CARDIOVASCULAR RISK IN HIGH ALTITUDE PEOPLE OF NEPAL

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Abstract

Background

Permanently living at high altitude (HA) directly affects the cardiovascular system because of lower arterial blood oxygen content compared to sea-level and other associated physiological changes. It is uncertain if there are clear-cut benefits or risks to cardiovascular health from living at HA and whether these benefits or risks, if they exist, vary in different populations. In Nepal, a comprehensive cardiovascular risk assessment of a sample of individuals representing a HA population has not previously been performed. The main aims of this project were to estimate, in residents at HA, the prevalence of coronary heart disease (CHD) and cerebrovascular disease; to estimate the distribution of key cardiovascular risk factors; and to estimate any possible relationships between CHD or blood pressure with altitude.

Methods

The study design was a cross-sectional survey. The sampling technique was cluster sampling of study areas on the basis of altitude level, population density and logistical support to undertake the study, but the participants within the study areas were randomly selected. The sample consisted of 521 residents aged 30 years or over from the Nepal districts of Mustang and Humla, permanently living at altitudes of 2800 metre (m), 2890 m, 3270 m, or 3620 m. Data was collected by administering the WHO STEPS interview questionnaire for non-communicable disease risk factors, a questionnaire for verifying stroke-free status (QVSFS), bio-physical measurements (blood pressure, height, weight, waist, hip), biochemical measurements (lipid profile and glycated haemoglobin), and a resting 12 lead electrocardiogram (ECG). The prevalence of CHD was defined as the presence of pathological Q waves in the ECG or self-report of personal history of CHD (previous event of myocardial infarction (MI) or chest pain from heart disease (angina)). ECG recordings were categorized as definitely abnormal (e.g. showing evidence of previous MI, borderline (e.g. non-specific T-wave inversion) or normal after review by a cardiologist using standard widely accepted criteria. Blood pressure (systolic/diastolic) was

classified as normal (<120/80 mmHg), pre-hypertension (HT) (120–39/80–89 mmHg), HT (≥140/90 mmHg), Stage I HT (140–159/90–99 mmHg), and Stage II HT (≥160/100 mmHg). Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models were used for the relationship between systolic blood pressure (SBP), diastolic blood pressure (DBP) and altitude. Logistic regression was used to estimate the association between an abnormal (or borderline abnormal) ECG and altitude in univariate and multivariate models.

Results

None of the participants showed definite electrocardiographic evidence of CHD. Overall, 5.6% of the participants gave a self-reported history of CHD. Altogether 19.6% of the participants had an abnormal (or borderline abnormal) ECG. The main categories of abnormality were right axis deviation (5.4%) and left ventricular hypertrophy by voltage criteria (3.5%). Observed ECG abnormalities differed between ethnic populations: suggestive of left sided cardiac abnormalities in the Mustang district with a majority population of Tibetans; and right sided abnormalities in the Humla district with a majority population of Khas-Arya. There was a moderate association between the probability of abnormal (or borderline abnormal) ECG and altitude, adjusted for potential confounding variables, with an odds ratio for a greater probability of an abnormal ECG (95% CI) of 2.83 (1.07 to 7.45), P=0.03 per 1000 m elevation of altitude.

A history of stroke or of symptoms of stroke (by positive self-report of at least one criterion of the QVSFS) was identified in 6.7% of the participants.

A multivariate model adjusting for potential confounding variables showed that there was moderate evidence of an association between SBP and altitude; mean SBP (95% CI) increase by 11.3 mmHg (-0.1 to 22.7), P=0.05 for every 1000 m elevation.

The distribution and prevalence of key cardiovascular disease-related risk factors did not differ by altitude level. Rather, they differed by ethnicity, residential settings (urban or rural) and cultural practices. The prevalence of HT or being on treatment for HT was higher in the Mustang district with dominant Tibetan-related populations (between 41% and 54.5%) than in the Humla district, with dominant Khas-Arya (29.1%). Only 3.3% to

10.3% participants in Mustang self-reported being current smokers, whereas this rate was 38.6% in Humla. The prevalence of current drinker was high at all altitude levels ranging from 45.4% (3620 m) to 63.9% (3270 m). The prevalence of abnormal lipid components, diabetes or being on treatment for diabetes, and overweight or obesity, were all higher in urban (2800 m and 3620 m) compared to rural (3270 m and 2890 m) residential settings.

Conclusion

The HA populations sampled in this study had a lower prevalence of CHD and a higher prevalence of stroke than that of relevant comparator low altitude populations. None of the participants had ECG evidence of past CHD. Cardiovascular risk profiles of HA populations may depend on altitude, ethnicity, cultural lifestyle practices, and residential setting (urban or rural). Altitude *per se* could be an important additional risk factor because of its association with SBP and abnormal (or borderline abnormal) ECG. Different ancestry-related physiological responses to the low oxygen environment at HA may affect cardiovascular health consistent with the evidence of different patterns of ECG abnormality. The findings of the present study suggest that ethnicity and associated lifestyle or cultural practices (such as salt and alcohol intake, smoking habit) and residential settings (mainly differences in physical activity and fruit and vegetable consumption in urban and rural participants), are also likely to be important determinants of cardiovascular health for HA residents.

Dissemination of and development of work performed for this thesis

Published peer-reviewed research papers

1. **Aryal, N**; Weatherall, M; Bhatta Y.K.D; Mann, S. (2016) Blood pressure and hypertension in adults permanently living at high altitude: a systematic review and meta-analysis. *High Altitude Medicine and Biology*, 17(3), pp. 185-193.

2. **Aryal, N**; Weatherall, M; Bhatta Y.K.D; Mann, S. Electrocardiography in people living at high altitude in Nepal. *Heart Asia,* 9 (1), pp. 48-53

Conference presentations and published peer-reviewed abstracts

1. *Are high altitude populations at high risk of heart disease ?A comparison of two high altitude areas of Nepal* (2016, 4-7 June). Poster presentation at World Congress of Cardiology and Cardiovascular Health organized by World Heart Federation in Mexico City, Mexico.

Aryal N, Weatherall M, Bhatta Y, Mann S. (2016) PS039 Are High Altitude Populations at High Risk of Heart Disease? A Comparison of Two High Altitude Areas of Nepal. *Global Heart,* 11(2):e22-e3.

2. *Are high altitude populations at high risk of heart disease ?A comparison of two high altitude areas of Nepal* (2016, 2-5 March). Poster presentation at 11th Asia Pacific Travel Health Conference, Kathmandu, Nepal.

3. *Are high altitude populations at high risk of heart disease ? A cross-sectional study in Nepal* (2015, 4-6 June). Poster presentation at annual scientific meeting of Cardiac Society of Australia and New Zealand (CSANZ) in Auckland, New Zealand.

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List of Abbreviations

AMS	Acute Mountain Sickness
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATP	Adenosine Triphosphate
AV	Atrioventricular
BMI	Body Mass Index
BP	Blood Pressure
CBS	Central Bureau of Statistics
CHD	Coronary Heart Disease
CMS	Chronic Mountain Sickness
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
ECG	Electrocardiogram
ESH-IP2	European Society of Hypertension International Protocol Revision 2010
FPG	Fasting Plasma Glucose
HA	High Altitude
HAPE	High Altitude Pulmonary Edema
HAPH	High Altitude Pulmonary Hypertension
HARS	High Altitude Renal Syndrome
HbA1c	Glycated Hemoglobin
HDI	Human Development Index
HDL	High-Density Lipoprotein-Cholesterol
HIF-1	Hypoxia Inducible Factor-1
HT	Hypertension
IDF	International Diabetes Federation

IFG	Impaired Fasting Glucose
IHD	Ischemic Heart Disease
ISH	International Society of Hypertension
LA	Low Altitude
LAD	Left Axis Deviation
LBBB	Left Bundle Branch Block
LDL	Low-Density Lipoprotein-Cholesterol
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MOOSE	Meta-analysis of Observational Studies in Epidemiology
NCD	Non-Communicable Disease
NHRC	Nepal Health Research Council
NRS	Nepalese Rupees
QVSFS	Questionnaire for Verifying Stroke Free Status
RA	Research Assistant
RAD	Right Axis Deviation
RBBB	Right Bundle Branch Block
RHD	Rheumatic Heart Disease
RMSE	Root Mean Square of Error
RVH	Right Ventricular Hypertrophy
SBP	Systolic Blood Pressure
SDU	Standard Drink Unit
SEAR D	South East Asia Sub-Region D
SI	Student Investigator
SOP	Safe Operational Procedure
TC	Total Cholesterol
TG	Triglyceride
TIA	Transient Ischemic Attack
USA	United States of America

UTI	Urinary Tract Infection
UVB	Ultraviolet B
VLDL	Very Low-Density Lipoprotein-Cholesterol
WC	Waist Circumference
WHO	World Health Organization
WHR	Waist to Hip Ratio
WHtR	Waist to Height Ratio

1 Introduction

This chapter is divided into eight sections:

1.1 Background on populations of the world living at high altitude (HA) and their environmental challenges.

1.2 Human physiological responses to low atmospheric pressure.

1.3 Health and diseases prevalent at HA.

1.4 A brief overview of cardiovascular disease (CVD) trends, mortality and morbidity at HA.

1.5 Life expectancy, CVD and risk factors for CVD in HA areas of Nepal.

1.6 A statement of the problem.

1.7 The significance of the study.

1.8 The aims and objectives of the study.

1.1 Background

The term 'high altitude' (HA) is not uniformly defined in the scientific literature. However, an altitude of 2500 metre (m) or above is the conventional demarcation for HA (Pawson & Jest, 1978) because people generally start to experience adverse symptoms such as shortness of breath and increased heart rate, nausea, dizziness, satiety and fatigue above this altitude (Lossio, 2006).

Using this definition of HA, more than 140 million people in the world permanently live at HA, comprising 2% of the global population (Moore, Niermeyer, & Zamudio, 1998). Established human populations living in the Ethiopian summits of Africa, the Himalayan mountains of Asia, and the Andean mountains of South America have a long history of HA residency: 70,000 years, 25,000 years, and 11,000 years respectively (Beall, 2007). The largest populations at HA are 80 million in the Himalayan mountains of Asia and 35 million in the Andean mountains of South America (Moore et al., 1998). The capitals of three of the four main Andean countries are located at HA: La Paz (Bolivia), Bogota (Columbia), and Quito (Ecuador). Between 2% and

45% of the populations of Asian Countries – China, India, Nepal, Kyrgyzstan, Afghanistan and Bhutan – live at HA. An estimated 80 million people live in four high plateaus of China alone: Qinghai (Tibet), Inner Mongolia, Yun-Gui and the Yellow land plateau (Niermeyer, Zamudio, & Moore, 2001).

La Rinconada, a mining village in Peru, at an altitude of 5100 m is the highest permanent settlement in the world, and has a population of around 7000. The Ma Gu area (altitude 5067 m) of Tibet, with a population around 800, and Dingboche area (4400 m) of Nepal, with a population of 200, are also other permanent human settlements at the extreme end of the range of HA residency (West, 2002).

Living at HA is associated with consequences of the geography, such as access problems due to mountainous and rugged terrain. However, it is also associated with other challenges to human life such as decreased partial pressure of oxygen, cold temperatures, and increased exposure to ultraviolet radiation. The most important physiological factor affecting the health and well-being of HA residents is likely the reduced partial pressure of oxygen.

Figure 1.1 shows the inverse relationship between atmospheric and inspired oxygen levels at increasing altitude.

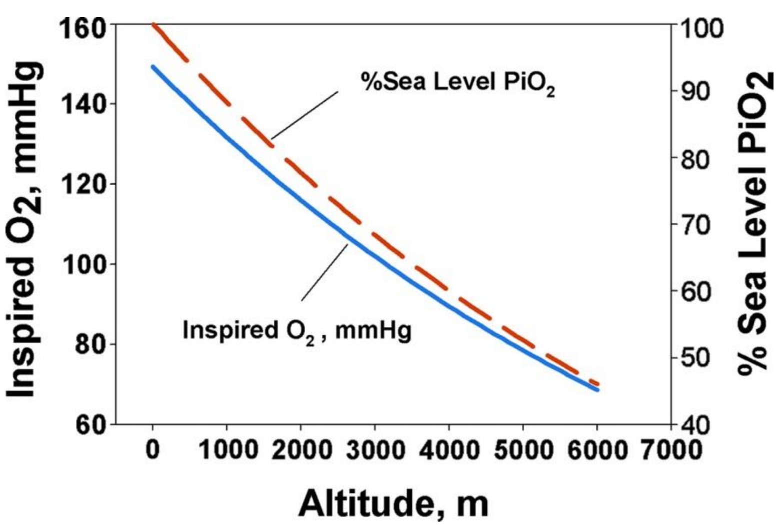

Figure 1.1: Ambient oxygen levels, measured by the partial pressure of oxygen (solid line) or as a percent of sea-level values (dashed line) decrease with increasing altitude

(Adapted from: Beall C. M. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci 2007;104(Suppl 1):8655-60).

Those born and habitually living at HA tend to adopt particular lifestyle characteristics. Most HA populations are involved in agricultural work and their living conditions are poor. They have very few options for nutrition because only a limited range of crops and vegetables can be produced in such extreme climatic conditions. Potatoes and highland barleys are perhaps the most commonly cultivated crops at HA. Fruits and green vegetables are difficult to grow at HA, particularly in the Himalayan regions of Asia. Most HA natives herd sheep, goats and yaks for meat, butter and cheese; use animal products such as wool and manure; and also use the animals as a means of transportation. Interestingly, in Tibet butter production was so universal that it was used to pay taxes and as an acceptable form of wages for daily labour (Stevens, 1996).

HA residents are usually physically active because of the physical demands of both arable and pastoral farming, although during the extremely cold winters people mostly stay inside their houses and outdoor activities virtually cease. Butter-laden salty tea and alcohol intake are central facets of lifestyle in HA residents of Tibetan cultural regions. The traditional diet of Tibetans consequently includes high levels of salt, at a minimum of 20 to 30 grams (g) per day (Sehgal, Krishan, Malhotra, & Gupta, 1968; Sun, 1986). This is five times more than the World Health Organization (WHO) recommendation for regular dietary intake. Traditional food consumption also comprises large quantities of meat and a high level of consumption of alcohol (Luobu, 2012; X. Zhao et al., 2012). In Andean HA areas, chewing coca (the raw material from which cocaine is produced) is popular among natives as they believe it is beneficial in combating the harsh climatic conditions (Hanna, 1974). These practices are strongly culturally embedded in social rituals, such as weddings, funerals and feasts.

Despite hostile environmental conditions and a reduced capacity for physical performance, HA native populations with the longest history of ancestry and residency have successfully adapted to their living situation. The extended time over which some populations have resided at HA means that natural selection may have led to beneficial genetic variants for optimal function under hypoxic conditions. A recent study reported that Tibetans, Andeans, and Ethiopian highlanders exhibit different adaptations to the hypoxic hypobaric situation, mediated in turn by different genes (Huerta-Sánchez et al., 2013). Consequently, different phenotypic responses of these populations to hypoxia have been observed. Andeans respond to HA primarily through hematological adaptations and Tibetans through respiratory changes. Both changes lead to the same outcome of improved tissue oxygen delivery (Beall, 2007). These differences may contribute to varying benefits and risks related to the cardio-pulmonary health of HA populations.

Most HA areas are rural and remote with very limited health care services and facilities. This contributes to late diagnosis or non-diagnosis of existing medical conditions, poorer outcomes of health conditions that are diagnosed, and limited accurate documentation of disease states and causes of death.

1.2 Acclimatization to high altitude

Acclimatization to HA is defined as the physiological adaptation of the body to a hypoxic hypobaric environment. Over generations, acclimatization may lead to 'adaptation', which involves genetic modifications (Lossio, 2006).

A growing consensus among relevant scientists is that full acclimatization cannot be achieved because it is impossible to achieve full physiological compensation for the physical and mental impairments triggered by chronic hypoxia (Jourdanet, 1875). A prominent HA physiologist states: "it is a serious misconception on acclimatization that it will reverse all ill health effects of HA" (West, 2003b). Acclimatization significantly improves arterial hypoxemia, but despite this arterial oxygen levels remain far below those achieved at sea level (West, 2003a). This contrasts with the belief of some earlier scientists that a path to full acclimatization would be through changes in blood over generations of exposure to hypoxia (Bert, 1878).

The distressing symptoms experienced by those living at or travelling to HA have been known for centuries. An example of a historical record is a report from the Himalayas of China by a Chinese official from between 37B.C. and 32B.C. (Gilbert, 1983b). There are reports of serious difficulties experienced by travellers over the western edge of the Himalayan Karakoram Range and in the Pamir Range during that period (Gilbert, 1983b). In the Andes, HA symptoms were first documented by Father Jose De Acosta in 1590 when he experienced nausea, headache, and heart and stomach pains while crossing the Andean Cordillera. He strongly suggested it might have been due to the thin air (Gilbert, 1983a). In 1878, a French physiologist, Paul Bert, scientifically demonstrated that distressing effects were indeed mainly attributable to the rarefied air (Rudolph, 1992), later confirmed by many other investigations.

It is not only reduced levels of inspired oxygen at HA that can induce health problems. Reports have documented that HA natives temporarily suffer health problems when descending to low altitude (LA) because of the 'excessive oxygen' (Lossio, 2006). Pulmonary edema is also found in HA residents when they return from LA back to their usual HA residence. This is termed 're-ascent high altitude pulmonary edema' (Moore et al., 1998). Thus, the process of acclimatization seems to apply to both environmental hypoxia and hyperoxia.

The main features of physiological adaptations to HA are hyperventilation, erythrocytosis and pulmonary vasoconstriction. The degree of these varies in different HA populations.

Hyperventilation is the most commonly observed feature. Increased breathing rates and volumes of ordinary ventilation act to increase alveolar ventilation (Moore et al., 1998). Tibetans who live at HA have a two-fold higher hypoxic ventilatory response compared to Andeans who live at HA (Beall, Strohl, et al., 1997). When compared to HA permanent residents, sojourners from LA generally show a greater degree of hyperventilation (Stuber & Scherrer, 2010).

Many HA populations produce a more erythrocytes; consequently hemoglobin concentration rises and both these act to offset oxygen deficiency by increasing the amount of oxygen carried by the blood. This phenomenon is particularly pronounced in Andean HA populations. Tibetan natives, on the other hand, compensate for their lower arterial oxygen by relatively a high flow rate of oxygen carrying blood to tissue and greater diffusion of oxygen from the blood stream into cells (Beall, 2007). Sherpa populations of Nepal, well-known HA dwellers of Tibetan ancestry, have a serum erythropoietin level at 3440 m similar to that in non-Sherpa at 1300 m (Hanaoka et al., 2012). An increased level of hemoglobin is not usually seen in populations living at an altitude of 1600 m or below when compared with those at sea level (Sullivan, Mei, Grummer-Strawn, & Parvanta, 2008). Table 1.1 shows the oxygen saturated levels, hemoglobin levels, and arterial oxygen contents of major HA populations.

Table 1.1: Oxygen saturation levels, hemoglobin levels, and arterial oxygen contents of major high altitude populations

	Oxygen saturation (%)	Hemoglobin conc. (adult men) (g/dL)	Arterial oxygen content (mLO_2/100 mL blood)
Sea level	97	15.3	21.1
Ethiopia (3530 m)	95	15.6	21.1
Tibet (4000 m)	89	15.8	19.2
Bolivia (4000 m)	92	19.1	24.4

Abbreviations: g/dL, gram per decilitre; mLO_2, millilitre of oxygen; mL, millilitre

Adapted from: Beall, C. M. (2006). Andean, Tibetan, and Ethiopian patterns of adaptation to high-altitude hypoxia. *Integrative and Comparative Biology*, 46(1), 18-24.

There is strong genetic evidence for differences in blood hemoglobin concentrations in Tibetan and Andean HA populations. The gene EPAS1, for hypoxia-inducible factor 2α, stimulates erythrocyte production in HA Tibetans (Beall et al., 2010) but there is no evidence of enriched EPAS1 variants in Andean HA populations (Bigham et al., 2009).

Pulmonary arterial vasoconstriction is another important characteristic of HA acclimatization. This acts to maintain alveolar perfusion and ventilation rate and to minimize systemic hypoxia (Stuber & Scherrer, 2010). However, excessive pulmonary vasoconstriction may lead to pulmonary hypertension (HT), right ventricular hypertrophy (RVH), right heart failure and pulmonary edema (Peñaloza & Arias-Stella, 2007). Pulmonary HT and consequent effects are more prominent in Andean HA populations than in Tibetans (Ostadal & Kolar, 2007). Hypoxic pulmonary vasoconstriction in Tibetan highlanders is minimal and pulmonary arterial pressure is the same as that of sea-level populations. This may be due to genetic adaptation to HA (Luobu, 2012; Yang et al., 1987). The high level of nitric oxide gas in the lungs of Tibetan and Aymara HA populations might be one adaptation that contributes to pulmonary artery vasodilation (Beall, 2007).

Overall, the two largest HA populations at present, Tibetans and Andeans, demonstrate different physiological changes in response to environmental hypoxia. Usually, Tibetan HA populations have better levels of hypoxic ventilation response, blood oxygen saturation, lung function, maximum cardiac output and sleep quality, and lower levels of pulmonary vasoconstriction and hemoglobin concentration when compared with Andean HA dwellers (West, 2011; Wu & Kayser, 2006). Tibetans show two major features that could have advanced their degree of adaptation further than Andeans; firstly, they have the longest generational history at HA, and secondly they have least a degree of genetic admixture. Andeans have substantial genetic admixture with South American Indian and European genes (Moore et al., 1998). The genetic basis of HA adaptation of Tibetan natives is relatively well understood (Wu & Kayser, 2006). There is little information on physiological responses of HA Ethiopians; however, available evidence indicates low levels of blood hemoglobin and pulmonary artery pressure, as in Tibetans, and higher levels of hemoglobin oxygen saturation and arterial oxygen content than in Tibetans and Andeans (Arestegui et al., 2011). Table 1.2 shows the comparison between physiological responses among the three major HA populations.

Table 1.2: Comparisons of physiological characteristics of Tibetan, Andean, and Ethiopian high altitude populations

	Tibetans	**Andeans**	**Ethiopians**
Basal metabolic rate	Normal	Normal	Unknown
Maximum oxygen consumption	Normal	Normal	Unknown
Ventilation (litre/minute)	15	10.5	Unknown
Hypoxia ventilatory response	Higher	Lower	Unknown
Oxygen saturation of hemoglobin	Lower	Higher	Highest
Hemoglobin	Lower	Higher	Lower
Arterial oxygen content	Lower	Higher	Highest
Pulmonary artery pressure	Lower	Higher	Lower
Pulmonary nitric oxide production	Higher	Lower	Higher
Peripheral capillary density	Higher	Lower	Unknown
Oxygen dissociation	Normal	Normal	Normal
Chronic mountain sickness	1.2%	8 to 15%	Unknown

Adapted from: Arestegui A. H., Fuquay R, Sirota J, Swenson E. R., Schoene R. B., Jefferson J. A., et al. (2011). High altitude renal syndrome (HARS). *Journal of the American Society of Nephrology*, 22(11), 1963-8.

1.3 Health and disease at high altitude

High levels of physical activity and some other features of a traditional lifestyle, as well as physiological adaptation to the hypoxemic hypoxia of HA, might be expected to be associated with better health for those living at HA. However, available data on mortality or life expectancy of HA populations is poor and inconsistent. A recent systematic analysis of the provincial level burden of disease in China estimated that in 2013, of all 33 provinces of China, Tibet province (mean altitude 4500 m above sea level) had the lowest life expectancy at birth (68.4 years) (Zhou et al., 2016). A similar finding of high mortality rate at HA for the period 1996 to 2000 was reported from the Andean region of Peru, which accounted for half of all mortality despite having only 32% of the total Peruvian population (Huicho, Trelles, Gonzales, Mendoza, & Miranda, 2009). The mortality rate in Bolivian highlanders is also higher than in other areas of Bolivia, increasing for every 1500 m elevation (Virues-Ortega et al., 2009). In contrast, the mortality rate is reported to be lower in mountainous region of Greece (950 m) than at sea level during the follow-up period of 15 years between 1981 and 1996 (Baibas, Trichopoulou, Voridis, & Trichopoulos, 2005). In the United States of America (USA), living at HA (equal to or greater than 1500 m) has no effect on net life expectancy (Ezzati et al., 2012). It may be that, as in other populations, lifestyle, genetic and environmental factors play an important role in health or disease at HA, rather than HA itself. This section will briefly discuss common health problems at HA.

1.3.1 High altitude illness

Chronic mountain sickness (CMS) and high altitude pulmonary hypertension (HAPH) are, by definition, seen in people in the HA environment, whether resident or visiting. Low birth weight in newborn children is observed in most HA populations. This sub-section will briefly discuss CMS, HAPH and low birth weight at HA.

CMS (sometimes known as ‘Monge's disease’) is typically diagnosed in long-term HA residents. This disease is clinically characterized by a greater concentration of erythrocytes (blood hemoglobin: ≥21 g/dL (decilitre) for men and ≥19 g/dL for women) and clinical symptoms include dizziness, headache, insomnia, loss of appetite, breathlessness and/or palpitations, cyanosis, and mental and cognitive impairment (León-Velarde et al., 2005). Usually the prevalence of CMS is higher in men, smokers, older adults, and at higher levels of altitude

(León-Velarde, Villafuerte, & Richalet, 2010). Andean HA populations are particularly affected with CMS (8% to 15%) while Tibetans have a far lower prevalence (around 1.2%), and it has not been reported among Ethiopian highlanders (Beall, 2007; Beall et al., 2002).

HAPH is often termed a CMS of a vascular type. Chronic or short-term hypoxia may induce an increased amount of smooth muscle cells in distal pulmonary arteries and arterioles, resulting in increased pulmonary vascular resistance, pulmonary vasoconstriction and consequent pulmonary HT (Ostadal & Kolar, 2007). Furthermore, these adaptations may lead to high altitude pulmonary edema (HAPE) and consequent fatal events (Lankford & Swenson, 2014). HAPH is generally considered to be present when mean pulmonary artery pressure exceeds 30 mmHg or systolic pulmonary artery pressure is >50 mmHg (measured at the residential altitude). Clinical signs are those of right heart failure such as dyspnoea, sleep disturbance or cyanosis (León-Velarde et al., 2005). A large body of evidence shows increased levels of HAPH among HA Andeans but it is uncommon in Tibetan HA dwellers (Stuber & Scherrer, 2010).

Low birth weight is another well-established effect of hypoxia at HA populations. From past studies conducted over 40 years, estimates are that birth weight declines by mean of 100 g for every 1000 m elevation of altitude (Moore et al., 1998). This is attributed to intra-uterine growth retardation due to oxygen deficiency in the fetal placenta (Moore, Charles, & Julian, 2011) rather than other risk factors like maternal age, prenatal care, or nutrition (Jensen & Moore, 1997). All HA populations have reduced birth weight compared to LA populations. However, this association is less prominent in populations with the longest ancestry at HA. For example, the association is least in Tibetans, intermediate in Andean HA populations, but most pronounced in populations with the shortest history of residence at HA, such as dwellers of the Rocky Mountains North America, Ladakh-India, and Han-China (Moore, Armaza, Villena, & Vargas, 2002).

Higher levels of neonatal, infant and maternal mortality are also reported in some HA populations, particularly in Peru and Bolivia (Gonzales, Tapia, & Carrillo, 2008; Pan American Health Organization, 1994). A large study of 22,662 residents of Peru reported five times higher odds for stillbirth rates at altitude of greater than 3000 m when compared to those at 150 m (Gonzales et al., 2008). However, there is some inconsistency in this association (Miller et al., 2007). Low birth weight at HA could also be due to other factors such as limited medical care, infectious diseases, and lack of good maternal education.

Several studies report growth retardation in HA children. Growth stunting was reported to persist in HA children in Peru between 1964 and 1999 (Pawson & Huicho, 2010), and in children of Tibetan origin in Nepal (Pawson, 1977). Although intra-uterine growth retardation and suboptimal nutrition in remote areas at HA may be relevant, increasing altitude is detrimental to the growth of children even after accounting for related socio-economic factors (Dang, Yan, & Yamamoto, 2008).

Taken together, these trends in HA-related diseases and morbidities generally show that HA residents with more favourable patterns of adaptation have fewer consequences from environmental hypoxia (Beall, 2007; Beall et al., 2002).

1.3.2 Other major diseases

Other important diseases related to HA-triggered body tissue hypoxemia and the HA environment are chronic obstructive pulmonary disease (COPD), cancer, and renal-related abnormalities.

The reported increased prevalence of COPD in hypoxic environmental conditions of HA is not uniform across HA populations. The association between altitude and the prevalence of COPD was positive in Colombia (Caballero et al., 2008) but negative in Latin American cities (Menezes et al., 2005) and in Mexico (Laniado-Laborin, Rendón, & Bauerle, 2011). The vast majority of the prevalence studies of COPD at HA are based on studies from South America. There is some evidence of a positive association between COPD mortality and altitude (Cote, Stroup, Dwyer, Horan, & Peterson, 1993; Ezzati et al., 2012). The tendency to use biomass fuel for household energy among HA dwellers may precipitate COPD (Norboo, Yahya, Bruce, Heady, & Ball, 1991; Pearce, Aguilar-Villalobos, Rathbun, & Naeher, 2009). CMS may also contribute to chronic respiratory illness because of decreased alveolar ventilation (León-Velarde et al., 2010).

The majority of epidemiological studies report lower cancer mortality and prevalence at HA. Higher levels of vitamin D produced by higher ultraviolet radiation at HA is proposed to be one mechanism providing protection from cancer (Hayes, 2010). This is biologically plausible because vitamin D could prevent cancer by inhibiting cell growth and increasing cell differentiation (van den Bemd, Pols, & van Leeuwen, 2000). Other adaptations, possibly related to increased levels of blood hemoglobin at HA, may intensify the progression of specific malignant tumours, including breast cancer (Bennett et al., 2008). However, large studies with samples from the USA (Youk, Buchanich, Fryzek, Cunningham, & Marsh, 2012) and another multi-national study (Burton, 1975) reported no particular association between cancer mortality and HA. The occurrence of some cancer types are reported to be higher in some HA populations. For example, the incidence and mortality from gastric cancer is associated with residence in HA areas of Central and Andean South America (Torres et al., 2013), and the prevalence of melanoma is also reported to be higher in mountainous regions of Spain (Aceituno-Madera, Buendía-Eisman, Olmo, Jiménez-Moleón, & Serrano-Ortega, 2011). There is no published evidence about cancer for the Himalayan region.

In summary, the existing evidence suggests that HA populations are not generally at greater risk from cancer-related morbidity and mortality (Burtscher, 2014; Hayes, 2010), but rather than providing direct protection, HA could be a surrogate marker for host genetic, bacterial, dietary, and environmental factors that may increase the risk of some forms of cancer (Torres et al., 2013).

A new clinical syndrome, high altitude renal syndrome (HARS), has been proposed as an entity consequent on the combined effects of HA induced polycythemia, systemic HT, hyperuricemia and microalbuminuria on kidney function (Arestegui et al., 2011). A marked increase in hematocrit level and hypoxemia at HA seems to mediate adverse renal function through mechanisms such as decreased renal plasma flow and consequent lower glomerular filtration rate (Lozano & Monge, 1965), increased production of uric acid (Schoutsen, De Jong, Harmsen, De Tombe, & Achterberg, 1983) and decreased urate clearance (Johnson et al., 2003). These findings are supported by a large Tibetan study, which found a greater prevalence of hyperuricemia, microalbuminuria, and proteinuria among HA residents compared to LA residents of Tibet (W. Chen et al., 2011). Glomerular hypertrophy was also seen in HA children (Naeye, 1965), which is likely to be related to the low birth weight at HA (Brenner, Garcia, & Anderson, 1988).

1.4 Cardiovascular disease mortality and morbidity at high altitude

Hypobaric hypoxia at HA directly affects the cardiovascular system because of the decline in arterial blood oxygen content and other physiological changes. A possible pathophysiological link between CVD and HA has always intrigued researchers, although studies over more than five decades have not resulted in any clear-cut resolution of benefits or risks to CVD health from living at HA (Ostadal & Kolar, 2007).

Although the current pool of evidence is inconsistent as to the association between coronary heart disease (CHD) mortality and morbidity rates at HA, a majority of studies report an association between stroke and congenital heart disease at HA when compared to LA populations. The relationship between CVD and HA was first reported in the 1960s when Hurtado showed that residents living at an altitude of 4540 m in Peru had lower rates of myocardial infarction (MI) and coronary thrombosis compared to those at sea level. Remarkably, this report only recorded one case of MI at HA over a period of 30 years (Alberto Hurtado, 1960). Subsequently, an analysis of 300 autopsies carried out on deceased who had lived at 4375 m in Peru also did not find any case of MI or significant CHD (Ramos, Krüger, Muro, & Arias-Stella, 1967). These Peruvian observations are consistent with a study at 4100 m in Milpo, which reported a significantly lower prevalence of HT, angina and electrocardiogram (ECG) abnormalities than at sea level (Ruiz, Figueroa, Horna, & Peñaloza, 1969). These earlier studies have not provided information on the role of possible confounding factors that might also lead to lower apparent rates of CHD.

Studies on some other HA populations also report lower CVD mortality and morbidity rates compared to LA. A retrospective analysis of mortality data in counties of the USA suggest that living at HA might have a protective effect on ischemic heart disease (IHD) (Ezzati et al., 2012). However, the vast majority of this study’s data came from low to intermediate altitudes of lower than 2500 m. Similarly, a hospital-based retrospective study in Saudi Arabia also suggested a lower incidence and mortality of acute MI in HA regions compared to the rest of the country (Ashouri et al., 1993).

The main proposed biologically plausible explanation for cardio-protection at HA is activation of a transcriptor modulator, hypoxia inducible factor (HIF-1), which induces the expression of multiple genes with cardioprotective properties (Semenza, 2006). Proposed mechanisms include stimulating nitric oxide synthesis (Ding et al., 2005), boosting erythropoietin (Cai et al., 2003), angiogenesis (Sasaki et al., 2002), increasing the efficiency of mitochondrial energy production (Essop, 2007), and other anti-oxidant functions (Abdias Hurtado, Escudero, Pando, Sharma, & Johnson, 2012). High levels of vitamin D due to an exponential increase in ultraviolet B (UVB) light at HA (J. D. Anderson & Honigman, 2011), improvement in coronary vasculature through increased number of branches and peripheral vessels (Arias-Stelalnad & Topilsky, 1971), increased levels of physical fitness and a low level of air pollution (Burtscher, 2014) have also been suggested as cardio-protective factors. A 'healthy individuals effect' is an alternative explanation for these findings from non-experimental studies of illness at HA because sick people often migrate away from HA to LA (Regensteiner & Moore, 1985).

