Hypertension treatment and control in Nepal: health care challenges and the potential of nonpharmacological interventions in the management of high blood pressure

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Abstract

Hypertension is among the leading preventable causes of cardiovascular diseases and deaths globally. Accumulating evidence suggested that the burden of hypertension is growing, particularly in low-and middle-income countries. Hypertension treatment and control remain challenging due to barriers associated with health system, healthcare providers, and patients.

There is a lack of country-specific information on factors influencing hypertension treatment and control in Nepal, a South-Asian lower-middle-income country. Besides, in Nepalese primary care practice, the uptake of guidelines to use non-pharmacological interventions alongside the anti-hypertensive medications for optimum control of blood pressure is low.

The aims of this thesis were: (1) to assess the gaps and associated barriers and enablers of hypertension treatment and control in Nepal; (2) synthesize the available evidence on non-pharmacological interventions for hypertension, including alcohol reduction, physical activity, salt reduction, potassium supplementation, weight control, and heart-healthy diet; and (3) explore the potential of yoga intervention, as one of promising non-pharmacological interventions, in the primary care setting in Nepal.

This thesis includes five studies. The first study was a secondary analysis of data from two national surveys in Nepal which assessed the prevalence and associated factors of screening, awareness, treatment, and control of hypertension. The second study was a systematic review conducted to assess barriers, enablers, and strategies for hypertension treatment and control in Nepal. The third study narratively synthesised the evidence on non-pharmacological interventions for hypertension in primary care. The fourth study was a randomised control trial, testing the effectiveness of yoga, as a non-pharmacological intervention in primary care, on reducing blood pressure in patients with hypertension. The fifth study was a mixed-methods study exploring the implementation potential of the yoga intervention for hypertension control in the primary care setting.

The findings of Study 1 suggested that the gap in cascade of hypertension care is prominent in Nepal, where the poor, the participants from remotely located provinces, those who received treatment from in primary health care centres and public hospitals, those who

did not have health insurance coverage, and those under the age of 30 years were at a higher risk of inadequate hypertension care. Furthermore, Study 2 found several barriers to hypertension treatment and control associated with health governance, health service delivery, health financing, medication, technologies, human resources, individual health care providers, and patients, which are the major challenges for improving hypertension management in Nepal. The narrative review (Study 3) showed that previous evidence supports the use of alcohol reduction, sodium intake reduction, physical activity, and weight reduction as non-pharmacological interventions for blood pressure reduction in primary care, but more research is needed on other types of promising interventions, such as yoga. The intervention trial (Study 4) found that a health-worker led yoga intervention is effective for blood pressure reduction among patients with hypertension, while Study 5 showed that it is feasible to implement such an intervention in the primary care setting in Nepal.

Overall, the thesis sheds light on imminent health care challenges related to hypertension treatment and control in Nepal. The findings may inform general practitioners, health administrators, and policymakers about the effectiveness, barriers, and facilitators of non-pharmacology interventions, including yoga. This may facilitate the implementation of such interventions in the standard primary care practice, and consequently improve the outcomes of hypertension treatment and control in Nepal.

Declaration

"I, Raja Ram Dhungana, declare that the PhD thesis entitled "Hypertension treatment and control in Nepal: health care challenges and the potential of nonpharmacological interventions in the management of high blood pressure" is no more than 100,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references and footnotes. This thesis contains no material that has been submitted previously, in whole or in part, for the award of any other academic degree or diploma. Except where otherwise indicated, this thesis is my own work. I have conducted my research in alignment with the Australian Code for the Responsible Conduct of Research and Victoria University's Higher Degree by Research Policy and Procedures. All research procedures reported in the thesis were approved by the VU Human Research Ethics Committee [Approval Number: HRE19-142]".

Signature

Date: 14 December 2021

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PART A:

DETAILS OF INCLUDED PAPERS: THESIS BY PUBLICATION

Please list details of each Paper included in the thesis submission. Copies of published Papers and submitted and/or final draft Paper manuscripts should also be included in the thesis submission

Item/ Chapter No.	Paper Title	Publication Status (e.g. published, accepted for publication, to be revised and resubmitted, currently under review, unsubmitted but proposed to be submitted)	Publication Title and Details (e.g. date published, impact factor etc.)
Chapter 4, Study 1	Hypertension screening, awareness, treatment, and control: a study of their prevalence and associated factors in a nationally representative sample from Nepal	Published	Global Health Action (Q1 journal) Published date: Feb 8, 2022
Chapter 4, Study 2	Barriers, enablers, and strategies for the treatment and control of hypertension in Nepal: a systematic review	Published	Frontiers in Cardiovascular Medicine (Q1 journal), Published date: Oct 11, 2022
Chapter 5, Study 3	Implementation of non-pharmacological interventions for blood pressure reduction in primary care: a review of effectiveness, cost-effectiveness, barriers, and facilitators	Under review	BMC Primary Care (Q1 journal) Submitted date: Apr 5, 2022
Chapter 6, Study 4	Effects of a health worker-led 3-month yoga intervention on blood pressure of hypertensive patients, a randomised controlled multicentre trial in the primary care setting	Published	BMC Public Health (Q1 journal) Published date: Mar 20, 2021
Chapter 6, Study 5	Yoga for hypertensive patients: a study on barriers and facilitators of its implementation in primary care	Published	Global Health Action (Q1 journal) Published date: Jan 1, 2021

Declaration by [candidate name]: Raja Ram Dhungana **Signature:** [redacted] **Date:** 14 December 2021

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Chapter 1. General introduction

This chapter presents the background about the burden of hypertension globally and in Nepal, and illustrates the evidence gap in the cascade of hypertension care in Nepal. This chapter also introduces the importance of nonpharmacological interventions for hypertension and provides a rationale for synthesising evidence on implementation of nonpharmacological interventions in primary care as well as generating country-specific evidence on the feasibility of using yoga for hypertension control in primary care in Nepal.

1.1. Background

1.1.1. Global burden of hypertension

Hypertension is among the key causes of non-communicable diseases in 2019 [1]. It is also the major cause of premature death globally [2]. Most importantly, the increasing trend in hypertension associated deaths and disability is a growing public health concern worldwide. Recent evidence suggests that deaths and disabilities due to hypertension have increased significantly in the last three decades: the deaths increased from 6.8 million in 1990 to 10.8 million in 2019; the disability-adjusted life years (DALYs) rose from 2,874 to 3,043 per 100,000 population in the same period [1].

Additionally, hypertension is also among the most common preventable causes of cardiovascular disease and death. Deaths and disabilities due to cardiovascular diseases accounted for large proportions of the total deaths (32.8% of total deaths) and total DALYs (15.5% of total DALYs) globally in 2019 [3, 4]. Cardiovascular diseases also cause a high economic burden to the individual, family, and nation due to the cost incurred from long-term and expensive care of diseases, where the annual cardiovascular diseases care costs exceed health expenditure per capita in most low-and middle-income countries [5]. The health and economic burdens of cardiovascular diseases are the sequela of hypertension, and the suffering will not be alleviated unless the prevention and optimal control of hypertension is achieved.

Recent evidence showed that more and more people are affected by hypertension globally. Compared to 1990, the absolute number of 30-79 years of hypertensive people doubled in 2019 [6]. Specifically, the cases of hypertension surged from 331 million to 626 million among women and 317 million to 626 million among men globally in the same period [6]. Not only did the cases of hypertension increase during this period but the uptrend in the age-standardised prevalence of hypertension was also observed particularly in low-and middle-income countries [7], indicating a burgeoning burden of hypertension.

1.1.2. Challenges in hypertension management

Amid the rising burden of hypertension, the only ways to reduce the risk of hypertension-related complications are either to prevent the disease or to improve cascade of hypertension care through effective detection, treatment, and optimal control of blood pressure [8]. However, the indicators of cascade of hypertension care such as the prevalence of screening (percentage of the individuals who have ever had their blood pressure measured by a doctor or another health worker), awareness (percentage of individuals who know they have high blood pressure, which have been diagnosed by the doctor or another health worker), treatment (percentage of individuals who use any antihypertensive medication to lower blood pressure), and control (percentage of individuals who have a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg) of hypertension remain low in most of the countries around the globe. The prevalence of hypertension treatment was below 25% and the prevalence of hypertension control was below 10% for some countries in sub-Saharan Africa, Oceania, and South Asia in 2019 [6]. Another study found that less than 25% of hypertensive people were under medication and below 10% had controlled blood pressure in north Africa, central and south Asia in 2019 [7] The low prevalence of hypertension awareness, treatment, and control indicate a huge gap in the cascade of hypertension care.

The poor performance in the cascade of hypertension care could be associated with several barriers associated with service delivery, health workforce, access to medicines, and financing [9-14]. Similarly, factors relating to poor knowledge and practices of hypertensive patients such as non-adherence to medicine, experienced or perceived adverse effects of antihypertensive drugs, and poor health-seeking behaviour can also affect the treatment and control of hypertension [14-16]. Therefore, hypertension management is often quite challenging and requires multifaceted approaches. In alignment with that fact, several global initiatives and programs including *Global Hearts Initiative* by the World Health Organization and *Hypertension Roadmap* by the World Heart Federation are being implemented to improve hypertension control globally [8]. Most of these technical packages have highlighted nonpharmacological interventions as an important component of hypertension management, along with other integrated strategies.

1.1.3. Nonpharmacological intervention

The behaviour modifications particularly limiting alcohol intake, increasing physical activity, salt reduction, potassium supplementation, and weight control are found to have a very

promising blood pressure-lowering effect in hypertensive patients. They could potentially reduce blood pressure by 4-11 mmHg in hypertension [17]. Owing to that fact, all available international guidelines for hypertension treatment and practice recommend them as nonpharmacological interventions for controlling blood pressure [18, 19]. Further, they are also recommended along with pharmacological treatment in individuals with hypertension to achieve better control of blood pressure and reduce the dosage of drugs or pill burden.

However, translating the recommendation of using nonpharmacological interventions into practice remains challenging. Evidence on the effectiveness of nonpharmacological interventions for hypertension control in a real-world setting is limited and inconsistent. Furthermore, there is very little evidence on the implementation potential of nonpharmacological interventions to improve hypertension management specific to low-and middle-income countries.

1.1.4. Context: hypertension in Nepal and nonpharmacological interventions

1.1.4.1. Burgeoning burden of hypertension and need for bridging the evidence gap

Nepal is considered a lower-middle-income country in South Asia. It is a multi-ethnic, multi-lingual, multi-religious, multi-cultural, and mostly mountainous country, with around 30 million inhabitants in 2021. Recently, the country reformed the political and organizational system, phasing out a unitary system and adopting a three-tiers federal system of government. Now Nepal has seven provinces and 753 local governments.

With federalization, the responsibility for health also shifted from the Central level to the Provincial government and local level and the transformation process is still in transition. For now, around 7000 public and private health facilities are providing promotive, preventive, curative, and rehabilitation care in Nepal. The public health facilities include hospitals (*n*=125), primary health care centres (*n*=198), health posts (*n*=3808), urban health centres (*n*=374), community health units (*n*=299), and other health facilities (*n*=59) [20]. District hospitals, primary health care centres, and health posts are the grass-root level health facilities for providing primary health care services at the levels of districts, municipalities, and wards. The community-based health services are provided by the three cadres of

community-level service providers: female community health volunteers, auxiliary nurse midwives, and auxiliary health workers.

Following the global epidemiological transition, the burden of diseases in Nepal has also shifted from communicable, maternal, neonatal and nutritional diseases to non-communicable diseases. The percentage of deaths due to communicable, maternal, neonatal and nutritional diseases has reduced from 63.6% in 1990 to 26.8% in 2017 [21], whereas the percentage of deaths due to non-communicable diseases increased from 29.9% in 1990 to 63.2% in 2017 [21]. It is an established fact that the growing burden of non-communicable diseases is mainly due to an increase in the ageing population; exposure to behavioural risk factors such as tobacco use, harmful alcohol consumption, unhealthy diet, and insufficient physical activity; and growing prevalence of metabolic risk factors including obesity, diabetes, and hypertension [2]. Evidence showed that there has been an increasing trend in the prevalence of harmful alcohol consumption, insufficient physical activity, obesity, diabetes, and hypertension in Nepal [22-24].

The increasing prevalence of hypertension is a growing public health concern in Nepal. Studies showed that nearly one-third of the population are affected with hypertension in Nepal in 2020 [24, 25]. The prevalence is almost 6 percent points larger than in 2000 [24]. Together with hypertension, deaths and disability attributed to cardiovascular diseases has increased significantly in the last three decades [1]. This has caused a significant increase in the government's health spending as well as out of pocket expenditure for people [26].

The burden of hypertension and its sequelae can be mitigated through the prevention and control of hypertension. Effective management and optimal control of hypertension require a quality cascade of hypertension care steps including screening, awareness, treatment, and control. Therefore, a systematic investigation of the distribution and determinants of screening, awareness, treatment, and control of hypertension is needed in Nepal which informs the stakeholders on gaps in the cascade of hypertension care. It also helps to identify those hypertensive persons who are most likely to be unaware of the elevated level of blood pressure they have, those who are aware of their hypertension status but are not likely to seek treatment, or those who have an uncontrolled blood pressure despite taking antihypertensive medication [27, 28].

Similarly, a comprehensive understanding of the factors influencing hypertensive treatment and control is important to address barriers and promote facilitators of hypertension

control. Further, a deeper insight into barriers and facilitators of hypertension control could also contribute to the development of contextual and problem-specific strategies for hypertension management. However, very little is known about the barriers and facilitators of hypertension control in Nepal. Thus, a systematic investigation of the factors influencing hypertension control can shed light on the range of barriers for hypertension treatment and control related to the health system, health providers, and patients in Nepal.

1.1.4.2. Potential nonpharmacological interventions and feasibility of implementing yoga in Nepal

As discussed above, despite a wealth of evidence on the importance of nonpharmacological interventions for hypertension management and strong recommendations for using them alongside the medication to further reduce blood pressure, they are not fully adopted in practice by primary healthcare providers. To understand the factors influencing uptake of evidence into practice in primary care settings, a thorough review of the evidence on the effectiveness, cost-effectiveness, barriers, and facilitators of nonpharmacological interventions for blood pressure reduction in primary care is necessary.

Furthermore, implementation of nonpharmacological interventions in a real-world setting can be challenging. Several country-specific contextual factors such as perspectives of hypertensive patients towards intervention, implementation settings, and implementer's characteristics can influence the implementation of interventions, affecting their outcome [29-31]. Likewise, the level of acceptability of the intervention among study participants and cost of implementation of interventions are also important in determining outcome and for translation of evidence to practice [30, 32, 33]. However, none of the nonpharmacological interventions have been tested in a real-world clinical setting in Nepal and nothing was known about factors influencing the implementation of these interventions. It is, therefore, essential to generate Nepalese context-specific evidence on the nonpharmacological interventions to maximise uptake of evidence in clinical practice.

Yoga is culturally acceptable and commonly practised nonpharmacological intervention in Nepal [34-36]. The Ministry of Health and Population has recognised yoga as a lifestyle therapy [34, 35]. Several yoga-based programs are implemented through health facilities in 77 districts to promote health and wellbeing of the population [35]. Recent evidence suggested that yoga can also be used as an antihypertensive therapy [37]. Two studies from Sweden have investigated the effect of yoga on hypertension in primary health care settings but none has involved primary health care staff in implementing yoga

interventions [38, 39]. Further, none of the studies have provided detailed insights into the barriers and facilitators of implementing yoga for hypertension in primary care settings. As yoga is the most culturally compatible and well recognised antihypertensive therapy in Nepal, assessing the effectiveness of yoga intervention on blood pressure reduction and uncovering the barriers and facilitators of its implementation in primary care settings could facilitate adoption of yoga interventions for hypertension in primary care in Nepal

1.2. Aims of the thesis

The overarching aim of the thesis was to assess the burden of hypertension in Nepal and identify potential non-pharmacological interventions for hypertension specific to the Nepalese context. Specific aims of the thesis were to:

a) assess the prevalence and associated factors of hypertension screening, awareness, treatment, and control in Nepal
b) identify the barriers, enablers, and strategies for hypertension treatment and control in Nepal
c) synthesise the evidence on non-pharmacological interventions for hypertension control at primary care
d) investigate the impact of yoga — as one promising non-pharmacological intervention — on blood pressure reduction in primary care settings in Nepal
e) explore the barriers and facilitators of implementation of yoga intervention for hypertension control in primary health care settings in Nepal

1.3. Structure of the PhD research projects: An overview

The overview provides a short description of the rationale, implications, and hierarchy of each research project, which compositely frames the structure and meaning of the overall PhD thesis. Table 1 provides information about evidence gap, objectives, studies conducted under this PhD thesis, and their relevance.

Table 1. An overview of the structure of PhD research projects

Evidence gap	Objectives	Studies	Relevance and applications	Chapter in PhD thesis
No detailed investigation of the gap in hypertension care using cascade of hypertension care framework in Nepal	To assess the prevalence and associated factors of hypertension screening, awareness, treatment, and control in Nepal	Study one: A secondary data analysis of nationally representative surveys	Informs gap in cascade of hypertension care in Nepal	Chapter 4, Study 1
Several studies with diverse study designs and populations are available on barriers, facilitators, and strategies for hypertension treatment and control that require systematic investigation and interpretation	To identify the barriers, enablers, and strategies for hypertension treatment and control in Nepal	Study two: Systematic review on barriers, enablers, and strategies for hypertension treatment and control	Informs barriers, enablers, and strategies of hypertension treatment and control in Nepal	Chapter 4, Study 2
No prior comprehensive synthesis of evidence on effectiveness, barriers, facilitators of non-pharmacological intervention in primary care	To synthesise the evidence on non-pharmacological interventions for hypertension control at primary care	Study three: Narrative review on non-pharmacological interventions for hypertension at primary care	Informs effectiveness, barriers, and facilitators of non-pharmacological intervention in primary care Provides a rationale for conducting Study 4	Chapter 5, Study 3
No evidence on implementation potential of health worker-led yoga intervention for hypertension	To investigate the impact of yoga on blood pressure reduction in primary care settings in Nepal	Study four: A pragmatic randomised controlled trial of yoga and hypertension in a primary care setting	Informs effectiveness of yoga intervention for hypertension in primary care settings	Chapter 6, Study 4
No evidence on barriers and facilitators of implementation of health worker-led yoga intervention for hypertension	To explore the barriers and facilitators of implementation of yoga for hypertension control in primary care settings in Nepal	Study five: A mixed-methods study to assess barriers and facilitators of implementation yoga intervention in primary care	Complement Study 4 to provide a clear picture of the feasibility of conducting yoga intervention for hypertension in primary care	Chapter 6, Study 5

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Chapter 2. Literature review

This chapter critically appraises the literature and summarises evidence on

a. the burden of hypertension including health system challenges, and program and policies responses for hypertension management in Nepal;
b. non-pharmacological intervention for hypertension including alcohol reduction, sodium reduction, potassium supplementation, physical activity, weight control, and heart-healthy diet; and
c. implementation of yoga intervention for hypertension

To illustrate the trend in burden of hypertension, data on the global burden of disease 2019 were extracted from the Institute of Health Metrics and Evaluation and compared using the data visualisation tool.

Similarly, to assess the policy responses to hypertension in Nepal, policy and program documents specific to hypertension management were reviewed and presented in a periodic timeline.

This chapter also includes a critical appraisal of six building blocks of the health system including governance, service delivery, health workforce, essential medicines, information system, and financing to assess health system gaps and challenges to service delivery specific to hypertension in Nepal.

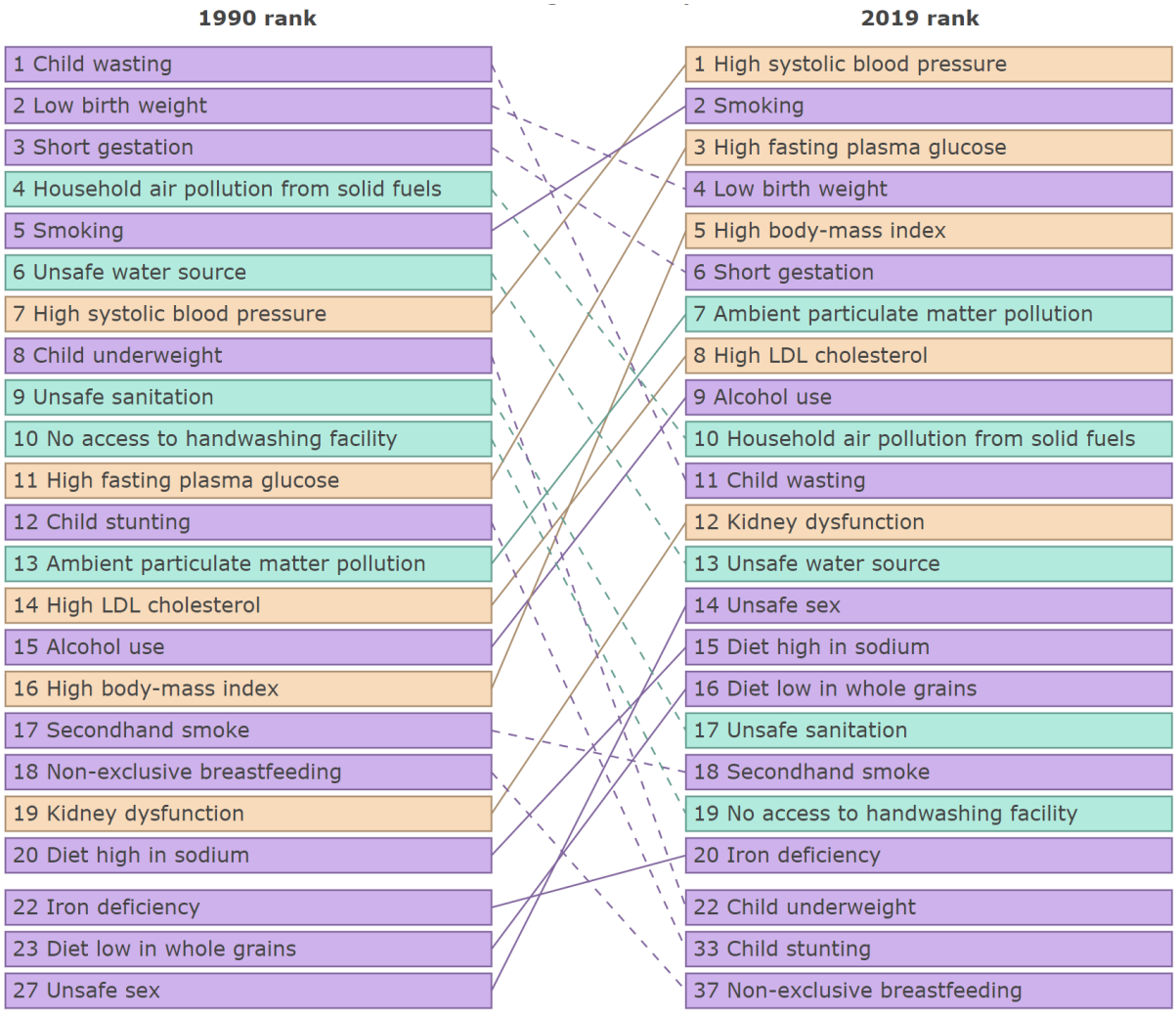
Lastly, for the review of literature on non-pharmacological interventions, a comprehensive literature search was performed in Google Scholar, PubMed, and Embase using appropriate keywords to identify the relevant evidence on the use of alcohol reduction, salt reduction, potassium supplementation, physical activity, weight control, heart-healthy diet, and yoga.

2.1. Burden of hypertension and healthcare challenges

2.1.1. Global burden of hypertension

According to recent estimates, hypertension is among the largest contributors to mortality and disability globally [1]. The mortality due to hypertension has increased significantly over the last 30 years. In 2019, high systolic blood pressure caused around 10.8 million deaths, which was four million higher than the estimated number of deaths due to the same cause in 1990 (6.8 million deaths) [2]. The burden of hypertension is also growing with high systolic blood pressure being the leading cause of DALYs in 2019 (Fig 1) [2].

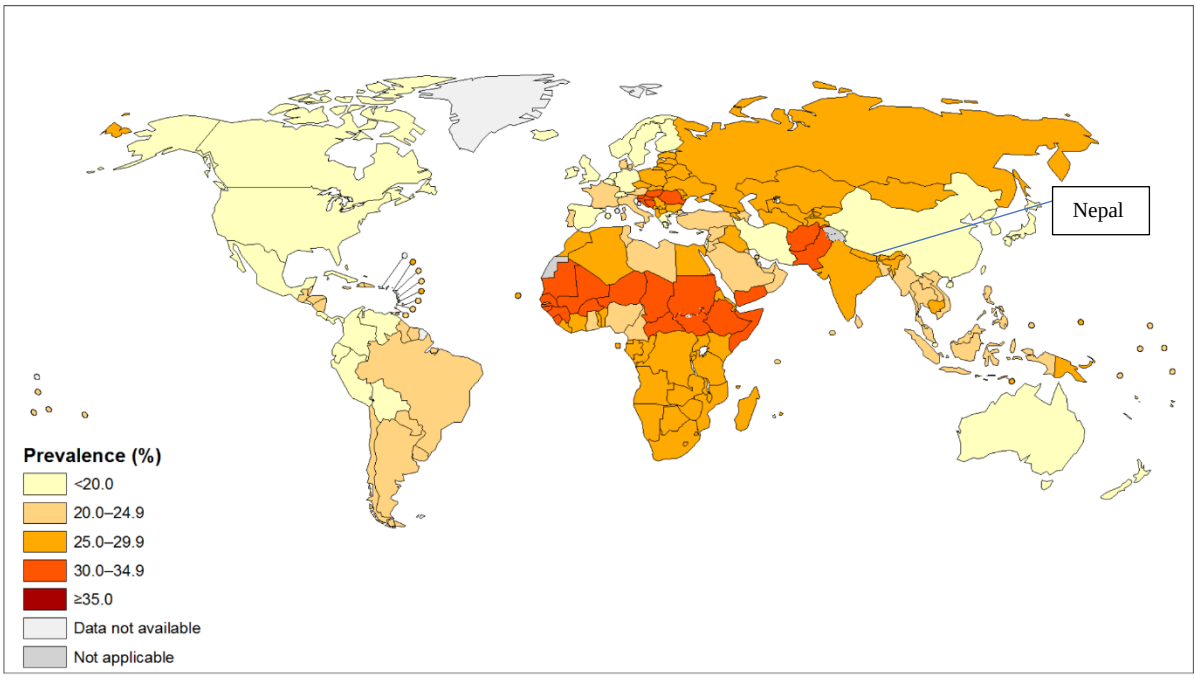
Figure 1. Comparing the risk factors as per their contribution to disability-adjusted life years globally between 1990 and 2019.



Note: source, Global Burden of Disease Collaborative Network [2]

Hypertension affects more than 20% of the World's adult population [3, 4], where 75% of all hypertensive individuals are currently living in lower-income and middle-income countries [5]. More importantly, World Health Organization's estimates on hypertension showed that low-income countries (28.4%) had the highest prevalence of hypertension, followed by lower-middle-income countries (25.5%), upper-middle-income countries (20.9%), and high-income countries (17.7%) in 2015 [4]. Even though the prevalence of hypertension has gradually decreased in high-income countries in the last few decades, it has an opposite trend in lower-income and middle-income countries. For example, in high-income countries, the prevalence of hypertension decreased from 37.6% to 17.7% between 1975 and 2015, whereas it increased from 26% to 28.4% in low-income countries during the same period [4]. Recent estimates also demonstrated that the prevalence of hypertension also increased by 7.7% between 2000 and 2010 in low-income and middle-income countries [5]. At the regional level, Africa has the highest estimated prevalence of hypertension (27.4 %) in 2015, followed by the Eastern Mediterranean (26.3%), and Southeast Asia (25.1%) (Fig 2). The Western Pacific (19.2%) and America (17.6%) had the lower prevalence of hypertension compared to other regions [4]. Based on the World Health Organization estimation for 2015, Nepal was ranked third in the prevalence of hypertension (29.4%) in South Asia, following Afghanistan (30.6%) and Pakistan (30.5%) [4].

Figure 2. Prevalence of hypertension (age 18+, both sexes, 2015)



Note: Source, World Health Organization [4]

The prevalence of hypertension screening, awareness, treatment and control are low in low-and middle-income countries, indicating gaps in the cascade of care of hypertension [5]. Among all hypertensive individuals in low-and middle-income countries in 2010, 37.9% were aware that they had high blood pressure, 29% were treated, and only 7.7% had controlled blood pressure [5]. The burden of untreated and uncontrolled hypertension was also found to be high in the countries around Nepal—Bangladesh, India and Pakistan, where 68.1% of hypertensive persons did not take treatment and 87.1% did not have optimal control of blood pressure between 2003 and 2009 [6].

2.1.2. Health and economic consequences of hypertension

2.1.2.1. Health consequences

It is an established fact that hypertension causes several cardiovascular diseases including stroke and ischemic heart diseases [7]. A lifetime risk of overall cardiovascular disease for hypertensive individuals at 30 years of age is 63·3% compared with 46·1% for those with normal blood pressure [7]. Hypertensive individuals can develop cardiovascular disease five years earlier than normotensives [7]. The effects of high blood pressure could vary by the different subtypes of cardiovascular diseases. For example, high systolic blood pressure is associated with an increased risk of intracerebral haemorrhage by 44%, subarachnoid haemorrhage by 43%, ischemic stroke by 25%, stable angina by 41%, myocardial infarction by 29%, heart failure by 27%, peripheral arterial disease by 35%, and end-stage of renal diseases by 44% [7, 8].

Other than cardiovascular diseases, recent evidence has suggested that long-standing hypertension is associated with dementia including Alzheimer disease- a condition with decreased cognitive abilities leading to functional decline and the inability to perform the usual activities for healthy individuals [9]. Likewise, some studies have reported an increased risk of incident all-cancer and cancer mortalities with high blood pressure. For example, a study that analysed the pooled data from the seven cohorts including 577,799 adults from Norway, Austria, and Sweden found that each 10 mmHg increase in systolic blood pressure would lead to a 5% increase in the risk of cancer and a 12% increase in cancer mortalities [10]. Recent systematic reviews have also suggested an association between hypertension and oral health disorders [11] and osteoporosis [12], however, the biological mechanisms underlying their relationship are yet to be elucidated.

2.1.2.2. Economic consequences

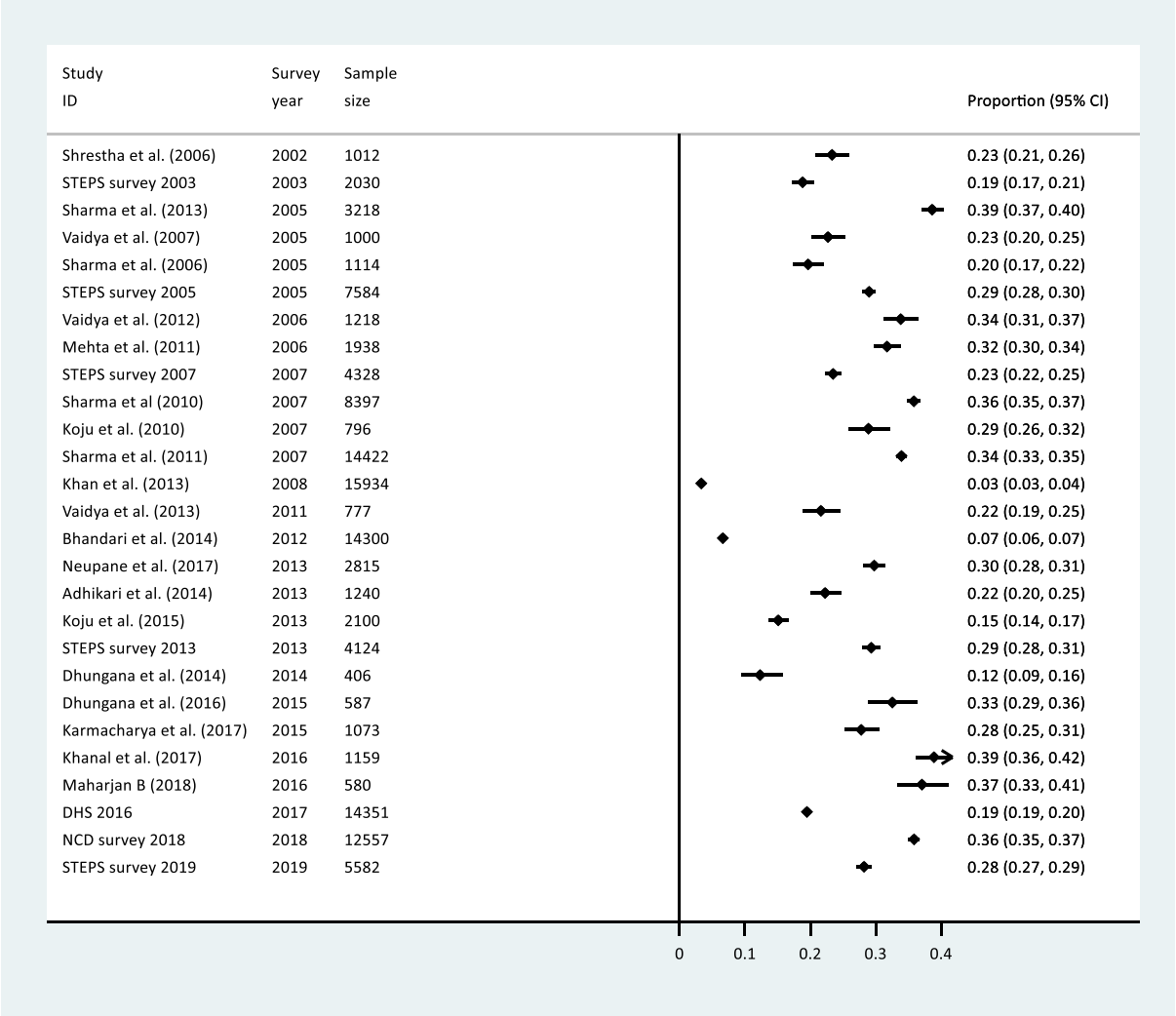
Hypertension causes a high economic burden to individuals and countries due to the direct cost incurred by treatment and management of hypertension and associated cardiovascular and other complications and the indirect costs such as productivity loss. According to the 2001 estimates, about 10% of the world's overall healthcare expenditures are attributable to sub-optimal blood pressure, where the percentage of healthcare expenditures attributed to high blood pressure was 22.6% in Europe and Central Asia, 16.4% in South Asia, and 12.3% in Middle East and North America [13]. A recent systematic review reported a range of costs per episode of hypertension and cardiovascular diseases between USD 500 and USD 1500 in low-and middle-income countries [14]. The average treatment costs for coronary heart disease and stroke were, however, higher than USD 5000 per episode [14]. The review showed that compared to the total health expenditure per capita, the annual direct cost could be as high as 5.9 times for for an individual with hypertension, 28 times for an individual with coronary heart disease, and 470 times for an individual with stroke [14]. The country-specific data also suggest costs of hypertension care account for the largest components of the total medical expenditure. In the USA, the annual cost attributable to patients with hypertension is USD 9089, causing additional expenses of USD 131 billion per year compared to the cost for the US population without hypertension [15]. In Ethiopia, the cost of hypertension was around USD 79 per patient per year in 2018 [16]. In Brazil, the direct cost of hypertension and associated cardiovascular diseases in 2019 was around USD 581.1 million [17].

As the burden of hypertension is growing in low-and middle-income countries, the cost associated with hypertension is likely to increase in future and exert enormous pressure on their health system. More than that, due to the lack of a robust financial protection system, hypertensive patients, particularly those from low socioeconomic status, have to incur a substantial and increasing amount of out-of-pocket expenditure causing a severe financial catastrophe. Even in upper-middle-income countries like Mexico, hypertension patients pay 52% of the total cost incurred by hypertension [18]; in Columbia, around 74% of hypertensive patients spend from their pocket for the treatment [19], and in China, about 24% of the households experienced catastrophic health expenditure (the total health expenditure larger than 10% of the annual income) due to hypertension [20].

2.1.3. Burden of hypertension in Nepal

Hypertension is a prevailing problem in Nepal. Recent studies showed that every third person has high blood pressure in Nepal [21, 22]. Nepal has a greater prevalence of hypertension than the other South Asian neighbouring countries India (25.8%) and Bangladesh (24.7%) and low-income countries (23.1%) [23]. However, there is a large discrepancy among the estimates of prevalence of hypertension reported across the studies in Nepal. Huang et al. found that the pooled prevalence of hypertension was 27.3% in Nepal in 2018 [24]. Other studies reported largely varied findings on hypertension ranging from 5% to 39% [25-30]. The distribution of prevalence estimates reported across the studies conducted between 2000 and 2020 are shown in figure 3. The heterogeneity in the estimates was mainly due to the variation in study settings and age and sex of the study participants [21]. Details of systematic search and analysis of the studies listed in figure 3 have been published elsewhere [21].

Figure 3. Distribution of prevalence estimates reported across the studies between 2000 and 2020



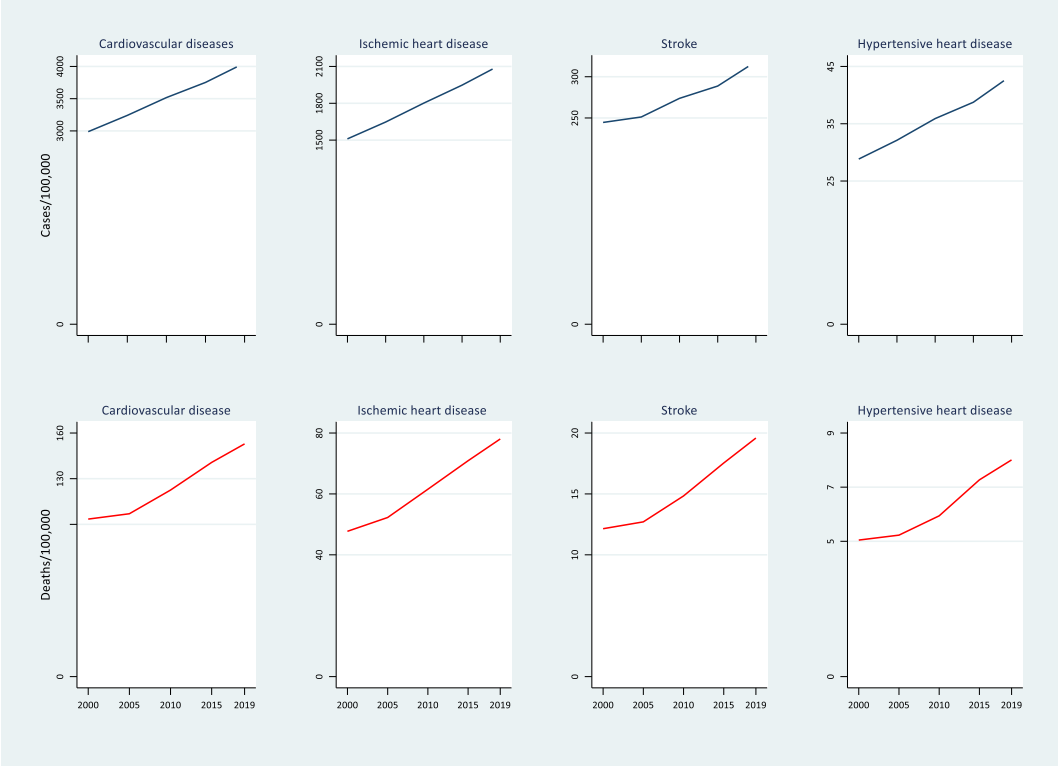
A meta-analysis including 23 studies was recently conducted in Nepal, to assess the burden of hypertension in the last two decades, and it found that the prevalence of hypertension increased by 6percentpoint in the last 20 years [21]. Vaidya et al. [25] also found a three-fold increase in hypertension prevalence in the suburb (Bhadrabas and Alapot villages) of Kathmandu in 25 years between 1980 and 2006. The periodic STEPwise approach to chronic disease risk factor surveillance (STEPS) surveys reported a 3 percent point increase in the prevalence of hypertension in Nepal between the 2007 [31] and 2013 [32] survey years.

To understand the burden of hypertension, it is also important to discuss the situation of cardiovascular diseases in Nepal. As discussed above, hypertension is the number one preventable risk factor for cardiovascular diseases, particularly for ischemic heart disease,

stroke, and hypertensive heart disease. For example, around 45% of deaths due to heart disease and 51% of stroke-related deaths are attributable to hypertension [33]. To depict the change in burden of cardiovascular diseases over the last two decades, this thesis extracted and analysed the publicly available data from the Global Burden of Diseases (GBD) 2019. A detailed description of the metrics, data sources, and statistical modelling for cardiovascular diseases are available elsewhere [34]. In brief, The GBD 2019 used the data sources from 204 countries and regions and provided a comprehensive assessment of burden of 369 diseases and injuries including cardiovascular diseases [35]. The GBD 2019 used 389 data sources from Nepal to estimate the disease burden.

The GBD data suggested that the burden of cardiovascular diseases is also significantly increasing in Nepal. In 2019, there were estimated to be 1,214,607 Nepalese with cardiovascular disease cases. Cardiovascular diseases caused 46,501 deaths and 1,104,474 DALYs in Nepal in 2019 [2]. As shown in Figure 4, all age mortality rate for cardiovascular diseases increased from 103.5 deaths per 100,000 population in 2000 to 152.9 deaths per 100,000 population in 2019. The proportional contribution of cardiovascular disease deaths to the total deaths increased from 13.9% to 24% from 2000 to 2019. Like cardiovascular diseases, the top three contributors of cardiovascular deaths: ischemic heart disease (12.3% of all deaths in 2019), stroke (7.9% of all deaths in 2019), and hypertensive heart disease (1.3% of all deaths in 2019) followed the similar trends during the period (Fig 4).

Figure 4. Trends of cardiovascular diseases and deaths between 2000 and 2019



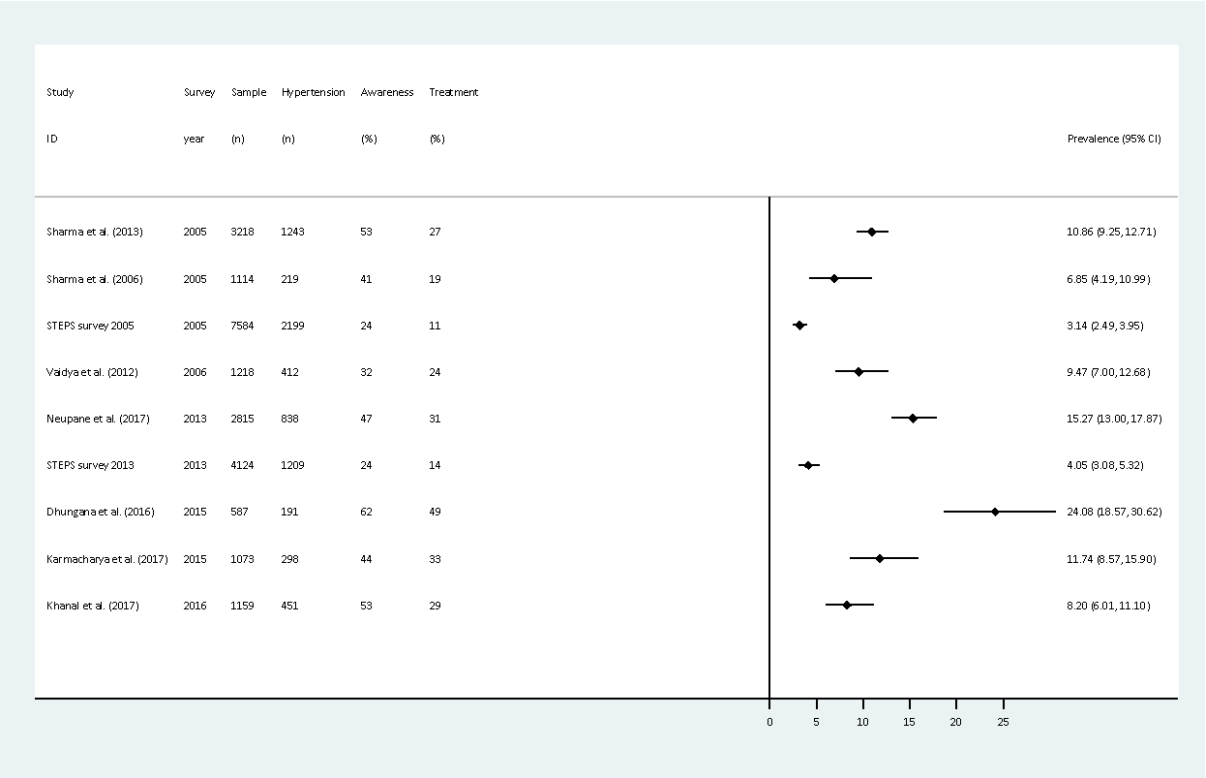
2.1.3.1. Cascade of hypertension care

The cascade of hypertension care includes screening, awareness, treatment, and control of hypertension. Hypertension screening is the measurement of blood pressure by a doctor or another health worker. Hypertension awareness is defined as self-report of any prior diagnosis of hypertension by a health care professional. Hypertension treatment is related to the use of any antihypertensive medication to lower blood pressure. Hypertension control is the condition when a hypertensive person has a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg. The use of the cascade of care framework helps to quantify the unmet need for services by tracking the loss of a proportion of service users in a particular stage of the cascade of care [36]. The application of the framework to identify the persons who are more likely to be unaware of their condition, aware but untreated, or treated but having sub-optimally controlled blood pressure would inform the health care providers and other stakeholders to locate gaps in hypertension control cascade and pair those in an at-risk population with effective interventions [37]. For example, if a large proportion of the population is not aware of their condition, blood pressure screening or other outreach services can be effective to identify persons with hypertension. Similarly, if the lack of treatment or control is the prevailing problem, the stakeholders require to identify and tackle health

systems, health providers, and individual level barriers for effectively linking and retaining the patient to the hypertension management services.

Some of the sub-national studies reported a wide range of estimates on awareness, treatment, and control of hypertension in Nepal [Fig 5]. They, however, unanimously suggested that the prevalence of hypertension awareness, treatment, and control are low in Nepal [25, 26, 28, 29, 31, 32, 38-40].

Figure 5. Awareness, treatment, and control of hypertension reported across studies in Nepal



A nationally representative survey- Demographic and Health Survey 2016 - found that 38% of hypertensive people in Nepal were aware of their high blood pressure status and 18% took antihypertensive medication [41].

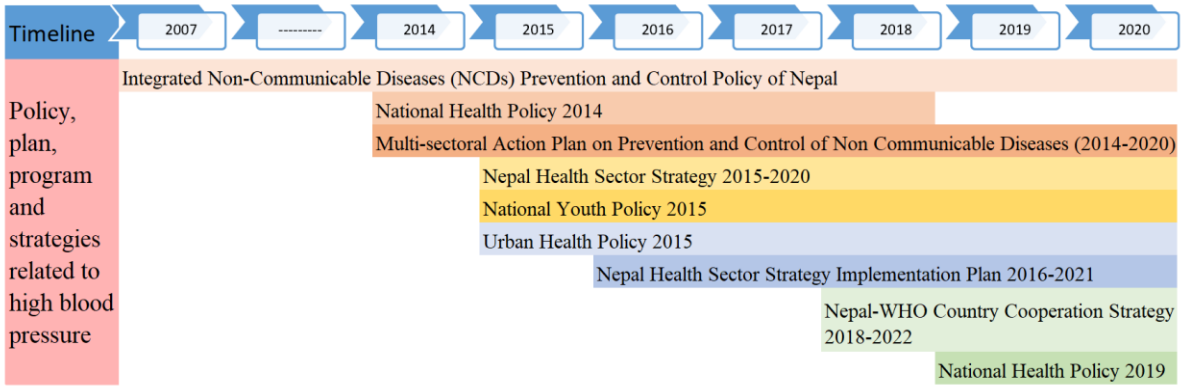
Evidence from outside of Nepal shows that the unmet need for hypertension care is disproportionately distributed across different socio-demographic groups in the community. The young, females, poor (lowest wealth quintile), those with low educational attainment, and those living in rural settings are more likely to be unaware, untreated or have uncontrolled high blood pressure [42]. An Indian study observed that those who are single, males, participants from rural areas, and individuals with lower household wealth had a poorer status at each step of the cascade of care process [43]. In Nepal, very little is known

about the unmet need for hypertension care. Further, there is a dearth of research that used the cascade of care framework to systematically investigate the gaps and the factors influencing hypertension treatment and control in Nepal.

2.1.4. Policies and program responses for hypertension control in Nepal

Very few policy documents issued in Nepal are specific to high blood pressure. Most of them are related to the prevention and control of noncommunicable disease and its risk factors including tobacco use, alcohol consumption, physical inactivity, and unhealthy diet (Fig 6).

Figure 6. Policies and programs related to hypertension in Nepal



The Multi-sectoral Action Plan for Prevention and Control of NCDs (2014-2020) was the first action plan that explicitly included high blood pressure as an indicator for monitoring the progress in prevention and control of non-communicable diseases in Nepal [44]. The action plan set a target of a 25% relative reduction of high blood pressure in Nepal by 2025. It contained four specific action areas: a) leadership, advocacy and partnership; b) health promotion and risk reduction; c) health system strengthening for early detection and management of non-communicable diseases and their risk factors; and d) surveillance, monitoring, evaluation, and research to reduce preventable morbidity, avoidable disability, and premature mortality due to non-communicable diseases in Nepal. It aimed to engage multiple sectors and develop population-wide interventions to promote a healthy lifestyle.

The Nepal Health Sector Strategy Implementation Plan 2016-2021 included the Package of Essential Non-communicable Diseases as a major intervention for the prevention and control of non-communicable diseases including hypertension in Nepal [45]. The

Package of Essential Non-communicable Diseases is a cost-effective approach for the early detection, prevention, treatment, and care of cancers, diabetes, hypertension and other cardiovascular risk factors in a primary care setting.

