioners oversaw and advised patients with COPD registering in their healthcare centers to quit smoking[31] and a community based integrated intervention that included systematic health education, intensive and individualized intervention, treatment, and rehabilitation for early prevention and management of COPD.[76] Results included higher rates of abstinence from smoking (46.4% vs. 3.4%, p<0.001)[31] and higher rates of smoking cessation (21% vs. 8%, p<0.004)[76] in intervention group compared to control group, lower annual rate of decline in forced expiratory rate in one second (FEV1) in the intervention group compared to the control group, with an adjusted difference of 19 ml/year and 0.9% of predicted values (all p<0.05),[76] and lower cumulative death rates from all causes (1% vs. 3%, p<0.009) in the intervention community than in the control community.[76]

Diabetes | There were two efficacious protocols aimed at the prevention of diabetes.[70; 77] One study focused on a culturally sensitive, diabetic specific smoking cessation intervention which resulted in significantly higher odds for quitting smoking as compared to an intervention group that only received a regular smoking intervention (odds ratio (OR) =8.4, 95% CI = 4.1-17.1; p<0.001).[70] Another study displayed the effectiveness of a CCM framework (Chronic Care Model) in terms of glycemic control and diabetes management for adults over the age of 20 in a low-to-middle income country (OR for HbA1c = 6.0, 95% CI = 2.4-15.1; p<0.001).[77]

Prematurity and low birth weight | There was one protocol that had an effect on neonatal morbidity, growth, and development.[80] The intervention aimed to see how effective in-hospital developmental care was among preterm infants with very low birth weight and found that the intervention groups had lower incidences of stage II-III retinopathy (OR = 0.34, p = 0.01) and feeding desaturation (OR = 0.32, p = 0.05).[80]

Hepatitis | There were two efficacious interventions that focused on the prevention of hepatitis.[71; 78] One intervention administered an intravenous Hepatitis B immune globulin (HBIG) to pregnant women, which resulted in newborns in the intervention group having significantly lower rates of Hepatitis B in umbilical cord blood (21.4%, p<0.01).[78] Another intervention administered a neonatal hepatitis B vaccination in order to measure the efficacy on liver cancer and other liver diseases.[71] In this study, newborns in China were given the vaccination, and the incidence rate of infant fulminant hepatitis was significantly lower in the intervention group as compared to the control group with efficacies of 69% (95% CI for hepatitis: 34%-85%; p = 0.0024).[71]

Cardiovascular disease and road traffic accidents had no rigorous and effective interventions published within this region.

Asia, South

WHO Region 4, South Asia, is part of the WHO super region South Asia and consists of the following six countries: Afghanistan, Bangladesh, Bhutan, India, Nepal, and Pakistan. There were 13 efficacious interventions included in our package, of which nine were conducted in India,[70; 83-90] one in Bangladesh,[91] one in Nepal,[92] and two in Pakistan.[93; 94] Quality scores ranged from 4 to 7 within this region.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 4,370,233)
2. Cardiovascular disease (n= 3,495,478)
3. Chronic obstructive pulmonary disease (n= 2,375,455)
4. Ischemic heart disease (n= 1,883,212)
5. Trachea, bronchus, lung cancers (n= 1,165,681)
6. Neonatal infections (n= 1,108,918)
7. Cerebrovascular disease (n= 1,027,755)
8. Road traffic accidents (n= 983,736)
9. Diabetes (n= 928,676)
10. HIV/AIDS (n= 712,589)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in South Asia

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Labetalol or methyldopa, standard care[83]	Maternal micronutrient supplementation[84]	Home –based neonatal care[85]
2. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
3. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
4. Ischemic heart disease	Polypill to reduce Cardiovascular Disease[86]	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]
5. Trachea, bronchus, lung cancers	Rural community-based smoking cessation[87]	Motivational interviewing[27]	Communities That Care program[59]
6. Neonatal infections	Trained birthing assistant-based intervention[93]	Chlorhexidine or soap and sanitary education[92]	Sunflower seed oil or Aquaphor on nosocomial infections in newborns[91]
7. Cerebrovascular disease	Community-based lifestyle intervention[94]	Exercise to Enhance Mobility Post-stroke[23]	Health Belief Model Telephonic Intervention[24]
8. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education
9. Diabetes	Diabetic smoking cessation program[70]	Metformin in obese children[32]	Tailored dietary advice and education[33]
10. HIV/AIDS	Frontiers Prevention Project[88]	HIV prevention in truck drivers[89]	HIV prevention education in RHANI wives[90]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; South Asia

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight				✓		✓✓				
Cardiovascular disease										
Chronic obstructive pulmonary disease										
Ischemic heart disease						✓				
Trachea, bronchus, lung cancers						✓				
Neonatal infections								✓✓✓		
Cerebrovascular disease							✓			
Road traffic accidents										
Diabetes							✓			
HIV/AIDS					✓					

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | There were three efficacious protocols aimed at alleviating prematurity and low birth weight.[83-85] In one study, pregnant women were given either labetalol or methyldopa as well as standard care in order to reduce pregnancy-induced hypertension, which is associated with adverse fetal outcomes.[83] The antihypertensive therapy proved to be significantly effective in reducing rates of severe pregnancy-induced hypertension ($p = 0.005$) and having lower incidence of adverse perinatal events ($p = 0.016$).[83] Another efficacious intervention gave undernourished pregnant women a multi-micronutrient supplement in a randomized, double-blind experiment, which resulted in heavier infants in the intervention group as well as a decline in the incidence of low birth weight compared to the control group ($p = 0.006$).[84] A home-based neonatal care intervention was also found effective among villages in India where the incidence and burden of both infectious and care-related neonatal morbidities were reduced by almost half as compared to a historical control group ($p<0.001$).[85]

Ischemic heart disease | One protocol was efficacious in reducing systolic blood pressure and LDL-cholesterol as risk factors for cardiovascular disease[86]. A randomized, double-blind placebo-controlled trial of a polypill (aspirin 75mg, lisinopril 10mg, hydrochlorothiazide 12.5mg, and simvastatin 20mg) in patients with an estimated 5-year cardiovascular disease risk over 7.5% found polypill treatment to reduce systolic blood pressure by 9.9 (95% CI: 7.7-12.1) mmHG and LDL-cholesterol by 0.8 (95% CI: 0.6-0.9) mmol/L, but with an excess of side effects known to component medicines (58% vs. 42%, $p = 0.001$).[86]

Trachea, bronchus, lung cancers | One intervention efficaciously reduced smoking prevalence in order to prevent trachea, bronchus, and lung cancers.[87] The protocol focused on in-person interviews and phone counseling with the goal of smoking cessation.[87] Study participants were middle-aged male community residents in India.[87] The protocol was a randomized control trial. Self-reported smoking abstinence prevalence was significantly higher in the intervention group as compared to the control group (relative risk (RR): 1.85 with 95% CI of 1.05 to 3.25; $p<0.05$).[87]

Neonatal infections | Three protocols focused on the prevention of neonatal infections through topical treatments.[91-93] Two of the interventions aimed to successfully prevent omphalitis and neonatal mortality through providing chlorhexidine as an umbilical cord-care regimen.[92;93] In newborn babies delivered in Pakistan, there was a significant reduction in risk of omphalitis (RR = 0.58, $p = 0.002$) and in infants enrolled within 24 hours of birth in a study in Nepal, mortality was significantly reduced by 34% (95% CI: 0.46-0.95) in those that received the chlorhexidine intervention.[92;93] A third successful intervention included a daily massage of sunflower seed oil for infants born before week 33 of gestation, which resulted in infants that were 41% less likely to develop nosocomial infections ($p = 0.032$).[91]

Cerebrovascular disease | One protocol focused on the prevention of cerebrovascular disease through using a community based lifestyle intervention for blood pressure.[94] Participants were children and young adults aged 5-39 in a developing country setting.[94] The intervention consisted of three monthly family based home health education sessions developed by lay health workers and was found to ameliorate the usual increase in blood pressure with age.[94] The systolic pressure increased by 1.5 mmHg in the control group and by 0.1 mmHg in the home health education group (p = 0.02).[94] The diastolic blood pressure increased by 1.5 mmHg more in the control group than in the intervention group (p = 0.002).[94]

Diabetes | One efficacious study focused on a culturally sensitive, diabetic specific smoking cessation intervention which resulted in significantly higher odds for quitting smoking as compared to an intervention group that only received a regular smoking intervention (OR=8.4, 95% CI = 4.1-17.1; p<0.001).[70]

HIV/AIDS | Three protocols focused on the prevention of HIV by improvement in HIV risk factors.[88-90] Interventions ranged from safe sex motivational counseling[89; 90] to a community-focused behavioral intervention (including condom programs and structural interventions).[88] Study participants included men who have sex with men,[88] female sex workers,[88] truck drivers,[89] and wives at risk for HIV.[90] Two out of the three interventions used an RCT study design[89; 90] while one intervention employed a two-point cross-sectional study design using a historic control group.[88] As compared to the control group, intervention participants reported more frequent condom use (p<0.05 for female sex workers[88]; p<0.001[89]; p = 0.01[90]), lower STI sero-positivity (syphilis among MSM: p<0.001[88]), and fewer total non-marital sexual partners (p<0.001).[89]

Cardiovascular disease, chronic obstructive pulmonary disease, and road traffic accidents had no rigorous and effective interventions published within this region.

Asia, Southeast

WHO Region 5, Southeast Asia, is part of the WHO super region East Asia and Pacific and consists of the following 11 countries: Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Maldives, Myanmar, Philippines, Sri Lanka, Thailand, and Timor-Leste. There were seven unique local efficacious interventions included in our package, of which two were conducted in Vietnam,[95; 96] two in the Asia Pacific region,[54; 55] one in Indonesia,[65] one in Philippines,[77] and one in Lao People's Democratic Republic.[81] Quality scores ranged from 3 to 9 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 1,338,972)
2. Prematurity and low birth weight (n= 941,120)
3. Cerebrovascular disease (n= 666,750)
4. Ischemic heart disease (n= 509,097)
5. Diabetes (n= 495,065)
6. Chronic obstructive pulmonary disease (n= 404,074)
7. Colon and rectum cancers (n= 373,106)
8. Road traffic accidents (n= 350,406)
9. Hypertensive heart disease (n= 340,969)
10. Trachea, bronchus, lung cancers (n=279,800)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Southeast Asia

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Prematurity and low birth weight	Maternal Nutrient Supplementation[65]	Pregnancy Deworming and iron-folate supplementation[95]	Micronutrient Supplementation[96]
3. Cerebrovascular disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Exercise to Enhance Mobility Post-stroke[23]
4. Ischemic heart disease	Distal Protection Device[52]	Celecoxib[53]	Oral antiplatelet therapy post percutaneous coronary intervention[20]
5. Diabetes	Integrated community management of diabetes[77]	Metformin in obese children[32]	Tailored dietary advice and education[33]
6. Chronic obstructive pulmonary disease	Practitioner education and smoking behavior[31]	Integrated education, treatment and rehabilitation[76]	Azithromycin[56]
7. Colon and rectum cancers	Flexible sigmoidoscopy screening[97]	Aspirin in cancer prevention[98]	Telephone counseling and screening[99]
8. Road traffic accidents	Road safety and helmet promotion[81]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
9. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Electronic follow-up nursing care system for coronary patients[75]
10. Trachea, bronchus, lung cancers	Smoking behavior intervention[31]	Motivational interviewing[27]	Communities That Care program[108]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Southeast Asia

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Prematurity and low birth weight				✓					✓✓	
Cerebrovascular disease				✓	✓					
Ischemic heart disease										
Diabetes					✓					
Chronic obstructive pulmonary disease										
Colon and rectum cancers										
Road traffic accidents			✓							
Hypertensive heart disease				✓	✓					
Trachea, bronchus, lung cancers										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | Three protocols focused primarily on nutrient supplementation for pregnant women in order to alleviate prematurity and low birth weight.[65; 95; 96] In one study, a double-blind cluster-randomized trial was conducted where Indonesian pregnant women were given nutrient supplementation and resulted in an 18% reduction in early infant mortality in the intervention group ($p = 0.010$).[65] Another study showed that infants had a higher birth weight ($p<0.001$) after women of reproductive age in Vietnam were given a monthly deworming and weekly iron-folic acid supplementation.[95] An efficacious intervention in Vietnam also showed the effectiveness of multiple micronutrient supplementation during pregnancy.[96] In this study, the mean birth weight of infants was significantly higher in the intervention group, which received multiple micronutrients, as compared to the control group, which only received iron-folic acid supplements ($p<0.05$).[96]

Cerebrovascular disease | Two randomized trial protocols focused on the prevention of cerebrovascular disease, addressing cardiovascular risk factors.[54; 55] Intervention subjects were hypertensive patients. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55] Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group ($p<0.001$),[55] greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, $p<0.001$) and non-Pacific Asian regions (-31.1% vs. -4.2%; $p<0.001$),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; $p<0.001$),[55] diastolic blood pressure (-10.5% vs. -5.3%; $p<0.001$),[55] total cholesterol (-17.4% vs. 0,7%; $p<0.001$),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; $p<0.001$).[55]

Diabetes | One efficacious study displayed the effectiveness of a Chronic Care Model framework in terms of glycemic control and diabetes management for adults over the age of 20 in a low-to-middle income country (OR for HbA1c = 6.0, 95% CI = 2.4-15.1; $p<0.001$).[77]

Road traffic accidents | One protocol was efficacious in increasing preventive measures to decrease road traffic injuries.[81] The intervention focused on road safety days promoting helmet usage, including safety videos, speeches, paper educational materials, a coconut helmet safety demonstration, and a street march.[81] The study population was Northwest Laos hospital staff, traffic police, and general road traffic users.[81] This protocol used observational longitudinal design with a historic control group from before the implementation of the road safety days.[81] Results ranged from reductions in severe road traffic injuries ($p = 0.0001$) to increased motorcycle helmet usage ($p = 0.0001$).[81]

Hypertensive heart disease | Two randomized trial protocols were effective in reducing risk of hypertensive heart disease. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55] Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55]greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Cardiovascular disease, ischemic heart disease, chronic obstructive pulmonary disease, colon and rectum cancers, and trachea, bronchus, and lung cancers had no rigorous and effective interventions published within this region.

