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Study, Design, and Rationale of Noncommunicable Diseases in Nepal (NCD Nepal) Study: A Community-Based Prospective Epidemiological and Implementation Study in Rural Nepal

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Abstract

Background: Noncommunicable diseases (NCDs) are the leading causes of deaths globally. Currently, there are limited high-quality data on the epidemiology and usefulness of community-based screening and treatment of NCDs in low-to-middle-income countries (LMIC), like Nepal. We describe the protocol of a community-based, longitudinal epidemiological study of screening and management of NCDs in rural Nepal.

Methods: We organize monthly mobile health clinics to screen NCDs among 40- to 75-year-old residents from municipal subdivision wards 3, 4, 6, and 7 of Ghorahi submetropolitan city, Dang, Nepal (approximately 406 km west of the capital, Kathmandu). We estimate a total of 7052 eligible participants. After obtaining informed consent, trained personnel will collect sociodemographic and lifestyle data, medical, medication, and family history using validated questionnaires, plus anthropometric measures and capillary glucose levels. We will screen for hypertension, diabetes, obesity, dyslipidemia, tobacco and alcohol use, self-reported physical activity, dietary habits, cardiovascular disease, stroke, chronic lung disease, cancer, and chronic kidney disease. We will also check hemoglobin A1C, lipid panel, serum creatinine, sodium, potassium, urine dipstick, and urine albumin-to-creatinine ratio in high-risk participants. We will offer lifestyle counseling,

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pharmacotherapy or refer to higher level care, where appropriate; routinely follow participants with NCDs for continuity of care; and follow individuals without NCDs but with elevated glucose, prehypertension or other risk factors every year, and those without risk factors every 2 years. We will monitor participants in the community to reduce attrition and to track all-cause and disease-specific mortality.

Discussion: Understanding the community burden of NCDs in resource-limited setting and testing effectiveness of community-based screening and management of NCDs will provide insights to develop national policy to address NCD burden in LMIC like Nepal.

Keywords

community-based intervention, disparity, low- and middle-income countries, Nepal, noncommunicable diseases, rural health, diabetes, hypertension, tobacco use, cardiovascular disease

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Background

Noncommunicable diseases (NCDs) are the leading cause of death globally.[1] Cardiovascular diseases (CVDs) account for most NCD deaths worldwide with over three quarters occurring in low-to-middle income countries (LMIC).[1] Several NCDs, including CVD, stroke, cancer, and chronic kidney disease (CKD) share hypertension, diabetes, obesity, dyslipidemia, tobacco consumption, alcohol drinking, low physical activity, and unhealthy diet as risk factors. Although more than 80% of the global burden of CVD occurs in LMIC, there is a paucity of high-quality data in LMIC about CVD, chronic lung disease, cancer, and their risk factors.[1–3] To fulfill the calls to mitigate the global burden of NCDs, a better understanding of the epidemiology of NCD in LMIC, especially in the rural areas, is needed.[4]

National disease burden paradigm is shifting toward NCDs in Nepal, posing an additional burden on a resource-limited health system.[5] Between 1990 and 2013, life expectancy in Nepal has increased by 12 years, and the burden of myocardial infarction and stroke has increased by >60%.[3] Deaths due to CVD, diabetes, cancer, and chronic lung disease accounted for 60% of all deaths with one fourth of all deaths caused by CVD.[1,6] Similarly, while CKD is underrecognized in Nepal, especially in rural communities, one study estimated its prevalence to be 19%, as compared with 7% in the United States.[7] It is thus possible that many rural community residents are living with undiagnosed and untreated NCDs.[8]

Community-based studies of NCDs in Nepal are limited to a few risk factors, have small sample size, are mostly cross-sectional in design, and often lack laboratory investigation because of logistic challenges.[9–21] Although a simple intervention can have a meaningful population benefit,[22] longitudinal studies involving community screening and treatment of common NCDs are very limited in Nepal. Furthermore, the effect of risk factor modification on NCD incidence, its trends and complications, and the cost-effectiveness of such programs are currently lacking. There is an increasing calls for epidemiological study combined with implementation study in capacity and infrastructure building to address NCDs.[23,24] We present a study protocol to understand the epidemiology of NCDs, and the effectiveness of community implementation approaches to manage common NCDs.

Methods

Ethical Approval and Patient consent

We obtained ethical board approval from the Nepal Health Research Council. Trained personnel will obtain informed written consent from each participant.

Setting. This study is conducted by a nonprofit organization, Health Foundation Nepal, that has sister organizations in both Nepal and the United States and has built goodwill in the community from prior work.[25] It has a stationary clinic ~406 km west of Kathmandu, the capital of Nepal. This study involves 4 wards (3, 4, 6, and 7) of Ghorahi Submetropolitan City, Dang, Nepal (Figure 1). Each ward is a subdivision of a municipality with administrative and political autonomy. Any resident aged 40 to 75 years from the area are eligible (wards 3–4 and 6–7 were previously in Laxmipur and Saudiyar Village Development Committee, respectively). The 2018 Municipal Household Data Survey estimated a total population of 27 807 in the study area and a total of 7052 people (3349 men and 3703 women) aged 40 to 75 years, which will be our target population.[26]