A number of studies also report higher CVD mortality and morbidity rates at HA. CVD related complications in Bolivia were more frequent in grandparents living at high (equal to or greater than 3000 m) and moderate (1500 m to 2999 m) altitude compared to LA counterparts (Virues-Ortega et al., 2009). In a Yemeni study on acute coronary syndrome patients, HA (1500 m to 3500 m) patients were more likely to have a history of IHD, younger age, hyperlipidemia and higher smoking rates (Al-Huthi, Raja'a, Al-Noami, & Rahman, 2006). A positive correlation between CHD morbidity and altitude was also found in an epidemiological study of CHD in provinces in China (D. Zhao, 1993). Higher hematocrit levels at HA were attributed for these adverse outcomes in some HA populations (Al-Huthi et al., 2006; Al Tahan et al., 1998). A 34-year follow up in the Framingham study demonstrated that a higher hematocrit level was significantly associated with the incidence of CHD, MI, and stroke (Gagnon, Zhang, Brand, & Kannel, 1994). Furthermore, a high prevalence of certain risk factors (for example, HT in Tibetan HA dwellers (Mingji, Onakpoya, Perera, Ward, & Heneghan, 2015)) may contribute to the adverse CVD related outcomes.

A preponderance of evidence suggests a greater risk of stroke and related morbidities in HA populations. A Pakistani hospital-based study showed that the relative risk of stroke among populations living at 4572 m was 10 times greater than for those living at 610 m (Niaz & Nayyar, 2003). The age-adjusted incidence of stroke in Tibet was one of the highest in China at 450.4 per 100,000 population (G. Xu, Ma, Liu, & Hankey, 2013). Another study in the Tibetan state of Ganzi using a representative sample of 7038 individuals reported the stroke morbidity rate was high at 1923 per 100,000 population (H.-T. Zhang, Gao, Ye, Pang, & Long, 2015). A very recent study estimated that age-standardized death rates from cerebrovascular diseases were highest among Tibetan women and second-highest in Tibetan men when compared with the populations of the other 32 provinces of China (Zhou et al., 2016). The rate of stroke was also observed to be high among those working at HA. A study in an army population deployed at an altitude of higher than 3000 m, with mean length of stay 10.2 months, reported 12.8 cases of stroke per 1000 hospital admissions as opposed to just 1.05 per 1000 hospital admissions in soldiers living at lower than 3000 m (S. K. Jha, Anand, Sharma, Kumar, & Adya, 2002). None of these studies reported lower mortality and morbidity rates of stroke at HA. One study at an altitude of greater than 3400 m in Peru reported stroke prevalence rates comparable to the world population (Jaillard, Hommel, & Mazetti, 1995).

Both lifestyle and physiological changes due to hypoxia may contribute to a higher risk of stroke at HA. Lifestyle factors such as diet and consequent HT and hyperlipidemia were suggested as causal for higher stroke rates in Tibet (G. Xu et al., 2013; H.-T. Zhang et al., 2015), whereas increased levels of polycythemia were implicated for other HA populations (Al Tahan et al., 1998; S. K. Jha et al., 2002). A Saudi Arabian study reported that of all stroke cases thrombotic stroke was 93.4% at an altitude of higher than 2000 m as opposed to 79.3% at an altitude lower than 2000 m (Al Tahan et al., 1998). HA polycythemia may increase blood viscosity and accelerate thrombosis (Fujimaki, Matsutani, Asai, Kohno, & Koike, 1986). Other factors such as dehydration caused by hyperventilation, cold temperature and lack of thirst (Basnyat et al., 2001); hypercoagulability due to marked increment in plasma fibrinogen levels (Singh & Chohan, 1973); and platelet adhesiveness (S. C. Sharma, Vijayan, Suri, & Seth, 1977) may raise the risk of thrombosis and resultant thrombotic stroke at HA. A systematic review suggests that HA populations of the Himalayas have a higher cerebral blood flow than both Andean populations and sea-level residents, but Andean populations have a lower cerebral blood flow values compared to sea-level populations (Jansen & Basnyat, 2011). Therefore, it is likely that Andeans and other populations who are less adapted to HA may have an increased risk of thromboembolic stroke due to increased level of hematocrit and reduced availability of nitric oxide (Jansen & Basnyat, 2011).

Large studies report an increased risk of congenital heart disease in children born at HA. Studies comprising 32,578 (Jin et al., 2008), 288,066 (Q. H. Chen et al., 2009) and 5,790 children (J.-Y. Zheng et al., 2013) all found an association between congenital heart disease and HA. However, these studies have been carried out only in the Tibetan HA region and data for other HA resident populations are unclear. Hospital-based data in La Paz (mean altitude 3650 m), Bolivia, showed that 66% of all cardiac related surgery was for congenital heart disease, and of these patients 91.5% were resident at altitude above 3000 m (Ponce-Caballero, Loma-Rodriguez, Villegas, & Laura, 1976). Lower oxygen tension and increased pulmonary vascular resistance at HA may result in impairment of normal neonatal development (Miao, Zuberbuhler, & Zuberbuhler, 1988; J.-Y. Zheng et al., 2013).

A large body of evidence suggests beneficial effects on CVD health in populations living at intermediate levels of altitude (Baibas et al., 2005; Faeh, Gutzwiller, & Bopp, 2009; Faeh et al., 2016; R. Gupta, Misra, Pais, Rastogi, & Gupta, 2006; Mahajan et al., 2004; Mortimer Jr, Monson, & MacMahon, 1977; Sinnett & Whyte, 1973; Voors & Johnson, 1979). IHD and stroke mortality was shown to be inversely and progressively related to altitude (259 m to 1960 m) in a retrospective data analysis of 1.64 million people in Switzerland (Faeh et al., 2009). Further analyses in Switzerland, encompassing 4.2 million people, reported that after accounting for all other environmental factors IHD mortality reduced by a significant 24% at an altitude higher than 1500 m compared to an altitude lower than 600 m (Faeh et al., 2016).

Taken together, the evidence is inconsistent, although majority report cardio-protection from living at HA. The retrospective and hospital-based nature of these studies means other factors may explain the apparent association between lower rates of CHD and living at HA. Evidence for the increased risk of stroke and congenital heart disease at HA is more robust. Studies of populations living at intermediate altitudes report better cardiovascular health at this level of altitude. More studies are needed of populations living at HA taking account of different ethnicities to improve understanding of the consequences of HA for cardiovascular health.

1.5 Life expectancy at high altitude in Nepal

The national health information system of Nepal is very rudimentary. Nepal is one of the 19% of the countries that do not have an established system to record cause-specific mortality (World Health Organization, 2014a). A vital registration system with sufficient information on causes of death is not in place. However, information on life expectancy is available. The Central Bureau of Statistics (CBS) reports that the mountain region of Nepal has the lowest life expectancy at birth (66.98 years) compared to the hilly region (69.02 years) or low-land region (68.85 years) (Central Bureau of Statistics, 2012). The proportion of people not expected to survive to age 40 years has also been estimated to be higher in the mountain region (10.62%) compared to the hilly (7.11%) or low-land regions (7.44%) (Government of Nepal & United Nations Development Programme, 2014). Research initiatives on CVD and related risk factors in Nepal are scarce and the information that does exist is reviewed in Section 2.6.

1.6 Statement of the problem

The risks and benefits for cardiovascular health in an environment of chronic hypobaric hypoxia induced by living at HA are uncertain. Increased angiogenesis and structural vascular changes caused by HA may be helpful in reducing blood pressure (BP) and promoting cardio-metabolic efficiency, but erythrocytosis (from chronically low inspired oxygen concentrations) and pulmonary HT among those living at HA may constitute important cardiovascular risk factors (Ostadal & Kolar, 2007; Stuber & Scherrer, 2010). The largest HA populations, Tibetans and Andeans, have different distributions of key CVD risk factors; for example, higher systemic HT in Tibetans (Mingji et al., 2015) but lower in Andeans (Makela, Barton, Schull, Weidman, & Rothhammer, 1978), and higher pulmonary HT in Andeans but lower in Tibetans (Beall, 2007). The differences in genetic, lifestyle and cultural factors among HA populations may all be relevant to this variation.

In Nepal, almost 2 million people live permanently in mountainous areas, representing 7% of the national population (Central Bureau of Statistics, 2012). A large proportion of the population of the hilly districts are also resident at altitudes greater than 2500 m. According to earlier estimates, around 35% of the total Nepalese population permanently live at higher than 2500 m of elevation (Moore et al., 1998). Populations with Tibetan ancestry are the dominant HA population in Nepal: for example, Sherpa, Thakali, Tibetan Gurung and Lama. They migrated from the Eastern part of Tibet about 500 years ago (Eagle, 2000).

No study has yet reported CVD incidence and there is little published information on diabetes, obesity, dyslipidemia and dietary risk in this group. A few studies have examined the prevalence of HT, mainly in Sherpas.

Two large studies have reported the prevalence of HT in mountainous districts of Nepal and compared it with that in populations living at moderate altitude in the hilly region and in the lowest terrain of the low-land region. A national representative survey among those aged between 18 and 65 years and including five mountainous districts showed that the prevalence of HT in mountain districts was more than double (29.5%) of that in the hilly (14%) and low-land (13.7%) regions (Koju et al., 2015). This study also noted that those living at an altitude of equal to or greater than 2000 m had an adjusted odds ratio with 95% confidence interval (CI) of 1.3

(0.9 to 1.9) for being hypertensive compared to those living at below 2000 m. Also, living at equal to or above 2000 m was reported to be associated with HT after adjustment for possible confounding variables in this study. In contrast, the WHO STEPS survey conducted in 2013 documented a slightly lower prevalence of HT in mountainous regions (22.2%) than in the hill areas (25.9%) or low-land areas (26.1%) (K. K. Aryal et al., 2015). It is likely that this discrepancy is caused by the confounding effect of sampling different ethnic populations and the consequent differential exposure to risk factors. In a study that compared BP and HT in opportunity samples of male Sherpas older than 18 years living at HA with those who migrated to a low-land area, the rate of HT was 25% in those living at between 3400 and 3900 m in the Everest region and 21.7% in Sherpas who migrated to Kathmandu (Smith, 1999). Diastolic blood pressure (DBP) was significantly higher in Sherpas currently living at HA. An earlier study reported the opposite association: that Sherpas and Tibetans living at HA (above 2980 m) had a lower systolic blood pressure (SBP) than those who were born at HA but later migrated to LA (Kathmandu) (Weitz, 1982). A very low prevalence of HT (3.8%) at HA (above 2650 m) among those aged over 14 years was also reported in the Humla district of Nepal (S. Shrestha, Shrestha, Shrestha, & Bhattarai, 2012). A proposed mechanism for an association between altitude and BP and HT is the tradition in Nepal for HA residents from Tibetan ancestry to consume large amounts of salty butter tea (Smith, 1999).

Two studies have reported blood glucose levels at HA in Nepal and both found a lower prevalence at HA than at LA. A national survey reported the prevalence of raised blood glucose (fasting plasma glucose ≥126 mg/dL (≥7.0 mmol/L) or on medication) was 1.9% in mountainous areas compared to 3.5% in hilly regions and 3.9% in low-land areas (K. K. Aryal et al., 2015). Similarly, 14.3% of Sherpa population aged 30 to 70 years and living at altitudes equal to or higher than 2900 m in the Everest region were shown to have impaired fasting glucose (IFG) (100 to 125 mg/dL) (5.6 to <7 mmol/L) and 2 hours plasma glucose <200 mg/dL (<11.1 mmol/L) compared to 42.1% in Sherpa living in the Kathmandu valley (Sherpa, Supamai, & Virasakdi, 2008). The adjusted odds ratio (95% CI) for IFG was 0.19 (0.08 to 0.44) for the Everest region compared to Kathmandu.

Studies on the prevalence of obesity at different altitudes in Nepal report inconsistent results. A recent national study among 13,369 women aged between 15 and 49 years reported that the prevalence of overweight (body mass index [BMI] ≥25 kg/m^2) in women from mountainous regions (24.8%) was higher than in the hilly (18.7%) and low-land (6.3%) areas (S. Bhandari et al., 2016). In another study among Tibetans in Nepal, those living at HA of equal to or higher than 2900 m had a greater prevalence of central obesity (waist circumference [WC] >102 cm for men and >88 cm for women) than those at 1200 m (57.1% versus 53.5%) (Sherpa, Stigum, Chongsuvivatwong, Thelle, & Bjertness, 2010). A lower expenditure of calories in Tibetan HA residents has been documented (Sherpa, Stigum, Chongsuvivatwong, Nafstad, & Bjertness, 2013), which transforms surplus calories into visceral fat. Another national survey reported a markedly lower prevalence of overweight or obesity (BMI ≥25 kg/m^2) in mountainous populations (9%) compared to hilly (26.2%) and low-land (18.9%) residents (K. K. Aryal et al., 2015).

One previous study investigated the lipid profile of HA residents in Nepal. The WHO STEPS survey 2013 in populations 15 years and over reported that the proportion of elevated total cholesterol (TC) was lowest in mountainous regions (14.1%) compared to 21.7% in hilly and 24.5% in low-land areas (K. K. Aryal et al., 2015). This study also reported a higher prevalence of current smokers (mountainous 24.6%, hilly 19.9%, low-land 16.5%), hazardous drinkers (mountainous 5.7%, hilly 3.1%, low-land 0.6%), but the least prevalence of low physical activity (mountainous 0.5%, hilly 2.2%, low-land 4.8%). A low consumption of fruit is more prevalent in mountainous regions. One study including 21,111 women of reproductive age from all ecological regions of the country showed that 4% of participants from mountainous districts, 16% from hilly districts, and 9.4% from low-land districts consumed fruit once a day (S. Bhandari et al., 2016). Another nationally representative study also reported a low intake of fruit and vegetables in mountainous regions (mountainous 99.3%, hilly 98.7%, low-land 0.6%) (K. K. Aryal et al., 2015).

Dietary practices vary significantly between the two major ethnic populations living at HA in Nepal – Tibetans and Khas-Aryas. Those from Tibetan origins (such as Sherpa and Thakali) have culturally derived food practices of consuming large amounts of alcohol, salt, meat products and oil (Smith, 1999; Stevens, 1996). However, during the field surveys this author has observed that the Khas-Aryas at HA have gradually acquired Tibetan dietary practices, particularly in consuming salty butter tea.

In summary, there is little robust data from population-based studies on CVD and related risk factors among HA populations in Nepal. Such studies that do exist have inconsistent findings. Differences in CVD-related risk in Nepal may depend as much on ethnicity (Tibetans versus Khas-Aryas) as on altitude. More evidence on both ethnic populations is required to understand the degree of CVD risk in HA populations of Nepal.

1.7 Significance of the study

This study is significant because:

First, it will be the first comprehensive survey of CVD and CVD risk factors in the population at HA in Nepal, which in turn may lead to development of important strategies to reduce this risk. Second, comparing the results of this study with results of studies in other HA populations will supply information on the potential role of altitude itself and other key environmental factors such as urban versus rural settings. Third, the comparison between Tibetan and non-Tibetan HA populations will enable understanding of whether HA itself has a protective or harmful effect on cardiovascular health or whether other factors such as ethnicity or lifestyle determine the risk.

1.8 Aims and objectives

Research Questions

This study investigates the following general research questions:

1. What is the prevalence of CHD in HA populations in Nepal?

2. What is the prevalence and distribution of key CVD risk factors among this group and do these differ by altitude?

The detailed aims are:

1. To estimate the prevalence of CHD by interpreting resting ECGs, to identify any distinct pattern of ECG abnormalities, and to estimate the association, if any, between changes consistent with CHD and altitude.

2. To estimate the prevalence of cerebrovascular disease.

3. To estimate the distribution of blood pressure and prevalence of HT and to determine the association, if any, between systolic and diastolic BP, and altitude.

4. To estimate the distribution of key CVD risk factors: lipid profile, glycated hemoglobin, body mass index, waist and hip circumference, tobacco use, alcohol use, salt use, fruit and vegetable consumption, and physical activity.

5. From this information, to determine the 10-year risk of fatal or non-fatal cardiovascular events using the WHO and International Society of Hypertension (ISH) risk prediction chart.

6. To compare the estimates of CHD, BP, HT, CVD risk factors, and CVD risk at HA with similar data from those living at LA.

2 Literature Review

The purpose of this chapter is to review and summarize the literature on cardiovascular disease (CVD) and related risk factors in high altitude (HA) populations. Five sections present various associations between CVD and risk factors and HA. Narrative reviews are presented for the associations between: (i) obesity, (ii) tobacco use, (iii) alcohol intake, (iv) diet, and (v) electrocardiogram (ECG) abnormalities; and altitude. There is a final section about CVD and risk factors specifically in Nepal.

2.1 Obesity at high altitude

Overweight and obesity are important public health concerns affecting both developed and developing countries. The World Health Organization (WHO) has considered it a global epidemic (World Health Organization, 2000). According to a recent WHO report, 13% of the world's adult population (men 11%, women 15%) were obese and 39% (men 38%, women 40%) were overweight in 2014 (World Health Organization, 2015b). Estimates for developed countries are that between 40% and 70% of the adult population are either overweight or obese (Ng et al., 2014). A rapid rise in the prevalence of severe obesity (obesity III, body mass index (BMI) ≥40 kg/m^2) is of particular concern; for example it is at 6.4% in the United States of America (USA) (Ogden, Carroll, Kit, & Flegal, 2014).

Obesity increases the risk of CVD, particularly via associated risk factors such as diabetes, hypertension (HT) and dyslipidemia (Solomon & Manson, 1997). Type II diabetes is particularly associated with obesity. More than 80% cases of type II diabetes can be ascribed solely to obesity (Napier, 2006). People with a BMI greater than or equal to 35 kg/m^2 are 20 times more likely to develop diabetes compared to individuals with a normal BMI during a 10-year period (Field et al., 2001). The suggested mechanism of type II diabetes in most of those with obesity is insulin resistance due to the elevated levels of serum fatty acids in the obese state (Boden, 2011; Papaetis, Papakyriakou, & Panagiotou, 2015).

It may be that obesity should be treated like any other chronic disease regardless of metabolic abnormalities (Hill & Wyatt, 2013). In a systematic review and meta-analysis of non-experimental studies conducted between 1950 and 2013, the relative risk of all-cause mortality or cardiovascular events was 1.24 (95% CI 1.02 to 1.55) in obese participants compared to the metabolically healthy normal weight participants (Kramer, Zinman, & Retnakaran, 2013). Obesity was a significant predictor of ischemic heart disease (IHD) in the Framingham study data involving 5209 participants (Hubert, Feinleib, McNamara, & Castelli, 1983). The INTERHEART study also showed that abdominal obesity could account for 20% of the population-attributable risk of first myocardial infarction (MI) (Joshi et al., 2007). Obesity-related comorbidities could be improved with weight loss of 5% to 10% (Padwal & Sharma, 2010). Although the net positive energy balance (overload less expenditure) is the most common cause of obesity, the etiology is highly complex and encompasses factors (among others) such as genetic, physiological, environmental and socio-economic (Napier, 2006; Wright & Aronne, 2012).

Obesity in HA populations

The preponderance of evidence suggests that HA populations generally have a lower BMI and less general obesity compared to low altitude (LA) populations. However, the rates of central obesity as defined by high waist circumference (WC) were actually higher in most of the HA populations studied. In addition to the known risks for obesity such as lifestyle, dietary and socio-economic factors, other environmental conditions at HA could influence obesity in native populations. These include hypoxia, cold temperature-induced changes in energy balance and metabolic rate, low birth weight, growth stunting, and a high level of vitamin D. However, the role of these factors for obesity in HA populations has not been fully elucidated. This review will discuss key findings on obesity-related studies in adult HA permanent residents, explain possible causes and the possible mechanism of this relationship, and also briefly describe the effects on obesity from short-term exposure to HA.

A large amount of evidence indicates an inverse association between BMI and altitude. In a nationally representative study comparing American adults living at lower than 500 metre (m) (n=322,681) and higher than or equal to 3000 m (n=236), LA residents had a greater risk for both men and women for obesity: odds ratio (95% CI) 5.1 (2.7 to 9.5), for men, and 3.1 (1.6 to 9.3), for women, after controlling for temperature, diet, urbanization, physical activity, smoking, and demographic factors (Voss, Masuoka, Webber, Scher, & Atkinson, 2013). Another study comparing Tibetan participants residing in Tibet and Nepal at three levels of altitude (1200 m, 2900 m, and 3700 m) found that a higher altitude level was significantly associated with lower

BMI even after adjusting for physical activity and calorie intake (Sherpa et al., 2010) (Table 2.1). This relationship was not observed for WC or waist to height ratio (WHtR). An inverse relationship between altitude and BMI, WC and waist to hip ratio (WHR) was found in an Indian study comparing the anthropometric measurements in a HA population (2438 m) in Himanchal Pradesh and a LA population in Delhi (253 m) (Tyagi, Tungdim, Bhardwaj, & Kapoor, 2008). Another Indian study comparing the populations with Tibetan ancestry at low (701 m), intermediate (1861 m), and high (3493 m) altitude also reported an inverse relationship of BMI with altitude (Mandal, Adak, Biswas, & Bharati, 2011). A Peruvian study on 210 women with similar ancestry but living at different altitudes (>3800 m and <1500 m) showed a similar BMI and WC at both levels (Lindgärde, Ercilla, Correa, & Ahrén, 2004).

Table 2.1: Prevalence of obesity and central obesity by altitude level

Altitude	**1200 m (N=127)**	**2900 m (N=119)**	**3660 m (N=371)**
		N (%)	
Obesity	25 (19.7)	14 (11.8)	36 (9.7)
Central obesity	68 (53.5)	68 (57.1)	92 (24.8)

Definitions: obesity, BMI ≥30 kg/m^2; central obesity, WC >102 cm for men and WC >88 cm for women. (Adapted from Sherpa et al. 2010).

Studies comparing the natives permanently living at different levels of HA populations also document a lower BMI with increasing levels of altitude (Negi et al., 2012; S. Shrestha et al., 2012). Negi et al. 2012 reported that the prevalence of obesity was 17.4% and central obesity (WC: >90 cm for men and >80 cm for women) was 19.4% in the participants living at 3100-3500 m but the corresponding values increased to 35.7% and 30.4% respectively in those living at higher than 3500 m in Spiti valley of India (Negi et al., 2012). In a Nepalese study of 137 participants, BMI was significantly lower at 2950 m compared to 2670 m, especially in men (S. Shrestha et al., 2012).

Studies carried out at a single altitude level of HA have also generally shown a low prevalence of obesity by BMI classification but higher central obesity. A study in Pakistan comprising 4203 adults living at 2438 m reported obesity in just 1.8% of the participants (Shah, Nanan, Rahbar, Rahim, & Nowshad, 2004). A Peruvian study at 4100 m on a small sample of 102 estimated an obesity prevalence of 2.6%, 18.2%, and 14.3% for the age groups 30 to 39 years, 40 to 49 years, and older than 50 years respectively (Mohanna, Baracco, & Seclén, 2006). The corresponding prevalence for central obesity (WC: >102 cm for men and >88 cm for women) were 36.8%, 36.4%, and 47.6% respectively. A study on HA farmers and herdsmen at 3700 m in Tibet reported the prevalence of central obesity (WC: ≥90 cm for men and ≥80 cm for women) in 46% of the 692 participants aged 30 to 80 years (Sherpa et al., 2013). This prevalence was higher in women than in men (64.3% versus 25%).

While the majority of the studies report lower BMI and general obesity at HA, studies conducted in Saudi Arabia have unequivocally shown a higher BMI, obesity, and central obesity at HA compared to LA populations. BMI levels were higher in both men and women at HA (3150 m, sample size 437) compared to LA natives (500 m, sample size 468) in the Asir province of Saudi Arabia (Khalid, 1995). This finding is corroborated by another study among 438 married and non-pregnant women born and permanently living at 2800 m to 3150 m in the Abha region of Saudi Arabia, which reported the prevalence of central obesity (WC: >88 cm) at 41.1% (Khalid, 2007). Participants at LA were physically more active than HA counterparts in both of the above studies. Interestingly, Saudi Arabian school children and adolescents aged 6 to 15 years also had significantly greater odds for being overweight and obese at HA compared to LA counterparts (Khalid, 2008).

Possible explanations for lower BMI and higher central obesity in HA populations

Altered metabolic processes, low birth weight, and a greater concentration of circulating vitamin D have all been proposed to contribute to lower mean BMI and rates of general obesity at HA. Metabolic expenditure varies according to energy imbalance in either very hot or cold temperatures (McAllister et al., 2009). To cope with a reduction of ambient temperature of 5°C, an increased annual calorie expenditure equivalent to 5.1 kg to 7.3 kg of adipose tissue is required (Hansen, Gilman, & Odland, 2010). The catabolic effect of physiological responses to cold temperature at HA may be responsible for lower body weight at HA.

Evidence suggests low birth weight at HA may reduce later deposition of subcutaneous tissue (Galan et al., 2001) and lower BMI in adulthood (Sørensen et al., 1997). Higher levels of circulating vitamin D because of increased exposure to ultraviolet radiation at HA (Holick, Chen, Lu, & Sauter, 2007) may confer a benefit that lowers the obesity rates in HA populations.

Vitamin D is hypothesized to suppress inflammatory cytokines Tumor Necrosis Factor alpha (TNF-alpha) and Interleukin-6 (IL-6) (Khoo et al., 2011; B. Li et al., 2013), which are elevated in the obese state (Kahn, Hull, & Utzschneider, 2006). A recently published meta-analysis also showed that obese people had 35% greater risk of vitamin D deficiency (Pereira-Santos, Costa, Assis, & Santos, 2015). In addition, there is also strong evidence that vitamin D may promote the outcomes of weight loss interventions (Rosenblum, Castro, Moore, & Kaplan, 2012; Villareal et al., 2011). It is thus plausible to argue that increased vitamin D levels may help prevent obesity in HA residents.

The levels of leptin, an adipose tissue-derived hormone, increases in hypoxia and this hormone reduces appetite and increases energy expenditure (Yingzhong, Droma, Rili, & Kubo, 2006). However, there is little published literature about the leptin-altitude relationship in native HA populations. It is possible that levels of leptin at HA decrease (Santos, 2000; Woolcott, Castillo, Torres, Damas, & Florentini, 2002). Although hypoxia promotes leptin secretion, cold temperature inhibits it (Sherpa et al., 2010) and ambient cold temperature may moderate the role of hypoxia for leptin secretion during the long-term exposure.

Despite having lower mean BMI and rates of obesity, a higher prevalence of central obesity (high WC) is observed in the majority of the studied HA samples compared to those seen in LA samples. This finding has important health implications because CVD risk factors are more prevalent in people with central adiposity than in those with fat in peripheral regions (National Institute of Health, 1998). Although BMI has a high correlation with body fat, it does not provide information on central fat deposition (Padwal & Sharma, 2010).

Possible causes of increased rates of central obesity may include physical inactivity, high alcohol consumption, and social deprivation. In some studies, participants at HA were physically less active than those living at LA and centrally obese participants were also less active (Khalid, 1995, 2007; Sherpa et al., 2013). A Tibetan study of residents at 3700 m found that only one-fourth of the participants had energy expenditure of greater than 2000 kcal/week (Sherpa et al., 2013), suggesting a low expenditure of calories. The surplus calories might have transformed to fat and accumulated in the visceral area. Outdoors ambient temperature is usually cold at HA and, particularly during the winter, people limit themselves to activities inside the house for months. It has also been shown that elderly HA residents had lower basic activities of daily living compared to LA elders (Matsubayashi et al., 2009).

Alcohol intake is very common in HA populations. In some HA populations, for example Tibetans, alcohol drinking is a cultural practice. The positive association between heavy or binge drinking and central obesity is reported in a number of studies (K. Lee, 2012; Wannamethee, Shaper, & Whincup, 2005). A plausible mechanism for this relationship may be alcohol-induced rise in appetite and consequent additive energy to that from other dietary sources (Yeomans, 2010).

Low socio-economic status or social deprivation has been linked to increased levels of anthropometric measurements including WC and WHR. A European study showed increasing rates of WC with increasing levels of socio-economic deprivation, particularly in women (R. Chen & Tunstall-Pedoe, 2005). Other studies also reported lower physical activity among men and women with lower socio-economic status (Ford et al., 1991). Because of limited opportunities and access, HA populations are more likely to be in a lower socio-economic stratum, which in turn may result in low levels of education and awareness about healthy lifestyle.

Obesity in short-term exposure to HA

Appetite suppression and body weight loss are frequently observed during an HA sojourn (Quintero, Milagro, Campion, & Martinez, 2010) and these are also components of chronic mountain sickness (CMS) (León-Velarde et al., 2010). The possible reasons include changes in leptin, glucagon-like peptide 1, protein synthesis, intestinal absorption and hypoxia-related genes (Quintero et al., 2010). There is also substantial evidence that people with a higher BMI or obesity lose more weight than people with normal BMI during short-term exposure to HA. For example, obese persons working temporarily at 4000 m reached their normal BMI level after 3 to 5 months of HA exposure (Wu et al., 2007). Thus, working or trekking at HA might be an effective strategy for losing body weight – except in those with other co-morbidities like CVD, or sleep apnea (Kayser & Verges, 2013). However, more evidence is required to support a therapeutic use of HA exposure for maintaining or reducing body weight.

Conclusion

Collectively, HA populations generally have lower mean BMI levels and reduced rates of obesity. However, higher rates of central obesity may increase the risk of CVD, and metabolic risk factors. The multi-factorial nature of obesity and lack of research preclude reaching definite conclusions about the relationship between obesity and HA. However, it is conceivable that hypoxia and cold temperature at HA affect energy balance and other obesity-related factors in HA populations.

2.2 Tobacco use at high altitude

Tobacco consumption is one of the world's biggest public health challenges. Tobacco causes the deaths of 6 million people every year and around 80% of more than one billion smokers in the world are from low and middle income countries (World Health Organization, 2015c). One estimate is that half of tobacco smokers will die prematurely due to their tobacco use (Peto, Boreham, & Lopez, 1996). Smoked tobacco accounts for about 65% to 85% of all tobacco produced globally and it causes more disease than the other forms of tobacco (World Health Organization, 1997). The prevalence of smoking is highest in Eastern Europe and Central, Southern, and Eastern Asia where 50% of adults smoke (P. Jha, Mony, Moore, & Zatonski, 2010). In 2012, the age standardized prevalence of current smoking in WHO's South-East Asia region was around 33% for men and 3% for women who were aged 15 years or over (World Health Organization, 2014b). The prevalence of smoking has reduced in developed countries in recent years but it is increasing in developing nations (Pipe, 2010).

An estimated 1.6 million cardiovascular deaths in 2000 were attributed to smoking, accounting for 11% (of these, men 17% and women 5%) of all CVD deaths of people aged 30 years or more in the worldwide population (Ezzati, Henley, Thun, & Lopez, 2005). Among all CVD deaths attributable to smoking, IHD comprised the largest proportion (54%) and was similar in developed and developing countries (Ezzati et al., 2005). A prospective study of one million participants in the USA reported a smoking-associated risk ratio (RR) of 2.5 (men) and 2.9 (women) for IHD, and 2.7 (men) and 3.4 (women) for cerebrovascular disease (Peto, Boreham, Lopez, Thun, & Heath, 1992).

Cigarette smoking directly contributes to the development of IHD, chiefly by impairing nitric oxide activity, increasing vascular inflammation, initiating and promoting deposition of inflammatory materials in vessel walls, contributing to plaque rupture, and oxidizing lipoproteins (Ambrose & Barua, 2004; Benowitz, 2003; Tonstad & Johnston, 2006). Smokeless tobacco users are more likely to have raised blood pressure (BP) levels compared with smokers and non-tobacco users (Bolinder & de Faire, 1998) due to the high sodium content and the presence of two pharmacologically active ingredients: nicotine and licorice (Westman, 1995).

Smoking prevalence and practices at HA

Available literature suggests that HA populations have a lower prevalence of smoking compared with those living at LA. Factors such as a culturally driven preference for alcohol intake rather than tobacco products, lack of availability of tobacco products and low purchasing capacity may be the reasons. Reports of smokeless tobacco use in HA are extremely rare and so this review is mainly focused on smoked tobacco.

Studies on HA populations of Tibetan ethnicity have mostly reported a smoking prevalence between zero and 15%. None of the 119 study participants in the age group of 30 to 70 years from the Sherpa population living at 2900 m in Nepal were smokers or past smokers (Sherpa et al., 2010). The prevalence of current smoking was 5.1% (of these, men 10.6%, women 1%) in a study among 701 members of a HA population living at 4300 m in Tibet, which was well below the national prevalence of China (X. Zhao et al., 2012). Another study among 692 farmers aged 30 to 80 years and living at 3700 m in Tibet reported the prevalence of smoking as 15.3% (of these, men 33.1%, women 0.3%) (Sherpa et al., 2013). Two studies on HA populations with Tibetan ancestry but living at higher than 3000 m in the Himanchal state of India showed a prevalence of 15% for current smokers (Negi et al., 2012) and just 5.9% for current and past tobacco consumers (Negi et al., 2014). A systematic review concluded that the low smoking rates in Tibet accounted for its lowest crude mortality rate from lung cancer among all regions of China (She, Yang, Hong, & Bai, 2013). Nonetheless, the prevalence of smoking has increased in the urban HA Tibetan population; for example, the capital city of Lhasa (3660 m) has a rate of 24.3% (Sherpa et al., 2010). Also, the prevalence of smoking was 25% in the older Tibetan population (≥60 years) living at greater than or equal to 3000 m in Qinghai, China; 43% and 25% for Mongolian and Han elders respectively (Matsubayashi et al., 2009).

There have been very few reports on tobacco use and smoking trends in Andean HA populations. In a study among 3246 participants aged 15 years or over in Peru (3380 m), 7.4% reported smoking at least one cigarette per day (Jaillard et al., 1995). The prevalence of smoking was similar, at 6.7%, among 506 participants (aged 35 to 75 years) living at 4100 m in Peru (Gonzales & Tapia, 2013).

In contrast to the Tibetan and Andean populations, studies on other HA populations showed a higher smoking prevalence. The prevalence of smokers was 43.7% in men and 5.5% in women in a study of 4203 adults living at 2438 m in Pakistan (Shah, Arif, Delclos, Khan, & Khan, 2001). In this study participants who reported consuming wine were 3.5 times more likely to be smokers. The odds ratio for smoking was 7.0 times higher in people aged 20 to 50 years living in a mountainous area of Taiwan compared to those living at low altitude (H.-W. Chen, Chu, Chen, & Yeh, 2014). In this study, a lack of tobacco control activities in mountainous areas was implicated for the higher smoking rates. A study conducted in the Appalachian mountains of the USA reported that adults generally showed a lesser degree of acceptance for adolescent tobacco consumption than for alcohol use (Meyer, Toborg, Denham, & Mande, 2008).