The remaining policy documents were developed to address the overall non-communicable disease burden in general rather than hypertension. The National Health Policy-2014 was the first national health policy to consider non-communicable disease as a major health challenge in Nepal [46]. The policy was then updated in 2019 as National Health Policy-2019 which envisaged to address the disease burden through the provision of basic health care services and health promotional activities in the new federal system [47]. Likewise, the Ministry of Health, Nepal promulgated the Urban Health Policy 2015 for promoting a healthy lifestyle for prevention of non-communicable diseases among urban poor and marginalised population [48]. The National Youth Policy 2015 also aimed to minimise risky behaviour among the youth in Nepal [49].

2.1.4.1. Health system gaps in hypertension management in Nepal

The health system functioning is evaluated particularly using the six building blocks framework designed by World Health Organization [50]. They include governance, service delivery, human resources, medical products, information system, and financing. The health system performance across the six building blocks would help determine the equity, access, coverage, efficiency, quality, safety and sustainability of health services.

Governance in health is more about the issues of accountability which is measured whether countries have appropriate policies, strategies, and approaches for health system strengthening. The policies and strategies help to set the vision for the future, define the objectives, prioritise the roles of different actors, inform and build consensus, and estimate the resources required to achieve goals. Therefore, the existence of effective national health strategies and policies that reflect national needs and priorities is the key indicator for governance. However, as discussed in the previous section, Nepal lacks sufficient policies, strategies, and plans particularly on cardiovascular diseases and hypertension (Table 2).

Table 2. Health system gaps in hypertension specific service delivery

Six building blocks	Indicators	Remarks
Governance	Policies in respective domains	The Multi-sectoral Action Plan for Prevention and Control of NCDs (2014-2020) is the only policy document that explicitly deals with

Six building blocks	Indicators	Remarks
		cardiovascular diseases and hypertension in Nepal [44].
Service delivery	Number and distribution of health facilities offering hypertension specific services	Nepal does not have clinical guidelines for prevention and management of cardiovascular diseases and hypertension. It has only two tertiary care centres specialized in cardiovascular diseases, which are located in the capital city [51]. Thirty out of 77 districts are implementing the Package of Essential Non-communicable Diseases for detection and management of cardiovascular diseases including hypertension [52].
Health workforce	Distribution of health workers by occupation/specialization, region, place of work, and sex	Health workforce at primary care centres and health posts are being trained for screening, diagnosing, treating, and referring services for cardiovascular disease risk and hypertension under the Package of Essential Non-communicable Diseases. Nepal has 154 cardiologists and 22 cardiothoracic surgeons registered (0.006 cardiologist/1000 population) in 2019 [53].
Essential medicines	Availability of selected essential medicines in public and private health facilities	Among 398 essential drugs listed on the National Essential Medicine List 2021, two antihypertensive drugs (amlodipine and enalapril) and one is diuretic (hydrochlorothiazide) are available as free medicines at public health centres [54].
Information system	Health information system	The Health Management Information System (HMIS) collects information on hypertension from routine health facility data, which is used by the Department of Health Services to report in the Annual Health Report. However, HMIS does not collect information on all cardiovascular diseases and they are not reported in the Annual Health Report [55].
Financing	Government expenditure on health as a proportion of general government expenditure	The total spending on cardiovascular diseases and hypertension were 2.6% and 0.9% of current health expenditure in the year 2016/17 [56]. In the same year, household's out-of-

Six building blocks	Indicators	Remarks
	The ratio of household out-of-pocket payments for health to total expenditure on health	pocket payment on non-communicable diseases including hypertension was almost half of the total household's out-of-pocket expenditure made for the diseases/health conditions [56].

Service delivery is the immediate output of the health system. Good service delivery is crucial for the achievement of goals set for specific programs and strategies. The service delivery is commonly evaluated by measuring access, availability, utilisation, and coverage of the services. Regarding the availability of hypertension specific health services, implementation of the Package of Essential Non-communicable Diseases in primary health care centres and health posts is vital for screening, detection, management, and referring cardiovascular diseases including hypertension [52]. The Package of Essential Non-communicable Diseases is being implemented in 30 out of 77 districts in Nepal. In addition to that, two tertiary cardiac care centres are catering specialized services in cardiovascular diseases in Nepal though they are located in the capital city [51]. However, clinical guidelines for prevention and management of cardiovascular diseases and hypertension are not available in Nepal until now. Likewise, there are a limited number of health professionals trained in cardiovascular disease management in Nepal where 154 cardiologists and 22 cardiothoracic surgeons (0.006 cardiologist/1000 population) were registered until 2019 [53]. The non-physician health workforces require training in prevention, detection, and management of hypertension and cardiovascular risk in Nepal [53]. Though health workers from the Package of Essential Non-communicable Diseases implemented districts are being trained to screen, manage, and refer individuals with risk of cardiovascular diseases and hypertension, the effectiveness of the package is yet to be evaluated.

An equitable access to essential medical products is one of the markers of a well-functioning health system. In Nepal, there are 398 essential drugs listed on the National Essential Medicine List 2021 [54]. Out of 398 essential drugs, 70 are free and are available in primary care centres and health posts. Two antihypertensive drugs amlodipine and enalapril and one diuretic (hydrochlorothiazide) are also available freely at primary care centres [54]. However, a regular, effective, and efficient supply of these medicines is uncertain [57]. The antihypertensive drugs such as atenolol and amlodipine were out of stock in 82% and 90% of health centres in 2015, respectively [58].

The Health Management Information System (HMIS) collects information on hypertension and reports them in the Annual Health Report under the section of '*Non-Communicable Diseases and Mental Health*. According to the Annual Health Report 2019/2020, 741,150 patients were diagnosed with hypertension and received treatment from health centres [55]. However, HMIS neither collects information on all cardiovascular diseases nor does the Annual Health Report report them [55]. Apart from HMIS, STEPwise Approach to NCD Risk Factor Surveillance (STEPS) surveys are vital to understand the trends of hypertension in Nepal. The STEPS surveys are periodically conducted nationally representative surveys designed to estimate non-communicable disease risk factors including hypertension in Nepal [22, 31, 32]. Additionally, the Demographic and Health Survey also started reporting the prevalence, treatment and control of hypertension in Nepal since 2018 [41]. Both national surveys do not collect data on cardiovascular diseases.

Health financing is defined as the "function of a health system concerned with the mobilization, accumulation, and allocation of money to cover the health needs of the people, individually and collectively, in the health system" [50]. The purpose of health financing is to ensure equitable access to care by allocating sufficient funds for health (such as government direct budget to health) and/or by providing financial risk protection to the population. The general government expenditure on health, one of the indicators related to the government's commitment to making funding available for health, was 7.1 % of the general government expenditure in Nepal in the year 2016/2017 [56]. It is generally expected that 15% of overall government expenditure should go to health [50]. Non-communicable diseases were the largest contributor of current health expenditure in Nepal in 2017 (30.2% of current health expenditure) whereas the total spending on cardiovascular diseases and hypertension were 2.6% and 0.9% of current health expenditure [56].

Household's out-of-pocket payment for health care contributed to 57.4% of current health spending in the health system of Nepal in 2016/2017, where 75.1% of household's out-of-pocket payment for health care was incurred for medicines and medical goods [56]. In the same year, household's out-of-pocket payment on non-communicable diseases was almost half of the total household's out-of-pocket expenditure made for the diseases/health conditions [56]. Despite the growing household's out-of-pocket payments of non-communicable diseases including hypertension, there is a nominal budgetary allocation for non-communicable diseases in Nepal. In 2016, the government direct budget for non-communicable disease-related programs was USD 1.3 million, which was 0.2% of the total

government budget on health [53]. Likewise, health insurance, one of the financial risk protection measures, has minimal impact on protecting the population from catastrophic health expenditure (the total health expenditure larger than 10% of the annual income). Until 2019, the National health insurance policy covered only 10% of the total population in Nepal [59].

2.2. Non-pharmacological interventions for hypertension

This section of the literature review provides details on six non-pharmacological interventions for hypertension, namely, alcohol intake reduction, salt intake reduction, increased potassium intake, physical activity, weight loss, and heart-healthy diets. The selection of these six non-pharmacological interventions was guided by the 2017 American College of Cardiology and American Heart Association Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults [60]. Additionally, this section also includes reviews of other potential non-pharmacological interventions such as stress reduction. To identify literature on alcohol reduction, salt reduction, potassium supplementation, physical activity, weight control, heart-healthy diet, and other non-pharmacological interventions, a thorough literature search was conducted in Embase, Google Scholar, and PubMed databases. The search keywords included “hypertension” or “blood pressure” combined with keywords for common non-pharmacological interventions for hypertension: “non-pharmacological intervention”, “lifestyle modification”, “alcohol”, “salt”, “potassium”, “physical activity”, “weight”, and “diet”. The most recent review papers and primary studies were reviewed.

2.2.1. Alcohol reduction

2.2.1.1. Association of alcohol intake and blood pressure

It is a fact that alcohol increases the risk of high blood pressure. The risk of hypertension is linearly associated with alcohol consumption in men. For example, the relative risks of hypertension for 50 and 100 grams of pure alcohol consumption per day are 1.57 and 2.47 respectively [61]. Likewise, compared to abstainers, the risk for hypertension increases by 19%, 51%, and 74% among those who consume 1 to 2, 3 to 4, and 5 or more standard drinks per day, respectively [62]. In contrast, in women, no increased risk of hypertension was observed for consuming less than 2 alcoholic drinks per day [63]. The magnitude and direction of the effects of alcohol vary based on the time after its consumption. A Cochrane review indicated that medium-dose (14-28 gm) of alcohol consumption could increase blood pressure within six hours of intake and the effect diminished >13 hours after consumption, whereas high-dose (>30 gm) of alcohol decreased systolic blood pressure by 3.49 mmHg

within 6 hours and increased it by 3.69 mmHg >13 hours after consumption [64]. The causal link between alcohol and blood pressure is also confirmed by a Mendelian randomisation study [65]. Recently, the single nucleotide polymorphism (SNP) rs671─a genetic determinant for alcohol drinking─ is found to be associated with an increase of 9.5 mmHg of systolic blood pressure and 7.5 mmHg of diastolic blood pressure in Chinese population [66].

2.2.1.2. Mechanisms

Several mechanisms have been proposed for alcohol-induced hypertension [67, 68]. These mechanisms are linked with an increased sympathetic outflow, diminished baroreflex, and impaired renin-angiotensin-aldosterone system [67]. Studies conducted in ethanol-induced hypertensive mouse model indicated that alcohol altered the vascular responsiveness by increasing intracellular Ca2+ levels and down-regulated nitric oxide generating system causing an impaired vascular relaxation [68].

2.2.1.3. Alcohol intake reduction and blood pressure

Studies showed that alcohol-reducing interventions can significantly reduce blood pressure. A systematic review that analysed pooled data from 15 clinical trials found that alcohol reduction (16%-100% reduction) was associated with the change of -3.31 mm Hg in systolic blood pressure and -2.04 mmHg in diastolic blood pressure [69]. Greater reduction in blood pressure was observed with low alcoholic drink substitution than behaviour counselling, in hypertensive individuals than normotensives, and in those with hypertensive medication than without medication [69]. Likewise, the higher the alcohol intake at baseline, the greater the impact on alcohol intake and blood pressure reduction [70]. Furthermore, the blood pressure-lowering effect of alcohol reduction is found to be dose-dependent. In a systematic review of 36 trials, Roerecke et al. found that partial or complete reduction in alcohol intake was associated with the reduction of systolic blood pressure by 1·18 mmHg, 3 mmHg, and 5.5 mmHg among those who consumed 3 drinks/day, 4-5 drinks/day, and ≥6 drinks/day, respectively [70]. However, a reduction in alcohol intake was not statistically significantly associated with the reduction in blood pressure among who drank ≤2 drinks per day, indicating that alcohol reducing intervention would only be effective in people who drink more than two drinks per day.

2.2.1.4. Implementation of alcohol intake reduction strategies

Most of the hypertension treatment guidelines stress assessing alcohol intake among hypertensive patients and providing alcohol-lowering advice to reduce intake. Among various

interventions, Alcohol Brief Intervention [71] has been successfully tested to reduce alcohol consumption. A recent study suggested that hypertensive patients at primary care could benefit from the physician-led alcohol-reducing brief intervention for blood pressure reduction [72]. Since the reduction in blood pressure and reduced alcohol would save millions of lives per year, Rehm et al. recommended several alcohol-reducing strategies among hypertensive patients in primary care [73]. The recommendations include the screening of harmful alcohol use and applying brief advice for newly diagnosed or uncontrolled hypertensive patients [73]. Studies have shown that implementing an Alcohol Brief Intervention in primary healthcare settings would be a cost-effective strategy to reduce alcohol consumption and thus reduce health burden [74]. Alongside delivering Brief Intervention for alcohol reduction, the study suggests that health workers need training, support, and financial reimbursement to increase the screening for alcohol consumption [75].

Evidence around the globe indicated that assessment of alcohol intake during hypertension screening and treatment is not widely practised in primary care. For example, in Germany, only 45% of the hypertensive patients were screened for alcohol and 13% of General Practitioners had never screened for alcohol in any of hypertensive cases [76]. Likewise, a study conducted among the General Practitioners from France, Germany, Italy, Spain, and the UK found that only 22.2% of General Practitioners screened and delivered brief interventions in hypertensive patients with hazardous drinking [77].

2.2.2. Salt reduction

2.2.2.1. Association of salt intake and blood pressure

Sodium is an essential micronutrient that helps the body to keep fluids and blood pressure in normal balance. It is also important for numerous physiological processes along with muscle and nerve function. However, evidence suggests that there is a positive association between increased sodium intake and several health conditions including hypertension, cardiovascular disease, and stroke [78, 79]. One-gram increment of sodium intake is linked to the increment of 2.58 mmHg of systolic blood pressure [80]. Likewise, an increase of 5 g/day in salt intake is associated with a 23% increase in the risk of stroke and a 14% increase in the risk of cardiovascular disease [81]. Furthermore, an estimated 1.65 million deaths due to cardiovascular diseases in 2010 were attributed to high sodium consumption [82]. Recent evidence shows that high dietary sodium is also associated all-cause of mortality [79].

According to the Global Burden of Disease (GBD) study estimation, the high intake of sodium, as a leading dietary risk factor, accounted for 3·20 million deaths globally in 2017 [83].

2.2.2.2. Estimations on salt intake

Globally, the average sodium intake per person was 3.95 gm/day in 2010 [84]. This estimation was twice the amount of sodium intake recommended by the World Health Organization (2 gm/day). Sodium intake is the highest in the Asian regions, where East Asia, Asia Pacific, and Central Asia recorded daily intake of sodium of 4.8, 5.0, and 5.5 gm respectively [84]. The average global and regional sodium intake increased significantly between 1990 and 2010 [84]. A recent review showed that the daily salt intake either reduced slightly or remained constant mainly in high-income countries and increased in many low and middle-income countries in 2018 compared to 2010 estimates [85]. Likewise, the variation in dietary sodium intake is also observed between urban and rural settings. Estimated sodium excretion (a surrogate of sodium intake) is significantly higher in rural areas than in urban areas, and inversely associated with per capita gross national income [80]. Along with the regional variation in salt intake, it is also important to note the dietary source of salt intake varied significantly across countries. For example, data from INTERMAP study suggested that large proportion of intake of the dietary salt (76%) in China belongs to the salt added in home cooking, whereas 63% of dietary sodium comes from four major food items namely soya sauce, sea food, soups, and preserved vegetables in Japan, and 95% of sodium intake is contributed by processed foods in the UK [86].

2.2.2.3. Mechanisms

Several hypotheses explain the link between increased sodium intake and hypertension. A high intake of dietary sodium induces a substantial increase in the plasma sodium concentration, extracellular fluid, cardiac output, and peripheral vascular resistance as it alters the way the kidney functions to filter the blood [87]. Other studies suggested that high sodium intake could have many deleterious effects particularly on blood vessels, heart, and renal system leading to hypertension and other cardiovascular diseases [78, 88-94]. It also causes massive albumin excretion, severe renal arteriolar damage, interstitial fibrosis, increased glomerular hydrostatic pressure, and end-stage renal disease [78, 88-93, 95].

2.2.2.4. Salt intake reduction and blood pressure

A wealth of evidence suggests that lowering dietary sodium intake is directly related to the reduction in blood pressure. Between 1997 to 2017, more than 10 systematic reviews were conducted comparing the effect of low salt intake vs high salt intake on blood pressure [96-103]. The summary results varied among the studies, where the mean difference of systolic blood pressure between intervention group and control group reported in individual reviews ranged from 3.9 mmHg to 5.9 mmHg. He et al. [102] estimated the age and ethnicity adjusted dose-response relation between the reduction in salt intake and fall in systolic blood pressure. The meta-regression analysis showed a reduction of salt intake by 6 gm/day could predict a decline of 5.8 mmHg of systolic blood pressure [102]. The same amount of salt reduction (6 gm/day) could have a greater blood pressure-lowering effect (10.8 mmHg of reduction in systolic blood pressure) among hypertensive individuals [102]. Few studies also found that the low salt intake not only affects hypertension, that also reduces the incidence of cardiovascular diseases, stroke, and all-cause mortality [79, 104]. A reduction of salt intake by 2-2.3 g/day could reduce cardiovascular events by 20% and all-cause mortality by 5-7% [104]. The effect would be double by 6 g/day reduction and tripled by 9 g/day reduction in daily salt intake [105].

2.2.2.5. Implementation of salt intake reduction strategies

Population-level salt reduction strategies have been widely adopted across the globe. A systematic review conducted in 2015 found that 75 countries have already introduced national salt reduction strategies by 2014, which was more than double the number of countries (*n*=32) reported in 2010 [106]. Among those 75 countries, most of them were either high-income countries (*n*=41) or upper-middle-income countries (*n*=21). In 2016, the World Health Organization introduced a technical package for salt reduction called SHAKE [107]. It is an initiative designed to assist the Member States with the implementation of the key interventions such as measuring and monitoring salt use, promoting reformulation of food products, regulating the labelling and marketing of food, empowering the individuals for less salt use, and creating a supportive environment for healthy eating. The initiative is in line with the Global Action Plan for the Prevention and Control of Non-communicable Diseases 2013-2020 that aims to achieve a 20% reduction in population salt intake by 2025 [108]. In line with World Health Organization strategy, the major salt reduction approaches are related to the behaviour changes interventions, food reformulations, and policy and population-level interventions [109, 110]. The interventions are often multifaceted and involve more than one

strategy [110], applied to hypertensive or general population [110, 111] at an individual, community or national level [112].

2.2.2.5.1. Behaviour change intervention

The behaviour change modalities mostly include health education to provide in-depth information about salt reduction delivered directly to groups of people or public awareness campaigns to change behaviour on a large scale using mass media, print, and digital media [113]. Some behaviour change interventions are implemented as parts of a multi-component education intervention which included both health education and awareness campaigns. In a systematic review conducted in 2017, Trieu et al. [113] identified 22 studies those tested different behaviour change interventions to cut down the salt intake, in which 14 studies evaluated health education, four studies used the public awareness campaign, and four studies included both.

2.2.2.5.1.1 Health education

Health education in the form of dietary counselling is one of the effective strategies to reduce salt intake at the individual level. In a meta-analysis, Hooper et al. [111] found that dietary counselling was associated with an overall reduction of 2.5 mmHg in SBP and 1.2 mmHg in DBP at six to 12 months of follow-up. Most of the health education interventions are delivered either in community, workplace or school settings [113]. A school-based intervention in which a curriculum-based structured education program on the harmful effect of salt was delivered to primary school children for 3.5 months in China was effective in reducing salt intake in children and their families [114]. A community-based intervention from Vietnam that utilised the Communication for Behavioural Impact (COMBI) framework and used an integrated mix of five communication action areas such as public, community mobilization, and sustained community-based social marketing found effective in lowering average population salt intake [115]. A multifaceted community-based program, based on the COMBI framework, was significantly associated with a 0.8 g/day reduction in salt consumption in an Australian regional town between 2011 and 2014 [116]. Most of the studies delivered health education through didactic group lectures, some also used interactive methods such as cooking demonstrations and workshops or practical approaches such as using a salt-restriction spoon in the kitchen [113]. For example, a study by Chen et al. replaced the kitchen spoons with the salt reduction spoons, calibrated to hold 2 grams of salt which showed promising results in lowering dietary salt intake [117]. Application of mobile health technologies has also shown positive results in changing dietary habits [118].

Morikawa et al. [119] investigated the effectiveness of self-monitoring of dietary sodium intake and dietary counselling among hypertensive male participants in the workplace in Japan and found that the intervention group participants had a greater reduction in diastolic blood pressure (4.6 mmHg) than the control group. It is important to note that the effect of health education on blood pressure varied largely by the types of study participants (hypertensive or normotensive) and duration of follow-up (short term or long-term follow-up) [111].

2.2.2.5.1.2 Public awareness

Globally, more than 70 countries have already started different public awareness campaigns to educate the consumer on salt reduction [106]. Most of the campaigns were conducted by the government and other stakeholders at a community or state level, in parallel with other salt reduction strategies such as structural changes in education, health, and food industry for a sustainable way of improving public awareness [112, 120]. Cyprus, Austria, Denmark, Finland, France, and Germany reported conducting consumer education on salt as a broader and sustainable way of improving public awareness [120]. Trieu et al. [113] found that more than one third (8/22) of studies evaluated public awareness campaigns nationwide or in a community, where 7 out of 8 studies showed the significant effect on changing the salt intake related behaviours. Those studies used multimedia tools such as TV, radio, website, and newspaper to deliver the key messages or advice or practical tips to reduce salt intake [113].

2.2.2.5.2. Policy interventions

Law and regulations are the key components of population-level salt reduction strategies globally. A Cochrane review conducted in 2016 identified six major jurisdictions as population-level interventions for dietary salt reductions [121]. The commonly introduced legislative action to reduce salt intake is food reformulation for limiting sodium contents particularly in bread, meat products, milk products, and tomato products. For example, some of the European countries like Belgium, Hungary, and the Netherlands introduced legal reequipment to limit the maximum level of sodium in bread [120]. In 2013, South Africa passed regulations to reduce the salt contents in several processed food [107]. Likewise, some countries started pricing interventions such as taxing high salt foods [120]. Another legislative action for salt reduction is the voluntary or mandatory labelling of sodium content in the food package. Finland has had national legislation for front-of-pack ‘warning labelling’ for high salt foods since 1980 [120]. In the UK, the front-of-pack labels are now voluntarily used on more than three quarters of supermarket foods since 2006 [122]. Adding to the list of

population level salt reduction intervention, Christoforou et al. [106] found that more than 20 countries regulated the salt procurement policies in public institution settings such as in school, workplace, prison, and hospital where a contained food service was functioning.

2.2.2.6. Impact of salt intake reduction strategies

Despite the widespread implementation of salt reduction initiatives, the outcome of salt limiting behaviour and its overall impact on hypertension and other cardiovascular health is not recorded effectively. Among the 75 countries as found to have dietary sodium reduction efforts implemented, McLaren et al could only retain data from15 to have quantitative analysis [121]. The limited availability of data and poor monitoring and evaluation of population-based initiatives are the challenges in building evidence-based strategies for salt reduction [121]. Nevertheless, the available data suggested that a few countries particularly China, Finland, Ireland, and the UK could significantly reduce the dietary sodium intake in the population [121]. Some countries like Switzerland, however, reported an increase in mean salt intake (8.4 gm/day to 9.2 gm/day) between 1984 and 2011 [121] which could be because the outcome was measured earlier than expected (the outcome was measured in 2011 and intervention was implemented in 2008). While comparing the salt reduction strategies and hypertension and deaths due to stroke and ischemic heart disease (IHD), He et al. [123] found that along with a decrease in salt intake by 1.4 gm/day, mortality of stroke and IHD reduced by 42% and 40% respectively in the UK between 2003 and 2011, indicating an association, though weak, between two events.

It is interesting that all salt reductions strategies are found to be cost-effective. A Palestine study found that the population strategies particularly population-wide health promotion campaigns, mandatory labelling of food packaging, and mandatory reduction of the salt content of processed food were found to be cost-effective compared with the do-nothing scenario [124]. In a systematic review, Hope et al. [125] identified 14 studies that evaluated the cost of the different salt reduction strategies in Vietnam, Syria, USA, England, Australia, Argentina, and Norway. The majority of the studies (8/14) conducted a cost analysis of multiple sodium reduction interventions including health education through mass media, reformulation of products, tax legislation, and voluntary agreements on food labelling. All of the fourteen studies concluded that their salt reductions interventions were cost-effective [125]. However, the findings of these studies were based on the simulation of intervention using economic modelling, not on actual data from the implementation and

evaluation of interventions. Recently, Webb et al. [126] also estimated the cost-effectiveness ratio of government-supported soft policy strategies combining targeted industry agreements and public education to reduce sodium intake across183 countries worldwide over 10 year period and found that the average cost-effectiveness ratio would be approximately $204 per DALY saved [126]. Furthermore, the study projected that a 10% reduction in sodium intake within each country over the same period could prevent approximately 5.8 million DALYs/year related to cardiovascular diseases. The cost-effectiveness ratio was lowest (best) for lower-middle-income countries and South Asia.

Overall, evidence suggests that limiting sodium intake may help lower blood pressure and reduce the risk of cardiovascular disease and stroke. Despite that fact, the average intake of dietary sodium is significantly higher than the recommended amount globally indicating a need for prompt intervention for assessing the population salt intake, monitoring existing programs, and developing and implementing evidence-based approaches for salt reduction. Evidence shows that multifaceted intervention (reformulation, food labelling, and media campaigns) or population-based approaches would give better results in reducing population sodium consumption than individually focused interventions [110]. Having said that, it is also equally important to consider the dietary pattern and socio-cultural issues of individuals and communities including other barriers attached with salt reduction before developing a scalable and effective intervention. For example, in countries with high non-discretionary use, reformulation of processed food would be more impactful for reducing sodium, whereas in countries with high discretionary use, an intervention targeting home cooking and table salt could be more relevant. Likewise, while aiming for behaviour change, intervention should be comprehensive and should address the consumers' knowledge and awareness about the harm/ benefit of high/low salt intake and create enabling environment to opt for a lower salt diet.

2.2.3. Potassium supplementation

2.2.3.1. Potassium supplementation and blood pressure

Potassium is an essential nutrient that is present intracellularly and is required to maintain resting membrane potential and intracellular osmolarity. Evidence shows that potassium also has a vital role in lowering blood pressure [127-133].

A systematic review conducted by the World Health Organization found that an increased potassium intake was associated with an average reduction in systolic blood

pressure of 4.68 mmHg (95%CI: 2.40, 6.96), specifically in individuals with hypertension [132]. Additionally, Filippini et al. [133] in a systematic review observed a higher blood pressure-lowering effect among those who had a lower (< 90 mmol/day) potassium intake at baseline. In a dose-response meta-analysis, a U-shaped relationship between potassium intake and blood pressure was identified, indicating both low and high potassium intake could result in an increased blood pressure level [134]. The study found that the reduction in blood pressure is maximum if the differences (before and after supplementation) in potassium excretion is around 30 mmol/day [134].

2.2.3.2. Mechanisms

The blood pressure-lowering effect of potassium supplementation is due to its role in decreasing proximal tubular reabsorption of sodium, inhibiting renin release, and increasing glomerular filtration rate [135]. Evidence suggests that potassium could counteract the negative effect of sodium on blood pressure by helping the kidney excrete sodium. Therefore, the effect of potassium supplementation on blood pressure reduction is higher among those who consume more salt. For example, a systematic review found that an increased potassium intake was associated with the reduction in systolic blood pressure by 1.97 mmHg and 6.91 mmHg when mean sodium intake was 2-4 gm/day and >4 g/day, respectively [132]. Furthermore, studies found that the ratio of sodium to potassium is strongly associated with blood pressure outcomes and subsequent risk of cardiovascular diseases, where the higher is the ratio of sodium to potassium excretion, the greater is the risk of hypertension and subsequent cardiovascular diseases [136, 137]. The other functions of potassium include vasodilating, increasing nitric oxide production, and promoting proliferation of vascular smooth cells reduces the risk of vascular injury [135, 138]. Studies have shown that an increase in dietary potassium significantly reduces the risk of stroke and associated mortality independent of blood lowering effect, indicating potassium might have vascular protective properties as well [135].

2.2.3.3. Implementation of potassium supplementation strategies

World Health Organization recommends potassium intake to at least 90 mmol/day (3.5 g/day) for adults [139] and American guidelines, however, set a higher target of daily potassium intake of >120 mmol/day (4.7 g/day) [140]. The daily intake of potassium is far below the recommended guidelines globally. Daily potassium intake is <3 g in Asian, African, Canadian, and European populations [141-144]. There is a dearth of information relating to population-based strategies for potassium supplementation globally. It may be because

accounting population's baseline potassium values, presence of underlying medical conditions, use of medications that alter potassium levels, dietary pattern, and ability to adhere to a therapeutic regimen before supplementing potassium is challenging [145]. However, the daily requirement of potassium can be achievable by eating large amounts of fruits and vegetables. For example, the Dietary Approaches to Stop Hypertension diet- a diet rich in fruits and vegetables reduced the blood pressure in hypertension [146], which has been discussed under the heading '*Heart-healthy diet*'.

2.2.4. Physical activity

2.2.4.1. Physical inactivity and hypertension

A plethora of epidemiological and intervention studies have explored an inverse relationship between physical activity and hypertension [147, 148]. Recent evidence showed that at least 8% of cases of hypertension in the population are attributable to physical inactivity at leisure time [147]. It has been documented that prolonged sitting induced the accumulation of extracellular fluids and reduced the dilation of associated arteries in the legs [149]. That could be linked to the fact that one additional hour of sedentary behaviours in a day increases systolic blood pressure and diastolic blood pressure by 0.06 mmHg and 0.20, respectively [150]. In contrast to the role of physical inactivity on hypertension, the time spent in sports, walking, and gardening reduces the risk of hypertension [148]. In a dose-response meta-analysis, Liu et al. [151] found that an increase of 10 metabolic equivalents of task h/wk was significantly associated with the 6% reduced risk of hypertension.

2.2.4.2. Global estimates on insufficient physical activity

Insufficient physical activity is a prevailing problem globally. Finding from a study that pooled the data from 358 surveys across 168 countries reported that 27.5% of adults did not meet the recommendation for physical activity in 2016 [152]. The proportion of sufficiently physically active population largely varies with gender, age, and geographical regions [153]. A study that analysed the data of 1.6 million 11 to 17-year-old students from 146 countries and found that more than 80% of adolescents were doing fewer than 60 minutes of physical activity of moderate to vigorous intensity per day [154]. The prevalence of insufficient activity in this age group was 84·9% (82·6–88·2) in low-income countries, 79·3% (77·2–87·5) in lower-middle-income countries, 83·9% (79·5–89·2) in upper-middle-income countries, and 79·4% (74·0–86·2) in high-income countries in 2016 [154]. Despite a global

voluntary target of a 15% relative reduction in the prevalence of insufficient physical activity by 2030, a recent study suggested that the prevalence of physical activity did not increase significantly worldwide between 2001 and 2016 [152]. Moreover, some countries like the USA and Thailand even observed an increasing trend of physical inactivity during the same period [154].

The increasing trend of physical inactivity is also linked with prolonged sitting behaviours at the workplace and after school sedentary time, and the use of passive modes of transportation. [155]. For example, a systematic review found that children and adolescents spent 41-57% of after school periods in sedentary time [156]. Prevalence of such sedentary behaviours ranges from 40-60% depending upon the age of the person [156, 157].

2.2.4.3. Mechanisms

Several possible mechanisms have been postulated to explain the relationship between physical activity and blood pressure [158-160]. Physical activities modulate the actions of autonomic nervous system, then reduce the peripheral resistance which results in a significant drop in blood pressure level [159]. Physical activity also acts on neurohormones and vasodilating substances such as norepinephrine, endorphins, and nitric oxide that exhibit blood pressure-lowering effect through vascular adaptations [158, 159, 161]. It is also found that the constant physical activities could inhibit the inflammatory cytokines that are responsible for endothelial dysfunction and proliferation of vascular smooth muscle [162-164]. The effect of physical activity on hypertension could be mediated by the reduction in overweight or improved insulin sensitivity, the other two pertinent risk factors for hypertension [159, 160].

2.2.4.4. Increased physical activity and hypertension

A large body of evidence suggests that physical activity could significantly reduce blood pressure. For example, a systematic review that synthesised evidence from nine RCTs with 24 weeks of follow-up found that increased physical activity reduced systolic and diastolic blood pressure by 5–10 mmHg and 1–6 mmHg, respectively [165]. Most used physical activity-related interventions include aerobic, resistant, handgrip or combined exercises [166]. Aerobic exercise was associated with a significant reduction in mean systolic and diastolic blood of 4.94 mmHg (95% CI: 2.70, 7.17) and 3.73 mmHg (95% CI: 1.77, 5.69), respectively in hypertensive patients [167]. More importantly, aerobic exercise is found to be equally effective to reduce blood pressure whether the persons are hypertensive individuals or

normotensives; normal weight or overweight; low, moderate or high-intensity exercise; biking, walking, jogging or mixed activities; exercised for <120 minutes/wk or >150 minutes/wk; and sustained exercise for <10 wk or >24 wk [167]. Owing to that fact, every hypertension treatment guideline around the globe recommends moderate to vigorous physical activity as one of the most effective non-pharmacological interventions for blood pressure reduction [168].

Besides aerobic exercise, studies have shown the positive impact of resistance training on blood pressure [169-172]. A meta-analysis of 28 RCTs found that both isometric resistance training and dynamic resistance training were able to reduce 3.9 mmHg (95% CI: 1.5, 6.2) of systolic and 3.6 mmHg (95% CI: 2.1, 5.0) of diastolic blood pressure [170]. In another meta-analysis, the isometric exercise, such as handgrip or lower limb extension, in bouts of <20 min, with a weekly exercise time of <1 h, was significantly associated with about 10/7 mm Hg of systolic/diastolic blood pressure reduction [171].

Studies found that shortening the sitting time or interrupting the prolonged sitting hours (such as 2 min bouts of moderate-intensity walking) could significantly reduce the blood pressure [173]. Additionally, 2.5 hours of light intensity activity, standing or walking during office hours are significantly associated with a greater reduction in ambulatory blood pressure compared to sitting [174, 175]. Effect of physical activity on blood pressure does not vary whether it is an accumulated or continuous exercise of the same total duration [176].

2.2.4.5. Implementation of physical activity promoting strategies

Several intervention strategies for promoting physical activity were found to be effective [177-179]. The strategies mostly include behavioural change intervention and policy and environmental approaches. This review particularly focuses on behavioural change intervention implemented at the health care centre, community or workplace among hypertensive or general population.

2.2.4.5.1. Behaviour change interventions

The behavioural change intervention particularly includes provider-based physical activity counselling or brief advice and mass education campaigns. These interventions either aimed to reduce sedentary behaviour or promote physical activity such as walking, cycling; were delivered through the health care workers (Nurse, Doctor, general practitioner), exercise specialist, mass media, smartphones or other multifaceted approaches, and implemented at the individual, workplace, school, primary care or community level [177-181]. For example,

Ogilvie et al. [177] identified six studies that provided brief face to face advice to individuals in workplace or primary care; three studies that evaluated remote support to individuals delivered by telephone or internet; six studies with group-based approaches; seven studies provided pedometers with various supporting measures; and five studies with community-based approaches that significantly increased the self-reported walking among the participants.

Evidence on the use of physical activity counselling for hypertensive patients is limited. A newly published pilot study demonstrated that physical activity counselling for 14 weeks could increase the number of steps per day and sitting time, but did not affect the blood pressure of hypertensive patients [182]. Interestingly, when physical activity and dietary counselling were used together, a greater reduction in blood pressure in hypertensive patients was observed. A systematic review showed that the behavioural counselling (physical activity and diet) significantly reduced 4.5 mmHg and 2.3 mmHg of systolic blood pressure during 12 months and 12-24 months of intervention respectively [183].

2.2.4.5.2. Policy approaches

To increase physical activity, the Global Action Plan on Physical Activity 2018-2030 has developed a framework of effective and feasible policy actions at all levels globally [184]. The plan contains four strategic objectives of creating active societies, environments, people, and systems, which are achievable through 20 policy actions that are universally applicable to all countries [184]. Most of the countries adopted World Health Organization physical activity guidelines, some have modified them to meet the need of specific groups such as children, adolescents, older adults, pregnant or breastfeeding women, and people with disabilities or people with chronic disease [185]. In a recently published cross-sectional study, Klepac Pogrmilovic et al. [186] collected data from 76 countries on national policy and guidelines related to promoting physical activity. The study found that 92% of the countries had formal written policies on physical activity. However, information on the impact and cost-effectiveness of the policy intervention is usually not readily available. Likewise, except for the recommendation issued by the hypertension treatment guidelines, no other physical activity policy and guidelines specific to hypertensive patients are recorded.

Overall, physical activity is effective to prevent and control hypertension. Interventions that included physical activity and dietary counselling together and with community support have shown promising results to reduce blood pressure. Nevertheless,

very less is known about the impact of the constant and long-term intervention of physical activity in blood pressure. Likewise, a systematic investigation of the evidence on the effectiveness of practitioners' physical activity counselling at health centres is required before recommending the use of physical activity promoting advice for hypertension at primary care.

2.2.5. Weight reduction

2.2.5.1. Weight and blood pressure

A preponderance of evidence suggested that overweight/obesity is related to blood pressure. Earlier in 1987, findings from the Framingham Heart study indicated an association between obesity and the risk of hypertension. The study reported that an increase of 4.5 kg of body weight was associated with a 4.4 mmHg and 4.2 mmHg increase of systolic blood pressure in males and females, respectively [187]. A cross-sectional sample collected from different regions (the Seychelles and Switzerland) showed that an elevation of 1 mmHg of systolic blood pressure was associated with a gain in body mass index of 1.7 kg/m2 in males and 1.25 kg/m2 in females [188]. A recent linear dose-response meta-analysis that pooled the data from 50 prospective cohort studies found that a 5-unit increment in body mass index was associated with a 49% higher risk of hypertension [189]. The study also indicated that a gain of weight equal to 1 kg/m2 increased the risk of hypertension by 16% [189]. In addition to body mass index, the other indices of abdominal adiposity such as waist circumference and waist-hip-ratio are also consistently associated with hypertension. The risk of developing hypertension increases by 27% per 10-cm increment in waist circumference and by 37% per 0.1-unit increment in waist-to-hip ratio [189].

2.2.5.2. Mechanisms

Several mechanisms have been proposed to explain the pathophysiological link between overweight/obesity and hypertension [190-192]. It has been found that the dysfunctional adipose tissues in obesity lead to overstimulation of the sympathetic nervous system, impair the renin-angiotensin-aldosterone system, and induce chronic vascular inflammation and thus raise the blood pressure [191]. By contrast, reversing the weight also reverses the altered neurohumoral and renal mechanism, ultimately reducing blood pressure [191, 193].

2.2.5.3. Reduction in weight and blood pressure

Studies showed that reducing weight also lowers blood pressure. In a meta-analysis, Neter et al. [194] found that an average of 5.1 kg reduction in body weight linked to 4.4 mmHg and 3.8 mmHg drop in systolic and diastolic blood pressure, respectively. A greater reduction in blood pressure was observed with 5-10% of weight loss over six months and longer duration [195]. It was also observed that participants who lost more than 5 kg of body weight or those under antihypertensive medication were more likely to have larger blood pressure reduction than others [194]. However, the long-term impact of weight loss on blood pressure reduction is not promising as blood pressure tends to revert to the initial level after certain years. A systematic review analysed the pooled data from 83 short term studies (follow-up period 6 to <12 months), 59 medium-term studies (follow-up time 12 to <24 months), and 18 long term studies (follow-up time ≥24 months) and found that the blood pressure-lowering effect of any weight loss intervention diminished with time despite sustained weight loss [195]. Aucott et al. [196] in their meta-analysis further clarified that initial reduction in blood pressure due to weight loss could be short-lived (≤3 years).

2.2.5.4. Implementation of weight control strategies in hypertension

Most of the weight control interventions are accomplished through either physical activity or diet control. Among all behavioural change interventions for weight loss, commercial community behavioural change intervention with or without replacement of diet showed a significant association with weight reduction. However, primary care-based weight reduction counselling did not show any significant effect in reducing weight [195]. A health care provider-led weight reduction discussion was associated with 5% greater weight reduction among overweight and obese patients [197]. Evidence also showed that low (810 kcal/day) and very low (<800 kcal/day) energy diets are also effective for weight loss [198, 199]. Evidence also suggested that these diets are more effective in weight reduction compared to behavioural therapy [198-200]. However, the low energy diets are recommended when rapid reduction in weight is required and to be only provided by the trained professional with medical monitoring due to the reported adverse events [199].

2.2.6. Heart-healthy diet

Evidence suggested that dietary modification is one of key components of prevention and control of hypertension. Different dietary approaches including Dietary Approaches to Stop

Hypertension (DASH) diet (high intake of fruits & vegetables, low-fat dairy products, and whole grains, and low in sodium), Mediterranean diet (high consumption of fruit, vegetables, olive oil, legumes, cereals, and fish), Nordic Diet (whole-grain products, abundant use of berries, fruit and vegetables, rapeseed oil, three fish meals per week, low-fat dairy products and avoidance of sugar-sweetened products), Palaeolithic diet (contains lean meat, fish, fruit, leafy and cruciferous vegetables, root vegetables, eggs and nuts, without dairy products, refined fats, sugar, candy, soft drinks, beer and extra addition of salt), low carbohydrate diet, and low-fat diet are associated with a significant reduction in blood pressure in hypertension [201, 202]. Compared to the control diet, the largest net blood pressure-lowering effect was seen among the DASH diet with a reduction of 7.4 mmHg of systolic blood pressure and 4.22 mmHg diastolic blood pressure [202]. The DASH diet was ranked the most effective dietary approach in reducing blood pressure, followed by the Palaeolithic, and the low-carbohydrate diet (for systolic blood pressure) or the Mediterranean diet (for diastolic blood pressure) [201]. It has also been indicated that dietary interventions along with exercise and weight loss could result in larger blood pressure reduction [203].

2.2.6.1. Mechanisms

Most of the dietary approaches are designed to be lower in carbohydrate, fat, sodium and higher in fruit and vegetables that contain fibre, potassium, calcium, zinc, magnesium, and other micronutrients. The combined effect of low calory, low fat, low sodium, and high potassium diet has been indicated to beneficially affect systematic inflammation, body weight, blood glucose level, cholesterol, and blood pressure, protecting against cardiovascular diseases, stroke, diabetes, and cancers [204-207], which are discussed under the separate headings of sodium reduction, potassium supplementation, and weight control.

2.2.6.2. Implementation of heart-healthy diet for hypertension

The most commonly applied dietary interventions are the DASH diet and the Mediterranean diet. They are mostly delivered by dietary education through face-to-face counselling [208]., telephone, email [209] and led by primary care physician [210], nurse, dietician [209], nutritionist [208], and other health workers [210]. The dietary interventions are often combined with exercise, weight loss, salt reduction or co-intervention to have better control of hypertension [203, 211].

Despite the proven benefit of DASH and other diets on hypertension, adherence to dietary recommendations is low among patients [212]. Primary care physicians from Canada

stated that the lack of time, difficulty in assessing patients' dietary patterns, patients' non-adherence to dietary advice, and inconsistent dietary guidelines were the major barriers to the implementation of DASH diet intervention at primary care [213]. They believed that the use of electronic medical record tools, access to dietitians, nutrition education in medical training would help facilitate them providing dietary advice to patients [213]. From a hypertensive patient's perspective, the major barriers to following a recommended diet are social and environmental factors such as eating outside the home or eating food cooked by others, and lack of food choice in social gatherings; lack of family support; lack of taste in the diet; and cost of diet [214].

2.2.7. Other promising non-pharmacological interventions

The body of evidence on other non-pharmacological interventions, such as yoga, stress reduction, and healthy drinks is growing [215, 216]. [195]. A recent meta-analysis of 49 clinical trials found that engaging in 3 sessions per week of yoga (including breathing techniques and meditation/mental relaxation) is associated with an average reduction in systolic blood pressure of 5 mmHg [216]. Likewise, a systematic review suggested that a mindfulness-based stress reduction program, which mostly includes mediation and yoga, could be a promising behavioural therapy for reducing blood pressure in hypertension [217]. Similarly, studies showed that moderate consumption of coffee and green tea could be beneficial for reducing blood pressure [218, 219]. The 2020 International Society of Hypertension global hypertension practice guidelines also included healthy drinks, stress reduction, and smoking cessation as recommended lifestyle modifications for blood pressure reduction [215]. A wealth of evidence suggested smoking as a preventable risk factor for cardiovascular diseases, where cessation of smoking reverses the disease progression [220].

2.3. Lifestyle-related risk factors and their modification interventions among hypertension patients in Nepal

As discussed above, alcohol consumption, unhealthy diet, physical inactivity, and overweight/obesity are some of the major lifestyle-related risk factors for hypertension. In Nepal, the prevalence of alcohol consumption was 29.7% in hypertensive individuals in

2019, a 7 percent point higher than the rate that was reported in the general population [22]. Nearly all Nepalese (97%) do not consume sufficient fruit and vegetables as recommended (400 gm/day). The average salt intake is 13.3 (±4.7) gm/person/day in Nepal [221], which is nearly three times higher than the recommended intake per day (5 gm/person/day). It is also found that 9.2% of Nepalese add salt to their foods while eating [22]. Around 7% of Nepalese had insufficient physical activity (<600 METs/week) in 2019 [22], which was twice the prevalence reported in 2013 [222]. The prevalence of insufficient physical activity was 8.4% in hypertensive individuals in 2019 [22]. Nearly one-fourth of Nepalese have overweight/obese (body mass index≥ 25 kg/m2). Overweight/obesity is more prevalent (27.3%) in hypertensive individuals than in the general population [22].

As summarised in the previous section, many interventions for lifestyle modifications exist globally. Details of the policy and program interventions for the prevention and control of non-communicable diseases in Nepal have been discussed above. Shortly, Nepal has developed Multi-Sectoral Action Plan that includes targets and plans to promote healthy lifestyles including alcohol intake reduction, salt intake reduction, increasing physical activity, and weight reduction. Additionally, Nepal also adopted the National Alcohol Regulation and Control Policy to regulate sales of alcohol in 2017. However, no clear guidelines on population-specific salt intake reduction, increasing potassium intake, and physical activity are available in Nepal. Further, the implementation and supervision of policies is weak, and no evaluation has been conducted yet to assess whether the implemented policies are effective for promoting healthy lifestyles. Apart from population policy interventions, a few studies have also investigated the effect of lifestyle modification interventions on blood pressure reduction among hypertensive patients in Nepal [223-227]. However, these health education interventions were designed to promote healthy behaviours in general rather than specifically modifying alcohol use, physical inactivity or overweight using established theories of behaviour change. None of these studies measured the change in risk behaviours. Gaudel et al. [228] investigated the effects of a lifestyle-related risk factor modification intervention on lifestyle changes among patients with coronary artery disease in Nepal and found a significant improvement in diet and physical activity in intervention group compared to control group. But the study did not report a change in blood pressure. Overall, there is a dearth of information regarding the use of non-pharmacological interventions for hypertension in Nepal. Therefore, it is required to systematically syntehsise the available evidence on non-pharmacological interventions globally and generate country-specific

evidence to inform stakeholders about the importance of lifestyle modification interventions for the prevention and control of hypertension in Nepal.

2.4. Yoga and blood pressure

2.4.1. Yoga

Evidence showed that yoga could be useful for improving several physical and mental health conditions. Recent studies investigated the effect of yoga on many physical conditions such as cancer, arthritis, menopausal disorders, diabetes, and cardiovascular diseases, among others [229, 230]. It has also been tested against depression [231], anxiety [232], stress [233, 234], attention-deficit/hyperactivity disorder [235] and dementia [236] and shown some promising results.

2.4.1.1. Yoga for hypertension

A number of individual studies and at least eight systematic reviews have investigated the effect of yoga on high blood pressure until 2020 [237]. The recent meta-analysis that synthesised the evidence from 49 clinical trials suggested that yoga could have a promising effect on blood pressure reduction [216]. However, the effect of yoga varied based on the contents, structures, and delivery of the yoga intervention [238]. Cramer et al. [239] analyzed data from 44 randomised control trials and found that seven of them used Hatha yoga and 13 studies applied different styles of yoga such as Iyengar Yoga, Sudarshan Kriya Yoga, Kundalini Yoga, Restorative Yoga, Silver Yoga, Ashtanga Yoga, Viniyoga, Vinyasa Yoga, and Yoga Synergy. All studies included physical postures in their intervention, 33 included breathing exercise (*Pranayama*), 36 used relaxation, and 18 applied meditation [239]. Breathing exercise alone was also associated with an average of 2-21 mmHg of systolic blood pressure reduction, and 1-7 mmHg of diastolic blood pressure reduction [240]. Furthermore, Brandani et al. [240] reviewed 13 clinical trials assessing the effect of breathing exercise and blood pressure and concluded that *Pranayama* with slower rhythms and manipulation of the nostrils associated with a greater reduction in blood pressure compared with the other types of yoga. Wu et al. [216] also found that reduction in systolic blood pressure was higher with the intervention that contained breathing exercise. They observed that yoga was associated with -5.0 mm Hg and -3.9 mm Hg reduction in systolic and diastolic blood pressure,

respectively. When yoga was practised 3 sessions per week with breathing techniques and meditation/mental relaxation, the systolic blood pressure/diastolic blood pressure reductions nearly doubled (11/6 mm Hg) [216]. In a subgroup analysis of a meta-analysis, Hagins et al. [241] found that yoga could have a significant effect on systolic and diastolic blood pressure if intervention includes all three components of yoga: postures, breathing exercise, and meditation. Yoga could also elicit promising results in blood pressure reduction if it is used with other complementary therapy such as biofeedback and music therapy [237].