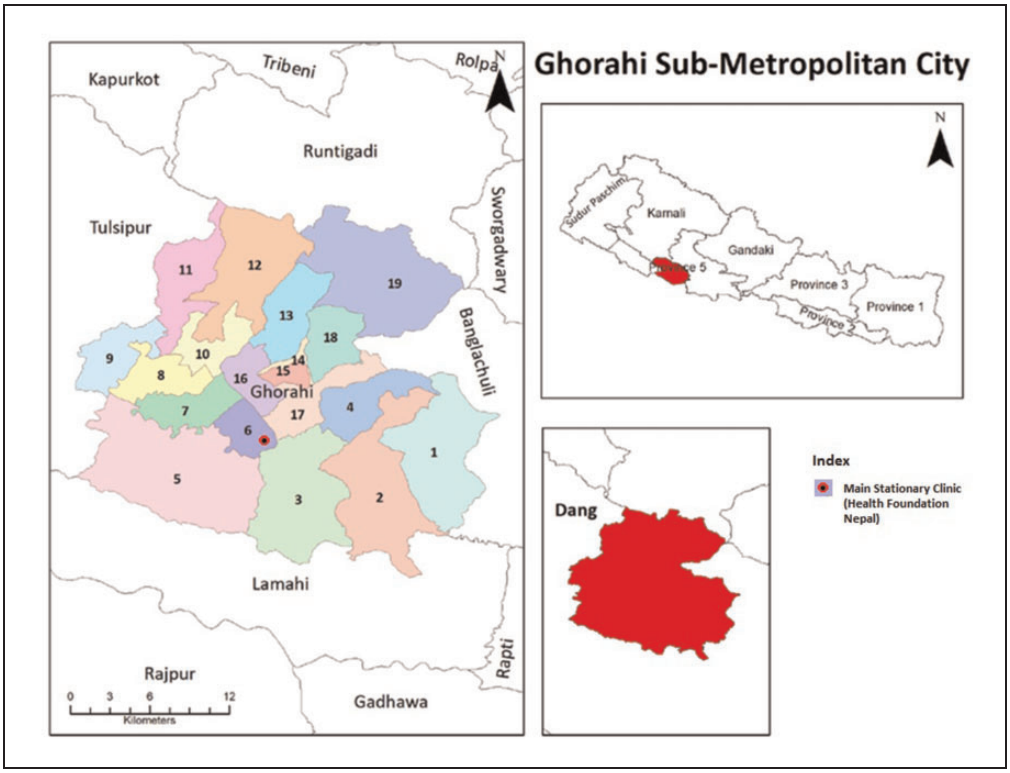

Figure 1. Map of the Broader Area and Study Site. Source: Data obtained from Ghorahi Municipal Profile 2018.[26]

Several active community resources like community leaders, mothers' group for health and female community health volunteers (FCHVs) are intimately involved with the study. They know all households and community residents because of their intricate connections.[27,28] Mothers' group for health is an active, women-led, local civil society group working on several social issues.[27] FCHVs have been working on family planning, maternal and child health, immunization, and nutrition.[28] There are 45 mothers' groups for health and 45 FCHVs in the study area.

We will conduct monthly mobile health clinics close to participants' neighborhood for ease of participation. Each mobile clinic will have 9 stations, managed by a team of physicians, nurses, health assistants, psychosocial counselors, laboratory technicians, administrative personnel, volunteers, and local community leaders (Figure 2). We first pilot tested mobile clinics to assess study feasibility and optimize workflow.

Participant Recruitment and Follow-up

Initial visit. We will first estimate a target population for each mobile clinic outreach area using the Municipal Household Data Survey, FCHVs, and mothers' group for health.[26] We will also estimate the number of people who are disabled and unable to attend the mobile clinic. We will invite community residents personally a week prior to the mobile clinic using the community network. For disabled people, we will offer community resources for transportation or visit their homes. Notified individuals not able to participate will be invited again to attend the next mobile clinic occurring in the adjoining community or they can participate directly by visiting the stationary clinic. This comprehensive approach should facilitate all eligible community residents to participate.

Follow-up visit. To maximize follow-up, 2 pathways are designed (Figure 3): one to treat and follow-up participants with established NCDs and the other for surveillance. For those with established NCDs (Figure 3, pathway 1), we will conduct the first follow-up visit within a few weeks using mobile clinic. Subsequent follow-up will be in the stationary clinic. We will coordinate with FCHVs and mothers' group to contact participants who missed their follow-up visits via phone or using a door-to-door visit, inviting them to follow-up at the next mobile clinic occurring at the adjoining area in a month or directly to the stationary clinic. Additional follow-up for continuity of care will be at the main stationary clinic and the frequency of follow-up depends on comorbidities, disease severity, laboratory requirements and other factors as per pre-specified protocols (Figure 4). All participants with established NCDs will also have yearly visit.

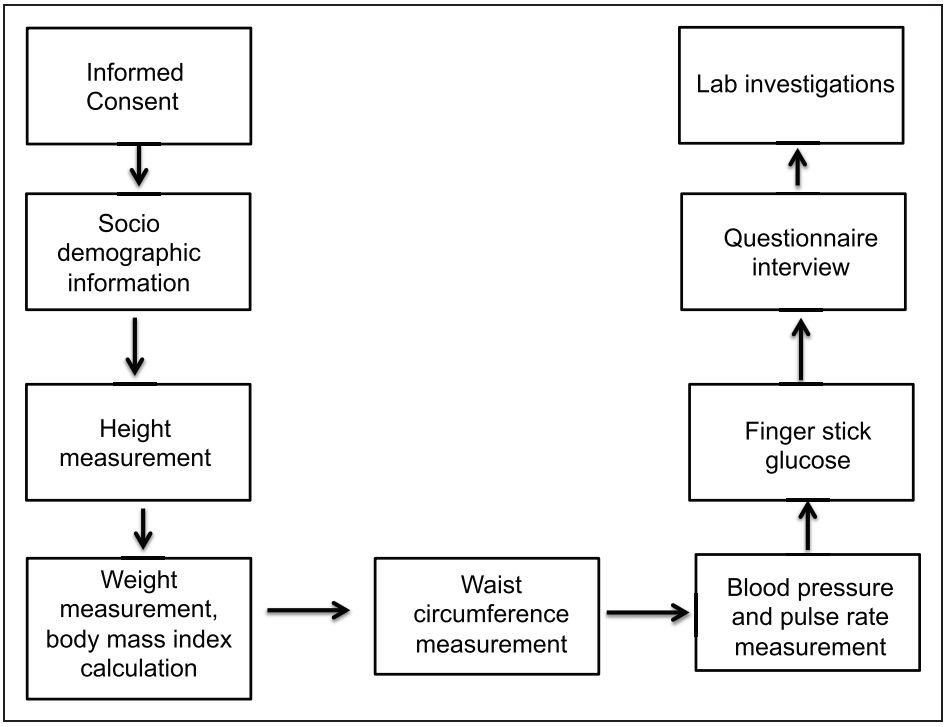

Figure 2. Mobile Clinic Setup.