Cultural norms and practices have an enormous influence on tobacco use in HA populations. For example, traditionally smoked tobacco is less common in Tibetan HA populations. Instead, nose-snuffing of powdered tobacco is customary cultural practice. This is also used as a remedy for common cold and related illnesses. Chewing coca is a popular practice in the Andean HA population as they believe it helps to combat the hard climatic conditions of HA (Hanna, 1974). These factors may contribute to the comparatively lower rates of smoking in Tibetan and Andean HA populations.

Effects of smoking at HA on sojourners and non-acclimatized populations

The current literature on sojourners and non-acclimatized populations at HA shows that although smokers may have a decreased risk of acute mountain sickness (AMS) compared with non-smokers, they may have impaired capacity to acclimatize at HA. A study on Han lowland individuals temporarily working in Tibet reported a lower incidence of AMS in smokers when compared to non-smokers, but they had an impaired capacity for long-term acclimatization compared to non-smokers (Wu et al., 2012). In a prospective cohort study among 1326 French sojourners, the odds for having AMS were significantly lower in smokers than in non-smokers during their ascent to 4000 m (Richalet, Larmignat, Poitrine, Letournel, & Canouï-Poitrine, 2012). However, during prolonged stays at HA smokers generally have more cases of mountain sickness. For example, a study among young Chinese male immigrants to Tibet showed a higher prevalence of CMS in the smoking group compared to the non-smoking group (Pei et al., 2012), and in Peru foreign workers who could not cope with work at 3200 m were all smokers (Lindgärde & Liljekvist, 1984), suggesting that smoking behaviour may impair long-term altitude acclimatization. Nonetheless, there are also studies showing no significant relationship between the prevalence of AMS and smoking status (Gaillard, Dellasanta, Loutan, & Kayser, 2004; Schneider, Bernasch, Weymann, Holle, & Bartsch, 2002).

Hypoxia-induced cerebral vasodilation, which is impacted by the increased levels of nitric oxide, is one of the main triggers of AMS headache. As nitric oxide levels go down in smokers, this may protect them from headache (Wu et al., 2012). Reduced levels of nitric oxide along with the effects of higher levels of nicotine and carbon monoxide in smokers may help to attenuate breathing instabilities and decrease sleep disturbance at HA (Wu et al., 2012).

An increased risk of frostbite among smokers during a sojourn to HA has also been documented. A retrospective study of frostbite cases over a 10-year period among mountaineers in Karakoram Mountain Range in Pakistan reported that tobacco smoking was a contributing factor to susceptibility to frostbite (Hashmi, Rashid, Haleem, Bokhari, & Hussain, 1998). A graded relationship between smoking frequency and frostbite incidence was reported in LA population as well (Ervasti et al., 2004).

Conclusion

In summary, available evidence suggests that the prevalence of smoking tobacco in the larger HA populations, Tibetans and Andeans, is generally low, but other HA populations may have higher smoking rates than LA residents. Cultural norms and practices have an important role in tobacco use at HA. Among sojourners and non-acclimatized population at HA, smokers have a decreased risk of AMS compared to non-smokers but have impaired capacity to acclimatize during a prolonged stay.

2.3 Alcohol intake at high altitude

Globally, 3.3 million deaths annually, or 5.9% of all deaths, are attributed to the harmful use of alcohol. A WHO report attributed these to alcohol-mediated CVD and diabetes (33.4%), cancers (12.5%), and gastrointestinal diseases (16.2%) (World Health Organization, 2014c). Alcohol consumption is causally implicated in more than 200 health conditions (Rehm et al., 2010).

Cardiomyopathy, atrial fibrillation, HT, and haemorrhagic stroke are identified as the main CVD related risks from heavy alcohol consumption (World Health Organization, 2007b). The biological mechanisms for these associations are unclear. It has been hypothesized that alcohol-induced toxicity in myocardial cells, cardiac conduction interference, refractory period shortening and increased sympathetic activity may be the possible reasons for alcoholic cardiomyopathy (Klatsky, 2015; Marchi, Muniz, & Tirapelli, 2014).

The views on risks and benefits of alcohol consumption on CVD health are controversial. The vast majority of epidemiological studies suggest that light to moderate alcohol consumption is associated with reduced risk of CVD outcomes (Ronksley, Brien, Turner, Mukamal, & Ghali, 2011; Smyth et al., 2015). A recent large prospective study on 114,970 participants from 12 countries with different income regions showed that current drinking was significantly associated with reduced MI, hazard ratio (95% CI) of 0.76 (0.63 to 0.93) (Smyth et al., 2015). Approximately half of this benefit is suggested to be mediated by the increased level of high-density lipoprotein-cholesterol (HDL) triggered by alcohol consumption (Rimm, Williams, Fosher, Criqui, & Stampfer, 1999). Nonetheless, there is robust evidence that episodic heavy drinking may raise the risk of IHD (Roerecke & Rehm, 2010), possibly due to an effect of increased triglyceride (TG) levels (Klatsky, 2015).

Alcohol consumption trend at HA

High alcohol consumption is common in some HA populations, particularly those of Tibetan origin. The trend has been inconsistent in other HA populations.

In an Indian study on 242 participants (aged ≥19 years) of Tibetan origin from the Lepcha community living in the Sikkim Himalayas, 80.8% were currently drinking and 22.1% were heavy drinkers, defined as consuming more than two standard drinks per day (Mukhopadhyay,

Mukhopadhyay, & Majumder, 1996). Among farmers and herdsmen at 3700 m in Tibet, the prevalence of current drinking was 46.8% (Sherpa et al., 2013). The proportion of current drinkers in this study was similar for men and women. A study among 119 Sherpas of Tibetan origin living at 2900 m in the Everest region of Nepal found that 35.5% were drinking alcohol more than five times a week (Sherpa et al., 2008). Another study comparing two HA populations reported that 44.4% of Tibetans living at 3660 m and 56.3% of the Sherpas living at 2900 m were drinking alcohol more than five times a week (Sherpa et al., 2010). In an Indian study among 413 participants (age >20 years) of Tibetan ancestry living at 3100 m and 3900 m the prevalence of current drinking was reported to be 32.4% (Negi et al., 2012). A Tibetan study reported that of 701 herdsmen living at 4300 m and aged 40 years or older, 9.1% were drinking alcohol at least once a week (X. Zhao et al., 2012). Studies on an older HA Tibetan population aged greater than or equal to 60 years, however, reported a low prevalence of current drinking status (16%) compared to HA-living Mongolian (24%) and Han (22%) counterparts (Matsubayashi et al., 2009).

A tendency towards high alcohol consumption among HA populations with Tibetan origin is associated with serious health consequences. Native Tibetans were found to have a higher incidence of alcoholic cirrhosis than LA populations and 60.9% of all cirrhosis was attributed to alcohol (G. Zhao & Li, 1989). A hospital-based study on acute first-ever stroke patients showed that the prevalence of heavy drinking was significantly higher in Tibetans compared to those from lowland areas (Fang et al., 2011). In a population-based study among 3171 participants in Lhasa (Tibet), 16.2% (of those, men 31.6% and women 9.6%) had alcohol use disorder (Guo et al., 2008). It has also been reported that alcohol drinking may exacerbate high altitude sickness among indigenous Tibetans who frequently travel between high and low or to extreme HA (S. Li et al., 2006).

Very few studies have reported data on alcohol consumption in other HA populations. A Peruvian study on 3246 participants aged greater than or equal to 15 years and living at 3380 m showed that 12.3% were heavy drinkers (consuming 120 to 300 g/week) (Jaillard et al., 1995). More than one-third (34%) reported drinking alcohol at least once a week in a study among HA miners in Argentina (Schinder & Ruder, 1989). A qualitative study at Nahuala (2467 m) in Guatemala concluded that during festivals and holidays many drinkers, especially men, drink until inebriation and the social environment encourages drinking (Kanteres, Lachenmeier, & Rehm, 2009).

Possible reasons for high alcohol consumption in HA

Although little research is available from which to draw conclusions about a general pattern of alcohol consumption in all HA populations, high consumption of alcohol has been consistently reported in populations with Tibetan ancestry, regardless of their living situation. There may be three strong reasons triggering alcohol consumption in HA: ancestral cultural habit, cold temperature, and physical hardship.

Alcohol consumption is culturally embedded in some HA populations, mainly Tibetan and Andean (Kanteres et al., 2009; Luobu, 2012; Meyer et al., 2008; X. Zhao et al., 2012). In these populations, alcohol is consumed for hours and in large quantities during social and religious functions (Kanteres et al., 2009; Mukhopadhyay et al., 1996). The use of alcohol by adolescents is also socially tolerated by adults (Meyer et al., 2008), which further develops alcohol use as a culturally and socially preferred norm. Alcohol is widely available in HA areas and brewed in most of the homes from HA crops such as millet and barley. There is also a strong belief that locally brewed alcohol has medicinal properties (Gorer, 1938).

HA is associated with cold temperatures and many HA populations believe that alcohol has thermogenic effects and helps to keep a body warm. Although alcohol consumption in cold weather has minor effects on core body temperature, it is well-established that perception of cold and concomitant discomfort from cold decrease after alcohol intake (Graham & Baulk, 1980; Martin, Diewold, & Cooper, 1977). The biological mechanism of this is unclear; however, vasodilation of the blood vessels after alcohol intake and consequent warming of the skin (Wasielewski & Holloway, 2001) or the direct effect of ethanol on the central nervous system (Yoda et al., 2008) may play a role in reducing cold sensation.

Because of environmental and physical adversities, HA living generally implies difficult working conditions and physical hardship. Previous reports suggest that these factors are strongly associated with alcohol consumption (Littman, 1970; Schinder & Ruder, 1989).

Impact of alcohol on HA sojourns

Few studies have examined the impact of alcohol consumption on health during HA sojourns. Alcohol consumption reduced acute ventilatory response in the initial stages of ascent to 3000 m from 171 m in a randomized crossover trial (Roeggla, Roeggla, Roeggla, Binder, & Laggner, 1995). In a study among construction workers on the Qinghai-Tibetan highway, gastrointestinal bleeding was higher among frequent drinkers compared to those drinking less (Wu, 2001). Another study suggested that the combination of alcohol drinking and smoking may inhibit HA long-term acclimatization but not AMS (Lindgärde & Liljekvist, 1984). Avoidance of alcohol has also been suggested to HA travellers as a preventive measure for high altitude pulmonary edema (HAPE) (Paralikar, 2012) and especially for cardiac patients aiming to go to HA (Higgins, Tuttle, & Higgins, 2010).

There are also some reports that AMS incidence may not differ between drinking and non-drinking HA sojourners (Honigman et al., 1993; Schneider et al., 2002), and alcohol intake may not be associated with high-altitude headache, the most common symptom in HA sojourners (Burtscher, Mairer, Wille, & Broessner, 2011).

Conclusion

Overall, some HA populations have a high rates of alcohol consumption, for example more than one-third of the adult Tibetan populations. It may be due to the combination of cultural, social and environmental factors. Hence, interventions through only health centers and educational institutions may be not sufficient to change these trends. Culturally and religiously driven preventive measures supported by appropriate government regulations should supplement these efforts.

2.4 Dietary habits at high altitude

A healthy diet is protective for CVD, cancer, obesity and diabetes (World Health Organization, 2015a). Up to 30% of deaths from coronary heart disease (CHD) are attributable to unhealthy diets (Lichtenstein et al., 2006). The WHO expert consultation on diet and prevention of chronic disease recommends that daily dietary edible fat intake should not exceed 40 g, dietary cholesterol less than 300 milligram (mg), salt consumption no more than 5 g, fruit and vegetables around 400 gram (g) to 500 g and the sodium to potassium intake ratio be equal to or lesser than 1 (Joint WHO/FAO Expert Consultation on Diet & Nutrition and the Prevention of Chronic Diseases, 2002).

The Global Burden of Disease study estimates that 1.65 million people die each year from conditions related to the excessive consumption of sodium (more than 2 g per day) (Mozaffarian et al., 2014). The INTERSALT study, which was conducted in 52 samples of population groups across 32 countries, reported a positive association between BP and salt intake in adults aged between 20 and 59 years (Elliott et al., 1996; Rose et al., 1988). One estimate is that reducing dietary salt intake by 1.15 g per day would lead to a 16% reduction in CHD deaths, a 22% reduction in stroke related deaths, and a marked 50% reduction in the number of people requiring antihypertensive medications (M. R. Law, Frost, & Wald, 1991). There is a controversy about the optimal amount of sodium intake, as several large and international prospective studies have reported an increased risk of cardiovascular events in people consuming both high (>5 g/day) and low amounts of sodium (<3 g/day), compared to those with moderate intake (3 g to 5 g/day) (O'Donnell et al., 2014; O'Donnell et al., 2011).

It has been suggested that total fat intake should not exceed 30% of total energy consumed (Grundy, 1997) and foods with high unsaturated fat (such as nuts, avocados, fish, olive, canola oils) are preferable to saturated high-fat foods (such as animal products, butter, cheese, fatty meats) (Reddy, 2010). The relationship between dietary fats and CVD may be due to atherogenic effects of plasma lipids, but fats may also have direct effects on thrombosis, endothelial function and inflammatory pathways (Ghafoorunissa, 1994; Kris-Etherton et al., 2001).

Existing evidence does not indicate any important association between carbohydrate intake and CVD (National Heart Foundation of Australia, 2006). However, excessive dietary carbohydrate may raise the CVD risk indirectly through overweight, obesity, and effects on lipids and blood glucose (Reddy, 2010).

Dietary patterns at HA

HA encompasses difficult climatic and agronomic conditions resulting in very limited food choice options. Potatoes, barley and buck-wheat are the staple foods in major HA communities such as Tibetan and Andean communities (Berti et al., 2010; Stevens, 1996). In the Everest region of Nepal, adult Sherpas consume more than one kilogram (kg) of tubers per day, of which 0.72 kg is potato, and more than 75% of crop land is dedicated to potato farming (Stevens, 1996). In the HA region of Ecuador more than two-thirds of daily food comprises potato and maize (Oyarzun, Borja, Sherwood, & Parra, 2013) and in the Bolivian Andes potatoes and tubers fulfill 54% of total dietary energy (Berti et al., 2010). In three large prospective studies in LA areas in the USA, a higher intake of baked, boiled or mashed potatoes was positively associated with an increased incidence of HT (Borgi, Rimm, Willett, & Forman, 2016). However, no research has been published on the association between BP and potato consumption at HA. In HA residents of both the Himalaya and Andes regions, fruit and vegetables are grown in small quantities due to adverse agronomic conditions (Berti et al., 2010; Stevens, 1996). One report states that Andes HA natives prioritize less nutritionally rich crops in terms of both production and consumption (Oyarzun et al., 2013).

The most striking difference in dietary habits between two major HA populations, Tibetan and Andean, is the amount of fat intake. Related literature unequivocally suggests that HA residents of Tibetan origin generally consume a high amount of fat, whereas Andean HA populations have a very low consumption. Tibetans consume an estimated 3 to 4 litres of yak butter tea daily (Cao et al., 2003) and meat consumption is also very high (Smith, 1999; Sun, 1986). Yak herding is a key subsistence activity in Tibetan cultural regions as the animals are used for both meat and transportation purposes (Stevens, 1996). Nak (female yak) are also prized sources of butter, cheese and meat. Butter is so popular in Tibet that formerly it was an acceptable currency for hiring workers and it was also used to pay taxes (Stevens, 1996). In contrast, fat intake is low in Andean HA regions. A systematic review of the nutritional adequacy of the diets in the Central Andes range reported that fat intake comprises less than 20% of total calories and in some settings less than 10% (Berti, Fallu, & Cruz Agudo, 2014). Although some Andean HA natives rear animals like cows, pigs, chickens, and guinea pigs, they rarely consume them (Oyarzun et al., 2013). An earlier report showed that about the half of the population in the Peruvian Andes region suffered from calorie deficiency and available food was unable to meet the calorie needs of the family (Ferroni, 1982).

Excessive consumption of salt is very common and embedded in Tibetan cultural dietary practices. This is largely influenced by the daily use of salty yak butter tea (Smith, 1999; Sun, 1986). Tibetan adults consume nearly four to five times the WHO recommended amount of 5 g of salt per day (Liu et al., 2001; Sun, 1986).

Consequences of poor diets in HA populations

Stunted growth is the predominant consequence of malnutrition problems observed in both Tibetan and Andean HA populations. A study reported that the prevalence of stunting and underweight in younger Tibetan children was 39% and 23.7% respectively (Dang, Yan, Yamamoto, Wang, & Zeng, 2004). The prevalence of malnutrition, and especially stunting, is higher in pre-school and school children in Tibet compared to the overall prevalence in China (Harris et al., 2001; National working committee on children and women, 2001). Studies in Andean regions also suggested stunting is a serious nutritional problem in children and adolescents (Bassett, Gimenez, Romaguera, & Sammán, 2013; Cossio-Bolaños et al., 2015). Other factors such as altitude (Dang et al., 2008) and poor socio-economic conditions (Leonard, 1989) may also contribute to child stunting at HA. Retarded growth, height, weight and BMI in early life may lead to the development of CVD in later life (Barker, Osmond, Forsén, Kajantie, & Eriksson, 2005; van Rooyen et al., 2005).

The high fat intake of Tibetan populations confers risk for CVD health. A worldwide longitudinal modeling study comprising data from 124 countries over the period 1980 to 2009 showed that availability of meat and dairy products as a proportion of the diet was independently and strongly associated with IHD mortality in adults (Green, Sutherland, Dangour, Shankar, & Webb, 2016).

Conclusion

HA natives have dietary habits that are associated with poor nutrition, possibly contributing to CVD risk. In addition to the limited food options because of the harsh weather and altitude, lack of proper utilization of available nutritional options is also important. A high risk of CVD due to the high intake of salt and a high-fat diet may be particularly relevant to HA populations of Tibetan ancestry.

2.5 Electrocardiographic abnormalities at high altitude

The most common ECG abnormalities in HA populations are right axis deviation (RAD), right bundle branch block (RBBB), and right ventricular hypertrophy (RVH). Research carried out on ECG abnormalities in HA residents reports a right-ward shift of the QRS frontal plane axis during both acute and chronic exposure to HA. RAD increased with increasing altitude levels in a Bolivian study, with mean levels of deviation of: +39° at 400 m, +70° at 3800 m, and +104° at 4780 m (Raynaud, Valeix, Drouet, Escourrou, & Durand, 1981). Another study comparing mean RAD among residents aged 13 to 20 years at different altitude levels reported +55° at sea level, +67° at 1600 m, +83° at 3100 m, and +125° at 4500 m (Pryor, Weaver, & Blount, 1965). A Peruvian study on children aged up to 14 years showed that RAD was frequently observed at 4540 m compared to their sea level counterparts (Peñaloza, Gamboa, Dyer, Echevarría, & Marticorena, 1960).

RAD is also commonly reported during short-term exposure to HA and in studies conducted in simulated HA chambers. For example, in a hypobaric chamber study, frontal plane QRS axis of eight volunteers deviated right-ward from +55° at sea level to +107° at a barometric pressure equivalent to that at 8848 m during the exposure of 40 days (Malconian et al., 1990). Another hypobaric chamber study in India reported that 15% of the 200 LA residents, when exposed to barometric pressure equivalent to 4500 m, showed a rise in RAD of between +20° and +30° during just 45 minutes of exposure (Akhtar, Bandopadhaya, Chatterjee, & Krishnamurti, 1978). RAD increased by more than 10° compared to RAD at sea level for more than half of 202 Indian soldiers deployed at 3600 m and 4200 m for around two years, but this change completely reversed in the majority of them within a month of returning to sea level (Kapoor, 1984).

Studies report frequent occurrence of RVH and RBBB in HA residents. In a study of 74 men the prevalence of RVH was 17% in Tibetans and 29% in Han natives living at 3658 m in Tibet (Halperin, Sun, Zhuang, Droma, & Moore, 1998). In another study among 120 healthy men living at 4540 m in Peru, the prevalence was 19.2% for RVH and 30.8% for RBBB (Rotta & Lopez, 1959). However, an Indian study of 984 healthy Tibetan participants living at 2745 m reported a prevalence of RVH of just 0.9% (Kaushal, DasGupta, Prashar, & Bhardwaj, 1995). A similar phenomenon of right heart burden has also been reported during short-term exposure to HA. For example, RSR pattern in ECG suggestive of RBBB was reported among 26% of 19 members of an American Medical Research Expedition to Mount Everest (Karliner, Sarnquist, Graber, Peters, & West, 1985). A sign of right ventricular overload was observed in all 10 participants, usually residents at sea level, during their one-year stay at an altitude of 4540 m in Peru (Peñaloza & Echevarría, 1957).

The main reason for right heart abnormalities during acute or chronic exposure to HA is likely to be hypoxia-induced increases in pulmonary vascular resistance and pulmonary HT. Depending on the levels of HA, pulmonary vascular resistance is reported to increase, perhaps by between 100% and 500% of baseline levels (Swenson, 2013). The magnitude and nature of the changes in pulmonary vascular resistance and right heart abnormalities vary in different HA populations. For example, pulmonary vascular resistance and pulmonary HT are well reported as being at a higher level among HA dwellers such as Andeans or North Americans (Pryor et al., 1965; Rotta & Lopez, 1959) but at a lower level in those with high degree of adaptation such as Tibetans (Groves et al., 1993; M. Gupta, Rao, Anand, Banerjee, & Boparai, 1992). This may suggest that natural selection of genetic traits providing protection from pulmonary vascular resistance might have occurred for populations with longer generational history at HA, such as Tibetans.

2.6 Cardiovascular disease and risk factors in Nepal

Cardiovascular diseases are the most common non-communicable diseases (NCDs) in Nepal (Vaidya, 2011). According to the WHO NCDs country profile 2011, CHD is the single most common cause of premature deaths in Nepal, responsible for 14.2% of all deaths with an age-standardized mortality rate of 152.6 per 100,000 population; stroke (age-standardized mortality rate of 82.6 per 100,000) and HT (age-standardized mortality of 40.4 per 100,000) being the third and fifth top causes of mortality respectively (World Health Organization, 2011). The annual death rate per 100,000 from CVDs and diabetes combined was estimated to be 400.2 per 100,000 for men and 301.3 per 100,000 for women (World Health Organization, 2011). The number of patients treated at the Shahid Gangalal National Heart Centre, the only government heart specialty hospital in Nepal, doubled between 2001 and 2008 (Shahid Gangalal National Heart Centre, 2008). A hospital-based cross-sectional study across 31 health institutions in Nepal reported that 40% of the hospital admissions among patients aged 35 years or older were related to CVD (Nepal Health Research Council, 2010). CVD is a substantial and growing public health problem in Nepal.

There are few large-scale representative studies of CVD in Nepal. The first case of MI in Nepal was documented in 1945 (Maskey, Sayami, & Pandey, 2003). A further 150 cases were identified between 1960 and 1968; 81.3% were smokers, 28% were hypertensives, 25.4% had hypercholesterolemia, and 14.3% were diabetics (Pandey, 1970). In 2003 an estimate based on hospital data was that 5% of the adult population in Kathmandu had IHD (Maskey et al., 2003). A population-based cross-sectional study of 1000 men aged 35 years or older using the WHO Rose angina questionnaire and ECG assessments estimated the prevalence of CHD in this group was 5.7% (Vaidya et al., 2009). The most significant risk factors identified in that study were tobacco use and a history of HT. No literature has been published about stroke prevalence in Nepal. Hospital audits of stroke cases report that ischemic stroke comprises around two-thirds of all stroke cases, stroke appears more frequently in men, and smoking is likely to be the main identifiable risk factor (Devkota, Thapa Magar, & Malla, 2006; Oli & Agrawal, 2001; A. Shrestha, Shah, Adhikari, Sapkota, & Regmi, 2011). An analysis of hospital data of stroke cases collected over five years reported that 15.3% of all stroke patients were below 45 years of age. This suggests that age of stroke onset may be younger in Nepal than in developed nations

(Devkota et al., 2006). Rheumatic heart disease (RHD) was a major cause of cardiac-related admissions, accounting for 22% cases in a specialist hospital (G. P. Bhandari, Angdembe, Dhimal, Neupane, & Bhusal, 2014). The prevalence of RHD is estimated to be two per 1000 school children in Nepal (Regmi & Wyber, 2013).

Nepalese also have a poor knowledge of heart-related diseases, their symptoms and risk factors. In a community-based study in two villages near Kathmandu, 60% of the respondents were not aware of any symptoms of heart attack and just 29.7% knew HT was a major risk factor for CVD (Vaidya, Aryal, & Krettek, 2013).

CVD risk factors in Nepal

HT: HT is the most studied risk factor of CVD in Nepal. A meta-analysis of population-based HT studies with a sample size of greater than 1000 estimated that nearly one-third (29.7%) of the adult Nepalese population had HT (SBP/DBP: ≥140/90 mmHg or were on treatment) (Neupane et al., 2014). A repeat cross-sectional study in the same community showed that the prevalence of HT increased three-fold over 25 years, from 6% in 1981 to 18% in 2006, using old WHO criteria for HT (SBP/DBP: ≥160/95 mmHg) (Vaidya, Pathak, & Pandey, 2012). Increased intake of salt and higher BMI were blamed for this rising trend. The growing prevalence of HT in Nepal was also corroborated by nationally representative NCD risk factors surveys of the population aged 15 years or older, which have noted the prevalence of HT increasing from 21.5% in 2007 (Ministry of Health and Population, Government of Nepal, Society for Local Integrated Development Nepal (SOLID Nepal), & WHO, 2008) to 25.7% in 2013 (K. K. Aryal et al., 2014). A huge unmet need for effective prevention and treatment of HT has been demonstrated by a nationally representative study, which showed 90% of participants with elevated levels of BP were not receiving any treatment (K. K. Aryal et al., 2014).

Obesity: Although population-based studies of overweight or obesity have been sparse in Nepal, trend analysis clearly indicates the rapid escalation of prevalence in recent years. Nationally representative studies noted that the prevalence of obesity (BMI ≥30 kg/m^2) was 1.7% in 2007 (Ministry of Health and Population et al., 2008) but increased by more than double in 2013 to 4% (K. K. Aryal et al., 2014). The prevalence rates for overweight (BMI ≥25 kg/m^2) tripled from 7.2% to 21.6% during this period. This is comparable to the nationally representative Nepal demographic health surveys repeated after a 10-year interval, which documented that the prevalence of overweight (BMI ≥25 kg/m^2) among women aged between 15 and 49 years rose from 6.4% in 2001 to 14% in 2011 after adjusting for age, parity and education (Kinnunen & Neupane, 2014). A large study including 14,425 participants from the community-based screening programmes in Eastern Nepal reported the prevalence of abdominal obesity at 34.7% according to the International Diabetes Federation (IDF) criteria for South Asians (WC >90 cm in men and >80 cm in women) (S. K. Sharma et al., 2011). The prevalence of overweight or obesity in specific population groups was also reported to be high; for example, 25.9% in school children from private schools studying in grades 1 to 6 (Koirala, Khatri, Khanal, & Amatya, 2015), 33.4% in civil servants (Simkhada, Poobalan, Simkhada, Amalraj, & Aucott, 2009), and 32.9% in men from the relatively well-off community (Vaidya et al., 2005). All of these studies identified higher family income and sedentary lifestyle as the main causes for the rise in obesity. Among Jhaukel-Duwakot Health Demographic Survey site participants, 43.3% had a low level of physical activity in their daily lives, particularly those with obesity, HT or diabetes (Vaidya & Krettek, 2014).

Almost all of these studies in Nepal followed the WHO guidelines on BMI classification (World Health Organisation, 1995). However, in the recent years, ethnicity specific BMI cut-points have been proposed for non-Caucasian populations. For example, BMI equal to or greater than 23 kg/m^2 and 25 kg/m^2 have been recommended as cut-points for overweight and obesity respectively for Asian Indian population (Misra et al., 2009). While considering these cut-points, overweight and obesity rates of Nepalese populations in published studies could have been significantly higher compared to commonly used WHO international classification.

Diabetes: IDF national estimates of diabetes prevalence for Nepal in the population aged between 20 and 79 years were 1.6% in rural areas and 10.7% in urban areas (International Diabetes Federation, 2015). Studies on type II diabetes in Nepal report the prevalence ranging from 4.1% to 9.5% (Mishra, Neupane, Bhandari, Khanal, & Kallestrup, 2015). A meta-analysis of diabetes studies in Nepal published between 2000 and 2014 with 30,218 subjects suggested the pooled estimate of type II diabetes prevalence (95% CI) of 8.4% (6.2 to 10.5), and pre-diabetes (impaired glucose tolerance) of 10.3% (6.1 to 14.4) (Gyawali et al., 2015). This study also estimated the pooled prevalence (95% CI) of type II diabetes at 1% (0.7 to 1.3%) in rural areas and 8.1% (7.3 to 8.9) in urban areas. Another systematic review and meta-analysis including only recent or nationally representative studies with a larger sample size estimated the prevalence of diabetes and pre-diabetes to be 9.5% and 19.5% respectively (Jayawardena et al., 2012). Notably, this report showed that the prevalence of pre-diabetes in Nepal was the highest among all South Asian countries.

From hospital-based data, it has been projected that diabetes prevalence will reach 17.5% in Nepal in 2025 (Dulal & Karki, 2009). In contrast to these estimations, a nationally representative study in 2014 of populations aged 15 years or older showed that 3.6% had raised fasting glucose (≥126 mg/dL) (≥7 mmol/L) or were on treatment (K. K. Aryal et al., 2014). Due to the lack of easy access to health care services and screening programmes a significant number of Nepalese populations may not be aware of their diabetic status. One study on 1012 participants from seven urban populations found that 54.4% of diabetics were not previously aware of their status (U. Shrestha, Singh, & Bhattarai, 2006). A high rate (25.9%) of diabetes has also been observed in elderly populations aged 60 years or more (M. Chhetri & Chapman, 2009). Studies have usually shown a greater risk of diabetes in women than in men (Gyawali et al., 2015).

Dyslipidemia: Population-based reports on lipid profile have been very limited in Nepal. The WHO STEPS survey for NCD risk factors 2013 has been the only representative study with data on lipid profiles for the country so far. This survey comprising participants aged 15 years or older and from 15 (of 75) randomly selected districts in Nepal showed that 22.7% had raised total cholesterol (TC) (≥190 mg/dL [4.9 mmol/L] or were on treatment), 79.3% of women and 61.2% of men had low HDL (<40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women), and 25.2% were affected with raised TG (≥150 mg/dL [≥1.7 mmol/L]) (K. K. Aryal et al., 2014). This study noted that those with higher education levels were more likely to have a higher prevalence of raised TC than those with no formal education. Another large study conducted in the Eastern part of Nepal reported a slightly lower prevalence of high TC (17.2%) and low HDL (56.7%) but a higher rate of high TG (48.3%) compared to national data (S. K. Sharma et al., 2011). A study among 4279 adolescents and young adults from rural Nepal found that a high TC/HDL ratio (>5.0) was prevalent in 17.4% of the cohort of those aged between 9 and 13 years, and 16% in those aged between 15 and 23 years; the prevalence of low HDL being strikingly high at 70.6% and 80.4% respectively for men and women (Stewart et al., 2013).

Although population-based studies have indicated that a low level of HDL is the most common lipid abnormality, hospital-based data from the urban areas have shown high TG to be most common (Karki, Neupane, Pradhan, & Magar, 2003; Takhelmayum, Thanpari, Kumar, Singh, & Sinha, 2014). None of the studies have investigated significant CVD risk associated with abnormal lipid components.

Smoking: Periodic evidence has demonstrated that smoking prevalence in Nepal has been falling dramatically in recent years. The comparison of two national surveys six years apart shows that the prevalence of current smoking had declined from 26.2% (of those, men 35.5%, women 15.9%) in 2007 (Ministry of Health and Population et al., 2008) to 18.5% (of those, men 27%, women 10.3%) in 2013 (K. K. Aryal et al., 2014). A national estimate of smoking prevalence for population aged 30 years or more in Nepal is 24.7% (of those, men 32.8% and women 16.8%) (K. K. Aryal et al., 2014). Nonetheless, the decreasing rate for the use of smokeless tobacco was marginal, from 18.6% down to 17.8%. This remarkable improvement in tobacco smoking prevalence can be substantially attributed to the Tobacco Control and Regulation Act 2011, which provided stringent measures such as a ban on smoking in public places, work places and public transport, and prohibition of all forms of tobacco advertising. At one time in the past, Nepal was one of the countries in the world with an alarmingly high prevalence of smokers with 73.7% daily smokers (of those, men 85.4%, women 62.4%) (Pandey, Neupane, & Gautam, 1988). Even today, the tobacco consumption rate is very high in some areas. For example, 43.6% of rural women in remote districts self-reported being a current tobacco user (Khatri, Mishra, & Khanal, 2015). A Nepal demographic health survey in 2011 identified a lack of formal education, older age, manual occupation and residency in low-land Terai as key determinants for tobacco use in men (Khanal, Adhikari, & Karki, 2013).

Alcohol intake: Like many others, Nepalese society has ambivalent views regarding alcohol consumption as many ethnic groups traditionally brew alcohol at home and alcohol consumption has been a preferred traditional cultural practice. Furthermore, alcohol is easily available in the market and there are no age restrictions on purchase. However, national surveys in recent years have shown a dramatic decline in alcohol consumption. The prevalence of ‘reported drinking in the past 30 days’ has gone down to 17.4% (of those, men 28%, women 7.1%) in 2013 (K. K. Aryal et al., 2014) from 28.5% (of those, men 39.3%, women 16.5%) in 2007 (Ministry of

Health and Population et al., 2008). The proportion of harmful use of alcohol (≥60 and ≥40 g mean consumption of pure alcohol per day for men and women respectively) was six times greater in mountain regions (6%) than in low-land areas (<1%) (K. K. Aryal et al., 2015). The influence of cultural practices on alcohol consumption has been shown to result in high alcohol intake in new generations as well. A study on adolescents (aged 11 to 17 years) in Kathmandu showed that those from ethnic groups that are traditionally alcohol users were twice as likely to have ever consumed alcohol (40.1%) compared to those from ethnic groups that were traditionally non-users of alcohol (19.4%) (Parajuli, Macdonald, & Jimba, 2015). Several studies have reported that parental alcohol use is the most significant predictor of alcohol consumption in youth (Dhital, 2001; A. Sharma & Khandelwal, 2000), and Nepalese initiated alcohol intake from a median age of just 10 years (Dhital, 2001).