Australasia

WHO Region 6, Australasia, is part of the WHO super region High Income and consists of the following two countries: Australia and New Zealand. There were seven unique local efficacious interventions included in our package, of which six were conducted in Australia[23; 100-104] and three in New Zealand.[100; 101; 105] Quality scores ranged from 4 to 9 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 66,371)
2. Birth asphyxia and birth trauma (n= 52,676)
3. Ischemic heart disease (n= 35,608)
4. Trachea, bronchus, lung cancers (n= 21,400)
5. Diabetes (n= 19,321)
6. Neurodegenerative disorder (n= 18,393)
7. Chronic obstructive pulmonary disease (n= 18,372)
8. Cerebrovascular disease (n= 17,534)
9. Prematurity and low birth weight (n= 8,007)
10. Colon and rectum cancers (n= 7,791)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Australasia

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
3. Ischemic heart disease	Pravastatin Therapy[101]	CHOICE[102]	Polypill to reduce Cardiovascular Disease[86]
4. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
5. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetes lifestyle prevention program[106]
6. Neurodegenerative disorder	Liquid flavanol consumption[107]		
7. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Individually-tailored integrated care[108]
8. Cerebrovascular disease	Exercise to Enhance Mobility Post-stroke[23]	8-week exercise program[105]	Health Belief Model Telephonic Intervention[24]
9. Prematurity and low birth weight	Long-term Preterm intervention[103]	Heparin and aspirin[104]	Maternal micronutrient supplementation[18]
10. Colon and rectum cancers	Flexible sigmoidoscopy screening[97]	Aspirin in cancer prevention[98]	Telephone counseling and screening[99]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Australasia

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Birth asphyxia and birth trauma										
Ischemic heart disease						✓	✓		✓	
Trachea, bronchus, lung cancers										
Diabetes										
Neurodegenerative disorder										
Chronic obstructive pulmonary disease										
Cerebrovascular disease				✓					✓	
Prematurity and low birth weight						✓✓				
Colon and rectum cancers										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Ischemic heart disease | Three protocols were efficacious in reducing ischemic heart disease events and/or risk factor outcomes.[86; 101; 102] Studies examined the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) and effects of pravastatin therapy through controlled-trial in LIPID patients with diabetes and patients with impaired fasting glucose (IFG),[101] a randomized controlled trial of the Choice of Health Options In prevention of Cardiovascular Events (CHOICE) program on cardiovascular risk factors (clinic visit plus telephone support, mandatory cholesterol lowering and tailored preferential risk modification) in acute coronary syndrome survivors,[102] and a randomized, double-blind placebo-controlled trial of a polypill (aspirin 75mg, lisinopril 10mg, hydrochlorothiazide 12.5mg, and simvastatin 20mg) in patients with an estimated 5-year cardiovascular disease risk over 7.5%.[86] Studies found pravastatin therapy reduced risk of major CHD event from 15.9 to 12.3% (p<0.001) and 19% in diabetic group (p = 0.11), reduced risk of any cardiovascular event by 21% (p<0.008) in diabetes group and 26% (p = 0.003) in the IFG group, reduced risk of stroke by 39% (p = 0.02) and by 42% (p = 0.09) in IFG group,[101] 12 month significantly better risk factor levels in CHOICE group vs. controls for total cholesterol (4.0 vs. 4.7 mmol/L, p<0.001), systolic blood pressure (131.6 vs. 143.9 mmHg, p<0.001), body mass index (28.9 vs. 31.2 kg/m^2, p = 0.025) and physical activity and better knowledge of risk factor targets,[102] and found polypill treatment to reduce systolic blood pressure by 9.9 (95% CI: 7.7-12.1) mmHG and LDL-cholesterol by 0.8 (95% CI: 0.6-0.9) mmol/L, but with an excess of side effects known to component medicines (58% vs. 42%, p = 0.001)[86].

Cerebrovascular disease | Two protocols used exercise programs to target risk factors related to cerebrovascular disease and to enhance mobility and prevent falls after stroke.[23; 105] Subjects for the first intervention were transient ischemic attack patients.[105] After an 8-week exercise program, individuals randomized to the exercise condition experienced a significantly greater reduction in resting heart rate (-5.4), systolic blood pressure (-6.7), and diastolic blood pressure (-2.8) (all p<0.05).[105] Subjects for the second intervention were community-dwelling people who had suffered one or more strokes.[23] The experimental group (EG) received a program aimed to improve walking, prevent falls, and increase physical activity.[23] At 12 months, the EG walked 34 m further in 6 minutes (p<0.001) and 0.07 m/s faster over 10 m (p = 0.03) than the control group.[23]

Prematurity and low birth weight | Two protocols were effective in reducing prematurity and low birth weight outcomes.[103; 104] One protocol focused on the benefits of home-based preventive care for infants that were born prematurely as well as their caregivers.[103] The study showed that long-term, caregivers have less anxiety from the intervention group (p = 0.01) and the pre-term infants in the intervention group also show reduced internalizing behaviors (p = 0.02).[103] Another study indicated that giving low-molecular-weight heparin and aspirin to pregnant women at less than 12 weeks gestation reduced recurrent hypertensive disorders (p = 0.012).[104]

Cardiovascular disease, birth asphyxia and birth trauma, trachea, bronchus, and lung cancers, diabetes, neurodegenerative disorder, chronic obstructive pulmonary disease, and colon and rectum cancers had no rigorous and effective interventions published within this region.

Caribbean

WHO Region 7, Caribbean, is part of the WHO super region Latin America and Caribbean and consists of the following countries: Antiguea and Barbuda, Bahamas, Barbados, Belize, Cuba, Dominica, Dominican Republic, Grenada, Guyana, Haiti, Jamaica, Saint Lucia, Saint Vincent and the Grenadine, Suriname, and Trinidad and Tobago. There were two local efficacious interventions included in our package, all of which were regional interventions.[61,62] Quality scores ranged from 4 to 5 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 101,014)
2. Prematurity and low birth weight (n= 71,309)
3. Birth asphyxia and birth trauma (n= 56,673)
4. Ischemic heart disease (n= 48,806)
5. Diabetes (n= 40,268)
6. Cerebrovascular disease (n= 35,605)
7. Chronic obstructive pulmonary disease (n= 27,413)
8. Road traffic accidents (n= 22,438)
9. Hypertensive heart disease (n= 16,834)
10. Trachea, bronchus, lung cancers (n= 15,400)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Caribbean

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Prematurity and low birth weight	Mebendazole supplementation[19]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation, daily in healthy women[18]
3. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
4. Ischemic heart disease	Cardiopulmonary rehabilitation[109]	Comprehensive smoking ban[110]	Oral antiplatelet therapy post percutaneous coronary intervention[20]
5. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
6. Cerebrovascular disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Exercise to Enhance Mobility Post-stroke[23]
7. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention [31]
8. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
9. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Losartan[40]
10. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[108]	State cigarette taxes[28]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Caribbean

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular Disease										
Prematurity and low birth weight										
Birth asphyxia and birth trauma										
Ischemic heart disease										
Diabetes										
Cerebrovascular disease				✓	✓					
Chronic obstructive pulmonary disease										
Road traffic accidents										
Hypertensive Heart Disease				✓	✓					
Trachea, bronchus, lung cancers										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cerebrovascular disease | Two randomized trial protocols focused on the prevention of cerebrovascular disease, addressing cardiovascular risk factors.[54; 55] Intervention subjects were hypertensive patients. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55] greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Hypertensive heart disease | Two randomized trial protocols were effective in reducing risk of hypertensive heart disease. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55]greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Cardiovascular disease, prematurity and low birth weight, birth asphyxia and birth trauma, ischemic heart disease, diabetes, chronic obstructive pulmonary disease, road traffic accidents, trachea, bronchus, and lung cancers had no rigorous and effective interventions published within this region.

Europe, Central

WHO Region 8, Central Europe, is part of the WHO super region Eastern Europe and Central Asia and consists of the following ten countries: Croatia, Czech Republic, Hungary, Macedonia, Montenegro, Poland, Romania, Serbia, Slovakia, and Slovenia. There were 5 unique local efficacious interventions included in our package, of which one was conducted in Poland,[111] two regional interventions,[61,62] and one in the Czech Republic.[21] Quality scores ranged from 4 to 5 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 653,535)
2. Ischemic heart disease (n= 288,255)
3. Cerebrovascular disease (n= 242,412)
4. Trachea, bronchus, lung cancers (n= 123,799)
5. Chronic obstructive pulmonary disease (n= 95,169)
6. Neurodegenerative disorder (n= 71,938)
7. Diabetes (n= 69,183)
8. Hypertensive heart disease (n= 65,023)
9. Birth asphyxia and birth trauma (n= 53,117)
10. Inflammatory heart disease (n= 48,794)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Central Europe

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Protein and glycemic control diet[15]	Metformin and Intensive lifestyle change[14]	Lifestyle counseling to obese groups[16]
2. Ischemic heart disease	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]	Rehabilitation with family support[22]
3. Cerebrovascular disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Tailored dietary advice and education[25]
4. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[108]	State cigarette taxes[28]
5. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
6. Neurodegenerative disorder	Liquid flavanol consumption[107]		
7. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
8. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	
9. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
10. Inflammatory heart disease	Laser illumination during percutaneous coronary intervention[111]	Atorvastatin for myocardial injury protection during angioplasty[112]	Nurse-led intervention[113]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Central Europe

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease					✓					
Ischemic heart disease										
Cerebrovascular disease				✓	✓					
Trachea, bronchus, lung cancers										
Chronic obstructive pulmonary disease										
Neurodegenerative disorder										
Diabetes										
Hypertensive heart disease				✓	✓					
Birth asphyxia and birth trauma										
Inflammatory heart disease					✓					

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cardiovascular disease | One protocol was efficacious in reducing cardiovascular biomarkers in order to prevent cardiovascular disease.[15] The intervention focused on heart-healthy diets to enhance child cardiovascular biomarker outcomes.[15] Study participants were European children of overweight or obese parents. The intervention was a randomized control trial with five groups: high protein diet, low protein diet combined with high glycemic index, low glycemic index, or a control diet.[15] Results included decreased mean waist circumference (p<0.007), decreased LDL-c (p<0.007), and decreased blood pressure (p<0.01).[15]

Cerebrovascular disease | Two protocols focused on the prevention of cerebrovascular disease by a proactive multifactorial intervention (PMI) approach, based on single-pill amlodipine/atorvastatin, addressing cardiovascular risk factors.[54; 55] Intervention subjects were hypertensive patients. One protocol found that PMI reduced coronary heart disease risk compared to usual care (UC) in Pacific Asian populations (-37.1% vs. -3.5%, p<0.001).[54] The other found that despite mean baseline blood pressure and Framingham CHD risk being higher in the proactive intervention group compared to the UC group, the mean CHD risk post-intervention was 12.5% in the PMI group compared to 16.3% in the UC group (p<0.001).[55]

Hypertensive heart disease | Two randomized trial protocols were effective in reducing risk of hypertensive heart disease. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine / atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55]greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Inflammatory heart disease | One protocol was effective in reducing inflammatory reaction among participants treated with percutaneous coronary intervention (PCI).[111] This randomized controlled trial included intravascular low-energy laser irradiation (= 808 nm) of dilated lesion during the PCI resulted in lower levels of IL 1β (p<0.05) as well as IL 6 (p<0.05) in the irradiated group during each analysis after the procedure were observed in addition and lower IL 10 level in irradiated group within 6 (p<0.001) and 12 hours (p<0.001) after PCI was observed.[111]

Ischemic heart disease, trachea, bronchus, and lung cancers, chronic obstructive pulmonary disease, neurodegenerative disorder, diabetes, and birth asphyxia and birth trauma had no rigorous and effective interventions published within this region.