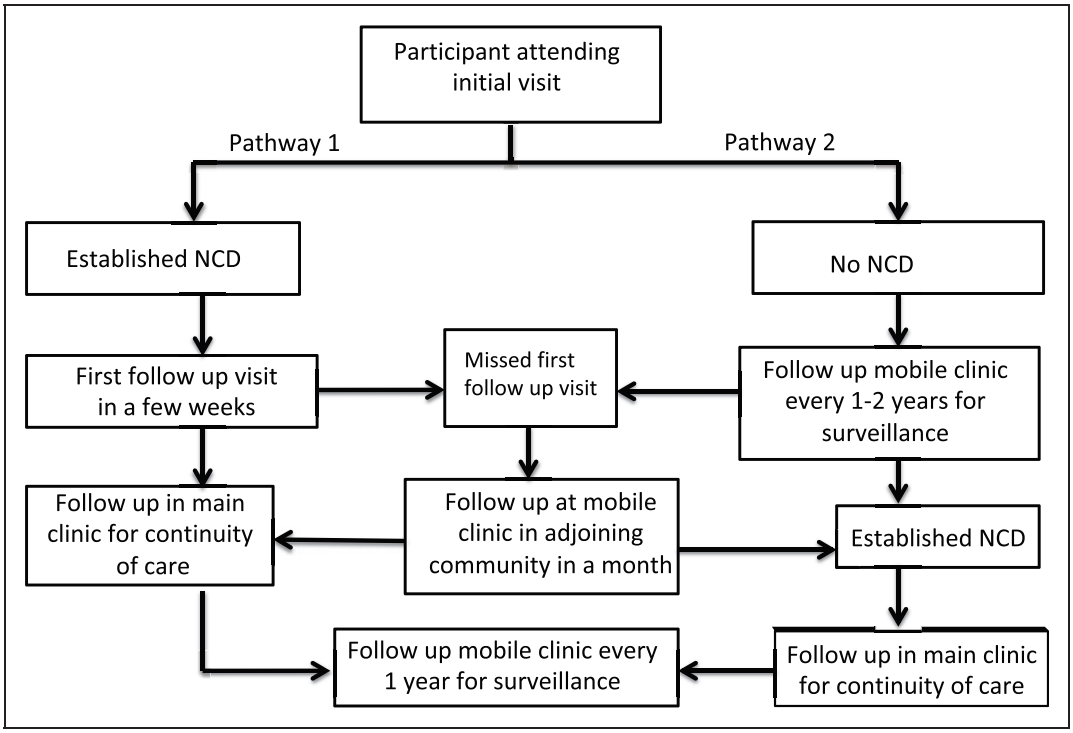

Figure 3. Follow-up Pathways. NCD, noncommunicable disease.