Diets: The few available reports have shown that the consumption of fruit and vegetables in the Nepalese population is extremely low. The latest national survey found that 98.9% of the participants consumed less than five mean portions of fruit and vegetables per day (K. K. Aryal et al., 2014). This is much higher than in the national survey conducted in 2007, which reported a prevalence of 61.9% (Ministry of Health and Population et al., 2008). An earlier WHO STEPS survey conducted among 2030 participants in Kathmandu also noted that almost all (99.3%) participants self-reported consuming less than five portions of fruits and vegetables per day (World Health Organization, 2003). Nepal is hugely dependent on India for fruit and vegetables due to low production in Nepal. Increasing market prices often makes them difficult to afford.

Very few studies report quantitative salt consumption and trends in the general Nepalese population. A door-to-door survey, repeated in the same community after 25 years, showed that 55.9% (n=1405) of the participants aged 21 years or older reported consuming more than 5 g of salt per day in 1981, increasing to 89.5% (n=1218) in 2006 (Vaidya et al., 2012). A national survey in 2013 also documented that 10.9% of the participants thought they were consuming an excessive amount of salt (K. K. Aryal et al., 2014).

Conclusion

Collectively, CVD and its risk factors are significant health problems and causes of mortality in Nepal. The actual burden and likely causes and risk factors are difficult to establish from the current literature. However, available evidence suggests that the rates of HT, obesity and diabetes have been increasing over time and a significant proportion of the population has undiagnosed disease and risk factors, and is unaware of its CVD health-related risk status. A low level of HDL and low intake of fruit and vegetables may be particular features of CVD risk factors in Nepal. Tobacco smoking has declined in Nepal recently, which is a positive factor for CVD prevention. Although alcohol intake is also decreasing, customary practice and social acceptance of drinking alcohol is a major challenge to healthy lifestyles in Nepal.

3 Systematic Literature Review

The purpose of this chapter is to systematically review and summarize the literature for the associations between: (i) blood pressure (BP), (ii) blood glucose, and (iii) lipid profile; and altitude. Meta-analyses of the association between BP and blood glucose and living at high altitude (HA) are also shown. These variables were selected for systematic review and meta-analysis because they are the key cardiovascular disease (CVD) risk factors that have direct impact from hypobaric hypoxic conditions of HA.

3.1 Blood pressure and hypertension at high altitude

Hypertension (HT) is an important risk factor for adverse health outcomes such as stroke and myocardial infarction (MI) and contributes globally to an estimated 9.4 million deaths and 7% of disease burden annually (Lim et al., 2012). Depending on the definition used, HT affects between 20% and 30% of the global population (Asia Pacific Cohort Studies Collaboration, 2003; Prospective Studies Collaboration, 2002). The world-wide prevalence of HT is likely to rise with time, in part because of the ageing of the global population but also because of the increasing prevalence of obesity. One estimate is that the current prevalence will increase from 26.4% currently to 29.2% by 2025 (Kearney et al., 2005). Regardless of any threshold, increasing BP has a graded relationship with the risk of CVD. One estimate is that for each increment of 20 mmHg in systolic blood pressure (SBP) or 10 mmHg in diastolic blood pressure (DBP) the risk of CVD doubles across the entire range of BP from 115/75 mmHg to 185/115 mmHg, even in the absence of other risk factors (Prospective Studies Collaboration, 2002).

The effect of chronic hypoxic hypobaric conditions, induced by living at HA, on BP is uncertain and may vary in different populations. Research on this relationship and other cardiopulmonary changes at HA has been ongoing for more than 50 years (Ostadal & Kolar, 2007), without a clear-cut resolution on whether the relationship between BP and HT and HA is causal, or a result of coincident lifestyle factors. An inverse association between altitude and systemic BP may be due to, separately or in combination with, structural changes in vasculature; and a number of socio-cultural, biological, chemical and physical factors (León-Velarde et al., 1993; Ruiz & Penaloza, 1977). However, the possible benefit from altitude related hypoxia on systemic BP may diminish when genetic and lifestyle related risk factors become dominant, as seen in Tibetan origin populations (Gesang et al., 2002; Mingji et al., 2015). An increased amount of smooth muscle cells in the distal pulmonary arteries in those living at HA may directly increase pulmonary BP (Arias-Stella, 1966). This may not be true for all HA residents, such as Tibetans and Ethiopians, possibly because of the higher levels of exhaled nitric oxide compared with Andeans or low altitude (LA) populations, suggesting different, possibly ancestry-based, physiological responses to HA (Beall, 2007; Beall et al., 2001).

This section of the literature review is a systematic review and meta-analysis that aims to estimate the association between BP and HT and altitude in adults permanently living at HA. This has been published in a peer-reviewed journal.

Methods

This section comprises a systematic review and meta-analysis.

Study inclusion and exclusion criteria

Inclusion criteria for the systematic review were: studies of BP and/or HT in populations living at an altitude of greater than or equal to 2400 metre (m), with a minimum sample size of 100 permanent residents, and in those aged 18 years or older. Only English language articles available in the full text were included. Studies on patients, not at population level, and not denoting the specific altitude level, were excluded. The search was completed on 1 December 2014.

Search and selection methods

A search was conducted in three major biomedical databases: PubMed, OvidSP (MedLine and EMBASE) and Scopus. The search terms: ‘blood pressure’ or ‘hypertension’, were combined with the words ‘altitude’ or ‘mountain’ or ‘himalaya’ or ‘highland’. These combinations were also assessed along with the names of major populations at HA: ‘Tibetans’ and ‘Andeans’, and the names of seven South American countries with HA areas – 'Bolivia', 'Chile', 'Colombia', 'Ecuador', 'Mexico', 'Peru', and 'Venezuela'. Studies were searched by title and/or abstract. In addition, reference lists from identified articles were scrutinized to find relevant published articles. The studies that published data on SBP and DBP or prevalence of HT were considered. The flow diagram for the article selection process is shown in Figure 3.1.

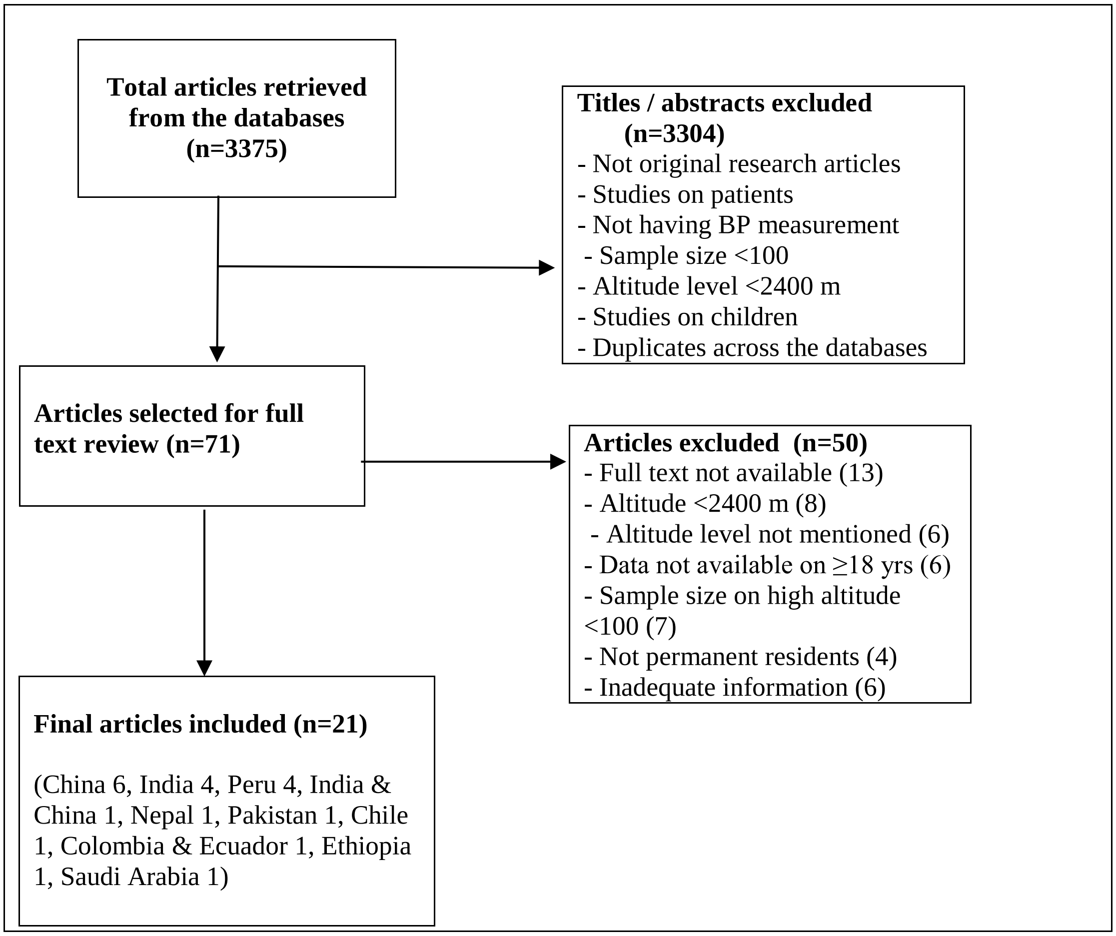

Figure 3.1: Flow diagram of identification and selection of the articles on blood pressure and hypertension at high altitude

Data extraction and quality appraisal

A data extraction table was developed using the Centre for Reviews and Dissemination guidance template (Khan, Ter Riet, Glanville, Sowden, & Kleijnen, 2001). The eligibility of identified papers was assessed and authors, year of publication, geographical locations, sample size, altitude of the study site, mean BP values and rates of HT were recorded. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist was followed for reporting (Stroup et al., 2000). Important and relevant risk-of-bias components are shown separately for each study.

Statistical analysis

Random effects meta-regression was used to evaluate the association between mean BP and HT prevalence by altitude. BP levels were treated as continuous Gaussian variables and a binomial distribution was used for the prevalence of HT. If a study reported an altitude range rather than a specific level, the mean of the range was recorded. For the meta-regression the reported mean BP was used as a response variable in a mixed linear model that used the particular study as a categorical variable, as a random effect, and the inverse variance of the mean BP as a weight. A pooled estimate of mean systolic and diastolic BP was estimated per 1000 m increment in altitude. For the meta-regression of HT prevalence a pooled odds ratio for HT per 1000 m increment in altitude was estimated using a similar random effects model. Sensitivity testing and sub-group analysis was also performed. Studies that reported data at different levels of HA, or from different ethnic populations, were treated independently during the analysis. Analysis was performed separately for the studies with participants from Tibetan and non-Tibetan origins because of well-known differences in genetics and physiological responses to environmental hypoxia.

Comprehensive Meta-analysis (CMA) version 3.0 was used.

Results

The search identified 3375 papers: 1612 from Scopus, 719 from Embase, 565 from Medline, 479 from PubMed, and 10 from a reference search. A search of the listed references was performed for 71 articles selected for full text review.

Twenty one studies were included in this review, including two studies published in each of the 1970s, 1980s and 1990s; four studies in the 2000s and eleven studies after 2010. The total number of participants was 40,854: nine studies including less than 500 participants, six studies with 500–1000 participants, five studies with 1000–5000 participants, and one with more than 5000 participants. Six studies were based in China (five on Tibetans); four in India (all on Tibetans); four in Peru; and one each in Colombia & Ecuador, China and India (including Tibetans); Chile; Pakistan; Ethiopia; Nepal (Tibetans); and Saudi Arabia. Ten studies each had Tibetan and non-Tibetan participants and one study had participants from both groups. All studies were cross-sectional. The altitude level ranged from 2438 to 4300 m. The key features of the selected studies are shown in Table 3.1.

Table 3.2 shows the risk of bias of each study, including sampling process, HT cut-points, BP measuring devices, number of BP readings, and body position during BP measurements. Briefly, participants were randomly selected in eleven studies, non-randomly in six studies, completely surveyed in two studies, and the sampling process was unclear in two studies. Fourteen studies reported the prevalence of HT, of which eleven used a cut-off point of greater than or equal to 140/90 mmHg, one considered a cut-point of greater than or equal to 130/85 mmHg, while two older studies adopted the cut point of greater than or equal to 160/95 mmHg for HT. The measurement device for BP was a standard mercury sphygmomanometer in ten studies, an aneroid sphygmomanometer in one study, an automated device in five studies, and the BP measuring device was unclear in five studies. Two readings of BP were taken and mean value was considered in seven studies, three readings were taken in four studies, and the number of readings was not mentioned in seven studies. In two studies, a second reading was only considered if HT was observed in the first reading. One study repeatedly measured BP until readings were stable within 2 to 3 mmHg. Body position during the BP measurements was sitting in 14 studies, supine in one study, and unclear in six studies.

Table 3.1: Key features of included studies on blood pressure and hypertension at high altitude

Author	Location	Sample Size	Altitude (m)	HT (%)	BP values (mean) (mmHg)
Clegg et al. 1976	Ethopia/ Siemien mountains	142 (18-65 yrs)	3000 m	Not reported	3000 m (Debarek) SBP:122.9, DBP:76.6 (M) SBP:120, DBP:75.7 (W)
Makela et al. 1978	Chile/ Andean mountains	139 (18-84 yrs)	>4000 m	Not reported	> 4000 m (Altiplano) SBP: 119.45, DBP: 78.23 (M) SBP: 112.23, DBP: 72.94 (W)
Dasgupta et al. 1982	India/ Himachal Pradesh	857 (20-74 yrs)	3050 m	1.9* (including ≥ 15 yrs sample)	SBP:111.28, DBP:74.88 (M) SBP:111.72, DBP:74.20 (W)
Sun 1986	China/ Tibet	25050 (≥ 25 yrs)	2500 m - 5000 m	15.2 M:13.4, W:16.6	Not reported
Khalid & Adzaku 1995	Saudi Arabia/Assir Province	189 (M) (21-60 yrs)	>3150m	Not reported	> 3150 m (AlSoda& AlSoga) SBP:114.79, DBP:76.38 (M)
Smith 1999	Nepal/ Khumbu	133 (M) (>18 yrs)	3400-3900 m	25	3400-3900 m (Khumbu) SBP:122.9, DBP:79.7
Shah et al. 2001	Pakistan/ Ghizar	4203 (> 18 yrs)	2438 m	15 M: 13.7, W:15.4	SBP:124.5, DBP:79.8 (M) SBP: 124.9, DBP: 77.8 (W)
Liu et al. 2001	China/ Tibet	125 (48-56 yrs)	3760 m	39.7 M:28.8, W:50.7	3760 m (Tibetan) SBP: 127.7, DBP:81.9 (M) SBP: 132.6, DBP:83.7 (W)
Lindgarde et al. 2004	Peru/ Cuzco	105 (W) (≥ 35 yrs)	3800 m	Not Reported	3800 m (Cuzco) SBP:97, DBP:59

Tripathy & Gupta 2007	India/ Leh	158 (> 20 yrs)	3521 m	39.9 M:43.8, W:38	3521 m SBP:134.55,DBP:81.59(M) SBP: 131.92, DBP:80.58 (W)
Matsubayashi et al. 2009	China/ Qinghai	247 (≥ 60 yrs)	3000-3300 m	Han: 58	Han SBP:141, DBP:86
Okumiya et al. 2010	China & India	Tibet:209 Ladakh:117 (≥ 60 yrs)	3700 m, 2900-3800 m	Tibet: 72 Ladakh:53	3700 m (Tibet) SBP:142, DBP:91 2900-3800 m (Ladakh) SBP:137, DBP:87
Hernandez-Hernandez et al. 2010	Colombia, Ecuador	Bogota:1553 Quito:1638	2600 m, 2850 m	Bogota:13.4 M:14.6,W:12.4 Quito :8.6 M:7.2,W:10.1	2600 m (Bogota) SBP:114, DBP:76.2(M) SBP:111.4,DBP:73.1 (W) 2850 m (Quito) SBP:114.5,DBP:72.7(M) SBP:112.3,DBP:70.5 (W)
Negi et al. 2012	India/ Himachal Pradesh	3100m: 171 3900m: 242 (> 20 years)	3100 m, 3900 m	3100m: 27.5 3900m: 19	3100 m SBP:130.7, DBP:83.1 3900 m SBP:120.98, DBP:80.05
Zhao et al. 2012	China/ Tibet	701 (≥ 40 yrs)	4300 m	55.9 M:66.1, W:48.3	SBP:151.6,DBP: 95.9(M) SBP: 142.8, DBP: 89 (W)
Zheng et al. 2012	China/ Tibet	1370 (≥ 18 yrs)	3650 m	51.2 M:56, W:48	SBP:141.80, DBP:92.38 (M) SBP:133.76, DBP:87.33 (W)
Sherpa et al. 2013	China/ Tibet	692 (30-80 yrs)	3700 m	37 M: 35.3, W: 38.4	Not reported

Gonzales et al. 2013	Peru/ Junin	506 (35-75 yrs)	4100 m	Not reported	SBP:117.4, DBP:74.7(M) SBP:114.2,DBP:72.38(W)
Caravedo et al. 2014	Peru/ Puno	519 (≥35 yrs)	3825 m	Not reported	SBP:115.31
Ojeda et al. 2014	Peru/ Cusco	Hispanic:395 (W) Quechas:376 (W)	2577-3570 m	Hispanic:10.9 Quechas:1.1	Not reported
Negi et al. 2014	India/ Himachal Pradesh	1017 (>20 yrs)	3000-4000m	27.3 M: 27.9, F:27	Not reported

Abbreviations: m: metre, M: men, W: women, BP: blood pressure, HT: hypertension, SBP: systolic blood pressure, DBP: diastolic blood pressure, HA: High altitude. *Excluded from the HT analysis.

Table 3.2: Risk of bias of included studies on blood pressure and hypertension at high altitude

Study	Sampling process	HT cut-point (mmHg)	BP measuring device	Number of BP readings	Body position during BP measurements
Clegg et al. 1976	Random	Not relevant	Unclear	Unclear	Unclear
Makela et al. 1978	Unclear	Not relevant	Mercury sphygmomanometer	Two	Sitting
Dasgupta et al. 1982	Complete survey	≥160/95	Mercury sphygmomanometer	One (if HT in first then second)	Sitting
Sun 1986	Non-random	≥160/95	Mercury sphygmomanometer	Multiple till stable within 2 to 3 mmHg	Sitting
Khalid & Adzaku 1995	Random	Not relevant	Mercury sphygmomanometer	Two	Sitting
Smith 1999	Non-random	≥140/90	Unclear	One (if HT in first then two)	Sitting
Shah et al. 2001	Random	≥140/90	Mercury sphygmomanometer	Three	Sitting
Liu et al. 2001	Random	≥140/90	Automated device	Three	Unclear
Lindgarde et al. 2004	Non-random	Not relevant	Mercury sphygmomanometer	Unclear	Supine
Tripathy & Gupta 2007	Random	≥140/90	Mercury sphygmomanometer	Unclear	Sitting
Matsubayashi et al.2009	Non-random	≥140/90	Automated device	Two	Sitting
Okumiya et al. 2010	Non-random	≥140/90	Automated device	Two	Sitting
Hernandez-Hernandez et al. 2010	Random	≥140/90	Mercury sphygmomanometer	Two (or until readings close to within 5 mmHg)	Sitting
Negi et al. 2012	Random	≥140/90	Mercury sphygmomanometer	Two	Sitting
Zhao et al. 2012	Non-random	≥140/90	Automated device	Three	Sitting
Zheng et al. 2012	Random	≥140/90	Mercury sphygmomanometer	Two	Sitting
Sherpa et al. 2013	Random	≥130/85	Automated device	Three	Unclear
Gonzales et al.	Random	Not	Aneroid	Unclear	Sitting

2013		relevant	sphygmomanometer		
Caravedo et al. 2014	Random	Not relevant	Unclear	Unclear	Unclear
Ojeda et al. 2014	Unclear	≥140/90	Unclear	Unclear	Unclear
Negi et al. 2014	Complete survey	Unclear	Unclear	Unclear	Unclear

BP in relation to HA

Seven studies compared the mean BP at HA (≥2400 m) and LA (<2400 m). Of these, five reported higher mean SBP and DBP values in HA for both genders (Clegg, Jeffries, & Harrison, 1976; Hernandez-Hernandez et al., 2010; Khalid & Adzaku, 1995; Liu et al., 2001; Smith, 1999). In one study, mean BP values were higher at HA except for DBP in women (Tripathy & Gupta, 2007). In a Peruvian study, mean SBP was marginally high at HA, but DBP was significantly lower (Lindgärde et al., 2004). For individual studies the mean difference was statistically significantly higher at HA for both SBP and DBP in three studies (Hernandez-Hernandez et al., 2010; Khalid & Adzaku, 1995; Liu et al., 2001), in DBP in a Nepalese study (Smith, 1999), and in DBP only for young female adults in an Indian study (Tripathy & Gupta, 2007). One study reported marginally higher mean values for both SBP and DBP at LA (Tripathy & Gupta, 2007).

Five studies reported mean BP values at different levels of HA (≥2400 m). Two showed decreasing BP values (Makela et al., 1978; Negi et al., 2012), and increasing BP values (Clegg et al., 1976; Okumiya et al., 2010) with higher elevation. In one study, SBP increased marginally but DBP decreased with altitude (Hernandez-Hernandez et al., 2010). Mean SBP levels varied from 97 mmHg (Lindgärde et al., 2004) to 146.6 mmHg (X. Zhao et al., 2012) and DBP from 59 mmHg (Lindgärde et al., 2004) to 92 mmHg (X. Zhao et al., 2012) at HA.

Fourteen studies reported the prevalence of HT in HA, in which seven studies showed the prevalence at over 30% (Liu et al., 2001; Matsubayashi et al., 2009; Okumiya et al., 2010; Sherpa et al., 2013; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012), including four where the prevalence was greater than 50% (Matsubayashi et al., 2009; Okumiya et al., 2010; X. Zhao et al., 2012; X. Zheng et al., 2012). Interestingly, all seven of these studies had participants of Tibetan race. Similarly, five studies reported a prevalence of HT between

15% and 30% (Negi et al., 2012; Negi et al., 2014; Shah, Luby, Rahbar, Khan, & McCormick, 2001; Smith, 1999; Sun, 1986), and two South American studies reported a prevalence of less than 15% (Hernandez-Hernandez et al., 2010; Ojeda, Blümel, Vallejo, & Lavín, 2014). The prevalence of HT by local definition ranged from 15.2% (Sun, 1986) to 71.8% (Okumiya et al., 2010) for Tibetan participants and between 1.1% (Ojeda et al., 2014) and 57.9% (Matsubayashi et al., 2009) in non-Tibetans.

Gender and BP in HA

Among the 10 studies that reported mean BP for genders separately, men had a higher value of both systolic and diastolic BP in seven studies (Clegg et al., 1976; Gonzales, Rubio, & Gasco, 2013; Hernandez-Hernandez et al., 2010; Makela et al., 1978; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012). Only one Tibetan study had a high mean of both systolic BP and diastolic BP in women (Liu et al., 2001). Of eight studies reporting HT for men and women, an equal number of studies found high prevalence in men (Negi et al., 2014; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012) and in women (Liu et al., 2001; Shah, Luby, et al., 2001; Sherpa et al., 2013; Sun, 1986).

In four studies the differences were significantly higher in men for at least one of SBP, DBP and HT (Clegg et al., 1976; Gonzales et al., 2013; X. Zhao et al., 2012; X. Zheng et al., 2012). By contrast, the differences were not significantly higher in the studies where women had higher values for mean SBP, DBP or HT. Overall, men tended to have a higher mean BP than women but no clear gender-based pattern was observed for HT.

Age and BP in HA

Thirteen studies reported an analysis of any relationship between BP at HA and age (Clegg et al., 1976; Dasgupta et al., 1982; Hernandez-Hernandez et al., 2010; Khalid & Adzaku, 1995; Makela et al., 1978; Negi et al., 2012; Shah, Luby, et al., 2001; Sherpa et al., 2013; Smith, 1999; Sun, 1986; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012). Among these only three did not show a positive association between age and BP (Clegg et al., 1976; Dasgupta et al., 1982; Makela et al., 1978). An Indian study showed a rise of BP at a younger age in women (Dasgupta et al., 1982), while a Pakistani study showed a more gradual increment between age and DBP (Shah, Luby, et al., 2001). An Ethiopian study showed no impact of age at HA except in high socio-economic status populations (Clegg et al., 1976).

Predictors of high BP in HA

Among the 10 studies that reported statistical analysis of predictors of BP in HA, six found body mass index (BMI) the best predictor (Negi et al., 2012; Shah, Luby, et al., 2001; Smith, 1999; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012). Likewise, body weight explained the rise of BP levels in two studies (Khalid & Adzaku, 1995; Makela et al., 1978). Other predictors were family history of HT (Shah, Luby, et al., 2001), higher socio-economic group (Clegg et al., 1976), alcohol intake (Smith, 1999), and packed cell volumes (Khalid & Adzaku, 1995).

Results from the closely relevant but excluded studies

There were six studies that would have met the criteria for this review, but included data from participants younger than 18 years (Baker, 1969; Beall, Gebremedhin, Brittenham, Decker, & Shamebo, 1997; He, Tell, Tang, Mo, & He, 1991; Murillo, Barton, Palomino, Lenart, & Schull, 1980; Otsuka et al., 2005; Ruiz & Penaloza, 1977). Of these, three studies from South America (Baker, 1969; Murillo et al., 1980; Ruiz & Penaloza, 1977), one study from Ethiopia (Beall, Gebremedhin, et al., 1997), and one study from China (He et al., 1991) showed low levels of BP in HA, whereas an Indian study found high levels (Otsuka et al., 2005).

Association of mean BP with altitude

Twenty population samples from 17 studies were included in the meta-regression of BP. Eleven samples were from non-Tibetan and nine from Tibetan origin participants. In Tibetans mean SBP (95% confidence interval (CI)) increased by 17 mmHg (0.2 to 33.8) per 1000 m, P=0.05, but decreased by 5.9 mmHg (-19.1 to 7.3), P=0.38, in non-Tibetans (Figure 3.2). The mean DBP (95% CI) also increased by 9.5 mmHg (0.6 to 18.4), P=0.04 in Tibetans but decreased by 4 mmHg (-13 to 5), P=0.38 in non-Tibetans, per 1000 m higher altitude. Compared to women both Tibetan and non-Tibetan men had higher mean values for both SBP and DBP. However, this difference was statistically significant for non-Tibetan participants only, with mean SBP difference (95% CI) of 2.5 mmHg (0.78 to 4.15), P=0.004 and DBP difference (95% CI) of 2.5 (1.78 to 3.19), P<0.001.

Six studies measured BP at both high (≥2400 m), N=7, and low (<2400 m), N=10, altitude levels. Random-effects meta-regression of this data showed that both mean SBP and DBP decreased with similar magnitudes per 1000 m higher altitude; SBP (95% CI) by 1.1 mmHg (-5.1 to 2.9), P=0.58; and DBP (95% CI) by 1.3 mmHg (-3.6 to 1), P=0.27. The point estimates suggested that SBP decreased more rapidly below 2400 m, -4 mmHg compared to -1.2 mmHg per 1000 m elevation, whereas DBP fell steeply above 2400 m (-3.7 mmHg vs. -2.5 mmHg per 1000 m elevation). However, no definite inflection points were noted.

Association of HT prevalence with altitude

Random-effects meta-regression of HT by altitude was performed in 18 population samples (from 14 studies); 11 had Tibetan and 7 had non-Tibetan origin. The estimated odds ratio (95% CI) for the association of the probability of HT in relation to altitude in participants of Tibetan origin was 2.01 (0.37 to 11.0) per 1000 m, P=0.45. For those of non-Tibetan origin the association was 4.05 (0.07 to 244.7) per 1000 m, P=0.49. The model-based point estimates reflect the gradient seen for the prevalence of HT by altitude of: 16.5% (2000 m), 28.5% (3000 m), and 44.6% (4000 m) for Tibetans; and 4.1% (2000 m), 14.9% (3000 m), and 41.4% (4000 m) for non-Tibetans. Sensitivity analysis excluding two studies with older populations (≥60 years) (Matsubayashi et al., 2009) (Okumiya et al., 2010) showed a similar result for Tibetans but for non-Tibetans the direction of the effect was reversed with odds ratio (95% CI) of 0.10 (0.004 to 2.22) per 1000 m, P=0.14. The estimated effect sizes were similar after excluding six studies that presented an altitude range, rather than an exact altitude. The point estimates from the individual studies were not combined for both BP and HT analysis because the heterogeneity statistics examined by tau, I^2, and the Q statistics showed a considerable degree of heterogeneity across the studies.

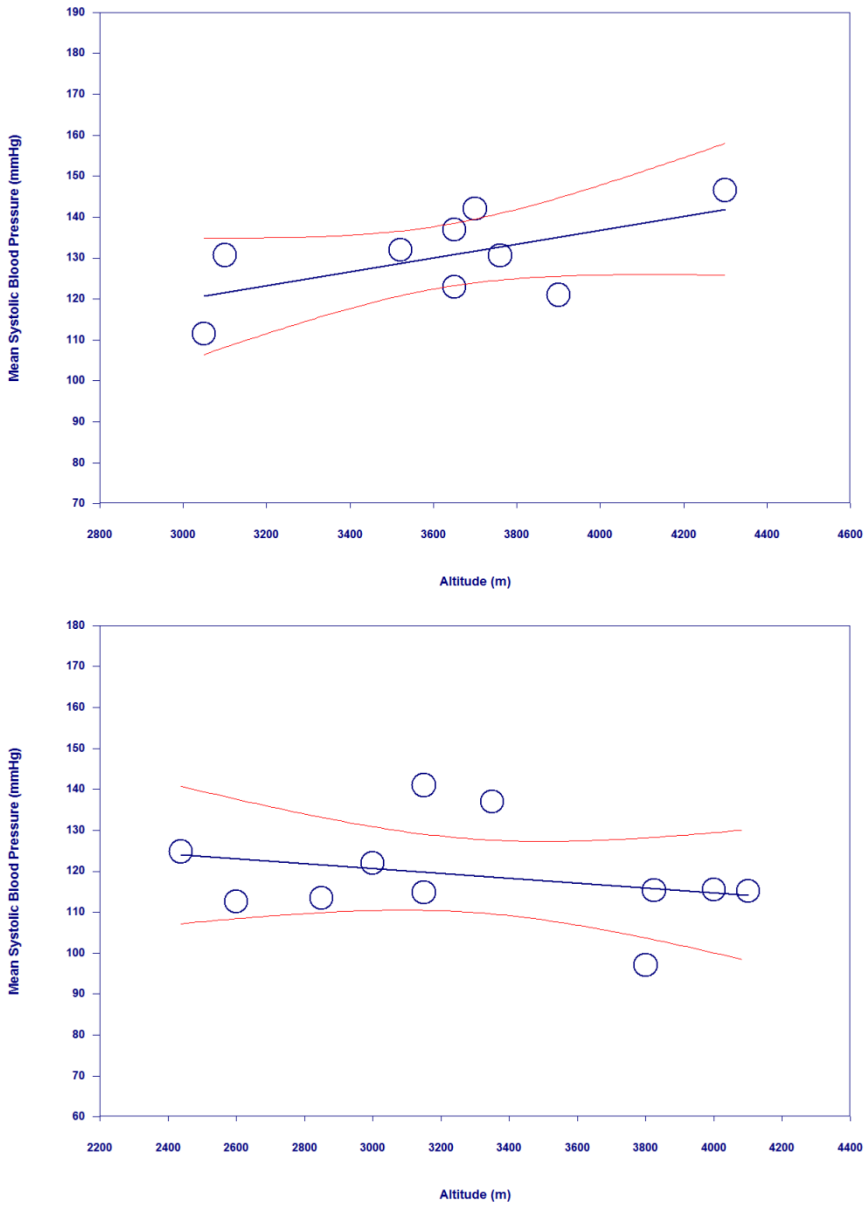

Figure 3.2: The relationship between altitude and mean systolic blood pressure in Tibetan (above) and non-Tibetan (below) participants in meta-regression analysis with 95% confidence interval

Discussion

This systematic review and meta-analysis of adult populations living at HA found weak evidence of a positive association between SBP and DBP and altitude in participants of Tibetan origin. In the analysis of non-Tibetan origin participants, both mean SBP and DBP tended to decrease with elevation, but the associations were not statistically significant. For HT, both Tibetan and non-Tibetan populations showed increasing prevalence with increasing altitudes. However, sensitivity analysis by excluding two studies with older participants gave a point estimate consistent with a reduction in HT prevalence in non-Tibetan participants. Model-based estimates were that more than a quarter of the Tibetan origin populations and less than 15% of the non-Tibetan origin populations had HT (by local definitions) at 3000 m. The estimated prevalence of HT for Tibetan populations at 3000 m is consistent with the estimated global rate of HT in the general population (Kearney et al., 2005). However, the prevalence is higher at higher altitudes; e.g., 44.6% for Tibetans at 4000 m. The analysis showed the known association that men have a higher value of SBP and DBP than women but the prevalence of HT was similar. BMI and body weight were the best predictors of higher BP in HA residents.

Tibetan and non-Tibetan (mainly Andean) ancestry populations have different physiological responses to environmental hypoxia and this may be because these populations have different genetic variants and adaptive phenotypic consequences for HA (Huerta-Sánchez et al., 2013). Physiological studies in Andean populations show a reduction of systemic BP under hypoxic hypobaric conditions due to the relaxation of smooth muscles, increase in collateral circulation and vascularization (León-Velarde et al., 1993; Ostadal & Kolar, 2007). Evidence from genetic studies in Tibetans also suggests associations between the D allele of the angiotensin-converting enzyme gene and HT, and higher frequency of the G allele in hypertensive Tibetans (Gesang et al., 2002; Kumar et al., 2003). Usually, Tibetan HA populations have a higher level of hypoxic ventilation response and blood oxygen saturation, better lung function, maximum cardiac output, better sleep quality and lower levels of pulmonary vasoconstriction and hemoglobin concentration compared with Andean HA populations (Wu & Kayser, 2006). Tibetans have also longer generational history at HA and a lesser degree of genetic admixture than Andeans, which could have advanced their degree of adaptation (Moore et al., 1998). The differences in the relationships between BP and HT and altitude between Tibetan and non-Tibetan HA populations in this systematic review and meta-analysis may also be related to lifestyle factors. The diet of Tibetans traditionally consists of high levels of salt, a minimum 20 to 30 gram (g) per day (Sehgal et al., 1968; Sun, 1986), which is five times more than the WHO recommendation. Traditional food consumption also comprises high amounts of meat and fat, high alcohol drinking, and low consumption of potassium, fruit and vegetables (Luobu, 2012; X. Zhao et al., 2012). These factors are associated with increased BP levels and the prevalence of HT (Furberg, Psaty, & Soliman, 2010). Lower mean BP in Andes HA population has also been suggested due to low socio-cultural status, increased intake of minerals such as zinc, healthier diets, lesser thickness of aorta and probable elasticity, and lower cardiac output (Ruiz & Penaloza, 1977). Earlier studies report a low prevalence of risk factors for HT, such as obesity and smoking, in Andean samples (Ruiz et al., 1969).