Europe, Eastern

WHO Region 9, Eastern Europe, is part of the WHO super region Eastern Europe and Central Asia and consists of the following seven countries: Belarus, Estonia, Latvia, Lithuania, Moldova, the Russian Federation, and Ukraine. There were three unique local efficacious interventions included in our package, of which one was conducted in Russia[114] and two were regional interventions.[54; 55] Quality scores ranged from 4 to 6 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 1,662,100)
2. Ischemic heart disease (n= 996,589)
3. Cerebrovascular disease (n= 511,299)
4. Self-inflicted injuries (n= 165,465)
5. Trachea, bronchus, lung cancers (n= 133,522)
6. Road traffic accidents (n= 122,998)
7. Prematurity and low birth weight (n= 111,277)
8. Neurodegenerative disorder (n= 109,672)
9. Chronic obstructive pulmonary disease (n= 104,166)
10. Hypertensive heart disease (n= 98,417)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Eastern Europe

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Ischemic heart disease	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]	Rehabilitation with family support[22]
3. Cerebrovascular disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Health Belief Model Telephonic Intervention[24]
4. Self-inflicted injuries	Depression management education program[115]	Postcard message intervention after hospital-treated self-poisoning[60]	Psychotherapy after self-poisoning[61]
5. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
6. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
7. Prematurity and low birth weight	Fish oil supplementation[114]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation[18]
8. Neurodegenerative disorder	Liquid flavanol consumption[107]		
9. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
10. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Family Healthware web-based tool[38]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Eastern Europe

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Ischemic heart disease										
Cerebrovascular disease				✓	✓					
Self-inflicted injuries										
Trachea, bronchus, lung cancers										
Road traffic accidents										
Prematurity and low birth weight						✓				
Neurodegenerative disorder										
Chronic obstructive pulmonary disease										
Hypertensive heart disease				✓	✓					

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cerebrovascular disease | Two randomized trial protocols focused on the prevention of cerebrovascular disease, addressing cardiovascular risk factors. .[54; 55] Intervention subjects were hypertensive patients. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55]greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Prematurity and low birth weight | One efficacious protocol focused on administering fish oil capsules to high-risk pregnant women, which resulted in a reduced hazard rate of spontaneous delivery by 44% as compared to olive oil capsules (95% CI = 14%-64%).[114] Among those with previous problems, the hazard of low gestational age was significantly lower in the fish oil group as compared to the olive oil group (adjust HR: 0.67, 95% CI: 0.67-0.93).[114]

Hypertensive heart disease | Two randomized trial protocols were effective in reducing risk of hypertensive heart disease. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group (p<0.001),[55]greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, p<0.001) and non-Pacific Asian regions (-31.1% vs. -4.2%; p<0.001),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; p<0.001),[55] diastolic blood pressure (-10.5% vs. -5.3%; p<0.001),[55] total cholesterol (-17.4% vs. 0,7%; p<0.001),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; p<0.001).[55]

Cardiovascular disease, ischemic heart disease, self-inflicted injuries, trachea, bronchus, lung cancers, road traffic accidents, neurodegenerative disorder, and chronic obstructive pulmonary disease had no rigorous and effective interventions published within this region.

Europe, Western

WHO Region 10, Western Europe, is part of the WHO super region High Income and consists of the following countries: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, and United Kingdom. There were 21 unique local efficacious interventions included in our package, of which three were conducted in Finland,[33; 116; 117] three in the Netherlands,[56; 118; 119] four in multiple countries within the region,[15; 21; 40; 120] two in Denmark, [121; 122] two in Italy,[39; 107] one in France,[123] one in the Greece,[124] one in Switzerland,[21] three in Spain,[58; 108; 125] and one in Sweden.[126] Quality scores ranged from 2 to 9 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 1,473,663)
2. Ischemic heart disease (n= 740,051)
3. Trachea, bronchus, lung cancers (n= 436,282)
4. Cerebrovascular disease (n= 410,318)
5. Neurodegenerative disorder (n= 399,991)
6. Chronic obstructive pulmonary disease (n= 399,916)
7. Diabetes (n= 338,635)
8. Prematurity and low birth weight (n= 246,653)
9. Hypertensive heart disease (n= 188,050)
10. Colon and rectum cancers (n= 162,340)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Western Europe

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Protein and glycemic control diet[15]	Targeted multifactorial intervention in patients with type II diabetes and microalbuminuria[122]	Fortified milk and lifestyle intervention[124]
2. Ischemic heart disease	Promotional stair-climbing program[21]	Sirolimus-eluting stent[121]	Pravastatin therapy[118]
3. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
4. Cerebrovascular disease	Exercise intervention[126]	Statin therapy[125]	Internet based nurse risk management[119]
5. Neurodegenerative disorder	Liquid flavanol consumption[107]		
6. Chronic obstructive pulmonary disease	Azithromycin[29]	Individually-tailored integrated care[108]	Tiotropium[30]
7. Diabetes	Tailored dietary advice and education[33]	Lifestyle intervention to prevent diabetes, through weight loss[116]	Lifestyle intervention to prevent diabetes[117]
8. Prematurity and low birth weight	Maternal micronutrient supplementation[18]	Cervical Pessary in short cervix cases[58]	Infant insultin treatment[127]
9. Hypertensive heart disease	Nurse care management[39]	Losartan[40]	Losartan for left ventricular atrophy[120]
10. Colon and rectum cancers	Flexible sigmoidoscopy screening[97]	Aspirin in cancer prevention[98]	Telephone counseling and screening[99]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Western Europe

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease			✓	✓	✓					
Ischemic heart disease									✓✓✓	
Trachea, bronchus, lung cancers										
Cerebrovascular disease		✓				✓	✓			
Neurodegenerative disorders					✓					
Chronic obstructive pulmonary disease							✓	✓		
Diabetes				✓✓					✓	
Prematurity and low birth weight							✓✓	✓		
Hypertensive heart disease					✓		✓	✓		
Colon and rectum cancers										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cardiovascular disease | Three protocols were efficacious in reducing cardiovascular biomarkers in order to prevent cardiovascular disease. [15; 122; 124] Interventions ranged from heart-healthy diets to a multi-component behavioral and pharmacologic intervention[122] to fortified milk supplementation.[124] Study participants included European children of overweight/obese parents,[15] type II diabetes and microalbuminuria patients,[122] and hyper-cholesterolemic adults.[124] All interventions employed randomized control trials. Results included decreased mean waist circumference (p<0.007[15]), decreased LDL-c (p<0.007[15]), decreased blood pressure (p<0.01[15]; p<0.001[122]), overall decreased risk of cardiovascular disease (HR: 0.47 with 95% CI of 0.24 to 0.73[122]), and decreased total fat intake (p<0.037[124]).

Ischemic heart disease | Three protocols that examined cardiovascular disease risk factor and ischemic heart disease outcomes were found efficacious.[21; 118; 121] One assessed a promotional campaign for stair use on employees at a university hospital[21], another tested a zotarolimus-eluting stent versus the sirolimus-eluting stent in a single-blind superiority trial with adult patients with chronic stable coronary artery disease or acute coronary symptoms[121], and a third used a placebo-controlled trial of pravastatin therapy in children with familial hypercholesterolemia[118]. Results found significant declines in waist circumference (p<0.001), weight (p = 0.022), fat mass (p = 0.035), diastolic blood pressure (p = 0.028), and low-density lipoprotein cholesterol (p = 0.026) in intervention group[21], a regression in carotid intima-media thickness (IMT) in pravastatin group (p = 0.049) and reduced mean low-density lipoprotein cholesterol levels in pravastatin group compared with placebo (p<0.001)[121], and at both 9- and 18-month follow-ups composite of major cardiac events occurred in higher proportion in patients with zotarolimus-eluting stent (p = 0.0002) and all-cause mortality was significantly different at 18-month follow-up (p = 0.035)[118].

Cerebrovascular disease | Three protocols focused on prevention of cerebrovascular disease through a lifestyle intervention program, a statin-based medical intervention, and an internet based, nurse led risk factor management program.[119; 125; 126] The first protocol evaluated the effect of a lifestyle intervention program in primary healthcare on cardiovascular risk factors.[126] Subjects were patients with moderate to high risk of cardiovascular disease.[126] At one year post-intervention, subjects in the intervention group significantly increased maximal oxygen uptake, physical activity, and quality of life and significantly decreased body weight (p<0.001), waist and hip circumference (p<0.001), body mass index (p<0.001), waist–hip ratio (p<0.01), systolic and diastolic blood pressure (p<0.001), triglycerides (p<0.05), and glycosylated haemoglobin (p<0.01).[126] Another protocol examined the effect of a statin-based medical intervention on the prevention of stroke recurrence and all-cause mortality.[125] Subjects were an aging Mediterranean population without known coronary heart disease.[125] Subjects who received statins had lower fatal/non-fatal recurrent stroke (p = 0.001) and mortality rate (p = 0.007).[125] The third protocol investigated the effect of an internet based, nurse led vascular risk factor

management program in reducing vascular risk factors in patients with clinically manifest vascular disease.[119] After 1 year, the relative change in Framingham heart risk score of the intervention group compared with the usual care group was -14% (95% CI, -25% to -2%).[119] A difference between groups was observed in low-density lipoprotein cholesterol (-0.3, -0.5 to 0.1, mmol/L; $p<0.001$) and smoking (-7.7%, -14.9% to -0.4%; $p = 0.038$).[119]

Neurodegenerative disorder | One protocol, in which individuals were randomized to receive a drink containing 990 mg (high flavanols), 520 mg (intermediate flavanols), or 45 mg (low flavanols) of cocoa flavanols once daily for eight weeks, was effective in improving cognitive function among elderly individuals with mild cognitive impairment.[107] The time required to complete Trail Making Test A and Trail Making Test B was lower in subjects receiving high flavanols (38.10 ± 10.94 and 104.10 ± 28.73 seconds, respectively) and intermediate flavanols (40.20 ± 11.35 and 115.97 ± 28.35 seconds, respectively) ($p<0.05$) compared to those receiving low flavanols (52.60 ± 17.97 and 139.23 ± 43.02 seconds, respectively).[107]

Chronic obstructive pulmonary disease (COPD) | Two protocols, both randomized controlled trials, were effective in improving COPD related outcomes. [29, 108] Interventions included a regimen of Azithromycin 250 mg three times a week among COPD-patients with chronic productive cough[29] and an integrated care (IC) intervention that included individually tailored care plan for exacerbated COPD patients upon discharge shared with the primary care team plus accessibility to a specialized nurse case manager through a web-based call center.[108] Results included greater mean increase in the Leicester Cough Questionnaire (1.3 ± 0.5; $p = 0.01$) as well as the St. George's Respiratory Questionnaire (7.4 ± 2.5; $p = 0.004$) total score after 12 weeks among the intervention group compared with placebo,[29] lower re-hospitalization rate during follow-up in the IC group than usual care (HR= 0.55; $p = 0.01$),[108] and greater percentage of IC group (49%) without admissions among survivors compared to the usual care group (31%; $p = 0.03$).[108]

Diabetes | There were three efficacious protocols that focused on alleviating diabetes in this region through lifestyle interventions. [33; 116; 117] One study looked at the effects of a lifestyle intervention in impaired glucose-tolerant individuals, which resulted in higher insulin secretion levels in the intervention group ($p = 0.02$).[33] Another study was geared towards a lifestyle intervention (an intensive diet-exercise program) in impaired glucose-tolerant individuals and found that weight reduction was greater in the intervention group ($p<0.0001$), thus resulting in a prevention or delaying of type II diabetes.[116] A third lifestyle intervention was shown to be efficacious in reducing weight in the intervention group ($p<0.001$), which was geared towards individuals with impaired glucose tolerance, and ultimately led to a reduction in the risk of diabetes ($p<0.001$).[117]

Prematurity and low birth weight | Three protocols were efficacious in alleviating prematurity and low birth weight.[18; 58; 127] One study focused on micronutrient supplementation being administered to seemingly healthy pregnant women, and resulted in infant birth weights increasing by 10% in the intervention group ($p = 0.03$).[18] Another intervention focused on cervical pessary and its effects on spontaneous delivery in pregnant mothers.[58] This study randomly assigned pregnant women with a short cervix (25 mm or less) to cervical pessary or expectant management and resulted in significantly less frequent spontaneous delivery in the pessary group (OR = 0.18, $p<0.0001$).[58] As low levels of insulin-like growth factor I in a newborn can cause neonatal morbidity, one study focused on the administration of an early insulin treatment in infants.[127] The study showed that early insulin treatment in infants was significantly effective in increasing IGF-I levels, which could improve health outcomes of low birth weight infants ($p = 0.028$).[127]

Hypertensive heart disease | Three randomized trial protocols were effective in reducing hypertensive heart disease related risk factors and/or outcomes.[39; 40; 120] Interventions included a nurse-led reminder program through email among hypertensive adults[39] as well as once-daily losartan- or atenolol-based antihypertensive therapy to hypertensive patients[40] and hypertensive patients with left ventricular atrophy.[120] Compared to the usual care group, the intervention group had a greater change in mean systolic blood pressure (10.0 vs. 14.9; $p<0.001$), had a lower percentage of participants with uncontrolled hypertension (45.9% vs. 14.0%; $p<0.001$), and had a greater change in mean LDL cholesterol (39.6 vs. 44.2; $p<0.001$) from baseline to 6 months of follow-up.[39] Lower risk of new on-set atrial fibrillation (RR= 0.67; $p<0.001$),[40] fewer composite end points (hazard ratio=0.60, p=0.03) and strokes (HR=0.49, $p = 0.01$) in patients who developed new-onset atrial fibrillation,[40] and lower risk of fatal (HR=0.65; 95% CI 0.43-0.96; $p = 0.032$)[120] as well as atherothrombotic stroke (HR=0.72; 95%CI 0.59-0.88; $p = 0.001$) [120] were found in those treated with losartan compared to those treated with atenolol.