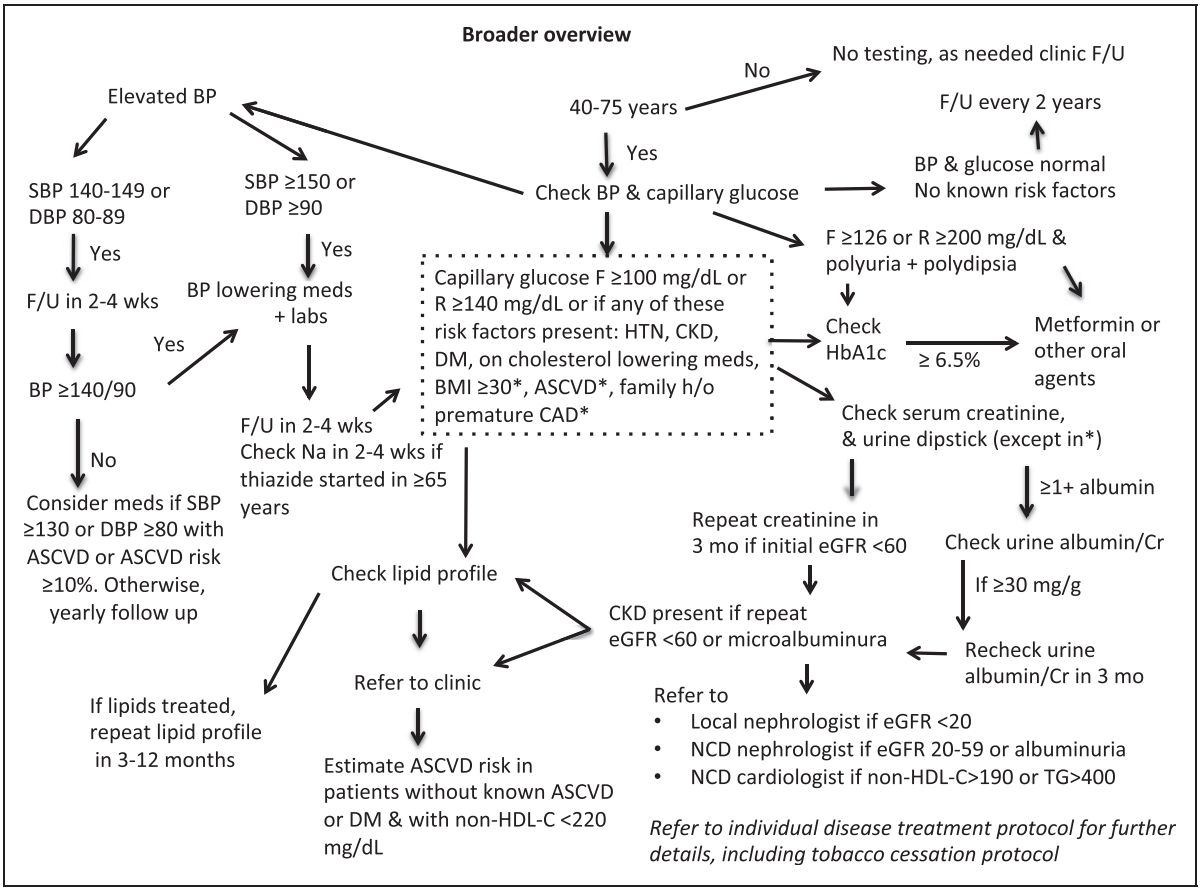

Figure 4. Broader Overview of Clinical Protocol. ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; NCD, noncommunicable disease; SBP, systolic blood pressure; TG, triglyceride. Note that (a) Lifestyle change is the cornerstone of cardiovascular disease prevention and we will counsel everyone about this. (b) We will confirm adherence to lifestyle changes and medications on each visit. (c) We will inquire all child bearing age women about pregnancy status by checking their last menstrual period prior to starting any medication unless with history of hysterectomy. We recommend reliable use of contraception, if medication is started in women with child-bearing age, and to report to clinic if planning pregnancy or found to be pregnant. (d) Additional circumstances are important in treatment decisions. The protocol is just a guide and nothing can replace clinical judgment and so clinicians will use this algorithm for general guidance and consult their counterpart NCD specialists for further guidance.

The second follow-up pathway for participants without NCDs will be performed in a mobile clinic similar to the initial visit. We will follow participants with prehypertension (systolic blood pressure [BP] 120–139 mmHg or diastolic BP 80–89 mmHg and not on pharmacotherapy), elevated glucose but without diabetes (fasting capillary glucose $\geq$100 mg/dL or random glucose $\geq$140 mg/dL without polyuria or polydipsia plus hemoglobin A1C $\leq$6.4% not on pharmacotherapy), any forms of tobacco use, unhealthy alcohol use (>1 drink per day for women or >2 drinks per day for men), family history of premature coronary artery disease, obesity (body mass index $\geq$30 kg/m^2 or waist circumference $\geq$102 cm in men or $\geq$88 cm in women), and microalbuminuria, but without CKD, every year.[29–35] Rest of the participants without NCDs will be followed every 2 years using the same questionnaire. The goal of the surveillance is to reinforce healthy lifestyle and to monitor and treat for interim NCDs (Figure 3, pathway 2). Similar to people with established NCDs, we will invite them to attend mobile clinics or into the main stationary clinic. We will provide home visits if they continue to miss follow-up. Any individual who develops incident NCD from this surveillance will join first pathway for continuity of care.

Study Outcomes

The major outcomes of interest include the incidence and prevalence of NCDs, including hypertension, diabetes, obesity, dyslipidemia, tobacco and unhealthy alcohol use, illicit drug use, household smoke exposure, low

physical activity, low fruits and vegetable consumption, and excessive salt intake. Other outcomes include all-cause and disease-specific mortality, incidence and prevalence of coronary artery disease, heart failure, peripheral artery disease, stroke, cancer, and CKD (Table 1). Additional outcomes of interest include assessment of patterns of health services use and control of NCDs in those with established disease. Using an itemized record of cost and the outcomes mentioned earlier will also allow us to examine the costs required to prevent common NCDs, including cost-utility ratios.

Pilot Testing and Questionnaire Development

We tested the study feasibility during 6 pilot mobile clinics. The initial draft of the questionnaire was partly derived from the World Health Organization STEPwise approach to surveillance survey,[11] the Demographics and Health Survey,[36] and a prior clinical trial of hypertension[22] (Table 2). These were previously translated and used in Nepali language. We added relevant questions that were translated from English to Nepali language by a bilingual investigator, which was edited by 8 additional bilingual personnel. We pretested this questionnaire in 12 individuals from diverse background and made iterations to improve clarity. Subsequently, we pre-tested the Nepali version of the questionnaire in 25 individuals from nearby local population attending a different health facility. After sequential editing to improve clarity, the final initial questionnaire has 320 variables (Table 2).

Similarly, we tested the feasibility of follow-up during 6 follow-up mobile clinics in those with NCD. We pretested the first draft of the Nepali version of the follow-up questionnaire in 28 individuals attending a nearby health facility and made iterations for clarification. The final follow-up questionnaire has 122 variables, which we will use for both continuity of care and surveillance.

Clinical Protocol

During the pilot testing of initially formulated clinical protocol, we added hemoglobin A1C, tobacco cessation protocol, and updated the pharmacological treatment algorithm (Figure 4 and Supplemental Figures 1 to 4). We will screen for hypertension, diabetes, obesity, tobacco use, low physical activity, and dyslipidemia (Figure 4). Clinical specialists from diverse backgrounds agreed on checking labs only in high-risk individual employing a pragmatic approach because checking labs in all participants can be expensive but with marginal value. We will check capillary glucose level and BP in all participants; and serum creatinine, lipid profile, urine dipstick, hemoglobin A1C, and urine albumin/creatinine ratio in high-risk people, such as those with preexisting or newly diagnosed NCD (Figure 4). We will also assess for presence of coronary artery disease, stroke, heart failure, peripheral artery disease, chronic lung disease, CKD, renal stone, cancer, and other lifestyle-related risk factors. All participants will receive counseling for healthier lifestyles, including physical activity, diet, salt intake, tobacco cessation and moderation of alcohol use, as appropriate. Therapeutic lifestyle modification will be personalized according to the presence of additional risk factors. We will use pharmacotherapy for hypertension, diabetes, dyslipidemia and tobacco use as feasible (Supplemental Figures 1 to 4).