Similarly, the duration of yoga sessions also varies across the studies. A systematic review of 49 controlled trials showed that on average, yoga was practised for 4.8±3.4 sessions per week for 13.2±7.5 weeks [216]. Each session lasted for 59±25.01 minutes, where the time of physical postures, breathing techniques, and meditation/relaxation (minutes/session) was around 30, 15, and, 15 minutes, respectively [216]. Blood pressure reduction was greater among those who practised yoga more than 3 sessions per week [216]. Similarly, the impact of yoga would be higher if it is practised for 12 weeks compared to less weeks of practice [239].

2.4.1.2. Mechanisms

Yoga affects the secretion of endocrine hormones such as cortisol, serotonin, oxytocin, and melatonin which are associated with stress, anxiety, depression, and other mental and physical health conditions [242, 243]. It also acts on the autonomic nervous system, balancing sympathetic and parasympathetic actives [244]. It is hypothesized that decreasing activation of sympathetic nervous system and increasing parasympathetic activity from yoga leads to the balance of neuro-humoral bio-feedback mechanism targeting baroreflex sensitivity, vasodilation, secretion of endocrine hormone, and regulation of bodily functions including blood pressure [245].

2.4.1.3. Implementation of yoga for hypertension control

Most of the studies with yoga interventions for blood pressure reduction were conducted in India, USA, UK, South Korea, Australia, and Iran. Out of 56 studies on yoga intervention for blood pressure reduction conducted between 1983 to 2018, 42.9% (*n*=24) were from India, 16.1% (*n*=9) were from South Korea, 41.1% (*n*=23) were from other non-Asian countries like the United States and the UK [216]. Few studies were also conducted in China, Japan, Thailand, Sweden, Cuba, and Jamaica [239].

Despite the preponderance of evidence on the efficacy of yoga on blood pressure, there are very few effectiveness trials conducted in real-world settings. A large number of the trials were conducted in the healthy or normotensive population [246-255], recruited the participants from the workplace [250, 252, 256] or academic setting [249, 251], and used the respective centres [249-252, 255, 257] or separate yoga studios [258-260] for the intervention. Most studies having hypertensive patients as the study participants recruited the sample from the clinical settings [261-267]. For example, McCaffrey et al. [263] enrolled 61 hypertensive participants from hospital mobile clinics and primary care units in Thailand. The intervention group participants practised yoga for 3 times per week for 8 consecutive weeks. The yoga session was for 63 minutes conducted in the yoga centre located outside the hospital. The yoga package consisted of postures, *Pranayama*, and relaxation. The participants were provided with a cassette and the practice sessions were guided by the trained Research Assistant. The control group received routine care and health education. Similarly, a study from Spain recruited 50 hypertensive patients diagnosed with hypertension in a public health care centre. Intervention group participants practised yoga two days each week for three months. Each session was for 90 minutes. But this study provided no information on setting for yoga practice, instruction or supervision, and other care available to the participants [265]. Murugesan et al. [264] also recruited hypertensive patients from a public hospital in India in 2000, but the intervention was delivered in a more controlled environment.

There are only two studies available that investigated the effect of yoga on blood pressure among hypertensive patients in primary care settings and utilized primary care physicians to instruct yoga. Both studies were conducted by Wolf et al. [262, 266] in the same setting in Sweden. In the first study, 83 hypertensive participants were recruited from the public health centre and randomised to yoga class, yoga at home and control groups [262]. Yoga class groups attended the health centre once a week for 60 minutes for 12 weeks. They were also asked to practise yoga at home daily. The yoga at home group received instructions (by the study physician who were not trained in yoga) for two yoga exercise (left nostril breathing and spinal flex) which they practised for the study duration. The control group received usual care. Findings showed that the physician instructed home-based yoga practice had a significant reduction in diastolic blood pressure compared to the control group. Later, the study team expanded the study to test whether the same home-based yoga program had a significant impact on blood pressure in patients with hypertension [266]. The study

recruited 191 patients and randomized them to treatment (two yoga instruction sessions from primary care physician and yoga practice for 15 minutes, twice daily for 12 weeks) and control group (usual care) [266]. However, the study did not find any significant difference in blood pressure between treatment and control groups.

It is important to highlight the fact that a few pragmatic approaches for yoga intervention for blood pressure reduction are available. Sarah et al. [268] investigated the telephone-based rehabilitation approach to maximize the adherence to home-based yoga practice. The study recruited 228 male cardiac patients from a rehabilitation centre in Germany and randomised them to tele-rehabilitation group and control group. Both groups received yoga intervention (breathing exercise and postures) once a daily (for 45 minutes), five times a week for three consecutive weeks. The tele-rehabilitation group additionally received six telephone counselling sessions. The findings suggested that tele-rehabilitation was significantly associated with higher adherence (adherence in intervention group = 36.5% vs. control group = 23.9%) to home-based yoga practice after one year [268].

To sum up, it is widely accepted that yoga could be a viable lifestyle intervention for hypertension control. However, there are various challenges in the uptake of evidence into practice. Globally, various forms, structures, and paths of yoga are being practised. Among them, yoga intervention comprising three components particularly postures, breathing exercise, and relaxation/meditation have shown promising results in reducing blood pressure. Similarly, many limiting factors to regular yoga practice have been identified. One of them is about the requirement of long-term time commitment which makes yoga as a laborious way for hypertension control. Likewise, most of the interventions were tested in ideal conditions. There are some important differences between generating evidence from an ideal environment and uptake of the evidence into practice [269]. Moving from efficacy trial to effectiveness trial and implementation research could take time, but that increases the likelihood of success of the intervention in real-world settings [270, 271]. This is an issue for future research to explore how yoga can be implemented in real-world clinical settings. One study implied that primary care staff could lead yoga intervention in a clinical setting and supervise home-based practice [266] or use tele-counselling [268] to increase adherence to home-based yoga practice. But further work is certainly required to develop more acceptable, scalable, and sustainable yoga interventions for hypertension in real-world clinical and community settings.

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Chapter 3. Methodology and conceptual framework

This chapter aims to provide a summary overview of five studies conducted under the current PhD thesis. Though the five studies had separate methods and frameworks, they were designed to complement each other to achieve the broader objectives of the thesis (Table 1).

This chapter also outlines the theoretical framework that aims to represent an overall concept of PhD thesis. The framework captures a complex pathway towards hypertension control, illustrating interactions and relationships of different factors that can positively or negatively affect hypertension control.

3.1. An overview of methodologies of the PhD projects

The summary overview of methodologies and conceptual frameworks of five studies are tabulated in Table 3 and briefly presented on each study heading below.

Table 3. A summary overview of methodologies of the research projects

Studies	Theoretical framework	Study design	Data collection/extraction	Data analysis/synthesis
Study 1	Cascade of hypertension care	Secondary data analysis of nationally representative surveys with 9682 participants	Sampling methods: multistage cluster sampling method Survey tools: structured questionnaires; and anthropometric, biochemical, and clinical measurements	Adjusted prevalence ratios were calculated using multivariable Poisson regression analysis
Study 2	Theoretical framework for hypertension control	Systematic review on barriers, enablers, and strategies for hypertension treatment and control Registration: registered in PROSPERO	Search strategy: six databases were searched for qualitative, quantitative, and mixed-methods studies Study selection: 15 studies were selected after primary and secondary screening of literature	Synthesised and reported the findings as per the PRISMA and Synthesis Without Meta-Analysis (SWiM) guidelines
Study 3	None, fitted with the main framework of the thesis	Narrative review on non-pharmacological interventions for hypertension at primary care	A thorough literature search was conducted to identify evidence on the use of alcohol reduction, salt reduction, potassium supplementation, physical activity, weight control, and heart-healthy diet for hypertension control in primary care	Narratively synthesise the findings
Study 4	None, fitted with the main framework of the thesis	Randomised controlled multicentre pragmatic trial Randomisation: 121 participants were randomised to yoga intervention (*n*=61) and wait-list control (*n*=60) groups	Data collection tools: structured questionnaires; and anthropometric, and clinical measurements at the first day and 90-day follow-up	Data were analysed on an intention-to-treat basis using linear mixed-effects regression models
Study 5	Consolidated Framework for Implementation Research and	Mixed-methods study Qualitative methods: focus group discussions, in-depth interviews, and key informant interviews	Data were collected from the 'Yoga and Hypertension'(YoH) trial (Study 4) participants, YoH intervention implementers, and officials from the	Qualitative data: template analysis Quantitative data: descriptive analysis

Studies	Theoretical framework	Study design	Data collection/extraction	Data analysis/synthesis
	theoretical framework of acceptability	Quantitative methods: telephone interview and documentary analysis	Ministry of Health and Population in Nepal Data collection tools: Semi-structured interview guide and structured questionnaires	

3.1.1. Study 1. Hypertension screening, awareness, treatment, and control: a study of their prevalence and associated factors in a nationally representative sample from Nepal

Data from two STEPwise approach to Surveillance (STEPS) surveys were analysed to quantify the gaps in hypertension treatment and control using the cascade of care framework.

The STEPS surveys were conducted in 2013 and 2019. They were the national representative surveys and used the multistage cluster sampling method to select the participants. STEPS 2013 collected data of 4,200 respondents selected from 210 clusters between January and June 2013. STEPS 2019 collected data from 5593 individuals from 737 clusters between October 2018 and March 2019. Details of survey methodology for STEPS 2013 [1] and STEPS 2019 [2] have been described elsewhere. The final dataset contained information related to hypertension screening, awareness, treatment, and control from 9682 participants.

Data were analysed using the STATA software version 16.0 (Stata Corporation, College Station, TX, USA). All estimations were adjusted for the complex survey design. Multivariable models were constructed using Poisson regression analysis to report the prevalence ratio. This study included all available explanatory variables in the multivariable models. All the models were adjusted for the survey year.

3.1.2. Study 2. Barriers, enablers, and strategies for the treatment and control of hypertension in Nepal: a systematic review

After quantifying the gaps in cascade of hypertension care, a systematic review was conducted to assess barriers, enablers, and strategies for hypertension treatment and control in Nepal. Data from qualitative, quantitative, and mixed methods studies were systematically extracted, synthesised, and reported findings following the PRISMA [3] and Synthesis Without Meta-Analysis (SWiM) guidelines [4].

Studies that provided information on barriers to, enablers of, and strategies for hypertension treatment and control in Nepal were selected based on the PICOS (P-Population; I- Intervention/Exposure; C-Control/Comparator; O-Outcome; S- Study design) model.

Literature was searched primarily in PubMed, Embase, Web of Science, CINAHL through EBSCOHost, ProQuest, and WorldCat databases. Mixed Methods Appraisal Tool was used to assess the methodological quality of the selected studies.

In data analysis, both qualitative and quantitative findings were synthesised to enrich the understanding of barriers, enablers, and strategies for hypertension treatment and control specific to "health system", "providers", and "patients" based on the theoretical framework for hypertension control. Qualitative data were analysed using template analysis [44]. Due to the limited information on the exposures and outcome and large methodological heterogeneity between the quantitative studies, the vote-counting method was applied to synthesise and narratively present the findings based on the Cochrane Handbook for Systematic Reviews of Interventions [5].

3.1.3. Study 3. Implementation of non-pharmacological interventions for blood pressure reduction in primary care: a review of effectiveness, cost-effectiveness, barriers, and facilitators

The third study was a narrative review of effectiveness, cost-effectiveness, barriers, and facilitators for the implementation of non-pharmacological interventions for blood pressure reduction in primary care.

Five electronic databases, including PubMed, Embase, Cochrane Library, Google Scholar, and Web of Science, were searched to find the relevant literature on non-

pharmacological interventions for hypertension in primary care settings. Studies that investigated the effectiveness of non-pharmacological interventions including alcohol reduction, physical activity, salt reduction, potassium supplementation, weight reduction, and heart-healthy diet for a reduction in systolic or diastolic blood pressure were critically appraised. Additionally, information related to barriers and facilitators for implementing the aforementioned interventions were also extracted and summarised narratively in the text, tables, and figures.

3.1.4. Study 4. Effects of a health worker-led 3-month yoga intervention on blood pressure of hypertensive patients: a randomised controlled multicentre trial in the primary care setting

As the third study had informed us about the lack of evidence on the implementation potential of yoga intervention for hypertension in primary care settings, Study 4 was conducted to assess the effect of yoga intervention on blood pressure reduction in hypertensive patients.

The Yoga and Hypertension (YoH) trial was a multicentric, two arms, randomised, nonblinded trial that was conducted in seven District Ayurveda Health Centres (DAHCs) in Nepal between March 2017 and June 2018. Study participants were hypertensive patients with or without antihypertensive medication attending the outpatient department (OPD) of the study sites. One hundred and forty participants were randomized into treatment and control groups by stratified block randomization. At the study site, participants received an intervention consisting of five days of structured yoga training and practised the same package at home with a recommendation of five days a week for the following 90 days. The control group received only two hours of health education on lifestyle modification related to blood pressure control. The primary outcome of this trial was the systolic blood pressure at follow up which was assessed before and after the intervention.

Analyses were performed based on the intention-to-treat (ITT) principle in Stata 16.0 (StataCorp LLC, College Station, TX, USA). Data on primary outcomes were analysed with mixed-effects linear regression models. Potential confounding variables including smoking,

alcohol consumption, and physical activity were also adjusted in the models. All tests will be two-tailed and $p < 0.05$ will be considered statistically significant.

3.1.5. Study 5. Yoga for hypertensive patients: a study on barriers and facilitators of its implementation in primary care

The fifth study was a retrospective evaluation of the implementation of the YoH trial (Study 4). A mixed-methods study design was used to assess factors influencing implementation of YoH trial conducted between 2017 and 2018.

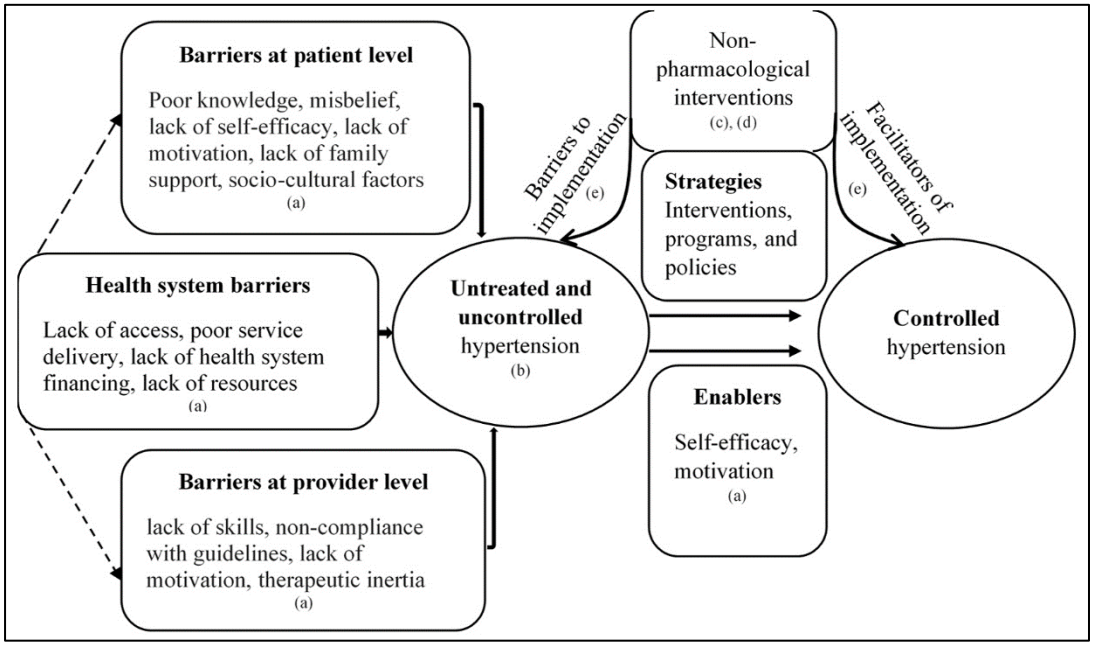
Data were collected using in-depth interviews (IDI), focus group discussion (FGD), key informant interview (KII), telephone interview, and documentary analysis. IDI was conducted among six implementors of YoH trial to understand their perspectives on and experience of implementation of intervention. For that, a semi-structured interview guide was used to collect data from six health workers who were involved in the implementation of YoH trial. Similarly, FGD was conducted among 16 YoH trial participants to assess participants' perspectives and experience regarding yoga intervention and explore enablers and barriers to intervention adherence. Additionally, four KIIs was conducted with the four leading government health professionals to assess organisational capacity to scale up yoga intervention in primary healthcare settings. In the telephone interview, 20% (12 out of 59) of the randomly selected trial participants from each centre were interviewed via telephone using a structured questionnaire.

For qualitative data analysis, the interview transcripts were translated into English and imported to NVivo 12 (QSR International Pty Ltd, Melbourne, Australia). Constructs of Consolidated Framework for Implementation Research and theoretical framework of acceptability were used to generate prior codes for the template analysis [6]. The coding and themes were generated using the prior template of codes and themes and constantly revised during the analysis. The quantitative data were presented as absolute frequencies and percentages of participant responses across different categories. Finding from both qualitative and quantitative components were discussed together for providing insights into the process, context, barriers, and facilitators of implementation of yoga intervention in a primary care setting in Nepal.

3.2. Conceptual framework

The multiple theoretical frameworks were fitted together to provide a clear understanding of factors related to health system, individual healthcare providers, patients, and interventions influencing hypertension control in Nepal as shown in figure 7.

Figure 7. Conceptual framework for hypertension treatment and control



Note: (a) refers to Study 2 where the framework is discussed; (b), Study 1; (c), Study 3; (d), Study 4; (e), and Study 5

3.2.1. Framework for hypertension control

This framework covers the major part of conceptual framework of the current PhD thesis. The concept was primarily derived from the theories used in previous studies on barriers [7-9]. Additionally, the framework was fitted with enablers and strategies, which are the major determining factors for hypertension control.

The framework recognises several barriers relating to different layers of the health system including healthcare providers and patients that impede hypertension treatment and blood pressure control [9]. The framework assumes that poor knowledge, misbelief, lack of self-efficacy, lack of motivation, and lack of family support among hypertensive patients lead to poor health-seeking behaviours or non-adherence to medication, causing poor control of

hypertension [8-10]. For example, lack of awareness of the 'normal' blood pressure target [11, 12] and lack of knowledge about possible complications of hypertension [12] were found to be associated with uncontrolled hypertension. Likewise, patients' false belief in adverse effects of antihypertensive medications and fear of long-term use refrained them from taking antihypertensive medications [11, 13]. Studies also suggested that lack of family support and certain socio-cultural factors contribute to uncontrolled hypertension [13].

On top of that, several factors related to healthcare providers also predispose patients to uncontrolled hypertension. Healthcare providers' lack of skills in detecting and managing hypertension, lack of compliance to national and international guidelines for hypertension management, lack of motivation, and failure to initiate or intensify therapy when appropriate are some of the precipitating factors for uncontrolled hypertension [8, 9, 14]. Additionally, failure of healthcare providers to deliver a clear health message to patients regarding lifestyle modifications, medications, and routine follow-up care also affects treatment adherence among hypertensive patients [15].

Similarly, health system-related factors that have been hypothesised to influence hypertension treatment and control are lack of physical and trained human resources, poor health system financing including lack of health insurance coverage or co-payments for medical care, and poor service delivery [7].

By contrast, certain contextual factors enable hypertensive patients to take actions or change behaviour for hypertension treatment and control. For example, family support for refilling medication or maintaining a regular follow-up visit to health providers could positively facilitate medication adherence and thus improve hypertension control [13]. Likewise, the positive personal attributes and factors such as good illness perception and self-efficacy enable hypertensive patients to engage in self-care behaviours including medication adherence, physical activity, and dietary changes [16, 17].

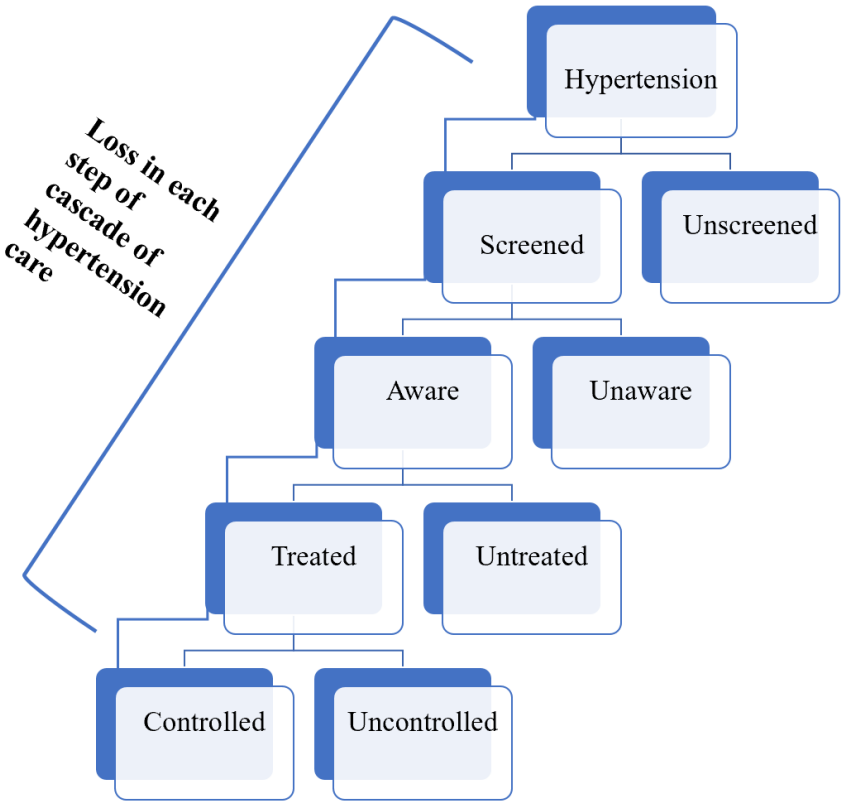
Improving hypertension treatment and control requires multifaceted strategies including pharmacological and non-pharmacological interventions, programs, and policies that could ensure accessible and appropriate hypertension care. Additionally, there are several other interventions designed to address the barriers to hypertension treatment particularly in low-and middle-income countries such as task shifting (delegating task from highly specialised to less specialised health workers) [18], team-based care (providing patient-centred care with the collaboration of various combinations of physicians, nurses,

pharmacists, social workers, and other health care professionals) [19], and health system financing [7].

3.2.2. Cascade of hypertension care framework

The cascade of care framework includes sequential steps including hypertension screening, awareness, treatment, and control (Fig 8).

Figure 8. Cascade of hypertension care



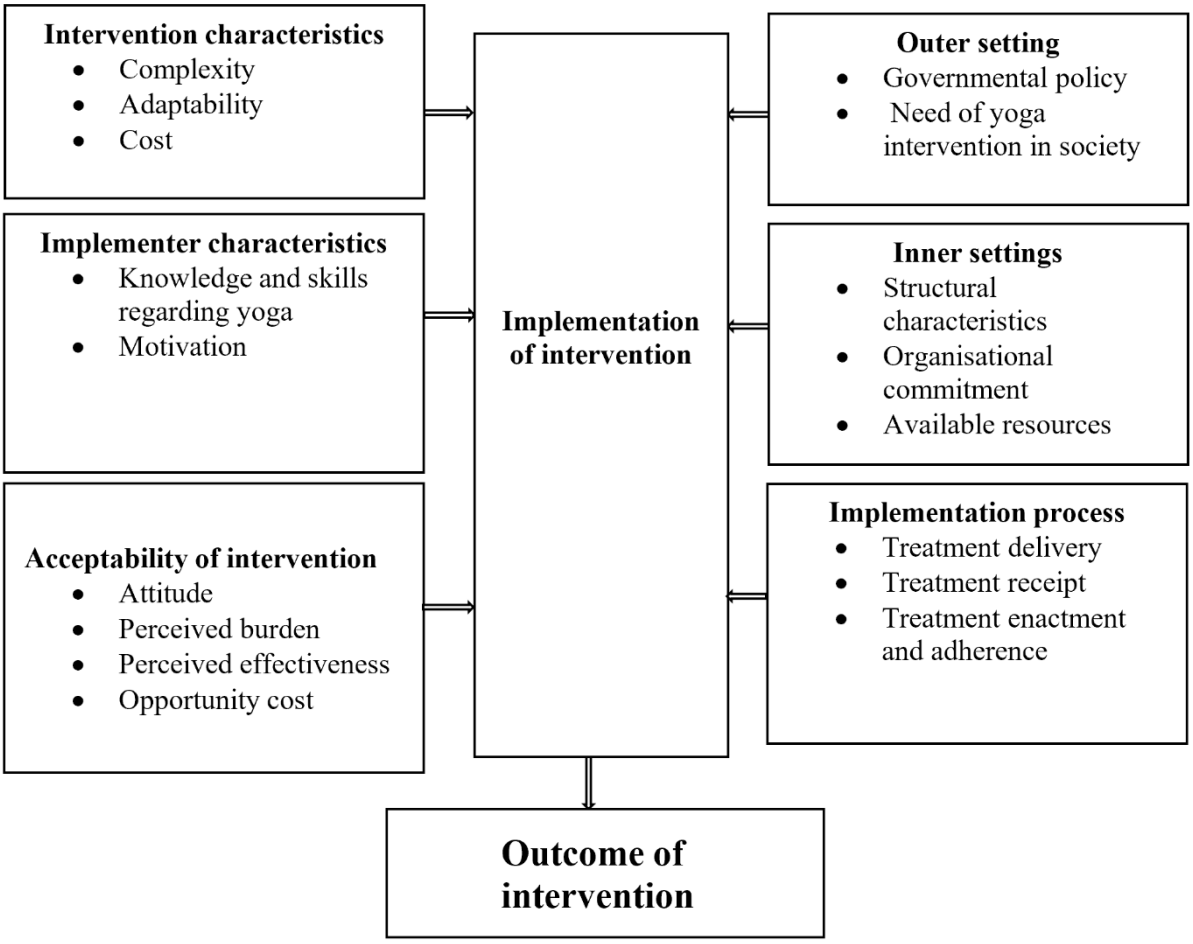
The framework enables service providers to detect and treat patients earlier than usual [20]. It also helps to quantify gaps in the continuum of care of hypertension which represent the proportions of people taking part in and leaving each step of care. [21]. For that, the proportion of people taking part in each step is calculated by keeping the denominator constant throughout sequential steps so that the cumulative losses in the cascade of care are visible. Therefore, the application of the framework is critical to identify persons who are more likely to be unaware of their hypertension, aware but untreated, or treated but having uncontrolled blood pressure. Locating the gaps in cascade of hypertension care informs the

health care providers and other stakeholders to pair those who are likely to drop out of care with effective interventions [22].

3.2.3. The Consolidated Framework for Implementation Research

The basic structure of the Consolidated Framework for Implementation Research consists of an interactive interplay of contents of intervention, context, and process of implementation [23]. It emphasises the importance of five major domains in implementation research, such as intervention characteristics, outer and inner settings of implementation, characteristics of individuals involved in implementation, and the process by which the implementation is accomplished (Fig 9).

Figure 9. Consolidated Framework for Implementation Research and Theoretical Framework of Acceptability



The first construct of the Consolidated Framework for Implementation Research is dedicated to the intervention characteristics. Stakeholders' understanding of the strength, quality, and relative advantages of implementing interventions may affect their outcome. Stakeholders could be reluctant to support the implementation of interventions, if they perceive that interventions are not backed by evidence or have a relatively less important outcome.

In this thesis, the framework was applied for understanding barriers and facilitators of implementation of yoga, a non-pharmacological intervention, in the Nepalese context. Stakeholders were invited to share their opinions about the intervention package using open-ended questions like "What do you think about the yoga intervention?". They were further asked about how complex the intervention package was to understand and deliver. The study participants were asked to share whether they felt comfortable with providing in-person

training of yoga to the participants, and whether the resources used in delivering the intervention such as posters, pamphlets, and videos were useful to them. These questions were designed to assess the perception of stakeholders about intervention characteristics, which may help reshape future similar interventions to be more adaptable and less complex.

The second and third constructs in the Consolidated Framework for Implementation Research are the outer and inner settings. The implementation of yoga intervention could have been affected by external factors, such as how government incorporates and acknowledges yoga as a complementary therapy in the existing health system. Does the health ministry allocate adequate resources for delivering yoga services in primary care? Are primary care centres resourced enough to deliver yoga programs? To find the answers to the questions, this study inquired leading government health authorities in Nepal. The inner setting construct of the Consolidated Framework for Implementation Research comprises of structural characteristics of implementing organisation such as staffing, organising, decision making, and roles and responsibility of staff involved in implementation. Similarly, organisational commitment and collective working culture may also determine the outcome of implementation. Regarding primary healthcare settings in Nepal, information related to resources, such as dedicated staff and place for yoga instruction, budget, and monetary incentives to health workers involved in implementation could be some major influencing factors for successful implementation. The study used an interview guide that was designed to collect information relating to the outer and inner settings from government officials and healthcare staff who worked as interventionalists.

The fourth construct of the Consolidated Framework for Implementation Research is the characteristics of individuals. The Consolidated Framework for Implementation Research highlights the importance of interventionalist's knowledge and skills on intervention in implementation research. Health-care worker's/interventionalist's familiarity with the intervention package can substantially affect the implementation process. Their attitude towards and the value placed on the intervention relate to the effective execution of the study. The key informant interview with an interventionalist started with the question "What is your level of understanding of yoga?". This question opened an opportunity to ask about their perspective on intervention, organisational position, coordination, and interpersonal relationship with other team members.

The last construct is the process of implementation. To assess the post-intervention implementation process including fidelity of the implementation of yoga trial, this thesis borrowed the concept of treatment delivery, treatment receipt, and treatment enactment from the Intervention Taxonomy guidelines [24]. Treatment delivery includes content fidelity of the implementation, as it asks about the extent to what the content of the intervention was delivered as intended. Similarly, treatment receipt is related to the participant's understanding of the treatment. Treatment enactment overlaps with the concept of self-efficacy, as described in the acceptability of the intervention framework [25].

3.2.4. Theoretical framework of acceptability

The Consolidated Framework for Implementation Research was supplemented using some of the constructs of the theoretical framework of acceptability [25]. Acceptability of the intervention is crucial for the effective implementation of the intervention [25]. Higher acceptability of the intervention leads to better adherence to treatment which eventually affects the outcome of the intervention [26]. Acceptability of the intervention depends on how an individual feels about the intervention (affective attitude) or to what extent the cost or benefits to be given up to engage in the study (opportunity cost) or do the participants perceive that the intervention is likely to achieve its purpose or not (perceived effectiveness) (Fig 9) [25].

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Chapter 4. Gaps and challenges in the cascade of hypertension care in Nepal

Chapter four assessed the gaps in cascade of hypertension care by estimating the prevalence of hypertension screening, awareness, treatment, and control and determining the distribution of unmet needs for hypertension control in the Nepalese population. Furthermore, this chapter highlighted the barriers to hypertension treatment and control, which are likely to be major challenges in the cascade of hypertension care. This chapter also identified the enablers and strategies for hypertension treatment and control in Nepal.

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DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

1. PUBLICATION DETAILS (to be completed by the candidate)

Title of Paper/Journal/Book:	Hypertension screening, awareness, treatment, and control: a study of their prevalence and associated factors in a nationally representative sample from Nepal
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2. CANDIDATE DECLARATION

I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

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3. CO-AUTHOR(S) DECLARATION

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The datasets generated during and/or analysed during the current study will be stored in Victoria University Research Repository (https://vuir.vu.edu.au/)

Name(s) of Co-Author(s)	Contribution (%)	Nature of Contribution	Signature	Date
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4.1. Study 1. Hypertension screening, awareness, treatment, and control: a study of their prevalence and associated factors in a nationally representative sample from Nepal

4.1.1. Abstract

Background

The growing burden of hypertension is emerging as one of the major healthcare challenges in low- and middle-income countries such as Nepal. Given that they are struggling to deliver adequate health services, some low-and middle-income countries have significant gaps in the cascade of hypertension care (including screening, awareness, treatment, and control). This results in uncontrolled hypertension, placing a high burden on both patients and healthcare providers.

Objective

The objective of this study was to quantify the gaps in hypertension screening, awareness, treatment, and control in the Nepalese population.

Methods

We used the data from a pooled sample of 9682 participants collected through two consecutive STEPwise approach to Surveillance (STEPS) surveys conducted in Nepal in 2013 and 2019. A multistage cluster sampling method was applied in the surveys, to select nationally representative samples of 15- to 69-year-old Nepalese individuals. Prevalence ratios were calculated using multivariable Poisson regression.

Results

Among the hypertensive participants, the prevalence of hypertension screening was 65.9% (95% CI: 62.2, 69.5), the prevalence of hypertension awareness was 20% (95% CI: 18.1,

22.1), the prevalence of hypertension treatment was 10.3% (95% CI: 8.8, 12), and the prevalence of hypertension control was 3.8% (95% CI: 2.9, 4.9). The unmet need of hypertension treatment and control was highest amongst the poorest individuals, the participants from Lumbini and Sudurpaschim provinces, those who received treatment in public hospitals, the uninsured, and those under the age of 30 years.

Conclusions

The gaps in the cascade of hypertension care in Nepal are large. These gaps are particularly pronounced among the poor, persons living in Lumbini and Sudurpaschim provinces, those who sought treatment in public hospitals, those who did not have health insurance, and young people. National- and local-level public health interventions are needed to improve hypertension screening, awareness, treatment, and control in Nepal.

4.1.2. Background

According to recent estimates, hypertension is the biggest single contributor to death and disability globally, accounting for 10.4 million deaths a year in 2017 [1]. Around 45% of deaths due to heart disease and 51% of deaths due to stroke are attributable to hypertension [2]. Hypertension affects more than 20% of the world's adult population [3, 4]. Among these hypertensive individuals, 75% are from low-income and middle-income countries. In low-and middle-income countries, the prevalence of hypertension increased by 7.7% between 2000 and 2010 [5].

The increasing prevalence of hypertension is also a growing concern in Nepal. Surveys conducted in different parts of Nepal between 2011 and 2016 suggest that the prevalence of hypertension has increased over the past decade [6-9]. A recent systematic review found that the prevalence of hypertension in Nepal increased by 6% between 2000 and 2020 [10].

The prevalence of hypertension screening, awareness, treatment, and control are low in low-and middle-income countries, indicating gaps in the cascade of hypertension care [5]. Among all hypertensive individuals in low-and middle-income countries in 2010, 37.9% were aware that they had high blood pressure, 29.0% were receiving treatment, and only 7.7% had controlled blood pressure [5]. The burden of untreated and uncontrolled hypertension was also found to be high in Nepal's neighbouring countries (e.g. Bangladesh, India, and Pakistan) in a study conducted between 2003 and 2009, where 68.1% of hypertensive persons did not receive treatment, and 87.1% of hypertensive persons did not have optimal control of their blood pressure [11]. Some of the sub-national study results suggest that the prevalence of hypertension awareness, treatment, and control are also low in Nepal [8, 12-14]. A secondary analysis of the Demographic and Health Survey (DHS) 2016 results demonstrated that 38% of hypertensive people in Nepal were aware of their high blood pressure status, while 18% of hypertensive people were taking antihypertensive medication [15].

Gaps in the cascade of hypertension care are disproportionately distributed across different socio-demographic groups. Studies have shown that hypertension control is significantly lower in younger South Asian individuals as compared with other age groups [11]. Similarly, women, poor members of society (lowest wealth quintile), individuals with

low levels of education, and those living in rural settings were more likely to have untreated and uncontrolled high blood pressure or be unaware of their hypertension [11]. An Indian study observed that single, men, participants from rural areas, and individuals with lower household wealth had a poorer status at each step in the cascade of care process [16].

Quantifying the unmet need to provide care and understanding its distribution in each step of the care process is critical for the effective management of the disease. The cascade of care framework is commonly used to describe and track the sequential steps across the continuum of care in the treatment of infectious diseases, and particularly in the treatment of HIV, hepatitis C, and tuberculosis [17]. In HIV infection, the concept of continuum care "seek, test, treat, and retain" emphasizes the importance of identifying and diagnosing conditions early on and subsequently linking these conditions to antiretroviral therapy [18]. In addition, applying this concept helps to quantify the unmet need for services, as it enables users to track the loss of a proportion of service users at a particular stage in the cascade of care [19]. Recently, the concept was applied to assess the gaps in detecting and treating people with diabetes and hypertension and retaining them in the care process [19-21]. Healthcare providers and other stakeholders can apply the framework to identify persons who are more likely to be unaware of their condition, who are aware but untreated, or who have received treatment but who have sub-optimally controlled blood pressure. This framework also allows to locate gaps in the hypertension control cascade and tailor interventions to those in at-risk population groups [21]. For example, if a large proportion of the population is unaware of their condition, blood pressure screening or other outreach services can be used effectively to identify persons with hypertension. Similarly, if the lack of treatment or control is the prevailing problem, the stakeholders will need to identify and tackle health systems, health providers, and individual level barriers, in order to effectively connect the patient with the hypertension management services and retain them in the process of care.

Several studies have reported the prevalence of hypertension in Nepal, including the two recent Nepalese STEPwise approach to Surveillance (STEPS) surveys [8, 22, 23]. However, these studies did not systematically investigate the gaps in hypertension care using the cascade of care framework. This study was, therefore, carried out to quantify the losses of the hypertensive participants which occurred at each step of hypertension care cascade, and to determine the distribution of screening, awareness, treatment, and control of hypertension across different population groups in Nepal.

4.1.3. Methods

4.1.3.1. Data source, study participants, and sampling

We analysed data from two STEPwise approach to Surveillance (STEPS) surveys conducted in Nepal in 2013 and 2019. Both were nationally representative surveys in which the multistage cluster sampling method was used to select a single individual with 15 to 69 years of age from each sampled household. STEPS 2013 collected data from 4200 respondents selected from 210 clusters between January and June 2013. STEPS 2019 collected data from 5593 individuals from 737 clusters between October 2018 and March 2019. The response rates were 98.6% in 2013 and 86.4% in 2019. Detailed information about the survey methodology for STEPS 2013 [22] and STEPS 2019 [23] have been described elsewhere. The available data from the two surveys were combined to form a single dataset that included information about 9682 participants.

4.1.3.2. Data collection

The STEPS survey was used to collect data with the World Health Organization NCD STEPS instrument, structured into STEP I, STEP II, and STEP III to measure the behavioural, anthropometric, and biological characteristics of the participants [22, 23]. For our study purpose, we extracted the socio-demographic (age, gender, marital status, education, occupation, and province), socio-economic (wealth quintile), behavioural risk factors (smoking, alcohol consumption, fruit and vegetable intake, and physical activity), and cardiometabolic risk factor (high body mass index, diabetes, and high cholesterol) data from the survey. We also included the STEPS survey 2019 data on health providers and health insurance in the subsequent analysis.

4.1.3.3. Outcome variables

The outcome variables were hypertension screening, awareness, treatment, and control, which are collectively defined as the cascade of hypertension care. To assess hypertension screening, the surveys asked if the individual participants had ever had their blood pressure measured by a doctor or another health worker. Participants were considered aware if they knew they had high blood pressure, which had to have been diagnosed by the doctor or another health worker. Hypertension treatment was defined as the use of any antihypertensive medication to lower blood pressure at the time of data collection. We considered that hypertension was controlled, if the participants had a systolic blood pressure below 140 mmHg and a diastolic blood pressure below 90 mmHg. The unmet need for the cascade of

care was categorised as: unscreened, unaware, untreated, and uncontrolled hypertension. This need was assessed using the reciprocal values of screening, awareness, treatment, and control of hypertension, respectively.

The systolic and diastolic blood pressure was measured using a digital, automated blood pressure monitor (OMRON digital device, OMRON, Netherlands) with a medium-sized cuff. Before blood pressure measurements were taken, the survey data enumerators asked the participants to rest for 15 minutes, roll up their clothing over their arm, sit up straight and quietly, and keep their legs uncrossed. The enumerators recorded three systolic and diastolic blood pressure readings at five-minute intervals. We averaged the second and third readings to obtain the final blood pressure readings. Participants were considered as hypertensive, if they had systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg or were taking anti-hypertensive medications as recommended by the Joint National Committee-VII [24].

4.1.3.4. Study variables

We used the pre-existing categories of age, gender, marital status, education, and occupation as defined by the survey. The 2019 survey was the first STEPS survey to record the household wealth index. This index was divided into quintiles, with the lowest quintile denoting the poorest subgroup. The 2019 survey was also the first one to collect data based on the new provincial system and data on health insurance.

The surveys followed the World Health Organization standard international guidelines to collect data on behavioural, clinical, and metabolic risk factors. A detailed description of the data collection methods used is available elsewhere [22, 23]. Briefly, survey data was collected on smoking, alcohol consumption; the frequency and amount of fruit and vegetable intake (using a food frequency questionnaire); physical activity (using the Global Physical Activity Questionnaire – GPAQ). In addition, participants' height and weight were measured, and blood samples were analysed to assess the fasting blood sugar and lipid levels.

"Current smokers" were considered as participants who had smoked tobacco at least once in the 30 days prior to the survey [25]. Alcohol users were considered those who had drunk at least one alcoholic drink in the 30 days prior to the survey [26]. Eating at least two servings of fruit and at least three serving of vegetables per day in a typical week was considered as a sufficient fruit and vegetable intake [27]. Sufficient physical activity was

defined as the involvement in moderate and/or vigorous physical activity equivalent to ≥ 600 MET minutes/week [28]. The body mass index (BMI) was calculated as the weight (in kg) divided by the height (in meters) squared and categorised into < 25.0 kg/m^2 (as not overweight or obese), 25.0 to 29.9 kg/m^2 (as overweight), and ≥ 30.0 kg/m^2 (as obese) [29]. The fasting blood sugar and blood cholesterol levels were determined using the Cardiocheck Plus Analyzer (PTS Diagnostics, Indianapolis, USA), based on blood samples obtained by the fingerstick method according to the World Health Organization STEPS manual [30]. The participants were instructed to fast for at least 12 hours before the blood samples were taken. Diabetes was diagnosed if the fasting blood sugar level was 126 mg/dL or higher or the participants were taking any anti-diabetic medications at the time of the interview [31]. The cut-off value for the high cholesterol level was ≥ 240 mg/dL [32].

4.1.3.5. Data analysis

We analysed the data using the STATA software version 16.0 (Stata Corporation, College Station, TX, USA). All estimations were weighted using the population weights to account for the complex survey design and were presented together with their 95% confidence intervals (CIs).

Gaps in the cascade of hypertension care were presented in the flow diagram that represents the percentages of people who took part in and left each step of care. To calculate the percentage of people taking part in each step, the denominator was held constant throughout the sequential steps, so that the cumulative losses in the cascade of care were visible. The differences in the prevalence of hypertension screening, awareness, treatment, and control by survey years were tested using the chi-square test.

To assess the degree of socio-economic inequalities in the cascade of hypertension care, we plotted a concentration curve using the cumulative percentage of each indicator (*y*-axis) against the cumulative percentage of wealth quintiles (*x*-axis). We estimated the concentration index for each indicator. Given the dichotomous nature of the outcome variables, we employed Erreygers Corrected Concentration Index and specified the limits as 0 and 1 [33].

We conducted a Poisson regression analysis to report the prevalence ratio, to allow for a straightforward interpretation of the data, and to account for the low prevalence of hypertension treatment and control [34]. We included all available explanatory variables in the multivariable models (as a model I). All of the models were adjusted for the survey year.

As a sensitivity analysis, we also conducted a subgroup analysis as a model II for hypertension treatment (among the aware hypertensive individuals only) and hypertension control (among the treated hypertensive individuals only); the results are shown in Supplementary table 1 and Supplementary table 2.

4.1.4. Results

4.1.4.1. Characteristics of the participants

The majority of the hypertensive participants (57.9%) were men. The mean (standard deviation) age of the participants was 40.2 years (14 years). Most of the participants (84.9%) were married. Nearly half of the participants (48.8%) had received no formal schooling or had not completed the primary level of education. Around three-fourths of the participants (75.7%) were either homemakers or self-employed. Only 3% and 7.4% of the participants consumed the recommended amounts of fruit and vegetables, respectively. A vast majority of participants (93.7%) engaged in the recommended level of physical activity per week. Of the hypertensive participants, 9% also had diabetes and 5.9% also had high cholesterol levels (Table 4).

Table 4. Characteristics of hypertensive participants

Variables	*N*	%*
Sex		
Women	1556	42.1
Men	1236	57.9
Age		
15–29 years	296	24.2
30–44 years	851	28.9
45–69 years	1645	46.9
Marital status		
Never married	123	10.2
Currently married	2451	84.9
Widowed	190	4.2
Other (separated, divorced)	27	0.6
Education		
No formal schooling	1305	37.7
Lower than primary school	328	11.1
Primary school	421	17.5
Secondary school	454	20.7

High school	174	8.3
Bachelor's degree and higher	109	4.8
Occupation		
Government employee	86	3.1
Non-government employee	170	8.1
Self-employed	788	33.2
Homemaker	1510	42.5
Student	61	5.3
Unemployed	63	3.3
Other (retired, non-paid job)	124	4.4
Smoking		
Yes[†]	610	22.0
No	2182	78.0
Alcohol consumption		
Yes[‡]	714	27.3
No	2078	72.7
Vegetable intake		
Sufficient[§]	196	7.4
Insufficient	2596	92.6
Fruit intake		
Sufficient[‖]	87	3.0
Insufficient	2705	97.0
Physical activity		
Sufficient[¶]	2575	93.7
Insufficient	184	6.3
Body mass index		
< 25 kg/m2	1718	63.9
25–29 kg/m2	799	27.8
≥ 30 kg/m2	261	8.3
Diabetes		
Yes[**]	263	9.0
No	2348	91.0
Cholesterol level		
High (≥ 240 mg/dL)	177	5.9
Not high	2470	94.1

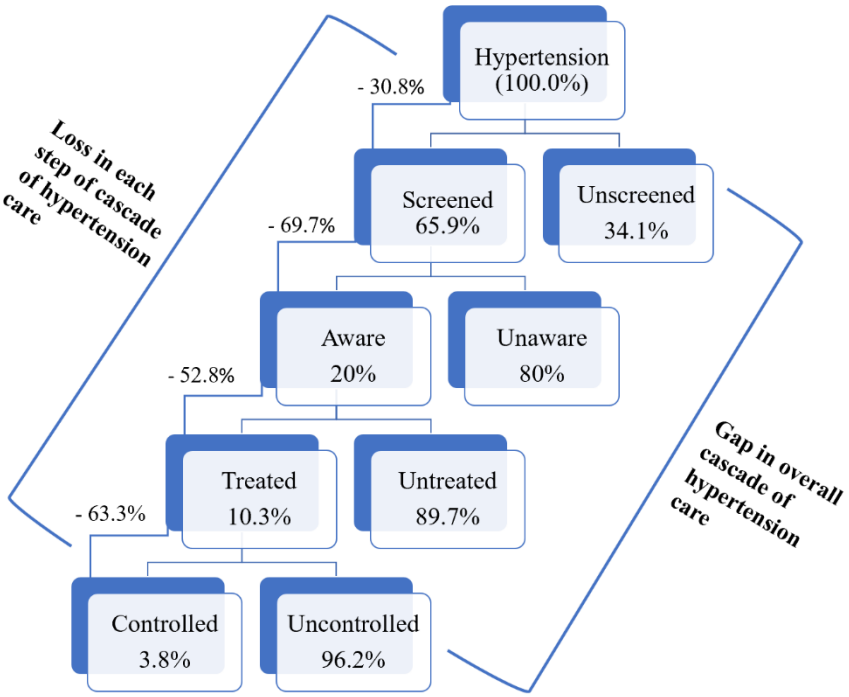
Note: [*] weighted percentage [†]Smoking tobacco at least once in the 30 days prior to the survey; [‡]At least one drink of alcohol in the 30 days prior to the survey; [§]Eating at least three servings of vegetables in a typical week; [‖] Eating at least two servings of fruit in a typical week; [¶] Involvement in moderate and/or vigorous physical activity of ≥ 600 MET minutes/week in a week; [**] Fasting blood sugar level of 126 mg/dL or higher or taking any anti-diabetic medications at the time of the interview.

4.1.4.2. Gaps in the cascade of hypertension care

The prevalence of hypertension was 25.4% (95% CI: 23.9, 27.0). Among the hypertensive participants, the prevalence of hypertension screening was 65.9% (95% CI: 62.2, 69.5), the

prevalence of hypertension awareness was 20% (95% CI: 18.1, 22.1), the prevalence of hypertension treatment was 10.3% (95% CI: 8.8, 12), and the prevalence of hypertension control was 3.8% (95% CI: 2.9, 4.9). In the cascade of care, 34.1% (95% CI: 30.5, 37.8) of the hypertensive participants did not have their blood pressure screened. Of those screened, 30.3% (95% CI: 27.6, 33.1) were aware of their hypertension (Fig 10). Among aware hypertensive individuals, less than half (47.2%; 95% CI: 41.9, 52.6) were receiving treatment. Of those who were receiving treatment, 36.7% (95% CI 30.1, 43.8) had controlled high blood pressure.