Trachea, bronchus, and lung cancers and colon and rectum cancers had no rigorous and effective interventions published within this region.

Latin America, Andean

WHO Region 11, Andean Latin America, is part of the WHO super region Latin America and Caribbean and consists of the following countries: Bolivia, Ecuador, and Peru. There was one local efficacious intervention included in our package, which was conducted in Peru.[25] The only recorded quality score was 8 within this region.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 78,362)
2. Cardiovascular disease (n= 61,107)
3. Birth asphyxia and birth trauma (n= 57,926)
4. Chronic obstructive pulmonary disease (n= 47,132)
5. Road traffic accidents (n= 38,662)
6. Diabetes (n= 38,350)
7. Ischemic heart disease (n=32,588)
8. Renal disease (n= 25,742)
9. Cerebrovascular disease (n=18,728)
10. Trachea, bronchus, lung cancers (n= 15,084)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Andean Latin America

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Mebendazole supplementation[19]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation, daily to healthy women[18]
2. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
3. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
4. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
5. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
6. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
7. Ischemic heart disease	Cardiopulmonary rehabilitation[109]	Comprehensive smoking ban[110]	Oral antiplatelet therapy post percutaneous coronary intervention[20]
8. Renal disease	Modified fat and protein diet in stage 4 chronic kidney disease patients[128]	HBV vaccination in formerly nonresponsive HBV vaccination patients[129]	
9. Cerebrovascular disease	Exercise to Enhance Mobility Post-stroke[23]	Health Belief Model Telephonic Intervention[24]	Tailored dietary advice and education[25]
10. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Andean Latin America

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight								✓		
Cardiovascular Disease										
Birth asphyxia and birth trauma										
Chronic obstructive pulmonary disease										
Road traffic accidents										
Diabetes										
Ischemic heart disease										
Renal disease										
Cerebrovascular disease										
Trachea, bronchus, lung cancers										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | One protocol was efficacious in reducing low birth weight in infants.[19] Pregnant women in their second trimester were given a combination of mebendazole and iron supplements, which resulted in the proportion of very low birth weight infants to be much lower in the intervention group as compared to the control (p = 0.007).[19]

Cardiovascular disease, birth asphyxia and birth trauma, chronic obstructive pulmonary disease, road traffic accidents, diabetes, ischemic heart disease, renal disease, cerebrovascular disease, and trachea, bronchus, and lung cancers had no rigorous and effective interventions published within this region.

Latin America, Central

WHO Region 12, Central Latin America, is part of the WHO super region Latin America and Caribbean and consists of the following countries: Colombia, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, and Venezuela. There were seven local efficacious interventions included in our package, of which two were conducted in Colombia,[130;131] two in Mexico,[132;133] one in Panama,[110] one in Honduras,[133] and one regional intervention.[54] Quality scores ranged from 5 to 8 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 322,522)
2. Diabetes (n= 311,237)
3. Prematurity and low birth weight (n= 216,730)
4. Ischemic heart disease (n= 186,234)
5. Road traffic accidents (n= 146,817)
6. Violence (n= 139,847)
7. Chronic obstructive pulmonary disease (n= 135,268)
8. Renal disease (n= 104,731)
9. Self-inflicted injuries (n= 102,631)
10. Cerebrovascular disease (n= 89,243)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Central Latin America

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
3. Prematurity and low birth weight	Mebendazole supplementation[19]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation[18]
4. Ischemic heart disease	Comprehensive smoking ban[110]	Cardiopulmonary rehabilitation[109]	Oral antiplatelet therapy post percutaneous coronary intervention[20]
5. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
6. Violence	Public transit development[130]	Ban on carrying firearms[131]	Thai Family Matters education program[134]
7. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
8. Renal disease	Modified fat and protein diet in stage 4 chronic kidney disease patients[128]	HBV vaccination in formerly nonresponsive HBV vaccination patients[129]	
9. Self-inflicted injuries	Postcard message intervention after hospital-treated self-poisoning[60]	Psychotherapy after self-poisoning[61]	Depression survey and screening[48]
10. Cerebrovascular disease	Proactive multifactorial intervention on CVD risk[54]	Energy restricted diet[132]	Mobile blood pressure monitoring[133]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Central Latin America

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Diabetes										
Prematurity and low birth weight										
Ischemic heart disease					✓					
Road traffic accidents										
Violence						✓		✓		
Chronic obstructive pulmonary disease										
Renal disease										
Self-inflicted injuries										
Cerebrovascular disease					✓	✓✓				

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Ischemic heart disease | One protocol evaluated the effect of a nationwide comprehensive smoking ban (CSB) and tobacco tax increase (TTI) on the risk of acute myocardial infarction (AMI) in Panama by use of AMI case data analysis[110]. Relative Risk of AMI reduced, using pre-CSB as a reference point, through first CSB period (p = 0.023), second CSB period (p = 0.000) and post-TTI (p = 0.041)[110].

Violence | Two protocols, a large-scale natural experiment[130] and an interrupted time-series study with multiple replications,[131] were effective in reducing homicide rates. A public transit system that was built to connect isolated low-income neighborhoods to the city's urban center reduced homicide rates by 66% greater in intervention neighborhoods than in control neighborhoods (rate ratio = 0.33, 95% CI: 0.18-0.61) and resident reports of violence decreased 75% more in intervention neighborhoods (OR = 0.25, 95% CI: 0.11-0.67).[130] A ban on carrying fire arms on weekends after pay days, on holidays, and on election days in two urban cities resulted in the incidence of homicide being lower during periods when the firearm-carrying ban was in effect compared with other periods (multivariate-adjusted rate ratio, 0.86, 95% CI: 0.76-0.97 for one city and 0.87, 95% CI, 0.77-0.98 for the other.[131]

Cerebrovascular disease | Three protocols focused on the prevention of cerebrovascular disease through improvement of cardiovascular risk factors.[54;132;133] The first protocol compared the effect of two energy-restricted diets, a low-fructose diet versus a moderate natural fructose diet, on weight loss and metabolic syndrome parameters and found that while both diets were associated with significant weight loss and improvements in secondary outcomes (including blood pressure, lipid profile, serum glucose, insulin resistance, uric acid, soluble intercellular adhesion molecule-1, and quality of life scores) compared with baseline, weight loss was higher in the moderate natural fructose group (4.19 kg) than the low-fructose group (2.83 kg) (p = 0.0016).[132] The second protocol examined the effect of using mobile technology and home blood pressure monitoring for hypertension management and found that compared with controls, intervention patients at follow-up reported fewer depressive symptoms (p = 0.004), fewer medication problems (p < 0.0001), better general health (p<0.0001), and greater satisfaction with care (p = 0.004).[133] A third protocol focused on the prevention of cerebrovascular disease by a proactive multifactorial intervention (PMI) approach, based on single-pill amlodipine/atorvastatin, addressing cardiovascular risk factors.[54] Intervention subjects were hypertensive patients. PMI was found to reduce coronary heart disease risk compared to usual care (UC) in Pacific Asian populations (-37.1% vs. -3.5%, p<0.001).[54]

Cardiovascular disease, diabetes, prematurity and low birth weight, road traffic accidents, chronic obstructive pulmonary disease, renal disease, and self-inflicted injuries had no rigorous and effective interventions published within this region.

Latin America, Southern

WHO Region 13, Southern Latin America, is part of the WHO super region High Income and consists of the following three countries: Argentina, Chile, and Uruguay. There were two unique local efficacious interventions included in our package, of which one was conducted in Argentina and Chile[135] and one in Uruguay.[136] Quality scores ranged from 3 to 5 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 145,355)
2. Chronic obstructive pulmonary disease (n= 77,729)
3. Ischemic heart disease (n= 65,936)
4. Prematurity and low birth weight (n= 57,886)
5. Birth asphyxia and birth trauma (n= 53,940)
6. Diabetes (n= 51,685)
7. Trachea, bronchus, lung cancers (n= 50,796)
8. Cerebrovascular disease (n= 45,748)
9. Road traffic accidents (n= 31,523)
10. Neurodegenerative disorder (n= 29,210)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Southern Latin America

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Individually-tailored integrated care[108]
3. Ischemic heart disease	Balloon angioplasty vs. coronary stenting[135]	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]
4. Prematurity and low birth weight	Maternal micronutrient supplementation[18]	Maternal tailored counseling sessions[57]	Cervical Pessary in short cervix cases[58]
5. Birth asphyxia and birth trauma	Tocolysis and delayed delivery[136]	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]
6. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
7. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
8. Cerebrovascular disease	Exercise to Enhance Mobility Post-stroke[23]	Health Belief Model Telephonic Intervention[24]	Tailored dietary advice and education[25]
9. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education for adolescents[137]
10. Neurodegenerative disorder	Liquid flavanol consumption[107]		

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Southern Latin America

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Chronic obstructive pulmonary disease										
Ischemic heart disease					✓					
Prematurity and low birth weight										
Birth asphyxia			✓							
Diabetes										
Trachea, bronchus, lung cancers										
Cerebrovascular disease										
Road traffic accidents										
Neurodegenerative disorder										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Ischemic heart disease | One protocol was found efficacious in analyzing the incidence of angiographic restenosis between percutaneous transluminal coronary angioplasty (PTCA) and stent in diabetic patients undergoing percutaneous coronary interventions (PCIs) for lesions in small reference diameter.[135] The randomized control trial found angiographic binary restenosis (45% with PTCA and 28% with stents, $p = 0.047$), net gain (0.74 mm with POBA and 0.94 mm with stents, $p = 0.008$) and freedom from target vessel failure (66% with POBA and 81.2% with stents ($p = 0.013$) significantly improved in patients initially treated with stent therapy, through comparison of incidence of angiographic restenosis.[135]

Birth asphyxia and birth trauma | One protocol found fetal intrauterine resuscitation using tocolysis and delayed delivery to have efficacious immediate neonatal results amongst fetuses with diagnosed intrauterine distress when compared to emergency delivery[136]. This prospective randomized study found a relative risk of base deficit in the emergency group higher than in the resuscitation group (RR= 1.48, $p = 0.04$), and relative risk of need for admission to the neonatal care unit was higher in the emergency delivery group than in the resuscitation group (RR=2.13, $p = 0.005$).[136]

Cardiovascular disease, chronic obstructive pulmonary disease, prematurity and low birth weight, diabetes, trachea, bronchus, and lung cancers, cerebrovascular disease, road traffic accidents, and neurodegenerative disorders had no rigorous and effective interventions published within this region.

Latin America, Tropical

WHO Region 14, Tropical Latin America, is part of the WHO super region Latin America and Caribbean and consists of the following two countries: Brazil and Paraguay. There were four local efficacious interventions included in our package, all of which were conducted in Brazil. [109; 138-140] Quality scores ranged from 7 to 8 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 416,041)
2. Prematurity and low birth weight (n= 193,804)
3. Ischemic heart disease (n= 188,290)
4. Diabetes (n= 186,935)
5. Chronic obstructive pulmonary disease (n= 150,685)
6. Cerebrovascular disease (n= 148,060)
7. Road traffic accidents (n= 146,043)
8. Violence (n= 102,6013)
9. Trachea, bronchus, lung cancers (n= 95,814)
10. Self-inflicted injuries (n= 85,528)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Tropical Latin America

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Prematurity and low birth weight	Mebendazole supplementation[19]	Maternal Micronutrient Supplementation[65]	Maternal micronutrient supplementation[18]
3. Ischemic heart disease	Statin intervention[138]	Cardiopulmonary rehabilitation[109]	Fluvastatin[140]
4. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
5. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention [31]
6. Cerebrovascular disease	Pharmaceutical care program[139]	Health Belief Model Telephonic Intervention[24]	Tailored dietary advice and education[25]
7. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
8. Violence	Public transit development[130]	Ban on carrying firearms[131]	Thai Family Matters education program[134]
9. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
10. Self-inflicted injuries	Postcard message intervention after hospital-treated self-poisoning[60]	Psychotherapy after self-poisoning[61]	Depression survey and screening[48]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Tropical Latin America

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Prematurity and low birth weight										
Ischemic heart disease							✓✓	✓		
Diabetes										
Chronic obstructive pulmonary disease										
Cerebrovascular disease							✓			
Road traffic accidents										
Violence										
Trachea, bronchus, lung cancers										
Self-inflicted injuries										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Ischemic heart disease | Three protocols focused on patient outcomes after coronary artery bypass surgery (CABG)[109], following successful first (Percutaneous Coronary Intervention) PCI with stable or unstable angina or silent ischemia[138], and after successful PCI in diabetic patients[140] through randomized double-blind placebo controlled design[138; 140] and randomized rehabilitation intervention[109]. Studies found major adverse cardiac events (MACE)-free survival time was significantly longer in fluvastatin group (p = 0.01) and 21.4% in fluvastatin group and 26.7% in placebo group had at least one MACE (RR= 0.78, p = 0.01)[138], fluvastatin reduced risk of MACE in diabetic patients by 51% (p =0.0088)[140], and cardiac rehab patients presented shorter time to endotracheal intubation (p =0.05), reduction in incidence of pleural effusion (RR = 0.2, 95% CI: 0.5-0.8; p = 0.03), atelecstasis (RR = 0.15, 95% CI: 0.03-0.8; p = 0.03), pneumonia (p = 0.01), and other outcomes[109].