We will begin pharmacotherapy for hypertension if initial systolic BP $\geq$150 mmHg and/or diastolic BP $\geq$90 mmHg (Figure 4 and Supplemental Figure 1).[30,32] We will also consider pharmacotherapy in high-risk individuals with systolic BP 130 to 149 mmHg and/or diastolic BP 80 to 89 mmHg at follow-up. Participants with known clinician-diagnosed diabetes or elevated capillary glucose (fasting $\geq$100 mg/dL or random $\geq$140 mg/dL) will have their hemoglobin A1c measured. We will begin pharmacotherapy if hemoglobin A1C $\geq$6.5% or if capillary glucose fasting $\geq$126 mg/dL or random $\geq$200 mg/dL in presence of both polydipsia and polyuria (plus check hemoglobin A1C; Figure 4, and Supplemental Figure 2).[31,35] For the latter group, if hemoglobin A1C <6.5%, we will stop pharmacotherapy and focus on lifestyle intervention. We will recommend statin therapy for people with atherosclerotic CVD, primary hypercholesterolemia, diabetes, and 10-year estimated coronary artery disease and stroke risk $\geq$7.5% (Figure 4 and Supplemental Figure 3).[37] We will consider non-high-density lipoprotein cholesterol for treatment decisions.[38] We will offer cessation counseling using motivational interviewing techniques and pharmacotherapy, when feasible to tobacco users (Supplemental Figure 4).[33,34] The treatment strategy will be tailored to provide personalized care taking into consideration age, comorbidities, socioeconomic status, and other pertinent variables.

Study Variables

Study variables leverage the World Health Organization and the US guidelines[29–33,35,37,39–41] (Table 1). For the initial visit, we will use the validated structured questionnaire for lifestyle, personal medical history, medication use and family history (Figure 2 and Table 2). Representative lifestyle variables include self-reported tobacco and alcohol use, household smoke exposure, red meat, fruits and vegetables intake, and work, commute, and leisure time-related physical activities. Personal medical history covers hypertension, diabetes, coronary artery disease, heart failure, stroke, lower

Table 1. Definition of Some Commonly Used Variables.

Lifestyle-Related Variables

Currently alcohol intake[11]

Any self-described alcohol drink in the last 30 days defines current alcohol use. One drink is approximately 10 g of alcohol, which is found in 250 mL of 5% beer, jand, tongba (latter 2 are local alcohol products) or 105 mL of 12% wine, or 30 mL of 40% hard liquor (such as vodka, gin, rum, or whisky) or 45 mL of 27% locally made alcohol called Raksi. Unhealthy alcohol is daily intake of >2 drinks in men and >1 drink in women.

Current smoking[11]

Any self-described smoking cigarette or locally available hand-made wrapped tobacco product such as Bindi in the last 30 days.

Recommended diet (diet not meeting following is considered unhealthy diet—all self-described)[11,29]

Salt intake <1.5 teaspoonful daily; Red meat <70 g daily; Fruit intake at least 1 standard serving of fruits daily (1 medium size fruit or 1/2 cup of chopped, cooked or canned fruits or 1/2 cup of fruit juice not artificially flavored); Vegetable intake at least 1 standard serving of vegetables daily (1 cup of raw, green leafy vegetables, 1/2 cup of cooked or chopped vegetables, or 1/2 cup of vegetable juice); Fat intake <6 to 9 teaspoon of ghee daily (ghee is the commonly used food rich in saturated fat).

Physical activities (all self-described)

Work-related physical activities[11]

Moderate-intensity activities: At least 10 minutes of activities that make a person breathe somewhat harder than normal such as cleaning, washing, gardening, milking cow with hands, planting and harvesting crops, digging dry soil, weaving, wood work such as chiseling and sawing, mixing cement, labor work such as pushing loaded wheelbarrow and operating jack hammer, walking with load on head, drawing water, tending animals, and so on.

Vigorous-intensity activities: At least 10 minutes of activities that make a person breathe much harder than normal such as chopping wood, carrying wood, sawing hardwood, ploughing, cutting crops, digging, grinding with pestle, shoveling sand, loading furniture, rickshaw driving, and so on.

Commute-related physical activities[11]

Walking or biking at least 10 minutes on a regular basis for commute (such as going to work-place, temple, and grocery shopping).

Leisure/spare time-related physical activities[11]

Moderate-intensity activities: At least 10 minutes of activities that make a person breathe somewhat harder than normal such as cycling, jogging, dancing, horse riding, yoga, pilates, low impact aerobics, and playing cricket.

Vigorous-intensity activities: At least 10 minutes of activities that make a person breathe much harder than normal such as playing soccer, rugby, tennis, high impact aerobics, ballet dancing, fast swimming, and so on.

Risk Factors/Diseases

Prehypertension[30,32]

Either systolic blood pressure 120 to 139 mmHg or diastolic blood pressure 80 to 89 mmHg plus not on pharmacotherapy during initial and first follow-up visit per hypertension protocol.

Hypertension[30,32]

Either SBP ≥150 mmHg or DBP ≥90 mmHg on initial visit; or persistently elevated BP at first follow-up visit with SBP ≥140 mmHg or DBP ≥90 mmHg; or patient reported but clinician diagnosed elevated blood pressure; or currently supposed to be taking antihypertensive medications.

Elevated glucose without diabetes[35]

Elevated capillary glucose level (either fasting ≥100 mg/dL or random ≥140 mg/dL without polyuria or polydipsia both) plus hemoglobin A1C ≤6.4% plus not on pharmacotherapy during initial and first follow-up visit as per diabetes protocol.

Diabetes mellitus[35]

Capillary glucose level ≥100 mg/dL (fasting), or ≥140 mg/dL (random) plus hemoglobin A1C ≥6.5%; capillary glucose level ≥126 mg/dL (fasting), or ≥200 mg/dL (random) plus both polyuria and polydipsia while hemoglobin A1C is pending; or patient reported but clinician diagnosed diabetes; or currently supposed to be taking medications for diabetes.