Figure 10. Gaps in the cascade of hypertension care



Note: The denominator for the overall loss in the cascade of care is the total number of hypertensive participants (n = 2792). The denominator for the gap at each step in the cascade of hypertension care is the number of the participants from the antecedent step. For example, the denominator for the loss in treatment is the total number of aware hypertensive participants (n = 682)

4.1.4.3. Trend in the cascade of hypertension care

The prevalence of awareness (19.7% vs 20.3%), treatment (11.7% vs 9.0%), and control (3.8% vs 3.8%) did not differ significantly ($p > 0.05$ for all) between the 2013 and 2019 surveys. The difference in the prevalence of hypertension screening between the two survey years (70.3 % vs 61.8%) was significant ($p = 0.036$).

4.1.4.4. Socio-demographic variation in the cascade of hypertension care

Unadjusted prevalence estimates indicated that hypertension screening ($p < 0.001$), awareness ($p < 0.001$), treatment ($p < 0.001$), and control ($p < 0.013$) significantly varied across the age categories (Table 5). The prevalence of hypertension awareness was significantly lower among men as compared to women (17.2% vs 23.9%, $p < 0.001$). Hypertension screening ($p = 0.035$), awareness ($p < 0.001$), and treatment ($p = 0.003$) varied significantly across the groups by marital status. The lowest prevalence of hypertension screening (54.4%), awareness (6.7%), and treatment (2.7%) was found among those who had never been married. The lowest prevalence of screening was found among those who had had no formal education. The prevalence of hypertension awareness ($p < 0.001$) and control ($p < 0.001$) varied significantly across the occupational groups, with the lowest prevalence found among students.

Table 5. Sociodemographic distribution of screening, awareness, treatment, and control of hypertension among hypertensive participants in Nepal

Variables	Screened	Aware	Treated	Controlled
	%	%	%	%
Age				
15–29 years	52.0	6.2	2.2	1.5
30–44 years	70.3	17.9	7.0	3.3
45–69 years	70.5	28.4	16.5	5.2
p-value*	< 0.001	< 0.001	< 0.001	0.013
Gender				
Men	64.9	17.2	9.3	3.1
Women	67.3	23.9	11.7	4.7
p-value*	0.407	< 0.001	0.105	0.105
Marital status				
Never married	54.4	6.7	2.7	2.5
Currently married	67.8	21.4	11.0	3.9
Widowed	56.1	25.1	13.7	5.4
Other (separated, divorced)	64.1	20.9	20.9	0.0
p-value*	0.035	< 0.001	0.003	0.595
Education				
No formal schooling	59.6	21.7	12.0	3.8
Lower than primary school	67.8	21.7	7.5	2.7
Primary school	69.9	20.5	9.2	3.6
Secondary school	67.6	15.9	8.4	4.3
High school	66.3	17.7	9.9	2.8
Bachelor's degree and higher	88.9	23.4	16.5	6.4
p-value*	0.004	0.303	0.083	0.706
Occupation				

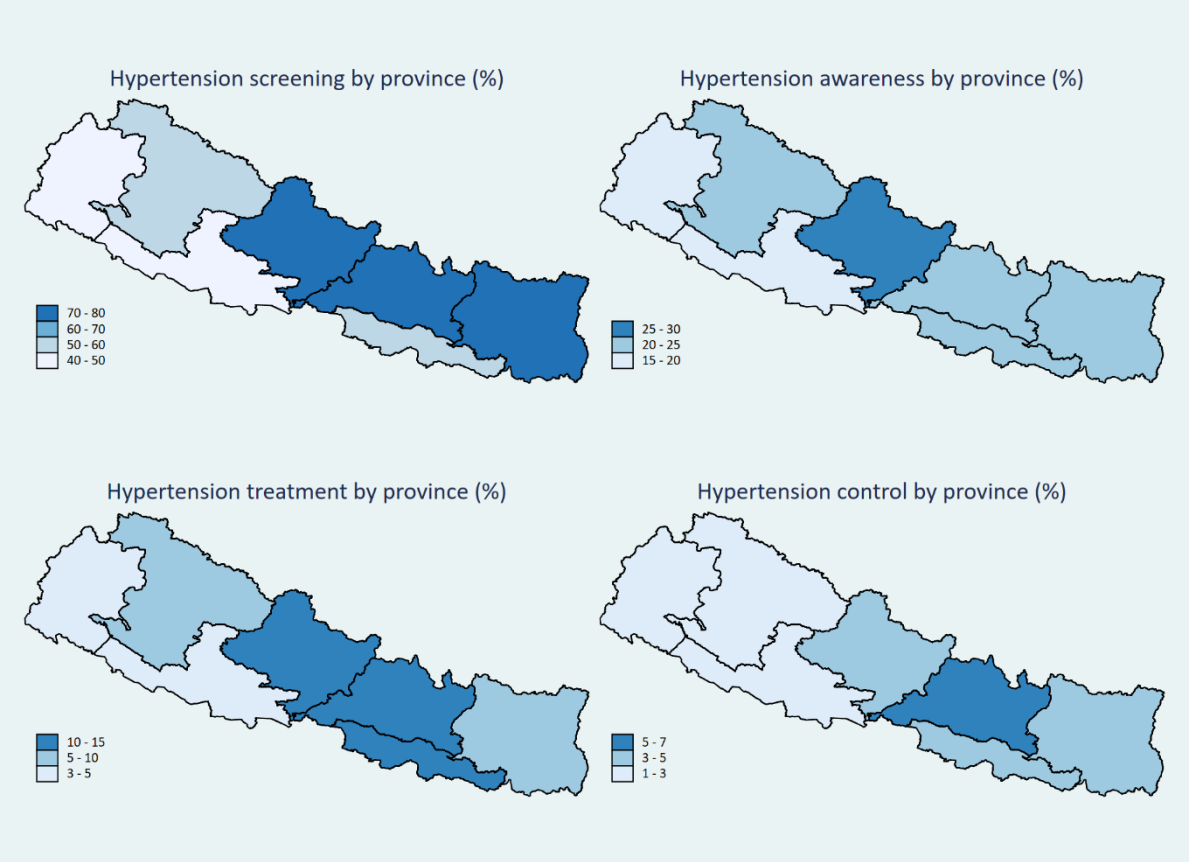
Government employee	78.6	28.1	18.8	7.9
Non-government employee	61.8	16.5	5.5	0.3
Self-employed	66.5	19.4	10.0	4.2
Homemaker	66.0	21.0	10.6	4.0
Student	55.2	4.1	2.1	2.1
Unemployed	59.1	8.3	3.6	3.3
Other (retired, non-paid job)	77.5	44.2	27.6	4.2
p-value	0.344	< 0.001	< 0.001	0.306

Note: * *p*-value from chi-square test

4.1.4.5. Geographical variation in the cascade of hypertension care

Gandaki Province had the highest prevalence of hypertension screening (76.3%) and hypertension awareness (26.4%) among the seven provinces (Supplementary table 3). Bagmati Province had the highest percentage of participants being treated (13.0%) and having optimal control of hypertension (7.1%). Hypertension screening, awareness, treatment, and control were relatively low in the Lumbini and Sudurpaschim provinces (Fig 11). We did not find a significant difference between rural and urban settings in the cascade of hypertension care.

Figure 11. Geographical variation in the cascade of hypertension care

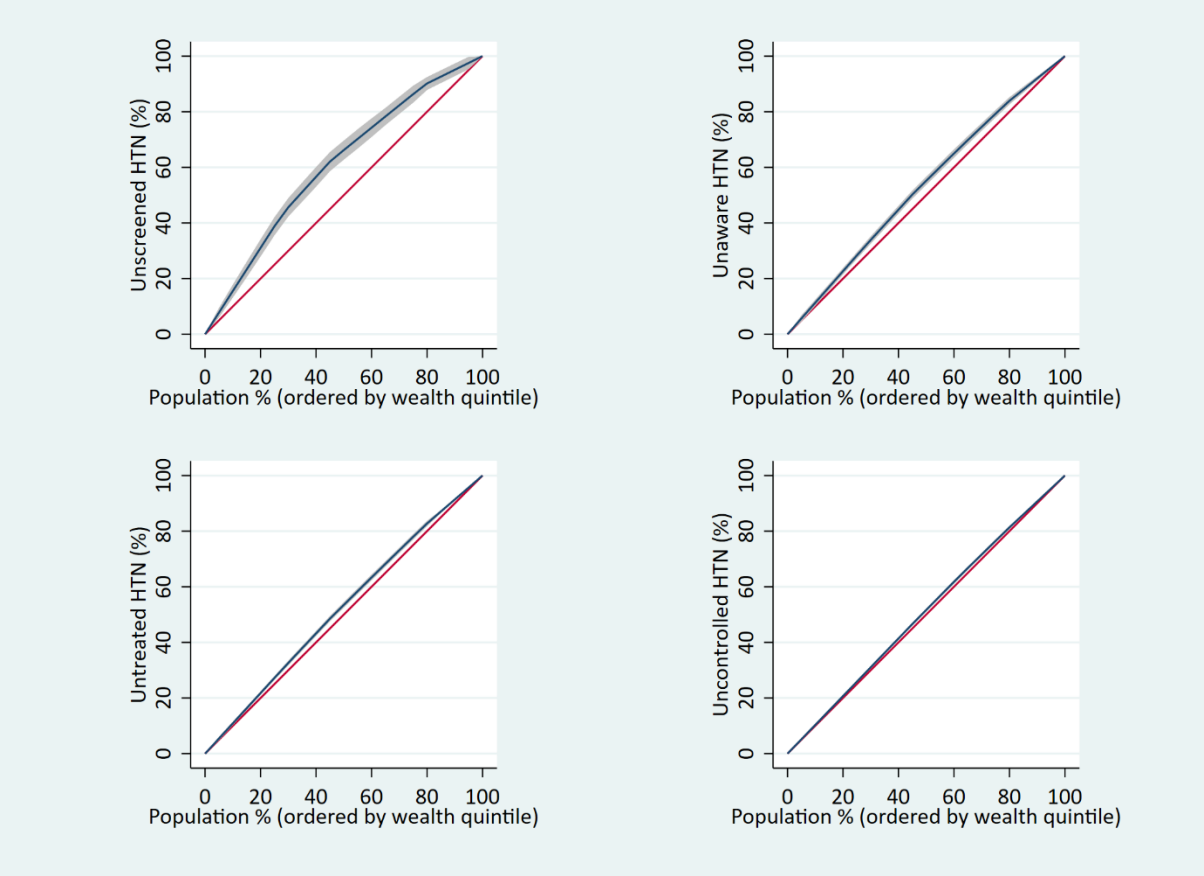


Note: From right to left, the provinces are named as Province 1, Province 2, Bagmati, Gandaki Lumbini, Karnali, and Sudurpaschim, separated by a black border (line)

4.1.4.6. Socio-economic inequalities in the cascade of hypertension care

Hypertension screening, awareness, treatment, and control were significantly associated with the wealth quintile (Supplementary table 3). The probability of being screened, aware, treated, and controlled for hypertension increased as the wealth quintile increased. The undesired outcomes—unscreened (concentration index [cin] = -0.19), unaware (cin = -0.16), untreated (cin = -0.11), and uncontrolled (cin = -0.06) hypertension)—were the highest among the poorest Nepalese (Fig 12).

Figure 12. Economic inequalities in the cascade of hypertension care

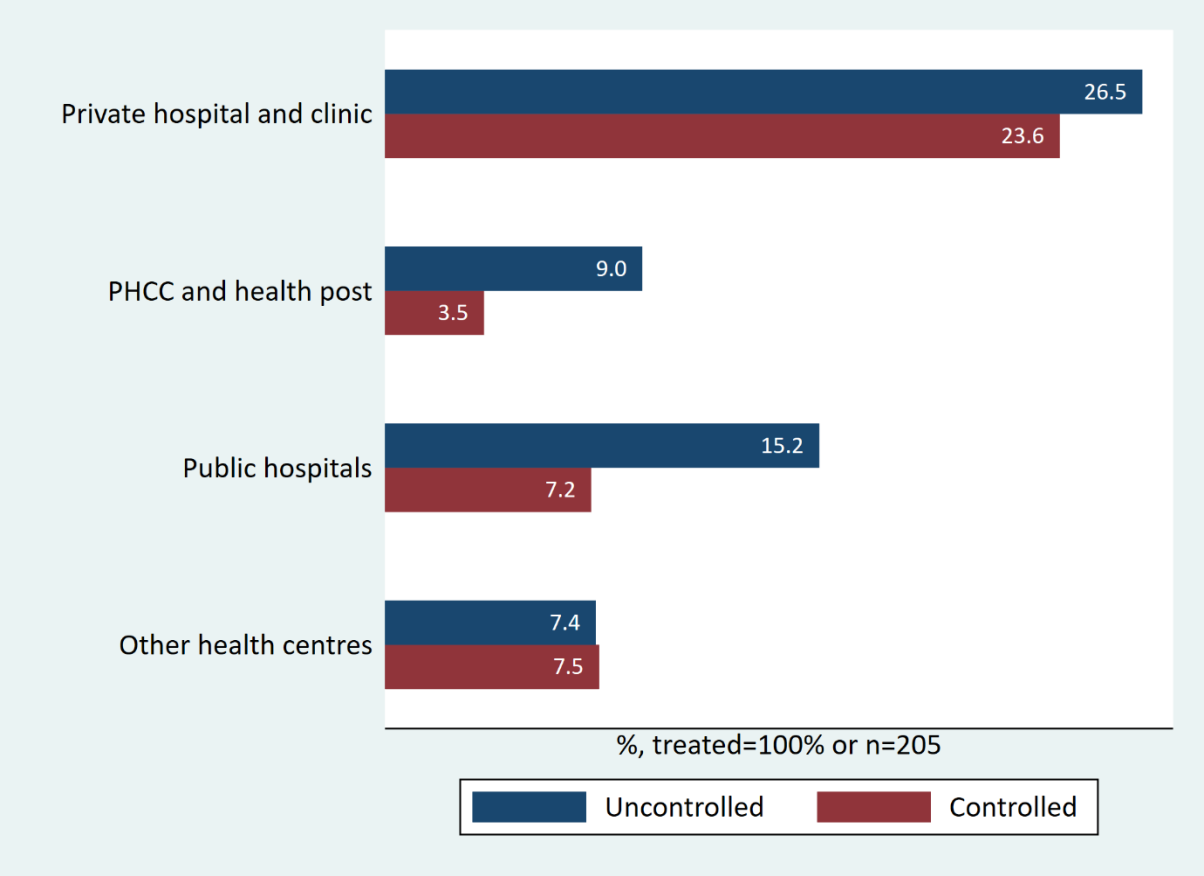


Note: *y*-axis is the cumulative percentage of the outcome variables, *x*-axis is the cumulative percentage of population ordered by the wealth quintile from the lowest to the higher quintile; HTN = hypertension. The concentration index (cin) is defined as twice the area between the concentration curve (blue) and the line of equality (the 45-degree red line). A positive cin (curve below the line of equality) indicates that ill/undesired health is more prevalent among the rich, and a negative one (curve above the line of equality) indicates that the outcome is more prevalent among the poor.

4.1.4.7. Gaps in the cascade of hypertension care by healthcare providers

Of the participants receiving medication, around half (50.2%) had sought treatment in private health centres, 34.9% had visited public hospitals and primary healthcare centres, and 14.9% had received treatment from other intuitions, such as community health centres, Ayurveda hospitals (i.e. Ayurveda health centres functioning at the district level under the Ministry of Health), and pharmacies (i.e. chemist shops) (Fig 13). The hypertension control rate was higher among those who had been treated in private health institutions (50.4%) as compared with those who had sought treatment in primary healthcare centres (27.8%) and public hospitals (32.2%) (Fig 13).

Figure 13. Hypertension treatment and control by the providers



Note: PHCC – Primary health care centres; Other health centres – community hospitals, Ayurveda health centres and pharmacies

4.1.4.8. Factors associated with the cascade of hypertension care

4.1.4.8.1. Factors associated with hypertension screening

The probability of being screened was positively associated with the age, education level, and body mass index. Screening was more prevalent in the people with diabetes, those who did not consume alcoholic drinks, and those who ate more fruits (Table 6).

Table 6. Factors associated with hypertension screening, awareness, treatment, and control

Variables	Adjusted prevalence ratio (95% CI*)			
	Screening	Awareness	Treatment	Control
Age				
15–29 years	Ref	Ref	Ref	Ref
30–44 years	1.34 (1.13, 1.58)	2.14 (1.22, 3.77)	3.22 (1.16, 8.95)	4.43 (0.71, 27.64)
45–69 years	1.41 (1.20, 1.67)	3.51 (2.06, 6.00)	7.25 (2.65, 19.86)	7.35 (1.14, 47.44)
Gender				
Men	Ref	Ref	Ref	Ref
Women	1.08 (0.97, 1.21)	1.65 (1.30, 2.10)	1.26 (0.87, 1.82)	1.62 (0.86, 3.03)

Variables	Adjusted prevalence ratio (95% CI*)			
	Screening	Awareness	Treatment	Control
Marital status				
Never married	Reference	Reference	Reference	Reference
Currently married	1.0 (0.77, 1.30)	0.95 (0.46, 1.95)	0.94 (0.32, 2.72)	0.38 (0.10, 1.47)
Widowed	0.85 (0.63, 1.16)	0.85 (0.39, 1.84)	0.83 (0.28, 2.47)	0.48 (0.13, 1.83)
Other (separated, divorced)	0.95 (0.56, 1.62)	0.82 (0.29, 2.32)	1.96 (0.51, 7.57)	
Education				
No formal schooling	Ref	Ref	Ref	Ref
Lower than primary school	1.19 (1.06, 1.35)	1.15 (0.86, 1.55)	0.73 (0.48, 1.12)	0.96 (0.44, 2.11)
Primary school	1.29 (1.15, 1.45)	1.30 (0.98, 1.72)	1.08 (0.72, 1.63)	1.70 (0.85, 3.38)
Secondary school	1.27 (1.12, 1.44)	1.14 (0.85, 1.54)	1.09 (0.68, 1.75)	2.09 90.98, 4.44)
High school	1.24 (1.02, 1.51)	1.38 (0.85, 2.25)	1.28 (0.68, 2.41)	1.48 0.43, 5.16)
Bachelor's degree and higher	1.51(1.24, 1.83)	1.36 (0.88, 2.09)	1.48 (0.78, 2.82)	2.57 (0.81, 8.11)
Occupation				
Government employee	Ref	Ref	Ref	Ref
Non-government employee	0.97 (0.76, 1.25)	0.89 (0.48, 1.64)	0.58 (0.25, 1.38)	0.07 (0.01, 0.39)
Self-employed	0.99 (0.81, 1.20)	0.86 (0.49, 1.50)	0.77 (0.35, 1.69)	0.73 (0.17, 3.03)
Homemaker	0.98 (0.80, 1.21)	0.69 (0.39, 1.21)	0.66 (0.30, 1.46)	0.59 (0.14, 2.52)
Student	0.95 (0.61, 1.50)	0.41 (0.08, 2.05)	0.68 (0.09, 5.24)	0.73 (0.08, 6.85)
Unemployed	0.92 (0.66, 1.29)	0.38 (0.12, 1.22)	0.34 (0.05, 2.30)	0.65 (0.07, 6.17)
Other (retired, non-paid job)	1.05 (0.85, 1.31)	1.34 (0.74, 2.43)	1.12 (0.50, 2.51)	0.42 0.10, 1.78)
Smoking				
Yes†	Ref	Ref	Ref	Ref
No	0.99 (0.90, 1.09)	0.93 (0.74, 1.18)	1.0 (0.70, 1.43)	0.72 (0.40, 1.27)
Alcohol consumption				
Yes‡	Ref	Ref	Ref	Ref
No	1.10 (1.00, 1.22)	0.99 (0.78, 1.25)	1.56 (1.05, 2.31)	2.59 (1.08, 6.22)
Vegetable intake				
Sufficient§	Ref	Ref	Ref	Ref
Insufficient	0.99 (0.89, 1.11)	0.98 (0.70, 1.38)	1.28 (0.79, 2.06)	1.13 (0.53, 2.44)
Fruit intake				
Sufficient‖	Ref	Ref	Ref	Ref
Insufficient	0.90 (0.80, 1.03)	0.68 (0.48, 0.97)	0.63 90.38, 1.05)	0.57 (0.23, 1.41)
Physical activity				
Sufficient¶	Ref	Ref	Ref	Ref
Insufficient	0.95 (0.84, 1.07)	1.51 (1.14, 1.99)	1.57 (1.04, 2.36)	1.82 (0.96, 3.45)
Body mass index				
< 25 kg/m2	Ref	Ref	Ref	Ref
25–29 kg/m2	1.12 (1.02, 1.22)	1.54 (1.26, 1.88)	1.82 (1.36, 2.43)	1.68 (1.00, 2.83)
≥ 30 kg/m2	1.33 (1.21, 1.47)	1.98 (1.51, 2.59)	2.18 (1.48, 3.20)	2.31 (1.20, 4.46)
Diabetes				
Yes**	Ref	Ref	Ref	Ref

Variables	Adjusted prevalence ratio (95% CI*)			
	Screening	Awareness	Treatment	Control
No	0.89 (0.81, 0.97)	0.68 (0.55, 0.85)	0.58 (0.43, 0.79)	0.82 (0.45, 1.50)
Cholesterol				
High (>239 mg/dL)	Ref	Ref	Ref	Ref
Not high	1.06 (0.93, 1.22)	0.80 (0.57, 1.11)	0.74 (0.49, 1.10)	0.56 (0.28, 1.11)

Note: *Prevalence ratio adjusted for all the remaining variables listed in the table, survey year, and responses to a question that combines ethnicity, historical "caste" groups, religion, and social disadvantage and its 95% Confidence interval; †Smoking tobacco at least once in the 30 days prior to the survey; ‡At least one drink of alcohol in the 30 days prior to the survey; §Eating at least three servings of vegetables in a typical week; ‖ Eating at least two servings of fruit in a typical week; ¶ Involvement in moderate and/or vigorous physical activity of ≥ 600 MET minutes/week in a week; ** Fasting blood sugar level of 126 mg/dL or higher or taking any anti-diabetic medications at the time of the interview.

4.1.4.8.2. Factors associated with hypertension awareness

Age was positively associated with the hypertension awareness. More men than women were aware of their hypertension. Less physically active, overweight, and obese participants had a higher prevalence of awareness than others (Table 6).

4.1.4.8.3. Factors associated with hypertension treatment

The probability of getting treatment was three and seven times higher among the groups of participants who were 30–44 years and 45–69 years of age as compared to the 15–29-year-old hypertensive participants. We found no significant association with gender in the whole sample. However, while considering only the participants who were aware of their hypertension, the prevalence of hypertension treatment among women was 28% lower than among men ($p < 0.021$); Supplementary table 2). The treatment rate was significantly higher among obese and diabetic participants and those who did not consume alcoholic drinks (Table 3).

4.1.4.8.4. Factors associated with hypertension control

The prevalence of hypertension control in the 45-years-and-above age group was six times higher than that of 15–29-year-old participants. The rate of hypertension control did not vary significantly by gender, marital status, and education. Compared to government employees, the prevalence of hypertensive participants with controlled blood pressure was significantly lower among those working in non-government sectors. The hypertension control rate was 2.59 times higher in hypertensive individuals who did not drink alcohol than among those who drank alcohol. The probability of having controlled blood pressure increased as the age increased (Table 6).

4.1.5. Discussion

This study found a low prevalence of screening, awareness, treatment, and control of hypertension in Nepal, indicating large gaps in the cascade of hypertension care. Only 3.8% of the participants were found to have controlled blood pressure. The cases of unscreened, unaware, untreated, and uncontrolled hypertension were more prevalent amongst the poorer participants, those living in the Lumbini and Sudurpaschim provinces, those who had sought treatment in primary health care centres and public hospitals, those who had no health insurance, and in younger age groups. These findings should facilitate the revision of the existing hypertension care strategies and reallocation of the existing resources to achieve a better control of blood pressure among hypertensive individuals in Nepal.

The prevalence estimates for hypertension awareness, treatment, and control found in the current study are the lowest ever reported in Nepal. The prevalence estimates reported in four previous studies conducted in different parts of Nepal ranged from 43% to 61.8% for hypertension awareness, from 29.0% to 48.7% for hypertension treatment, and from 8.2% to 24.1% for hypertension control [35-38]. The prevalence estimates from the Nepalese Demographic Health Survey on awareness (40.0%), treatment (19.2%), and control (10.5%) were also higher than those found in the current study [39]. The reason for such differences in the estimates may be due to the differences in the study populations across the studies. For example, the participants in the Dhungana et al. [8] and Karmacharya et al. [12] studies were from Bagmati province only, where – as our study findings suggest – the prevalence of hypertension control is higher than in the other provinces. Likewise, the Nepalese Demographic Health Survey also included participants aged 70 years and above [39]. Given the fact that the sample in the current study was restricted to adults aged 15–69 years, direct comparisons between our findings and those of the Nepalese Demographic Health survey would not be justified. As suggested by our results, the prevalence of hypertension awareness, treatment, and control is higher in older age groups. It is, therefore, not surprising that the prevalence estimates from the Nepalese Demographic Survey are higher than those we found.

The study findings also suggest that Nepal has the poorest performance in the cascade of hypertension care as compared with the neighbouring countries. For example, hypertension control rates in India [16] and China [40] are nearly twice as high as those in Nepal.

In comparison, USA (53%) and Canada (66%) have the highest prevalence of hypertension control and are examples of countries that provide effective hypertension care [41]. After introducing the Canadian Hypertension Education Program, Canada was able to improve hypertension treatment from 35% to 80% and hypertension control from 13% to 68% between 1992 and 2013 [42]. Some strategies used in this program might also be applicable to the Nepalese context.

The gaps in the cascade of hypertension care were inversely related to wealth. A higher prevalence of hypertension screening, awareness, treatment, and control was associated with higher wealth quintiles. The socio-economic inequalities in health and healthcare utilization are common in low- and middle-income countries [43-45]. A study conducted among 163,397 participants from 21 countries found that better economic development (as measured as gross national product (GNP) per capita) of the countries and higher socio-economic status (as expressed in wealth quintiles) of the individuals were positively associated with awareness, treatment, and control of hypertension [46]. Based on these findings, the lower rate of treatment and control in the Lumbini and Sudurpaschim provinces could also be explained by their geographical remoteness and high poverty rates.

Our study also found that the prevalence of hypertension treatment and control was significantly higher in people who had health insurance coverage. Previous studies showed that patients with health insurance are less likely to report barriers in accessing hypertension care [47] and achieve greater reductions in blood pressure than uninsured persons [48]. These findings suggest that improving the accessibility of health insurance may positively affect hypertension care in Nepal. However, further studies are required to evaluate and confirm the benefit of the current health insurance policy in terms of improving access to health care and disease control. Likewise, the association observed between PHC and government hospitals and a poor control of hypertension indicates a need to improve the quality of services at these institutions, which would also help minimize the socio-economic inequalities in hypertension care [49].

An age disparity in the cascade of hypertension care was prominent. Participants in the lower age group (< 30 years) were less likely to be screened, aware, treated, and have controlled blood pressure, results that are consistent with those of American studies that found that young adults had a 33% lower rate of being diagnosed [50] and a 44% lower rate of medication initiation [51]. The literature shows that young adults think hypertension

develops during old age and that taking medication makes them feel older [52]. Hypertension treatment and control did not vary significantly across gender, marital status, education, and occupation groups. However, the probability of being enrolled in antihypertensive treatment was higher for men than for women, if they were aware that they had hypertension.

Except for alcohol consumption, other behavioural risk factors such as smoking, fruits and vegetable intake, and physical activity were not significantly associated with hypertension control. Those who did not drink alcohol were more likely to take medication and have controlled blood pressure. Participants with a higher body mass index (BMI) and those with diabetes were more likely to seek hypertension treatment than others. However, hypertension control was not associated with diabetes. Although most of the study variables were not significantly associated with hypertension control, it is important to note that all the participants who had controlled blood pressure had also been taking antihypertensive drugs. However, studies have shown that several barriers to hypertension treatment exist in Nepal that potentially impede the initiation of treatment and adherence and lead to uncontrolled blood pressure among hypertensive patients [53, 54]. Therefore, along with the interventions to reduce exposure to risk factors, it is prudent to develop strategies that can dismantle the barriers associated with hypertension treatment and control in order to achieve the target of a relative 25% reduction in hypertension by 2025 in Nepal [55].

This study had some limitations. The surveys were not primarily designed to assess gaps in the cascade of hypertension care. Therefore, this study lacked some potentially important explanatory variables, such as medication adherence. Furthermore, the findings on fruits and vegetable intake, physical activity, smoking, and alcohol consumption might have been influenced by the recall and social desirability biases, as the responses were collected via self-reports. In addition, the blood pressure was measured on a single occasion only, which may have resulted in a miscategorization of some participants. Similarly, the finding is limited to the quantitative assessment of the gaps. Further qualitative studies are required to gain a deeper understanding of the contextual factors (e.g. perceived barriers and facilitators) that are likely to be associated with the gaps in the cascade of hypertension care in Nepal.

The main strength of the study is the representative nature of the data we used for the analysis. STEPS surveys follow the standard framework and methods of the World Health Organization STEPwise Approach to Noncommunicable Disease Risk-Factor Surveillance to collect nationally representative data. Furthermore, this study represents an original

contribution to the knowledge base in that it quantifies the gap in hypertension care and depicts its distribution across different population groups, particularly because a large variety of participant characteristics were taken into account.

4.1.6. Conclusions

The gaps in the cascade of hypertension care in Nepal are large, and the rate of hypertension control is critically low. The gaps are particularly pronounced among the poor, those living in Lumbini and Sudurpaschim provinces, those who had sought treatment in primary healthcare centres and public hospitals, those who did not have health insurance, and young people. National- and local-level public health interventions are needed to improve hypertension screening, awareness, treatment, and control in Nepal. Mass screening that targets the most heavily affected areas and population groups, increasing access to quality care services at public primary healthcare centres and public hospitals, and applying behavioural interventions to address the barriers to hypertension treatment and control are recommended. Expanding the role of community health workers in supporting hypertension management and medication adherence could be a feasible strategy to help patients overcome barriers to hypertension treatment and control in the Nepalese context.

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DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

1. PUBLICATION DETAILS (to be completed by the candidate)

Title of Paper/Journal/Book: Barriers, Enablers and Strategies for the Treatment and Control of Hypertension in Nepal: A Systematic Review

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2. CANDIDATE DECLARATION

I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

[redacted] 03/12/2021

Signature **Date**

3. CO-AUTHOR(S) DECLARATION

In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

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3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to a) granting bodies, b) the editor or publisher of journals or other publications, and c) the head of the responsible academic unit; and
5. The original data will be held for at least five years from the date indicated below and is stored at the following **location(s)**:

The datasets generated during and/or analysed during the current study will be stored in Victoria University Research Repository (https://vuir.vu.edu.au/)

Name(s) of Co-Author(s)	Contribution (%)	Nature of Contribution	Signature	Date
Zeljko Pedisic	10%	Conception of study, analysis and interpretation of data, and manuscript development	[redacted]	12 Dec 2021
Achyut Raj Pandey	5%	Data extraction, interpretation of findings, and manuscript development		06 Dec 2021
Nipun Shrestha	5%	Data extraction, interpretation of findings, and manuscript development		02 Dec 2021
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4.2. Study 2. Barriers, enablers, and strategies for the treatment and control of hypertension in Nepal: a systematic review

4.2.1. Abstract

Background

Understanding country-specific factors influencing hypertension care is critical to address the gaps in the management of hypertension. However, no systematic investigation of factors influencing hypertension treatment, and control in Nepal is available. This study aimed to systematically review the published literature and synthesise the findings on barriers, enablers, and strategies for hypertension treatment and control in Nepal.

Methods

Embase, PubMed, Web of Science, CINAHL, ProQuest, WorldCat, Nepali journals, and government websites were searched for qualitative, quantitative, and mixed-methods studies on factors or strategies related to hypertension treatment and control in Nepal. Information from qualitative studies was analysed using template analysis, while results from quantitative studies were narratively synthesised. Summary findings were framed under “health system”, “provider”, and “patient” domains. The protocol was registered in PROSPERO (registration number: CRD42020145823).

Results

We identified 15 studies; ten related to barriers and enablers and five to strategies. The identified barriers associated with the health system were: lack of affordable services and lack of resources. The barriers at the provider’s level were: communication gaps, inadequate counselling, long waiting hours for appointments, lack of national guidelines for hypertension treatment, and provider's unsupportive behaviours. Non-adherence to medication, irregular follow-up visits, lack of awareness on blood pressure target, poor help-seeking behaviours, reluctance to change behaviours, perceived side-effects of anti-hypertensive medication, self-medication, lack of family support, financial hardship, lack of awareness on blood pressure complications, and comorbidity were barriers identified at patient level. The following

enablers were identified: free essential health care services, family support, positive illness perception, and drug reminders. Strategies implemented at the health system, provider, and patient levels were: establishing digital health records at health centres, health worker's capacity development, and health education.

Conclusions

There is a range of barriers for hypertension treatment and control in Nepal pertaining to the health system, health providers, and patients. Comprehensive interventions are needed at all three levels to further improve management and control of hypertension in Nepal.

4.2.2. Background

A political declaration on the prevention and control of non-communicable diseases, adopted by the General Assembly of the United Nations in 2011, emphasises the importance of developing national capacities to deal with non-communicable diseases, particularly in low- and middle-income countries [56]. Though more and more focus of the health system is placed on tackling non-communicable diseases, the rate of hypertension treatment and control in low-and middle-income countries is low [21]. Compared to high-income countries, low- and middle-income countries reported substantially lower proportions of hypertension treatment (55.6% vs. 29.0%) and control (28.4% vs. 7.7%) in 2010 [5]. In three South Asian countries, namely, Bangladesh, India, and Pakistan, 31.9% of the hypertensive population was on anti-hypertensive medication and only 12.9% had controlled blood pressure [11].

Nepal, a South Asian lower-middle-income country landlocked between China and India hosts a population of 28 million, with 125 ethnic groups living mostly in rural areas [57, 58]. Under the Ministry of Health and Population, the public health system in Nepal delivers health services to the community through the tertiary, district, and primary care centres and health posts. Alongside public health services, private for-profit sectors and non-governmental organisations provide health services in Nepal [59].

With the growing burden of hypertension, untreated and uncontrolled hypertension is prevalent in Nepal [8, 12-15]. The majority of hypertensive individuals were not aware of their condition (awareness = 40.0%); a half of those that were aware were not treated (treatment = 20.2%), and a half of those on treatment, the blood pressure was not controlled (control = 10.5%) in 2016 [60].

Gaps in hypertension treatment and control can be due to various factors associated with the health system, health care providers, and individual patients. Systematic reviews and other studies from outside of Nepal suggest that lack of access, poor service delivery, unaffordability of health services, and limited resources are common health system-related barriers [41, 61-65]. Similarly, studies also found that the factors pertaining to patients and providers, such as lack of awareness and treatment, non-adherence to medicine, adverse drug effect, therapeutic inertia, and communication gaps, were contributing to uncontrolled hypertension [63, 65-75].

The quantity and the scope of primary research on barriers, enablers, and strategies for hypertension control are growing in Nepal. While new evidence from primary studies is evolving, a systematic review is needed for a comprehensive identification, understanding and synthesis of the factors affecting hypertension treatment and control in the Nepali context. Therefore, this review aimed to systematically synthesise evidence on barriers, enablers, and strategies for hypertension treatment and control in Nepal. By providing a comprehensive understanding of health system- and individual-level barriers and enablers and strategies of hypertension treatment and control, this review aims to inform the policymakers and related stakeholders about the gaps in hypertension care and contribute to the development of the contextual and problem-specific strategies to increase hypertension control in Nepal.

4.2.3. Theoretical framework

A framework was used to organize patient, health care provider, and health system (excluding patients and providers) barriers, enablers, and strategies for improving blood pressure control. The framework was derived from the theories used in previous studies on barriers [41, 65, 76], and adapted to also fit the enablers and strategies (Fig 7).

By "barriers", we considered factors that prevent hypertension treatment and adequate blood pressure control [76]. These have previously been linked with hypertensive patients, providers, and health system [76]. Patient-reported barriers include, for example, knowledge, perception, beliefs, practices, self-efficacy, motivation, family support, affordability, and socio-cultural factors such as social dining and drinking [65, 77]. These factors may affect health-seeking behaviours, treatment adherence, and follow-up care among patients, ultimately affecting blood pressure control [76]. The commonly cited barriers by the providers comprise a lack of skills, non-compliance with guidelines, lack of motivation, and therapeutic inertia [65, 75, 76]. An interaction of patient and provider factors can sometimes lead to a communication gap and a poor relationship, affecting treatment adherence and follow-up care.

Furthermore, enablers are the personal or contextual factors that facilitate actions or a required behaviour for hypertension treatment and control. They include, for example, perceived severity of illness and family support [78].

Strategies to improve blood pressure control include interventions, programs, or policies targeted at the providers, patients, or other components of the health system. Some of the proposed evidence-based strategies are: task shifting [79]; team-based care [80]; health system financing, including insurance coverage and co-payments of medical care [41]; health system arrangement, including improved service delivery [81]; using combination therapy [82] or polypill [83]; home-based blood pressure monitoring [84]; and educational interventions for patients and physicians [85].

4.2.4. Methods

We systematically searched the literature, selected eligible studies, assessed methodological quality, extracted relevant data and synthesised findings in accordance with the PRISMA [86] and Synthesis Without Meta-Analysis (SWiM) guidelines [87]. The protocol has been registered in PROSPERO (registration number: CRD42020145823).

4.2.4.1. Eligibility criteria

We used the PICOS (P-Population; I- Intervention/Exposure; C-Control/Comparator; O-Outcome; S- Study design) model to frame our research questions and applied the same model to define the eligibility criteria for study selection.

4.2.4.2. Population

We included studies that provided information on any factors limiting or facilitating the performance of hypertension treatment and control in Nepal. These factors were associated with hypertensive patients, health care providers (physicians, nurses, health care workers, and others), or health system. We did not restrict studies according to participants' age, gender, ethnicity, or comorbidity.

4.2.4.3. Exposure/Intervention

We defined the exposure as any factors that reportedly impede or facilitate hypertension treatment and control in Nepal [41, 76], excluding the non-modifiable personal attributes such as age, gender and ethnicity of patients and providers. Strategies were any interventions, program or policies targeted to the providers or patients or other components of health system and delivered at the community or health facility level for improving hypertension treatment and control.

4.2.4.4. Comparator/ control

We included studies with or without comparators or control groups. Some of the comparators or controls were untreated, uncontrolled hypertensive individuals, general population, or patients who receive usual care.

4.2.4.5. Outcomes

The outcomes of interest were hypertension treatment, hypertension control, and treatment adherence. By "hypertension treatment" we considered the use of at least one antihypertensive medication by hypertensive patients [41]. We defined "hypertension control" as maintaining systolic blood pressure of <140 mmHg and diastolic blood pressure of <90 mmHg in individuals under antihypertensive medication [41]. "Medication adherence" was defined as consistently taking antihypertensive medication as prescribed by the health care provider [41].

4.2.4.6. Types of study

We included observational (qualitative, quantitative, and mixed-methods) and experimental studies that assessed and quantified barriers, enablers, and strategies for hypertension treatment and control in Nepal. Qualitative studies that provided information on views and experiences of patients, providers, and other related stakeholders regarding barriers and enablers of hypertension treatment and control were also included in the review. Studies were included regardless of language of publication or sample size. Reviews, case reports, case series, and conference abstracts were not deemed eligible for inclusion.

4.2.4.7. Search strategy

The primary literature search was conducted in PubMed, Embase, Web of Science, CINAHL through EBSCOHost, ProQuest, and WorldCat databases. We used a comprehensive search strategy to identify hypertension-related literature published between 2000 and 2020 in Nepal. Barriers, enablers, and strategies for hypertension treatment and control are likely to change over time. Therefore, to provide the most relevant data for informing changes in health system, this review focused on the current situation, and we only searched for the recent literature (i.e. published in the last 20 years). We combined the search terms "hypertension" and "blood pressure" with the search term "Nepal". The full search syntax is provided in Supplementary table 4.

The secondary search was done through Nepal Journals Online, Journal of Nepal Health Research Council, Journal of Kathmandu Medical College, Nepal Medical College Journal, Journal of Nepal Medical Association, and Chitwan Medical College Journal to identify any relevant citations we may have missed in the primary search. We also accessed websites of the Nepali Government, professional and regulatory organisation, and national and international agencies. Finally, we conducted forward citation searching for included studies using Google Scholar database and screened the reference lists of the included studies, as part of a backward citation search.

4.2.4.8. Data management

We used EndNote X8 (Clarivate Analytics, Philadelphia, PA, USA) and Rayyan QCRI [88] to manage the records and other data throughout the review. At first, we exported the citations to EndNote X8 to identify and remove the duplicates. The citations were then imported to Rayyan QCRI, to carry out screening and data extraction.

4.2.4.9. Selection process

Initially, two authors (RRD and ARP) independently screened the titles and abstracts of the articles and labelled them as 'included', 'maybe', and 'excluded'. Full-texts of all records except the ones that were labelled 'excluded' by both reviewers were reviewed. The screening process was blinded, and all disagreements in study selection were settled by consensus between the two authors. A PRISMA flow chart illustrating the study selection process is presented in figure.

4.2.4.10. Data extraction

Using a pre-designed form, two authors (RRD and ARP) independently extracted the following data from the included publications: study design; study types; study participants; study setting; statistical method; year of publication; information to assess the risk of bias; types and/or prevalence of barriers, enablers, and strategies; and the effects on hypertension awareness, treatment, and control. For strategies, we additionally extracted data related to the comparator group.

4.2.4.11. Quality assessment

We used the Mixed Methods Appraisal Tool (MMAT) to assess the methodological quality of the selected studies. MMAT includes a five-item checklist for different types of study design, with 'Yes' 'No', and 'Can't tell' response options (Supplementary table 5). For each

‘Yes’ response, the given study was assigned a star (*). A study could, therefore, get an overall score between zero and five stars. For the purpose of this review, we used the following scoring system for overall methodological quality: 0-1 star = ‘low’; 2-3 stars = ‘fair’; 4-5 stars = ‘good’. Two authors (RRD and ARP) independently checked the quality of the studies. To resolve discrepancies between assessment scores provided by the two authors, a third author (NS) also assessed the quality of the studies using the same tools. All conflicts were resolved by consensus. We did not exclude studies from the review based on the outcome of quality assessment.

4.2.4.12. Data synthesis

Both qualitative and quantitative findings were discussed together to enrich the understanding of barriers and enablers of hypertension and control specific to health system, health care providers, and patients in the Nepalese context. To enable such a mixed-methods approach to synthesise the evidence, we incorporated both qualitative and quantitative data within the domains of previously described theoretical framework. This allowed us to provide a joint summary of both quantitative and qualitative findings from individual studies for each of the domains.

Extracted qualitative data were analysed using template analysis [89]. Two authors of the current study used the pre-defined template to extract the meta code/code and associated text from the primary qualitative study and enable merging them into three major domains. The list and definition of the prior codes used in template analysis are given in Supplementary table 6. The final list of codes was further categorized as “health system-related”, “Provider-related” and “Patient-related” barriers and enablers. The code relating to the institution, resource, finance and services were categorised as health system-related factors. Attitudes, perceptions, practices, behaviours, and beliefs of patients and providers were listed under their respective domains.

We calculated the odds ratios and their 95% confidence interval (CI) using the proportions of exposure and outcomes, where available. Due to the limited information on the exposures and outcome and large methodological heterogeneity between the selected studies, we did not conduct a meta-analysis. Instead, in attempt to identify the most prominent factors, we applied the vote counting method to count the frequency of their mentions across the studies, as suggested in the Cochrane Handbook for Systematic Reviews of Interventions [90]. Before that, the factors for which ≥60% of studies showed a positive or negative

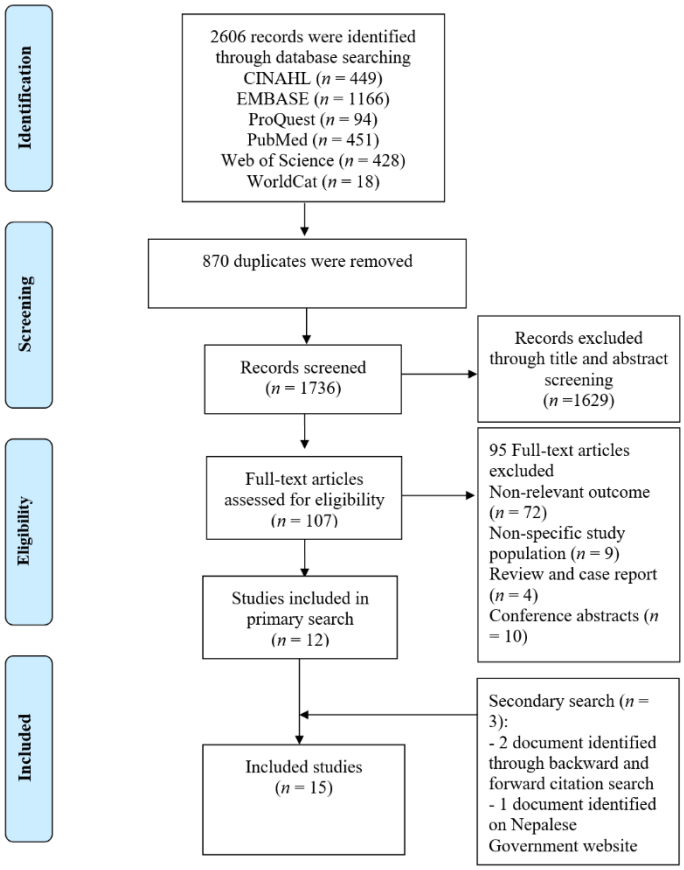
association were assigned to the domains of health system, providers, and patients, in accordance with the framework.

4.2.5. Results

4.2.5.1. Study selection

The systematic search of six electronic databases resulted in a total of 2606 records. We removed 870 duplicates in Endnote and exported the remaining 1736 records to Rayyan QCRI for the title and abstract screening. We excluded 1629 ineligible titles and abstracts and retrieved the full-texts of the remaining 107. Out of 107 full-text articles that we assessed, 95 had either ineligible outcomes such as pulmonary hypertension, were conducted among non-hypertensive or non-Nepali participants, or were reviews, case reports or conference abstracts. We did the forward and backward citation tracking for the remaining 12 studies and identified two additional records [91, 92]. One additional study eligible report was identified on the Nepalese Government website. No additional eligible studies were found in Nepalese journals and on websites of Nepali professional and regulatory organisations, and national and international agencies. Finally, we included 15 studies [23, 91-104] for qualitative synthesis (Fig 14). None of the studies were included in the quantitative synthesis of effect sizes because of the significant differences in their aims, methods, interventions/exposures, and outcome measures.

Figure 14. Study selection flow diagram



4.2.5.2. Study characteristics

The included studies were conducted in Bagmati province (Kathmandu and its periphery, *n* = 8), Gandaki province (Kaski, *n* = 4), province 1 (Sunsari, *n* = 2), and Sudurpaschim province (Achham, *n* = 1). The numbers of studies conducted in hospital (*n* = 8) and community (n = 7) settings were nearly equal. All the community-based studies included participants from the peri-urban (*n* = 3) and urban (*n* = 3) areas. Only a study conducted in Acham (hospital and community-based) included participants from a rural area [95]. More than half of the studies were completed in 2015 or later. Ten studies assessed the barriers and enablers of hypertension treatment and control [23, 91, 92, 98-104]. Of these, three studies applied qualitative methods [99-101], six used quantitative methods [23, 91, 92, 98, 103, 104], and one was conducted using mixed methods [102]. The majority of these studies investigated hypertension treatment as an outcome of interest (Supplementary table 7). Three studies also discussed adherence to antihypertensive medications [92, 103, 104]. Most studies collected data from hypertensive participants, except one study that interviewed community health workers to explore the barriers and enablers in utilising health care among the patients [101].

Five of the included studies that assessed the effectiveness of hypertension treatment and control strategies [93-97] were prospective comparative studies (*n* = 1) [97], randomised trials (*n* = 2) [94, 96], and uncontrolled before and after studies (*n* = 2) [93, 95]. Four out of these five studies reported systolic and diastolic blood pressure as outcome measures [93, 94, 96, 97]. The studies tested the effectiveness of health education [93-97] and combined, antihypertensive medication, and yoga [96] interventions (Supplementary table 8).

The total number of participants in the included studies was 3279, with the individual sample sizes ranging from *n* = 13 to *n* = 1638. Only three studies applied multivariable analysis and reported adjusted effect sizes [94, 103, 104]. Most of the qualitative and mixed methods studies (3 out of 4) applied a thematic analysis. Three studies [94, 95, 99] reported non-response rates, and they ranged between 9% and 27.8%.

4.2.5.3. Study quality

In quality assessment, all studies received three or more stars, suggesting they were of fair or good methodological quality (Supplementary table 5). Only three out of 11 quantitative studies [94, 103, 104] adjusted for confounding.

4.2.5.4. Barriers and enablers of hypertension treatment and control

4.2.5.4.1. Barriers to hypertension treatment and control

We identified several barriers to hypertension treatment and control discussed in both qualitative and quantitative studies. They are tabulated separately in Supplementary table 9 and Supplementary table 10. We categorised all the barriers into three major domains: health system-related barriers, provider-related barriers, and patient-related barriers (Table 7).