Cerebrovascular disease | One protocol focused on the prevention of cerebrovascular disease through examining the effect of a 36-month pharmaceutical care program on coronary heart disease risk.[139] Subjects were elderly diabetic and hypertensive patients.[139] While no significant changes were observed in the control group, subjects in the intervention group experienced significant reductions in the mean values of systolic blood pressure (156.7 mmHg vs. 133.7 mmHg; p<0.001), diastolic blood pressure (106.6 mmHg vs. 91.6 mmHg; p<0.001), fasting glucose (135.1 mg/dL vs. 107.9 mg/dL; p<0.001), hemoglobin A1C (7.7% vs. 7.0%; p<0.001), triglycerides (206.0 mg/dL vs. 152.5 mg/dL; p<0.001), low-density lipoprotein (LDL) cholesterol (112.4 mg/dL vs. 102.0 mg/dL; p<0.001), high-density lipoprotein cholesterol (55.5 mg/dL vs. 65.5 mg/dL; p<0.001), total cholesterol (202.5 mg/dL vs. 185.9 mg/dL; p<0.001), body mass index (26.2 kg/m2 vs. 26.1 kg/m2; p<0.001), and abdominal circumference (103.2 cm vs. 102.5 cm; p = 0.001) 36 months post-intervention compared to baseline.[139] The mean Framingham risk prediction score was unchanged in the control group but decreased from 6.8% at baseline to 4.5% after 36 months in the intervention group (p<0.001).[139]

Cardiovascular disease, prematurity and low birth weight, diabetes, chronic obstructive pulmonary disease, road traffic accidents, violence, trachea, bronchus, and lung cancers, and self-inflicted injuries had no rigorous and effective interventions published within this region.

North Africa / Middle East

WHO Region 15, North Africa and Middle East, is part of the WHO super region North Africa and Middle East and consists of the following countries: Algeria, Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Morocco, Occupied Palestinian Territory, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, Turkey, United Arab Emirates, and Yemen. There were ten unique efficacious interventions included in our package, of which six were conducted in Iran,[22; 141-146] two regional interventions,[54; 55] and one in Turkey[143]. Quality scores ranged from 5 to 9 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 995,241)
2. Prematurity and low birth weight (n= 545,700)
3. Ischemic heart disease (n= 493,213)
4. Diabetes (n= 326,678)
5. Cerebrovascular disease (n= 312,984)
6. Chronic obstructive pulmonary disease (n= 306,723)
7. Road traffic accidents (n= 296,146)
8. Trachea, bronchus, lung cancers (n= 190,598)
9. Hypertensive heart disease (n= 189,321)
10. Congenital disease (n= 183,580)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in North Africa, Middle East

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
2. Prematurity and low birth weight	Magnesium sulfate treatment[141]	Nurse-led relaxation sessions[142]	Erythromycin vs. ursodeoxycholic[143]
3. Ischemic heart disease	Rehabilitation with family support[22]	Vaccinium arctostaphylos L. fruit extract[144]	Isfahan Healthy Heart Programme[145]
4. Diabetes	Vitamin D supplementation on gestational diabetes[146]	Metformin in obese children[32]	Tailored dietary advice and education[33]
5. Cerebrovascular disease	Isfahan Healthy Heart Programme[145]	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]
6. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
7. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education[69]
8. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[59]	State cigarette taxes[28]
9. Hypertensive heart disease	Proactive multifactorial intervention on CVD risk[54]	Proactive multifactorial intervention on CVD risk[55]	Losartan for left ventricular atrophy[120]
10. Congenital disease	Prenatal alcohol use intervention[147]	Multi-component physician intervention [148]	Folic acid post first trimester[149]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; North Africa, Middle East

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease										
Prematurity and low birth weight						✓✓	✓			
Ischemic heart disease						✓	✓		✓	
Diabetes						✓				
Cerebrovascular disease				✓	✓	✓				
Chronic obstructive pulmonary disease										
Road traffic accidents										
Trachea, bronchus, lung cancers										
Hypertensive heart disease					✓	✓				
Congenital disease										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | Three RCT study design protocols were efficacious in reducing low birth weight in premature infants.[141-143] One study investigated the effects of administering magnesium sulfate to pregnant women and discovered that it increased the active phase of labor up to 77% and also reduced the risk of respiratory distress syndrome significantly ($p = 0.002$) as compared to a control group.[141] Another successful intervention focused on administering routine prenatal care along with applied relaxation training sessions to high anxiety level pregnant women and resulted in significant reductions in low birth weight in comparison with the control group, who just received routine prenatal care ($p = 0.009$).[142] A third study looked at the effectiveness of erythromycin and ursodeoxycholic acid in preterm infants and showed that the time it took to reach full feeding was significantly shorter in infants in the erythromycin group as compared to that of infants from the placebo group ($p = 0.014$).[143]

Ischemic heart disease | Three protocols were efficacious in reducing risk factors for coronary artery disease.[22; 144; 145] One study examined improving lifestyle behaviors in an at-risk population[145], another physical activity coupled with familial support in patients with coronary heart disease post-discharge[22], and the effects of fruit extract of *Vaccinium arctostaphylos L.* (a plant rich in anthocyanins) in hyperlipidemic adult patients[144]. Methods included controlled trials. [22; 144; 145] Protocols found increased physical activity in the intervention group($p<0.001$)[22], *V arctostaphylos* fruit extract to significantly reduce total cholesterol ($p < 0.001$) compared to placebo[144], and prevalence of major risk factors for coronary artery disease (CAD) decreased in both intervention and reference groups, while nutritional habits and smoking behaviors decreased more significantly in the intervention group as compared to the reference group ($p<0.05$ and $p<0.03$, respectively).[145]

Diabetes | One efficacious study focused on how vitamin D supplementation would have an effect on metabolic status of gestational diabetes.[146] The study resulted in a significant decrease in concentrations of fasting plasma glucose in the intervention group ($p<0.001$) as well as in serum insulin ($p = 0.01$).[146]

Cerebrovascular disease | Three protocols focused on the prevention of cerebrovascular disease by prevention of cardiovascular disease risk factors.[54; 55; 145] The first examined the efficacy of the Isfahan Healthy Heart Programme in improving lifestyle behaviors in a population at risk for developing cardiovascular diseases.[145] After 5 years of intervention, members in the intervention group improved their nutritional habits with respect to fruit and vegetable consumption and used more unsaturated fat and less salt in their diets (all $p<0.05$).[145] Two additional protocols focused on the prevention of cerebrovascular disease by a proactive multifactorial intervention (PMI) approach, based on single-pill amlodipine/atorvastatin, addressing cardiovascular risk factors.[54; 55] Intervention subjects were hypertensive patients. One protocol found that PMI reduced coronary heart disease risk compared to usual care (UC) in Pacific Asian populations (-37.1% vs. -3.5%, $p<0.001$).[54] The other found that despite mean baseline blood pressure and Framingham CHD risk being higher in the proactive intervention group compared to the UC group, the mean CHD risk post-intervention was 12.5% in the PMI group compared to 16.3% in the UC group ($p<0.001$).[55]

Hypertensive heart disease | Two randomized trial protocols focused on the prevention of hypertensive heart disease, addressing cardiovascular risk factors.[54; 55] Intervention subjects were hypertensive patients. Interventions included a proactive multifactorial intervention (PMI) using single-pill amlodipine/atorvastatin among hypertensive patients.[54; 55]Results include mean absolute Framingham 10-year coronary heart disease risk at week 52 of 12.5% in PMI group and 16.3% in the usual care group ($p<0.001$),[55] greater reduction in calculated coronary heart disease risk compared with usual care in both hypertensive patients living in Pacific Asian (-37.1% vs. -3.5%%, $p<0.001$) and non-Pacific Asian regions (-31.1% vs. -4.2%; $p<0.001$),[54] greater change from baseline at week 52 in PMI group compared to the usual care group for systolic blood pressure (-19.8% vs. -10%; $p<0.001$),[55] diastolic blood pressure (-10.5% vs. -5.3%; $p<0.001$),[55] total cholesterol (-17.4% vs. 0,7%; $p<0.001$),[55] as well as LDL cholesterol (-25.6% vs. 2.7%; $p<0.001$).[55]

Cardiovascular disease, chronic obstructive pulmonary disease, road traffic accidents, trachea, bronchus, lung cancers, and congenital disease had no rigorous and effective interventions published within this region.

North America, High Income

WHO Region 16, North America High Income, is part of the WHO super region High Income and consists of the following countries: Canada and the United States. There were 23 unique efficacious interventions included in our package, of which 19 were conducted in the United States[14; 16; 20; 24; 27; 28; 30; 35; 38; 40; 57; 59; 106; 120; 150-157] and 2 in Canada.[20; 138; 154] Quality scores ranged from 4 to 10 within this region.

Top 10 causes of death in 2013 (deaths)

1. Cardiovascular disease (n= 958,837)
2. Ischemic heart disease (n= 598,941)
3. Trachea, bronchus, lung cancers (n= 367,207)
4. Neurodegenerative disorder (n= 343,422)
5. Diabetes (n= 304,169)
6. Chronic obstructive pulmonary disease (n= 297,530)
7. Cerebrovascular disease (n= 181,761)
8. Prematurity and low birth weight (n= 174,471)
9. Road traffic accidents (n= 148,035)
10. Hypertensive heart disease (n= 116,810)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in High Income North America

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Lifestyle counseling to obese groups[16]	Exercise program for overweight children[150]
2. Ischemic heart disease	Oral antiplatelet therapy post percutaneous coronary intervention[20]	B-blockade and nurse management[151]	Statin intervention[138]
3. Trachea, bronchus, lung cancers	Motivational interviewing[27]	Communities That Care program[158]	State cigarette taxes[28]
4. Neurodegenerative disorder	Liquid flavanol consumption[107]		
5. Diabetes	Diabetes lifestyle prevention program[106]	Lifestyle behavior education program[152]	Lifestyle intervention and/or statins in type II diabetes[153]
6. Chronic obstructive pulmonary disease	Tiotropium[30]	Smoking cessation program[154]	Azithromycin[56]
7. Cerebrovascular disease	Health Belief Model Telephonic Intervention[24]	Multicomponent warfarin management program[155]	Gemfibrozil[156]
8. Prematurity and low birth weight	Maternal tailored counseling sessions[57]	Maternal behavioral intervention[157]	Maternal micronutrient supplementation[18]
9. Road traffic accidents	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]	Road safety education for adolescents[137]
10. Hypertensive heart disease	Family Healthware web-based tool[38]	Losartan[40]	Losartan[120]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; High Income North America

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Cardiovascular disease				✓	✓	✓				
Ischemic heart disease								✓	✓	✓
Trachea, bronchus, and lung cancers						✓	✓	✓		
Neurodegenerative disorders										
Diabetes					✓		✓✓			
Chronic obstructive pulmonary disorder						✓	✓			
Cerebrovascular disease								✓✓✓		
Prematurity and low birth weight						✓	✓			
Road traffic accidents						✓				
Hypertensive heart disease							✓✓	✓		

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Cardiovascular disease | Three protocols were efficacious in reducing cardiovascular biomarkers in order to prevent cardiovascular disease.[14;16;150]Interventions ranged from metformin supplementation[14] to meal replacements and weight loss medications[16] to child exercise programs examining oxidative stress.[150] Study participants included individuals with impaired glucose tolerance,[14] obese adults,[16] and overweight/obese children.[150] All interventions employed randomized control trials. Results included decreased triglycerides ($p<0.01$[14]; $p<0.05$[16]), increased HDL-C ($p<0.01$[14]; $p<0.05$[16]), increased weight loss ($p<0.05$)[16] decreased BMI ($p<0.01$[14]; $p<0.001$[150]), and decreased mean waist circumference ($p = 0.001$[150]).