Elevated cholesterol[37]

Patient reported but clinician diagnosis of elevated cholesterol/dyslipidemia or if currently supposed to be taking medications for cholesterol, such as statins, bile acid binding resins, ezetimibe or niacin, or other cholesterol specific lowering medications. This will also include specific levels of total and low-density lipoprotein cholesterol, which we will explore later.

Coronary artery disease[41]

Presumed atherosclerotic obstruction in the arteries of the heart resulting in substernal chest pain that is worse with exertion and better with rest or sublingual nitroglycerin. It includes stable angina, unstable angina, myocardial infarction, or sudden unexplained death. Anyone with patient reported but physician diagnosed coronary artery disease or new diagnosis of coronary artery disease.

Peripheral artery disease of lower extremity[40]

Presumed atherosclerotic obstruction of artery supplying lower extremity that classically causes pain with walking that goes away with rest. Anyone with patient reported but physician diagnosed lower extremity peripheral artery disease; or new diagnosis of lower extremity peripheral artery disease.

(continued)

Table 1. Continued

Stroke[37]
Neurological symptoms lasting ≥24 hours either from presumed obstruction of or bleeding in the arteries in the brain. Anyone with patient reported but physician diagnosed stroke or new diagnosis of stroke.
Atherosclerotic cardiovascular disease[37]
Coronary artery disease, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin.
Chronic kidney disease[39]
Estimated glomerular filtration rate of <60 mL/min/1.73 m^2 or presence of markers of kidney damage (eg, ≥microalbuminuria = 30–300 mg/g albumin in urine) ≥3 months.
Macroalbuminuria[49]
>300 mg/g albumin in urine
Obesity[50]
Body mass index ≥30 kg/m^2
Family history of premature coronary artery disease[37]
Father/brother/son with coronary artery disease at ≤55 years of age or mother/sister/daughter with coronary artery disease at ≤65 years of age.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

extremity peripheral artery disease, chronic lung disease, CKD, and cancer. We will ask everyone to bring all the medical documents and current medications and record them. Family history includes hypertension, diabetes, coronary artery disease, stroke, dialysis, and cancer. Similarly, for follow-up visits, we will use a standardized questionnaire to assess for lifestyle changes, medication adherence and interim development of NCDs, perform anthropometric measurements, prescribe medications and provide laboratory investigations, as needed. In the future, we will explore additional definitions and cut-points for risk factors that may be more contextually meaningful. Furthermore, we will examine heterogeneity of risks, such as according to age, sex, socioeconomic, and other locally pertinent variables.

Physical Examination

Trained staff will measure BP using a standardized protocol with appropriate-sized automated BP cuff on bare skin/over a thin clothing after participants sit quietly with legs uncrossed for 15 minutes and then take 2 more measurements at 3-minute intervals.[42,43] We will measure height with a portable stadiometer after participants remove shoes, slippers and hat, and stand looking straight ahead with their knees straight, feet together, and heels against backboard.[42,43] We will record height to the nearest 0.1 cm. We will measure weight with a portable weighing scale on a flat surface. Participants will remove their shoes, wear light clothes, stand facing forward with arms at side, and record weight to the nearest 0.1 kg.[42,43] We will measure waist circumference with a measuring tape at midpoint between the lower margin of last rib and top part of iliac crest on bare skin or over a thin clothing at normal end expiration and record it to the nearest 0.1 cm.[42,43]

Laboratory Investigation

In partnership with National Reference Laboratory, a category level 'A' certified laboratory from the national accreditation agency,[44] we will centrifuge specimens on-site and transport aliquots to a nearby laboratory (170 km away) maintaining a strict temperature of 2°C to 8°C. We will discuss the lab results in person with study participants within 2 weeks at mobile clinic.

Study Monitoring and Training

All staff are required to review study-related video materials about research ethics, methods, protocols and data management. Their knowledge will be ascertained through annual testing. Investigators will monitor strict adherence to the protocol during mobile clinics. External investigators, physicians, and public health personnel will make periodic impromptu visits during mobile clinics to conduct audits. Investigators will review videos of one study participant from every initial and follow-up mobile clinic to monitor interview quality.

We will perform periodic research and clinical training of staff using formal and informal training programs. We will also perform anonymous surveys of randomly selected participants from initial and follow-up visits, community leaders, mothers' group, FCHVs, and all study staff to assess process evaluation and perception toward the study to help address important gaps and to make program activities more community centric.

Table 2. Domains and Variables Included in the Questionnaire and Their Validation Methods.

Domains	Example Variables and Validation Methods
Initial Visit	
Basic demographics	Age,[a,b] sex,[a,b] marital status,[a,b] race/ethnicity,[a] religion, profession,[a] family members,[a,b] income,[a] education,[a] migration plan, access and distance to health-care center,[b] traditional health-care seeking behavior
Lifestyle	Alcohol use,[a] tobacco use[a] (various forms, smoke and smokeless), passive smoke exposure,[b] household-related smoke exposure, illicit drug use, vegetable[a] and fruit[a] use, ghee use, red meat use, salt[a] and salty food[a] use, physical activity (work, commute, and leisure time related)[a]
Readiness to change lifestyle	Barriers to increase fruits and vegetable use, readiness to lower salt use,[a] readiness to increase leisure time physical activity,[a] readiness to reduce/stop alcohol and tobacco use,[a] barriers and preparedness to reduce home smoke exposure
Personal medical history	Hypertension,[a] diabetes,[a] coronary artery disease, heart failure, stroke, peripheral artery disease, chronic lung disease, renal stone, chronic kidney disease, end stage renal disease, cancer, bleeding symptom
Medication history	Nonsteroid anti-inflammatory drugs, aspirin,[a] anti-hypertensives,[a] anti-diabetes,[a] any other medication, Ayurvedic and medicinal herbs, medication adherence
Family history	Hypertension, diabetes, coronary artery disease, stroke, end stage renal disease, cancer
Treatment and counseling	Personalized lifestyle counseling,[c] medication prescription, and referral
Follow-up Visit	
Basic demographics	Follow-up reason
Lifestyle	Change in alcohol use,[a] tobacco use[a] (various forms, smoke and smokeless), passive smoke exposure, household-related smoke exposure, illicit drug use, vegetable and fruit use, ghee use, red meat use, salt use, physical activity (work, commute, and leisure time related)
Interval disease	Hypertension, diabetes, coronary artery disease, heart failure, stroke, peripheral artery disease, chronic lung disease, chronic kidney disease, end stage renal disease, cancer, other disease
Lab test	Explanation of lab results
Medication use	Any new medication, medication adherence
Treatment and counseling	Personalized lifestyle counseling,[c] medication prescription, and referral