Table 7. Barriers to hypertension treatment and control in Nepal

Domain	Barriers (category)	Barriers identified in		Study count
		qualitative study	quantitative study	
Health system-related	Unaffordability of services and medicines	Unaffordable services [99]	Expensive (vs. affordable) medicine [103], high cost of medicine [23]	+++
	Lack of human resources, diagnostic tools and medicines	Lack of human resources and diagnostic tools [101]	Unavailability of medicine [23]	++
Health care provider-related	Communication gap between patients and providers regarding	Communication gap between patients and providers regarding medication use and follow-up visits [99-102]	-	++++

Domain	Barriers (category)	Barriers identified in		Study count
		qualitative study	quantitative study	
	medication use and follow-up visits			
	Inadequate counselling on lifestyle modifications	Inadequate counselling on lifestyle modifications [99-102]	No counselling [102]	++++
	Long waiting hours	Long waiting hours [99, 102]	long waiting hours (>20 minutes vs. ≤ 20 minutes) [102]	++
	Lack of national guidelines for hypertension treatment	Lack of national guidelines for hypertension treatment [102]	-	+
	Provider's unsupportive-behaviours	Provider's unsupportive-behaviours [99]		+
Patient-related	Non-adherence	Non-adherence [99, 102]	Poor adherence to medication (low adherence vs high adherence) [102], Non-adherence to medication [98]	+++
	Irregular follow-up visits	Irregular follow-up visits [101, 102]	Lost to follow up (irregular vs regular) [103], Lost to follow up (no follow up vs regular follow-up) [102], lack of blood pressure monitoring [98]	++++
	Lack of awareness on blood pressure target	-	Lack of awareness on blood pressure target [102], Not aware of normal blood pressure [98]	++
	Poor help-seeking behaviours	Poor help-seeking behaviours [101]	-	+
	Reluctance to change behaviours	Reluctance to change behaviours [99]	-	+
	Perceived side-effects of anti-hypertensive medication	Perceived side effects of anti-hypertensive medication [99, 102]	Perceived side effect of drugs [23]	+++
	Self-medication	Self-medication [101]	-	+
	Lack of family support	Lack of family support [99]	-	+
	Financial hardship	Financial hardship [100]	-	+
	Lack of awareness on blood pressure complications	-	lack of awareness on high blood pressure complications [98]	+
	Comorbidity	-	Comorbidity (yes vs no) [104]	+

Note: "+" indicates the number of studies that reported the barriers.

4.2.5.4.1.1 Health system-related barriers

The unaffordability of health services and medicines [23, 99, 103] and lack of human resources, diagnostic tools and medicines [23, 101] were the most often cited health system barriers.

4.2.5.4.1.2 Provider-related barriers

The most frequently cited barriers at providers' level were the communication gap between providers and patients [99-102], health worker's lack of interest in counselling for lifestyle modifications [99-102], and long waiting hours for the appointment [99, 102]. Health care providers failed to deliver clear information to patients regarding medication dosage and duration, behaviour modification and need for routine monitoring. A hypertensive male participant from the study conducted by Shrestha et al. [99] complained that the doctor did not explain enough about his condition.

"….. *After check-up, I was told to take medicine. …..I was not told anything. So, I asked people who have heart disease to get the information regarding what food to eat, which food increases it, and which food controls pressure*." [99]

In addition, other provider-related factors affecting hypertension treatment and control were: lack of national guidelines in hypertension treatment [102] and provider's unsupportive behaviours [99].

4.2.5.4.1.3 Patient-related barriers

Both quantitative and quantitative studies reported various individual/patient-level factors that were significantly associated with untreated or uncontrolled hypertension. The most prominent barriers were: non-adherence to medication [98, 99, 102], irregular follow-ups [101-103], and patients' lack of awareness of the 'normal' blood pressure target [98, 102] (Table 1). For example, a 55 years old participant with uncontrolled hypertension from a study in Kathmandu reported not visiting the doctor for one and a half years since her last visit [102], as the doctor did not recommend regular visits.

"*I have not gone for follow-up. I am following the same regimen from the last one and a half years. My doctor told me to visit him only if I had problems.*" [102]

Additionally, a wide variety of themes evolved from the qualitative analysis of the findings on patient's beliefs and practices that affect hypertension treatment and control (Supplementary table 9). The factors impeding initiation of anti-hypertensive treatment were poor help-seeking behaviours [101] and reluctance to take medication due to perceived side effects and fear of long-term use [99, 102].

4.2.5.4.2. Enablers of hypertension treatment and control

Three qualitative studies discussed facilitating factors for improved hypertension treatment. Among them, family support, positive illness perception, and using drug reminder were the most frequently cited ones [99, 100].

The remaining enablers were: provision of free essential medicine [101] and patient's motivation to control hypertension [99] (Table 8).

Table 8. Enablers and strategies for hypertension treatment and control in Nepal

Domain	Enablers			Strategies
	Category	qualitative study	quantitative study	
Health system-related	Free essential medicines	Free essential medicines at health centre [101]		Strengthening data recording systems at the health care centre [95]
Health care provider-related				Capacity development of health worker [95, 97]
Patient-related	Family support	Family support [99, 100]		Health education for hypertensive patients [93-95, 97], yoga [96]
	Positive illness perception	Perceived seriousness of the illness	Positive illness perception [92]	
	Self-motivation	Self-motivation [99]		
	Drug reminder (packaging and text)	Use of medication containers [99]		
		Use of reminders for medication [99]		

Similarly, only one quantitative study discussed enablers separately. The study found that scores of dimensions of illness perception particularly timeline, treatment control, and

coherence were positively correlated with medication adherence [92]. The higher the participant perceived high blood pressure as a chronic condition (Spearman correlation coefficient (r) = 0.23, p<0.05), the better the medication adherence was. The more the participant believed that the treatment can control the blood pressure (r = 0.51, p<0.05), the higher the medication adherence score they had. The better the understanding of hypertension (r = 0.22, p<0.05), the higher the medication adherence was [92].

4.2.5.5. Strategies for hypertension treatment and control

Out of five eligible studies in this category, all studies intervened at the patient level, two studies also investigated the effect of workforce strengthening (training and continuing education for integrated of non-communicable disease care), and one study evaluated the impact of new data recording systems at the health care centre (Table 8). The most frequently tested antihypertensive strategy was the health education for hypertensive patients [93-95, 97], and three out of four studies found it to be effective for reducing blood pressure (Table 9). Health education particularly related to lifestyle modification and medication reconciliations was applied as a component of comprehensive blood pressure management strategies [94, 95, 97] or as a single intervention [93]. One study [97] also compared hydrochlorothiazide, enalapril, and amlodipine as first-line antihypertensive drugs. The reduction in mean systolic and diastolic pressure was significantly higher with enalapril and amlodipine, compared with hydrochlorothiazide [97]. The participant under amlodipine reported more adverse events such as peripheral oedema, shortness of breath, and headache than the enalapril group.

Table 9. Findings of the studies on the effectiveness of strategies to improve hypertension treatment and control in Nepal

Study ID	Comparison	Sample size total (treatment/control)	Participants in analysis	Outcome	Findings	Overall MMAT score
Humagain et al. (2015)	Comparison 1: hydrochlorothiazide 25 mg vs amlodipine 5 mg	172 (NA/NA)	172	Outcome1: Systolic blood pressure	Before and after difference of mean(sd) 14.6(5.1) mmHg vs 21.9(5.9) mmHg, p<0.01	***
				Outcome 2: Diastolic blood pressure	Before and after difference of mean (sd) 8.8(2.5) mmHg vs 14.2 (2.8), p<0.01	
	Comparison 2: hydrochlorothiazide 25 mg vs enalapril 5 mg	172 (NA/NA)	172	Outcome 1: Systolic blood pressure	Before and after difference in mean (sd) 14.6 (5.1) mmHg vs 21.8 (7.4), p<0.01	
				Outcome 2: Diastolic blood pressure	Before and after difference in mean (sd) 8.8(2.5) mmHg vs 14.2(2.9) mmHg, p<0.01	

Study ID	Comparison	Sample size total (treatment/control)	Participants in analysis	Outcome	Findings	Overall MMAT score
	Comparison 3: amlodipine 5 mg vs enalapril 5 mg	172 (NA/NA)	172	Outcome 1: Systolic blood pressure	Before and after difference in mean (sd) 21.9 (5.9) mmHg vs 21.7 (7.4) mmHg, p = 0.92	
				Outcome 2: Diastolic blood pressure	Before and after difference in mean (sd) 14.2 (2.8) mmHg vs 14.3 (2.9), p=0.86	
Khadka et al. (2010)	yoga vs routine care	14 (7/7)	14	Outcome 1: Systolic blood pressure	Before and after difference in median was 21 mmHg in yoga vs 12 mmHg in control group, p<0.05	***
				Outcome 2: Diastolic blood pressure	Before and after difference in median 18 mmHg in yoga group vs 0 mmHg in control group, p<0.05	
Kumar et al. (2019)	multilevel intervention, no comparison group	340 (340/-)	340	Hypertension control	No statistically significant difference between baseline and endline outcome; hypertension control rate decreased from 75% (254 out of 340) to 73% (249 out of 340)	***
Neupane et al. (2018)	Health education, blood pressure monitoring, and referral vs usual care	1638 (939/699)	1468	Outcome 1: Systolic blood pressure	Before and after difference in mean was 6·47 mmHg in the intervention vs 2·85 mmHg in the control group	****
				Outcome 2: Diastolic blood pressure	Before and after difference in mean was 2·90 mmHg in the intervention group vs 1.11 mmHg in control group	
Sharma et al. (2014)	Health education, no comparison group	50 (50/-)	50	Outcome 1: Systolic blood pressure	The mean (sd) reduced from 150.1 (7.8) mmHg to 137.7 (9.9 mmHg), p<0.01	***
				Outcome 2: Diastolic blood pressure	The mean (sd) reduced from 104 (9.5) mmHg to 94.5 (7.7) mmHg, p<0.01	

One study studied yoga as an adjuvant therapy to medication and compared it with usual care [96]. The yoga group had a significant reduction in both systolic and diastolic blood pressure, compared with the 'medication-only' group after six weeks of follow-up.

One of the two studies that intervened at the level of health care providers found a significant improvement in blood pressure amongst their clients. The study trained and involved female community health volunteers for health education, blood pressure monitoring, and referral of hypertensive cases. The intervention was effective in reducing blood pressure. The mixed-effect regression coefficient was –4.9 (95% CI: –7.8 to –2.0) for systolic blood pressure and –2.6 (95% CI: –4.6 to –0.7) for diastolic blood pressure [94]. One study implemented the intervention program at health system level, by establishing a new digital and electronic health record system along with capacity development for health care workers and providing health education to the patients. The intervention had no statistically significant effect on hypertension control [95].

4.2.6. Discussion

We systematically reviewed 15 studies to identify barriers, enablers, and strategies of hypertension treatment and control in Nepal. Ten of them investigated various barriers and enablers within three domains: the health system, health care providers, and patients. The remaining five studies investigated the effectiveness of different hypertension treatment and control strategies, including health education and yoga. Our study identified several barriers for hypertension treatment and control in Nepal. Most of them were related to health care providers and hypertensive patients such as communication gaps, inadequate counselling, long waiting hours for appointments, lack of national guidelines for hypertension treatment, provider's unsupportive behaviours, non-adherence to medication, irregular follow-up visits, lack of awareness on blood pressure target, poor help-seeking behaviours, reluctance to change behaviours, perceived side-effects of anti-hypertensive medication, self-medication, lack of family support, financial hardship, lack of awareness on blood pressure complications, and comorbidity. To improve hypertension treatment and control, these barriers need to be addressed in future interventions targeting hypertensive patients and health care providers.

The synthesis of the findings reported in qualitative studies generated two themes on health system-related barriers for hypertension control and treatment. They were the lack of affordable services and health system resources including human and physical assets. Barriers relating to the availability and affordability of hypertension care services are common in low-income countries [41, 65]. The health system factors are complex and can have a strong influence on health service delivered by the provider and patient's access to care [41]. The unaffordability of the services and financial hardship at the individual level were associated with poor help-seeking behaviours, non-adherence to medication and irregular follow-up visits to health centres among hypertensive patients. The quantitative studies that investigated barriers to hypertension treatment and control also showed a significant association between high cost of drugs and non-adherence to medication. The odds of not adhering to taking antihypertensive drugs were 5.2 times higher among the patients who reported the cost of medicine as expensive [103]. This study identified the provision of free essential medicines at government health facilities as a single facilitating factor relating to the Nepali health system. Providing free essential antihypertensive medicines at the primary health care centres was supposed to increase access to treatment of hypertension. Some of the calcium channel blockers and beta blockers are freely available at primary health care centres. However, regular, effective, and efficient supply of these medicines is uncertain [105]. For example,

most of the health facilities (HF) reported unavailability of atenolol (82% of HF) and amlodipine (90% of HF) in 2015 [106].

None of the strategies from the selected studies aimed either to minimise the financial burden associated with hypertension treatment or to increase access to hypertension care. Only one study evaluated the effects of a strategy implemented at health system level. It developed and evaluated a new hospital-based health-records system, but the strategy failed to show a significant impact on blood pressure control. To increase access to care and minimise excessive health expenditures, different health system financing approaches, including health insurance coverage and co-payments for medication, have been evaluated globally [41]. Nepal recently enacted the National Health Insurance Act 2017 and is moving towards universal health coverage for equitable access to high quality and affordable health care [107]. However, its overall impact on treatment and control of hypertension and its related complications has yet to be studied.

The communication gap between health workers and patients was one of the most frequently studied barriers associated at provider level. The lack of clear messages on medication, dosage, lifestyle modification, and follow-up visits was reported as causes of non-adherence to medication and irregular follow-up visits, ultimately leading to suboptimal control of blood pressure. A recent study found that less medication (antihypertensive drugs) discussion between providers and patients was associated with six-fold increased odds of poor adherence to medication [108]. Jolles et al. also emphasised that effective communication between providers and patients could increase medication adherence and contributes to better control of high blood pressure [109].

Capacity development of the female health community volunteers and involving them for health education, blood pressure monitoring and linking the cases to health services was the only effective intervention implemented at the provider level. involvement of female community health volunteers in screening the high-risk population and monitoring the hypertensive patients is cost-effective [110] and could minimise the burden of exhausted health care workers. After a very acclaimed performance on improving maternal and child health [111], new evidence suggests that community health workers could potentially work as the frontline cadres to fight against the burden of non-communicable diseases, including hypertension [112]. Task sharing, particularly with other non-physician health workers in understaffed and resource-poor settings, is an effective strategy for the management of

hypertension [79]. Additionally, other approaches such as including pharmacists and nurses in a team and providing team-based hypertension care also showed positive effects on controlling high blood pressure [80].

Most of the barriers at the patient level were related to their knowledge, beliefs, and practices. Being unaware of the normal blood pressure target, perceived side effects of drugs, fear of long-term use of medication, reluctance to take medicine, self-medication, non-adherence to medication, lack of regular follow-up visits, lack of blood pressure monitoring, and not minimising risky health behaviours were the key barriers to hypertension treatment and control. Similar to our findings, Khatib et al. in their systematic review reported several patient-related barriers to hypertension treatment and control [65]. The authors categorised them as capability barriers (e.g. lack of skills and knowledge), intention and motivation barriers (e.g. lack of motivation to adhere to a treatment, false belief, such as drug dependency), and medication barriers (e.g. self-perceived side effects, taste and dosage), among others [65]. Interestingly, for most of the reported barriers they did not find large differences between low-and middle-income countries and high-income countries. The only exception were availability barriers, such as lack of health care facilities and resources, which were more prominent in low-and middle-income countries [65] as well as in Nepal.

Health education was the most commonly investigated strategy. One study used yoga as an adjuvant therapy to the medication and found that yoga was effective in blood pressure reduction. Globally, barriers relating to patient's knowledge, belief, and practices have been tackled effectively using different approaches, such as simplifying the treatment using polypill [83] and increasing adherence to medication, routinely and conveniently monitoring hypertension through home-based blood pressure measurement [84] and providing education interventions to patients and physicians [85]. Future studies should evaluate the effectiveness of these strategies in the context of Nepali health system.

The current study provided a comprehensive insight into factors influencing hypertension treatment and control at the health system, health provider, and patient levels. The findings may be used to inform and guide relevant stakeholders while designing strategies for improving hypertension treatment and control in Nepal. Enabling access to essential antihypertensive medications at primary health care facilities and developing hypertension treatment protocols and guidelines for primary health care providers may be needed to improve curative care of hypertension in Nepal. Providing health education to

hypertensive patients seems to be a viable strategy to improve hypertension care in Nepal. Increasing the involvement of female community health volunteers in the provision of health education may be helpful. Additionally, yoga could be recommended as a lifestyle therapy to manage hypertension as part of primary care. However, more research is needed to evaluate the effectiveness and feasibility of yoga interventions for hypertension treatment and control in the Nepalese context.

The use of information and communication technology-enabled integrated care has shown promising effects on blood pressure reduction in hypertensive patients [113, 114]. Therefore, it may be worthwhile to explore the effectiveness and feasibility of telephone follow-ups, web-based and computer-tailored solutions, home-use devices for blood pressure monitoring, smartphone applications, and telemedicine in the Nepalese context. A recently published protocol announced a study that will aim to recruit 200 hypertensive patients in Nepal and evaluate feasibility of a mobile phone text messaging intervention [95] [115].

A recent study indicated that there is a growing burden of non-communicable disease multimorbidity (i.e. occurrence of two or more chronic conditions) in Nepal [116]. In response to this challenge, it would seem worthwhile to evaluate integrated chronic care models for non-communicable diseases, including hypertension [95].

Some limitations of this review stem from the characteristics of the included studies. Although the majority of studies scored three out of five in MMAT checklists, nearly all of them were subject to inadequate reporting of research methods. For example, out of six comparative or intervention studies, three studies did not present clear information on the estimation of the required sample size and participant selection. Furthermore, only two quantitative studies adjusted their analyses for confounding. These methodological limitations of the included studies may have affected their findings and consequently the findings of our review.

A meta-analysis could not be performed due to a large methodological heterogeneity and variation in outcome measures between the included studies. For example, the data on barriers and enablers were extracted from qualitative, quantitative, and mixed methods studies. The data on antihypertensive strategies were from prospective comparative studies, randomised trials and uncontrolled before and after studies. The intervention modalities also varied across studies from health education to yoga.

4.2.7. Conclusions

By reviewing 15 individual studies of fair-to-good methodological quality, we found a range of factors at the health system, health care provider, and patient levels that are likely to impede or facilitate hypertension treatment and control in Nepal. We also found that health education (provided by female community health volunteers and health workers) and yoga are promising interventions for hypertension treatment and control in Nepal. However, further studies are required to confirm their effectiveness and feasibility, before incorporating them in the clinical practice. Overall, the findings of our systematic review may assist policy makers and other public health stakeholders in designing future interventions to improve hypertension treatment and control in Nepal.

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Chapter 5. Implementation of non-pharmacological interventions for blood pressure reduction in primary care

This chapter narratively synthesises evidence on implementation of non-pharmacological interventions for hypertension in primary care settings. The chapter included the non-pharmacological interventions particularly alcohol intake reduction, sodium intake reduction, increased potassium intake, physical activity, weight loss, and heart-healthy diet and discussed their effectiveness, barriers, and facilitators while implementing them in primary care settings.

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DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

1. PUBLICATION DETAILS (to be completed by the candidate)

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Institute: Institute for Health and Sport Candidate's Contribution (%): 85%

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2. CANDIDATE DECLARATION

I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

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Signature **Date**

3. CO-AUTHOR(S) DECLARATION

In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

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5. The original data will be held for at least five years from the date indicated below and is stored at the following **location**(**s**):

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Name(s) of Co-Author(s)	Contribution (%)	Nature of Contribution	Signature	Date
Zeljko Pedisic	10%	Conception of study and manuscript development	[redacted]	12 Dec 2021
Maximilian de Courten	5%	Manuscript development		14 Dec 2021

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5.1. Study 3. Implementation of non-pharmacological interventions for blood pressure reduction in primary care: a review of effectiveness, cost-effectiveness, barriers, and facilitators

5.1.1. Abstract

Background

Hypertension is the leading and preventable cause of cardiovascular diseases and deaths. Alongside the medication, several non-pharmacological interventions have shown promising results in controlling high blood pressure. Though primary care is the first point of contact for hypertension care, the use of nonpharmacological interventions for hypertension control in primary care is still obscure. This review aimed to critically appraise and narratively synthesise evidence on non-pharmacological intervention for hypertension in primary care.

Methods

A thorough literature search was conducted to identify evidence on the use of alcohol reduction, salt reduction, potassium supplementation, physical activity, weight control, heart-healthy diet, and other non-pharmacological interventions for hypertension control in primary care.

Results

There is very limited guiding evidence on the use of non-pharmacological interventions for hypertension in primary care. Available evidence suggested that alcohol reduction, sodium intake reduction, physical activity, and weight reduction could be viable interventions for hypertension reduction in primary care. However, implementation of these interventions remains a challenge due to several barriers associated with providers and patients. The barriers are specific to types of intervention but in general, they are mainly related to competing priorities and a lack of knowledge, skills and motivation in providers, and a lack of professional, peer, and family support in patients.

Conclusions

More evidence is required to recommend the use of non-pharmacological interventions for hypertension in primary care. Future studies should focus on assessing implementation potential of all types of effective non-pharmacological interventions for blood pressure reduction in primary care.

5.1.2. Background

There is a wealth of literature on alcohol intake, physical inactivity, high salt intake, and obesity as key lifestyle determinants of high blood pressure. A recent systematic review demonstrated that consumption of five or more standard alcoholic drinks per day is associated with a 74% greater risk for hypertension [1]. Likewise, physical inactivity was found to be associated with an increased risk of hypertension [2]. The population attributable fraction of hypertension due to physical inactivity is 13% [2]. A pooled analysis of 133,118 individuals showed that an additional gram of dietary sodium intake per day is associated with an average increase in systolic blood pressure of 2.58 mmHg [3]. Jayadi et al. [4] performed a meta-regression analysis with a pooled sample of 2.3 million participants from 57 prospective cohort studies and observed a significant relationship between body mass index (BMI) and blood pressure. A five-unit increase in BMI was associated with a 49% higher risk of hypertension [4]. Importantly, these risk factors are modifiable, and their modification (i.e. reducing alcohol consumption, increasing physical activity, reducing salt intake, and reducing body weight) may, therefore, play an important role in the prevention and management of high blood pressure.

A recent review found that a reduction in alcohol of 16-80% across 14 intervention trials was associated with an average reduction in systolic blood pressure of 3 mmHg [5]. The effect seems to be greater in hypertensive and medicated patients [5], and among those who drink more than two standard alcoholic drinks per day [6]. Several systematic reviews have consistently reported that salt reduction is associated with a significant reduction in blood pressure [7-14]. Salt reduction strategies were found to be associated with an average change in systolic blood pressure of -3.9 mmHg to -5.9 mmHg [7-14]. The blood pressure-lowering effect induced by a reduction in salt intake was found to be greater among hypertensive individuals [13]. The negative effect of high salt intake on blood pressure was found to be attenuated by potassium supplementation, as it may facilitate the removal of excess sodium from the body. The importance of potassium supplementation on blood pressure reduction has been substantiated by the findings of a systematic review [15]. The study reported that an increased potassium intake achieved through changes in diet or the use of dietary supplements was associated with an average reduction in systolic blood pressure of 4.7

mmHg, and that the reduction was greater among those who consumed more dietary salt [15]. Likewise, various types of physical activity, such as aerobic exercise [16], isometric and dynamic resistance training [17-20], and light-intensity incidental physical activity such as standing or walking at work [21, 22] are significantly associated with blood pressure reduction. A loss in weight was found to be associated with an average reduction in systolic blood pressure of 2.68 mmHg [23]. In addition to these modifications of lifestyle risk factors, heart-healthy diets including dietary approaches to Stop Hypertension (DASH) diet, Mediterranean diet, low-carbohydrate diet, diet with low-glycaemic index, low-sodium diet, and low-fat diet are associated with a greater reduction in blood pressure compared to a control diet in hypertensive and pre-hypertensive participants [24].

Taking into account the evidence on their effectiveness, the 2017 Guideline for the prevention, detection, evaluation, and management of hypertension recommended major six non-pharmacological interventions for hypertension including moderation in alcohol intake, reduced intake of dietary sodium, enhanced intake of dietary potassium, physical activity, weight loss, and heart-healthy diets that could potentially reduce 4-11 mmHg of systolic blood pressure in hypertension [25]. The body of evidence on other non-pharmacological interventions, such as yoga, healthy drinks, and stress reduction, is growing[26, 27]. The International Society of Hypertension (ISH) guidelines issued in 2020 also highlighted the importance of lifestyle modifications for blood pressure reduction and recommended them to use along with the antihypertensive medications for optimum control of hypertension [26]. Additionally, accumulating evidence suggested that some of the non-pharmacological interventions could also seem to help reduce the needed dosage of antihypertensive medication or and could have resulted in a greater reduction in blood pressure if they are used combined with medications [28-30].

However, non-pharmacological interventions are still not widely used in primary care. For example, less than one in four general practitioners in France, Germany, Italy, Spain, and the UK assesses alcohol intake and recommend alcohol reduction among their hypertensive patients [31]. Similarly, around one-third of primary care providers in the USA reported that their patients were unlikely to comply with the advice to reduce salt intake [32]. Also, in the UK, 90% of the overweight patients did not receive weight management intervention at primary care [33].

In this paper, we, therefore, thoroughly reviewed and summarised the evidence on the effectiveness, cost-effectiveness, barriers, and facilitators of non-pharmacological interventions for blood pressure reduction in primary care. Based on the summary findings, we also discussed possible strategies to facilitate the use of non-pharmacological interventions for blood pressure reduction in primary care and provided recommendations for future research in this area.

5.1.3. Methods

A thorough literature search was conducted in Google Scholar, PubMed, and Embase. The search keywords included “hypertension or blood pressure” combining the words that represent the non-pharmacological interventions for hypertension including “non-pharmacological intervention”, “lifestyle modification”, “alcohol”, “salt”, “potassium”, “diet, “physical activity”, “weight”, “yoga”, “DASH”, “Mediterranean diet”, and “stress reduction”. Additionally, forward and backward reference searches were also performed to identify the relevant evidence on the use of alcohol reduction, salt reduction, potassium supplementation, healthy diets, physical activity, weight control, and yoga.

5.1.4. Results

5.1.4.1. Alcohol reduction

Brief Alcohol Intervention with the aim to reduce alcohol consumption has shown to be effective when delivered in the primary care setting [34]. A systematic review found that this intervention reduces alcohol intake by on average 38 grams per week [35]. Kaner et al. [36], in their recent systematic review, found a slightly lower overall effect size. The participants who received a brief intervention reduced the alcohol intake on average by 26 gram. The intervention was found to be more effective among the individuals who are at a lower risk of alcohol dependence [37, 38], or if the intervention is delivered by a nurse [39]. A recent study also suggested that hypertensive patients at primary care could benefit from Brief Alcohol Intervention delivered by physicians with the aim to reduce blood pressure [37]. Rehm et al. recommended several strategies to reduce alcohol intake among hypertensive patients in primary care [40]. The recommendations include screening of harmful alcohol use and applying Brief Advice for newly diagnosed or uncontrolled hypertensive patients in primary

care [40]. Studies have shown that implementing Brief Alcohol Intervention in the primary healthcare setting is a cost-effective strategy to reduce alcohol consumption [41]. However, evidence on the effectiveness of this intervention among individuals with severe alcohol dependence, women, older adults, younger adults, minority groups, and those from low- and middle-income countries is scarce [34, 38].

Several challenges have been identified when implementing Brief Alcohol Intervention in the primary care setting. The common barriers to its implementation include physician's time constraints, hesitancy to provide counselling to patients on alcohol reduction, the stigma attached to alcohol use, and a lack of skills and knowledge [42-44]. The use of electronic devices and mobile phones to deliver the intervention may address some of the barriers in the implementation process [45-48], but further research is required to confirm their usefulness specifically in the primary care setting. Likewise, it was suggested that specialised training, support, and financial reimbursement could also encourage medical practitioners in primary care units to routinely assess patients' alcohol consumption [44, 49]. Furthermore, delegating work to non-physician specialists and tailoring interventions to patient needs could also facilitate the implementation of Brief Alcohol Intervention in primary care (Table 10) [44].

Table 10. Summary of findings on non-pharmacological interventions for the treatment of hypertension in primary care

Type of intervention	Common implementation strategies in primary care	Key findings on effectiveness, barriers, and facilitators
Alcohol intake reduction	1. Brief alcohol intervention	Effectiveness Average reduction in alcohol intake: 26 g/week (95% CI: -37, -14) [36]. Cost-effectiveness The incremental cost-effectiveness ratio of at least AU$ 650 per QALY/life-year gain [41]. Barriers Existing workload, limited resources and support, and perceived lack of knowledge and confidence among providers [44]. Facilitators Adequate resources, availability of training for providers, and tailoring interventions to patient needs [44].
Salt intake reduction	1. Advice-based intervention 2. Dietary counselling	Effectiveness Advice-based intervention: average reduction in systolic blood pressure of 1.1 mmHg and urinary sodium excretion of 35.5 mmol/day [50].

Type of intervention	Common implementation strategies in primary care	Key findings on effectiveness, barriers, and facilitators
		Dietary counselling: average reduction in sodium intake by 73 to 93 mmol/day across the intervention groups vs. 3.2 to 12.5 mmol/day among controls. An average reduction in blood pressure of -4 to -27mmHg [51]. Cost-effectiveness No studies available Barriers Poor adherence to low-salt diet among patients [52], low self-efficacy among patients [53], difficulties associated with monitoring salt intake in primary care [54], perceived lack of time among primary care workers, and lack of reimbursement for providing the service [32]. Facilitators No studies available
Potassium intake	1. Advice to increase intake of potassium-rich fruit and vegetables 2. Advice to use potassium-containing supplements	Effectiveness Advice to increase intake of potassium-rich fruit and vegetable: Inconsistent findings on the effect of an advice-based intervention promoting potassium-rich fruit and vegetable intake on blood pressure in primary care settings [55-57]. Advice to use potassium-containing supplements: in another study, potassium supplementation decreased systolic blood pressure on average by 4.48 mmHg [58]. Cost-effectiveness No studies available Barriers Low patient motivation, lack of provider time, and lack of patient-directed educational resources. Facilitators No studies available
Physical activity	1. Brief Intervention 2. Exercise referral schemes	Effectiveness Brief intervention: Brief Intervention resulted in a small increase in physical activity (standardized mean difference of 0.17) [59]. Cost-effectiveness The incremental cost per QALY of Brief Intervention is AU$ 3160 [60]. Exercise referral schemes: resulted in an increase in physical activity of on average 55 minutes per week [61]. Cost-effectiveness Exercise referral led to an increase of 0.003 quality-adjusted life-years (QALYs) at an additional cost of AU$ 458 per person [61]. Barriers Lack of time, limited resources, and lack of financial incentives for healthcare workers [59, 62]. Lack of professional support for learning and practising physical activity, lack of peer support, lack of family and social support, and lack of motivation for patients [59, 62, 63].

Type of intervention	Common implementation strategies in primary care	Key findings on effectiveness, barriers, and facilitators
		Facilitators Health workers' perception of physical activity as an effective intervention, and financial incentives for healthcare workers [59, 62, 63].
Weight reduction	1. Behavioural therapy 2. Restrictive diet	Effectiveness Behavioural therapy: led to an average weight reduction of 1.4 kg [64]. Cost-effectiveness The cost was AU$ 170 per kg lost [65]. Restrictive diet: compared with a behavioural programme alone, very low energy diet combined with a behavioural programme reduced weight by 3.9kg at one year, 1.4kg at two years, and 1.3kg at 38-60 months.[66]. Cost-effectiveness The incremental cost-effectiveness ratio of low energy dietary replacement was AU$ 5882(4738-7060), assuming that the weight reduced by one kilo is maintained for at least 5 years [67]. Barriers Lack of self-motivation, lack of self-control, inability to afford healthy foods and exercise equipment, inability to resist the temptation to eat 'junk' food, competing priorities, and comorbidities in patients [68, 69]. Reluctance to discuss weight management with patients, insufficient confidence, knowledge, and skill to help patients manage their weight, lack of clear guidelines for weight management in primary care, and limited resources and time among health professionals [69, 70]. Facilitators Peer support, professional support, social support, self-motivation to adhere to the dietary intervention, incentives and rewards are facilitators found for patients [69, 70].
Heart-healthy diets	Dietary counselling	Effectiveness Inconsistent findings on the effectiveness of diets for blood pressure reduction in primary care settings. Cost-effectiveness No studies available Barriers low patient motivation, lack of provider time, lack of patient-directed educational resources [71], difficulty in assessing patient's dietary pattern, patient's non-adherence to dietary advice, inconsistent dietary guidelines [72]. Facilitators Using electronic tools for monitoring, access to dietitians, and availability of educational resources [72].

5.1.4.2. Salt intake reduction

Informational interventions and dietary counselling are the most common strategies applied to reduce salt intake in hypertensive patients [73].

Hooper et al. [50], in their systematic review, demonstrated that advice-based intervention for salt reduction was significantly associated with a reduction in systolic blood pressure of on average 1.1 mmHg and urinary sodium excretion of on average 35.5 mmol/day at 13- to 60-month follow-ups. Similarly, Ferrara et al. [74] investigated the effectiveness of a lifestyle education intervention among 188 hypertensive patients at an outpatient clinic in Italy over a period of two years. They found that the intervention significantly reduced sodium intake and systolic blood pressure [74]. Lin et al. [75] also assessed the effects of a physician and patient targeted education intervention for reducing blood pressure among hypertensive patients in a clinical setting. Both patient and physician targeted interventions significantly reduced sodium intake and blood pressure[75].

In a systematic review, Ruzicka et al. [51] evaluated the feasibility of implementing effective sodium reduction strategies to treat hypertension in primary care settings. They found that most of the counselling interventions were supplemented with the provision of prepared food, community cooking classes, and intensive inpatient training sessions, which may not be implementable by primary care providers. Therefore, they concluded that such interventions may not be feasible for application in the primary care setting. Furthermore, no information on the cost incurred to implement salt reduction intervention specific to primary care is available.

Low adherence to sodium reduction interventions is a key barrier for their implementation in primary care [52]. The low adherence of patients to such interventions is usually due to their poor knowledge, attitude, and behaviour related to dietary salt intake [52, 76]. Some of the reasons for non-adherence to dietary advice are a lack of clear labelling of food products and limited choice of low-salt foods [77] and low self-efficacy for low sodium diet among hypertensive individuals [53]. A systematic review found that people are not fully aware that the food they are eating daily, such as bread and rolls, pizzas, sandwiches, tacos and burritos, cured meats and cold cuts, chicken, eggs and omelettes, soups, and cheese often contain a high amount of salt [76, 78]. Some studies have shown that even those who are aware of the salt/sodium intake guidelines often do not follow them, as they do not want to

compromise their preferred taste of food [56]. Liem et al. found that consumers added more salt to a soup when it had a “reduced-salt” label, to compensate for the perceived lack of salt in the product [79]. At primary care physician level, the barriers to implementation of dietary sodium reducing counselling are lack of time and lack of reimbursement [32]. Furthermore, the implementation of salt-reduction interventions in primary care may be further complicated by challenges in the monitoring of dietary salt intake. For example, the use of multiple 24-hour urine sodium tests may not always be feasible in primary care, particularly in low resource settings [54].

Despite these challenges, health worker-led brief advice and counselling seem to be best-buy salt reduction strategies. Increasing number of health care providers have positive attitudes towards their role to provide guidance on salt reduction to their patients [32]. For health workers, capacity building is required to facilitate patient counselling about sodium reduction in primary care. The World Health Organization highlighted the importance of behaviour change communication in reducing salt intake, which would work best in the environment that promotes healthy eating [80].

5.1.4.3. Potassium supplementation

The common potassium supplementation interventions in hypertensive individuals include increasing potassium intake from fruit and vegetables or using potassium supplements [15, 58].

Studies examined the effects of a potassium-rich diet and combined interventions that promoted potassium-rich diet, physical activity, and salt reduction on blood pressure. A study conducted in a primary care unit in Finland investigated the effect of a behavioural intervention consisting of a nurse-led counselling session to increase intake of dietary potassium, promote physical activity, and reduce salt intake on blood pressure among hypertensive patients [57]. They found no significant effects of the intervention on potassium intake and blood pressure [57].

Most of the potassium supplementation trials were conducted in controlled clinical settings rather than in primary care settings [58]. Therefore, there is a dearth of information relating to the implementation and cost of potassium supplementation interventions in primary care. Cohn et al. [81], in their review, discussed the challenges of potassium supplementation interventions in clinical practice. Before providing potassium

supplementation, several factors related to the patients should be accounted for, including baseline potassium values, presence of underlying medical conditions, use of medications that alter potassium levels, dietary patterns, and ability to adhere to a dietary regimen. For example, a higher blood-pressure-lowering effect was observed among those who had a lower (< 90 mmol/day) potassium intake at baseline [58]. Furthermore, there is a U-shaped relationship between potassium intake and blood pressure, indicating that both low and high potassium intake could result in an increased blood pressure level [82]. Patients with a comorbid condition such as congestive heart failure or chronic kidneys diseases who need to strictly maintain a given potassium level and those who use non–potassium-sparing diuretics should take precautions before commencing with potassium supplementation [83]. Recently, potassium-enriched salt substitutes were found to be effective in reducing high blood pressure [84]. This is a promising strategy to deal with both high dietary sodium intake and low potassium intake, while ensuring higher patient adherence, compared with low salt-high potassium diet. However, further studies are required to confirm its safety and long-term benefits in the context of hypertension.

5.1.4.4. Physical activity

Brief interventions and exercise referral schemes are two common physical activity promoting approaches in primary care patients. Brief interventions include a brief verbal advice, discussion, and encouragement with the aim to increase patient's physical activity. Such interventions are mostly delivered by primary care practitioners such as exercise professionals, general practitioners, health coaches, health visitors, mental health professionals, midwives, pharmacists, physiotherapists, and general practice nurses [59]. A systematic review found that Brief advice on physical activity is more effective than usual care in increasing physical activity among patients [59]. The brief intervention is also cost-effective [60]. However, there is insufficient evidence regarding its effect on blood pressure, feasibility, and acceptability [85].

An exercise referral scheme, that is, a referral by a primary care or allied health professional to a physical activity specialist or service [86] was also found to be effective in increasing physical activity [61, 87]. The patients who received exercise referrals increased their time in physical activity on average by 55 minutes more than the patients who received

usual care [61]. Evidence also suggests that the compliance to physical activity recommendations following exercise referral is higher than for brief interventions [87].

However, further studies are required to confirm its cost-effectiveness. Importantly, there is a lack of evidence on the impact of exercise referral on blood pressure in hypertensive patients. It is also challenging to provide a generic recommendation for the use of exercise referral schemes in primary care, because various forms of exercise referral are being practised globally [88].

Several other types of interventions have been utilised with the aim to increase physical activity in primary care. However, they generally showed inconsistent results in increasing physical activity and lowering blood pressure. For example, three out of five studies included in the systematic review by Eden et al. [89] found a significant increase in patients' physical activity following a clinician-led counselling intervention. In another systematic review, an intervention delivered face-to-face by health professionals was not found to be effective in increasing physical activity among patients [90]. However, for a similar intervention implemented by non-health professionals (peer health facilitators, exercise trainers) this review found a significant positive effect on physical activity [90]. Likewise, a recently published pilot study suggested that physical activity counselling for 14 weeks increases the number of steps taken per day, but has no effect on the blood pressure of hypertensive patients [91]. Significant effects on blood pressure of hypertensive patients can be expected when physical activity is combined with dietary counselling [92]. A systematic review showed that behavioural counselling on physical activity and diet reduces systolic blood pressure by on average 4.5 mmHg after 12 months and 2.3 mmHg after 12-24 months of the intervention [92].

Healthcare workers reported a lack of time and limited resources as key barriers for promoting physical activity among their patients [62]. Another study found that common facilitators and barriers for the implementation of physical activity counselling in the primary care setting are related to: practitioners' perception of the effectiveness of physical activity in reducing hypertension; practitioners' perception regarding patients' interest and motivation to change their behaviour; available resources; financial incentives; conflicting priorities; and practitioners' knowledge and confidence for prescribing physical activity [59]. The key influencing factors at the patient-level are related to their motivation, the level of understanding and recall of the received advice on physical activity, fitness level, cost, lack

of time, and professional, peer, family, and social support [59, 63]. To address some of the barriers to promoting physical activity, Patrick et al. [93] in their review recommended healthcare delivery models that link clinical and community resources. For example, healthcare centre-based screening and advice on physical activity, followed by community support, could be a viable strategy to promote physical activity among primary care patients. Additionally, physical activity training for health workers, increased support for patients provided by providers, peers and family, and interventions tailored to the individuals' and social needs and interests could facilitate physical activity promotion in primary care.

5.1.4.5. Weight control

Behaviour change interventions and restrictive diets are commonly used with the aim to reduce the weight of primary care patients. For example, a meta-analysis of 15 randomised controlled trials found an average weight reduction of 1.4 kg following a behavioural change intervention (mainly by promoting low calory diet and exercise) for weight loss [64]. The behavioural change interventions are usually delivered by primary care physicians and nurses, psychologists, health educators, and nutritionists [64]. They encompass self-monitoring of diet and exercise behaviour, followed by behavioural goal setting and barrier identification or problem-solving [64]. A recent study found that a health care provider-led weight reduction discussion was associated with 5% greater weight reduction among overweight and obese patients, compared with patients who did not participate in such discussion [94]. Likewise, a brief counselling provided by a primary care physician resulted in an average weight loss of around 2.5 kg at 6 to 12 months follow-ups [95]. Daumit et al. [65] further suggested that a primary care-based behavioural change intervention (reducing calorie intake, increasing physical activity, and self-monitoring) would be more cost-effective if it is administered remotely (e.g. by telephone) than in person.

Furthermore, a study compared the costs of doctor's referral to a commercially provided restrictive diet and a nurse-led behaviour change support for reducing body weight in obese patients [67]. The former was found to be more cost-effective for the routine treatment of obesity in healthcare settings [67]. Evidence also indicates that low-energy diets are more effective for weight reduction in the short term, compared with behavioural therapy [66, 67, 96]. However, their use is recommended only when a rapid weight reduction is required, and they should only be provided by trained professionals and alongside regular

medical monitoring to prevent adverse events [66]. This may reduce their feasibility in the primary care setting. It is also important to note that a large regain of lost weight (>40% for low-energy diets and >60% for very-low-energy diets) is expected within 1-5 years [97]. Although restrictive diets are associated with a reduction in blood pressure [98-100], very little is known about their long-term impact on other aspects of health of people with hypertension [98].

A lack of self-motivation, a lack of self-control, inability to afford healthy foods and exercise equipment, inability to resist the temptation for unhealthy foods, competing priorities, and comorbidities are some of the impediments for weight loss [68, 69]. By contrast, higher self-motivation, incentives, rewards, and peer, professional, and social support could facilitate weight loss in the long term [68]. Barriers at the level of primary care workers include: the reluctance to discuss weight management with patients; insufficient confidence, knowledge and skill to manage weight; lack of clear guidelines for weight reduction; limited resources; a lack of time; and physicians' pessimism about patients' weight loss success [69, 70].

Primary care-based weight-reduction interventions consisting of both reduced energy intake and increased physical activity are more effective than interventions with any of these components individually [101]. Enabling access to dieticians and exercise professionals, and addressing barriers at the levels of providers and patients should be a priority in future interventions.

5.1.4.6. Heart-healthy diets

Heart-healthy diets particularly include the diets with high intake of fruits & vegetables, low-fat, whole grains, and low in sodium. The two most commonly used dietary approaches for hypertension control are the DASH and Mediterranean diet [24, 102]. They are mostly delivered by dietary education through face-to-face counselling [56], telephone, email [55] and led by primary care physician [103], nurse, dietician [55], nutritionist [56] and other health workers [103]. The dietary interventions are often combined with exercise, weight loss, salt reduction or co-intervention to have better control of hypertension [104, 105]. The effectiveness of DASH diet for reducing blood pressure in primary care is limited. For example, recent studies from Brazil [56] and Hong Kong [106] showed that dietary counselling had no effect on blood pressure in primary care patients. Furthermore,

implementation of dietary intervention in a primary care setting is challenging due to the lack of provision of food, prepared meals, and intensive counselling [51]. It is found that adherence to dietary recommendations is low among patients [107]. Some of the reasons for the non-adherence to the DASH diet as perceived by the healthcare providers are low patient motivation, lack of provider time, and lack of patient-directed educational resources [71]. Primary care physicians from Canada stated that the lack of time, difficulty in assessing patient's dietary patterns, patient's non-adherence to dietary advice, and inconsistent dietary guidelines were the major barriers to implementation of DASH diet intervention at primary care [72]. They believed that the use of electronic medical record tools, access to dietitians, nutrition education in medical training would help facilitate them providing dietary advice to patients [72]. From a hypertensive patient's perspective, the major barriers to following a recommended diet are social and environmental factors such as eating outside the home or eating food cooked by others, and lack of food choice in social gathering; lack of family support; lack of taste in diet; and cost of diet [108].

5.1.4.7. Other promising non-pharmacological intervention

An emerging body of evidence suggested that other non-pharmacological interventions such as yoga, stress reduction, and healthy drinks could be beneficial for reducing blood pressure [26, 27]. [23]. For example, a recent meta-analysis of 49 clinical trials found that engaging in 3 sessions per week of yoga (including breathing techniques and meditation/mental relaxation) is associated with an average reduction in systolic blood pressure of 5 mmHg [27]. A systematic review suggested that a mindfulness-based stress reduction program could be a promising behavioural therapy for reducing blood pressure in hypertension [109]. Similarly, studies showed that moderate consumption of coffee and green tea could be beneficial for reducing blood pressure [110, 111].

However, evidence on the effectiveness of these interventions in primary care settings is limited. Only two studies investigated the effects of yoga interventions delivered in the primary care setting on blood pressure among hypertensive patients while utilising a primary care physician to provide yoga instruction. For example, Wolf et al. conducted two such studies in Sweden [112, 113]. Their first study found an average reduction in diastolic blood pressure of around 4 mmHg, following a 12 weeks intervention. However, in their subsequent study, they did not find a statistically significant effect [113]. Regarding stress reduction, a private clinic-based study found that eight 2.5-hour weekly mindfulness-based stress reduction sessions were associated with a reduction of around 12 mmHg of systolic blood

pressure [114]. Though there is a dearth of evidence on the effect of stress reduction interventions on blood pressure particularly in primary care settings, a number of studies indicated that mindfulness-based interventions are promising for improving mental health and are feasible to be implemented in primary care settings [115, 116].

5.1.4.8. Conclusions

Non-pharmacological interventions for blood pressure reduction in primary care with proven effectiveness include alcohol reduction, sodium intake reduction, physical activity, and weight reduction. Evidence on the effectiveness of potassium intake and heart-healthy diets is limited and inconsistent.

Given that studies have estimated only the overall cost-effectiveness of implementing non-pharmacological interventions (e.g. reduced alcohol intake, increased physical activity, weight loss), there is a lack of specific information on the cost-effectiveness of these interventions in the treatment of hypertension.

The most common barriers for such interventions related to healthcare providers include competing priorities and a lack of knowledge, skills, and motivation. The most common barriers related to patients include, a lack of motivation, comorbidities, and a lack of professional, peer, and family support future studies should provide further evidence on the effectiveness of weight control, potassium intake, and heart-healthy diets. More research is also needed on the implementation and cost-effectiveness of all types of effective non-pharmacological interventions for blood pressure reduction in primary care.

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Chapter 6. Implementation potential of a non-pharmacological intervention for hypertension in primary care in Nepal

This chapter investigated the effectiveness of yoga, a non-pharmacological intervention, for blood pressure reduction among hypertension patients in primary care settings. This chapter also assessed the implementation potential of yoga intervention for hypertension in primary care using the Consolidated Framework for Implementation Research.

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DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

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3. CO-AUTHOR(S) DECLARATION

In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

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5. The original data will be held for at least five years from the date indicated below and is stored at the following location(s):

The datasets generated during and/or analysed during the current study will be stored in Victoria University Research Repository (https://vuir.vu.edu.au/)

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6.1. Study 4. Effects of a health worker-led 3-month yoga intervention on blood pressure of hypertensive patients: a randomised controlled multicentre trial in the primary care setting

6.1.1. Abstract

Background

Hypertension control remains a major challenge globally. A recent systematic review suggested that yoga has beneficial effects on reducing blood pressure. However, the role of yoga in hypertension management in primary health care has received little attention, and no studies have evaluated the impact of a yoga program fully delivered by health care staff on hypertension. This study, therefore, assessed the effects of a health worker-led yoga intervention on blood pressure reduction among hypertensive individuals patients in the primary care setting.

Methods

This was a multicentric, two-arm, randomised trial conducted among hypertensive patients in seven Ayurveda Health Centres in Nepal between March 2017 and June 2018. One hundred and twenty-one participants who were on or without medications were randomised to intervention (*n*=61) and wait-list control (*n*=60) groups using stratified block randomisation. Participants in the intervention arm received an intervention consisting of an initial five-day structured yoga training at the centres and then a further home-based practice of yoga for five days a week for the following 90 days. Both intervention and control groups also participated in a 2-hour health education session. The primary outcome of this trial was systolic blood pressure at 90-day follow-up. Data were analysed on an intention-to-treat basis using linear mixed-effects regression models.

Results

We included all 121 study participants (intervention/control=61/60) in the primary analysis (52.1% males; mean ± SD age = 47.8 ± 10.8 years). The difference in systolic blood pressure

between the intervention group and the control group was -7.66 mmHg (95% CI: -10.4, -4.93). For diastolic blood pressure, the difference was -3.86 mmHg (95% CI: -6.65, -1.06). No adverse events were reported by the participants.

Conclusions

A yoga program for hypertensive patients consisting of a five-day training in health centres and 90 days of practice at home is effective for reducing blood pressure. Significant benefits for hypertensive patients could be expected if such programmes would become a part of the standard treatment practice.

Trial registration

This trial was prospectively registered with the Clinical Trial Registry of India [CTRI/2017/02/007822] on 10/02/2017.