Ischemic heart disease | Three protocols focused on cardiac outcomes by intervention of low-dose carvedilol coupled with nurse management in hospitalized patients with heart failure[151], fluvastatin regimen following successful first (Percutaneous Coronary Intervention) PCI with stable or unstable angina or silent ischemia[138], and clopidogrel regimen in patients undergoing PCI or deemed high likelihood of undergoing PCI[20] by randomized double-blind placebo controlled design[20;138] and randomized trial design[151]. Studies found major adverse cardiac events (MACE)-free survival time was significantly longer in fluvastatin group ($p = 0.01$) and 21.4% in fluvastatin group and 26.7% in placebo group to have at least one MACE (RR= 0.78, $p = 0.01$)[138], New York Heart Association class improved ($p = 0.01$) and total heart failure re-hospitalizations were reduced ($p = 0.02$)[151] and clopidogrel therapy associated with 26.9% reduced in the combined risk of death, myocardial infarction or stroke ($p = 0.02$).[20]

Trachea, bronchus, and lung cancers | Three interventions efficaciously reduced smoking prevalence in order to prevent trachea, bronchus, and lung cancers.[27;28;158] Protocols included motivational interviewing,[27] a community-based substance use prevention,[158] and a tax increase.[28] Studies drew participants from Baltimore City Head Start caregivers,[27] public school fifth-grade students,[158] and recent mothers.[28] One study found that self-reported smoking abstinence prevalence was significantly higher in the intervention group as compared to the control group (adjusted RR: 1.13 with 95% CI of 1.01-1.27; $p<0.05$).[158] Another found that household air nicotine levels were significantly lower in the motivational interviewing intervention group as compared to the control group ($p<0.05$).[27] The last study found that for each $1.00 increase in cigarette tax, the lowest educated women decreased their smoking by 14 to 22 cigarettes per month.[28]

Diabetes | There were three efficacious protocols that were focused on the prevention of diabetes.[106; 152; 153] One study focused on a peer-led lifestyle intervention for overweight, prediabetic adults and resulted in a significant weight loss in the intervention group compared to a control group ($p<0.01$).[106] Another study also focused on a lifestyle behavior intervention led by community health workers, which led to statistically significant differences between the intervention and control groups in regards to dietary habits ($p = 0.009$) and waist circumference ($p = 0.04$) in low-income Latina women.[152] Another intensive lifestyle intervention resulted in a significant change in C-reactive protein levels in the lifestyle intervention group ($p<0.001$) (regardless of statin status) as compared to the standard care.[153]

Chronic obstructive pulmonary disease (COPD) | Two protocols, both randomized controlled trials, were effective in improving COPD related outcomes.[30,154] Interventions included a regimen of once-daily tiotropium (18 g) for 6 months for COPD patients[30] and a 10-week smoking cessation program for patients with asymptomatic airway obstruction that included a strong physician message and 12 group sessions using behavior modification and nicotine gum, plus either ipratropium or a placebo inhaler.[154]

Results included lower number of COPD exacerbations in intervention group compared to control group (27.9% vs. 32.3%, $p = 0.037$)[30] and higher mortality rate in the usual care group compared with the special intervention group (hazard ratio = 1.18; 95% CI, 1.02-1.37; $p = 0.03$).[154]

Cerebrovascular disease | Three protocols focused on the prevention of cerebrovascular disease with interventions ranging from a behavioral telephonic intervention[24], to the use of gemfibrozil[156], to a warfarin management program[155]. The first protocol tested the effectiveness of a brief behavioral telephonic intervention in an ongoing community stroke prevention screening program on health care seeking for stroke risk.[24] Subjects in the intervention arm were 1.85 times more likely to visit a primary care physician than controls ($p = 0.02$) and were also more likely to discuss stroke screening results ($p<0.01$).[24] Another protocol examined the effect of gemfibrozil on reduction in stroke.[156] Subjects were men with coronary heart disease and low HDL cholesterol.[156] Subjects in the gemfibrozil group were less likely to have stroke compared to subjects in the placebo group, with a relative risk reduction, adjusted for baseline variables, of 31% ($p = 0.036$).[156] A third protocol compared the effect of a multicomponent warfarin management program[155] to the standard care protocol and achieved a significant decrease ($p<0.05$) in major bleeding, after six months, among the intervention group as compared to the standard of care.[155]

Prematurity and low birth weight | There were two efficacious protocols in reducing low birth weight in premature infants.[57; 157] One study utilized a cognitive-behavioral intervention aimed at reducing environmental tobacco smoke exposure and improving pregnancy outcomes for African-American women.[57] The intervention was successful in significantly improving the rates of very low birth weight (OR = 0.11 and 95% CI = 0.01-0.86; $p = 0.07$) and very preterm birth (OR = 0.22 and 95% CI = 0.07-0.68; $p = 0.01$).[57] Another study focused on an integrated behavioral intervention aimed at reducing psycho-behavioral risks in African-American women and resulted in a significant reduction of very preterm births in the intervention compared to the control group (OR = 0.42 and 95% CI = 0.19-0.93).[157]

Road traffic accidents | One protocol was efficacious in increasing preventive measures to decrease road traffic injuries.[35] The study population was made up of parent-teen American dyads.[35] The intervention involved class sessions focused on exposing parent-teen dyads to a video and lesson on a parent-teen driving agreement to aid in safe driving during the first year of driving as a teen.[35]This protocol used a group-randomized trial design.[35] The protocol resulted in increased likelihood of reporting driving restrictions during bad weather (heavy rain: $p<0.001$; snow or ice: $p<0.05$; fog: $p<0.01$).[35]

Hypertensive heart disease | Three randomized trial protocols were effective in reducing hypertensive heart disease related risk factors and/or outcomes.[38; 40; 120] Interventions included a web-based tool that assessed familial risk for diseases and provided personalized risk-tailored messages[38] as well as once-daily losartan- or atenolol-based antihypertensive therapy to hypertensive patients[40] and hypertensive patients with left ventricular atrophy.[120] Individuals in the intervention group were more likely to increase daily fruit and vegetable consumption from 5 or fewer servings a day to 5 or more servings a day (OR= 1.29; 95% CI, 1.05-1.58), increase physical activity to 5-6 times a week for 30 minutes or more a week (OR=1.47, 95% CI: 1.08-1.98), and less likely to move from not having cholesterol screening in the last 5 years to having their cholesterol measured within 5 years (OR= 0.34, 95% CI: 0.17-0.67).[38] Lower risk of new on-set atrial fibrillation (relative risk= 0.67; $p<0.001$),[40] fewer composite end points (hazard ratio=0.60, p=0.03) and strokes (hazard ratio=0.49, $p = 0.01$) in patients who developed new-onset atrial fibrillation,[40] and lower risk of fatal (hazard ratio=0.65; 95%CI 0.43-0.96; $p = 0.032$) [120] as well as atherothrombotic stroke (hazard ratio=0.72; 95%CI 0.59-0.88; $p = 0.001$) [120] were found in those treated with losartan compared to those treated with atenolol.

Neurodegenerative disorders had no rigorous and effective interventions published within this region.

Oceania

WHO Region 17, Oceania, is part of the WHO super region East Asia and Pacific and consists of the following countries: Fiji, Kiribati, Marshall Islands, Micronesia, Samoa, Solomon Islands, Tonga, and Vanuatu. There were no rigorous and effective interventions published within this region.

Top 10 causes of death in 2013 (deaths)

1. Colon and rectum cancers (n= 494,095)
2. Birth asphyxia and birth trauma (n= 55,451)
3. Prematurity and low birth weight (n= 32,983)
4. Cardiovascular disease (n= 18,456)
5. Diabetes (n= 16,891)
6. Ischemic heart disease (n= 10,675)
7. Chronic obstructive pulmonary disease (n= 9,651)
8. Road traffic accidents (n= 4,899)
9. Trachea, bronchus, lung cancers (n= 4,381)
10. Diarrheal diseases (n= 3,886)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Oceania

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Colon and rectum cancers	Flexible sigmoidoscopy screening[97]	Aspirin in cancer prevention[98]	Telephone counseling and screening[99]
2. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
3. Prematurity and low birth weight	Maternal Micronutrient Supplementation[65]	Pregnancy Deworming and iron-folate supplementation[95]	Micronutrient Supplementation[96]
4. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
5. Diabetes	Integrated community management of diabetes[77]	Metformin in obese children[32]	Tailored dietary advice and education[33]
6. Ischemic heart disease	Oral antiplatelet therapy post percutaneous coronary intervention[20]	Promotional stair-climbing program[21]	Rehabilitation with family support[22]
7. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
8. Road traffic accidents	Road safety and helmet promotion[81]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
9. Trachea, bronchus, lung cancers	Smoking behavior intervention[31]	Motivational interviewing[27]	Communities That Care program[158]
10. Diarrheal diseases	Hand washing promotion program[159]	Ceramic water purifiers[160]	Zinc supplementation to low birth weight infants[161]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

There were no rigorous and effective interventions published within this region.

Sub-Saharan Africa, Central

WHO Region 18, Central Sub-Saharan Africa, is part of the WHO super region Sub-Saharan Africa and consists of the following countries: Angola, Central African Republic, Congo, the Democratic Republic of Congo, Equatorial Guinea, and Gabon. There were three local efficacious interventions included in our package, of which one was conducted in the Democratic Republic of Congo,[67] one in Equatorial Guinea,[162] and one regional intervention.[163] Quality scores ranged from 4 to 7 within this region.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 817,466)
2. Chronic obstructive pulmonary disease (n= 155,126)
3. Malaria (n= 130,363)
4. Cardiovascular disease (n= 127,459)
5. Birth asphyxia and birth trauma (n= 127,219)
6. HIV/AIDS (n= 125,845)
7. Diarrheal diseases (n= 121,867)
8. Neonatal infections (n= 115,719)
9. Congenital disease (n= 82,927)
10. Diabetes (n= 61,174)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Central Sub-Saharan Africa

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Iron/folic acid supplementation and malaria prophylaxis[163]	Chloroquine prophylaxis or iron-folic acid supplementation[164]	Sulphadozine-pyrimethamine and malaria treatment[165]
2. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
3. Malaria	Insecticidal bed nets and residual spraying[162]	Community-based larviciding[166]	Intermittent Preventive Therapy and artemether-lumefantrine[167]
4. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
5. Birth asphyxia and birth trauma	WHO Essential Newborn Care program[67]	Performance-based payment of health care providers[66]	Tranexamic Acid on Clopidogrel[68]
6. HIV/AIDS	Male circumcision and HIV risk education[168]	Male circumcision[169]	HIV and alcohol risk reduction program[170]
7. Diarrheal diseases	Diapering, Food-Preparation, Hand-Washing Equipment[171]	Ceramic water filter[172]	Water disinfection and safe storage[173]
8. Neonatal infections	WHO Essential Newborn Care program[67]	Iron/folic acid supplementation and malaria prophylaxis[163]	Trained birthing assistant-based intervention[93]
9. Congenital disease	Folic acid fortification of staple foods[174]	Prenatal alcohol use intervention[147]	Multi-component physician intervention[148]
10. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Central Sub-Saharan Africa

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight				✓						
Chronic obstructive pulmonary disease										
Malaria							✓			
Cardiovascular disease										
Birth asphyxia and birth trauma					✓					
HIV/AIDS										
Diarrheal disease										
Neonatal infections				✓			✓			
Congenital disease										
Diabetes										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI = 0.58-0.99).[163]

Malaria | One intervention, which focused on distributing long-lasting insecticidal nets (LLIN) and biannual indoor residual spraying (IRS) in households in Equatorial Guinea and used historical control groups, found that children 1-4 years old had a lower prevalence of Malaria due to the intervention (OR for LLIN = 0.64, 95% CI = 0.55-0.74 and OR for IRS = 0.80, 95% CI = 0.62-1.03).[162]

Birth asphyxia and birth trauma | One protocol analyzing the effect of training birth attendants in rural Democratic Republic of Congo using the WHO Essential Newborn Care (ENC) program and an adaptation of the neonatal resuscitation program (NRP) was found efficacious in reducing neonatal morality[67]. The secondary analysis, using an active baseline design and a cluster-randomized trial found a decline in the risk of perinatal mortality during the year following ENC training (RR=0.73, 95% CI= 0.56-0.96)[67].

Neonatal infections | Two efficacious protocols focused on the enhanced training of birth attendants as well as iron and folic acid supplements.[67;163] One intervention succeeded in reducing perinatal mortality in a rural area of the Democratic Republic of Congo by using the WHO Essential Newborn Care program to train birth attendants (RR = 0.8, 95% CI: 0.66-0.97).[67] Another intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI = 0.58-0.99).[163]

Chronic obstructive pulmonary disease, cardiovascular disease, diarrheal disease, HIV/AIDS, congenital disease, and diabetes had no rigorous and effective interventions published within this region.