In addition to above, all variables from the initial and follow-up visits were validated during the pilot phase of this study.
[a]World Health Organization STEPwise approach to surveillance survey.[11]
[b]Demographics and Health Survey.[36]
[c]Effectiveness of a lifestyle intervention led by female community health volunteers versus usual care in blood pressure reduction.[22]

Ascertainment of NCDs

We will ascertain NCDs using multiple methods. We will review participants' possession of the most recent medical records from all health-care facilities they have visited. In addition to the scheduled follow-up mentioned earlier, we will instruct participants to come to the clinic after any major change in health. Using their community network, our community resources (FCHVs, mothers' group for health, community leaders) will notify study team if participants develop any major health events, such as stroke, myocardial infarction, initiation of dialysis, cancer, and death. We will invite participants with new NCDs to visit main stationary clinic, obtain additional history and, perform physical exams and laboratory testing. If the participant does not come for follow-up in the clinic 1 month after notification of major health events, we will visit the participants' home within another 2 weeks. To ascertain cause of death, we will meet with family, other caregivers or neighbors and learn about circumstances leading to death and try to obtain pertinent medical records and death certificates, if available. If this cannot be obtained, we will conduct an interview with the next of kin, other caregivers, neighbors, or local health-care worker following the World Health Organization verbal autopsy questionnaire that elicits information on signs, symptoms, medical history and circumstances preceding death.[45] An automated

software will assign cause of death based on this information.[45]

Quality Control

During each mobile clinic, we will use the same set of empty bottles, glasses, cups, and teaspoons to standardize measurements. We will also use a show card with relevant pictures and other information.[11]

We will calibrate the sphygmomanometers 1 day prior to monthly mobile clinics or at least once a month. We will measure BP of 1 individual with multiple but same brand/models of automated sphygmomanometers taking 5 BP measurements per device in an alternate manner. We will use the sphygmomanometer only if the mean difference in either SBP or DBP between the devices is $\leq \pm 5$ mm Hg.[46]

We will calibrate weighing scale 1 day prior to the mobile clinics or at least once a month by taking 5 measurements of a certified 5-kg metal ball. If the mean weight difference is $>\pm 0.1$ kg, we will calibrate the weighing machine until the weight difference is $<\pm 0.1$ kg. In addition, every 6 months, we will measure the weight of the metal ball against a separate certified 5-kg metal ball for 5 measurements with a goal mean weight difference $<\pm 0.1$ kg.

We will run quality control for glucometer and strips using manufacturer recommended control solution before each clinic or at least once a month. We will repeat lab tests for randomly selected 10% of participants who had any labs performed.

Sample Size

For sample size calculation, we used the incidence rates when available from a recent trial of hypertension[22] or prevalence rate from the STEPwise approach to surveillance survey.[11] We used the formula $Z^2 \times P \times (1-P)/d^2$, where $Z = 1.96$ at 5% level of significance, $P =$ incidence/prevalence of risk factor, and margin of error (desired precision, $d) = 0.05$. As a conservative sample size estimate, we accounted the design effect in this study by assuming 3 times larger variance than the earlier studies [11,22] and 40% drop-out rates. This gives us an adjusted sample size range of 151 to 1638 with at least 1638 individuals to estimate incidence/prevalence of common NCDs (Table 3). All the individuals enrolled in the study will be followed up for at least 5 years or drop-out. The estimated conservative sample size will allow, in future, to conduct longitudinal analysis to examine relevant hypotheses related to hard NCD outcomes with sufficient statistical power.

Data Analysis

We will estimate prevalence and incidence of NCDs using appropriate methods. We will conduct appropriate weighted multivariable regression analyses, risk prediction models, and dominant analysis ranking risk factors by importance. We will examine differences in demographic, socioeconomic, clinical, and laboratory factors between those adherent with scheduled follow-up from those followed-up outside scheduled visits to better understand factors associated with attrition. We will consider appropriate model building strategies. As

Table 3. Sample Size Calculation.

Risk Factors	Incidence/ Prevalence	Unadjusted Sample Size	Design Effect-Adjusted Sample Size	Drop-Out Adjusted Final Sample Size
Smoking[a]	0.160	206.5	619.6	1032.6
Smokeless tobacco	0.308	327.5	982.5	1637.6
Alcohol[a]	0.100	138.3	414.9	691.5
No Fruits and vegetables consumptions[a]	0.980	30.1	90.4	150.6
None vigorous physical activity[a]	0.090	125.9	377.6	629.3
Too much salt consumption[a]	0.860	185.0	555.0	925.1
Overweight	0.177	223.8	671.5	1119.2
Obesity	0.040	59.0	177.0	295.0
Hypertension (on medication)	0.257	293.4	880.3	1467.1
Hypertension (not on medication)	0.883	158.8	476.3	793.8
Diabetes	0.036	53.3	160.0	266.6
Hypercholesterolemia	0.227	269.6	808.9	1348.2
Raised triglycerides	0.252	289.7	869.0	1448.3
Multiple risk factors (1–2)	0.845	201.3	603.8	1006.3
Multiple risk factors (3+)	0.151	197.0	591.0	985.0

$Z = 1.96$ at .05 level of significance; precision, $d = 0.05$; drop-out rates = 40%.
[a]Used incidence rates when available.

needed, we will check fit statistics, area under the curve and/or information criteria. We will also examine cost for prevention of each NCD and death, and cost-utility ratios using various perspectives. We will perform hypothesis testing at .05 level of significance.