A recent systematic review estimates the prevalence of HT in HA populations of Tibet ranges between 23% and 56% and that there is a 2% increment in the prevalence of HT for every 100 m increment of altitude (Mingji et al., 2015). The same review suggests that rates of HT may be increasing over time in some populations living at HA. For example, the prevalence of stage II HT has increased by two to three times in Tibet between 1979 (Sun, 1986) and 2009 (X. Zhao et al., 2012). This is consistent with the impact of lifestyle factors rather than genetic factors for raised BP and HT.

Despite this latter suggestion, population origin, reflecting ancestry, rather than the country of residence seems to be an important factor for BP variation in those living at HA. Populations with Tibetan ancestry living at HA in China, India and Nepal, but following their traditional cultural practices, have elevated BP (Matsubayashi et al., 2009; Okumiya et al., 2010; Sherpa et al., 2013; Smith, 1999; Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012). One large Tibetan study of 25,000 adults reported stage II HT (≥160/95 mmHg) among 15% of the participants (Sun, 1986). Studies based on populations from South America have identified a low prevalence of HT and lower mean BP (Hernandez-Hernandez et al., 2010; Lindgärde et al., 2004; Makela et al., 1978). In Nepal, highland residents of Tibetan origin had a HT prevalence of 25%, as opposed to just 3.7% in other HA population groups (S. Shrestha et al., 2012; Smith, 1999).

An environmental factor that may influence systemic BP is ambient temperature. A large British study reported exposure to the colder climate, combined with poor housing quality, is associated with diastolic HT (Mitchell, Blane, & Bartley, 2002). By contrast, hot and humid conditions may cause vasodilation and lower BP (Ladell, 1964). Thus, BP could be related to both altitude and the temperature at any particular altitude.

Obesity is an important risk factor for HT (Furberg et al., 2010). This was also found in the studies identified in this systematic review. The mechanism by which obesity is linked with HT is not properly understood. However, an increase in sympathetic activity, sodium retention, insulin resistance, hyperleptinemia, and renal abnormalities are thought to be the likely underlying pathways (Hall, 2000; Mark, Correia, Morgan, & et al., 1999). Among the studies included in this review that compared BMI at high and low altitude levels, BMI was similar at both levels in four studies (Khalid & Adzaku, 1995; Lindgärde et al., 2004; Negi et al., 2012; Smith, 1999), lower in HA in one study (Hernandez-Hernandez et al., 2010), and no specific trend was observed in one study (Okumiya et al., 2010).

Limitations of this review were that it was limited to published and electronically available studies written in English. The 'grey literature' and in particular theses, conference papers and government reports were not sought. Publication bias may be present, specifically with regards to Chinese language papers and studies from Andean countries published in Spanish.

Implications for clinical practice, policy and research

The major implications of these findings for clinical practice, policy and research are that clinicians and those concerned with public health should note an increased HT risk in HA populations of Tibetan origin, whatever their current living situation. Culturally driven excessive consumption of salt, alcohol and dietary fats may be the key reasons behind the increased levels of BP among HA Tibetans. Thus, health education and lifestyle modification interventions may be particularly important in this population. For example, strategies to reduce sodium and increase potassium, e.g. with salt substitutes, might be appropriate (X. Zhao et al., 2014). In light of the relatively poor availability of health care services at HA, it is recommended that health policy planners consider strategies such as health camps to identify and treat individuals with high risk of HT.

Conclusions and unanswered questions

This study presented the evidence of a positive association of BP and altitude in adult HA populations of Tibetan origin. This could be due to the additive effects of hypoxia, lifestyle habits (particularly diet), and genetic predisposition. Non-Tibetan HA populations were generally found to have a low risk of raised BP. In both population groups, men were more likely than women to have increased BP. Regions with HA countries, particularly South Asia, Central Asia, and Africa, have insufficient epidemiological data on BP and other cardiovascular risk factors in their HA residents. More population-specific prevalence studies are needed to estimate the comprehensive risk of CVD in these regions.

3.2 Blood glucose levels and diabetes at high altitude

Diabetes mellitus (DM) is a key global public health problem. A recent estimate is that the global age-standardized prevalence of DM has increased from 4.3% in 1980 to 9.0% in 2014 among men, and from 5% to 7.9% among women (NCD Risk Factor Collaboration, 2016). During this period the number of people living with DM has also increased four-fold, from 108 million to 432 million (NCD Risk Factor Collaboration, 2016). Another estimate reports that a large proportion of those with DM remain undiagnosed and this is particularly so in low and middle income countries (Beagley, Guariguata, Weil, & Motala, 2014). Blood glucose levels have a continuous dose-response relationship with the risk of CVD (Meigs, Nathan, Wilson, Cupples, & Singer, 1998). This incremental risk does not depend on a formal diagnosis of DM (Gerstein & Punthakee, 2010), although those with DM themselves have a four-fold risk of CVD and develop CVD approximately 15 years earlier than those without DM (Booth, Kapral, Fung, & Tu, 2006). Permanently living at HA confers a metabolic adaptation of high glucose uptake (Holden et al., 1995). However, changing diets and lifestyle factors for residents at HA may result in increased mean blood glucose levels despite this metabolic adaptation (Sherpa et al., 2013).

This section comprises a systematic review and meta-analysis of the relationship between blood glucose and residence at HA. Potential factors that influence blood glucose at HA and also blood glucose responses to short-term exposure to HA will be discussed.

Methods

A search was conducted in three major biomedical databases: PubMed, OvidSP (Medline & Embase) and Scopus. The MeSH terms ‘diabetes mellitus’ or ‘hyperglycemia’ with major subheading 'epidemiology' were combined with words ‘altitude’, or ‘mountain’ or ‘himalaya’ or ‘highland’ or 'Tibetan' or 'Andean' in titles and/or abstracts. All relevant English language studies published until the end of May 2016 were scrutinized. Inclusion criteria were the studies with altitude level greater than or equal to 2400 m, sample size of greater than or equal to 100 and age of participants 18 years or over. Studies conducted on patients and not at population level, and among pregnant women were excluded.

Random-effects meta-regression was used to assess the relationship between each of fasting plasma glucose (FPG) levels and DM prevalence by altitude. FPG was treated as a continuous

Gaussian variable and pooled estimate of mean FPG was estimated per 1000 m elevation. For meta-regression, a mixed linear model was used with reported mean FPG as a response variable that used the particular study as a random effect, and the inverse variance of the mean FPG as a weight. For the meta-regression of DM prevalence a pooled odds ratio for DM per 1000 m elevation in altitude was estimated using a similar random-effects model. If a study reported an altitude range rather than a specific level, the mean of the range was recorded. Sensitivity testing and sub-group analysis was also performed. Data at different levels of HA or from different ethnic populations in a particular study were treated as an independent study during the analysis if sample size was greater than or equal to 100, or otherwise excluded as per the eligibility criteria. Population samples of those of Tibetan and non-Tibetan origin were analysed separately because of the background of known differences in degree of adaptation and physiological response against environmental hypoxia, for these different ancestry groups. Tibetans and Andeans, the latter comprising the highest proportion among non-Tibetans, have the largest total populations living at HA at the present time (Moore et al., 1998).

The measurement unit of blood glucose is mainly presented in mg/dL because the majority of the studies included in this review report FPG using this scale of measurement. The conversion factor from the International System of Unit (SI) is: 1 mmol/L=18 mg/dL.

Results

The search retrieved 262 papers; 84 from Scopus, 71 from PubMed, 61 from Medline and 46 from Embase. A reference search was performed for 39 articles selected for full text review. A flow diagram for the selection of articles is presented in Figure 3.3.

Eleven studies met eligibility criteria and were included in this review. Of these, seven were identified from a database search and four from a reference search. The selected studies were published between 2004 and 2016. Two studies were published each in 2008 and 2012. The total number of participants in included studies was 9884; five studies included fewer than 500 participants, two studies had 500 to 1000 participants and four studies had more than 1000 participants. Four studies were from China, three from Peru, and one each from Nepal, India, China and India combined, and seven from Latin American countries. The altitude level ranged from 2577 m to 4500 m. The risk of bias is presented in Table 3.3, which included consideration of the sampling process, DM definitions, DM cut-point definitions, and the fasting state during blood glucose measurements. Briefly, participants were selected randomly in six studies and non-randomly in five studies. The vast majority of the studies considered FPG ≥126 mg/dL (≥7.0 mmol/L) as a DM cut-point. The key features of the selected studies are shown in Table 3.4.

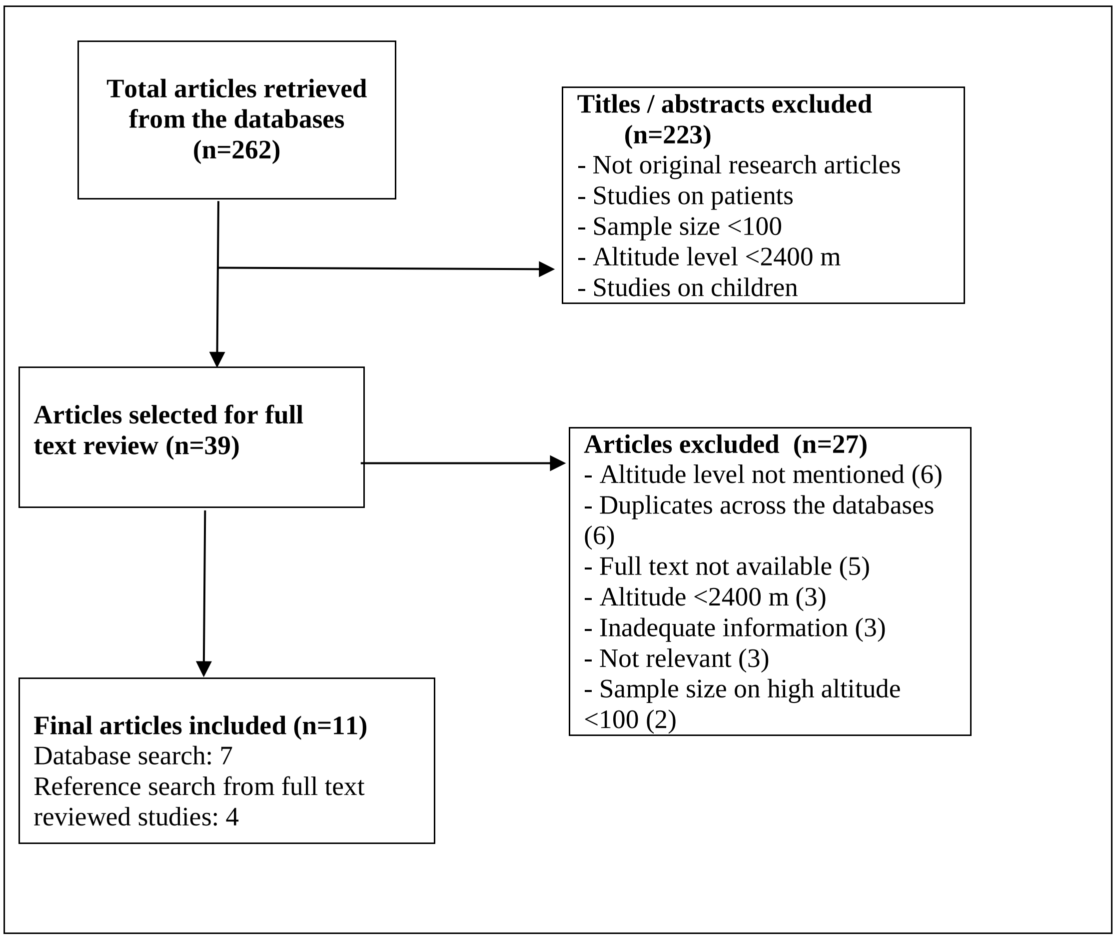

Figure 3.3: Flow diagram for identification and selection of articles on blood glucose levels and diabetes at high altitude

Age and gender

Only two recent studies reported the age-related prevalence of DM at HA and both reported a positive relationship between the prevalence of DM and older age (Okumiya et al., 2016; S. Xu et al., 2015). Of three studies that reported prevalence of DM by gender, two reported a higher prevalence in men than in women (Gonzales & Tapia, 2013; S. Xu et al., 2015). A Latin American study showed higher prevalence in women in both HA samples (Schargrodsky et al., 2008). Only one study reported mean FPG by gender, showing a higher mean FPG in women compared to men (Gonzales & Tapia, 2013).

High and low altitude comparison

Two studies compared populations from HA (≥2400 m) and LA (<2400 m) for each DM and FPG. Mean FPG was lower in HA samples than in LA samples in both studies (Lindgärde et al., 2004; Sherpa et al., 2008). A Nepalese study found a higher prevalence of new DM cases in an HA population (Sherpa et al., 2008) whereas a Latin American study comprising data from two HA and five LA samples reported inconsistent results (Schargrodsky et al., 2008).

Association of DM prevalence and mean FPG with altitude

The prevalence of DM at HA was given in 16 population samples (from nine studies): nine with samples of Tibetan origin and seven with samples of non-Tibetan origin. Random-effects meta-regression estimated odds ratio (95% CI) for DM prevalence in Tibetan origin population of 1.49 (0.49 to 4.48) per 1000 m, P=0.49 (Figure 3.4). For non-Tibetan origin populations this association was 0.82 (0.22 to 3.0) per 1000 m, P=0.80 (Figure 3.5). These point estimates suggest the gradient for DM prevalence of 2.9% (2000 m), 3.8% (3000 m), and 6.5% (4000 m) for a Tibetan population; and 5.7% (2000 m), 4.8% (3000 m), and 3.8% (4000 m) for a non-Tibetan population. Sensitivity analysis by excluding population samples with older populations (≥60 years) (Matsubayashi et al., 2009; Okumiya et al., 2010) yielded a similar result. There were no significant changes in effect size when the populations samples specifying an altitude range rather than an exact altitude were excluded (W. Chen et al., 2011; Okumiya et al., 2010; S. Xu et al., 2015); odds ratio (95% CI) was 1.35 (0.13 to 13.46), P=0.79 for Tibetan origin samples.

Random-effects meta-regression of FPG was performed in eight population samples, four each from Tibetan and non-Tibetan origin participants, from six studies. Consistent with the trends observed for DM, mean FPG increased by 5.2 mg/dL (-8.3 to 18.8) per 1000 m, P=0.45 in Tibetan populations but decreased by -7.9 mg/dL (-55 to 39.3) per 1000 m, P=0.74 in non-Tibetans. Heterogeneity statistics examined by tau, I^2, and the Q statistics showed a high heterogeneity across the studies. Hence the point estimates from the individual studies were not combined for either DM prevalence or FPG analysis.

Table 3.3: Risk of bias for selected studies on blood glucose levels and diabetes at high altitude

Study	**Sampling process**	**Definition**	**DM Cut-point**	**Fasting**
Lindgarde et al. 2004	Non-random	Not relevant	Not relevant	Yes
Lhamo et al. 2008	Random	ADA 2008	Fasting ≥126 mg/dL or 2hpg ≥200 mg/dL	Yes
Matsubayashi et al. 2009	Non-random	WHO (exact year not given)	≥126 mg/dL or 2hpg ≥200 mg/dL	Yes
Okumiya et al. 2010	Non-random	Not given	≥126 mg/dL or 2hpg ≥200 mg/dL	Yes
Chen et al. 2011	Random	Not given	Fasting ≥126 mg/dL or OGTT ≥200 mmol/L or self- report of treatment	Yes
Negi et al. 2012	Random	Not given	Fasting >126 mg/dL	Yes
Gonzalez & Tapia 2012	Random	Not given	Fasting >126 mg/dL	Yes
Xu et al. 2015	Random	Chinese guidelines	Fasting ≥126 mg/dL or OGTT ≥200 mg/dL or self-report of diabetes or on medication	Yes
Okumiya et al. 2016	Non-random	WHO 2006	Fasting ≥126 mg/dL	Yes
Schargrodsky et al. 2008	Random	Not given	Fasting ≥126 mg/dL or self-report	Yes
Ojeda et al. 2014	Non-random	Not given	Fasting >125 mg/dL or on treatment	Yes

DM, Diabetes Mellitus; ADA, American Diabetes Association; WHO, World Health Organization; 2hpg, 2 hour plasma glucose; OGTT, Oral Glucose Tolerance Test. 126 mg/dL=7.0 mmol/L; 200 mg/dL=11.1 mmol/L. Few studies define DM cut-point in mmol/L.

Table 3.4: Key features of included studies on blood glucose levels and diabetes at high altitude

Author	Location	Altitude (m)	Sample size	DM (%)	Mean FPG (SD)
Lindgarde et al. 2004	Peru	3800 m (Cuzco), 150 m (Lima)	3800 m: 105 150 m: 105 (≥35 years) (W)	Not reported	(mmol/L) 3800 m: 3.8 (1.1) 150 m: 4.6 (0.7)
Lhamo et al. 2008	Nepal	2900 m (Everest region), 1200 m (Kathmandu)	2900 m: 119 1200 m: 121 (30-70 years)	2900 m: 3.6 1200 m: 2.4 (New DM only)	(mg/dL) 2900 m: 97 (14.8) 1200 m: 100.4 (12.3)
Schargrodsky et al. 2008	Venezuela, Colombia, Argentina, Peru, Mexico, Ecuador, Chile (seven Latin American countries)	<u>High altitude</u> 2600 m (Bogota), 2850 m (Quito) <u>Moderate or low altitude</u> 566 m (Barquisimeto), 25 m (Buenos Aires), 1550 m (Lima), 2250 m (Mexico City), 520 m (Santiago)	<u>High altitude</u> 2600 m: 738 (M), 815 (W), 2850 m: 813 (M), 825 (W) <u>Moderate or low altitude</u> 566 m: 713 (M), 1135 (W), 25 m: 734 (M), 748 (W), 1550 m: 769 (M), 883 (W), 2250 m: 833 (M), 889 (W), 520 m: 783 (M), 872 (W) (25-64 years)	<u>High altitude</u> 2600 m: 8.1 (M:7.4, W:8.7), 2850 m: 5.9 (M: 4.6, W:7.3) <u>Moderate or low altitude</u> 566 m: 6 (M: 5.6, W: 6.3), 25 m: 6.2 (M:7.9, W:4.8), 1550 m: 4.4 (M: 4.3, W:4.6), 2250 m: 8.9 (M:8.0, W:9.7), 520 m: 7.2 (M:6.8, W:7.6)	Not reported
Matsubayashi et al. 2009	China	3000-3300 m (Qinghai)	393 Tibetan: 97 Mongolian: 49 Han: 247 (≥60 years)	Tibetan: 6.6 Mongolian: 9.4 Han: 7.9	(mg/dL) Tibetan: 91 (30.9) Mongolian: 84.4 (17.6) Han: 87.1 (33.4)
Okumiya et al. 2010	China & India	3000-3200 m (Qinghai/China), 3700 m	423 3000-3200 m: 97 3700 m: 209	3000-3200 m: 7 3700 m: 13 2900-3800 m: 8	(mg/dL) 3000-3200 m: 90 (29) 3700 m: 110 (34)

		(Qinghai/China), 2900-3800 m (Ladakh/India)	2900-3800 m: 117 (≥60 years)		2900-3800 m: 104 (21)
Chen et al. 2011	China	3658 m-4200 m (Tibet)	1289 (≥18 years)	2.9 (M: 3.1, W: 2.5)	Not reported
Negi et al. 2012	India	3100 m, 3900 m (Himachal Pradesh)	3100 m: 171 3900 m: 242 (>20 years)	3100 m: 4.1 3900 m: 0.4	(mg/dL) 3100 m: 102.6 (9.9) 3900 m: 100.3 (10.6)
Gonzales & Tapia 2012	Peru	4100 m (Carhuamayo & Junin)	M: 158 W: 348 (35-75 yrs)	M: 5.4 W: 4.3	(mg/dL) M: 92.1 (16.3) W: 95.1 (25.9)
Ojeda et al. 2014	Peru	2577-3570 m (Cusco)	Hispanic: 395 Quechas: 376 (40-59 yrs, W)	Hispanic: 2.8 Quechas: 0.5	Not reported
Xu et al. 2015	China	3200-4500 m (Tibet)	3200-3500 m: 444 (M), 463 (W) ≥3500 m: 378 (M), 374 (W) (≥18 years)	3200-3500 m: 7.3 (M:8.5, W:6.4) ≥3500 m: 4.9 (M:6.6, W:3.4) (age standardized)	Not reported
Okumiya et al. 2016	China	2900-4800 m (Tibet)	2900-3499 m: 240 (M), 334 (W) 3500-4499 m: 210 (M), 317 (W) ≥4500 m: 91 (M), 66 (W) (40-87 yrs)	2900-3499 m: 3.1 3500-4499 m: 9.5 ≥4500 m: 8.9	Not reported

m, metre; M, men; W, women; DM, diabetes mellitus; FPG, fasting plasma glucose; SD, standard deviation. The units of FPG (mg/dL or mmol/L) are presented as in respective studies.

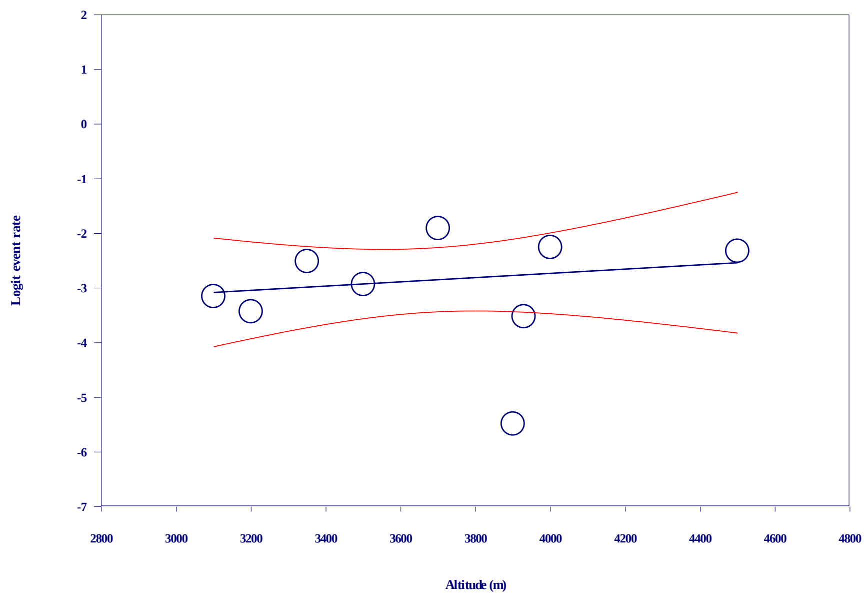

Figure 3.4: Meta-regression of logit event rate of diabetes on altitude for Tibetan origin populations

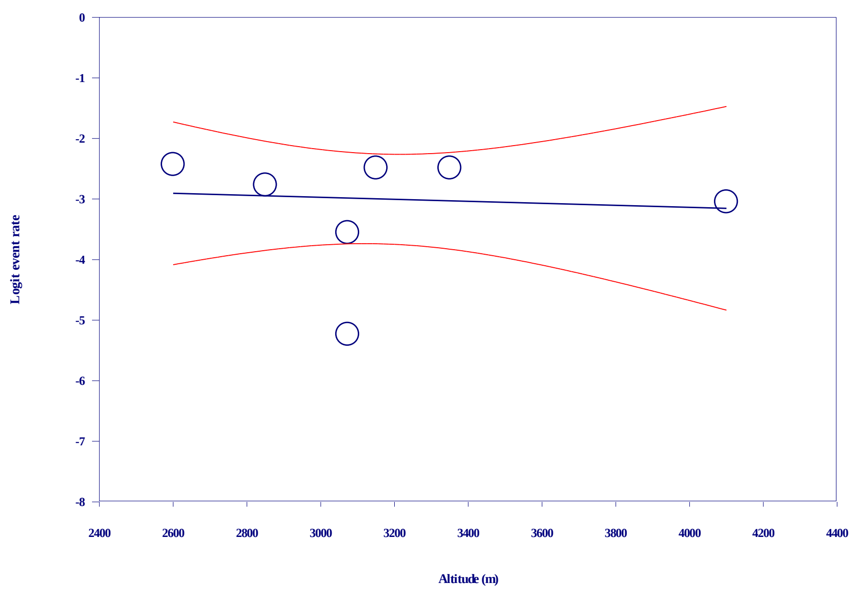

Figure 3.5: Meta-regression of logit event rate of diabetes on altitude for non-Tibetan origin populations

Discussion

This systematic review and meta-analysis showed no evidence of statistically significant associations between FPG, DM prevalence, and altitude in adult HA populations living at an altitude of 2400 m or higher. However, the point estimates for FPG and DM prevalence increased with increasing altitude in Tibetans but decreased with increasing altitude in non-Tibetan origin populations. A difference between the different populations, should one in fact exist, may be due to genetic differences in pathways affecting glucose metabolism in these ethnic groups (Xing et al., 2008). An important point is that the systematic review-based estimates of the point prevalence of DM at different levels of HA were usually lower than the global estimate of DM in general the adult population (8.5%) (NCD Risk Factor Collaboration, 2016). It is difficult to draw conclusions about the influence of age and gender on DM and FPG at HA because very few studies presented these data.

With regard to the studies reporting a high prevalence of DM, a recent study in Tibet reported the prevalence of 9.5% at 4000 m and 8.9% at 4500 m (Okumiya et al., 2016). A strong association between polycythemia and glucose intolerance was observed in this study. A Peruvian study involving a sample of older adults (≥60 years) at HA also reported the odds ratio (95% CI) for being diabetic or having impaired glucose tolerance as 3.0 (1.2 to 7.8) in those with polycythemia compared to non-polycythemic participants (Okumiya et al., 2011). Polycythemia may be associated with glucose intolerance because poor adaptation to hypoxia or polycythemia may be a compensatory response to insufficient oxygen supply during glucose metabolism (Okumiya et al., 2011). The evidence for this hypothesis is inconsistent. No association between hemoglobin concentration and blood glucose was found in another Peruvian study, although there was an association between DBP and hemoglobin concentration (Gonzales & Tapia, 2013).

A Tibetan study reported fasting hyperglycemia (>100 mg/dL) (>5.5 mmol/L) in 57.5% of 692 HA farmers and herdsmen (Sherpa et al., 2013). This has important health implications because people with pre-diabetes have an almost five-fold higher risk of future diabetes (Gerstein et al., 2007). Increasing availability and consumption of sugary carbonated drinks, processed foods and instant noodles at HA may be responsible for this high rate of fasting hyperglycemia. A study in Taiwan found the prevalence of DM was highest in a mountainous region compared with the other regions surveyed (Pan, Yeh, Chang, Hwu, & Ho, 2003). A Saudi Arabian study conducted in the Asir region at an altitude of 3150 m showed that diabetes was one of the most common risk factors among 124 patients admitted for diagnosed acute MI (Ashouri et al., 1993). A Swiss study of those under the age of 20 years found twice as many diabetics in the mountain region compared to two other geographical regions (Zuppinger, Teuscher, & Lüscher, 1975).

There are many potential reasons for lower DM and FPG in non-Tibetan (particularly Andean) populations at HA. A sub-analysis of 29,806 Peruvian people living at greater than or equal to 3000 m found that an inverse association between altitude and diabetes was not statistically significant after adjusting for a number of potential confounding variables: wealth index, age and sex. This suggests that lower socio-economic status may be relevant to lower rates of diabetes at HA (Mori, Seclén, Rosas, & Arias, 2015). Several types of glucose tolerance tests have also shown that HA residents had a more rapid decline in glucose levels compared to LA residents for both an intravenous glucose tolerance test (Picón-Reátegui, 1963) and an oral glucose tolerance test (Srivastava, Kumria, Grover, Sridharan, & Malhotra, 1975). HA residents were also found to have higher insulin sensitivity compared to LA residents (Lindgärde et al., 2004). Lower hepatic glucagon sensitivity (Sutton & Garmendia, 1976) and higher glucose disposal in the skeletal muscle (Woolcott, Ader, & Bergman, 2015) might also contribute to lower glucose levels in HA dwellers. Colder ambient temperatures at HA may affect glucose metabolism because carbohydrates are a key thermogenic fuel during shivering (Haman et al., 2005).

There is a broad consensus in the literature that acclimatization to HA results in an increased preference for the use of glucose as a metabolic substrate. This is because using glucose as a metabolic substrate has high oxygen efficiency. Glucose derives more adenosine triphosphate (ATP) per unit of oxygen consumed compared with lipids when oxidized (Braun, 2008; Roberts et al., 1996). A study in two aboriginal HA dwellers, Andean Quechuas and Nepalese Sherpas, found that the preference for glucose as a substrate in the heart correlated positively in these populations but negatively among LA residents (Holden et al., 1995). Furthermore, that study reported that glucose metabolism in myocardium was 25% to 50% more oxygen efficient than free fatty acids. There is also evidence that intermittent hypoxia reduces hepatic glucose output by 50% in rats (Freminet, Megas, & Puceat, 1990). Similar phenomena are plausible among human HA residents.

Plants and crops produced and consumed in HA regions may possess anti-diabetic properties. Some traditional plants are recommended by traditional healers as an integral part of folk medicine practices. One study identified three plants found in the Eastern Himalayan belt that have hypoglycemic properties (Mosihuzzaman et al., 1993). Some of the 46 plants used by local people to treat diabetes in the Himalayan region of India also had anti-diabetic effects in rodent models (Tag, Kalita, Dwivedi, Das, & Namsa, 2012). A Chinese study showed that a bean (Vigna angularis) when grown at HA may have both antioxidant and anti-diabetic properties (Yao, Cheng, Wang, Wang, & Ren, 2012). Another Chinese study conducted at HA areas found hypoglycemic effects in a tea (Kucha), which may be due to a reduction in disaccharidase activity (Xie et al., 2009). An Indian study in a Himalayan region of Sikkim and Darjeeling reported that out of 37 species being used as an anti-diabetic agent, 19% were included as hypoglycemic agents in the dictionary of Indian Folk Medicine and Ethnobotany (D. Chhetri, Parajuli, & Subba, 2005). Serviceberry plant, which has been used by the Blackfeet Indian tribe of the Rocky Mountains in Montana, United States of America (USA), reduced post-prandial glycemic response (A. J. Zhang, Rimando, Fish, Mentreddy, & Mathews, 2012). Buckwheat, one of the major crops at HA, (Stevens, 1996), was shown to lower blood glucose levels in a hospital-based experimental study in China (C. J. Lu, 1993). This benefit is mainly attributed to the unique protein structure and amino acid composition of buckwheat (S.-Q. Li & Zhang, 2001).

Environmental and physiological factors are likely to be more important than genetic factors in explaining blood glucose levels at HA. For instance, studies of Peruvian (Lindgärde et al., 2004) and Nepalese (Sherpa et al., 2008) participants report comparisons between populations of similar genetic background but residing at different altitudes. In both studies, participants living at lower altitudes had a higher prevalence of increased blood glucose levels. Related examples are findings from studies of genetically similar American and Mexican Pima Indians with groups living at HA, in a Sonora mountain area, who had lower fasting insulin levels compared to those of similar ethnicity living in a lowland area of the USA, even after adjusting for age, sex, and obesity (Esparza-Romero et al., 2010). Another study of migrants carried out in the Republic of Dagestan found that when highlanders migrated to lower altitudes the prevalence of DM increased from its original lower rate to the higher rate of the lowlander population (Abusuev, Khachurov, & Akhmedkhanov, 1992).

In studies that also reported on obesity there was an expected increased prevalence of high blood glucose levels at HA (Málaga, Zevallos-Palacios, Lazo, & Huayanay, 2010; Pan et al., 2003). In a Nepalese HA study, waist circumference (WC) was a significant predictor for impaired fasting glucose (IFG) (Sherpa et al., 2008). In common with international recommendations (Mozaffarian, 2016), these findings suggest that nutritional interventions of HA dwellers should target both obesity and diabetes.

Evidence for the effect of short-term exposure to HA on glucose metabolism

Many people are exposed to HA for short periods for work or recreational purposes. A number of studies on short-term residents at HA, including both healthy people and those with illness, report lower glucose concentrations with short-term exposure to HA.

A report of fasting blood glucose levels in seven Indian male lowlanders during their stay at 4000 m found an initial increase in blood glucose that decreased gradually after 10 months and increased again on return to sea level (Srivastava et al., 1975). A Taiwanese study found even a stay of only three days at HA (4000 m) improved glucose tolerance (W.-C. Lee et al., 2003). The authors suggested that HA living conditions and activities may serve as a potential natural remedy for diabetes.

Blood glucose levels tend to become lower among diabetic patients during short-term stays at HA. A Saudi Arabian study found that HA living at 2400 m, but not at extreme altitude, improved glycemic control in type II diabetic patients (Hessien, 2013). Some studies even highlight the risk of hypoglycemia among type I diabetics under treatment during short-term exposure to HA (Brubaker, 2005). Exposure to very HA (5000 m) may also affect glycemic control in both type I and type II diabetic patients (de Mol et al., 2011).

Not all studies report a positive effect on glucose metabolism with increasing altitude during HA sojourn. An Indian study of 25 men found no changes in glucose tolerance during measurements at sea level, repeated tests after 10, 30, and 300 days at HA (3500 m), and again 14 days after a return to sea level (Brahmachari, Malhotra, Joseph, & Krishnan, 1973). Some studies report that blood glucose concentrations increase rapidly on arrival at HA and later gradually decrease toward sea level values (Sawhney, Malhotra, & Singh, 1991; Williams, 1975). This could be due to the protective effects of HA on blood glucose being overwhelmed by increased hepatic glycogenolysis and glucose release due to the activation of the sympatho-adrenomedullary and adrenocortical system, or alternatively due to the increment in the rate-limiting enzymes (pyruvate kinase and pyruvate phosphotransferase) in glucose metabolism (Hance et al., 1980).

Conclusion

The evidence presented in this section suggests that long-term residence at HA usually has a beneficial effect on glucose metabolism although this may vary by ethnicity. Although the point estimates from meta-analysis were consistent with a positive association between DM prevalence and FPG and HA in Tibetan origin populations, and with the opposite association in non-Tibetan origin populations (mainly Andeans), the estimates of association had wide confidence limits and were not statistically significant. These findings should be interpreted with the following caveats: first, only studies published in the English language were included. Thus, there may be a publication bias for papers published in the local language of HA countries, mainly Chinese language papers from China and Spanish language papers from Andean countries. Second, because of small sample sizes included studies often had limited statistical power to detect important effects.