Sub-Saharan Africa, East

WHO Region 19, East Sub-Saharan Africa, is part of the WHO super region Sub-Saharan Africa and consists of the following countries: Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Madagascar, Malawi, Mauritius, Mozambique, Rwanda, Seychelles, Somalia, Sudan, Tanzania, Uganda, and Zambia. There were 12 local efficacious interventions included in our package, of which two were conducted in Uganda,[164; 175] two in Malawi,[167; 176] one in Mozambique,[165] two in Kenya,[169; 177] two in Tanzania,[166; 178] one in South Africa and Zimbabwe,[172] one in Rwanda,[66] and one regional intervention.[163] Quality scores ranged from 4 to 10 within this region.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 2,285,003)
2. HIV/AIDS (n= 615,993)
3. Cardiovascular disease (n= 381,046)
4. Malaria (n= 377,115)
5. Chronic obstructive pulmonary disease (n= 355,959)
6. Neonatal infections (n= 353,318)
7. Diarrheal diseases (n= 249,847)
8. Birth asphyxia and birth trauma (n= 249,683)
9. Road traffic accidents (n= 208,870)
10. Tuberculosis (n= 172,085)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in East Sub-Saharan Africa

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Chloroquine prophylaxis or iron-folic acid supplementation[164]	Sulphadozine-pyrimethamine and malaria treatment[165]	Intermittent Preventive Treatment[175]
2. HIV/AIDS	Male circumcision[169]	Metronidazole for potential HIV+ patients[177]	Poverty reduction[176]
3. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
4. Malaria	Community-based larviciding[166]	Intermittent Preventive Therapy and artemether-lumefantrine[167]	Sulphadozine-pyrimethamine and malaria treatment[165]
5. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
6. Neonatal infections	Iron/folic acid supplementation and malaria prophylaxis[163]	WHO Essential Newborn Care program[67]	Trained birthing assistant-based intervention[93]
7. Diarrheal diseases	Ceramic water filter[172]	Diapering, Food-Preparation, Hand-Washing Equipment[171]	Water disinfection and safe storage[173]
8. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
9. Road traffic accidents	Road safety education[69]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
10. Tuberculosis	Intradermal M. vaccae immunization[178]	Isoniazid preventive therapy[179]	Cotrimoxazole prophylaxis[180]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; East Sub-Saharan Africa

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight					✓	✓✓				
HIV/AIDS					✓		✓	✓		
Cardiovascular disease										
Malaria							✓	✓✓		
Chronic obstructive pulmonary disease										
Neonatal infections				✓						
Diarrheal disease										✓
Birth asphyxia and birth trauma						✓				
Road traffic accidents										
Tuberculosis							✓			

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | One efficacious intervention looked at the effects of the combination of weekly chloroquine prophylaxis and daily iron-folic acid supplementation on infant birth weight and resulted in a significant increase in mean birth weight (p = 0.03) and a reduction in low birth weight (p = 0.009) than the control group.[164] One protocol looked at the effects of a double dose of sulphadoxine-pyrimethamine on malarial infection during pregnancy as well as low birth weight in infants and found a relative risk of 1.39 (95% CI = 0.80-2.40) for low birth weight infants.[165] An intermittent preventive treatment of malaria in pregnancy also showed to have effects on low birth weight in infants.[175] The study indicated that in pregnant women, an intermittent preventive treatment of malaria led to a 6.3% proportion of low birth weight in the intervention group compared to the control group (p<0.03).[175]

HIV/AIDS | Three protocols focused on the prevention of HIV by improvement in known modifiable HIV risk factors.[169; 176; 177] Interventions ranged from male circumcision[169] to oral treatment[177] to cash payments aimed at reducing HIV-related poverty.[176] Study participants included young men,[169] reproductive-aged women at risk for HIV,[177] and young school-aged girls.[176] All interventions used an RCT study design, comparing an intervention to a control group.[169; 176; 177] As compared to the control group, intervention participants reported lower sexually transmitted infections sero-positivity (HR of bacterial vaginosis: 0.55 with 95% CI: 0.49-0.63, p<0.001[177]; HSV-2 adjusted OR: 0.24 with 95% CI: 0.09-0.65[176]) and lower HIV prevalence (p = 0.02[169]; adjusted OR: 0.36 with 95% CI: 0.14-0.91[176]).

Malaria | There were three efficacious protocols for preventing Malaria in this region.[165-167] One intervention focused on larviciding in certain areas of Dar es Salaam, Tanzania and found that the odds of individuals living in these areas being infected with Malaria was 21% lower than those who lived in untreated areas (OR: 0.79, 95% CI: 0.66-0.93).[166] Another intervention focused on intermittent preventive therapy post-discharge (IPTpd) in children aged 4-59 months who were admitted to hospitals in Malawi for severe malarial anaemia.[167] The study found that the intervention had the greatest protective effect 1-3 months into the study period, where less primary events occurred in children in the intervention group (p = 0.01) as compared to the control group.[167] One protocol looked at the effects of a double dose of sulphadoxine-pyrimethamine on malarial infection during pregnancy and found that after a second dose the prevalence of malaria in the placebo group compared to the intervention group had a relative risk of 2.24 (95% CI: 1.34-3.75).[165]

Neonatal infections | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI = 0.58-0.99).[163]

Diarrheal disease | One protocol that was found efficacious in reducing diarrheal disease entailed the use of a ceramic water filter among households in rural South Africa and Zimbabwe.[172] In the households that received the intervention, drinking water showed reduced E. coli counts (RR = .67, 95% CI: 0.5-0.89; $p = 0.006$) and the incidence for diarrhea was much lower among filter users (IRR 0.20, $p<0.001$).[172]

Birth asphyxia and birth trauma | One protocol assessed a performance-based payment of health-care providers and was found efficacious in the use and quality of child and maternal care services in health-care facilities in Rwanda[66]. A survey of facilities found the intervention group to have a 23% ($p = 0.017$) increase in number of institutional deliveries and a 56% ($p = 0.004$) increase in number of preventive care visits by children aged 23 months or younger and 132% ($p = 0.000$) and an increase in preventive care visits by children between 24 and 59 months[66].

Road traffic accidents | One protocol was effective in improving road traffic compliance among motorcyclists through a road safety educational program.[69] Three months after the intervention, compliance among the intervention arm was at 70% an among the control 18%, as statistically significant difference ($p<0.05$).[69]

Tuberculosis | One protocol was efficacious in the prevention of tuberculosis.[178] This randomized, placebo-controlled trial administered five intradermal doses of *M.vaccae* or placebo to HIV-infected patients with CD4 cell counts of at least 200cells/ml and a Bacille Calmette–Guerin scar and resulted in hazard ratio of 0.61 ($p = 0.03$) for definite tuberculosis comparing vaccine to placebo.

Cardiovascular disease and chronic obstructive pulmonary disease had no rigorous and effective interventions published within this region.

Sub-Saharan Africa, Southern

WHO Region 20, Southern Sub-Saharan Africa, is part of the WHO super region Sub-Saharan Africa and consists of the following countries: Botswana, Lesotho, Namibia, South Africa, Swaziland, and Zimbabwe. There were six unique local efficacious interventions included in our package, of which six were conducted in South Africa[168; 170; 179-181] and one regional intervention.[163] Quality scores ranged from 4 to 7 within this region.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 473,818)
2. HIV/AIDS (n= 302,128)
3. Cardiovascular disease (n= 119,521)
4. Birth asphyxia and birth trauma (n= 97,617)
5. Chronic obstructive pulmonary disease (n= 94,238)
6. Diabetes (n= 79,353)
7. Cerebrovascular disease (n= 45,645)
8. Road traffic accidents (n= 43,202)
9. Neonatal infections (n= 38,881)
10. Tuberculosis (n= 38,068)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in Southern Sub-Saharan Africa

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Iron/folic acid supplementation and malaria prophylaxis[163]	Chloroquine prophylaxis or iron-folic acid supplementation[164]	Sulphadozine-pyrimethamine and malaria treatment[165]
2. HIV/AIDS	Male circumcision and HIV risk education[168]	HIV and alcohol risk reduction program[170]	HIV prevention motivational counseling[181]
3. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
4. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
5. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
6. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]
7. Cerebrovascular disease	Exercise to Enhance Mobility Post-stroke[23]	Health Belief Model Telephonic Intervention[24]	Tailored dietary advice and education[25]
8. Road traffic accidents	Road safety education[69]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
9. Neonatal infections	Iron/folic acid supplementation and malaria prophylaxis[163]	WHO Essential Newborn Care program[67]	Trained birthing assistant-based intervention[93]
10. Tuberculosis	Isoniazid preventive therapy[179]	Cotrimoxazole prophylaxis[180]	Intradermal M. vaccae immunization[178]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; Southern Sub-Saharan Africa

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight				✓						
HIV/AIDS							✓	✓✓		
Cardiovascular disease										
Birth asphyxia and birth trauma										
Chronic obstructive pulmonary disease										
Diabetes										
Cerebrovascular disease										
Road traffic accidents										
Neonatal infections		✓								
Tuberculosis					✓	✓				

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI: 0.58-0.99).[163]

HIV/AIDS | Three protocols focused on the prevention of HIV by improvement in HIV risk factors.[168; 170; 181] Interventions ranged from safe sex motivational counseling[181] to male circumcision[168] to alcohol-focused risk-reduction counseling.[170] Study participants included uncircumcised HIV-negative young men, [168] men and women in Cape Town, South Africa,[170] people living with HIV on ART[181]. As compared to the control group, intervention participants reported more frequent condom use (p<0.05[170]; p<0.001[181]), lower HIV incidence (p = 0.00049[168]), and fewer acts of drinking in sexual contexts (p<0.05[170]).

Neonatal infections | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI: 0.58-0.99).[163]

Tuberculosis | Two protocols were effective in preventing tuberculosis related outcomes. One was a randomized trial that included self-administration of isoniazid, 300 mg/d, by HIV-infected male employees of a gold-mining company[179] and the other was a cohort study using historical controls that included a regimen of cotrimoxazole prophylaxis 960 mg once daily for adults with active TB.[180] The incidence rate ratio for the effect of clinic enrollment on TB incidence was 0.68 (p = 0.03),[179] the mortality at 6 months was 29% lower in intervention group than that in the control group (p<0.001),[180] a higher percentage of individuals from control group (12.1%) had sputum positive TB compared to intervention group (8.9%) (p=0.02),[180] and intervention group had more time to death (98 mean days) compared to the control group (58.5 mean days) (p<0.001).[180]

Cardiovascular disease, birth asphyxia and birth trauma, chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, and road traffic accidents had no rigorous and effective interventions published within this region.

Sub-Saharan Africa, West

WHO Region 21, West Sub-Saharan Africa, is part of the WHO super region Sub-Saharan Africa and consists of the following countries: Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Cote d'lvoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome and Principe, Sierra Leone, and Togo. There were two unique local efficacious interventions included in our package, of which one was conducted in Nigeria[69] and one regional intervention.[163] The quality score of all interventions within this region was 4.

Top 10 causes of death in 2013 (deaths)

1. Prematurity and low birth weight (n= 2,609,557)
2. Malaria (n= 941,975)
3. Neonatal infections (n= 479,470)
4. Road traffic accidents (n= 445,867)
5. Chronic obstructive pulmonary disease (n= 417,511)
6. HIV/AIDS (n= 412,288)
7. Cardiovascular disease (n= 340,390)
8. Birth asphyxia and birth trauma (n= 335,898)
9. Congenital disease (n= 309,095)
10. Diabetes (n= 267,653)

TABLE 1. Top Three Interventions per the Top 10 Causes of Death in West Sub-Saharan Africa

TOP 10 CAUSES OF DEATH	INTERVENTIONS		
1. Prematurity and low birth weight	Iron/folic acid supplementation and malaria prophylaxis[163]	Chloroquine prophylaxis or iron-folic acid supplementation[164]	Sulphadozine-pyrimethamine and malaria treatment[165]
2. Malaria	Community-based larviciding[166]	Intermittent Preventive Therapy and artemether-lumefantrine[167]	Training on bed net utilization[182]
3. Neonatal infections	Iron/folic acid supplementation and malaria prophylaxis[163]	WHO Essential Newborn Care program[67]	Trained birthing assistant-based intervention[93]
4. Road traffic accidents	Road safety education[69]	The Checkpoints Program[35]	"Skipper" Designated Driver Program[37]
5. Chronic obstructive pulmonary disease	Azithromycin[56]	Tiotropium[30]	Smoking behavior intervention[31]
6. HIV/AIDS	Male circumcision and HIV risk education[168]	Male circumcision[169]	HIV and alcohol risk reduction program[170]
7. Cardiovascular disease	Metformin and Intensive lifestyle change[14]	Protein and glycemic control diet[15]	Lifestyle counseling to obese groups[16]
8. Birth asphyxia and birth trauma	Performance-based payment of health care providers[66]	WHO Essential Newborn Care program[67]	Tranexamic Acid on Clopidogrel[68]
9. Congenital disease	Folic acid fortification of staple foods[174]	Prenatal alcohol use intervention[147]	Multi-component physician intervention[148]
10. Diabetes	Metformin in obese children[32]	Tailored dietary advice and education[33]	Diabetic smoking cessation program[70]

Notes. green = intervention was studied within WHO region; red = intervention was studied outside of region

TABLE 2. Intervention quality score distribution by causes of death; West Sub-Saharan Africa

CAUSES OF DEATH	INTERVENTION QUALITY SCORE									
	1	2	3	4	5	6	7	8	9	10
Prematurity and low birth weight				✓						
Malaria										
Neonatal infections				✓						
Road traffic accidents				✓						
Chronic obstructive pulmonary disease										
HIV/AIDS										
Cardiovascular disease										
Birth asphyxia and birth trauma										
Congenital disease										
Diabetes										

Notes. Intervention color key: behavioral interventions are in orange, structural interventions in black, and therapeutic/medicinal are in green

Select efficacious intervention descriptions evaluated and published within region

Prematurity and low birth weight | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI: 0.58-0.99).[163]

Neonatal infections | One efficacious intervention looked at the effects of the combination of iron and folic acid supplements and prenatal antimalaria prophylaxis on neonatal mortality in countries in Sub-Saharan Africa.[163] Infants of mothers who received this intervention during pregnancy showed a significant reduction in neonatal death (HR = 0.76, 95% CI: 0.58-0.99).[163]