Ethics and dissemination

This study was approved by the Ethical Review Board of the Nepal Health Research Council Nepal (Ref No: 1185, 06 January 2017).

6.1.2. Background

Hypertension is a major public health problem globally affecting around 22% of the world's adult population in 2015 [1]. Together with the growing burden of hypertension, the prevalence of untreated and uncontrolled hypertension is also very high, particularly in low-and middle-income countries. Among all hypertensive individuals in low-and middle-income countries in 2010, 29.0% were treated, and only 7.7% had controlled blood pressure [2]. In Nepal, for example, more than half of those who are treated still have uncontrolled blood pressure [3-5].

Beyond medication, several non-pharmacological measures are available that can contribute to the effective management of hypertension. To reduce systolic blood pressure by 4-11 mmHg in hypertensive individuals, the new American College of Cardiology/American Heart Association guidelines recommend weight loss, "heart-healthy" diet, potassium supplementation, sodium reduction, increasing physical activity and limiting alcohol intake [6]. Using culturally accepted and evidence-based non-pharmacological measures alongside the medication may further achieve optimal control of high blood pressure in low resource primary care settings. Niu et al. [7] found that combining non-drug therapies with antihypertensive medications could further improve blood pressure reduction targets.

The use of yoga for controlling high blood pressure is an increasingly popular intervention [8-10]. It has shown positive effects not only on hypertension but also on a wide range of other health conditions [9, 11-14]. In the most recent systematic review of 49 clinical trials, Wu et al. [15] suggested that yoga is a viable antihypertensive lifestyle therapy. The findings showed that practising yoga at least three times a week is associated with a reduction in systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 10 mmHg and 6 mmHg, respectively [15]. Despite a large number of clinical trials on the effects of yoga on hypertension, there are relatively few studies conducted in primary care settings [16, 17], and none of them has involved existing health workers in implementing yoga programs. If yoga is to be used as an adjunct or primary initial lifestyle therapy to control hypertension in clinical settings, primary care facility-based yoga training led by clinical staff could be a feasible approach.

Given that the studies conducted in a real-world setting are more likely to be translated into practice and to minimize the gap between the evidence and practice [18, 19],

this study aimed to assess the effects of structured yoga practice on blood pressure reduction among hypertensive patients in primary healthcare facilities.

6.1.3. Methods

6.1.3.1. Trial design

This was a multicentric, two-arm, randomised, wait-list controlled, nonblinded trial comparing structured yoga practice (alongside health education) against health education only over three months. It was conducted among 121 hypertensive participants in seven Ayurveda Health centres (AHCs) in Nepal between March 2017 and June 2018. The study is reported using CONSORT and Intervention Description and Replication (TIDieR) guidelines.

6.1.3.2. Study participants

Study participants were first-stage hypertensive patients attending outpatient departments at the trial centres, who had high blood pressure (SBP of ≥140 mmHg and <160 mmHg or DBP of ≥85 mmHg and <100 mmHg) or had been taking antihypertensive medication with SBP of ≥130 mmHg and <160 mmHg or DBP of ≥85 mmHg and <100 mmHg based on clinical measurements on two occasions, 1-2 weeks apart. The criteria for participant selection were age (≥18 years and ≤ 70 years) irrespective of gender and medication history. Persons with diabetes, those with a known case of secondary hypertension and/or other cardiovascular diseases/conditions, pregnant women, and those who practised yoga for 30 days or more in the previous 6 months were excluded. The hypertensive patients at each AHC were screened for eligibility criteria. Once the patients agreed to enrol in the study by providing their written informed consent, their de-identified codes and study sites were shared to the statistician (recruited outside the author team) who performed randomisation. The statistician did not have access to any other data about the participants. We used the centrally generated stratified block randomisation list to allocate the participants in the intervention and wait-list control groups, with recruiting site as a stratifying variable. A total of 121 hypertensive participants were recruited and allocated to intervention (n = 61) and control (n = 60) groups using the above-mentioned randomisation method. As per the published intervention protocol, the target sample size for the trial was 140 participants [20]. However, we managed to recruit 121 participants during the study period (Supplementary table 11). This sample size was large enough to ensure statistical power of 80% in a regression analysis with 15 independent variables (for two-tailed alpha $p < 0.05$ of a regression coefficient), if the true

intervention effect in the population was of at least small to medium size ($f^2 < 0.07$) according to Cohen [21].

6.1.3.3. Study settings

The trial was conducted in purposively selected AHCs located in Dhading, Nuwakot, Kaski, Ramechap, Surkhet, Rolpa and Rupandehi districts. Ayurveda Health Centres (AHCs) are the primary care facilities functioning at the district level in Nepal. Currently, 61 District AHCs are in operation throughout Nepal and they provide basic preventive and curative services. One of the AHC's regular health promotion programs includes yoga training to school children and senior citizens, to promote health and wellbeing. Between 2015 and 2018, some of the health workers from AHCs were trained in yoga by the Department of Ayurveda and Alternative Medicines. Our study investigators who were also experienced yoga teachers provided training to the same health workers on the intervention package and appointed them as instructors to deliver yoga intervention to the study participants. The instructors were not certified yoga instructors, but they were trained in medical sciences, Ayurveda and yoga for three to six years. The instructors were also permanent public employees, and they agreed to implement the study without altering their usual work routines at the centres. Among the seven trial centres, AHCs located in Kaski, Nuwakot, and Surkhet were able to recruit the initially planned number of participants (n=20) during the study period [20], whereas AHCs from Dhading, Ramechap, Rupandehi, and Rolpa had fewer study participants (Supplementary table 11).

6.1.3.4. Intervention

6.1.3.4.1. Health centre based five-day training

The first component of the intervention was a five-day training delivered to the intervention group participants at the trial centres. The participants were invited to attend two-hour yoga training sessions every day for five consecutive days. The instructors (i.e. health care workers from each centre), delivered the yoga training. The wait-list control group participants received the training after the completion of the study.

6.1.3.4.2. Two hours of health education

In addition to the five-day yoga training session, the participants in the intervention group also received a two-hour health education session. The contents of health education were adopted from the Information, Education and Communication materials endorsed by the National Health Education Information and Communication Center, Ministry of Health and

Population, Nepal. The materials contained behavioural and lifestyle modification education targeted to hypertensive participants. The wait-list control group also took part in the health education session.

6.1.3.4.3. Home-based yoga practice

The intervention group participants were encouraged to practise yoga at home for 30 minutes per day on five days a week, for the following 90 days from the last day of the training. They were also instructed to visit their trial centres once every 30 days for health assessment and monitoring purposes. The instructors were available over the phone, if the participants needed any help in yoga postures and procedures. The participants were also provided with recorded yoga videos with exercise instructions they could follow if needed.

The yoga program consisted of postures, breathing exercise and meditation structured for 30 minutes of practice (Supplementary table 12). Stretching exercise, lateral arc pose and twist pose were included in the initial 9 minutes of the session. This was followed by breathing exercises for the next 9 minutes. The remaining 12 minutes were allocated for meditation and relaxation activities. Evidence suggested that postures (*Asana*) [22-25], breathing exercise (*Pranayam*) [23-26], relaxation [25, 27] and meditation [22, 23, 27] are effective for reducing hypertension while practising them in combination or individually. However, studies found the combination of posture, breathing excise and relaxation/meditation has a greater effect [15, 28]. The yoga session in the current study, therefore, used the combined approach.

The wait-list control group did not receive yoga intervention. They required to visit the trial centres once every 30 days for routine observation.

6.1.3.5. Outcomes

SBP at follow up was the primary outcome of the study. Baseline SBP was recorded just before the intervention started and follow-up SBP was measured at 90 ± 5 days counting from the last day of yoga training. We used an aneroid sphygmomanometer (BP AG1-20, Microlife Corp., Taiwan) to record the blood pressure at the Outpatients Department of each trial centre. We initially recorded three blood pressure readings from the participants in each five-minute interval and then averaged the last two readings to get the final measurement. Alongside SBP, we also measured DBP of every individual at baseline and follow-up.

6.1.3.6. Data collection

Data were collected by face-to-face interviews, anthropometric measurements and clinical examinations. Blood pressure, body height, body weight and resting heart rate were measured at baseline and follow up. Information on socio-demographic characteristics (age, gender, marital status, ethnicity, education, occupation and income), smoking, alcohol consumption, physical activity and the use of antihypertensive medication were collected before the intervention. We applied structured questionnaires to record socio-demographic characteristics, smoking and alcohol consumption related behaviours, and seven days history of physical activity as previously described in the protocol paper in detail [20]. We measured height and weight using portable stadiometers and digital weighing machines respectively. Radial pulse was taken in the sitting position. Participants were advised to report any change in smoking, alcohol consumption and the use of medications during the study period. The data were collected by the same researcher at baseline and follow-up. The outcome assessors were aware of intervention group allocation.

6.1.3.7. Data analysis

The collected data were compiled, edited and entered in Epidata 3.1. We used Stata 16.0 (StataCorp LLC, College Station, TX, USA) to analyse the data. The analysis was performed based on the intention-to-treat (ITT) analysis. To check the distribution of missing data, we created indicator variables for missing outcome variables and dichotomised them on the basis of missing and non-missing. Logistic regression was performed for each indicator variable to check whether missing outcome variables could be predicted by any other study variables. A separate t-test was conducted to check whether the auxiliary variables significantly varied by the missing status of the indicator variables, but none of them was associated with the missingness of data. We used Multiple Imputation by Chained Equations (MICE) model to create 10 imputed datasets (seed of 1234). The imputation included all the variables that were in the estimation model, except income and physical activity. Separate imputation models were built for SBP and DBP. The Fraction of Missing Information (FMI) and Relative Efficiency (RE) were 11.5% and 98.9% for the model with SBP and 6.5% and 99.4% for the model with DBP (Supplementary table 13).

Baseline characteristics are presented as absolute frequencies, percentages, medians, arithmetic means and standard deviations. We used mixed-effects linear regression with follow-up SBP and DBP as the outcome variable to analyse the intervention effect. We conducted three analyses (Models 1-3) with a dichotomous independent variable representing

belonging to the intervention group (“1”) or control group (“0”). The unstandardized regression coefficient (B) for this dichotomous variable represents the estimated effect of the intervention. In all three models, the trial centre was considered as a second-level variable, and it was allowed to have a random intercept. Other than that, Model 1 (main analysis) was adjusted for baseline outcome measurements (baseline SBP in the analysis with follow-up SBP as the outcome variable and baseline DBP in the analysis with follow-up DBP as the outcome variable). In Model 2, we additionally adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, baseline body mass index (BMI), baseline resting heart rate and antihypertensive medication. For adjusting BMI as a time-varying covariate, along with the variables from Model 2, we added ‘BMI difference’ (calculated as BMI difference=baseline BMI - follow-up BMI) in Model 3.

For sensitivity analysis, we did a complete-case analysis. We simultaneously conducted a mediation analysis to test whether BMI had a significant mediation effect on the outcome. We conducted subgroup analyses based on the level of adherence to the protocol from the trial centre while delivering the intervention. No per-protocol analysis was done, as data on intervention compliance were not available at the individual level. A visual inspection was done to examine whether there was any interaction between covariates and intervention effects, and their average marginal (partial) effects were plotted in the marginal plots. All tests were two-tailed and $p < 0.05$ was considered to indicate statistical significance.

6.1.3.8. Fidelity assessment of the trial

We conducted a post-intervention survey to retrospectively assess the fidelity of intervention. Fidelity assessment was performed in three domains: intervention delivery (i.e. whether the contents of the intervention were delivered in line with the protocol), intervention receipt (i.e. whether participants understood or learned intervention components) and intervention enactment (i.e. whether participants were able to perform home-based yoga practice as instructed) [29, 30]. For this purpose, information on the contents delivered during the five-day yoga training session was collected by a thorough review of the training documents, attendance sheets and log-books from each centre. The collected information was then used to calculate the actual score of content delivery using a checklist (Supplementary table 14). The checklist contains the names of 10 structured yoga items and 5 health education topics that were to be covered during the intervention. Covering each yoga item and health education topic was assigned one point, so the maximum total score was 15 points. If the trial

centre included any additional yoga items other than the ones specified in the protocol they were given a negative point. The level of agreement between the contents that were actually delivered and those that were supposed to be delivered was assessed using the percentage of agreement (PoA), expressed as the ratio of the actual score of the items and topics covered in the training session (numerator) and the total score of all yoga items and health education topics as per the protocol (denominator). The percentage was expected to be at least 90% for each centre [31].

Similarly, to assess whether the participants learned the proper yoga skills during the training sessions (i.e. intervention receipt) and applied the same skills while practising at home (i.e. intervention enactment), we interviewed randomly selected 20% of participants from the intervention group using a structured questionnaire. The participants were asked whether the training provided by the instructor was sufficient for them to learn yoga properly and whether they had practised yoga at home as instructed by the trainer (i.e. as per protocol). The responses were provided on a scale from 1 to 5, with 1 indicating low and 5 indicating high sufficiency of the training. The findings of the survey guided the sensitivity analysis.

6.1.3.9. Data and safety monitoring

A clinical doctor who led the data monitoring and quality assurance team monitored the implementation of the trial, including participant recruitment and intervention delivery. The doctor provided necessary feedback to the study team. He was also responsible for reviewing data safety and quality, and he was the first person to report missing information and errors during data collection.

Regarding participants' safety, participants were instructed to report any serious adverse events during the intervention to the researchers located in each district. These researchers together with the clinicians from their centres were responsible for reviewing and responding to any reported adverse event and for reporting it to the Principal Investigator and Ethical Review Board.5

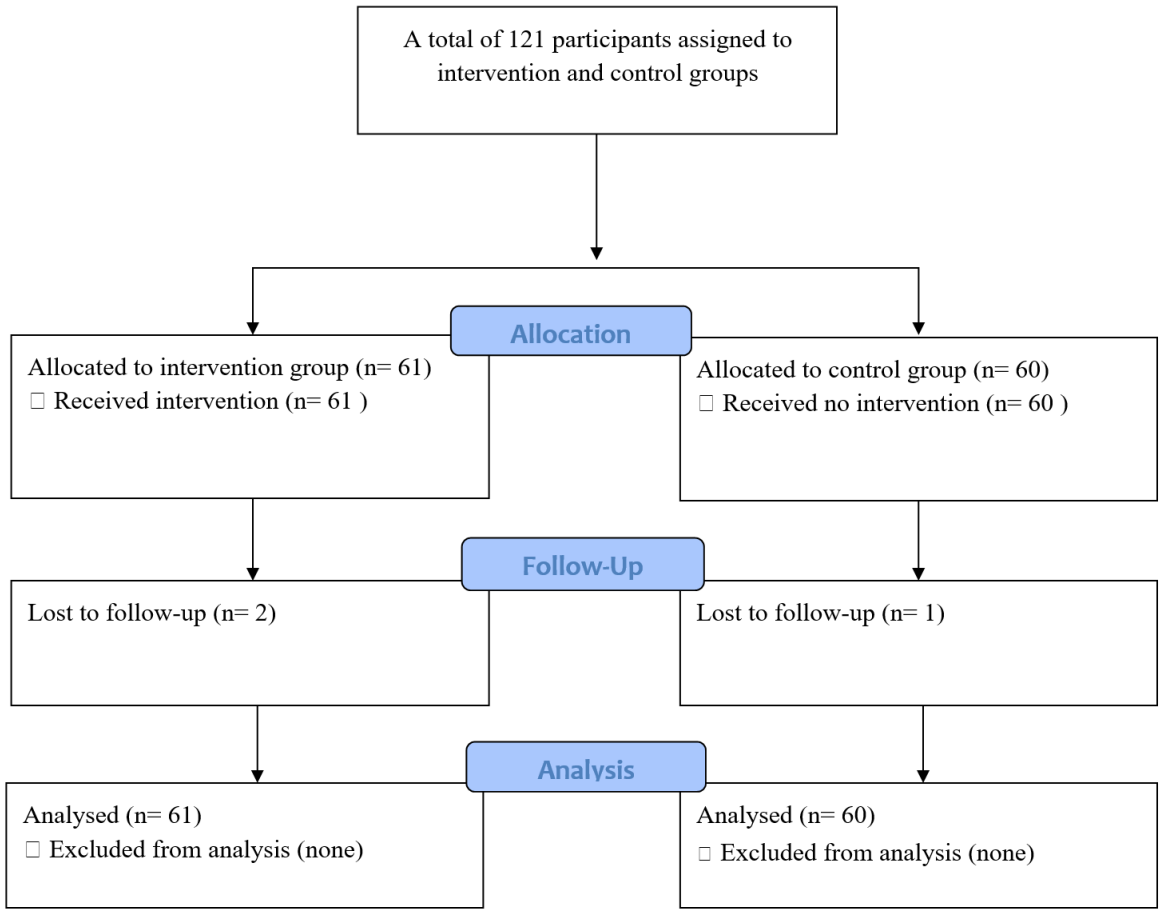
6.1.4. Results

6.1.4.1. Intervention effects

Data on the primary outcomes were available for a total of 118 participants (Fig 15). Three participants, two from intervention group (males) and one (female) from control group were lost to follow-up. None of the participants reported any changes in medication, tobacco use

and alcohol consumption during the study period. Participants also did not report experiencing any adverse events as a result of the intervention.

Figure 15. Participant flow diagram



Fifty-two percent of the participants were males. The mean (standard deviation [SD]) age of the participants was 47.7 (10.7) years. The median (interquartile range [IQR]) of years of formal education was 5 (11), where more than one third (35.5%) of participants had no formal schooling. Smoking and alcohol consumption were reported by 14.9% and 29.7% of participants, respectively (Table 11).

Table 11. Baseline characteristics of the participants

Characteristics		Intervention group	Control group
		n (%)* or mean (SD)† or median (IQR)‡	*n* (%)* or mean (SD)† or median (IQR)‡
Age (years)		47.1 (11.0)	48.4 (10.7)
Gender	Female	35 (57.4)	23 (38.3)
	Male	26 (42.6)	37 (61.6)

Marital status	Married	55 (90.2)	56 (93.3)
	Others (unmarried, widow)	6 (9.8)	4 (6.7)
Education (years)		5 (11)	6 (11.5)
Occupation	Paid job	15 (24.6)	9 (15.0)
	Self-employed	20 (32.8)	25 (41.7)
	Homemaker	24 (39.3)	16 (26.7)
	Others	2 (3.3)	10 (16.6)
Annual household income (Nepalese rupees)		300000 (400000)	200000 (325000)
Smoking	Yes	7 (11.5)	11 (18.3)
	No	54 (88.5)	49 (81.7)
Alcohol consumption	Yes	13 (21.3)	23 (38.3)
	No	48 (78.7)	37 (61.7)
Physical activity (MET-minutes/week)		1800 (2340)	1530 (2580)
Body mass index (kg/m^2)		27.3 (4.7)	27.5 (5.0)
Resting heart rate (beats per minute)		77.4 (5.1)	77.6 (6.1)
Systolic blood pressure (mmHg)		141. 7 (9.1)	136.9 (9.0)
Diastolic blood pressure (mmHg)		90.3 (5.4)	89.4 (5.1)
Antihypertensive medication	Yes	35 (57.4)	36 (60.0)
	No	26 (42.6)	24 (40.0)

* mean and standard deviation (SD) were shown for age, body mass index, resting heart rate, systolic blood pressure and diastolic blood pressure

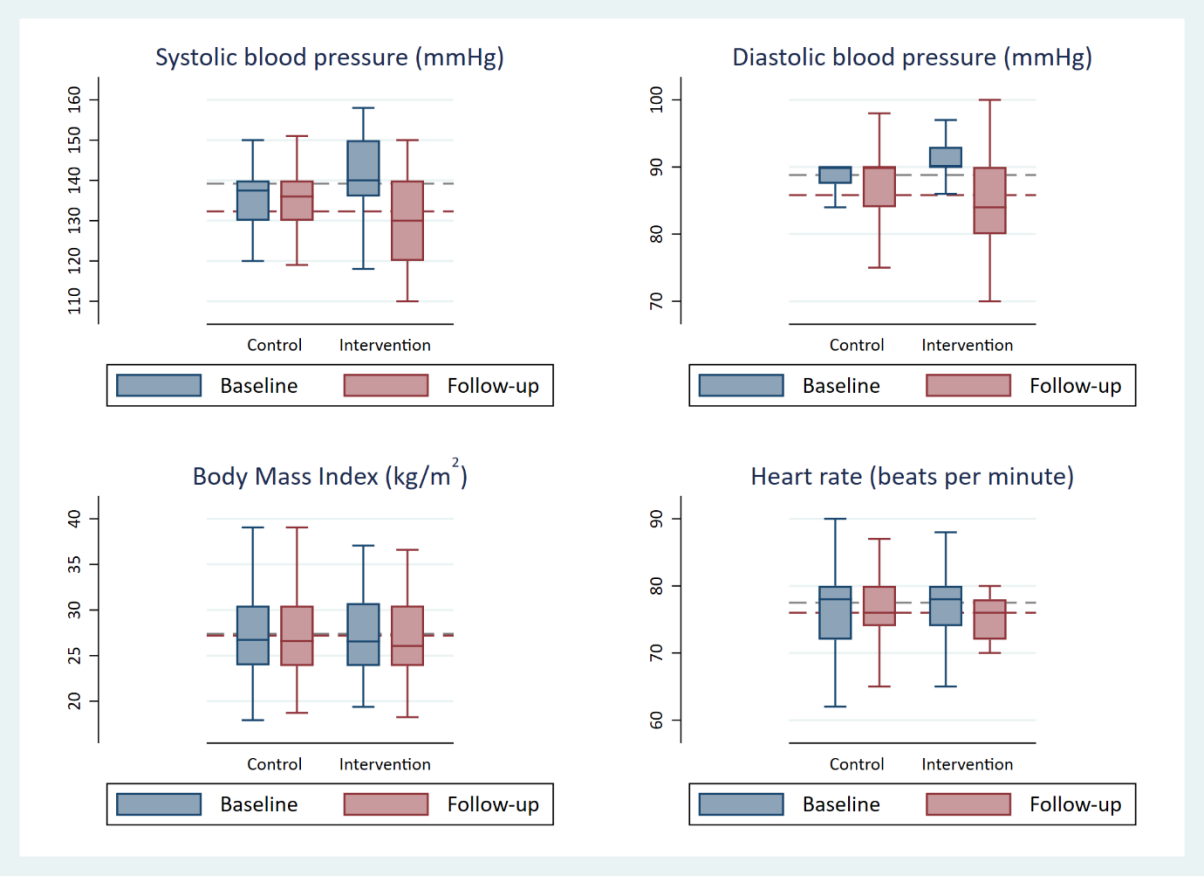
† number (*n*) and percentage (%) for gender, marital status, ethnicity, occupation, smoking, alcohol consumption and antihypertensive medication

‡ median and interquartile range (IQR) are given for education, annual household income and physical activity (moderate and vigorous activities)

The median (IQR) physical activity level expressed in MET-minutes per week was 1800 (2340) and 1530 (2580) for the intervention and control group respectively. The mean (SD) BMI was 27.4 (4.8) in kg/m^2. The mean (SD) of baseline SBP was 141.7 (9.1) mmHg in the intervention group and 136.9 (9.0) mmHg in the control group (Table 1). More than half (58.7%) of the participants were on antihypertensive medications.

At follow-up, the mean (SD) of SBP was 130.1 (9.3) mmHg and 134.6 (11.0) mmHg in intervention and control group, respectively. The mean of post-intervention DBP was 84.1(6.3) mmHg in the intervention group and 87.6 (7.0) mmHg in the control group (Fig 16).

Figure 16. Baseline and follow-up blood pressure, BMI and resting heart rate



Note: Grey dash line= Baseline mean; Maroon dash line= Follow-up mean.

The average reduction in SBP in the intervention and control group was 11.5 mmHg and 2.2 mmHg respectively (Table 12). The mean reduction in DBP in the intervention and control group was 6.1 mmHg and 1.9 mmHg. Compared to baseline BMI and resting heart rate, the follow-up BMI and resting heart rate in the intervention group decreased by 0.37 kg/m^2 (vs 0.7 kg/m^2 in control group) and 1.9 beats per minute (vs 1.2 beats per minute in control group), respectively.

Table 12. Changes in outcome variables from baseline to follow-up

Characteristics		Change in SBP*		Change in DBP†	
		Intervention group	Control group	Intervention group	Control group
		Mean	mean	mean	Mean
Total		11.5	2.3	6.1	1.8
Gender	Female	10.1	5.0	5.3	3.9
	Male	13.5	0.6	7.2	0.6

Marital status	Married	11.5	1.8	6.0	1.7
	Others (unmarried, widow)	10.8	8.3	7.0	3.8
Occupation	Paid job	11.0	-0.4	5.1	-0.6
	Self-employed	13.5	1.0	7.9	2.4
	Homemakers	9.7	7.1	5.3	4.7
	Others	16.5	0.5	5.0	-1.6
Smoking	No	11.3	1.9	5.9	2.0
	Yes	12.7	3.9	7.5	1.1
Alcohol consumption	No	11.3	3.4	5.9	2.8
	Yes	12.2	0.4	7.0	0.3
Antihypertensive Medication	No	14.0	2.0	7.3	1.0
	Yes	9.6	2.4	5.2	2.4

[*] systolic blood pressure; [†] diastolic blood pressure.

In the main analysis, being in the intervention group was associated with an average 7.66 mmHg (95% CI: 4.93, 10.4) greater reduction in SBP between baseline and follow-up, compared to the control group (Table 3: Model 1). After adjusting for age, gender, ethnicity, marital status, education, occupation, household income, smoking, alcohol consumption, physical activity, baseline body mass index, antihypertensive medication, baseline resting heart rate, and baseline SBP (Table 3: Model 2), being in the intervention group was associated with an average 7.41 mmHg (95% CI: 5.06, 9.76) greater reduction in SBP between baseline and follow-up, compared to the control group. In Model 3, the change in BMI from baseline to follow-up was significantly associated with SBP (B = -2.49 mmHg, 95% CI: -3.74, -1.20; Supplementary table 15). The unstandardized regression coefficient (B) representing the effect of the intervention in Model 3 was -6.36 (95% CI: -8.63, -4.10), again favouring the intervention group (Table 13). Detailed outputs of Model 2 and Model 3 are provided in Supplementary table 15 and Supplementary table 16.

Table 13. Intervention effects: results of multilevel mixed-effects linear regression

Outcome variable	Model 1[†]		Model 2[†‡]		Model 3[‡§]	
	B[§]	95% CI[‖]	B[§]	95% CI[‖]	B[§]	95% CI[‖]
Systolic blood pressure	-7.66[***]	-10.4, -4.93	-7.41[***]	-9.76, -5.06	-6.36[***]	-8.63, -4.10

Diastolic blood pressure	-3.86**	-6.65, -1.06	-3.49**	-6.13, -0.86	-2.73*	-5.06, -0.41

* Model included a dichotomous independent variable representing belonging to the intervention group ("1") or control group ("0") and trial centre as a second-level variable, and was adjusted for baseline systolic or diastolic blood pressure (depending on the outcome variable)
† Adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, body mass index (BMI), resting heart rate, and baseline systolic or diastolic blood pressure (depending on the outcome variable)
‡ Additionally adjusted for the difference in BMI between baseline and follow-up
§ Unstandardized regression coefficient
‖ 95% confidence interval for B
* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

The reduction in DBP between baseline and follow-up was 3.86 (95% CI: 1.06, 6.65) units higher for the intervention group, compared to the control group. In Model 2, we also found that being in the intervention group was associated with on average 3.49 mmHg (95% CI: 0.86, 6.13) greater reduction in DBP between baseline and follow-up, compared with being in the control group. The unstandardized regression coefficient (B) representing the effect of the intervention in Model 3 was -2.73 (95% CI: -5.06, -0.41), again favouring the intervention group (Supplementary table 16).

The regression coefficients in the complete-case, sensitivity analysis (using Model 1) were nearly the same as in the main analysis (-7.62 vs. -7.66 for SBP and -3.88 vs. -3.86 for DBP.). In mixed-effects mediation analyses, the mediating effects of the change in BMI from baseline to follow-up on the primary intervention outcomes were not significant.

The change in resting heart rate from baseline to follow-up was not significantly associated with SBD and DBP (Supplementary table 17 and Supplementary table 18). The marginal plots for gender, medication status, smoking and alcohol consumption by intervention allocation did not visually show any sign of interaction effect (Supplementary figure 1).

6.1.4.2. Findings from fidelity assessment

The PoA was 100% for five health centres and 90% for the two remaining centres. The difference in PoA between the health centres was not significantly associated with the primary intervention outcomes. The average score for intervention receipt was 4.3 out of five (the score provided by the participants in response to the question on whether the training was sufficient for them to learn yoga or not; Supplementary table 19). Similarly, 100% of the

participants reported they could perform home-based yoga practice in the same way as they were trained to do by the yoga instructor.

6.1.5. Discussion

In this multicentre randomised controlled trial, we found that a 3-month yoga intervention reduces systolic and diastolic blood pressure among hypertensive patients. This implies that yoga programmes can be promoted through primary care settings as an effective non-pharmacological therapy to treat hypertension.

Our findings are consistent with a recent systematic review that found an average reduction of SBP by 7.9 mmHg and DBP by 4.3 mmHg among the participants who received a yoga intervention including breathing techniques and meditation [15]. In another review, Cramer et al. found that yoga interventions lasting eight weeks or more, reduced SBP on average by −9.65 mmHg [32]. The pooled effect from the Cramer et al. meta-analysis may seem somewhat higher than the average effect found in our study. However, due to a relatively small pooled sample size and large heterogeneity between individual studies included in the meta-analysis, the confidence interval of the pooled effect from Cramer et al. [32] study was very wide, and it largely overlaps with our narrower confidence interval for the respective effect in our study. A smaller blood pressure-lowering effect in our study compared to the Cramer et al. [32] meta-analysis might be because of the attenuation of the intervention effect due to its implementation in a real-world clinical setting. Likewise, the implementation of yoga intervention in our study was done by health workers. It might be that the effect of yoga on blood pressure reduction would be higher, if the intervention was implemented by certified yoga instructors or kinesiologists.

Studies have investigated several possible underlying mechanisms for clinical effects of yoga on hypertension [33-35]. One of the hypothesized mechanisms is that yoga affects the autonomic nervous system by stimulating activity of parasympathetic and reducing activity of sympathetic nervous system [33]. It is also postulated that yoga increases bioavailability and blood levels of nitric oxide and promotes vasodilation [33]. Additionally, participation in yoga as a “mind-body” activity has been associated with improved physiological markers, reduced symptoms of stress, and better mood [36, 37]. Pascoe et al. [36] in their systematic review concluded that mindfulness-based activities, including yoga, lead to decreased cortisol level, a stress hormone that has been linked to high blood pressure.

Thoroughly investigating the mechanism of the effect of yoga on blood pressure was beyond the scope of this study. Nevertheless, we considered the possible mediating effect of the change in BMI and resting heart rate between baseline and follow-up, and we found no strong indication either of these would constitute the underlying mechanism. Given that yoga is a complex activity, it might be challenging to determine a single mechanism that would explain antihypertensive effects of all components of yoga. Therefore, to illuminate the underlying causal pathways, future studies will need to assess in detail different physiological, biomedical and stress biomarkers in relation to specific yoga components

The main strength of the current study was that the intervention was evaluated in a real-world clinical setting. The number of such studies is generally limited. Moreover, to the best of our knowledge, this was the first study that investigated the effects of a primary health care staff-led yoga intervention on high blood pressure among the patients attending public health centres in a low-income country. One of the benefits of conducting the trial in a real-world setting is that the study could have good external validity and it could enhance the likelihood that it is translated into practice [18, 19]. The current study has the potential to be scaled up nationwide in Nepal, as the remaining AHCs are also equipped with both physical and human resources to implement yoga intervention. The situation is likely to be similar in many other low-and middle-income countries. In Nepal, the national policy and mechanisms of using yoga as a health promotion tool are also already in place. The Multisectoral Action Plan for Prevention and Control of NCDs (2014-2020) and Urban Health Policy (2015) integrated yoga as a strategy for non-communicable diseases prevention and control. Similarly, the Department of Ayurveda and Alternative Medicines have launched yoga-based interventions such as '*Swatha Jiwan karyakram'*(informal translation: Healthy Life Program) and '*Vidhaylaya yoga shiskya karyakram'* (informal translation: School Yoga Education Program) in 75 districts of Nepal to promote health and wellbeing of elderly and school children. The current intervention could also be an economically viable approach, as it can utilize existing resources and can also be integrated into the ongoing program that has similar modalities, such as '*Swatha Jiwan karyakram'*. However, further studies are required to test the cost-effectiveness of upscaling the program. Furthermore, the current study also had well-structured intervention packages comprising different components of yoga, including postures, breathing exercises, relaxation and meditation. Previous evidence showed that these components in combination were likely to have a better positive impact on health than individual components [15, 28]. Likewise, the session timing (i.e. 30 minutes) and frequency

(i.e. five sessions per week) were selected to be in line with the World Health Organization physical activity guidelines (i.e. 150 or more minutes a week of moderate-to-vigorous physical activity). This study had a shorter session timing compared to previous studies in which the average session time was 59.2 minutes [15]. This might have positively affected participant compliance. Lastly, as this trial was conducted in several centres, representing large geographical areas of Nepal, the findings could be generalized beyond the trial participants and centres.

The current study has some limitations. Firstly, hypertension was diagnosed based on blood pressure measured on two occasions only that were 1-2 weeks apart. Although most participants were previously diagnosed hypertensive patients, it might be that we misclassified some of the newly diagnosed participants. We did not manage to collect information on r adherence to the study protocol from all participants. Evidence shows that the effect of yoga may vary depending on the frequency and duration of yoga practice [15]. Future studies on the effects of yoga on blood pressure should aim to collect such data, to enable conducting per-protocol analysis. Furthermore, the post-intervention blood pressure measurements were not done on the same day for all participants, as this was not feasible. It was measured between the 85^{th} and the 95^{th} day of the intervention, as not all participants were available for the follow-up measurement on the 90^{th} day. Besides, the variation in the level of yoga competency of the health workers who provided training to the participants might have also influenced the study outcomes. Likewise, the pre and post-intervention data were collected by the same people and they used aneroid blood pressure machines to assess blood pressure. This might have introduced rater bias. We did not assess long-term effects of the intervention. It might be that the intervention would not be as efficient and sustainable over a longer period, as participant compliance to the protocol would likely reduce over time. Lastly, as the study included only first-stage hypertensive patients, study findings cannot be generalised to patients with higher stages of hypertension.

6.1.6. Conclusions

A simple, 3-month yoga intervention delivered by health workers in primary care centres and coupled with home-based practice is effective in lowering high blood pressure among hypertensive patients. Given that the study was conducted in real-world clinical settings, our

findings suggest the intervention strategy should be considered as adjuvant or initial lifestyle therapy for hypertension in primary care.

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DECLARATION OF CO-AUTHORSHIP AND CO-CONTRIBUTION: PAPERS INCORPORATED IN THESIS

This declaration is to be completed for each conjointly authored publication and placed at the beginning of the thesis chapter in which the publication appears.

1. PUBLICATION DETAILS (to be completed by the candidate)

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Institute: Institute for Health and Sport Candidate's Contribution (%): 75%

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2. CANDIDATE DECLARATION

I declare that the publication above meets the requirements to be included in the thesis as outlined in the HDR Policy and related Procedures – policy.vu.edu.au.

[redacted] 08/12/2021

Signature **Date**

3. CO-AUTHOR(S) DECLARATION

In the case of the above publication, the following authors contributed to the work as follows:

The undersigned certify that:

1. They meet criteria for authorship in that they have participated in the conception, execution or interpretation of at least that part of the publication in their field of expertise;
2. They take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

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3. There are no other authors of the publication according to these criteria;
4. Potential conflicts of interest have been disclosed to a) granting bodies, b) the editor or publisher of journals or other publications, and c) the head of the responsible academic unit; and
5. The original data will be held for at least five years from the date indicated below and is stored at the following **location**(s):

The datasets generated during and/or analysed during the current study will be stored in Victoria University Research Repository (https://vuir.vu.edu.au/)

Name(s) of Co-Author(s)	Contribution (%)	Nature of Contribution	Signature	Date
Shiva Ram Khatiwoda	5%	Implementation of study, data analysis, and manuscript development	[redacted]	08 Dec 2021
Yadav Gurung	5%	Data analysis, and manuscript development		07 Dec 2021
Zeljko Pedisic	10%	Interpretation of findings and manuscript development		12 Dec 2021
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6.2. Study 5. Yoga for hypertensive patients: a study on barriers and facilitators of its implementation in primary care

6.2.1. Abstract

Background

International guidelines for hypertension treatment recommend the use of yoga, particularly among low-risk patients. However, evidence is lacking on the implementation potential of health-worker-led yoga interventions in low-resource, primary care settings.

Objective

To assess barriers to and facilitators of the implementation of a yoga intervention for hypertensive patients in primary care in Nepal.

Methods

The study was conducted using focus group discussions, in-depth interviews, key informant interviews, and telephone interviews. Data were collected from the 'Yoga and Hypertension'(YoH) trial participants, YoH intervention implementers, and officials from the Ministry of Health and Population in Nepal.

Results

Most YoH trial participants stated that: (1) it was easy to learn yoga during a five-day training period and practise it for three months at home; (2) practising yoga improved their health; and (3) group yoga sessions in a community centre would help them practise yoga more regularly. Most YoH intervention implementers stated that: (1) they were highly motivated to implement the intervention; (2) the cost of implementation was acceptable; (3) they did not need additional staff to effectively implement the intervention; (4) providing remuneration to the staff involved in the intervention would increase their motivation; and (5)

the yoga programme was '*simple and easy to follow*' and '*easily performed by participants of any age*'. The government officials stated that: (1) yoga is considered as a key health promotional activity in Nepal; and (2) the integration of the yoga intervention into the existing health care programme would not be too challenging, because the existing personnel and other resources can be utilised.

Conclusions

While there is a good potential that a yoga intervention can be implemented in primary care, capacity development for health workers and the involvement of community yoga centres in the delivery of the interventions may be required to facilitate this implementation.

6.2.2. Introduction

Yoga is a lifestyle therapy that is commonly used globally to improve physical and mental health. It encompasses different forms of practice, whereby the most widely used one commonly includes postures, breathing, and meditation exercises [38]. Results of a recent meta-analysis indicate that yoga is a promising antihypertensive lifestyle therapy that reduces systolic blood pressure and diastolic blood pressure in hypertensive individuals on average by 10 mmHg and 6 mmHg, respectively [15]. The blood pressure reduction seems to be greater among those who practise all three components of yoga combined more than three times per week as compared with those who practise only one component of yoga [15]. Similarly, the health benefit is greater following 12 weeks of yoga practice as compared with a shorter intervention period [39].

Most of the evidence on yoga and hypertension has emerged from a few countries. Wu et al. [15] found that, out of 56 yoga interventions for blood pressure reduction conducted between 1983 and 2018, 42.9% (n = 24) were from India, 16.1% (n = 9) were from South Korea, and 41.1% (n = 23) were from non-Asian countries such as Australia, the UK, and the US. A few studies are also available from China, Cuba, Jamaica, Japan, Sweden, and Thailand [39]. More studies from other countries are needed on the topic. This recommendation is in accordance with the United Nations declaration [40] that emphasises the importance of improving national capacities for dealing with non-communicable diseasesin low- and middle-income countries, such as Nepal. Findings on the effectiveness and implementation potential of yoga interventions in the primary care setting in Nepal may partially be generalised to other low- and lower-middle income countries with similar low-resource, primary care settings.

Many of the previous trials were conducted in healthy or normotensive populations [25, 41-49], recruited participants from the workplace [44, 46, 50] or academic settings [43, 45], and used the respective centres [43-46, 49, 51] or separate yoga studios [52-54] for the intervention. However, little evidence is available to demonstrate the impact of health-worker-led yoga interventions on blood pressure reduction in low-resource, primary care settings.

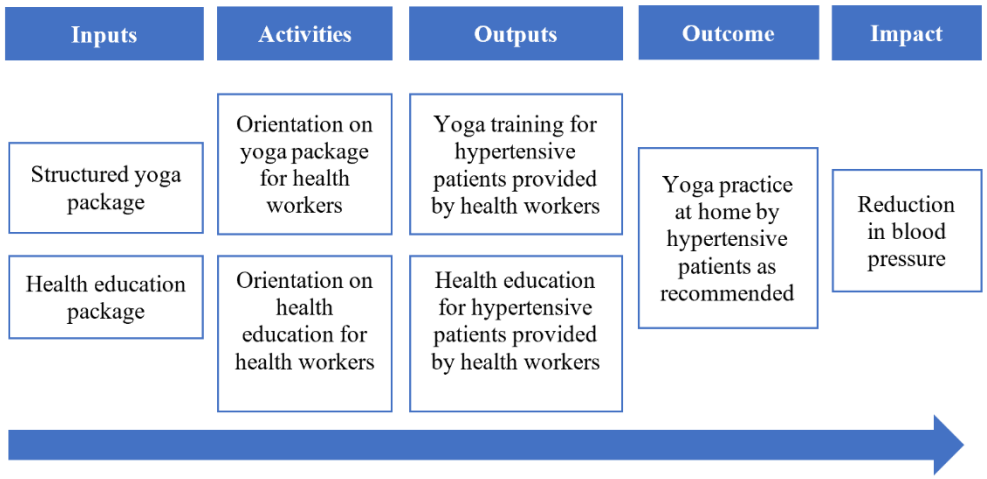
An intervention tested under ideal clinical trial conditions may fail to show the same effect(s) when implemented in real-world settings due to the dilution of effects and barriers

associated with the implementation of the intervention [55]. The quality of the implementations of the interventions in real-world clinical settings is likely to be affected by various factors related to the implementation process, external environments, internal settings related to the implementing organisation, the stakeholders' perspectives towards the intervention, policy priorities, and the level of acceptability of the intervention [56, 57]. For example, a high acceptability of the intervention may positively affect the adherence to the treatment and, therefore, improve the outcomes of the intervention [58]. Likewise, high costs associated with an intervention may impede its implementation as well as its sustained delivery [59, 60]. Therefore, having a good understanding of the factors that can influence the implementation of an intervention may improve the interpretation of its effectiveness [61]. It may be helpful when informing the relevant stakeholders and maximising the effectiveness when scaling up the intervention.

Between 2017 and 2018, a clinical trial entitled "Impact of a structured yoga program on blood pressure reduction among hypertensive patients" (YoH) was conducted in seven Ayurveda Health Centres in Nepal [20]. This trial was carried out to test whether a health-worker-led yoga intervention implemented in the clinical practice setting could effectively reduce blood pressure in hypertensive patients. One hundred and twenty-one participants were randomised to the intervention (n = 61) and control (n = 60) groups. The intervention group received an intervention consisting of an initial five-day structured yoga training at the centres, followed by home-based practice of yoga (yoga postures for nine minutes, breathing exercise for nine minutes, and meditation and relaxation for twelve minutes) for five days a week over a period of 90 days (Fig 17). The study found that, after the intervention, the mean differences in systolic blood pressure and diastolic blood pressure between the intervention group and the control group were −7.66 mmHg and −3.86 mmHg, respectively [62].

The aim of this study was to investigate barriers to and facilitators of the implementation of the yoga intervention for blood pressure reduction among hypertensive patients in the primary care setting in Nepal.

Figure 17. Logical framework of YoH trial



6.2.3. Methods

6.2.3.1. Study design and theoretical framework

From 2019 to 2020, we conducted focus group discussions, in-depth interviews, key informant interviews, and telephone interviews to collect qualitative and quantitative data from the YoH trial intervention group participants, YoH intervention implementers, and officials from the Ministry of Health and Population in Nepal. To report the qualitative component of the study, we applied the COnsolidated criteria for REporting Qualitative research (COREQ) checklist [63]. We used the Consolidated Framework for Implementation Research (CFIR) [56] and the Theoretical Framework of Acceptability (TFA) [57] to guide the collection, analysis, and interpretation of the qualitative data. The basic structure of the CFIR encompasses an interactive interplay between the intervention contents, context, and process of implementation. To gain a more comprehensive insight into the factors influencing implementation, the CFIR model was supplemented using TFA constructs (Fig 9). The TFA consists of seven constructs, including affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy.

6.2.3.2. Study setting

This study used data from the seven Ayurveda Health Centres where the original YoH trial was conducted. For the purpose of the current study, we collected additional data from six of the health centres located in Dhading, Kaski, Nuwakot, Ramechap, Rolpa, and Surkhet. These centres provide various preventive, promotive, and curative primary care services for

people. The school yoga health programme, for example, is one programme that is delivered as a routine health promotion activity.

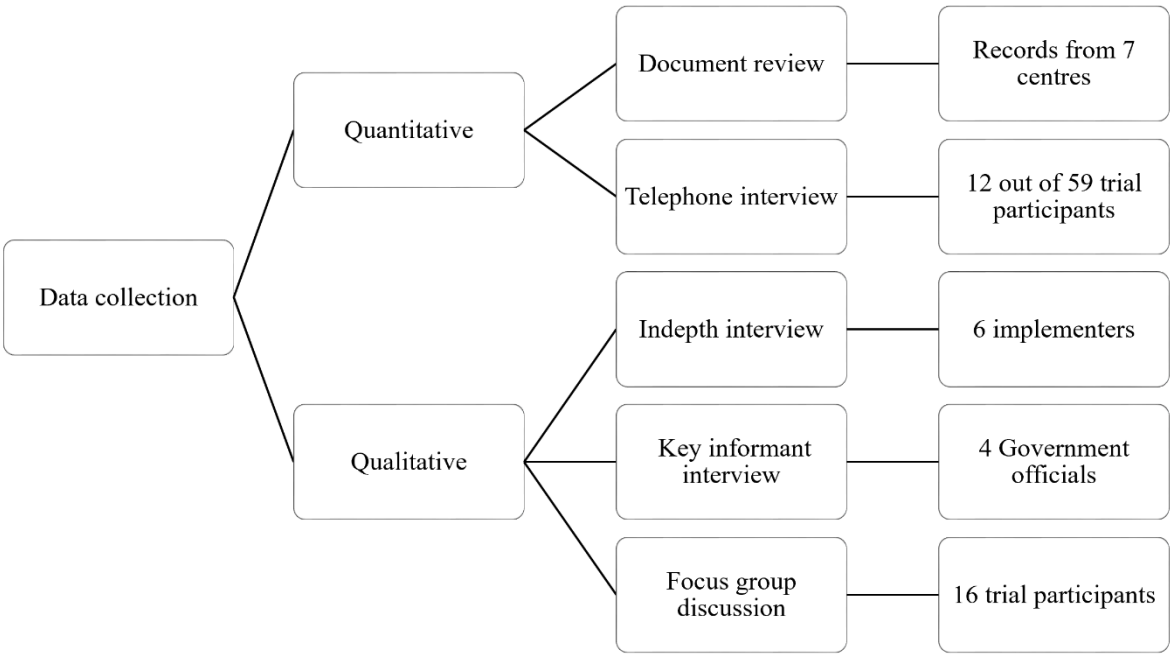
6.2.3.3. Study participants

Data were collected from key stakeholders in the YoH trial, including the intervention group trial participants and the trial implementers (i.e. medical officers). To identify the government's position on the use of yoga-related programmes in primary care settings, we also invited key officials from the Ministry of Health and Population and the Department of Ayurveda and Alternative Medicine to participate in the study.

6.2.3.4. Data collection

We collected qualitative data by carrying out focus group discussions, in-depth interviews, and key informant interviews, while quantitative data were collected by telephone interviews and by reviewing the YoH trial documentation (Fig 18). The data collection tools were initially developed in English by one author (RRD) and reviewed independently by two other authors (MdC and ZP). The data collection tools were then translated into Nepali by a certified translator. We conducted a pilot focus group discussion and an interview to pre-test the tool. The information collected during the pilot test was used to revise the tool prior to the study.

Figure 18. Data collection methods



6.2.3.4.1. Focus group discussions

Three focus group discussions were carried out, one in each of three randomly selected health centres in which the YoH trial was implemented. A total of 16 participants (six from the first trial centre, six from the second trial centre, and four from the third trial centre), who were originally in the intervention group of the YoH trial, were involved in the focus group discussions. We used a semi-structured interview guide to collect information about the participants' perspectives and experiences regarding the yoga intervention.

6.2.3.4.2. In-depth interviews

In-depth interviews were conducted to explore the implementers' perspectives and experiences regarding the implementation of the YoH trial. The implementers were health workers who recruited and monitored the trial participants and delivered the intervention. We also invited six medical officers who implemented the intervention in their trial centre to the interview.

6.2.3.4.3. Key informant interviews

We conducted four key informant interviews with leading officials from the Ministry of Health and Population. We asked them about: a) the government policy on implementing yoga for health promotion; and b) the likelihood that a yoga intervention can be scaled-up in the primary health care.

6.2.3.4.4. Telephone interviews

We conducted telephone interviews with twelve randomly selected individuals who were members of the intervention group in the YoH trial. The participants in the subsample were of similar age as the participants in the YoH study intervention group. However, the distributions of gender, historical "caste" groups, and occupation categories differed between the samples (Supplementary table 20). We used a structured questionnaire to gain an insight into yoga skills that participants acquired during the training sessions (treatment receipt) [64] and how they applied these skills while practising yoga at home (treatment enactment) [64].

6.2.3.4.5. Examination of records from the YoH trial

Data on the inner context of health centres and characteristics of the people who implemented the intervention were also extracted from the records of the YoH trial.