Environmental and physiological factors are likely to be more important than genetic factors for maintaining normoglycemia at HA. However, as HA populations are changing from traditional lifestyle and diet to other lifestyle habits a higher risk of elevated blood glucose levels may result. Lifestyle factors may overwhelm protective effects induced by physiological phenomena.

3.3 Lipid profile at high altitude

Dyslipidemia is a very powerful predictive factor for ischemic heart disease (IHD) (Simons, 1986). HA living may alter lipid concentrations due to hypoxia (Garmendia, Arroyo, & Muro, 1970; Roberts et al., 1996). This section will briefly outline the relationship between individual components of lipid profile and CVD, and then review the effects of HA living on lipid profile.

There is a positive association between IHD mortality and increasing total cholesterol (TC) levels (Prospective Studies Collaboration, 2007). There is also a very strong association between the risk of IHD and higher TC levels with no apparent lower threshold of risk (M. Law, 2010). Among different components of the lipid profile an elevated level of low-density lipo-protein (LDL) is particularly associated with increased IHD risk. The carrier protein (apolipoprotein B) of LDL is highly atherogenic (Superko, 1996). There is an inverse association between IHD risk and high-density lipo-protein (HDL) (Prospective Studies Collaboration, 2007). The association between triglyceride (TG) and IHD is uncertain. TG levels may be a conditional risk factor for IHD in those with low HDL, central obesity or DM (Foody, 2006; Padwal & Sharma, 2010). Large studies have not confirmed a strong positive association between lipid components and stroke mortality (Prospective Studies Collaboration, 2007) and incident ischemic stroke (Willey et al., 2009). However, strong positive relationships were found between incident cardiovascular morbidity and mortality, and the TC to HDL ratio after adjustment for other risk factors (Kappelle, Gansevoort, Hillege, Wolffenbuttel, & Dullaart, 2011).

Hypoxic and hypobaric conditions of HA alter the use of energy producing metabolic fuels (Gonzales, 2001), which may secondarily affect lipid profiles. As discussed in the previous section (3.2), hypoxia causes a preference for glucose utilization and decreases uptake of free fatty acids because of oxygen-efficient adaptation (Holden et al., 1995; Roberts et al., 1996). There could also be a physiological phenomenon of energy compensation in the form of increased concentrations of lipids in hypoxemia (Garmendia et al., 1970). Hypoxia alters hepatic lipid oxidation and can increase the levels of TG (Muratsubaki, Enomoto, Ichijoh, & Yamamoto, 2003) and HDL (Meerson, Tverdokhlib, Nikonorov, Filippov, &

Frolov, 1988). This section comprises systematic review only because there are not enough studies on lipid components at HA to perform a meta-analysis.

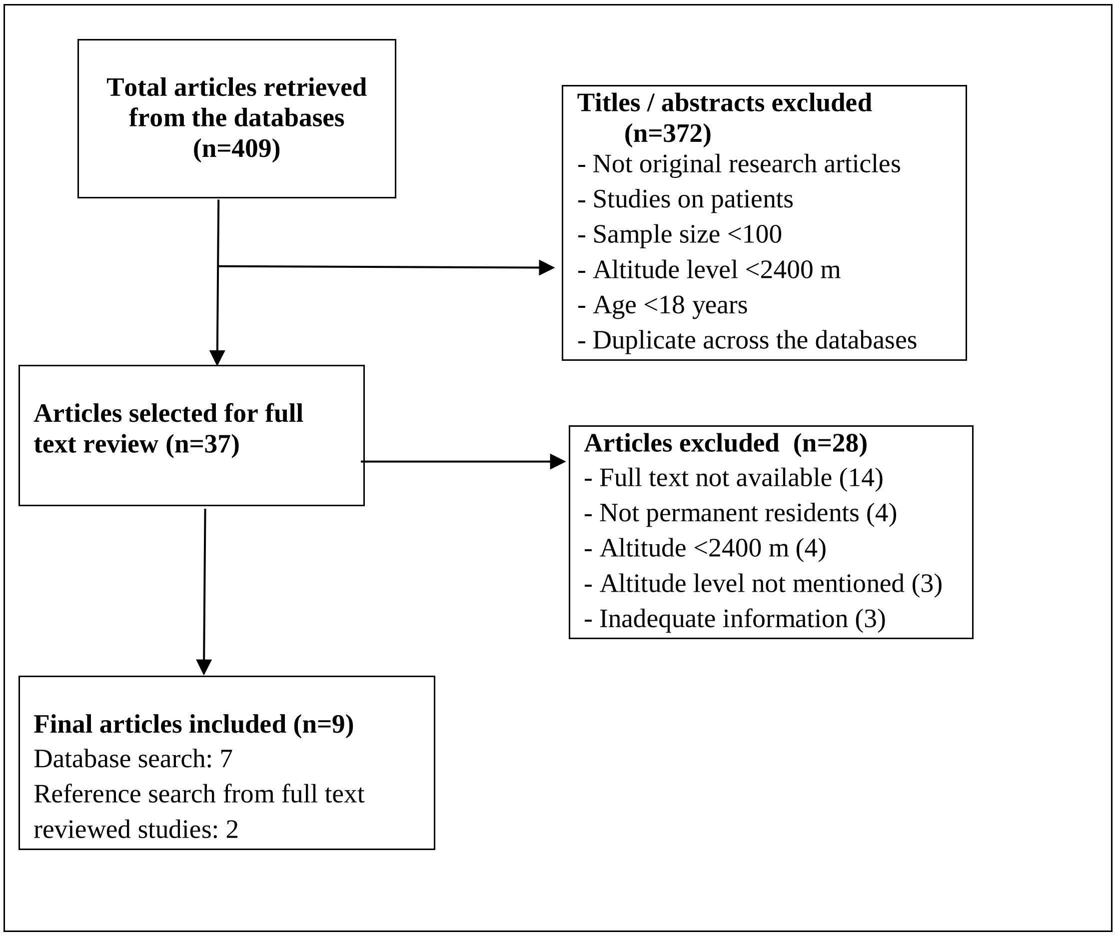

Figure 3.6 : Flow diagram for identification and selection of articles on lipid profiles at high altitude.

Methods

In order to identify relevant literature about lipids at HA, a search was conducted in three major biomedical databases: PubMed, OvidSP (Medline & Embase) and Scopus (Figure 3.6). The search terms 'lipid profile', 'lipids', 'metabolic syndrome' and individual components of lipid profiles; 'TC', 'LDL', 'HDL' and 'TG' (both words and abbreviations) were combined with the words 'altitude', or 'mountain', or 'himalaya', or 'highland' in titles and/or abstracts. Inclusion criteria were studies published in any language with at least the abstract available electronically in English, participants aged 18 years or older, and availability of data on prevalence or mean values of lipid components at HA. Studies conducted on patients rather than at population level, and those not denoting specific altitude levels were excluded. All relevant studies published until the end of January 2014 were scrutinized.

The measurement units for lipid components are presented in mg/dL because the majority of the included studies report it this way. The conversion factor from the SI unit is: 1 mmol/L=38.67 mg/dL for TC, LDL, and HDL; and 1 mmol/L=88.57 mg/dL for TG.

Results

A total of nine studies met the selection criteria. The key features of the selected studies are summarized in Table 3.5. Five studies are from Peru, two from China (Tibet), and one each is from Venezuela and Central Asia. Most studies are relatively small, less than 500 participants, and so have limited statistical power to examine confounding variables influencing lipid profiles. Three of the studies had a sample size of less than 100, between 100 and 500, and between 500 and 700 respectively. The levels of altitude ranged from 3200 m to 4100 m. Three studies compared lipid levels between HA (≥2400 m) and LA (<2400 m). Six studies provided data on prevalence and used the cut-points as per Adult Treatment Panel III (ATP III) criteria (Grundy et al., 2002). However, one study used the HDL cut-point of less than 40 mg/dL (<1.0 mmol/L) for both sexes (Gonzales & Tapia, 2013), and two used greater than or equal to 160 mg/dL (≥4.1 mmol/L) as a LDL cut-point (Gonzales & Tapia, 2013; Sherpa et al., 2011).

The studies identified by the literature search variably identify higher (Baracco, Mohanna, & Seclén, 2007; Gonzales & Tapia, 2013; Málaga et al., 2010; Mohanna et al., 2006; Sherpa et al., 2011) and lower lipid levels in association with HA (Caceres Pilares, Rojas Bravo, Caceres Espinoza, & Ortiz Martinez, 2004; De Mendoza et al., 1978; Fiori et al., 2000; Sherpa et al., 2013). The studies reporting dyslipidemia in HA also had many participants who were overweight or obese, or had central adiposity (Gonzales & Tapia, 2013; Málaga et al., 2010; Mohanna et al., 2006; Sherpa et al., 2011). It may be that in these studies lifestyle and dietary patterns affected the lipid profile of HA residents.

Some studies report exceptionally high levels of some of the lipid components. A Peruvian study of 74 adult permanent residents living at 3600 m reported low levels of HDL in 93.5% of women and 50% of men, and elevated level of TC in 40.6% including both sexes (Málaga et al., 2010). Another Peruvian study of 506 participants aged between 35 and 75 years living at 4100 m altitude reported a high prevalence of TG: men 60.4% and women 66.8%; and low levels of HDL, men 66.9% and women 63.2% (Gonzales & Tapia, 2013). This study also reported an association between higher hemoglobin levels and higher levels of TC, LDL, TG and non-HDL levels. Other studies reported different and usually lower levels of lipid profile components; however, levels of TG were elevated (Caceres Pilares et al., 2004).

Six studies reported the prevalence of 'abnormal levels' or mean values of lipid components by sex. The trend was observed for high mean values or prevalence of high TG and LDL in men and low HDL values in women. An equal number of studies reported high and low values of TC. Only three studies compared lipid values at low and high altitude. Distinctive patterns of lipid components varying by altitude of residence were not seen, other than high values of TG at HA.

Table 3.5: Key features of included studies on lipid profile at high altitude

Author	Location	Altitude (m)	Sample size	Prevalence (%)	Mean±SD (mg/dL)
De Mendoza et al. 1979	Venezuela	1000, 3500	1000 m: 136 3500 m: 94 (20-59 years)	-	1000 m TC, M: 190 (38), W: 192 (37); TG, M: 130 (53), W:125 (52); HDL, M: 41 (10), W:44(10); LDL, M:122 (35), W:122(37) 3500m TC, M:172(38),W: 164 (35); TG, M: 141(49), W:149(50); HDL, M: 36 (10), W:37(8); LDL, M:108(37),W:97(35)
Fiori et al. 2000	Central Asia	600, 900, 2100, 3200	600 m:72, 900 m: 91, 2100 m: 117, 3200 m: 94 (18-66 years)	-	600 m TC: 150 (28), TG:116 (70) 900 m TC:158(32),TG:107(69) 2100 m TC:153(29),TG:107(32) 3200 m TC:153(28),TG:103(57)
Caceres et al. 2004	Peru	3400	120 (30-39 years)	-	TC: 191, TG: 158, HDL: 46.8, LDL:113
Mohanna et al. 2006	Peru	4100	102 (≥30 years)	High TC: 34.3 High TG: 53.9 Low HDL:30.4 HighLDL:11.8	TC: 192.5(36.5) TG: 192.1(104.0) HDL: 53.3(10.5) LDL: 101.0(35.2)
Baracco et al. 2007	Peru	101, 4100	101 m: 99 4100 m: 172 (≥30 years)	101 m High TG: 29.7 (M:29, W: 30) Low HDL: 22.7 (M:11.3, W: 29.1) 4100 m High TG: 56.6 (M: 61.1, W: 54.4) Low HDL: 30.3 (M:5.6, W:44.4)	101 m TG: 134.6 (53.1) HDL: 54.3 (10.3) 4100 m TG: 194.2 (104.7) HDL: 53(10.3)

Malaga et al. 2010	Peru	3600	74 (>18 years)	High TC: 46.3 (M), 38.3(W) High TG: 50 (M), 47.8 (W) Low HDL: 50 (M), 93.5 (W)	-
Sherpa et al. 2011	China	3660	537 (30-70 years)	High TC: 31 (M:30.8, W: 32.3) High TG: 12.2 (M:18.8,W:8.3) Low HDL: 22.4 (M:15.1, W:26.7) High LDL: 4.8(M:7.9, W:3.0)	-
Gonzales & Tapia 2013	Peru	4100	506 (35-75 years)	High TC: 25.3 (M), 27.2 (W) High TG: 60.4 (M), 66.8 (W) Low HDL: 66.9 (M), 63.2 (W) High LDL: 9.1 (M), 8.8 (W)	TC, M: 168.8 (45.7), W: 170.8 (56.5); TG, M:183.8 (90), W: 182.1 (104); HDL, M: 36.2(10), W:36.8 (12.8); LDL, M:100.9 (35), W: 103.4 (40.8)
Sherpa et al. 2013	China	3700	692 (30-80 years)	Low HDL: 3.9 (M: 0.6, W: 6) High TG: 7.6 (M:9.8, W:5.8)	-

Abbreviations: m, metre; M, men; W, Women; SD, standard deviation; TC, total cholesterol; TG, triglycerides; LDL, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol

Discussion

HA living, with either short-term or long-term exposure, has been reported to be associated with increased TG levels (Brito et al., 2007; Siqués et al., 2007). A Taiwanese national survey found that TG levels were highest in mountainous parts of all regions surveyed (Chang, Yeh, Chang, Tsai, & Pan, 2002). Dietary factors may confound this relationship. HA residents often drink large amounts of alcohol and consume large amounts of carbohydrate (Baracco et al., 2007; Sherpa et al., 2013; Sherpa et al., 2010). High uptake of alcohol raises TG levels because of the increased secretion of its carrier protein (very low-density lipoprotein (VLDL)), impaired lipolysis, and increased free fatty acid from adipose tissue (Klop, do Rego, & Cabezas, 2013). Studies in France and Northern Ireland (Ruidavets et al., 2010), and in Switzerland (Foerster et al., 2009) show an increase in TG levels even in light drinkers, and the highest increment in heavy drinkers. Another study reported that a high consumption of fat and alcohol synergistically raises plasma TG (Barson et al., 2009). Alcohol intake increased the risk of hyperlipidemia by 2.4 fold in a Chinese study among 1425 people living at a moderate altitude of 1500 m to 2500 m (Deng, Luo, Huang, Shen, & Ma, 2012). Nonetheless, raised levels of TG were also reported in 29% of 330 Argentinean children living at an altitude of 3750 m who were unlikely to consume a significant amount of alcohol (Maccallini et al., 2012). TG levels may also rise when dietary carbohydrate accounts for more than 55% of the total energy (Parks, 2001). Carbohydrate-laden foods such as potatoes, barley and buckwheat are the mainstay of HA dietary patterns (Baracco et al., 2007; Sinnett & Whyte, 1973; Stevens, 1996).

Ambient cold temperature may also confound the lipid profile relationship with HA. Cold temperature is associated with catabolism of TG in both muscle and adipose tissue, although it is not certain whether this affects plasma TG (Vallerand & Jacobs, 1990). The concentration of HDL was lowest in the coldest months in a Wales study of 2036 men – the Caerphilly prospective study (Eldwood et al., 1993).

No clear relationship between ethnicity and lipid profile at HA has been identified, unlike the evidence identified for BP. In studies of Tibetans living at HA, high lipid values were observed in urban Tibetans of Lhasa (Sherpa et al., 2011), compared to low values among Tibetan farmers and herdsmen (Sherpa et al., 2013). In Peru, an older study among HA residents reported a low prevalence of dyslipidemia (Caceres Pilares et al., 2004). Recent studies from Peru consistently show high levels of lipids (Gonzales & Tapia, 2013; Luis Enrique Macias Bustes, Cabrera Valentin, & Blas Posada, 2011; Málaga et al., 2010). These examples suggest that acculturation with modernity and associated behavioural and lifestyle factors could be more important than ethnicity in affecting lipid status in HA people. Nevertheless, there is some evidence to show some role of ethnicity and genetic variation on lipid profiles during short exposure to HA (Vats et al., 2013).

Lipid values at intermediate altitude and after short-term exposure to HA

In short-term exposure to HA, studies have used exposure times of between three weeks and four years. No consistent patterns of changes to lipid profile in association with altitude have been reported. Some studies report a decrease in TC and LDL values, and an increase HDL values (Ferezou, Richalet, Coste, & Rathat, 1988; Tin'kov & Aksenov, 2002). Some studies report increased TC levels (S. K. Jha et al., 2002), and marked increases in TG (Brito et al., 2007; Siqués et al., 2007). One study of nearly 20,000 young male soldiers found no increase in TC with short-term living at HA (Ruhli et al., 2008).

In studies of the effects of intermediate altitude, between 1500 m and 2400 m, there is no particular relationship between HA and lipid profiles. In a Chinese study conducted among 1415 participants at an altitude of 1500 m to 2500 m, hyperlipidemia was found in 49.3%, hypercholesterolemia in 23.3% and hypertriglyceridemia in 34.1% (Deng et al., 2012). In the Aymara adults of Northern Chile, who live at an altitude of greater than 2000 m, the prevalence of serum hypercholesterolemia in men was 36.8% and in women 37.4%; low HDL, men 26.3% and women 24.4%; and TC/HDL ratio greater than or equal to 5, men 28.2% and women 30.5%) (Santos, Pérez-Bravo, Carrasco, Calvillán, & Albala, 2001). A study of 779 participants from Papua New Guinea living at altitudes of between 1828 and 2590 m, reported low mean TC values; however, hypertriglyceridemia was frequent in both genders (Sinnett & Whyte, 1973).

Conclusion

There is insufficient robust literature to draw robust conclusions about the association between lipid profiles and living at HA. Lifestyle factors rather than ethnicity or genetic factors seem likely to be the main influences on lipid components. The most consistent finding in the literature is that both short-term and long-term exposure to HA increase TG levels.

4 Methodology

The study was a cross-sectional sample survey. This chapter discusses the geographical area where the study was performed, the target population, sampling design, data collection procedures, instruments, data processing and analysis, ethical considerations, and the candidate’s role in this study.

4.1 Geographical study area

Nepal has 75 districts, 16 of which are part of a mountainous ecological region. Two mountainous districts, Mustang and Humla, were sampled using *a priori* information on their geography, altitude, population ethnicity, and feasibility of administering the study procedures. Particular areas of these districts were selected primarily for altitude levels, population density, and logistical support such as transportation and availability of electricity. The selected study areas were Jomsom, 2800 metre (m), which is an urban setting; Jharkot (3270 m), a rural setting; Muktinath (3620 m), another urban setting of the Mustang district (Figure 4.1); and Simikot (2890 m) which is a rural setting of the Humla district (Figure 4.2). Climate is 'cold temperate' at 2800 m in Mustang and at 2890 m in Humla, and 'alpine' at 3270 m and 3620 m in Mustang. Life expectancy at birth is 64.15 years in Mustang and 65.04 years in Humla, both lower than the national figure of 68.8 years (Government of Nepal & United Nations Development Programme, 2014). Tourism and its natural resources mean that Mustang people are relatively wealthy and the dominant Thakali ethnic group has the highest human development index (HDI) score in Nepal (Government of Nepal & United Nations Development Programme, 2014). In contrast, Humla is a district with the lowest HDI score (Government of Nepal & United Nations Development Programme, 2014) and it is the only district of Nepal without any road access. Both districts border China and the Tibetan culture is influential in these districts. The district health office records for 2013/2014 report that gastritis and urinary tract infection (UTI) were the main health problems in both districts. Among cardiovascular disease (CVD) related risk factors hypertension (HT) ranked eighth as a leading cause for hospital visits in the Mustang district but no CVD risk factors were in the top 10 leading causes for hospital visits in Humla.

Figure 4.1: Map of Mustang district indicating study areas Jomsom and Muktinath (Source: google image)

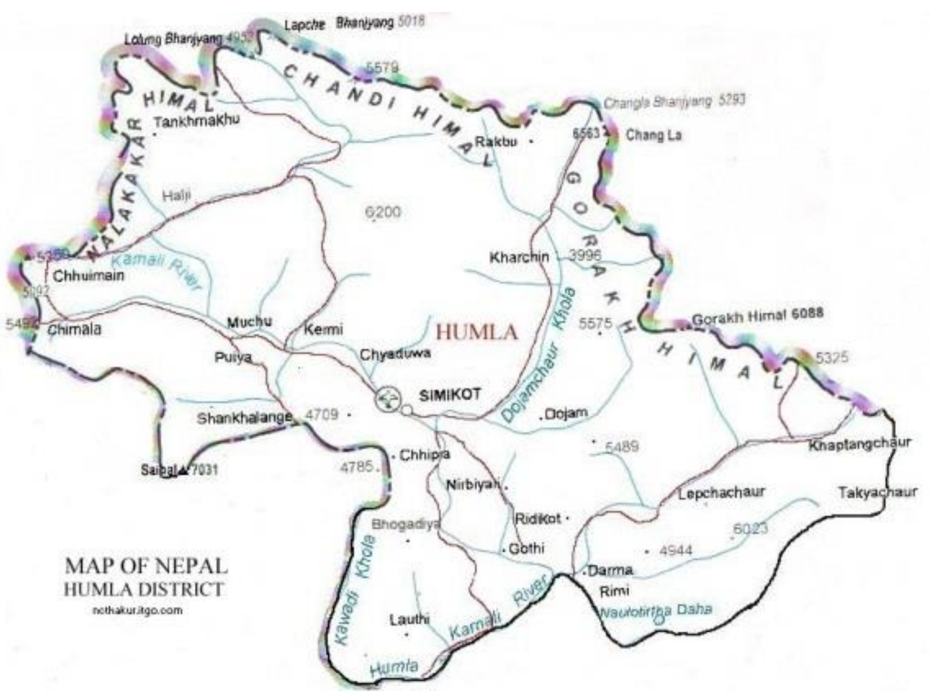

Figure 4.2 : Map of Humla district indicating study area Simikot (Source: google image)

4.2 Study population

A description of the study's target populations for all four study areas are presented in Table 4.1. All of these figures describe permanent residents. All study target populations were from two ethnicities – Tibetan and Khas-Arya. As a group, Tibetans migrated to the high mountains of Nepal some 500 years ago. Tibeto-Burman is their native language and they practise Buddhism (Rambal, 2012). Thakali, Tibetan Gurung, and Lama of the study's population belong to this category. Khas-Arya migrated to Nepal some 2000 years ago, speak the Nepalese language, and the majority of them are Hindu (Eagle, 2000). Brahmins, Chettris, and Dalits are mainly categorized as Khas-Arya (Gellner, 2016).While in New Zealand ethnicity is assigned by self-report, which may not strongly reflect ancestry, Tibetans and Khas-Aryas are distinctive in appearance, language, and name. In this thesis, the terms 'ethnicity' and 'ancestry' are used interchangeably to describe associations with being Tibetan or Khas-Arya.

Table 4.1: Household number and population in study areas

Study area	Altitude	Total household number	Total population	Total 30+ population
Mustang		3354	13452	6767
Jomsom	2800 m	145	775	502
Jharkot	3270 m	57	385	228
Muktinath	3620 m	37	255	169
Humla		9479	50858	17577
Simikot	2890 m	215	1161	688
Total		**454**	**2576**	**1587**

Source : Profile of Jomsom, Muktinath and Simikot village development committees 2011 and consultation with local people

4.2.1 Inclusion and exclusion criteria

Inclusion criteria

- Age 30 years and above

- Speak and understand Nepalese language

- Permanently living at high altitude (HA)

Exclusion criteria

- Unable or unwilling to provide written or verbal consent

- Impairments in hearing and speaking

- Pregnant

Inclusion and exclusion criteria were determined through participants' self-reported responses. The pregnancy status of female participants was queried only when pregnancy was suspected, consistent with culturally appropriate questioning in this study group. Female research assistants were assigned to confirm whether women were pregnant. Six female participants were withdrawn from the study during data collection when it became apparent that they were pregnant.

4.3 Sample design

4.3.1 Sample size calculation

The desired sample size within each group was around 250 individuals. This gives a margin of error for a proportion based on anticipated prevalence of HT of around 25% (K. K. Aryal et al., 2014) of plus or minus 5% after adjusting for the design effect and an expected non-response rate of 10%.

4.3.2 Sampling technique

Sampling was carried out in two stages. In the first stage, three areas of Mustang and one area of Humla were purposively sampled on the basis of altitude levels, population density and availability of logistical support to undertake the study. In the second stage, a list of households was developed, and a unique number was assigned to each of them. We estimated that 25% of the households in each study area would need to be sampled to achieve the planned sample size. Household numbers were randomly selected with the help of a computer-based randomization technique. All eligible family members of the randomly selected households were considered. Where none of the household members was eligible or none agreed to take part in the study, a household in close proximity was selected.

This sampling technique is a cluster sampling scheme by household; however, the analysis treats the data as being from a simple random sampling scheme. This is because of the absence of a robust sampling frame, low population size and very low population density of the study areas.

4.4 Instruments

This study employed three main instruments to address the research questions:

i) World Health Organization (WHO) STEPS questionnaire for non-communicable disease (NCD) risk factors

ii) Questionnaire for verifying stroke-free status (QVSFS)

iii) Electrocardiogram (ECG)

4.4.1 World Health Organization non-communicable disease risk factors STEPS interview questionnaire

Cardiovascular risk-related sections of the WHO NCD risk factors STEPS questionnaire version 2.2 were used. The Nepal Health Research Council (NHRC) has already translated it into Nepalese language, validated through a pilot study in a community, and approved by expert meetings (K. K. Aryal et al., 2014). This questionnaire has three sections. The first section has questions on socio-demographic and lifestyle factors, a second section consists of blood pressure and anthropometric (height, weight, waist, hip) measurements, and the third section contains measurements of blood glucose and lipids.

Demographic and socio-economic information

This initial section included questions related to age, sex, ethnicity, education, occupation, household income, and marital status. The ethnicity question further asked whether participants were from Tibetan ancestry. Altitude-related questions (origin of birth, duration at HA) were also included.

Tobacco use

Questions on both smoking and non-smoking forms of tobacco use were included. Questions were related to current (in the last 30 days) and past tobacco use. Duration of smoking was also noted among current smokers by asking what age they started smoking.

In Nepal, the most common types of smoked tobacco are manufactured cigarettes, bidis (unprocessed tobacco wrapped in leaves), and pipes (locally called *hookah*, *tamakhu*). Among non-smoked types, commercially or non-commercially manufactured chewing items from tobacco leaves locally known as *khaini*, *surti*, *gutkha*, *zarda*, *paan* are the most popular. Nose-snuffing of ground tobacco leaf (locally called *Nas*) is also common in mountain areas of Nepal, and especially among those from Tibetan culture.

Alcohol consumption

Alcohol consumption-related questions were about current, past and 'ever drinking' status, frequency of drinking, and the number of standard drink units (SDU) consumed in the past 30 days. Current drinkers were defined as those drinking alcohol in the past 30 days. A hazardous drinker was defined as weekly consumption of ≥21 and ≥14 SDUs of alcohol for men and women respectively (Piccinelli et al., 1997).

SDU of alcohol was calculated by the formula:

Amount of drink (litre)(l) × percent of volume of alcohol (%) × density of ethanol at room temperature (0.789) (Health Promotion Agency New Zealand, 2015).

A glass with 90 millilitre (mL) volume was a popular size in the study areas. The few participants who consumed alcohol in different-sized glasses were asked to estimate the volume with reference to a 90 mL glass. Traditionally home-made and locally brewed alcoholic beverages were popular in the study areas, mainly *jaad* (made of rice), *chang* (also made of rice but using a different method), and *raksi* (made of rice, millet or barley). The percentage of volume of alcohol was determined as 12% for jaad and chang, 25% for raksi (Pradhan et al., 2012), and 5.5% for beer and 40% for vodka as labelled.

Fruit and vegetables, salt and oil consumption

Participants were asked to estimate how many days they consumed fruit or vegetables in a typical week and the mean consumption of fruit or vegetables portions on those days. One portion of fruit and vegetables was defined as 80 gram (g) as per the WHO recommendation (World Health Organization : Joint WHO/FAO expert consultation, 2003) – for example, an apple, a banana, 10 grapes, or one *panyu* (tablespoon) of vegetables.

The amount of salt and oil consumption was determined by asking how much participants estimated their household consumed in a month, and this amount was divided by the number of family members currently sharing the kitchen for the main meal. Salt was usually available in one kilogram (kg) packets and oil in a 500 mL packet.

Physical activity

Physical activity was classified into vigorous and moderate levels. Vigorous physical activity was defined as any activity, such as carrying heavy loads, lifting heavy weights, digging or ploughing fields etc., causing a significant rise in breathing and heart rate for at least 10 minutes. Moderate physical activity was defined as continuous involvement in an activity for at least 30 minutes that caused a slight increment in breathing or heart rate, such as brisk walking, cleaning, washing clothes by hand, gardening, and any domestic chores. Participants were asked on average time they spent in vigorous and moderate physical activity per day in a typical week. Participants who were involved in a vigorous physical activity only at particular times in a year, such as during crop harvesting or other agriculture-related work were also considered.

The physical activity-related questions also included mean walking and sedentary time per day. Sedentary time was defined as behaviours such as reading a book, watching television, or sitting with friends.

History of CVD, HT, diabetes and high cholesterol

Information on personal and family history of CVD was collected. A family member was defined as being first-degree blood relations (parents, siblings, or children). Participants were also asked if they currently or previously had HT, diabetes and high cholesterol, or if they were currently on treatment for these.

Anthropometric measurements

Among anthropometric components, height, weight, waist and hip were measured. Weight was measured by a portable digital weighing scale (Seca, Germany) placed on a hard, flat surface. Weight was measured without shoes, heavy clothing and mobile phone, and participants were asked to empty their pockets. Participants were asked to stand steadily on the machine with their head facing forward and weight evenly distributed between both feet. Weight was recorded to the nearest 0.5 kg in accordance with the Frankfurt Plane technique (Cogill, 2003).

Height was measured by a portable standard stature scale. Participants were asked to take off their shoes, head caps and head ornaments. They were asked to stand with head looking forward, legs straight and heels together, arms to the side and shoulders relaxed. The research team members ensured that heels, buttocks, scapulae and the back of the head were against the wall. The participants and the research team member faced each other while measuring the participants' height. The participants were asked to inhale deeply and hold their breath while standing in an erect position. A ruler was lowered to the participant's highest point with enough pressure for the participant to feel their hair compressed and height was noted to the nearest 0.5 centimeter (cm) as per the Frankfurt Plane technique (Cogill, 2003). The classification of body mass index (BMI) was based on WHO established guidelines (World Health Organization, 1995); $\geq$30 kg/m^2: obese, $\geq$25 kg/m^2: overweight, 18.5 to 24.9 kg/m^2: normal, <18.5 kg/m^2: underweight.

Waist and hip were measured with soft fabric tapes as per WHO recommendation (World Health Organization, 1995). A room was partitioned off with a curtain to ensure privacy. Waist circumference was measured at the end of normal expiration at a level of midway between the lowest rib and the superior border of the iliac crest. Participants were asked to roll up their inner garments above the waist, loosen tight garments around the waist, including belts, and empty their pockets. Hip circumference was measured at the level of most protrusion. Participants were asked to roll down their lower garments, except for underwear.

Both waist and hip circumferences were measured with the participants' feet fairly close together, around 12 cm to 15 cm apart. Two members of the study team were assigned; one person measured the tape at eye level with one finger between tape and participant's body and the second person checked that the tape was horizontal around the body with no folds anywhere. For cultural reasons only female research assistants measured the waists and hips of female participants.

High waist circumference (WC) was defined as >90 cm (men) and >80 cm (women) using International Diabetes Federation (IDF) criteria for South Asian populations (Alberti, Zimmet, & Shaw, 2006). High waist to hip ratio (WHR) was defined as ≥0.90 (men) and ≥0.85 (women) according to the WHO recommendation (World Health Organization, 2008).

Blood pressure

BP was measured by oscillometric method using an automatic blood pressure measuring device (Omron HEM-7221). The recommended operating ambient pressure conditions of this machine are from 700 to 1060 hectopascals. This is the atmospheric pressure at around 3000 m, which was further verified with the manufacturer (Rudi Fernandez, personal communication, JA Davey Pty Ltd, 3rd October, 2016). Moreover, Omron BP monitoring machines have also passed the validation criteria at 3650 m as proposed by the European Society of Hypertension International Protocol Revision 2010 (ESH-IP2) (Cho, Tian, Lan, Zhao, & Yan, 2013). Three readings were recorded from left arm of each participant in sitting position with at least 10 minutes elapsing in between. The first measurement was taken a minimum of 10 minutes after the questionnaire was administered. If the readings differed by more than 10 units, a fourth measurement was taken and the lowest three were considered for mean calculation.

BP (systolic/diastolic) was classified as normal (<120/80 mmHg), pre-HT (120–39/80–89 mmHg), HT (≥140/90 mmHg), Stage I HT (140–159/90–99 mmHg), and Stage II HT

(≥160/100 mmHg) according to the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP (Chobanian et al., 2003).

Blood glucose and lipids

Glycated hemoglobin (HbA1c) and lipid profiles were measured using a Cobas b 101 device (Roche Diagnostics). Cobas b 101 uses immunoassay method for HbA1c and enzymatic method for lipid profile measurements (Cobas b 101 system : operator's manual software version 1.0). This device is validated for use at up to 3200 m and thus participants at 3620 m were requested to come down to the measurement facility set up at 3270 m. A small amount of capillary whole blood was taken by single finger-prick and processed by the device, which provided results for both HbA1c and lipids within 15 minutes. Single use only disposable lancets (Accu-Chek safe-T-Pro-Plus, Roche Diagnostics) were used for finger-prick. This lancet has 1.3 mm, 1.8 mm and 2.3 mm depth settings. Third or fourth finger of the non-dominant hand was selected for finger-prick. Firstly, the selected finger was massaged from the base to the tip to ennsure good blood flow. The lancing area (top side of the finger) was cleaned with an alcohol swab and dried with a tissue. The first drop of blood was wiped away and the finger was again massaged gently until a second large drop of blood formed.

A quality control check of this device was performed after every 100 participants, using the manufacturer's operating guidelines.

HbA1c was classified as diabetes (≥48 mmol/mol) and pre-diabetes (≥39 to 47 mmol/mol) according to the guidelines of the American Diabetes Association (American Diabetes Association, 2016). The National Cholesterol Education Program (NCEP), Adult Treatment Panel III (ATP III) guidelines were used to classify lipid profile; high total cholesterol (TC) (≥5.2 mmol/L), high triglyceride (TG) (≥1.7 mmol/L), high low-density lipoprotein-cholesterol (LDL) (≥3.4 mmol/L), low high-density lipoprotein-cholesterol (HDL) (<1.3 mmol/L for women, <1.0 mmol/L for men), and high non-HDL (≥4.1 mmol/L) (Grundy et al., 2002). High TC to HDL cholesterol was defined as the ratio ≥5.0.