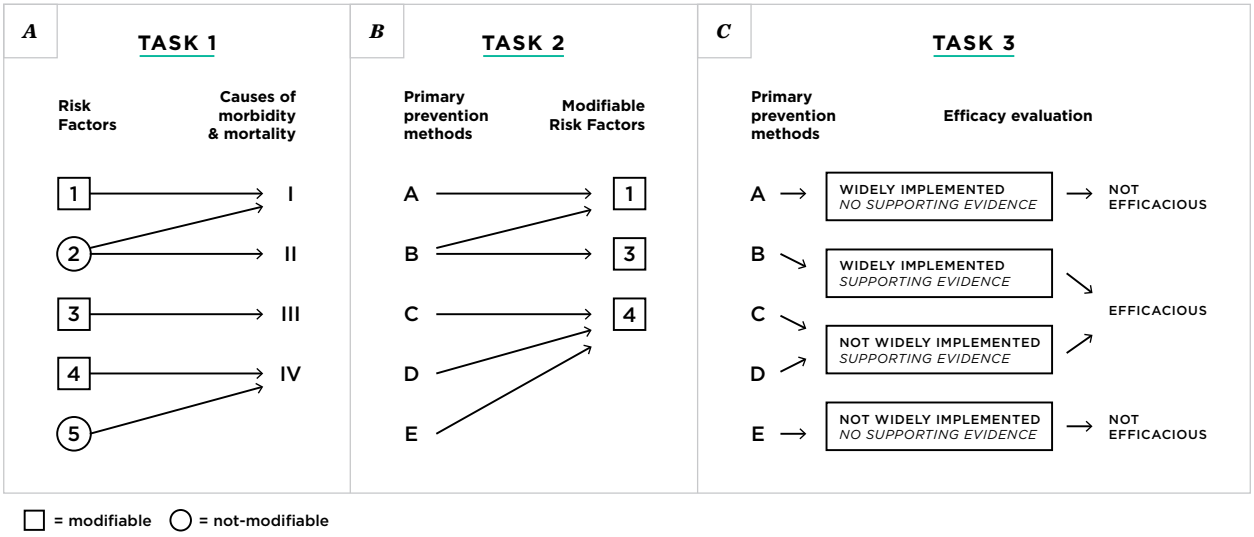
Road traffic accidents | One protocol was efficacious in increasing preventive measures to decrease road traffic injuries.[69]The study population was motorcyclists in Uyo, Southern Nigeria.[69] The intervention emphasized the importance of obeying road safety signs.[69] This protocol used experimental-control trial design with the control group selected from a town with similar characteristics to the intervention town.[69] The intervention resulted in increased motorcyclist helmet intervention compliance ($p<0.05$).[69]

Malaria, chronic obstructive pulmonary disease, HIV/AIDS, cardiovascular disease, birth asphyxia and birth trauma, congenital disease, and diabetes had no rigorous and effective interventions published within this region.

Appendix A — Detailed Methods Description

We identified the proximal modifiable risk factors (Task 1); systematically reviewed (Task 2) and evaluated (Task 3) the peer-reviewed scientific literature for efficacious primary prevention interventions; and identified (Task 4) primary prevention packages based on the literature for the top ten causes of mortality by WHO region.

FIGURE 1. Literature review work-plan



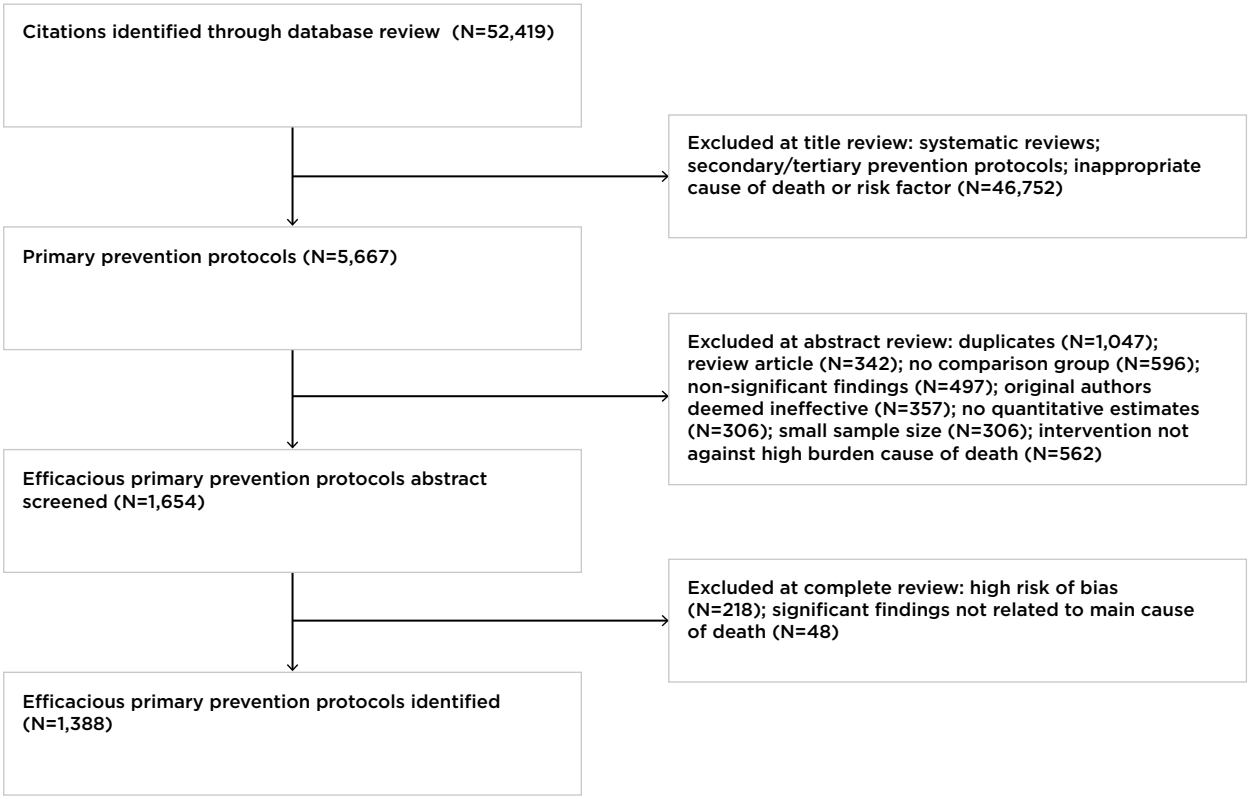
The above figure details the overall methods employed in this literature review.

Task 1 | Under Task 1, first we reviewed and compiled a list of the top 10 causes of death in 2013 (most recent global mortality estimates available), by WHO region.[183] Table 1 presents the top 10 causes of death by global region, organized by global relative mortality burden (1 to 10 indicating largest to smallest mortality burden). Cardiovascular disease (labeled as A in the table) was the largest underlying cause of death in 2013, responsible for 17,330,838 deaths. Of the top 10 causes of death globally, seven were attributed to non-communicable causes, with one cause each related to maternal and child health, human-made, and infectious diseases. Consistent with the epidemiologic transition, higher income regions have few to no infectious diseases among their top ten causes of death, while those in lower resource regions, such as Sub-Saharan Africa, have more infectious diseases among their top ten list. Most notably, Eastern Sub-Saharan Africa has four (HIV/AIDS, malaria, diarrheal diseases, and tuberculosis) infectious diseases among its top ten causes of death while thirteen of the remaining twenty regions have no infectious diseases among their top ten causes of death. Beyond differences in disease categorization (infectious, non-infectious, etc.) across regions, there are differences with the relative burden of mortality causes. Cardiovascular disease ranks among one of the top ten causes of death for each region, while hepatitis, inflammatory heart disease, and stomach cancer only appear in the top ten lists for one region (East Asia, Central Europe, and High Income Asia Pacific, respectively).

After identifying the top ten causes of death per region, risk factors for each of these main twenty-four causes of death were searched and identified from *UpToDate*, a medical information database for clinicians of prevention protocols.[16] Twenty-five modifiable proximal risk factors were thus documented.

Task 2 | For Task 2, we systematically searched the existing peer-reviewed literature for all primary prevention methods, published from 2000 to 2014 and catalogued in Medline (searched via PubMed.gov website). Based on subcategories of main causes of death, 49 causes of death and 25 risk factors were searched. From the 52,419 citations we initially title screened, 1,388 (2.6%) rigorous efficacious interventions were identified (see Figure 2 for complete literature review process).

FIGURE 2. Primary prevention literature review process, universal primary prevention imperative, 2000 – 2014



The above figure presents the results of the literature review process, from title and abstract review to final primary prevention protocol identification.

Task 3 | In Task 3 we evaluated the peer-reviewed scientific literature for efficacious primary prevention interventions creating a quality ranking score informed by bias assessment tools from the Cochrane Collaboration's review process;[184] GRADE quality assessment tool;[185] Downs and Black scale;[186] Newcastle Ottawa scale;[187] and NICE guidelines for quality assessment (GATE checklist)[188; 189]. See Appendix B for a detailed description of the quality score generation process. The quality score could theoretically range from 0 to 17 with a maximum of six points allotted to sample selection and recruitment, five points to study design, four points for intervention assessment, and one point for analytic technics. Figure 3 shows the mean and range of quality scores for interventions addressing the top 10 causes of death, globally. For the top three interventions for the top 10 causes of death globally, the mean quality scores ranged from 4.1 (road traffic accidents) to 6.6 (chronic obstructive pulmonary disease) with 10 as the highest individual study quality score reported for ischemic heart disease, diabetes, and HIV/AIDS.

Task 4 | Task 4 identified 21 primary prevention packages (one for each WHO region), drawing on 77 unique primary prevention intervention protocols. Rigorous published intervention evaluations were not equally available across WHO region. Figure 4 shows the proportion of interventions included in the final report out of those reviewed, by region. Oceania, at 0.0%, has the lowest percentage of included interventions and South Asia, at 52.0%, has the highest percentage. Interventions (noted as n next to the region) reviewed by region range from Eastern Europe with 6 interventions to High Income Asia Pacific at 1,194.

Appendix B — Quality Score Description

The quality score developed and used to evaluate each extracted article in this project was informed by existing bias assessment tools from the Cochrane Collaboration's review process[184]; GRADE quality assessment tool[185]; Downs and Black scale[186]; Newcastle Ottawa scale[187]; and NICE guidelines for quality assessment (GATE checklist)[188; 189]. First, we reviewed all items of the existing tools and relative ranking systems. Second, we removed items from the list that were redundant across tools, did not apply to the literature we were reviewing, or were of low priority in evaluating quality studies (as determined by authors of this study). Third, we applied the point system to a few articles, reviewed their relative scores and agreed on the final quality scoring system. Below is a table of items in the score and the amount of points an article could receive if it had that item. The authors consider the points in the scale to have no intrinsic value, but rather their utility is in the ability to discern levels of rigor across studies.

DOMAIN	ITEM	POINTS
Study design	Longitudinal design	**1**
Study design	Controlled trial	**2**
Study design	Quasi-experimental	**1**
Study design	Source population, eligible population and study population well described and appropriate	**1**
Sample	Response rate between 80-100%	**2**
Sample	Response rate between 60-79%	**1**
Sample	Intervention and comparison groups similar in all categories, with respect to age, sex, socio-demographics, racial or ethnic group representation, geographic region, and number of participants.	**2**
Sample	Intervention and comparison groups similar in five out of six categories, with respect to age, sex, socio-demographics, racial or ethnic group representation, geographic region, and number of participants.	**1**
Intervention	Intervention assessment utilized a validated survey	**1**
Intervention	Intervention assessment utilized an adapted pre-existing intervention and all participants and researchers were blinded to participant group allocation	**2**
Intervention	Intervention assessment utilized two out of three of the following: adapted pre-existing intervention; participants were blinded to group allocation; and researchers were blinded to participant group allocation	**1**
Intervention	Intervention outcome assessment was based on a locally validated survey	**1**
Analysis	Final analysis was adjusted or stratified for at least one appropriate covariate	**1**
	Total theoretically possible	**17**

Appendix C — Abbreviations

AMI	Acute myocardial infarction
aOR	Adjusted odds ratio
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCM	Chronic Care Model
CHD	Coronary heart disease
CHOICE	The Choice of Health Options In prevention of Cardiovascular Events
CK-MB	Creatine kinase-MB
COPD	Chronic obstructive pulmonary disease
CSB	Comprehensive smoking ban
cTnI	Cardiac troponin I
CVD	Cardiovascular disease
DCPDC	Disease Control Priorities in Developing Countries
DP	Distal protection
EG	Experimental group
ENC	Essential Newborn Care
FEV1	Forced expiratory rate in one second
HbA1c	Hemoglobin A1c
HBIG	Hepatitis B immune globulin
HBV	Hepatitis B virus
HDL-c	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HR	Hazard ratio
HSV-2	Herpes simplex virus 2
IC	Integrated care
IFG	Impaired fasting glucose
IGF-I	Insulin-like growth factor I
IL 10	Interleukin 10
IL 1ß	Interleukin 1ß
IMT	Intima-media thickness
IPTpd	Intermittent preventive therapy post-discharge
IRR	Incidence rate ratio

IRS	Indoor residual spraying
LDL	Low density lipoprotein
LDL-c	Low-density lipoprotein cholesterol
LIPID	The Long-Term Intervention with Pravastatin in Ischemic Disease
LLIN	Long-lasting insecticidal nets
MACE	Major adverse cardiac events
MAP	Mean arterial pressure
NRP	Neonatal resuscitation program
OR	Odds ratio
PCI	Percutaneous coronary intervention
PMI	Proactive multifactorial intervention
POBA	Plain old balloon angioplasty
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized controlled trial
RD	Risk difference
RR	Relative risk
RR	Risk ratio or relative risk
TB	Tuberculosis
TIMI	Thrombolysis In Myocardial Infarction
TTI	Tobacco tax increase
UC	Usual care
WHO	The World Health Organization
WHO-CHOICE	WHO-CHOosing Interventions that are Cost-Effective

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