6.2.3.5. Data management and analysis

Focus group discussions and interviews were conducted in a closed room, without any potential distractions from bystanders, at the study sites. Two trained researchers (RRD and SK) were involved in interviewing, recording, note-keeping, and transcribing the interview records. The transcripts were translated into English and imported into NVivo 12 (QSR International Pty Ltd, Melbourne, Australia) for further analysis. We used the five domains of CFIR and five domains of TFA as themes for the template analysis [65]. One of the two researchers (RRD) then generated the first coding template by thoroughly reading and considering each statement in the two transcripts; one was from focus group discussion and the other, from in-depth interview. Detailed information about the themes and codes is available in Supplementary table 21. Two other researchers (ZP and MdC) independently reviewed the codes and revised the first template. Field notes and analytic memos were used to interpret the findings. At the end of the process, as a means of validation, two authors (SK and YG) independently rechecked the final template and the underlying codes.

In addition, one author developed an analytic-summary cross table that contained contextual issues and included seven thematic areas in its rows and two intervention components in its columns. The factors were determined and labelled as barriers or facilitators based on their potential negative or positive influence on the implementation of the intervention. Quality checks were performed independently by an external reviewer who, for this purpose, reviewed the codes and coding results.

The quantitative data were presented as absolute frequencies and percentages of the participant responses across different categories. The analysis of quantitative data was performed using the IBM Statistical Package for the Social Sciences (SPSS) software, version 27 (SPSS Inc., an IBM Company, Chicago, IL, USA).

6.2.4. Results

6.2.4.1. Participant characteristics

Of the 16 focus group discussion participants, the majority were females (Table 14). Half of the participants from the focus group discussion had either attended primary school or not had any formal education and were homemakers, whereas all of the in-depth interview participants and key informants had a postgraduate degree and were government employees.

Table 14. Participant characteristics

Characteristics		FGD	IDI	KII	Telephone interview
		n (%)	*n* (%)	*n* (%)	*n* (%)
Age	30–40 years	3 (18.8)	5 (83.3)	1 (25.0)	3 (25.0)
	40–50 years	6 (37.5)	1 (16.7)	3 (75.0)	3 (25.0)
	50 years and older	7 (43.7)	0 (0)	0 (0.0)	6 (50.0)
Sex	Female	10 (62.5)	3 (50.0)	1 (25.0)	8 (66.7)
	Male	6 (37.5)	3 (50.0)	3 (75.0)	4 (33.3)
Education	No formal education	5 (31.3)	0 (0)	0 (0)	7 (58.3)
	Primary	3 (18.8)	0 (0)	0 (0)	0 (0)
	Secondary	6 (37.5)	0 (0)	0 (0)	3 (25. 1)
	Bachelor	1 (6. 2)	0 (0)	0 (0)	1 (8.3)
	Post-graduate	1 (6.2)	6 (100.0)	4 (100.0)	1 (8.3)
Occupation	Employed	7 (43.7)	6 (100.0)	4 (100.0)	5 (41.7)
	Homemaker	8 (50.0)	0 (0)	0 (0)	7 (58.3)
	Retired	1 (6.3)	0 (0)	0 (0)	0 (0)

Note: FGD, focus group discussion; IDI, in-depth interview; KII, key informant interview

6.2.4.2. General findings from the qualitative component of the study

Factors that are likely to influence the implementation of the yoga intervention were grouped into seven principal themes, namely, the (1) acceptability of the intervention among participants, (2) characteristics of the intervention, (3) external context, (4) inner context of health centres, (5) characteristics of implementers, (6) implementation process, and (7) sustainability of the intervention (Fig 19).

Figure 19. Factors influencing the implementation of yoga intervention in the primary care setting

1. **Acceptability of the intervention among participants**
   - 1.1. Attitudes towards the intervention
   - 1.2. Perceived effectiveness of the intervention
   - 1.3. Participant burden
   - 1.4. Opportunity cost
2. **Characteristics of the intervention**
   - 2.1. Complexity of the intervention
   - 2.2. Cost of implementation
   - 2.3. Adaptability of the intervention
3. **External context**
   - 3.1. Policy priority
   - 3.2. Demand for yoga in the community
4. **Inner context of health centres**
   - 4.1. Leadership engagement
   - 4.2. Personnel resources
   - 4.3. Physical space (yoga studio)
   - 4.4. Experience in implementing yoga programmes
5. **Characteristics of implementers**
   - 5.1. Knowledge and skills of yoga
   - 5.2. Motivation
6. **Implementation process**
   - 6.1. Intervention delivery
   - 6.2. Intervention receipt
   - 6.3. Intervention enactment and adherence to home-based yoga practice
7. **Sustainability of the intervention**
   - 7.1. Sustained practice of yoga intervention
   - 7.2. Institutionalising the use of yoga intervention

The findings across the seven thematic areas are summarized in Table 15 as barriers (n = 5) to or facilitators (n = 21) of the implementation of the yoga intervention.

Table 15. Barriers and facilitators of effective implementation of yoga intervention

Barriers and facilitators	Intervention components	
	Five-day, health-centre-based yoga training	Home-based yoga practice
Attitude towards yoga intervention		
Positive attitude towards intervention	+	+
Burden		
Short duration of a single yoga session (30 minutes)	+	+

Barriers and facilitators	Intervention components	
	Five-day, health-centre-based yoga training	Home-based yoga practice
Weekly frequency of home-based yoga sessions and overall duration of the intervention (5 days a week for 90 days)		-
Opportunity cost		
Competing priorities (e.g. household work)		-
Perceived effectiveness		
Belief that yoga has a positive health impact	+	+
Prioritising "instant relief" types of treatment	-	-
Intervention characteristics		
Brevity and simplicity of the yoga programme	+	+
Low cost of implementation	+	+
Adaptability in regard to the mode of intervention delivery and time schedule (i.e. participants are free to practise yoga at home at any time of the day)	+	+
External context		
High priority of yoga in the government policy	+	+
High demand in the community	+	+
Low awareness of yoga as a health-promotion activity in rural communities	-	-
Health-centre-related		
Active participation of the health centre leadership in the implementation of the intervention	+	+
Existing personnel resources	+	+
Other available resources	+	+
Previous experience in implementing yoga programmes	+	+
Dedicated staff for yoga	+	+
High priority given to yoga	+	+
Implementer characteristics		
Good knowledge	+	+
High skills	+	+
High motivation (among lead implementers)	+	+
Low motivation (among supporting staff) due to a lack of financial incentive	-	-
Implementation process		
Delivery of the intervention according to its protocol	+	+
Ability of participant to perform yoga	+	+
Sustainability of the intervention		
Sustained practice of yoga	+	+
Institutionalising the use of yoga intervention	+	+

Note: "+" sign denotes a facilitator; "-" sign denotes a barrier

6.2.4.2.1. Acceptability of trial

6.2.4.2.1.1 *Attitude towards yoga intervention*

The intervention participants showed a positive attitude towards the yoga intervention in general, yoga training they received in the health care centres, yoga instructors, and yoga home-based practice. They were happy to be involved in the intervention. They considered yoga to be a healthy lifestyle intervention and considered it as highly important in their daily routines. They believed that by practising yoga, one could help prevent various chronic diseases. Most participants were also satisfied with the training they received from the trial centre. They preferred group-based training, as they thought practising yoga in a group is more interactive and fun than practising alone. They liked practising relaxing or meditating postures the most. They said that practising *Savasana* [Dead body pose] and *Yoganidra* [Yogic sleep] made them feel happy and relaxed. The majority of them also believed that 30 minutes was the optimal duration of yoga sessions for them. Few participants mentioned that they would rather have had shorter practice sessions.

6.2.4.2.1.2 Perceived effectiveness of the intervention

Almost all intervention participants said that they experienced improvements in their health after doing yoga. The commonly perceived improvements were: *blood pressure reduction*; *feeling calm, light, fresh, relaxed, and well; having a good appetite; anger reduction; and reduced pain, stiffness, and discomfort in muscles and joints*. The participants who had a positive attitude towards the intervention reported more benefits than others.

6.2.4.2.1.3 Participant burden

Some yoga intervention participants perceived attending yoga training at the health centre for five days as a time-consuming and burdensome task. They also reported that engaging in the same yoga programme every day was tiring. Intervention participants also mentioned that the schedule for home-based yoga practice overlapped with their household and business activities and that they sometimes needed to appoint someone to take over their duties while they practised yoga.

6.2.4.2.1.4 Opportunity cost

None of the intervention participants explicitly mentioned opportunity costs incurred in the YoH trial. However, some of the YoH trial implementers thought that three months of follow-up might have been too long for them. They said it was difficult to track patients for

three months and expressed concerns about the costs associated with the additional staff time needed to monitor the home-based yoga practice over such a long period.

6.2.4.2.2. Intervention characteristics

6.2.4.2.2.1 Complexity of the intervention

When responding to the questions about the complexity of the intervention, most YoH trial implementers stated that the yoga programme was '*well-structured'* (in-depth interview participant 1 [IDI-1]), '*simple and easy to follow*' (IDI-5), '*without too many and too complicated postures*' (IDI-2), and '*easily performed by participants of any age*' (IDI-3). The intervention participants generally considered the intervention package to be '*easy*' to practise, and they felt '*comfortable*' while doing it.

6.2.4.2.2.2 Adaptability of the intervention

Some implementers suggested that the yoga programme should be made more adaptable, as they noticed that some of the young intervention participants requested more strenuous yoga activities than the relaxing ones. The implementers said they could not fulfil the request, because they followed the strict intervention protocol.

Some implementers also reported that the trial participants who lived near the trial centres wished to engage in the yoga training under their supervision at the health centre for longer than just five days. The implementers could not fulfil the request, because they had to follow the intervention protocol.

6.2.4.2.2.3 Cost of implementation

Implementers of the intervention said that the cost of implementation was acceptable. They said there were '*no major expenses'* (IDI-1) other than the '*cost of printing [protocol, training manual] and papers'* (IDI-2), which was easily covered from the '*internal/organisational funds*' (IDI-3). They mentioned that all supporting staff agreed to work voluntarily, which otherwise would have been challenging to manage from the available funds. However, most of the implementers mentioned that paying the supporting staff in the intervention by the hour motivated them even more strongly to implement the intervention (more details about this provided in the section entitled "Characteristics of Implementers / Motivation").

6.2.4.2.3. External environment and context

6.2.4.2.3.1 Policy priority

The government officials unanimously agreed that yoga is considered to be a key health promotional activity in Nepal and that several yoga-related programmes have been implemented in Ayurveda Health Centres. They also stated that, alongside the Ministry of Health and Population, other ministries such as the Ministry of Education and the Provincial Government had also assigned due priority to yoga and supported the inclusion of yoga-related activities in the school health programmes.

A few implementers thought otherwise and argued that the local government was not assigning due importance to yoga programmes.

> '*They [government] do not give as much priority [to yoga] as they give to other programmes like immunization and reproductive health programmes*.' (IDI-2)

6.2.4.2.3.2 Demand for yoga intervention in the community

The intervention participants generally thought that a high demand for yoga programmes existed among the hypertensive individuals in the community. They said that some of their hypertensive friends and acquaintances had expressed interest in taking part in the intervention. Most of the government official and implementers of the intervention also agreed that more and more people in the community seem to be interested in doing yoga. Some intervention participants also suggested that yoga interventions should be offered as part of the routine health care, so that the wider hypertensive community can reap the benefits they gained during the intervention.

An implementer of intervention from Rolpa, a relatively remote, rural place in Nepal, however, had a different opinion. This implementer thought that the people from Rolpa were not clearly aware of the benefits of yoga and said that these people wanted instant relief for their ailments instead.

A government officer expressed the same opinion by stating that people in remote areas have a relatively low health literacy and need to prioritise maintaining the security of their livelihoods.

'*Usually, yoga is advised to be practised in the morning. In rural areas, women often take care of family and livestock. They often cook [for the family], cut hay for cattle, and collect firewood and water.*' (KII-1)

One focus group participant from a rural area also expressed their concern regarding the competing priorities and said:

'*I had to do a lot of household work. I had to look after children. I sometimes could not follow the routine of [yoga] practice at home*.'

6.2.4.2.4. Inner contexts and setting of trial centres

6.2.4.2.4.1 Leadership engagement

All implementers of the intervention who were also in charge of their health centres stated that they were actively involved in planning and implementing the intervention (Table 16). They also provided yoga training to the intervention participants, mobilised the supporting staff to coordinate recruitment, organised the training sessions, and monitored the participants.

Table 16. Characteristics of health centres that implemented the yoga intervention

Centre	Leadership engagement[†]	Personnel resources (Instructors) [‡]	Yoga studio[§]	Experience in implementing yoga programme[‖]
Dhading	Yes	health assistant and medical officer	Yes	Yes
Kaski	Yes	medical officer	Yes	Yes
Nuwakot	Yes	health assistant	No	Yes
Ramechap	Yes	medical officer	Yes	Yes
Rolpa	Yes	medical officer	No	Yes
Rupendehi	Yes	health assistant	Yes	Yes
Surkhet	Yes	health assistant and medical officer	Yes	Yes

[†] Involvement of the medical officer in planning and execution of the trial
[‡] Dedicated personnel resources for instructing yoga
[§] Whether the yoga training studio is inside the trial centre

6.2.4.2.4.2 Personnel resources

The health centres had at least seven staff each, including a medical officer, *Kaviraj* [Ayurvedic health assistant], *Vaidya* [axillary health assistant], and other staff. Of these staff, the medical officer and health assistants had knowledge and skills in yoga and were involved in providing yoga training to the intervention participants. Most of the intervention implementers felt that they did not need additional staff to effectively implement the intervention. For example, IDI-1 said:

'We don't need separate staff. Available staff can handle that [yoga intervention].'

6.2.4.2.4.3 Physical space (yoga studio)

Five centres had their own yoga studio where they could provide training to the participants. The health centre located in Rolpa did not have a yoga studio, but the participants used the outpatient department room to organise the yoga training in the YoH trial. The intervention implementers from Nuwakot stated that they organised the yoga training outside the health centre. The yoga studios in the remaining five health centres are well-equipped.

6.2.4.2.4.4 Experience in implementing yoga programmes

The implementers of the intervention and government officials noted that many District Ayurveda Health Centres, including the seven trial centres, had been implementing different yoga-related programmes like *Swostha Jivan Karyakram* [Healthy Life Programme] and *Vidyalaya Yog Shiskya Karyakram* [School Health Programme]. They also reported that yoga interventions have a relatively high priority as compared to other, similar programmes.

6.2.4.2.5. Implementers' characteristics

6.2.4.2.5.1 Yoga knowledge and skills among health workers

All intervention implementers were trained in yoga and had a medical degree (Table 17). Some of them were volunteering as yoga instructors in the community outside of their office hours. They stated that the supporting health care workers, such as *Kaviraj* [Ayurvedic health assistant] and *Vaidya* [auxiliary health assistant], who were involved in implementing the yoga intervention, also had previous knowledge and skills in yoga.

Table 17. Implementers' characteristics

Participants	Yoga knowledge		Yoga skill		Motivation for implementation	
Health centre	Lead implementer†	Other staff‡	Lead implementer	Other staff‡	Lead implementer	Other staff‡
Dhading	Yes	Yes	Yes	Yes	Yes	NS§
Kaski	Yes	Yes	Yes	Yes	Yes	Yes
Nuwakot	Yes	Yes	Yes	NS	Yes	NS
Ramechap	Yes	Yes	Yes	NS	Yes	NS
Rolpa	Yes	Yes	Yes	Yes	Yes	Yes
Rupendehi	Yes	Yes	Yes	Yes		
Surkhet	Yes	Yes	Yes	NS	Yes	Yes

† Lead implementer of YoH trial and participant in the current study; ‡ Supporting staff ; § Not sufficient

However, some of the intervention implementers questioned whether the supporting health workers would be competent enough as yoga instructors, unless they would receive adequate professional training.

> '*Our assistants are not fully competent in yoga… If we give them good orientation and train them for 7-8 days, they can implement the yoga programme very well.*' (IDI-5)

One of the implementers said that yoga instructors need a good knowledge of yoga as well as a '*flexible*' body, which would only be possible if they regularly practised yoga. They added that the health workers lacked practical experience in yoga instruction. Accordingly, two government officials suggested providing yoga training to health care workers before scaling up the yoga intervention in other centres.

6.2.4.2.5.2 Motivation

The implementers of the intervention were highly motivated to contribute to the delivery of the intervention. They believed that Ayurveda Health Centres and their employees should offer yoga programmes for patients. However, some of the intervention implementers stated that their supporting staff were less motivated to implement the intervention. They suggested that providing remuneration or other incentives to the staff involved in the intervention would increase their motivation.

6.2.4.2.6. Implementation process

6.2.4.2.6.1 Intervention delivery

All intervention implementers stated that they followed the protocol and provided five days of training to the participants, as planned. The training was provided one-on-one or in a group session. All the centres provided yoga training to the participants in the morning (before their office work). Although this was not specified in the intervention protocol, they thought it would be best for the patients to learn yoga in the morning.

6.2.4.2.6.2 Intervention receipt

The intervention participants were satisfied with the five-day yoga training. Most of them reported that they could understand and perform yoga as instructed during the training. The intervention implementers were also confident that the intervention participants were interested in attending the five-day yoga training and that they were able to gain sufficient yoga skills during the training.

6.2.4.2.6.3 Intervention enactment and adherence to home-based yoga practice

Most of the intervention participants found it easy to practise yoga during the three-month, home-based part of the intervention. Most of them also reported that they regularly practised yoga during the intervention. Some participants stated they could not practise yoga regularly, although they were motivated to do so. The most frequently cited challenges to practising yoga at home were time constraints and competing priorities (e.g. looking after children and grandchildren). Participants sometimes skipped their yoga sessions or shortened the sessions by only practising *Pranayam* [breathing exercise], if they were in a rush.

The intervention implementers also agreed that some participants may not have strictly followed the intervention protocol. They mentioned that the reasons for this could be a lack of commitment to the yoga practice, the low perceived effectiveness of the yoga intervention, a lack of family support, and competing, work-related priorities.

Most of the participants suggested that offering group yoga sessions in a community centre would help them practise yoga more regularly. Those who worried that they would disturb their household members if they practised yoga early in the morning and those who felt distracted by their children were particularly in favour of the idea of group sessions in a community-based yoga centre.

6.2.4.2.7. Sustainability of the intervention

6.2.4.2.7.1 Sustained practice of yoga

A year after the completion of the yoga intervention trial, the majority of the intervention participants reported that they had continued practising yoga. Some of the participants stated that they are motivated to continue practising yoga over a long term. A few participants quit practising yoga after the study period due to time constraints.

6.2.4.2.7.2 Institutionalising the use of yoga intervention

One intervention implementer stated that, after the YoH trial, his health centre incorporated the yoga intervention into their routine practice. They mentioned that the centre now recommends all eligible hypertensive patients to practise yoga. The government officials and intervention implementers suggested that the integration of the yoga intervention into the existing health care programme would not be too challenging. Moreover, the yoga intervention would not require additional resources, if it could utilise the existing personnel and other resources.

6.2.4.3. Quantitative findings

More than two-thirds of the participants found the training useful for them, considered that it helped them to learn yoga, and were satisfied with the training they received. The most commonly reported barriers to regular home-based yoga practice were the burden of repeating the same routine over and over again (cited by 16.7% of participants), comorbid conditions (cited by 16.7% of participants), and other priorities at home (cited by 16.7% of participants; Table 18).

Table 18. Results of telephone interviews with intervention participants

Question	*n* (%)
Did you attend yoga training?	
Yes	12 (100)
How useful was the training for you to learn yoga?	
Very useful	7 (58.3)
Useful	2 (16.7)
Somewhat useful	3 (25.0)
Not useful	0 (0)
Not at all useful	0 (0)
How satisfied were you with the yoga training?	
Very satisfied	9 (75.0)
Satisfied	3 (25.0)
Somewhat satisfied	0 (0)

Not satisfied	0 (0)
Not at all satisfied	0 (0)
Did you practise yoga at home regularly as instructed?	
Yes	12 (100)
No	0 (0)
Did you find any barriers in home-based yoga practice?	
Yes	6 (50.0)
No	6 (50.0)
What were the barriers? (n = 6)	
The routine is difficult to follow	2 (333)
I don't have necessary skills	0 (0)
I have other medical conditions	2 (33.3)
I feel too lazy	1 (16.7)
I am not convinced about its positive effects	0 (0)
I have family/work commitments	2 (33.3)
It is too physically demanding	0 (0)
I lack motivation	1 (16.7)
I lack time	1 (16.7)
It is too inconvenient	0 (0)
It is boring	1 (16.7)
I am too tired	0 (0)

6.2.5. Discussion

The main finding of this study is that a simple, health-worker-led yoga intervention for blood pressure reduction among hypertensive patients has a good potential for implementation in the primary care setting. Specifically, we found that implementers, trial participants, and government officials perceived yoga as an effective, simple, low-cost, and scalable intervention for hypertension control.

Our results show that study participants had a positive attitude towards the intervention, a positive perception of the effectiveness of yoga for blood pressure reduction, and a relatively low participant burden. This indicates that the yoga intervention was highly acceptable. The positive attitudes that the participants expressed toward the intervention could be explained by the fact that yoga has a long tradition in Nepal [66]. Yoga originated and spread across South Asia, including Nepal, around 2000 years ago [38, 67]. It is now a culturally accepted and widely practised lifestyle therapy in Nepal. Given its popularity, yoga has recently been included in the secondary school curriculum [66, 68, 69]. Because yoga is a very popular activity in many other countries in South Asia, such as India [70], similarly positive attitudes of individuals towards yoga interventions could be expected across South Asia. It should be noted that yoga is also one of the most common exercise forms and recreational activities in a number of other countries. For example, in 2016, around 10% of the US population practised yoga [38]; therefore, it can be assumed that a positive attitude towards yoga interventions is likely to be held in the primary care settings in a range of other countries as well. This assumption, however, needs to be confirmed in future studies.

The stakeholders' perceptions of the complexity and relative advantages and disadvantages of an intervention may influence the effectiveness of its implementation [71]. The interventions that are being perceived as less complex are more likely to be implemented effectively [71]. In our study, the stakeholders perceived the intervention package as '*easy to follow*' and '*not complicated*', which is promising for its future implementation. Furthermore, the implementation cost is negatively associated with the effectiveness of implementation and sustained delivery of an intervention [59, 60]. We found that the cost associated with the implementation of yoga intervention was negligible, as the health centres largely relied upon the existing personnel and other resources. Although the low complexity and cost of implementation of the yoga intervention suggest that it has a good potential for implementation in the primary care setting in Nepal, our findings indicate that the

adaptability of the intervention package should be improved to meet varying patient requirements. In addition, health centres should incentivise the supporting staff to increase their motivation to adequately deliver the intervention.

This study confirmed some of the previously identified external and intra-organisational factors that are likely to facilitate the effective implementation of a health-promoting intervention [72]. Mendel et al. described six sets of factors that indicate the ability of an organisation to implement and maintain the delivery of a new intervention [73]. Organizational structure, resource availability, and policies are some examples. In the current study, we found that the government policy assigns high priority to the use of yoga for health promotion, that a high demand exists for yoga among hypertensive patients, and that Ayurveda Health Centres have adequate personnel and other resources required for the implementation of a yoga intervention. This suggests that implementation readiness for a yoga intervention is present at all levels in Nepal, from the government to individual health centres. Nevertheless, it is essential to improve the knowledge and skills of health workers in yoga instruction.

Our study also shed light on barriers associated with home-based yoga practices among hypertensive patients. The most commonly cited barriers were a lack of a daily routine, time constraints, and competing priorities (particularly household work and occupational commitments), findings that are in line with those of a previous study [74]. The use of educational videos to guide home-based yoga practice family support and replacing home-based yoga practice with group-based yoga practice in community centres are two commonly recommended possible strategies to overcome the challenges of home-based yoga practice.

The findings of our study may have implications regarding the inclusion of yoga interventions in the routine practices at health centres. An improved understanding of the factors influencing the effectiveness of implementation of the yoga intervention may contribute to scaling-up the YoH and similar interventions in other primary health-care centres in Nepal and potentially other countries. Nepal already has national policy and mechanisms that promote yoga as a lifestyle therapy. For example, the Multisectoral Action Plan for Prevention and Control of NCDs (2014-2020) and the Urban Health Policy (2015) envision yoga as a health promotional tool for non-communicable disease prevention and control. Similarly, there are several yoga-based health promotional interventions, such as the

Swatha Jiwan karyakram [English: Healthy Life Program] and *Vidhaylaya yoga shiskya karyakram* [School Yoga Education Program], that are supported by the Ministry of Health. The current study findings may help policymakers extend the existing yoga-based community interventions to the primary care setting for the management of hypertension and potentially other non-communicable diseases. Our findings may also be used to encourage policymakers in other countries to consider designing policies that would promote the use of yoga interventions in the primary care setting.

The limitations of the study are due to its retrospective design, which does not allow the study findings to be used to address concerns encountered during the implementation of YoH trial. The findings may, however, be used to improve the future implementation of the YoH intervention and similar health-promotion initiatives. The retrospective design of the study may also have resulted in a recall bias among the participants. If possible, future interventions should consider combining prospective, real-time, and retrospective feedback from participants, health workers, and other stakeholders.

6.2.6. Conclusions

The majority of the evaluated factors, such as the acceptability of the intervention, external environment, organisational attributes, and characteristics of implementers, indicate that there is a good potential for the implementation of the yoga intervention in a low-resource, primary care setting. The wider implementation of yoga interventions may require the capacity development of health workers and involvement of community yoga centres in the delivery of the interventions. These findings have greater implications in Nepal and other countries that have similar settings in terms of understanding how the factors influence the implementation of yoga in primary care as a lifestyle therapy. However, as the contextual factors may vary across different countries, the study findings may not necessarily be generalisable outside Nepal. Future studies on this topic in other countries are needed to confirm our findings.

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Chapter 7. General discussion

In this chapter, I have summarized and interpreted the key findings of the five studies presented in chapters four, five and six. While discussing the findings, I have also highlighted the overall strengths and limitations of the conducted studies. With constant comparison and triangulations across the findings of those five studies included in PhD, I have coherently discussed how the findings are useful and important for policy, practice, theory, and subsequent research regarding hypertension and non-pharmacological intervention in Nepal and other low-and middle-income countries.

7.1. Health care challenges due to hypertension in Nepal

7.1.1. Growing burden of hypertension and related diseases in Nepal

Study 1 demonstrated that hypertension is a prevailing problem in Nepal. Hypertension affected one in every four adult Nepalese in 2019. The study finding is more or less similar to the prevalence of hypertension in South Asian counterparts particularly in India (25.8%) and Bangladesh (24.7%) and other low-income countries (23.1%) [1]. It is interesting to note that the South Asian countries including Nepal have observed an increasing trend of the burden of hypertension [2]. One of the recent meta-analyses found that hypertension had increased by 6 percentage points between 2000 and 2020 in Nepal [3]. India observed an increase of 6.6 percentage points in the prevalence of hypertension between 1991 and 2015 [4]. Contrary to Nepal and India, high-income countries are witnessing a decreasing trend in the prevalence of hypertension [2], where the prevalence of hypertension decreased from 29.5% to 24.1% in men and 26.1% to 20.1% in women between 1975 and 2015 [2].

As discussed in chapter two, the number of patients suffering from cardiovascular diseases, many of which are caused by hypertension, is also increasing in Nepal. Cardiovascular diseases affected around 5% of the population and accounted for almost one-fourth of all deaths that occurred in Nepal in 2019 [5]. The proportional contribution of cardiovascular deaths to the total deaths nearly tripled in the last three decades in Nepal [5]. The increasing trend in all age mortality rate was also observed globally (increased by 6%), and in South Asia (increased by 30%) [5]. It was also increased in India, Bhutan, and Bangladesh by 32%, 70%, and 61% during the same period, respectively [5]. Cardiovascular deaths are mainly due to ischemic heart disease, stroke, and hypertensive heart disease in Nepal and globally [5].

The growing burden of hypertension and cardiovascular diseases has been linked to population ageing [6] and a higher prevalence of risk factors such as smoking, physical inactivity, obesity, diabetes, and dyslipidaemia, among others [7-9]. In Nepal, all most all (97%) Nepalese did not consume the recommended amount of fruit and vegetables (five servings of fruit and vegetables a day); 17% were current smokers; 6.8% used to drink 60 grams and more alcohol daily; 7.4% had low physical activity level; 24.3% were

overweight/obese, and 5.8 % had raised blood glucose in 2019 [10]. A significant surge in the prevalence of behavioural and metabolic risk factors was observed recently in Nepal. The prevalence of harmful alcohol intake increased thrice, and the prevalence of insufficient physical activity, obesity and diabetes were doubled in Nepal between 2013 and 2019 [10, 11].

7.1.2. Gaps in the cascade of hypertension care

In Study 1, a gap in awareness, treatment, and control of hypertension was assessed using the cascade of hypertension care framework. The study found that among all hypertensive participants, only around one-fifth knew they had hypertension, around one-tenth were under antihypertensive medication, and less than 4% had optimal control of blood pressure. The hypertension control rate in Nepal is the lowest compared to its overall prevalence in lower- and middle-income countries (7.7%) [12], the combined rate of Bangladesh, India and Pakistan (12.9%) [13], that of India alone (7.9%) [14], China (7.2%) [15], USA (53%) [16], and Canada (66%) [16].

The finding suggested huge disparities in cascade of hypertension care in Nepal. The most concerning part of the findings was that the unmet need for hypertension control was more prevalent amongst the vulnerable and hard to reach population including the poor and those who lived in relatively remote areas. Those who visited public health centres for the treatment or who had no health insurance were also among the most affected population in terms of gaps in hypertension care.

7.1.3. Barriers to treatment and control of hypertension

The assessment of the cascade of hypertension care in Study 1 helped us quantify the gap in hypertension treatment and control in Nepal. But it was critical to explain the rationale behind poor performance in hypertension care and identify the factors influencing treatment and control of hypertension in Nepal. To answer these questions, I conducted a systematic review (Study 2) on barriers, enablers, and strategies for hypertension treatment and control. The review applied a framework to categorise barriers, enablers and strategies into three major domains: health system, providers, and individual level. The barriers are the main challenges associated with health system, health providers, and hypertensive individuals for

treatment and control of hypertension in Nepal, which are discussed in detail under the following broad headings.

7.1.3.1. Low availability of health services

The low availability of health services regarding hypertension care is identified as an important system-level challenge for accessing treatment of hypertension in Nepal. To ensure an appropriate care of hypertension, policies, strategies, and approaches specific to hypertension are required. As discussed in chapter two, there are some policy initiations to ensure universal access to hypertension care in Nepal. The Multi-sectoral Action Plan for Prevention and Control of NCDs (2014-2020) and the Nepal Health Sector Strategy Implementation Plan 2016-2021 were the first two policy documents that recognized hypertension as a health indicator and developed strategies to prevent, detect and treat hypertension in Nepal. The implementation of the Package of Essential Non-communicable Diseases is one of the strategies endorsed by the Nepal Health Sector Strategy Implementation Plan 2016-2021 [17]. However, the Package of Essential Non-communicable Diseases is being implemented as a pilot project in only 30 out of 77 districts in Nepal and its effectiveness for improving hypertension control is yet to be evaluated. The low availability of services and poor implementation of policies and programs indicate that Nepal's health system has not been fully prepared to respond to the burgeoning burden of hypertension and its related complications [18].

7.1.3.2. Lack of resources

The low availability of the services is also linked to the lack of diagnostic tools and skilled health workers. Nepal has only two fully-equipped cardiac care centres that were established to provide specialized services in cardiovascular diseases. However, these centres are located in the capital city, which are barely accessible for those living in remote areas [19]. Recently, while implementing the Package of Essential Non-communicable Diseases, health workers from primary health care centres and health posts were also trained for screening, detection, and management of non-communicable diseases including hypertension [17]. However, it is too early to be confident about the positive impact of implementation of the Package of Essential Non-communicable Diseases on detection and control of hypertension as the large majority of the hypertensive population is unaware of their blood pressure level or are not willing to take antihypertensive treatment. Likewise, in the absence of guidelines for hypertension management, it is doubtful that health worker can effectively and systematically

contribute to identification, risk stratification, management, and referral of hypertension and its associated complication in Nepal.

7.1.3.3. Inadequate supply of essential medicines

Access to free essential medicines was the only health system-related enabler identified in Study 2 (a systematic review) of the thesis. The National Essential Medicine List 2021 includes two antihypertensive drugs namely amlodipine and enalapril and one diuretic, which are also available freely at primary care centres [20]. It is important to note that universal access to essential medical products is the prerequisite of a well-functioning health system. However, it has been frequently reported that the supply of essential medicine is not regular and efficient in Nepal [21]. In a survey conducted in 2015, over 80% of health facilities reported a shortage of antihypertensive medicines in Nepal [22]. The limited supply of essential medicines is a challenge for improving hypertension care in Nepal. Furthermore, the essential medicine list in Nepal is only 80% compatible with the World Health Organization list of essential medicines [23]. The fixed-dose combination of antihypertensive medications (such as lisinopril + amlodipine), atenolol, and telmisartan those are available in the World Health Organization 22nd list (updated in 2021) of essential medicines are not included in Nepalese National Essential Medicine List 2021 [20, 24], indicating a need for revision in the national essential medicine list of antihypertensive medications in Nepal.

7.1.3.4. Unaffordability of health services

Lack of affordability of services is another health system-related barrier in Nepal. The cost incurred for utilization of health services is mainly borne by out of pocket spending from patients in Nepal. In 2017, around half of the current health spending in the health system of Nepal was borne by the patients for buying medicines and medical goods [25]. Spending on hypertension and its related cardiovascular disease was 3.5% of current health expenditure [25]. The National health insurance policy scheme is available for protecting the population from catastrophic health expenditure (the total health expenditure is more than 10% of the annual income). However, the coverage, enrolment, and retention rate of the National insurance policy is very low. Until 2019, the National health insurance policy was expanded to 46 districts, covering 10% of total population with the dropout rate of about 38.4% [26]. Some of the reasons for the poor implementation of the National health insurance program are the limited number of service providers and health packages and lack of co-payment policy in different types of health services [26]. Limited coverage of insurance policy and skyrocketing out-of-pocket expenditure for non-communicable diseases including

hypertension are the challenges for financial risk protection among hypertensive patients in Nepal.

7.1.3.5. Non-adherence to medication and lifestyle modification

The above-discussed challenges are particularly related to the factors that determine health service delivery. The performance of the health system and utilisation of health care also depend upon different factors associated with patients. Non-adherence to antihypertensive medications and lifestyle modifications is one of the most cited individual-level barriers to treatment and control among hypertensive individuals. Likewise, poor communication and unsupportive behaviours from health providers also negatively impact hypertension treatment and control. Therefore, despite the improvement in the supply of service delivery, it might be challenging to improve the cascade of hypertension care unless the demand for services is increased through behavioural change interventions among hypertensive patients.

7.1.3.6. Poor knowledge, understanding and practice of hypertension management

This thesis found that hypertension treatment and control were linked with a lack of knowledge, negative perception, and poor practices of hypertension management among hypertensive individuals. The knowledge, perception, and practices that impeded the hypertension treatment were the lack of awareness on blood pressure targets and blood pressure complications, perceived side-effects of antihypertensive drugs, poor help seeking behaviours, reluctance or inability to change unhealthy behaviours, irregular follow-up visits, and self-medications, among others.

7.1.3.7. Lack of evidence on Nepal specific strategies for hypertension treatment and control

In a systematic review, this thesis found that there is a dearth of evidence on public health interventions for hypertension control in Nepal. There are a few studies that investigated the effect of behavioural change education on hypertension control among hypertensive patients [27-30]. Another study tested the effect of yoga on blood pressure reduction [31]. Except for the study by Neupane et al. [28], other studies were not strong enough to inform policy recommendations.

7.1.3.8. Co-morbid conditions and hypertension control

It was also found that control of hypertension was challenging if the hypertensive individuals had comorbidities. Evidence suggested that major NCDs share risk factors, hence they are interrelated [32, 33]. As with the growing burden of NCDs, more and more individuals with

hypertension are likely to have comorbidities, which may affect the individual and entire health system potentially leading to poorer hypertension outcomes, high treatment burden for the management of multiple chronic diseases [34, 35], and increased healthcare costs and workload for health workers [34, 36, 37]. Therefore, a coordinated and integrated health service delivery system is needed that deals with the comorbidity in an organised way as opposed to the existing fragmented model. Sustainable intEgrated chronic care modeLs for multi-morbidity (SELFIE) is one of the evidence-based frameworks designed to guide the development of integrated care [38], which is also applicable to the management of hypertension with comorbidities.

7.2. Non-pharmacological interventions for hypertension treatment and control

In the previous section, this thesis discussed the growing burden of hypertension and the inevitable enormous health care challenge in Nepal in terms of ensuring appropriate and accessible hypertension management and care for patients. Beside antihypertensive medications, non-pharmacological interventions including alcohol reduction, sodium reduction, potassium supplementation, physical activity, weight reduction, and diet could play an important role in hypertension management. The international guidelines for hypertension treatment have also acknowledged them as the indispensable components in the management of hypertension [39, 40]. However, despite the recommendation from the international guidelines and having unequivocal evidence on the benefit of non-pharmacological interventions for hypertension control, it is very uncommon to see them in the standard care of practice in primary care settings. Therefore, to answer the question of whether it is feasible to implement a non-pharmacological intervention in primary care, this thesis first narratively synthesised evidence on anti-hypertensive non-pharmacological interventions available throughout the globe and selected yoga as one of those non-pharmacological interventions for hypertension for the feasibility study in Nepalese context. The discussion based on the findings of studies three, four and five are as follows

7.2.1. Non-pharmacological interventions for hypertension in primary care settings

In the narrative review, this thesis found that alcohol reduction is one of the common non-pharmacological interventions implemented in primary care settings. The alcohol reduction strategies at primary care included the Brief Alcohol Interventions (BAI). The BAIs are the behaviour change theoretical practices that comprise of one or more continuous steps of screening and motivating the patients through brief advice or counselling [41]. Studies have shown that BAI was effective to reduce alcohol intake by on average 38 grams per week when delivered in the primary care setting [42, 43]. The feasibility of BAI in primary care settings in Nepal should also be explored further as a significant proportion of Nepali (6.8%) were found to drink 60 grams and more alcohol daily in 2019 [10]. Additionally, as the BAI

has shown a significant blood pressure-lowering effect in hypertension [44] and is also found to be cost-effective [45], the intervention may be useful to control blood pressure among Nepalese hypertensive individuals with harmful alcohol use.

Similarly, brief advice-based intervention and counselling were the two effective strategies implemented for dietary salt reduction among the patients attending primary care settings. The dietary salt-lowering effect of the interventions was significantly associated with a reduction in systolic blood pressure by at least 2-4 mmHg [46, 47]. In the case of promoting physical activity among the patients attending primary care, in addition to the brief intervention, exercise referral schemes were found to be effective in increasing the time spent in physical activity by an average of 55 minutes per week [48].

In the same way, behaviour change intervention and total dietary replacement were the two dominants primary care-based interventions that were found to be effective for losing weight [49, 50]. Despite a plethora of evidence regarding potassium supplementation and yoga intervention in population settings, there are hardly any relevant studies on these areas conducted in a primary care setting.

The implementation of non-pharmacological interventions in a primary care setting, however, remains challenging. Several factors associated with health care providers and patients can influence the implementation of non-pharmacological interventions in primary care. For example, health workers' competing priorities is one of the major barriers to implementation of non-pharmacological intervention in primary care. This is mainly because of understaffing of health workers in primary care settings. In 2017, the average number of physicians per 100,00 population was 16 globally, three in low-income countries, and eight in lower-middle-income countries [51]. Evidence shows that task sharing/shifting [52] and team-based care [53] approaches could facilitate the implementation of primary care-based intervention by overcoming the challenges of understaffing. Similarly, lack of skill, motivation, and resources among health care providers can impede the implementation of intervention [54-56]. In contrary to that, motivation, capacity building training, financial incentives, and adequate resources could facilitate them for effectively implementing the non-pharmacological intervention in primary care [56-59]. At the level of patients, non-adherence, low self-esteem, lack of motivation, lack of professional, peer and family support, and comorbidities are some of the barriers to non-pharmacological intervention in a primary care setting. Some of the strategies such as linking primary care patients to community-based

health and social services or professional program and resources [28, 60] or using electronic and mobile technologies [61-63] could be useful for long term monitoring and management of hypertensive patients, thereby increasing adherence and effectiveness of interventions.

7.2.2. Implementation potential of yoga intervention for hypertension in primary care settings

Since Study 3 informed that there is a dearth of information regarding the use of yoga for hypertension management in a primary care setting, Study 4 was designed to investigate whether yoga is effective if it is implemented by health workers in a primary care setting. The study found that a health worker-led yoga intervention in primary care setting could significantly reduce systolic and diastolic blood pressure by 7.7 mmHg and 3.9 mmHg, respectively. The findings were slightly lower than those were reported in a recent systematic review [64]. The review found that yoga intervention was significantly associated with an average reduction of systolic blood pressure by 7.9 mmHg and diastolic blood pressure by 4.3 mmHg among the participants [64]. It is a fact that an effect of intervention implemented in real-world settings could significantly vary with the finding of a study conducted in ideal conditions due to dilution of effects [65]. Various contextual factors related to the implementation process including external environments, study settings, and stakeholders' perspectives influence the implementation of the real-world setting-based intervention, thereby can affect the outcome of the study [66, 67]. Therefore, to understand the factors influencing the implementation of yoga in a primary care setting, Study 5 was conducted.

The factors identified in Study 5 were related to the overall acceptability of the yoga intervention among hypertensive patients, interventional characteristics, implementation settings, and implementer's characteristics, among others. Overall, study participants had a positive attitude towards the intervention. They perceived that yoga had some beneficial effect on blood pressure reduction. It can be assumed that various contextual factors related to yoga intervention such as yoga being a long-established tradition in Nepal [68] and being culturally accepted or widely practised in the community [68-70] might have influenced the acceptability of intervention among the participants [71]. Likewise, the implementers and government officials also indicated that yoga intervention has a good implementation potential in the primary care setting in Nepal as the intervention was '*simple'*, '*adaptable'* and economically viable. However, Study 5 findings indicate the health workers need

incentives and capacity building training on yoga to increase their motivation to adequately deliver the intervention.

7.3. Strength and limitations of the thesis

The PhD thesis is the first comprehensive investigation in terms of depicting a clear picture of the existing burden of hypertension and informing about the potential and feasible non-pharmacological interventions for hypertension management in a primary care setting in Nepal. The strengths and limitations of the individual studies are discussed in the '*Discussion*' section of the respective studies. In brief, to my best knowledge, no other studies have ever provided a deeper insight into the burden and health care challenges of hypertension in Nepal as the current thesis did. This thesis used the two sets of nationally representative data derived from the World Health Organization STEPwise Approach to Non-communicable Disease Risk-Factor Surveillance to quantify the gap in hypertension care and assess the distribution of unmet needs of hypertension care across different population groups in Nepal. The large datasets helped us generate precise estimates of the population parameters. In the same way, this thesis systematically synthesised the evidence on barriers, enablers, and strategies of hypertension treatment and control in Nepal. The new things about the study were that I constructed a new conceptual framework, triangulated the findings from both qualitative and quantitative studies and mapped the factors related to the health system, health care provider, and patient levels that were likely to impede or facilitate hypertension treatment and control in Nepal.

The scope of the thesis is not just limited to defining and analysing the health care challenges of hypertension in Nepal, rather it provides a detailed illustration of how a non-pharmacological intervention can be implemented for the management of hypertension in primary care settings. For that, I evaluated a pragmatic randomised controlled multicentre trial to test whether a health-worker-led yoga intervention could be effective in reducing blood pressure among hypertensive patients. The main strength of the study was that it was conducted in a real-world clinical setting, which means the study had a good external validity and the findings is more likely to be translated into practice [72, 73]. Furthermore, that was the first study to investigate the effects of a primary health care staff-led yoga intervention on high blood pressure among the patients attending public health centres in a low-income

country. Following the implementation of the clinical trial, this thesis retrospectively evaluated the implementation potential of the yoga intervention for hypertension in primary care settings. The main strength of the study is related to the use of an implementation research framework to design a mixed-methods evaluation study and providing an actionable finding on barriers and facilitators of the implementation of yoga intervention in primary care.

There are several limitations of this PhD thesis. Firstly, the PhD research questions were broad and required multiple studies with different methodologies and study populations to address them. It was challenging to interweave the issues discussed in individual studies and develop a bigger picture that could address the overall PhD research questions. Apart from that, the remaining limitations originate from the individual studies. For example, in the systematic review, I could not perform a meta-analysis because of the methodological heterogeneity and variation in outcome measures among the included studies. Similarly, as the pre-intervention and post-intervention data were collected by the same person, the clinical trial could have reported the biased estimation on the effect of yoga intervention for blood pressure reduction due to rater bias. The trial also lacked the information on the level of adherence to the study protocol from all participants, which otherwise would allow us to explore the dose-response relationship between frequency and duration of yoga practice and level of blood pressure reduction. Lastly, the retrospective design (one year after the completion of YoH trial) of Study 5 may also have resulted in a recall bias among the participants.

7.4. Implications of findings

The findings of the PhD research projects have significant implications for identifying the population at risk for unmet need for hypertension care and implementing the non-pharmacological intervention for improving hypertension management in Nepal. Firstly, the quantification of the unmet need for hypertension care informs the stakeholders about the loss of a proportion of hypertensive individuals in a particular stage of the continuum of care in Nepal. Though the concept of cascade of care framework is anew to hypertension management [74-76], it has been commonly used for early identification and diagnosis of chronic infectious diseases such as HIV/AIDS and tuberculosis and subsequently linking the

patients to the care [77, 78]. Adopting the same framework for hypertension management could be useful for identifying the hypertensive populations who are more likely to be unaware of their condition, aware but untreated, or treated but having sub-optimally controlled blood pressure [76]. The findings, therefore, may help the health care providers and other stakeholders locate the gaps in hypertension care in Nepal and pair those in an at-risk population with effective interventions. For example, based on study 1 findings, more than four million (n=4,280,495) of 15 to 69 years of Nepalese were affected with hypertension in 2019, where only less than a million (n=870,648) were aware of hypertension, 384,792 were treated, and 161,006 had controlled blood pressure. The loss of significant number of hypertensive individuals in each step of cascade of care indicated that Nepal needs an improved hypertension care for better control of hypertension in the population.

Similarly, the detailed mapping of the barriers, enablers and strategies of hypertension reported in this thesis would guide stakeholders to be more specific towards the intervention required to address barriers or re-enforce enablers or redirect the existing intervention to improve hypertension treatment and control in Nepal. For example, stakeholders could focus on increasing universal access to essential antihypertensive medications at primary health care facilities as the current thesis has identified it as an enabling factor for seeking treatment for hypertension. Stakeholders could also promote female community health volunteer-led community health education as the only intervention that was found to be effective to reduce blood pressure among hypertensive individuals in Nepal [28]. Additionally, evidence suggests that task shifting [52], team-based care [53], combination therapy [79], home-based blood pressure monitoring [80], and eHealth based monitoring and care [81, 82] could address some of the barriers identified in the thesis such as shortage of skilled human resources and poor adherence to hypertension care, thereby ultimately improving hypertension control.

The findings on non-pharmacological intervention for hypertension complement those of studies discussed above and strengthen the knowledge base on their effectiveness and feasibility as adjuvant therapies to reduce blood pressure among hypertensive patients in the primary care setting. The results of this thesis suggest that a significant reduction in blood pressure could be achieved through the modification of unhealthy lifestyle behaviours such as alcohol reduction, salt reduction, physical activity promotion, and weight maintenance. However, further studies are required to translate these findings to the Nepalese context.

This thesis also found that yoga as a non-pharmacological intervention is feasible to be implemented for blood pressure reduction among hypertensive patients in a primary care setting of Nepal. The results of this thesis demonstrated that a health worker-led 3-months yoga intervention was effective for reducing blood pressure among hypertensive patients attending primary care settings in Nepal. Positive perspectives towards yoga intervention among hypertensive patients, implementers and government officials, adequate policy priority for yoga as a health promotional lifestyle therapy, and existing skilled human and other resources indicated that there is a good potential for the implementation of the yoga intervention in a low-resource, primary care setting in Nepal. Moreover, the initiation has already been taken to translate research findings into practice. One of the health centres (trial centre) has already incorporated the yoga intervention for hypertension into routine care. Lastly, the detailed audits of barriers and facilitators of implementation of yoga intervention have implications for planning and developing similar interventions in Nepal and other countries that have similar settings.

7.5. Conclusions

Overall, the thesis sheds light on imminent health care challenges related to hypertension treatment and control in Nepal. The findings may inform general practitioners, health administrators, and policymakers about the effectiveness, barriers, and facilitators of non-pharmacology interventions, including yoga. This may facilitate the implementation of such interventions in the standard primary care practice, and consequently improve the outcomes of hypertension treatment and control in Nepal.