CVD risk prediction

Estimated 10-year risks of fatal or non-fatal cardiovascular events (myocardial infarction (MI) or stroke) were calculated using the validated risk prediction chart designed by WHO and the International Society of Hypertension (ISH) for the WHO region of South-East Asia, sub-region D (Mendis et al., 2007). The risk categories were defined as low (less than 10%), moderate (equal to or greater than 10% and lower than 20%), high (equal to or greater than 20% and lower than 30%), and very high (equal to or greater than 30%) (World Health Organization, 2007a). This risk prediction chart follows the total cardiovascular risk assessment approach and requires six components: presence or absence of diabetes, gender, smoker or non-smoker, age, systolic blood pressure (SBP), and TC.

4.4.2 Questionnaire for Verifying Stroke-Free Status

The QVSFS was administered to estimate prevalence of cerebrovascular disease – stroke or transient ischemic attack (TIA) (Jones, Williams, & Meschia, 2001). This questionnaire was chosen because it has high face validity and was developed by the American Heart Association. Efforts are also underway to use it in low-and middle-income countries where people have a low literacy level and very limited knowledge of stroke and its symptoms (Sarfo et al., 2016). The questionnaire consists of eight structured questions related to the history of stroke or TIA as confirmed by a medical doctor, and positive symptoms of stroke (sudden weakness and numbness on one side of the body, sudden loss in one or both eyes or one-half vision, sudden loss of ability to understand and express verbally or in writing).

Questions were modified for the local context and culture. Content validity was assessed by discussion with clinical members of Shahid Gangalal National Heart Hospital, Nepal. The accuracy of the English–Nepalese translation was checked by back-translation. Face validity was tested by piloting the questionnaire during the training session for the local research assistants.

4.4.3 Electrocardiography recordings

The 12-lead ECG was recorded using a portable Edan SE-600 instrument. Participants were asked to remove clothing from the chest area, lie flat with face up, arms at sides and legs uncrossed. Oily, sweaty, or clammy skin was wiped with alcohol swabs. Electrodes were placed on the chest in accordance with standard practice and connected with colour-coded leads. Artefacts due to alternating current (AC) interference was a particular problem, which was solved by using only the battery back up of the instrument. Qualified female nurses recorded the ECG results and other team members assisted when required.

The prevalence of coronary heart disease (CHD) was defined as the presence of pathological Q waves in the ECG or self-report of personal history of CHD (previous event of MI or chest pain from heart disease (angina)). Left ventricular hypertrophy (LVH) was assessed using the commonly used Sokolow-Lyon (Sokolow & Lyon, 1949) and the stricter definition of Romhilt and Estes (Romhilt & Estes, 1968). After review by a cardiologist using standard widely accepted criteria, ECG recordings were categorized as definitely abnormal, for example showing evidence of previous MI; borderline, non-specific T-wave flattening/inversion or one or more features suggesting possible LVH that did not fully meet accepted criteria defined by the published definitions we used; or normal. If there was a consistent QRS vector in the bipolar leads (I, II, III, aVR, aVL, aVF) then axis could be assessed. QRS axis was otherwise determined using the conventional frontal plane system with the leftward-pointing horizontal axis ascribed an axis of 0^o, positive axes the following in a clockwise direction and negative values anticlockwise. Left axis deviation was determined if the QRS axis was lower than -30° and right axis deviation was determined if the QRS axis was greater than +90°.

4.5 Data collection procedures

4.5.1 Training and standardization of research personnel

The Student Investigator (SI) and Research Assistants (RAs) were trained and standardized regarding data collection measurements. RAs were public health graduates, nurses with previous research experience, and local community health workers.

Training sessions were organized for three days with three hours of sessions each day. On the first day, the SI provided orientation on the aims and protocol of the study, contents of the questionnaires, and ethical considerations. RAs practiced the full-length questionnaire. On the second day, they were provided with blood pressure and anthropometric measurement training. Finally, they were oriented on the operation of the Cobas b 101 instrument for HbA1c and lipid profile, and ECG.

The SI was earlier provided training on the use of the Cobas b 101 instrument by manufacturer staff members (Roche Diagnostics NZ). He also got ECG-related training from a cardiac physiologist and a biomedical technician at Wellington Regional Hospital, New Zealand.

4.5.2 Data collection techniques

The research team held a consultation meeting with local community leaders and apprised them of the aims of the study. The community leaders were asked to disseminate information about the study through their channels. Local RAs also informed the communities about the study. Administering the questionnaires and BP measurements were carried out at the selected participants' homes. Practically, it was not feasible to undertake blood sample testing, ECG recordings and bio-physical measurements in individual houses so a local community hall was used as the measurement facility. Participants were asked to come for these measurements at a time suitable for them.

Blood samples were processed separately in a disc for blood lipids and HbA1c. After use all discs and ECG electrodes were stored in a closed container and deposited in the clinical waste bins of the local health facility. Finally, they were disposed of according to the current Safe Operational Procedure (SOP) for blood disposal in the clinical setting of Nepal.

Data was collected from June to August (summer) 2014 in the Mustang district and March to May (spring) 2015 in the Humla district. The ambient temperature was between 25 and 31 degrees Celsius in Mustang and around 15 degrees Celsius in Humla on most of the study days.

The non-response rate was 18/521 (3.4%). The most common reason for non-participation was unwillingness to provide a blood sample due to the cultural belief that it would make you sick.

4.6 Data processing and statistical methods

The data from questionnaires, and the bio-physical and bio-chemical measurements were captured on a single form. Data was entered into a spreadsheet programme after the field level data was collected. The SI double-checked the accuracy of the data and then exported it into the statistical package.

Data was analyzed in three stages. In the first stage, descriptive statistics were generated using mean, standard deviation, frequency and percentages. The Clopper-Pearson method was used to estimate an exact confidence interval for a single proportion. All results are presented for each level of altitude. In the second stage, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models for the relationship between SBP, diastolic blood pressure (DBP) and altitude are shown. In the third stage, logistic regression was used to estimate the association between an abnormal (or borderline abnormal) ECG and altitude in univariate and multivariate models. Relevant parametric and non-parametric tests of quantitative and categorical data, and the odds ratios (OR) for the comparisons of the groups are shown as appropriate. Altitude was treated as a continuous variable in the multivariate models. The strength of the associations is described as strong, moderate, and weak at the significance level of $P < 0.01$, $P = 0.01$ to 0.05, and $P = 0.06$ to 0.10 respectively.

Assumptions for the statistical analysis of ANOVA and ANCOVA models were examined. Normality assumptions were examined by inspecting standardized residual plots. Linearity and homoscedasticity assumptions were examined by inspecting studentized residuals versus predicted value plots. Outliers were reviewed by inspection of leverage versus residuals squared plots. Particular data points were reviewed carefully if more than 5% of the cases had a standardized residual value of greater than 2. Sensitivity analysis tests were also performed by examining changes in regression parameters with or without outliers. For logistic regression models, assumption of linearity between logarithm of odds of abnormal (or borderline abnormal) ECG and explanatory variables were examined by LOWESS plot.

STATA version 12 was used for statistical analysis.

4.7 Ethical considerations

This study was approved by the ethical review board of the Nepal Health Research Council (NHRC) and the University of Otago Human Ethics Committee. Information sheets and consent forms were provided in Nepalese language. The participants were informed that they could ask questions at any stage, had the right to withdraw at any point without giving any reason, and their decision on whether or not to participate would not have any consequences whatsoever. A written consent was sought where possible. In cases where participants were not literate, witnessed oral consent was given.

There was no significant risk involved with this research, although the finger-prick blood taking process can be painful for some people. Participants were informed of this risk. Privacy of information was maintained. Temporarily stored paper or electronic data was partially de-identified with reference to participants by using a numerical code known only to the SI and kept securely in the University of Otago, Wellington, New Zealand.

The preliminary findings of the study were presented at the District Health Office of Mustang district and among local community health workers in the Humla district.

4.8 Candidate's role in the study

The candidate was involved in the design, development of the proposal, the ethical approval process, field level data collection, data entry, statistical analysis and report writing with the help of his supervisors.

5 Results

This chapter is divided into three sections. The first section presents descriptive results for (i) socio-economic and demographic characteristics (ii) lifestyle-related characteristics (smoking and alcohol consumption patterns, physical activity, dietary habits) (iii) anthropometric measures (height, weight, waist and hip measurements) (iv) bio-chemical measures (lipid profile and glycated hemoglobin (HbA1c)) (v) stroke and cardiovascular disease (CVD) risk prediction. In the second and third sections descriptive, univariate and multivariate models are presented for blood pressure (BP) and electrocardiogram (ECG) recordings respectively. Results have been presented for each level of altitude and compared with the national prevalence where possible.

5.1 Descriptive statistics

5.1.1 Socio-economic and demographic characteristics

Table 5.1: Sample size and age distribution of the participants

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Sample size	251	165	61	44
Age group (years)	**N (%)**			
30–39	105 (41.8)	46 (27.9)	6 (9.8)	16 (36.4)
40–49	71 (28.3)	40 (24.2)	16 (26.2)	10 (22.7)
50–59	50 (19.9)	36 (21.8)	15 (24.6)	6 (13.6)
60 +	25 (10.0)	43 (26.1)	24 (39.3)	12 (27.3)
Age Mean (SD)	42.9 (11.0)	50.3 (13.7)	55.4 (13.2)	48.3 (12.5)

Table 5.1 shows the distribution of study sample and age at each altitude level. Participants were sampled from four altitude levels; 2800 metre (m), 2890 m, 3270 m, and 3620 m in the two districts of Mustang and Humla. The sample sizes were lower at 3270 m and 3620 m due to the low population size at those altitudes.

More than a quarter of the study participants at the altitudes of 2800 m, 3270 m and 3620 m were aged 60 years or older. Age differed by altitude levels: Kruskal-Wallis test Chi-square (3 df) 59.1, P <0.01. Women comprised a greater proportion than men at all levels of altitude (Figure 5.1) but this difference was not statistically significant, Chi-square (3 df) 2.5, P=0.47.

Women and older participants were more likely to be sampled partly because the sampling of the households was irrespective of age and sex, and because women and older adults were more likely to be at home.

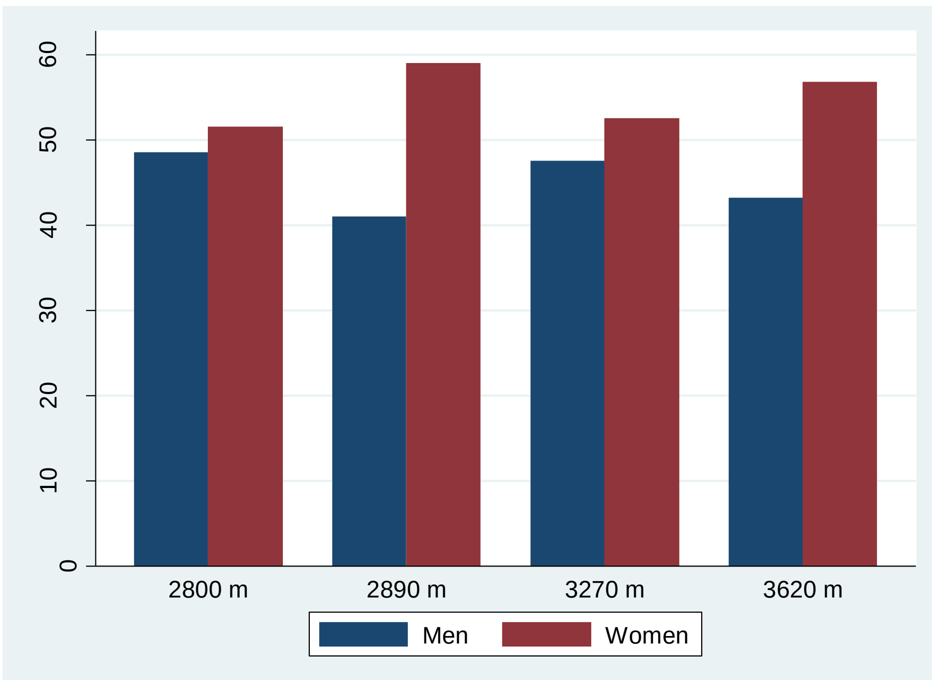

Figure 5.1: Sex distribution of the study participants at each altitude level

Table 5.2: Educational status of the study participants at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Education attainment		**N (%)**		
No formal education/illiterate	168 (66.9)	67 (40.6)	41 (67.2)	29 (65.9)
Less than primary level	18 (7.2)	45 (27.3)	19 (31.1)	6 (13.6)
Primary level completed	20 (8.0)	25 (15.1)	0 (0)	4 (9.1)
Secondary level or higher completed	45 (17.9)	28 (17.0)	1 (1.6)	5 (11.4)

Table 5.2 describes the educational status of the study participants at each level of altitude. Participants at an altitude of 2800 m were more literate and a higher proportion had completed at least primary school level of education compared with the participants at other altitude levels. More than two-thirds of the study participants at an altitude level of 2890 m, 3270 m, and 3620 m were illiterate or had no formal education.

Table 5.3: Occupation and household income of the study participants at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Occupation types		**N (%)**		
Govt or non-govt employee	39 (15.5)	25 (15.1)	1 (1.6)	7 (15.9)
Self-employed	21 (8.4)	86 (52.1)	6 (9.8)	14 (31.8)
Agriculture/daily waged labour	135 (53.8)	41 (24.8)	39 (63.9)	21 (47.7)
Unemployed/retired/ homemaker	56 (22.3)	13 (7.9)	15 (24.6)	2 (4.5)
Household income (per year)				
NRS <200,000	136 (54.2)	37 (22.4)	22 (36.1)	6 (13.6)
NRS 200,000 to 400,000	58 (23.1)	43 (26.1)	23 (37.7)	17 (38.6)
NRS >400,000	57 (22.7)	85 (51.5)	16 (26.2)	21 (47.7)

•1 NZ $ = NRS 77 (as of 6th December 2016)

As shown in Table 5.3, participants at all altitude levels were usually more involved in agriculture or daily waged labour work. Altitudes of 2800 m and 3620 m are tourist areas, so a significant proportion of the participants from these altitudes were self-employed in hotels, lodges, shops and other tourist-related businesses. Correspondingly, a higher proportion of the participants from these two altitudes also self-reported having the highest annual household income, greater than 400,000 Nepalese Rupees (NRS). Although there was no obvious trend of household income by level of altitude, the differences in proportions in the different income bands across altitude levels were statistically significant: Chi-square (6 df) 67.9, P <0.01.

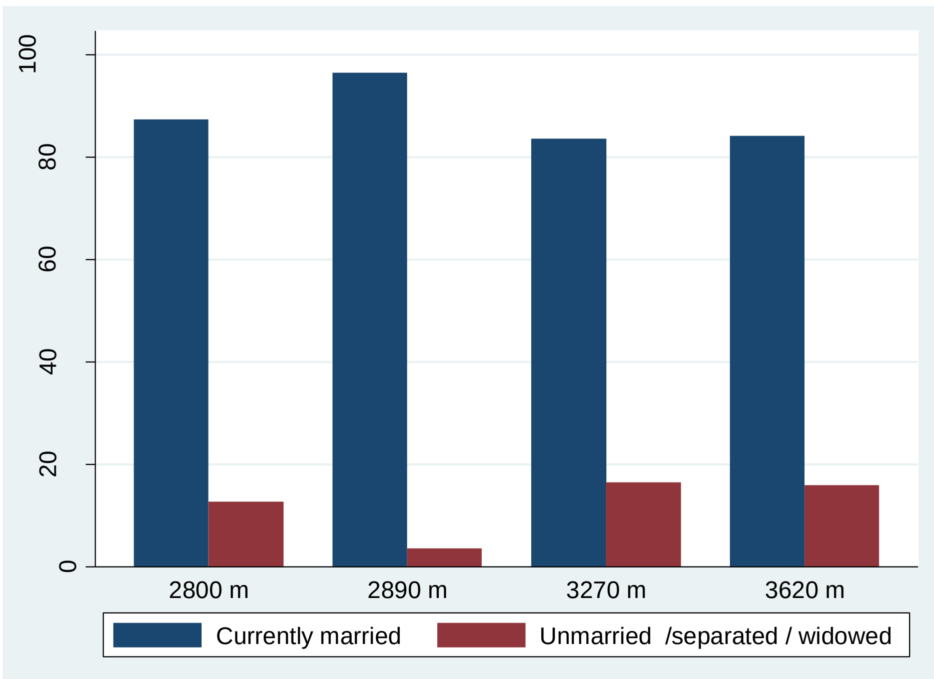

Figure 5.2: Marital status of the study participants by altitude level

Figure 5.2 shows that the vast majority of the participants at every altitude level were married.

Table 5.4: Birthplace and duration of high altitude residence of study participants by altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Birth place		**N (%)**		
Same district as current residence	246 (98.0)	148 (89.7)	59 (96.7)	38 (86.4)
District elsewhere	5 (2.0)	17 (10.3)	2 (3.3)	6 (13.6)
Duration at high altitude (≥ 2800 m)				
For lifetime	246 (98.0)	148 (89.7)	59 (96.7)	38 (86.4)
>10 years	2 (0.8)	17 (10.3)	2 (3.3)	6 (13.6)
5 to 10 years	3 (1.2)	0 (0)	0 (0)	0 (0)

Table 5.4 shows the birthplace of study participants and duration of residence at high altitude (HA) at each altitude level. The vast majority of the study participants were both born in the district of their current residence and had been living there most of their life. Of the participants who were born elsewhere, most of them had been living at their current residence for more than 10 years.

Table 5.5: Ethnicity of the study participants by altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Ethnicity		**N (%)**		
Tibetan	82 (32.7)	132 (80.0)	58 (95.1)	37 (84.1)
Khas-Arya	169 (67.3)	33 (20.0)	3 (4.9)	7 (15.9)

The majority of participants were Tibetan at all three altitude levels of the Mustang district and participants were mostly Khas-Arya at 2890 m in the Humla district (Table 5.5). Particular ethnic groups amongst Tibetans were Thakali, Tibetan Gurung and Lama; and for Khas-Aryas Brahmin, Chhetri, and Dalit.

5.1.2 Lifestyle-related characteristics

Table 5.6: Smoking-related characteristics of the study participants by altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
Current smoker	97/251 (38.6)	17/165 (10.3)	2/61 (3.3)	4/44 (9.1)
Current smokeless tobacco user	27/251 (10.8)	49/165 (29.7)	19/61 (31.1)	11/44 (25.0)
Past smoker	29/154 (18.8)	23/148 (15.5)	11/59 (18.6)	11/40 (27.5)
Past smokeless tobacco user	6/224 (2.7)	12/116 (10.3)	14/42 (33.3)	4/33 (12.1)
	Mean (SD)			
Number of years of smoking	24.4 (12.1) N=97	21.4 (14.4) N=17	22.5 (10.6) N=2	20.3 (18.6) N=4

Table 5.6 shows that fewer participants at an altitude level of 2800 m, 3270 m and 3620 m in Mustang reported currently smoking compared to more than one-third (38.6%) at 2890 m in Humla. This trend was opposite for the consumption of smokeless tobacco: it was greater at all three altitude levels in Mustang and lower at 2890 m in Humla. Of the smokers in Humla, 87.3% self-reported smoking tobacco daily. None of the women participants at 3270 m and 3620 m were current smokers, whereas 2.3% women at 2800 m and 31.1% at 2890 reported being current smokers. Nose snuffing of tobacco was a popular cultural practice at all altitude levels and particularly at 2800 m (21.2%). Of the non-smoking groups, at least 15% were past smokers at each altitude level.

Rural participants were significantly more likely to self-report being current smokers than the urban participants, rural 31.7% and urban 10.05%, the proportion difference of 21.6% (95% confidence interval (CI) 15 to 28.6), P <0.001; whereas urban participants were significantly more likely to self-report being current smokeless tobacco users, urban 28.7% and rural 14.7%, the proportion difference of 14% (95% CI 6.7 to 21.3), P <0.001.

For those in Nepal aged over 30 years, the national prevalence of current smokers is 24.7% and users of smokeless tobacco is 23.2% (K. K. Aryal et al., 2014).

Table 5.7: Self-reported alcohol intake characteristics of the study participants at every altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables		**N/N (%)**		
Current drinker	123/251 (49.0)	84/165 (50.9)	39/61 (63.9)	20/44 (45.4)
Past drinker	74/251 (29.5)	57/165 (34.5)	19/61 (31.1)	20/44 (45.4)
Never a drinker	54/251 (21.5)	24/165 (14.5)	3/61 (4.9)	4/44 (9.1)
Daily drinker	43/123 (34.9)	44/84 (52.4)	30/39 (76.9)	11/20 (55.0)
Hazardous drinker	24/123 (19.5)	26/84 (30.9)	22/39 (56.4)	8/20 (40.0)

•Current drinker: participants who drank alcohol in the past 30 days •Hazardous drinker: participants drinking ≥21 (males) or ≥14 (females) standard drink units of alcohol per week

In Table 5.7, self-reported alcohol intake by altitude level is shown. Approximately half of the participants at all altitude levels self-reported being current drinkers, which is greater than the national prevalence of 21.5% for the Nepalese population aged older than 30 years (K. K. Aryal et al., 2014). In general, participants in older age groups at all altitude levels were most likely to report being current drinkers. The exception was that the proportion of current drinkers at 2800 m was highest in the age group 40 to 49 years. A similar proportion of rural (51.9%) and urban (49.8%) participants self-reported being current drinkers, the proportion difference of 2.2% (95% CI -6.7 to 10.7), P=0.63.

Figure 5.3 shows the box plots of average daily consumption of alcohol in standard drink units (SDU) and bar charts of proportions of current drinkers by sex. A higher proportion of men were current drinkers compared to women at every altitude level. Participants at an altitude of 3270 m self-reported drinking more than four average SDU of alcohol daily, nearly twice that reported by current drinkers at other altitudes. Self-reported alcohol consumption in SDU differed by altitude level: Kruskal-Wallis test Chi-square (3 df) 28.1, P <0.01.

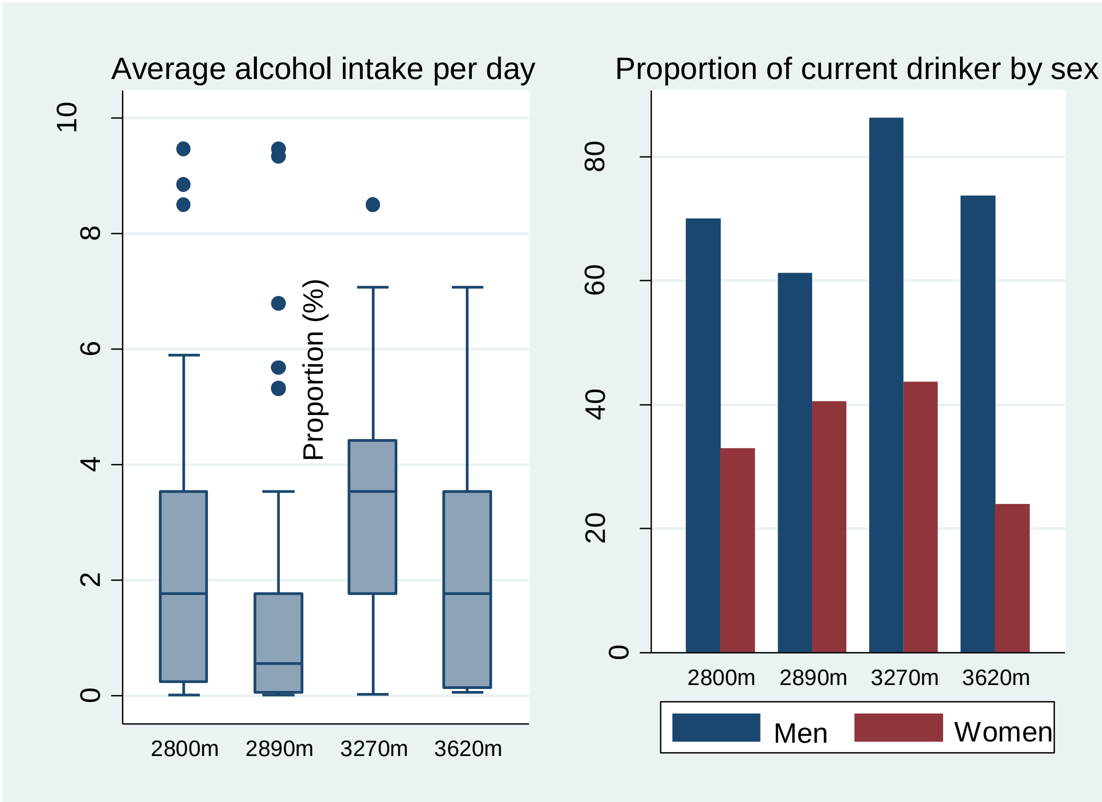

Figure 5.3: Average consumption of alcohol per day and the proportions of current drinker by sex at each altitude level

Table 5.8: Self-reported physical activity-related characteristics at each altitude level

	Humla		**Mustang**	
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables		**Mean (SD)**		
Vigorous physical	33.3 (18.9)	10.3 (32.9)	8.9 (14.0)	4.8 (9.5)
activity / week (hour)	N=167	N=165	N=61	N=44
Moderate physical	15.4 (10.6)	19.2 (16.0)	16.5 (12.8)	16.2 (10.7)
activity / week (hour)	N=204	N=165	N=61	N=44
Walk time /day	89.4 (89.6)	53.0 (44.8)	95.6 (79.9)	73.2 (53.0)
(min)	N=251	N=165	N=61	N=44
Sedentary time / day	2.8 (2.1)	3.6 (23)	3.7 (2.3)	4.0 (2.0)
(hours)	N=251	N=165	N=61	N=44

●Vigorous physical activity: activity (such as carrying heavy loads, digging) causing large increases in breathing or heart rate for at least 10 minute continuously ● Moderate physical activity: activity (such as brisk walking, cleaning, washing clothes by hand) causing small increases in breathing or heart rate

As shown in Table 5.8, vigorous physical activity decreased and sedentary hours increased with increasing levels of altitude. Men were more likely to be sedentary than women at all altitude levels except at 3270 m. Three-quarters of participants at each altitude level self-reported that they walked mean duration of at least 30 minutes per day. Urban participants self-reported having significantly higher sedentary hours per day than the rural particpants, urban 3.7 hours and rural 3.0 hours, the proportion difference of 0.7 hour (95% CI 0.3 to 1.1), P <0.001. Urban participants were also significantly less likely to have recommended levels of walk (minimum 30 minutes per day) than the rural participants, urban 77% and rural 89.7%, the proportion difference of -12.7% (95% CI -5.3 to -18.7), P <0.01.

Table 5.9: Self-reported fruit, vegetable and salt intake by altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
<5 fruit & vege portions / day	137/251 (54.6)	120/165 (72.7)	59/61 (96.7)	40/44 (90.9)
>5 gram of salt intake / day	224/236 (94.9)	135/150 (90.0)	54/54 (100)	27/28 (96.4)
	Mean (SD)			
Fruit & vege portions / day	4.5 (1.8) N=251	3.7 (2.0) N=165	2.7 (1.2) N=61	3.2 (1.2) N=44
Individual salt intake / day (gram)	13.3 (6.9) N=236	11.0 (5.7) N=150	10.4 (3.7) N=54	10.8 (4.1) N=28

Table 5.9 shows that the vast majority of the participants at every altitude level self-reported consuming fewer portions of fruit and vegetables and higher amounts of salt per day than internationally recommended levels (see Chapter 4, section 4.4.1). For every altitude level, the mean consumption of salt was at least two times greater than the recommended level of 5 grams (g) per day. Rural participants were significantly more likely to consume recommended level of fruit and vegetables (five portions per day) than the urban participants, rural 37.2% and urban 23.4%, the proportion difference of 13.8%

(95% CI 6.2 to 21.8), P <0.01; and rural participants were also more likely to consume more than the recommended level of salt per day, rural 95.9% and urban 91%, the proportion difference of 4.9% (95% CI 0.2 to 9.8), P=0.03.

5.1.3 Anthropometric measurements

Table 5.10 shows a summary of anthropometric measures among the participants at each altitude level. In general, participants at 2800 m and 3620 m had a greater proportion of values above the obesity and overweight cut-points for all of the measured anthropometric variables, compared to participants at other altitude levels. A large proportion of the participants in the youngest age group of 30 to 39 years from these two altitude levels were overweight or obese – 60% at 2800 m and 43.7% at 3620 m. At 2890 m, despite having the lowest proportion of participants who were overweight, obese, or with a high waist circumference (WC), more than three-quarters of the participants at this altitude had a high waist to hip ratio (WHR), related to a low hip circumference. Urban participants had significantly higher mean body mass index (BMI) compared with the rural participants, urban 25.5 kg/m^2 and rural 22.5 kg/m^2, mean difference of 3.0 kg/m^2 (95% CI 2.3 to 3.7), P <0.001.

The proportion of participants who were overweight or obese was higher at 2800 m and 3620 m but lower at 2890 m and 3270 m when compared with Nepal's national prevalence for those aged over 30 years (28.3%) (K. K. Aryal et al., 2014). Figure 5.4 shows the box plots of BMI by sex at each altitude level. Women comprised a greater proportion of those with a higher BMI than men for every altitude level; however, this difference was statistically significant only at 2800 m – mean difference (95% CI) 2.2 kg/m^2 (1.00 to 3.50), P <0.01.

Table 5.10: Proportions of anthropometric variables at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
Overweight or obese	52/251 (20.7)	81/143 (56.6)	16/60 (26.7)	21/44 (47.7)
High waist circumference	43/251 (17.1)	88/142 (62.0)	16/60 (26.7)	17/44 (38.6)
High waist–hip ratio	190/251 (75.7)	94/142 (66.2)	39/60 (65.0)	19/44 (43.2)

Overweight or obese: BMI ≥25 kg/m^2, high waist circumference: >90 cm for men and >80 cm for women, high waist–hip ratio: ≥0.90 for men and ≥0.85 for women

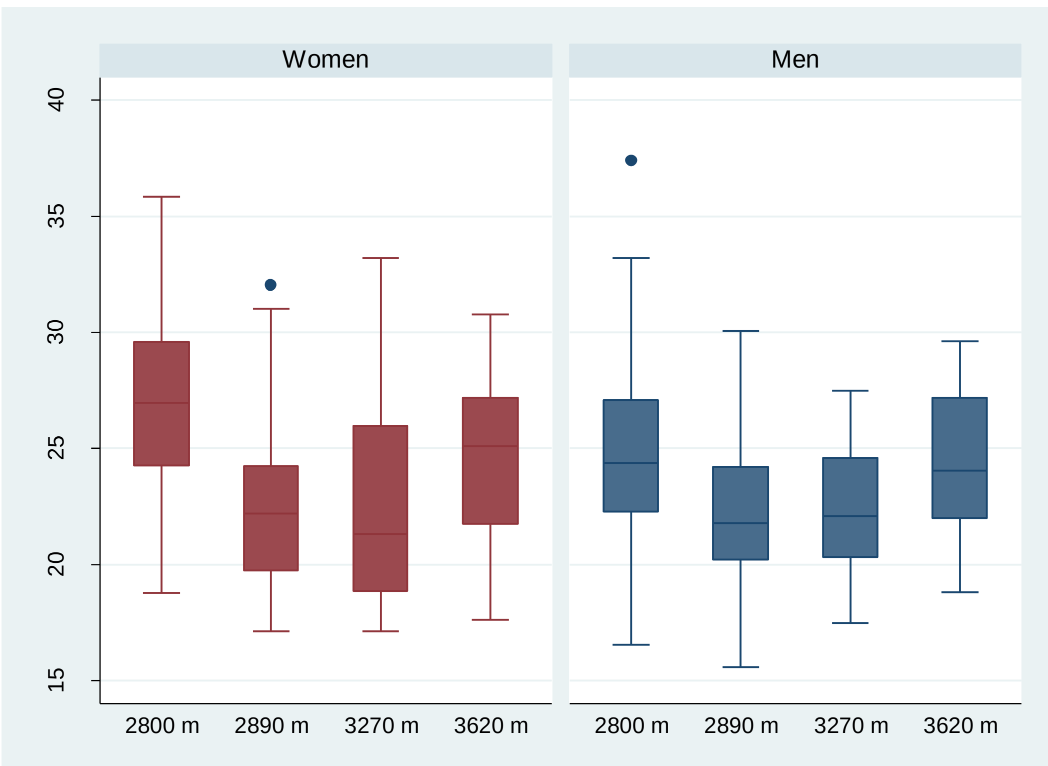

Figure 5.4: Body mass index by sex at each altitude level

5.1.4 Bio-chemical measurements

Table 5.11 shows lipid profiles of the study participants at each altitude level. No clear trend in lipid components by altitude level is present. Residents at 2800 m and 3620 m had higher total cholesterol (TC) and triglyceride (TG), and those at 2890 m had a lower high-density lipoprotein-cholesterol (HDL). Based on cut-points (see Chapter 4, section 4.4.1), a higher proportion of women had low HDL, whereas men were more likely to have high

TC, TG, low-density lipoprotein-cholesterol (LDL) and non-HDL cholesterol. The proportions of participants with high TC and low HDL were lower at all altitude levels compared with Nepal's national prevalence of 29.8% and 74.5% respectively in those aged 30 years or older. The proportion of participants with high TG was higher than the national prevalence (33.4%) at all altitude levels except 2890 m (K. K. Aryal et al., 2014).