Data Management

We will record data in case report forms during in-person interviews and then extract into excel spreadsheet from each visit in a password-protected computer that is stored in a securely locked office. Study staff will upload the spreadsheets into a securely encrypted and password-protected research data management server, which is accessible only to key study investigators. We will securely store original case report forms for back up. After data abstraction, we will routinely reenter 5% of randomly sampled data to assess inter- and intra-observer variability and report percent agreement and Kappa's statistics. The study team will meet every 3 months to discuss remediation about shortcomings and challenges in data abstraction.

Discussion

To our knowledge, the NCD Nepal study is a novel and unique community-based prospective cohort study in Nepal. This study will assess the epidemiology of NCDs in rural Nepal and concurrently examines effectiveness of implementation of pragmatic, but evidence-based management of common NCDs. The study will examine trends in NCD following lifestyle and pharmacological management. It will provide an opportunity to examine relationships of various lifestyle and biological factors with NCDs unique to local sociodemographic and cultural practices in Nepal. Its prospective design and continuous surveillance for NCDs allows for the opportunity to develop risk models to guide therapy in Nepal. It will provide a cost-effectiveness framework to better develop policy to address NCDs in LMIC. The study will provide clinical services to rural residents and, identify and refer people with advanced conditions to higher centers, who otherwise may not have this opportunity. While this may influence the natural history of CVD in the participants, it will also provide an important incentive for continued engagement with the community and an important insight into health promotion strategies in Nepal.

Most community-based epidemiological studies from Nepal are cross-sectional in design.[9–19] Although these studies provide meaningful information about prevalent NCDs, they impart no information about NCD incidence. A repeat cross-sectional study of same location in rural Kathmandu showed hypertension was 3 times more prevalent 25 years apart.[47] To our knowledge, there are only limited prospective studies in Nepal and are focused only on specific NCDs[20,21] and do not have concurrent intervention program like ours. The NCD Nepal study is uniquely poised to examine the effect of risk factor modification on the incidence and trends of NCDs and their control. Furthermore, it will also assess the effectiveness of community-based treatment and surveillance program. These data are important when planning policies to address increasing burden of NCDs in an already restraint health system. Recently, the government of Nepal has introduced the Package of Essential Noncommunicable Diseases for early detection and management of chronic disease.[48] However, implementing such program can be challenging in rural areas and can only provide services to selected people presenting to health centers. Since, many NCDs are asymptomatic, active screening and surveillance like proposed in this study can truly identify asymptomatic people. Furthermore, our study combining an epidemiological and implementation research will provide a robust research platform to better understand management of NCDs in Nepal. Study like ours can be extended elsewhere in and outside Nepal.

The NCD Nepal study also has limitations. For practical reasons, we are checking labs only in high-risk individuals. However, as feasible, we will consider checking them in all participants in the future. Although this is not a randomly selected sample, the study will enroll all eligible residents of 4 wards. It should be noted that it is ethically challenging to do random sampling in an area with poor medical infrastructure by depriving some participants of NCD treatment opportunities, and hence we did not perform random sampling. Despite having a comprehensive population census to calculate eligible population, and providing transportation for people with disability and extreme morbidity, those not motivated may not attend health clinics. Therefore, it is possible that our eventual sample may be somewhat self-selected, motivated, and healthier. It is also possible that individuals who develop new NCDs such as CVD, stroke, heart failure, and other NCDs may not come to our clinic but we believe that our comprehensive community network will minimize this bias. Furthermore, the findings of this study may not be representative of urban Nepal, where the lifestyle and environmental exposures are different. Because of the lack of a robust medical health records and national registry, we have to rely on nonconventional ways to confirm and ascertain NCDs such as CVD and mortality. Although we acknowledge the limitations of this strategy with potential for misclassification error and missing future NCDs, our model to capture incident events is inexpensive and has been used and validated in many other resource-limited setting.[45] In the future, we will consider using more objective ascertainment methods, including

imaging modalities, additional laboratory tests and other diagnostic tools. Despite a well-planned strategy to reduce attrition, we acknowledge this can be a challenge.

Conclusion

This longitudinal study emphasizes on thoughtful screening and management of NCDs and will help us better understand the epidemiology of NCD burden and effectiveness of management of common NCDs in a LMIC like Nepal. Systematic data collection about NCDs and their trends will examine benefits of preventive service delivery in rural Nepal and its cost effectiveness. Data from this study could guide the development of national policy in addressing NCDs in a LMIC like Nepal.

Author Contributions

All authors helped design the study, directed its implementation, including quality assurance, and control. GN, SA, MBhattarai, LT, and YP wrote the initial draft of the manuscript. All authors interpreted the data and critically reviewed and revised the final version of the manuscript. All authors read and approved the final version of the manuscript.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics and Consent

The ethical approval for this study was obtained from Nepal Health Research Council Ethical Review Board (Reg. No. 455/2017; Ref. No. 2483). All participants are required to complete a written informed consent form.

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Authors' Note

In light of expected increasing burden of NCDs and paucity of high-quality data on the epidemiology of NCDs in low- to middle-income country like Nepal and the potential usefulness of community-based screening and treatment of NCDs, we describe a protocol of a community-based longitudinal epidemiological study of screening and management of NCDs in rural Nepal.

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Supplemental Material

Supplemental material for this article is available online.

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