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Supplementary files

Supplementary table 1: Chapter four, Section A. Factors associated with hypertension treatment among all (model I) and aware (model II) hypertensive individuals

Variables	Model I		Model II	
	Adjusted prevalence ratio	95% CI*	Adjusted prevalence ratio	95% CI*
Age				
15-29 years	Reference			
30-44 years	3.22	1.16, 8.95	1.49	0.68, 3.28
45-69 years	7.25	2.65, 19.86	2.1	0.95, 4.66
Gender				
Men	Reference			
Women	1.26	0.87, 1.82	0.72	0.54, 0.95
Marital status				
Never married	Reference			
Currently married	0.94	0.32, 2.72	0.97	0.45, 2.07
Widowed	0.83	0.28, 2.47	1.06	0.48, 2.37
Other (separated, divorced)	1.96	0.51, 7.57	1.86	0.80, 4.32
Education				
No formal schooling	Reference			
Lower than primary school	0.73	0.48, 1.12	0.61	0.41, 0.91
Primary school	1.08	0.72, 1.63	0.8	0.56, 1.13
Secondary school	1.09	0.68, 1.75	1.01	0.75, 1.36
High school	1.28	0.68, 2.41	0.9	0.53, 1.52
Bachelor and higher	1.48	0.78, 2.82	1.0	0.63, 1.58
Occupation				
Government employee	Reference			
Non-government employee	0.58	0.25, 1.38	0.71	0.39, 1.28
Self-employed	0.77	0.35, 1.69	0.78	0.46, 1.32
Homemaker	0.66	0.30, 1.46	0.88	0.52, 1.46
Student	0.68	0.09, 5.24		
Unemployed	0.34	0.05, 2.30	1.0	0.21, 4.77
Other (retired, non-paid job)	1.12	0.50, 2.51	0.81	0.48, 1.39
Smoking				
Yes†	Reference			
No	1.0	0.70, 1.43	1.12	0.87, 1.45
Alcohol consumption				
Yes‡	Reference			
No	1.56	1.05, 2.31	1.71	1.22, 2.39
Vegetable intake				
Sufficient§	Reference			

Variables	Model I		Model II	
	Adjusted prevalence ratio	95% CI*	Adjusted prevalence ratio	95% CI*
Insufficient	1.28	0.79, 2.06	1.08	0.69, 1.69
Fruit intake				
Sufficient‖	Reference			
Insufficient	0.63	0.38, 1.05	0.81	0.61, 1.07
Physical activity				
Sufficient¶	Reference			
Insufficient	1.57	1.04, 2.36	1.11	0.79, 1.56
Body mass index				
<25 kg/m2	Reference			
25-29 kg/m2	1.82	1.36, 2.43	1.16	0.93, 1.45
≥30 kg/m2	2.18	1.48, 3.20	1.12	0.86, 1.45
Diabetes				
Yes**	Reference			
No	0.58	0.43, 0.79	0.96	0.69, 1.35
Cholesterol				
High (>239 mg/dL)	Reference			
Not high	0.74	0.49, 1.10		

Note: *Prevalence ratio adjusted for all the remaining variables listed in the table, survey year, and responses to a question that combines ethnicity, historical "caste" groups, religion, and social disadvantage and its 95% Confidence interval; †Smoking tobacco at least once in the last 30 days; ‡At least one drink of alcohol in the last 30 days; §Eating at least three serves of vegetables in a typical week; ‖ Eating at least two serves of fruit in a typical week; ¶ Involvement in moderate and/or vigorous physical activity of ≥600 MET-minutes/week in a week; ** Fasting blood sugar level of 126 mg/dL or higher or taking any anti-diabetic medications at the time of the interview.

Supplementary table 2: Chapter four, Section A. Factors associated with hypertension control among all (model I) and treated (model II) hypertensive individuals

Variables	Model I		Model II	
	Adjusted prevalence ratio	95% CI*	Adjusted prevalence ratio	95% CI*
Age				
15-29 years	Reference			
30-44 years	4.43	0.71, 27.64	1.59	0.53, 4.76
45-69 years	7.35	1.14, 47.44	1.28	0.42, 3.87
Gender				
Men	Reference			
Women	1.62	0.86, 3.03	1.07	0.62, 1.86
Marital status				
Never married	Reference			
Currently married	0.38	0.10, 1.47	0.34	0.18, 0.65
Widowed	0.48	0.13, 1.83	0.42	0.18, 0.95
Other (separated, divorced)				
Education				
No formal schooling	Reference			
Lower than primary school	0.96	0.44, 2.11	1.83	1.07, 3.16
Primary school	1.70	0.85, 3.38	1.92	1.10, 3.34
Secondary school	2.09	0.98, 4.44	2.17	1.24, 3.80
High school	1.48	0.43, 5.16	1.26	0.44, 3.63
Bachelor and higher	2.57	0.81, 8.11	1.59	0.65, 3.90
Occupation				
Government employee	Reference			
Non-government employee	0.07	0.01, 0.39	0.18	0.04, 0.79
Self-employed	0.73	0.17, 3.03	1.0	0.41, 2.48
Homemaker	0.59	0.14, 2.52	1.13	0.37, 3.44
Student	0.73	0.08, 6.85	2.33	0.39, 13.91
Unemployed	0.65	0.07, 6.17	5.06	1.17, 21.88
Other (retired, non-paid job)	0.42	0.10, 1.78	0.42	0.12, 1.49
Smoking				
Yes†	Reference			
No	0.72	0.40, 1.27	0.81	0.53, 1.24
Alcohol consumption				
Yes‡	Reference			
No	2.59	1.08, 6.22	1.97	0.97, 4.01
Vegetable intake				
Sufficient§	Reference			
Insufficient	1.13	0.53, 2.44	0.76	0.37, 1.58
Fruit intake				
Sufficient‖	Reference			
Insufficient	0.57	0.23, 1.41	0.79	0.35, 1.79

Physical activity				
Sufficient[¶]	Reference			
Insufficient	1.82	0.96, 3.45	1.29	0.67, 2.50
Body mass index				
<25 kg/m2	Reference			
25-29 kg/m2	1.68	1.00, 2.83	0.7	0.49, 1.00
≥30 kg/m2	2.31	1.20, 4.46	0.9	0.56, 1.44
Diabetes				
Yes[**]				
No	0.82	0.45, 1.50	1.51	0.83, 2.73
Cholesterol				
High (>239 mg/dL)	Reference			
Not high	0.56	0.28, 1.11	0.87	0.58, 1.29

Note: [*]Prevalence ratio adjusted for all the remaining variables listed in the table, survey year, and responses to a question that combines ethnicity, historical "caste" groups, religion, and social disadvantage and its 95% Confidence interval; [†]Smoking tobacco at least once in the last 30 days; [‡]At least one drink of alcohol in the last 30 days; [§]Eating at least three serves of vegetables in a typical week; [‖] Eating at least two serves of fruit in a typical week; [¶] Involvement in moderate and/or vigorous physical activity of ≥600 MET-minutes/week in a week; [**] Fasting blood sugar level of 126 mg/dL or higher or taking any anti-diabetic medications at the time of the interview.

Supplementary table 3: Chapter four, Section A. Distribution of cascade of hypertension care in Nepal in 2013 and 2019

Distribution of cascade of hypertension care in Nepal in 2013												
Characteristic	Total	Screening		*p*	Awareness		*p*	Treatment		*p*	Control		*p*
		Yes	No		Yes	No		Yes	No		Yes	No	
Age													
15-29 years	118	54.2	45.8		4.6	95.4		3.3	96.7		2.9	97.1	
30-44 years	371	70.8	29.2	<0.01	15.3	84.7	<0.001	8.4	91.6	<0.001	3.2	96.8	*0.63*
45-69 years	739	75.9	24.1		29.2	70.8		17.2	82.8		4.4	95.6	
Gender													
Men	509	67.1	32.9	0.17	15.7	84.3	*<0.01*	10.5	89.5	0.33	3.3	96.7	0.49
Women	719	72.3	27.7		24.6	75.4		12.7	87.3		4.3	95.7	
Marital status													
Never married	53	53.3	46.7		3.5	96.5		2.6	97.4		2.3	97.7	
Currently married	1071	71.4	28.6	0.05	20.5	79.5	<0.01	12.1	87.9	0.04	3.7	96.3	0.69
Widowed	98	63.2	36.8		30.6	69.4		14.1	85.9		5.8	94.2	
Other (separated, divorced)	5	89.3	10.7		34.4	65.6		34.4	65.6		0	100	
Education													
No formal schooling	582	65.3	34.7		23.4	76.6		13.4	86.6		3.8	96.2	
Lower than primary school	146	71.2	28.8		21.7	78.3		11.1	88.9		3.9	96.1	
Primary school	147	74.3	25.7	0.01	19.3	80.7	0.09	10.0	90.0	0.54	3.2	96.8	0.99
Secondary school	212	67.8	32.2		14.2	85.8		8.2	91.8		3.7	96.3	
High school	81	59.4	40.6		13.3	86.7		11.8	88.2		3.7	96.3	
Bachelor and higher	60	95.5	4.5		22.0	78.0		14.6	85.4		3.7	96.3	
Distribution of cascade of hypertension care in Nepal in 2019													
Characteristic	Total	Screening		*p*	Awareness		*p*	Treatment		*p*	Control		*p*
		Yes	No		Yes	No		Yes	No		Yes	No	
Age													
15-29 years	183	47.3	52.7	<0.001	7.4	92.6	<0.001	1.0	99.0	<0.001	0.1	99.9	<0.001

30-44 years	488	68.6	31.4		19.9	80.1		5.6	94.4		3.4	96.6	
45-69 years	915	65.1	34.9		27.6	72.4		15.5	84.5		6.0	94.0	
Gender													
Men	737	61.2	38.8	0.756	18.3	81.7	0.107	7.8	92.2	0.142	2.8	97.2	0.109
Women	849	62.5	37.5		22.9	77.1		10.6	89.4		5.0	95.0	
Marital status													
Never married	72	53.7	46.3	0.278	9.5	90.5	0.048	2.8	97.2	0.075	2.7	97.3	0.799
Currently married	1,399	63.4	36.6		21.8	78.2		9.5	90.5		3.9	96.1	
Widowed	93	47.1	52.9		18.9	81.1		12.9	87.1		4.8	95.2	
Other (separated, divorced)	22	57.2	42.8		17.1	82.9		17.1	82.9		0.0	100.0	
Education													
No formal schooling	731	54.6	45.4	0.069	20.1	79.9	0.683	10.7	89.3	0.038	3.8	96.2	0.078
Lower than primary school	184	64.8	35.2		21.4	78.6		4.1	95.9		1.6	98.4	
Primary school	278	66.3	33.7		20.9	79.1		8.6	91.4		3.8	96.2	
Secondary school	247	62.7	37.3		16.8	83.2		7.9	92.1		4.6	95.4	
High school	94	78.2	21.8		24.9	75.1		6.5	93.5		1.1	98.9	
Bachelor and higher	51	75.2	24.8		28.3	71.7		19.7	80.3		11.8	88.2	
Occupation													
Government employee	45	91.5	8.5	0.126	39.3	60.7	0.09	22.1	77.9	0.012	9.0	91.0	0.459
Non-government employee	110	58.3	41.7		17.5	82.5		2.5	97.5		0.6	99.4	
Self-employed	429	66.7	33.3		23.1	76.9		10.2	89.8		4.2	95.8	
Homemaker	864	59.5	40.5		19.8	80.2		9.8	90.2		4.5	95.5	
Student	37	46.9	53.1		9.3	90.7		0.0	100.0		0.0	100.0	
Unemployed	49	51.9	48.1		7.2	92.8		0.6	99.4		0.0	100.0	
Other (retired, non-paid job)	52	73.1	26.9		31.6	68.4		19.1	80.9		4.2	95.8	
Wealth quintile													
Lowest	443	48.8	51.2	0.004	11.7	88.3	<0.001	4.2	95.8	<0.001	1.5	98.5	<0.001
Second	277	61.3	38.7		17.3	82.7		5.3	94.7		1.4	98.6	
Middle	275	61.2	38.8		18.6	81.4		7.9	92.1		2.1	97.9	
Fourth	265	63.3	36.7		20.3	79.7		9.1	90.9		4.5	95.5	

Higher	326	76.4	23.6		35.2	64.8		19.2	80.8		9.8	90.2	
Residence													
Urban	246	58.2	41.8	0.676	21.9	78.1	0.766	11.5	88.5	0.418	4.4	95.6	0.706
Rural	1,340	62.2	37.8		20.2	79.8		8.7	91.3		3.7	96.3	
Province													
Province 1	268	71.0	29.0	0.001	22.9	77.1	0.289	10.4	89.6	0.038	3.6	96.4	0.079
Province 2	183	60.2	39.8		22.5	77.5		11.4	88.6		5.4	94.6	
Bagmati	232	74.6	25.4		21.4	78.6		13.0	87.0		7.1	92.9	
Gandaki	273	76.3	23.7		26.4	73.6		12.6	87.4		4.0	96.0	
Lumbini	246	47.4	52.6		14.7	85.3		5.0	95.0		1.9	98.1	
Karnali	180	54.1	45.9		21.9	78.1		7.5	92.5		1.3	98.7	
Sudurpaschim	204	49.9	50.1		17.7	82.3		3.2	96.8		1.7	98.3	
Health insurance													
Yes	140	81.0	19.0	0.002	38.1	61.9	<0.001	23	77	<0.001	9.7	90.3	<0.001
No	1446	59.8	40.2		18.5	81.5		7.6	92.4		3.2	96.8	

Supplementary table 4: Chapter four, Section B. Search strategies

Sn	Search Engine	Syntax
1	PubMed	(hypertension OR "blood pressure") AND Nepal* NOT animal
2	CINAHL	TX (hypertension OR “blood pressure”) AND TX Nepal NOT TX animals
3	Web of Science	((hypertension OR "blood pressure")) AND TOPIC:(Nepal) NOT TOPIC: (Animal)
4	Embase	(hypertension OR “blood pressure”) AND Nepal NOT animal
5	ProQuest	(Hypertension OR "blood pressure") AND Nepal NOT Animal
6	WorldCat	(Hypertension OR "blood pressure") AND Nepal NOT Animal

Supplementary table 5: Chapter four, Section B. Qualitative assessment of the studies using MMAT 2018

Category	Study ID	Items					Overall stars
Qualitative study checklist		1.1	1.2	1.3	1.4	1.5	
	Devkota et al. (2016)	*	*	*	*	*	*****
	Khanal et al. (2017)	#	#	*	#	*	**
A	Oli et al. (2014)	*	*	*	*	*	*****
	Shrestha et al. (2018)	*	*	#	*	*	****
Randomized controlled trials checklist		2.1	2.2	2.3	2.4	2.5	
	Neupane et al. (2018)	*	*	#	*	*	****
B	Khadka et al. (2010)	##	*	*	#	*	***
Nonrandomized studies checklists		3.1	3.2	3.3	3.4	3.5	
	Bhandari et al. (2015)	*	*	*	*	##	****
A	Devkota et al. (2016)	*	*	*	#	##	***
	Dhimal et al. (2020)	*	*	*	#	##	***
	Khan et al. (2013)	#	*	*	#	##	**
	Maharjan S (2016)	#	*	*	#	##	**
	Roka et al. (2020)	#	*	*	*	##	***
	Simkhada R (2012)	#	*	*	#	##	**
	Humagain et al. (2015)	#	*	*	#	*	***
B	Kumar et al. (2019)	*	*	#	#	*	***
	Sharma et al. (2014)	#	*	*	#	*	***
Mixed method study check list		5.1	5.2	5.3	5.4	5.5	
A	Devkota et al. (2016)	#	*	*	#	*	***
A, studies assessed facilitators and barriers; B, studies investigated strategies for hypertension treatment and control							
Responses: *, Yes; #, No; ##, Can't tell							
Items for qualitative study checklist							

1.1. Is the qualitative approach appropriate to answer the research question?
1.2. Are the qualitative data collection methods adequate to address the research question?
1.3. Are the findings adequately derived from the data?
1.4. Is the interpretation of results sufficiently substantiated by data?
1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?
Items for quantitative randomized controlled trials
2.1. Is randomization appropriately performed?
2.2. Are the groups comparable at baseline?
2.3. Are there complete outcome data?
2.4. Are outcome assessors blinded to the intervention provided?
2.5 Did the participants adhere to the assigned intervention?
Items for quantitative nonrandomized studies
3.1. Are the participants representative of the target population?
3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?
3.3. Are there complete outcome data?
3.4. Are the confounders accounted for in the design and analysis?
3.5. During the study period, is the intervention administered (or exposure occurred) as intended?
Items for mixed method study
5.1. Is there an adequate rationale for using a mixed methods design to address the research question?
5.2. Are the different components of the study effectively integrated to answer the research question?
5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?
5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?
5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?

Supplementary table 6: Chapter four, Section B. Template used for qualitative analysis

Keywords	Definition
Barriers	Factors that prevent hypertension treatment and adequate blood pressure control
Enablers	Enablers are the personal or contextual factors that facilitate actions or a required behaviour for hypertension treatment and control
Strategies	Strategies are to improve blood pressure control including interventions, programs, or policies targeted at the providers, patients, or other components of the HS

Health system excluding provider and patient (HS)	A health system consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health through provision of health care services, resource generation, financing, and stewardship, among other. The health care providers and patients are listed in the separate domains for our study purpose.
Health care provider	Healthcare providers are institutions or individuals providing healthcare services.
Patient-related	Hypertensive patient reported barriers include, for example, knowledge, perception, beliefs, practices, self-efficacy, motivation, family support, affordability, and socio-cultural factors
Lack of access	When hypertensive patients cannot access the hospital or clinician or could not receive medical care due to transportation, distant or lack of healthcare facilities
Lack of medicine	Short supply of antihypertensive medication in primary health care centre or health post
Lack of health care financing	Refers to the lack of payments regarding hospital care, physician care, dental care, prescriptions, and other personal medical services
Lack of hypertension treatment guidelines	Lack of country-specific hypertension treatment guidelines
Lack of motivation	Lacking motivation to treat, monitor and counselling to patients among health care provider
Lack of communication	Gap in communication between health care providers and patients
Lack of physician counselling	Physician or health care workers not providing enough counselling for lifestyle modification and drug use
Lack of knowledge	Lacking of knowledge on hypertension and related treatment and lifestyle management among patients
Misbelief	It is about wrong belief about hypertension, medication and practices to control high blood pressure among patients
Lost to follow up	Patients quitting the follow-up visit to health care providers

Lack of adherence	Patient's compliance over drug and lifestyle medication
Medication side effect	Self-perceived adverse effects of antihypertensive medication among patients
Lack of family support	Not getting supports from family members in areas such as physician appointment, diet, exercise and medication adherence among others
Outreach services	Delivering health services to hard to reach population by mobilizing the health workers away from the location where they usually work and live
Co-payment	A fixed amount paid by a patient to the provider of service before receiving the service.
Task shifting	Delegation of non-specialized medical tasks to less specialized health workers
Team based care	Providing health services by a team of physicians, nurses or other health workers collaboratively
Health education	Imparting information to patients about prevention and control of hypertension
Home based BP monitoring	To monitor their blood pressure at home and use those readings in their day-to-day care, recommend a team of experts.
Polypill	Administering multiple, low-dose hypertension medications

Supplementary table 7: Chapter four, Section B. Characteristics of the studies on barriers and enablers of hypertension treatment and control

Sn	Study ID	Study types	Sampling method	Data collection method	Participants	Sample size total (m/f)	Survey year	Survey site	Area	Outcome	Comments	MMAT scores
1	Bhandari et al. (2015)	Cross-sectional, quantitative study	Random sampling (154 from 975 hypertensive participants)	Semi-structured interview	Hypertensive persons of age 35 years and above	154 (NA/NA)	September 2009 to February 2010	Dharan sub-metropolitan city	Urban	Adherence to medication, hypertension control	Sex, education, occupation, family history of hypertension were adjusted. No information on gender distribution	****
2	Devkota et al. (2016)	Cross-sectional, mixed-methods study	Stratified random sampling for the quantitative part	Structured interview	Hypertensive persons of age between 18 years and 70 years -	118 (54/64)	January to July 2015	Kathmandu, Nepal	Peri-urban	Hypertension awareness, hypertension treatment,	No adjustment of confounding in analysis	***
			purposive sampling in the qualitative component	Key informant interview	Cardiologist	2 (2/0)	January to July 2015	Kathmandu, Nepal	Peri-urban	Hypertension awareness, hypertension treatment,		*****
				Focus group discussion, Key	Uncontrolled hypertensive persons of age 18-70 years	20 (10/10)						
3	Dhimal et al. (2020)	Cross-sectional, quantitative study	Multistage cluster sampling	Structured interview	Initially sampled 6328 participants of age 15-69 years. Among them, 296 hypertensive participants who were prescribed antihypertensive medication by health workers, but stopped taking antihypertensive medications at least from last 12 days	296 (120/176)	February to May 2019	Nationwide	-	Adherence to medication	Nationally representative sample for assessing the non-communicable disease risk factors. This study was not specifically designed for assessing barriers to treatment and control of hypertension	***
4	Khan et al. (2013)	Cross-sectional, quantitative study	Not clear	Structured interview	Treated hypertensive persons	79 (44/35)	2012	Pokhara	Urban	Hypertension control	No clear explanation on sampling procedures, no adjustment of confounding in analysis	**

5	Khanal et al. (2017)	Cross-sectional, qualitative study	Purposive sampling	In-depth interview	Health care providers (health assistants, pharmacy assistants, nurse, specialised nurse, practising pharmacists, chief hospital pharmacist, doctors, and specialised doctor)	9 (4/5)	March 2015	Lekhnath Municipality, Kaski	Not specified	Hypertension treatment	Small sample size, participants are not the hypertensive patients	**
6	Maharjan S (2016)	Cross-sectional, quantitative study	Purposive sampling	Structured interview	Hypertensive patients of age 18 years and above and who were on treatment	85 (53/32)	January and March 2016	Sahid Gangalal National Heart Center	Urban	Treatment adherence	No adjustment of confounding in analysis	**
7	Oli et al. (2014)	Cross-sectional, qualitative study	Non-probability sampling	In-depth interviews	Patients with confirmed hypertension, diabetes, heart disease for at least one year, Age 20 years and older	13 (6/7)	May and July 2013	Bhaktapur	Peri-urban	Hypertension treatment	Participants belonged to non-hypertensive patient as well	*****
8	Roka et al. (2020)	Cross-sectional, qualitative study	Sequential sampling	Structured interview	Hypertensive participants attending an outpatient clinic at the study centre	216 (110/106)	July to August 2017	Shree Birendra hospital	Not specified	Treatment adherence	Non-probability sampling	***
9	Shrestha et al. (2018)	Cross-sectional, qualitative study	Random sampling	Focus group discussion	Newly diagnosed hypertensive patients of age 18 years and above	35 (26/9)	Dec 2015 to Feb 2016	Dhulikhel Municipality	Peri-urban	hypertension awareness, hypertension treatment, hypertension control	Non-response rate is 27.8	****
10	Simkhada R (2012)	Cross-sectional, quantitative study	Random sampling	Structured interview, clinical measurements	Hypertensive participants diagnosed and under medication at least from last 6 months	147 (83/64)	1 Feb 2011- 31 July 2011	Bir Hospital, Kathmandu, Nepal	Not specified	Hypertension control	Small sample size; no age and sex-adjusted analysis	**

Supplementary table 8: Chapter four, Section B. Characteristics of the studies on the effectiveness of strategies to improve hypertension treatment and control in Nepal

Sn	Study ID	Study types	Study date and sites	Participants	Participant recruitment	Intervention	Sample size total (treatment/ control)	Outcome	MMAT score
1	Humagain et al. (2015)	Prospective comparative study	January 2015 to April 2015; Dhulikhel Hospital, Kathmandu University Nepal	Hypertensive patients of 40-80 years of age attending cardiology OPD	Enrolled all the hypertensive patients who attended the study site during the study period and divided them into three groups based on the three antihypertensive medication they used: hydrochlorothiazide 25 mg or amlodipine 5 mg or enalapril 5 mg	Participants received an antihypertensive medication (any of hydrochlorothiazide 25 mg or amlodipine 5 mg or enalapril 5 mg) and health education.	172 (NA/NA)	Systolic blood pressure Diastolic blood pressure	***
2	Khadka et al. (2010)	Randomised controlled trial	2000-2002; Yoga and lifestyle clinics, Department of Physiology, BPKIHS	Essential hypertensive patients of 30-60 years of age, without diabetes	Purposively selected the participants and Systematically randomised them into yoga and control group	Treatment group participants underwent for yoga practice scheduled for half an hour at least for 6 days in a week for 6 weeks; yogic practices were strengthening exercise (5 min), yogic asanas (6-7 minutes), Shavasan (5 minutes), meditation (5 minutes), pranayam (4 minutes)	14 (7/7)	Systolic blood pressure Diastolic blood pressure	***
3	Kumar et al. (2019)	Uncontrolled Before and After study	1 December 2016–31 May 2018; Achham, Nepal	Hypertensive patients of age 18 years and above	Among the 488 hypertensive patients enrolled in the non-communicable diseases program, the study selected 86% (340 out of 488) patients (all) with at least two follow up visits and having at least 12 week interval between baseline and endline	Intervention includes non-communicable diseases management capacity development for healthcare workers, establishment of digital and electronic health records in the centre and individual (patient) level counselling for preventive and treatment of non-communicable diseases.	340 (340/-)	Hypertension control	***
4	Neupane et al. (2018)	Clustered randomised trial	2015-2016; Lekhanath municipality, Kaski	General population (normotensive, pre-hypertensive, hypertensive) of 25-65 years of age	Participants were selected from 14 clusters. The municipality was divided into 15 clusters out of which 14 clustered were randomised into intervention and control group; 1:1 ratio.	The treatment group participants received health education on major non-communicable disease risk factors, had their blood pressure measurement and were referred (only for hypertensive participants) to health centre by the trained Female Community	1638 (939/699)	Systolic blood pressure Diastolic blood pressure	****

						Health Volunteer in every four months/year.			
5	Sharma et al. (2014)	Uncontrolled Before and After study	August 2012 to April 2013; Sankalpa Pharmacy, Kaski, Nepal	Hypertensive patients of 31 years and above attending the pharmacist run hypertension clinic	Enrolled all the eligible hypertensive patients who attended the study site	Healthcare workers (pharmacist) led one- to one counselling - contained three counselling session at 0 date, two months and four months. The contents of counselling were lifestyle modification, treatment, and control of hypertension	50 (50/-)	Systolic blood pressure Diastolic blood pressure	***

Supplementary table 9: Chapter four, Section B. Barriers and enablers of hypertension treatment and control reported in qualitative studies

Domain	Barriers	Enablers
Health system-related (excluding provider and patient)	Unaffordable services [1]; Lack of human resources and diagnostic tools [2]	Free essential medicines at health centre [2]
Health care provider-related	Communication gap between patients and providers regarding medication use and follow-up visits [1-4]; Inadequate counselling on lifestyle modifications [1-4]; Long waiting hours [1, 3]; Lack of national guidelines for hypertension treatment [3]; Provider's unsupportive behaviours [1]	-
Patient-related	Non-adherence [1, 3]; Irregular follow-up visits [2, 3]; Poor help-seeking behaviours [2]; Reluctance to change behaviours [1]; Reluctance to take medication [1].; Perceived side effects of anti-hypertensive medication [1, 3]; Self-medication [2]; Lack of family support [1]; Financial hardship [4]	Family support [1, 4]; Perceived seriousness of the illness [1]; Self-motivation [1]; Use of reminders for medication [1]; Use of medication containers [1]

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Supplementary table 10: Chapter four, Section B. Barriers to hypertension treatment and control in quantitative studies

Domain	Barriers	variables studied	Effect on outcome variables		Voting	Study quality
			Treatment non-adherence	Uncontrolled hypertension		
Health system related	High cost of medicine	Expensive (vs. affordable) medicine [1]	Odds ratio = 5.2; 95% CI: 1.1-23.9	-	++	Good
		Expensive medicine [2]	5% of those who did not take medicine			Fair
	Unavailability of medicine	Medicine is not available [2]	1.7% of those did not take medicine		+	Fair
Provider related	Long waiting time at hospital for appointment	long waiting hours (>20 minutes vs. ≤ 20 minutes) [3]		Odds ratio = 2.7; 95% CI: 1.1-6.8;	+	Fair
	Lack of behavior change counselling from the health providers	No counselling [3]		Odds ratio = 2.6, 95% CI 1.2-6.4	+	Fair
	Multiple pills prescription	Multi-pills (more than one vs. one antihypertensive drug prescription) [1]	Odds ratio = 6.4; 95% CI: 1.2-33.4		+	Good
Patient related	Lack of follow-up consultations	Lost to follow up (irregular vs regular) [1]	Odds ratio = 6.4; 95% CI: 1.2-33.4		++	Good
		Lost to follow up (no follow up vs regular follow-up) [3]		Odds ratio = 3.3, 95% CI: 1.2-9.1		Fair
		lack of blood pressure monitoring [4]		Odds ratio = 2.9, 95% CI: 1.0-8.0		Fair
	Poor adherence to medication	Non-adherence to medication (low adherence vs high adherence) [3]		Odds ratio = 9.1, 95% CI: 3.5-24.1;	++	Fair
		Non-adherence to medication [4]		Odds ratio = 5.8, 95% CI: 2.7-12.6;		Fair
	Lack of awareness on blood pressure target	Lack of awareness on blood pressure target [3]		Odds ratio = 3.2; 95% CI: 1.3-8.2;	++	Fair
		Not aware of normal blood pressure [4]		Odds ratio = 2.8, 95% CI: 1.3-6.1;		Fair

	Lack of awareness on blood pressure complications	lack of awareness on high blood pressure complications [4]		Odds ratio = 2.6, 95% CI: 1.2-6.1;	+	Fair
	Comorbidity	Comorbidity (yes vs no) [5]	Odds ratio = 2.5; 95% CI: 1.3-4.9		+	Fair
	Others	Do not think drug is necessary [2]	37.8% of those who did not take medicine		+	Fair
		Perceived side effect of drugs [2]	6.1% of those who did not take medicine		+	Fair

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Supplementary table 11. Chapter six, Section A. Number of participants across trial centres

	Intervention group		Control group	
Trial centre	Target sample size	Recruited	Target sample size	Recruited
Dhading	10	9	10	8
Kaski	10	10	10	10
Nuwakot	10	10	10	10
Ramechap	10	9	10	10
Surkhet	10	10	10	10
Rolpa	10	5	10	4
Rupandehi	10	8	10	8
Total	70	61	70	60

Supplementary table 12: Chapter six, Section A. Yoga Module for Hypertensive Patients

	Practices	Duration (min)
1.	Starting with “omkar”	1 min
2.	Warm-up exercises with synchronization of breathing in the sitting position: 1. Toe bending 2. Ankle bending 3. Knee bending 4. Half butterfly 5. Finger bending 6. Wrist bending 7. Elbow bending 8. Shoulder rotation 9. Neck bending up and down	5 min
3.	Yogic abdominal awareness, breathing and feeling in “shavasana”	3 min
4.	“Ardhakatichakrasan” (Lateral Arc Pose)	2 min
5.	“Vakrasana” (Twist Pose)	2 min
6.	“Chandravedi Pranayam” (Left nostril breathing)	2 min
7.	“Sheetali Pranayam” (Cooling breathing)	2 min
8.	“Nadi Suddhi Pranayama” (Alternate Nostril breathing)	2 min
9.	“Bhramari” (Humming bee breathing)	2 min
10.	Yoga “nidra” (Yogic sleep)	9 min
	Total Time	30 min

Supplementary table 13: Chapter six, Section A. Imputation variance information for systolic blood pressure

	Imputation variance					
Variables	Within	Between	Total	RVI	FMI	Relative efficacy
Age	0.009826	0.000038	0.009868	0.004202	0.004188	0.999581
Female	2.8767	0.11946	3.0081	0.045679	0.044089	0.99561
Marital status						
Others	4.36113	0.420532	4.82371	0.10607	0.09774	0.990321
Education	0.014923	0.000657	0.015646	0.048433	0.046648	0.995357
Occupation						
Self employed	1.96841	0.253266	2.247	0.141532	0.126961	0.987463
Homemakers	5.54746	0.112635	5.67136	0.022334	0.02195	0.99781

Others	4.95901	0.135234	5.10776	0.029997	0.029307	0.997078
Income	6.70E-14	5.30E-16	6.70E-14	0.008675	0.008617	0.999139
Smoking						
Yes	4.07474	0.232305	4.33028	0.062712	0.059739	0.994062
Alcohol consumption						
Yes	1.93501	0.172866	2.12516	0.09827	0.091092	0.990973
Physical activity	2.50E-08	1.60E-09	2.60E-08	0.072499	0.068544	0.993192
BMI baseline	0.025952	0.001298	0.02738	0.055023	0.052726	0.994755
BMI difference	0.378505	0.036402	0.418548	0.105791	0.097504	0.990344
Antihypertensive medication						
yes	1.92209	0.063736	1.9922	0.036476	0.035457	0.996467
Heart rate	0.022505	0.000172	0.022695	0.008409	0.008355	0.999165
SBP baseline	0.009674	0.000079	0.009762	0.009015	0.008952	0.999106
Group						
Intervention	1.17849	0.137016	1.3292	0.127891	0.115912	0.988542
_cons	161.666	0.396209	162.101	0.002696	0.00269	0.999731

Supplementary table 14: Chapter six, Section A. Checklist for assessing content fidelity

	Yoga exercises	Score	Health education topics	Score
1.	"Omkar"	1	Assessing the level of participants' understanding of high blood pressure	1
2.	Warm-up exercises	1	Introduction about high blood pressure	1
3.	Yogic abdominal awareness	1	Risk factors for high blood pressure	1
4.	Lateral arc pose	1	Complications of high blood pressure	1
5.	Twist pose	1	Behavioural approaches for the management of high blood pressure	1
6.	Left nostril breathing	1		
7.	Cooling breathing	1		
8.	Alternate nostril breathing	1		
9.	Humming bee breathing	1		
10.	Yogic sleep	1		
	Maximum score	10		5

Supplementary table 15: Chapter six, Section A. Intervention effects on systolic blood pressure, results of multilevel mixed-effects linear regression

Characteristic		Unadjusted model†		Model 2‡		Model 3§	
		B	CI‖	B	CI‖	B	CI‖
Age (years)		0.1	-0.10, 0.31	0.06	-0.15, 0.28	0.14	-0.06, 0.33
Gender	Male						
	Female	0.06	-5.21, 5.34	1.81	-1.70, 5.32	2.86	-0.54, 6.26
Marital status	Married						
	Others	1.19	-1.86, 4.23	-0.72	-5.83, 4.39	-1.02	-5.33, 3.29
Education		-0.05	-0.42, 0.31	-0.01	-0.24, 0.23	0.05	-0.19, 0.30
Occupation	Job						
	Self-employed	-1.71	-5.88, 2.47	-2.85	-5.79, 0.09	-2.01	-4.96, 0.93
	Homemaker	-2.03	-6.66, 2.59	-3.23	-7.95, 1.49	-3.41	-8.08, 1.25
	Others	2.7	-2.53, 7.92	-0.95	-5.49, 3.58	-0.38	-4.81, 4.05
Household income (Nepali Rupees)		-1.10e-06	-1.90e-06 -2.89e-07	-7.58e-07 ***	-1.09e-06, -4.28e-07	-9.93e-07***	-1.50e-06, -4.85e-07
Smoking	No						
	Yes	3.2	-2.65, 9.06	0.08	-4.62, 4.78	-0.98	-5.06, 3.10
Alcohol consumption	No						
	Yes	1.55	-1.86, 4.96	1.1	-1.51, 3.70	1.52	-1.34, 4.38
Physical activity (METs-minute)		0.00034	-0.0006, 0.0013	-0.00028	-0.0007, 0.00014	-0.00007	-0.00039 0.00025
Baseline BMI (kg/m^2)		0.06	-0.23, 0.34	0.35*	0.04, 0.66	0.36*	0.04, 0.69
Difference in BMI (kg/m^2)						-2.47***	-3.74, -1.20

antihypertensive medication	No						
	Yes	-0.46	-3.96, 3.04	-0.08	-2.87, 2.70	-0.93	-3.70, 1.83
Baseline heart rate (beats/minute)		-0.01	-0.37, 0.35	-0.05	-0.34, 0.25	-0.02	-0.31, 0.28
Baseline diastolic blood pressure (mmHg)		0.54***	0.36, 0.72	0.67***	0.45, 0.90	0.63***	0.43, 0.82
Treatment allocation	Control						
	Intervention	-4.53	-9.88, -0.73	-7.41***	-9.76, -5.06	-6.36***	-8.63, -4.10

Note: †, Model included a dichotomous independent variable representing belonging to the intervention group ("1") or control group ("0") and trial centre as a second-level variable;
‡, Adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, body mass index (BMI), resting heart rate, and baseline systolic blood pressure;
§, Additionally adjusted for the difference in BMI between baseline and follow-up;
‖, 95% confidence interval for B;
*, p <0.05; **, p <0.01; ***, p<0.001

Supplementary table 16: Chapter six, Section A. Intervention effects on diastolic blood pressure, results of multilevel mixed-effects linear regression

Characteristic		Unadjusted model †		Model 2‡		Model 3§	
		B	CI‖	B	CI‖	B	CI‖
Age (years)		0.04	-0.07,0.15	0.04	-0.10, 0.17	0.11	-0.02, 0.24
Gender	Male						
	Female	-0.71	-3.62, 2.20	-0.13	-2.01, 1.74	0.71	-1.06, 2.47
Marital status	Married						
	Others	1.14	-1.03, 3.32	-1.41	-4.31, 1.50	-1.58	-3.36, 0.21
Education		0.06	-0.14,0.26	-0.06	-0.23, 0.12	-0.01	-0.15, 0.13
Occupation	Job						
	Self-employed	-3.71*	-7.13, -0.3	-3.83***	-5.71, -1.95	-3.03***	-4.56, -1.49
	Homemaker	-2.44	-5.73, 0.84	-2.32*	-4.38, -0.26	-2.39*	-4.28, -0.49
	Others	1.01	-3.11, 5.13	0.67	-2.15, 3.48	1.07	-1.59, 3.73
Household income (Nepali Rupees)		-6.33e-07	-1.09e-06, -1.74e-07	-5.53e-07***	-8.56e-07, -2.49e-07	-7.61e-07***	-1.19e-06, -3.30e-07
Smoking	No						
	Yes	1.62	-1.86, 5.09	0.02	-4.02, 4.05	-1.15	-3.53, 1.23
Alcohol consumption	No						
	Yes	1.42	-1.17, 4.0	0.83	-1.07, 2.72	1.19	-0.70, 3.08
Physical activity (METs-minute)		0.00031	-0.0004, 0.00104	-1.51e-06	-.000782, 0.00078	0.00017	-0.00038, 0.00073
Baseline BMI (kg/m^2)		-0.04	-0.22,0.14	0.04	-0.19, 0.27	0.08	-0.18, 0.35
Difference in BMI (kg/m^2)						-2.33***	-3.49, -1.16
antihypertensive medication	No						
	Yes	-0.55	-2.78, 1.68	-0.2	-2.53, 2.12	-1.14	-3.23, 0.95

Baseline heart rate (beats/minute)		0.1	-0.12,0.32	0.08	-0.07, 0.23	0.1	-0.04, 0.24
Baseline diastolic blood pressure (mmHg)		0.41**	0.15,0.67	0.42**	0.13, 0.70	0.41**	0.15, 0.67
Treatment allocation	Control						
	Intervention	-3.49*	-6.4, -0.59	-3.49**	-6.13, -0.86	-2.73*	-5.06, -0.41

Note: †, Model included a dichotomous independent variable representing belonging to the intervention group ("1") or control group ("0") and trial centre as a second-level variable;
‡, Adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, body mass index (BMI), resting heart rate, and baseline diastolic blood pressure;
§, Additionally adjusted for the difference in BMI between baseline and follow-up;
‖, 95% confidence interval for B;
*, p <0.05; **, p <0.01; ***, p<0.001

Supplementary table 17: Chapter six, Section A. Models adjusted for the difference in heart rate between baseline and follow-up

Characteristic		Model 4†	
		B	CI§
Age (in years)		0.15	-0.06, 0.36
Gender	Male		
	Female	2.94	-0.59, 6.47
Marital status	Married		
	Others	-0.82	-4.87, 3.22
Education		0.07	-0.17, 0.32
Occupation	Job		
	self-employed	-2.01	-4.69, 0.68
	Homemaker	-3.41	-7.95, 1.13
	Others	-0.55	-5.05, 3.95
Household income (Nepali Rupees)		-9.58e-07 ***	-1.53e-06, -3.88e-07
Smoking	No		
	Yes	-1.33	-5.50, 2.85
Alcohol consumption	No	0	0.00, 0.00
	Yes	1.6	-1.20, 4.39
Physical activity (METs/min)		-0.00011	-0.00042 0.0002
Baseline BMI (kg/m^2)		0.37*	0.04, 0.71
Difference in BMI (kg/m^2)		-2.28**	-3.87, -0.70
Antihypertensive medication	No		
	Yes	-1.09	-4.11, 1.94
Baseline heart rate (beats/minute)		0.12	-0.27, 0.50
Difference in heart rate		-0.24	-0.67, 0.20
Baseline systolic blood pressure		0.62***	0.42, 0.82
Treatment allocation	Control		
	Intervention	-6.18***	-7.93, -4.42

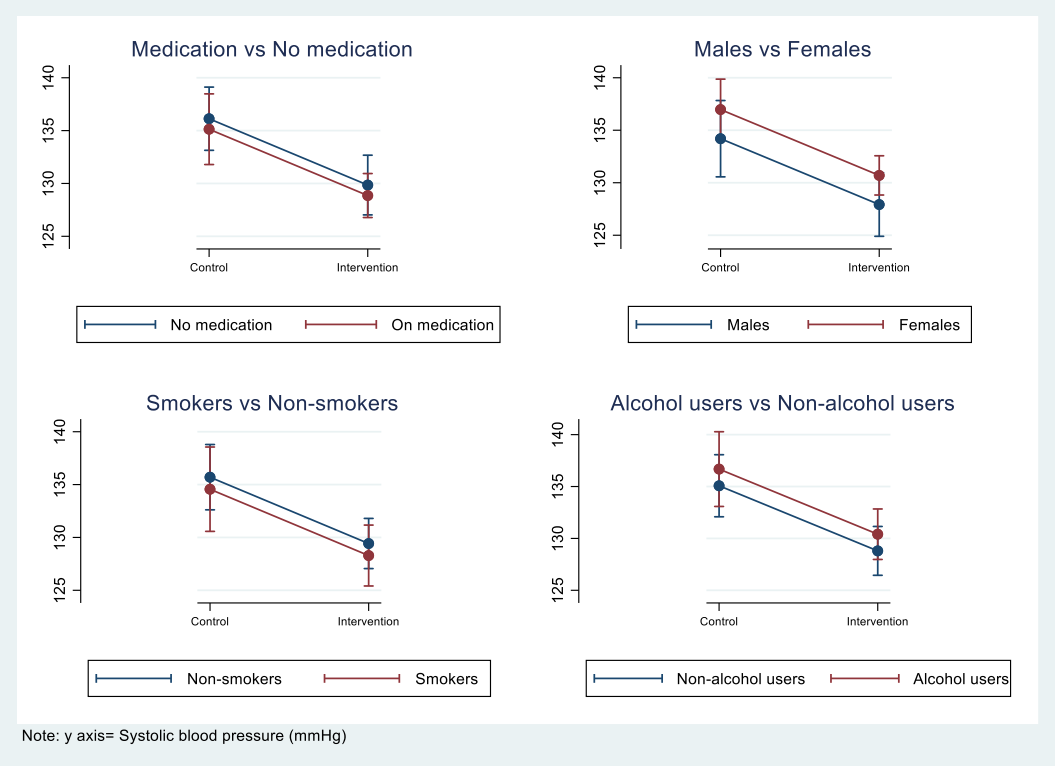
Note: †, Model included a dichotomous independent variable representing belonging to the intervention group ("1") or control group ("0") and trial centre as a second-level variable; Adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, body mass index (BMI), change in resting heart rate, and baseline systolic blood pressure;
§, 95% confidence interval for B;
*, p <0.05; **, p <0.01; ***, p<0.001

Supplementary table 18: Chapter six, Section A. Intervention effects on diastolic blood pressure

Characteristic		Model 4†	
		B	CI§
Age (years)		0.11	-0.03, 0.24
Gender	Male		
	Female	0.71	-1.17, 2.60
Marital status	Married		
	Others	-1.64*	-2.96, -0.33
Education		0.02	-0.16, 0.16
Occupation	Job		
	self-employed	-3.02***	-4.34, -1.71
	Homemaker	-2.37*	-4.24, -0.49
	Others	1.04	-1.53, 3.62
Household income (Nepali Rupees)		-7.43e-07 ***	-1.18e-06 -3.08e-07
Smoking	No		
	Yes	-1.23	-3.70, 1.24
Alcohol consumption	No		
	Yes	1.24	-0.45, 2.93
Physical activity (METs/min)		0.00017	-0.00034 0.00067
Basline BMI (kg/m^2)		0.08	-0.19, 0.35
Difference in BMI (kg/m^2)		-2.30***	-3.57, -1.03
Antihypertensive medication	No		
	Yes	-1.13	-3.26, 0.99
Baseline heart rate (beats/minute)		0.15	-0.04, 0.34
Difference in heart rate (beats/minute)		-0.08	-0.42, 0.25
Baseline diastolic blood pressure		0.41**	0.16, 0.67
Treatment allocation	Control		
	Intervention	-2.65*	-4.84, -0.46

Note: †, Model included a dichotomous independent variable representing belonging to the intervention group ("1") or control group ("0") and trial centre as a second-level variable; Adjusted for age, gender, marital status, ethnicity, education, occupation, income, smoking, alcohol consumption, physical activity, body mass index (BMI), change in resting heart rate, and baseline systolic blood pressure;
§, 95% confidence interval for B;
*, p <0.05; **, p <0.01; ***, p<0.001

Supplementary figure 1: Marginal plots for antihypertensive medication, gender, smoking, and alcohol consumption



Note: y axis= Systolic blood pressure (mmHg)

Supplementary table 19: Chapter six, Section A. Findings from fidelity assessmen

	Question	Response	n (%)
1.	Have you attended the yoga training conducted by a District Ayurveda Health Centre?	Yes	12 (100.0)
		No	0 (0.0)
2.	For how many days did you attend the training?	5 days	12 (100.0)
		< 5 days	0 (0.0)
3.	Was the training useful for you to learn yoga? Please rate its usefulness on the scale from 0 to 5, where 0 stands for “not at all useful” and 5 stands for “extremely useful”.	Average score (mean)	4.3
		Standard deviation	0.9
4.	Were you satisfied with the yoga training provided at the health centre? Please rate your satisfaction level on the scale from 0 to 5, where 0 stands for “not satisfied” and 5 stands for “extremely satisfied”.	Average score (mean)	4.6
		Standard deviation	0.5
5.	Did you practise yoga at home as part of the YoH trial, as recommended?	Yes	12 (100.0)
		No	0 (0.0)
6.	How often did you practise yoga at home in this period?	Regularly	12 (100.0)
		Sometimes	0 (0.0)
		Rarely	0 (0.0)
		Never	0 (0.0)
		I don’t remember	0 (0.0)

7.	During your home-based yoga sessions, did you follow the structure recommended by the health workers?	Yes	12 (100.0)
		No	0 (0.0)
8.	Which yoga exercises did you practise regularly?	"Omkar"	12 (100.0)
		Warm-up exercises	12 (100.0)
		Yogic abdominal awareness	12 (100.0)
		Lateral Arc Pose	12 (100.0)
		Twist Pose	12 (100.0)
		Left nostril breathing	12 (100.0)
		Cooling breathing	12 (100.0)
		Alternate nostril breathing	12 (100.0)
		Humming bee breathing	12 (100.0)
		Yogic sleep	12 (100.0)
		Other (please list)------	0 (0.0)

Supplementary table 20: Chapter six, Section B. Characteristics of the YoH intervention group and its subsample used in the current study.

Table 1. Characteristics of the YoH intervention group and its subsample used in the current study			
		Total (*n*=59)	Subsample (*n*=12)
Characteristics			
Age in years; mean (SD)		47.1 (1.4)	49.5 (3.8)
Gender	Male	42.6	33.3
	Female	57.4	66.7
Occupation	Employed	57.4	41.7
	Homemakers	39.3	58.3
	Others	3.3	0.0

Supplementary table 21: Chapter six, Section B. Template of prior themes and codes with definitions

Name of themes and codes	Definition
1. Acceptability of the intervention among participants	
1.1. Attitudes towards the intervention	Attitudes of the intervention participants towards yoga training, yoga instructors, and home-based practice
1.2. Perceived effectiveness of the intervention	Whether the participants experienced any changes in their health as a result of the intervention
1.3. Participant burden	Burden to intervention participants caused by the intervention
1.4. Opportunity cost	The loss of potential gain while participating in the yoga intervention
2. Characteristics of the intervention	

2.1. Complexity of the intervention	Implementers' perspectives regarding the complexity of the intervention
2.2. Cost of implementation	Costs associated with the implementation of the intervention
2.3. Adaptability of the intervention	To what extent was the intervention adaptable to different circumstances and situations
3. External context	
3.1. Policy priority	Government's policy regarding yoga in Nepal
3.2. Demand for yoga in the community	The demand for a yoga intervention among hypertensive people
4. Inner context of health centres	
4.1. Leadership engagement	Whether any officials from the health centres were involved in implementing the intervention or not
4.2. Personnel resources	Personnel resources for implementing a yoga intervention, particularly the availability of yoga instructors
4.3. Physical space (yoga studio)	Whether yoga studios are available in the health centres
4.4. Experience in implementing yoga programme	Previous experience of the health centres in implementing yoga-related programmes
5. Characteristics of implementers	
5.1. Knowledge and skills of yoga	Implementers' knowledge and skill, particularly regarding the academic or vocational training in yoga instruction
5.2. Motivation	The motivation of the intervention implementers for participating in the delivery of the intervention
6. Implementation process	
6.1. Intervention delivery	Whether the 5-day yoga training was delivered as intended
6.2. Intervention receipt	Whether the participants received or learned yoga intervention as planned
6.3. Intervention enactment and adherence to home-based yoga practice	Whether the participant could perform home-based yoga intervention regularly or not
7. Sustainability of the intervention	
7.1. Sustained practice of yoga intervention	Whether participants kept practising yoga even after the completion of the intervention
7.2. Institutionalising the use of yoga intervention	Health centre integrating yoga intervention in routine care