Table 5.11: Lipid profiles of the participants at each altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**Mean (SD)**			
TC (mmol/L)	4.1 (1.1)	4.5 (0.9)	4.2 (0.8)	4.5 (1.1)
	N=168	N=142	N=56	N=38
TG (mmol/L)	1.7 (0.9)	1.9 (0.9)	1.5 (0.9)	2.4 (1.5)
	N=168	N=140	N=56	N=38
HDL (women)	1.0 (0.3)	1.2 (0.5)	1.4 (0.3)	1.3 (0.3)
(mmol/L)	N=111	N=75	N=30	N=22
HDL (men)	1.1 (0.4)	1.1 (0.5)	1.3 (0.3)	1.1 (0.4)
(mmol/L)	N=56	N=64	N=24	N=15
LDL (mmol/L)	2.3 (0.7)	2.4 (0.7)	2.2 (0.7)	2.2 (0.9)
	N=164	N=135	N=53	N=34
Non-HDL	3.1 (0.9)	3.3 (0.8)	2.8 (0.8)	3.3 (1.2)
(mmol/L)	N=167	N=139	N=54	N=37
	N/N (%)			
High TC	23/168 (13.7)	34/142 (23.9)	7/56 (12.5)	6/38 (15.8)
High TG	62/168 (36.9)	74/142 (52.1)	17/56 (30.4)	22/38 (57.9)
Low HDL	120/168(71.4)	91/142 (64.1)	22/56 (39.3)	21/38 (55.3)
High non-HDL	23/167 (13.8)	23/140 (16.4)	4/55 (7.3)	7/37 (18.9)

High TC: ≥5.2 mmol/L, high TG: ≥1.7 mmol/L, high LDL: ≥3.4 mmol/L, low HDL: <1.3 mmol/L for women and <1.0 mmol/L for men, high non-HDL: ≥4.1 mmol/L

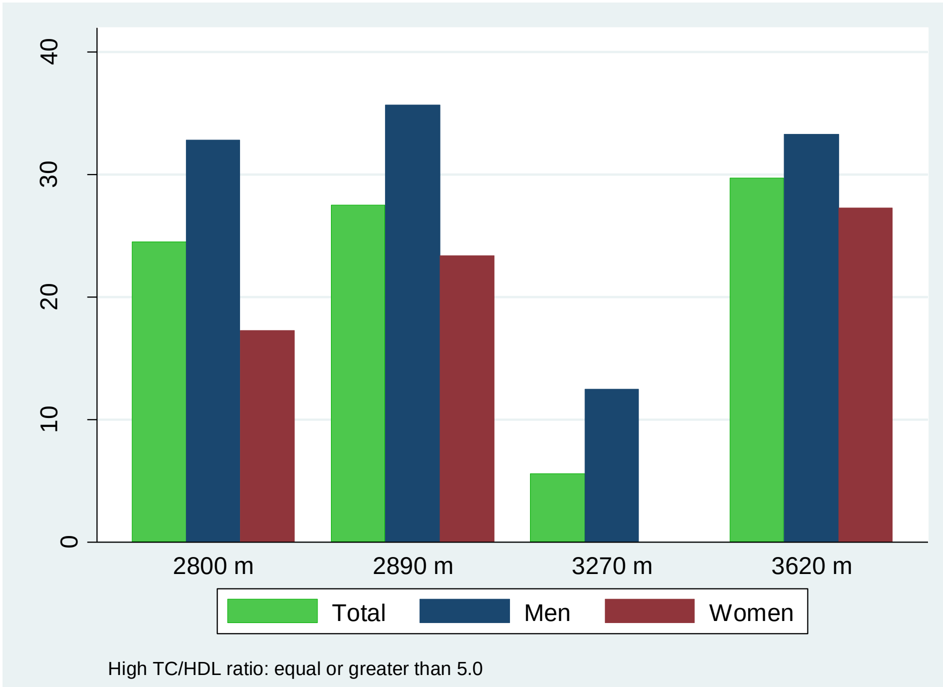

Figure 5.5: Proportions of high total cholesterol to high-density lipoprotein-cholesterol (TC/HDL) ratio by sex at each altitude level

Overall more than one-third (35.3%) of participants had abnormal results, based on cut-points (see Chapter 4, section 4.4.1), for at least two lipid variables. Only four (0.8%) participants were being treated with cholesterol lowering drugs.

As shown in Figure 5.5, more than one-quarter of the participants had a TC to HDL ratio higher than the cut-point of 5.0 at all altitude levels except at 3270 m. A higher proportion of men had a high TC to HDL ratio at all altitude levels; however, the difference in proportions compared to women was statistically significant at 2800 m only: proportion difference (95% CI), 16% (2 to 30), P=0.03. Compared to rural participants, urban participants had significantly higher proportion of high TC (urban 22.2% and rural 13.4%) and high TG (urban 53.3% and rural 35.3%). The proportion differences were 2.2% (95% CI 1.5 to 16.5), P=0.02 for high TC; and 18% (95% CI 8.4 to 27.6) , P <0.01 for high TG. Although the proportions of high LDL and high TC to HDL ratio were also higher in urban participants and the proportion of low HDL was higher in rural participants, these differences were not statistically significant.

An instrument failure at 2890 m meant that lipid components were available from 168/251 (67%) participants at this altitude level.

Table 5.12: Glycated hemoglobin and diabetes related characteristics at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables		**N/N (%)**		
Diabetes or medication	6/172 (3.5)	15/142 (10.6)	2/61 (3.3)	6/44 (13.6)
Diabetes	5/171 (2.9)	13/141 (9.2)	2/61 (3.3)	5/44 (11.4)
Impaired glucose tolerance	63/171 (36.8)	31/141 (22.1)	24/61 (39.3)	11/44 (25.0)
Diabetes newly diagnosed	1/171 (0.6)	5/141 (3.5)	2/61 (3.3)	3/44 (6.8)
		Mean (SD)		
HbA1c (mmol/mol)	38.1 (4.9) N=171	38.7 (10.6) N=141	38.0 (5.4) N=61	39.2 (8.8) N=44

Impaired glucose tolerance: HbA1c ≥39 to 47 mmol/mol, Diabetes: HbA1c ≥48 mmol/mol, Diabetes or medication : HbA1c ≥48 mmol/mol or on anti-diabetic medication

HbA1c and diabetes-related characteristics are presented in Table 5.12. There was no significant trend in diabetes-related characteristics by altitude level. The proportion of participants with diabetes was higher at 2800 m and 3620 m compared to all other altitude levels and compared to national prevalence in those aged over 30 years (5.9%) (K. K. Aryal et al., 2014). However, mean HbA1c were similar at all altitude levels. Men were more likely to be diabetic or on treatment than women at every altitude level, but the differences in proportions between men and women were not significantly different at any level. Three-quarters (74.5%) of the participants had never had a blood sugar test before and 2.7% were currently on anti-diabetic treatment. Urban participants were significantly more likely to be diabetic or on treatment than the rural counterparts, urban 11.3% and rural 3.4%, the proportion difference of 7.9% (95% CI 2.5 to 12.7), P=0.002.

Technical measurement problems at 2890 m meant that HbA1c levels were measured from 171/251 (68%) participants at this altitude level.

5.1.5 Stroke and cardiovascular disease risk prediction

Table 5.13 shows that 6.7% (35/521) participants had self-reported "yes" for at least one of the eight questions in the Questionnaire for Verifying Stroke Free Status (QVSFS) and higher proportions of participants who were residents at altitude of 2800 m and 3270 m reported a positive answer consistent with cerebrovascular disease. Eleven of 521 (2.1%) participants reported having a stroke history confirmed by a doctor. No obvious patterns were observed by altitude level. A higher proportion of men (8.2%) reported a positive stroke symptoms or history for at least one question than women (5.5%) but this difference was not statistically significant: Chi-square (1 df) 1.5, P=0.22.

Table 5.13: Stroke-related symptoms according to the questionnaire for verifying stroke free status for every altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
At least one symptom	7/251 (2.8)	17/165 (10.3)	9/61 (14.7)	2/44 (4.5)
Symptoms				
Told by physicians having stroke	0/251 (0)	3/165 (1.8)	6/61 (9.8)	2/44 (4.5)
Told by physicians having mini-stroke or transient ischemic attack	0/251 (0)	0/165 (0)	0/61 (0)	0/44 (0)
Sudden painless weakness on one side of the body	4/251 (1.6)	7/165 (4.2)	7/61 (11.5)	2/44 (4.5)
Sudden numbness on one side of the body	4/251 (1.6)	8/165 (4.8)	7/61 (11.5)	1/44 (2.3)
Sudden painless loss of vision in one or both eyes	5/251 (2.1)	5/165 (3.0)	5/61 (8.2)	1/44 (2.3)
Suddenly lost one half of the vision	4/251 (1.6)	8/165 (4.8)	3/61 (4.9)	1/44 (2.3)
Suddenly lost ability to	2/251 (0.8)	10/165 (6.1)	5/61 (8.2)	1/44 (2.3)

understand				
Suddenly lost ability to express verbally or in writing	3/251 (1.2)	7/165 (4.2)	6/61 (9.8)	1/44 (2.3)

Table 5.14 shows the proportions of participants with World Health Organization (WHO) / International Society of Hypertension (ISH) 10-year risk of future fatal or non-fatal major cardiovascular events (myocardial infarction (MI) or stroke) in different risk categories, based on the assessment for the WHO South East Asia sub-region D (SEAR D). This assessment incorporates age, sex, BP, TC, smoking status and presence or absence of diabetes. Overall, 3.9% (16/408) of the participants had a high or very high risk (equal to or greater than 20%) of a fatal or non-fatal major cardiovascular event within the next 10 years but this risk was not consistent by level of altitude. Although residents living in urban areas (2800 m and 3620 m) were more likely to develop this risk than those living in rural areas (2890 m and 3270 m) – urban 5.6% and rural 2.2% – the difference in proportion by residential areas was not statistically significant: Chi-square (1 df) 3.04, P=0.08.

Table 5.14: Proportions of World Health Organization / International Society of Hypertension (WHO/ISH)-10 year risk of a fatal or non-fatal major cardiovascular events by altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Sample size	**173**	**141**	**56**	**38**
WHO/ISH risk categories	**N (%)**			
Low (<10%)	164 (94.8)	125 (88.6)	49 (87.5)	31 (81.6)
Moderate (≥10% to <20%)	4 (2.3)	10 (7.1)	6 (10.7)	3 (7.9)
High (≥20% to <30%)	4 (2.3)	2 (1.4)	0 (0)	1 (2.6)
Very high (≥30%)	1 (0.6)	4 (2.8)	1 (1.8)	3 (7.9)

In summary, no strong relationships were found between the presence of CVD risk factors and altitude. Higher proportions of participants with CVD risk factors were found at altitudes of 2800 m and 3620 m, particularly for anthropometric, lipid and diabetes-related characteristics. Men were more likely to have CVD-related risk factors than women. Alcohol drinking was very common at all levels of altitude and more than twice as high as the national prevalence in Nepal.

5.2 Blood Pressure

This section is divided into two parts. In the first part, BP and hypertension (HT) are described in relation to altitude, socio-demographic, lifestyle and clinical characteristics. In the second part, analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models for the relationship between systolic blood pressure (SBP) and diastolic blood pressure (DBP) and altitude are shown.

Table 5.15 describes SBP and DBP at each altitude level. The mean SBP and DBP were highest at the highest altitude of 3620 m but did not consistently increase with increasing altitude. There was strong evidence that SBP and DBP were different across the altitude levels. The F-statistics from the ANOVA with SBP as the response variable and altitude as a categorical predictor variable was 12.6 (3 df,517), P<0.01; and for DBP, 3.64 (3 df,517), P=0.01. For a comparison between similar altitude levels, 2800 m and 2890 m, the mean differences (95% CI) were for SBP 9.6 (5.8 to 13.3) mmHg, t 5.1, P<0.01; and for DBP, 2.9 (0.5 to 5.3) mmHg, t 2.4, P=0.02. Figure 5.6 shows boxplots of SBP and DBP by the levels of altitude.

Table 5.15: Systolic and diastolic blood pressure by the level of altitude

	Humla	**Mustang**			
Variable	**2890 m**	**2800 m**	**3270 m**	**3620 m**	**Total (Mustang)**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**	
			Mean (SD)		
Systolic	116.9 (18.3)	126.5 (19.5)	125.1 (20.4)	131.5(23.6)	127.02 (20.5)
BP	N=251	N=165	N=61	N=44	N=270
Diastolic	83.8 (12.2)	86.7 (12.3)	83.8 (12.5)	89.2 (15.1)	86.5 (15.1)
BP	N=251	N=165	N=61	N=44	N=270

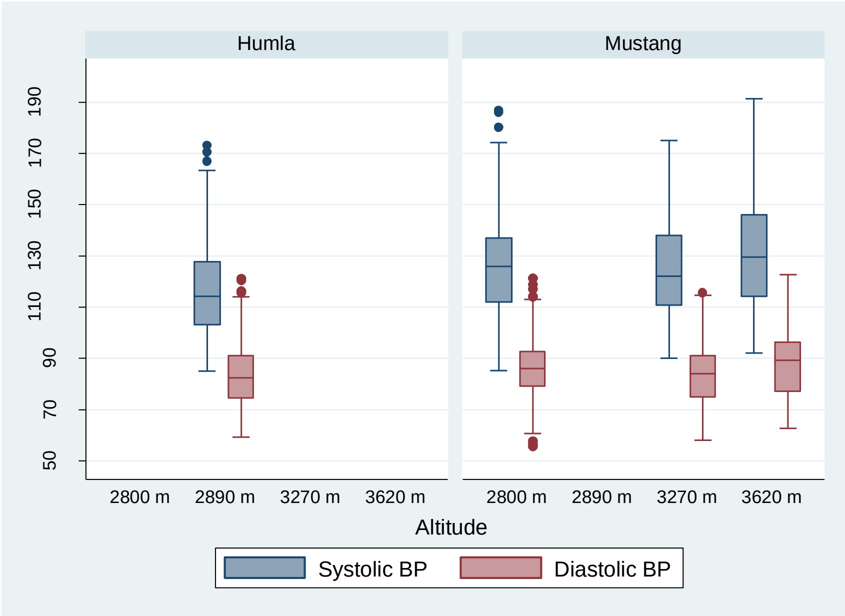

Figure 5.6 : Boxplot of mean systolic and diastolic blood pressure values by altitude level

Summaries of HT-related characteristics at different altitude levels are shown in Table 5.16. Residents at 3620 m had higher proportions of participants with HT and related characteristics than those at lower altitude. When altitude was treated as a continuous variable the age and sex adjusted odds ratio (95% CI) for being hypertensive or on anti-hypertensive medication was 1.54 (0.72 to 3.29), P=0.26 for every 1000 m increment in altitude. Residents at 2800 m had higher odds for HT or for being on anti-hypertensive medication compared to residents at 2890 m with age and sex adjusted odds ratio (95% CI) of 1.49 (0.96 to 2.33), P=0.07.

Altitudes of 2800 m and 3620 m are tourist areas and people have a modern lifestyle, whereas 2890 m and 3270 m are rural areas. For residents with modern lifestyle compared to those with a rural lifestyle the age and sex adjusted odds ratio (95% CI) for HT (or being on anti-hypertensive medication) was 1.68 (1.15 to 2.47), P=0.008.

The national prevalence of HT (or being on anti-hypertensive medication) for those aged 30 years or older living in Nepal is 36.8% (K. K. Aryal et al., 2014) and so the prevalence of HT at 2800 m, 3270 m and 3620 m in Mustang were higher than this, and lower at 2890 m in Humla. Nearly one-quarter of the study participants and two-thirds of hypertensives were diagnosed with HT, based on the measurements done for this study, for the first time. Overall, only 17/521 (3.3%) participants were on anti-hypertensive medication.

Table 5.16: Blood pressure and hypertension related characteristics by altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
	N=251	**N=165**	**N=61**	**N=44**
Variables	**N (%)**			
HT or on medication	73 (29.1)	76 (46.1)	25 (40.9)	24 (54.5)
HT	73 (29.1)	66 (40.0)	20 (32.8)	22 (50)
HT stage I	46 (18.3)	41 (24.8)	10 (16.4)	13 (29.5)
HT stage II	27 (10.8)	25 (15.1)	9 (14.7)	9 (20.4)
Pre-HT	69 (27.5)	59 (35.8)	21 (34.4)	10 (22.7)
HT new	63 (25.1)	30 (18.2)	13 (21.3)	18 (40.9)
HT ever	21 (17.2)	51 (34.0)	17 (29.8)	7 (16.7)
BP measured ever	123 (49.0)	150 (90.9)	57 (93.4)	42 (95.4)

•HT or on medication: SBP ≥140 or DBP ≥90 mmHg or on anti-hypertensive medication;
•HT stage I: SBP 140-159 or DBP 90-99 mmHg; •HT stage II: SBP ≥160 or DBP ≥100 mmHg;
•pre-HT: SBP 120-139 or DBP 80-90 mmHg.

Table 5.17 shows the proportion of HT (or those on anti-hypertensive medication) by socio-economic and demographic characteristics at each altitude level. Participants who were men, in older age groups, with formal school education, higher self-reported annual household income and currently married were more likely to have HT (or be on anti-hypertensive medication). The trend was inconsistent for different types of occupation. Men had almost two-fold higher odds than women for being hypertensive or on anti-hypertensive medication: age adjusted odds ratio (95% CI) of 1.96 (1.34 to 2.86), P<0.01. For every decade, older age was associated with sex adjusted odds ratio (95% CI) of 1.67 (1.44 to 1.94), P<0.01 for HT (or on anti-hypertensive medication). When compared with participants with a self-reported annual household income of less than NRS 200,000, the age and sex adjusted odds ratio (95% CI) for HT or being on anti-hypertensive medication was 1.25 (0.77 to 2.02), P=0.36 for those with annual household income of between NRS

200,000 to 400,000, and 1.79 (1.14 to 2.81), P=0.01 for those with greater than NRS 400,000.

Table 5.17: The proportion of hypertension (or those on anti-hypertensive medication) by socio-economic and demographic characteristics at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
HT or on medication	**N=73**	**N=76**	**N=25**	**N=24**
Variables	**N/N (%)**			
Age group (years)				
30–39	18/105 (17.1)	12/46 (26.1)	0/6 (0)	5/16 (31.2)
40–49	22/71 (30.9)	16/40 (40.0)	7/16 (43.7)	6/10 (60.0)
50–59	23/50 (46.0)	18/36 (50.0)	6/15 (40.0)	4/6 (66.7)
≥60	10/25 (40.0)	30/43 (69.8)	12/24 (50.0)	9/12 (75.0)
Sex				
Male	42/103 (40.8)	41/80 (51.2)	14/29 (48.3)	11/19 (57.9)
Female	31/148 (20.9)	35/85 (41.2)	11/32 (34.4)	13/25 (52.0)
Education				
No formal education / illiterate	49/168 (29.2)	27/67 (40.3)	17/41 (41.5)	15/29 (51.7)
Less than primary level	3/18 (16.7)	18/45 (40.0)	8/19 (42.1)	2/6 (33.3)
Primary level completed	8/20 (40.0)	16/25 (64.0)	0/0 (0)	4/4 (100.0)
Secondary level completed or more	13/45 (28.9)	15/28 (53.6)	0/1 (0)	3/5 (60.0)
Occupation				
Govt or non-govt employee	16/39 (41.0)	15/25 (60.0)	0/1 (0)	6/7 (85.7)
Self-employed	8/21 (38.1)	37/86 (43.0)	4/6 (66.7)	6/14 (42.9)
Agriculture/daily waged labour	39/135 (28.9)	19/41 (46.3)	14/39 (35.9)	10/21 (47.6)
Unemployed/retired/ homemaker	10/56 (17.9)	5/13 (38.5)	7/15 (46.7)	2/2 (100.0)

Household income (per year)				
<NRS 200,000	37/136 (27.2)	15/37 (40.5)	9/22 (40.9)	2/6 (33.3)
NRS 200,000 to 400,000	18/58 (31.0)	15/43 (34.9)	10/23 (43.5)	11/17 (64.7)
NRS >400,000	18/57 (31.6)	46/85 (54.1)	6/16 (37.5)	11/21 (52.4)
Marital Status				
Unmarried/divorced/ widowed	3/9 (33.3)	7/21 (33.3)	4/10 (40.0)	3/7 (42.9)
Currently married	70/242 (28.9)	69/144 (47.9)	21/51 (41.2)	21/37 (56.8)

•1 NZ $ = NRS 77 (as of 6th December 2016)

The relationship between HT (or being on anti-hypertensive medication) and ethnicity by altitude level is shown in Table 5.18. Participants from Tibetan ethnicity were predominant at all three altitude levels in Mustang. Khas-Aryas were the majority ethnic group of those living in Humla. Overall, participants with Tibetan ethnicity had a higher proportion of HT (or being on anti-hypertensive medication) compared to Khas-Aryas; however, when adjusted for age and sex the odds ratio (95% CI) for HT (or being on anti-hypertensive medication) among participants with Tibetan compared to Khas-Arya ethnicity was 0.86 (0.58 to 1.29), P=0.49.

Table 5.18: Hypertension (or on anti-hypertensive medication) by ethnicity at each altitude level

	Humla		**Mustang**		**Total**
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**	
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**	
Variables			**N/N (%)**		
Tibetan	20/82 (24.4)	63/132 (47.7)	24/58 (41.4)	18/37 (48.6)	125/309 (40.4)
Khas-Arya	53/169 (31.4)	13/33 (39.4)	1/3 (33.3)	6/7 (85.7)	73/212 (34.4)

• Tibetan = Thakali and Tibetan Gurung in Mustang and Lama in Humla, Khas-Arya = Dalit, Brahmin and Chhetri in both Mustang and Humla.

The proportion of participants with HT (or on anti-hypertensive medication) in relation to self-reported smoking and alcohol-related characteristics for each altitude level is described in Table 5.19. At least a quarter of the current drinkers and current smokers were hypertensive or on anti-hypertensive medication at all altitude levels. HT residents at 3270 m self-reported consuming markedly higher mean SDUs of alcohol than participants at all other altitudes. Overall, the age and sex adjusted odds ratio (95% CI) for HT or being on anti-hypertensive medication was 0.87 (0.54 to 1.37), P=0.54 for current smokers compared to non-smokers, and 0.82 (0.55 to 1.22), P=0.34 for current drinkers compared to non-drinkers.

Table 5.19: Hypertension (or on anti-hypertensive medication) by self-reported tobacco and alcohol-related characteristics and standard drink units of alcohol at each altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
Smoking status				
Current smoker	32/97 (32.9)	7/17 (41.2)	1/2 (50.0)	1/4 (25.0)
Past smoker	6/29 (20.7)	10/23 (43.5)	5/11 (45.4)	4/7 (57.1)
Current smokeless tobacco user	10/27 (37.0)	25/49 (51.0)	6/19 (31.6)	5/11 (45.4)
Past smokeless tobacco user	5/6 (83.3)	6/12 (50.0)	8/14 (57.1)	1/4 (25.0)
Alcohol status				
Current drinker	35/123 (28.5)	38/84 (45.2)	17/39 (43.6)	14/20 (70.0)
Ever a drinker	58/197 (29.4)	65/141(46.1)	23/58 (39.7)	24/40 (60.0)
Hazardous drinker	8/24 (33.3)	13/26 (50.0)	12/22 (54.5)	6/8 (75.0)
	Mean (SD)			
Standard drink units of alcohol in past 30 days	91.4 (187.9) N=35	68.9 (89.7) N=38	167.9 (193.1) N=17	70.9 (64.4) N=14

•Current drinker: participants who drank alcohol in the past 30 days •Hazardous drinker: participants drinking ≥21 (males) or ≥14 (females) standard drink units of alcohol per week

Table 5.20 describes physical activity-related variables in those with HT (or on anti-hypertensive medication) at each altitude level. Among those with HT there was no consistent trend in reports of sedentary behaviour by altitude levels, except that the participants at higher altitudes of 3270 m and 3620 m reported having more sedentary hours per day than the participants from 2800 m and 2890 m. Generally, those with HT (or on anti-hypertensive medication) were physically less active and sedentary at all altitude levels (data not shown).

Table 5.20: Physical activity-related variables in hypertensive (or on anti-hypertensive medication) participants by altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**Mean (SD)**			
Vigorous physical activity / week (hour)	35.8(18.9) N=41	5.6 (10.8) N=76	7.3 (12.1) N=25	2.8 (4.8) N=24
Moderate physical activity / week (hour)	12.5 (9.6) N=61	18.2 (14.3) N=76	12.6 (13.9) N=25	16.0(11.3) N=24
Walk time /day (min)	81.5(90.9) N=73	50.3 (44.4) N=76	99.4 (94.0) N=25	75.6(45.6) N=24
Sedentary time / day (hour)	3.3 (2.5) N=73	3.6 (2.4) N=76	4.9 (2.6) N=25	4.4 (1.6) N=24

•Vigorous physical activity: activity (like carrying heavy loads, digging) causing large increases in breathing or heart rate for at least 10 minutes continuously • Moderate physical activity: activity (such as brisk walking, cleaning, washing clothes by hand) causing small increases in breathing or heart rate

Table 5.21 shows the self-reported fruit and vegetable consumption and salt intake of those with HT (or on anti-hypertensive medication) by altitude level. Hypertensive residents at all altitude levels usually reported that they consumed less fruit and vegetables than the recommended five portions per day, and more salt than the recommended 5 g per day. Consumption of fruit and vegetables was lower in those with HT (or on anti-hypertensive medication) compared to non-hypertensives at all altitude levels, but this trend was not observed for salt consumption (data not shown).

Table 5.21: Self-reported fruit, vegetable and salt intake among hypertensive (or on anti-hypertensive medication) participants by altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
<5 fruit & vege portions / day	39/73 (53.4)	59/76 (77.6)	25/25 (100.0)	22/24 (91.7)
>5 gram of salt intake / day	65/68 (95.6)	64/70 (91.4)	21/21 (100.0)	15/16 (93.7)
	Mean (SD)			
Fruit & vege portions / day	4.3 (1.8) N=73	3.3 (1.7) N=76	2.7 (0.9) N=25	3.0 (1.2) N=24
Individual salt intake / day (gram)	13.8 (6.7) N=68	10.9 (4.6) N=70	9.9 (3.4) N=21	9.2 (4.1) N=16

BMI among those with HT (or on anti-hypertensive medication) at different altitude levels is shown in Table 5.22. BMI was higher at 2800 m compared to other altitude levels but there was no obvious trend by altitude. At least half of the participants who were overweight or obese (BMI ≥25 kg/m^2) had HT (or were on anti-hypertensive medication) at all altitude levels (Figure 5.7). Overall, overweight or obese participants had nearly three-fold higher odds for presence of HT (or being on anti-hypertensive medication) compared to the participants with normal BMI (<25 kg/m^2), age and sex adjusted odds ratio (95% CI) of 2.97 (1.95 to 4.52), P<0.01.

Table 5.22: Body mass index in hypertensive participants at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**Mean(SD)**			
Body mass index (kg/m^2)	23.6 (3.8) N=73	26.4 (4.1) N=65	23.2 (4.3) N=24	25.3 (3.1) N=24

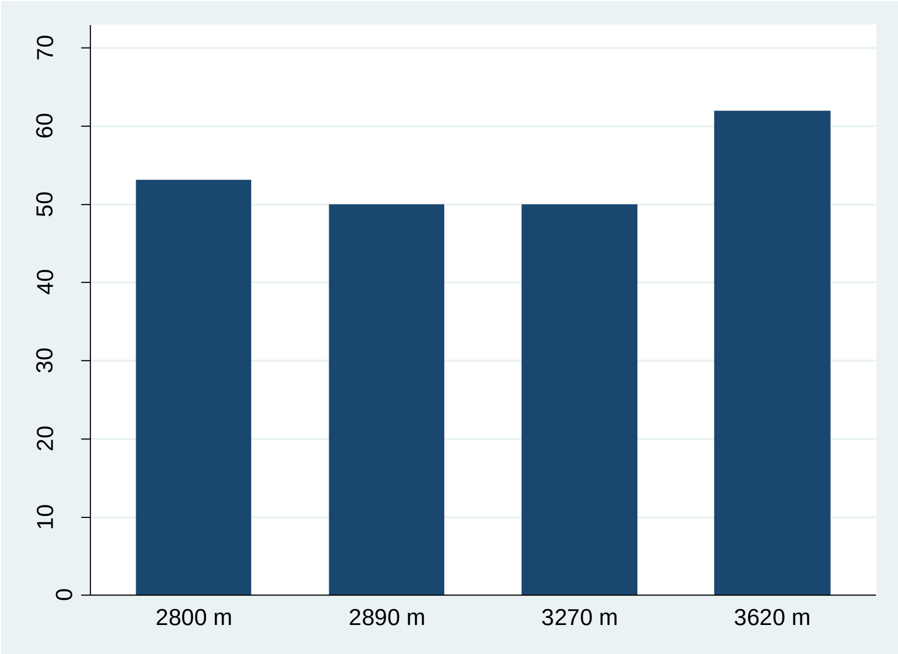

Figure 5.7: The proportion of hypertensive (or on anti-hypertensive medication) participants among those overweight or obese at each altitude level

5.2.1 Blood pressure and altitude

Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) models were used to estimate the nature and strength of associations between SBP and DBP and altitude. In a univariate ANOVA model four altitude levels were considered as explanatory variables and treated as categorical variables with 2800 m nominated as the reference level and compared to altitude levels 2890 m, 3270 m and 3620 m.

In the ANCOVA models predicting BP age, sex, weight, self-reported salt intake, and self-reported alcohol intake (standard drinks in the past 30 days) were used as possible confounding variables and altitude was treated as a continuous variable. There were four values of altitude (2800 m, 2890 m, 3270 m, and 3620 m). Overall normality and other statistical assumptions for ANOVA and ANCOVA were reasonably well met.

In a univariate model there was strong evidence of a relationship between SBP and altitude: $F(3,517)$ 12.6, $P<0.001$, with root mean square of error (RMSE) 19.4 and an R-squared of 6.8% (adjusted R-squared 6.3%). However, the relationship was only moderate between DBP and altitude: $F(3,517)$ 3.6, $P=0.01$, with a RMSE of 12.5 and R-squared 2.1% (adjusted R-squared 1.5%). Table 5.23 shows the estimates of the difference in mean BP for each altitude level compared to 2800 m in a univariate model.

Table 5.23: Estimates of the difference in mean systolic and diastolic blood pressure by altitude level in a univariate ANOVA model

Variables	Comparison	Estimate (95% CI)	P value
Systolic BP	Altitude 2890 m versus 2800 m	-9.6 (-13.4 to -5.7)	<0.001
	Altitude 3270 m versus 2800 m	-1.4 (-7.1 to 4.3)	0.62
	Altitude 3620 m versus 2800 m	5.0 (-1.5 to 11.5)	0.13
Diastolic BP	Altitude 2890 m versus 2800 m	-2.9 (-5.4 to -0.5)	0.02
	Altitude 3270 m versus 2800 m	-2.9 (-6.6 to 0.7)	0.12
	Altitude 3620 m versus 2800 m	2.5 (-1.7 to 6.7)	0.24

In a multivariate model adjusting for potential confounders there was moderate evidence of a relationship between SBP and altitude (Table 5.24). Mean SBP (95% CI) increased by 11.3 mmHg (-0.1 to 22.7), P=0.05 for every 1000 m elevation. For the ANCOVA model as a whole, as anticipated, the potential confounding variables were associated with SBP, overall F (6,222) 10.3, P<0.001 with a RMSE of 17.9 and R-squared of 21.8% (adjusted R-squared of 19.7%). Older age and self-reported units of standard drinks of alcohol in the past 30 days were associated with higher mean SBP. Unexpectedly, higher self-reported salt intake was moderately associated with a lower mean SBP.

Table 5.24: Estimates of the mean systolic blood pressure for altitude in a multi–variate ANCOVA and associations for confounding variables

Variable and Comparison	Estimate (95% CI)	P value
Altitude (per 1000 m higher)	11.3 (-0.1 to 22.7)	0.05
Weight (per kg higher)	0.2 (-0.03 to 0.5)	0.08
Salt intake (per gram higher)	-0.4 (-0.8 to -0.1)	0.02
Age (per decade older)	5.0 (3.2 to 6.8)	<0.001
Sex (male compared to female)	2.6 (-2.7 to 7.9)	0.33
Alcohol intake (per standard drink higher)	0.03 (0.003 to 0.05)	0.005

For the data used in the adjusted model, data were missing for 76 participants for the confounding variables weight and self-reported salt intake. The mean SBP was higher in missing data points for confounding variable weight (129.2 mmHg compared to 121.8 mmHg) with a mean difference (95% CI) of 7.3 mmHg (-1.0 to 15.8), t -1.7, P=0.08. It was also higher in missing data points for self-reported salt intake (123.6 mmHg compared to 122.0 mmHg) with a mean difference (95% CI) of 1.6 mmHg (-4.1 to 7.4), t -0.5, P=0.57 when compared with fully observed data points.

Table 5.25 shows the estimates of the associations between DBP and altitude and other covariates. In the multivariate model adjusting for the potential confounders, the relationship between DBP and altitude was positive, albeit with wider confidence intervals. Mean (95% CI) DBP increased by 5.4 mmHg (-1.7 to 12.6) per 1000 m higher altitude. The ANCOVA model as a whole has F (6, 222) 4.85, P<0.001 with R-squared 11.6% (adjusted R-squared 9.2%) and a RMSE 11.2.

Interaction analyses in multivariate models adjusting for potential confounding variables showed that the differences in SBP and DBP between urban and rural participants per 1000 m elevation of altitude were statistically not significant; the difference was 19.6 mmHg (95% CI -4.4 to 43.7), P=0.11 for SBP; and 1.0 mmHg (95% CI -0.1 to 2.2), P=0.08 for DBP.

Table 5.25: Estimates of mean diastolic blood pressure for altitude in a multivariate ANCOVA and associations for confounding variables

Variable and Comparison	Estimate (95% CI)	P value
Altitude (per 1000 m higher)	5.4 (-1.7 to 12.6)	0.14
Weight (per kg higher)	0.2 (0.06 to 0.4)	0.007
Salt intake (per gram higher)	-0.1 (-0.4 to 0.1)	0.21
Age (per decade older)	1.3 (0.2 to 2.4)	0.02
Sex (male compared to female)	0.4 (-2.9 to 3.8)	0.79
Alcohol intake (per standard drink higher)	0.02 (0.002 to 0.03)	0.02

In the multivariate analysis, a greater number of standard drinks of alcohol in the past 30 days, older age, and higher body weight were associated with higher DBP. As for SBP, there were 76 participants missing full data for the multivariate ANCOVA analysis, particularly for confounding variables such as weight and self-reported salt intake. The mean DBP was higher in missing data points for confounding variable weight (88.6 mmHg compared to 85.0 mmHg) with a mean difference (95% CI) of 3.6 mmHg (-1.6 to 8.9), t -1.3, P=0.18. It was also higher in missing data points for self-reported salt intake (86.7 mmHg compared to 84.9 mmHg) with a mean difference of 1.8 mmHg (-1.9 to 5.3), t -0.9, P=0.35 when compared with fully observed data points.

In summary, multivariate ANCOVA models suggested moderate evidence of a relationship between SBP and altitude, and no evidence of a relationship between DBP and altitude, after adjustment for potential confounding variables. Variables associated with mean SBP were age and self-reported alcohol intake; and age, self-reported alcohol intake and body weight for mean DBP. Surprisingly, salt intake was associated with decreased mean SBP.

Nearly one-quarter of the study participants and two-thirds of hypertensives were diagnosed with HT for the first time.

The prevalence of HT (or being on anti-hypertensive medication) was higher at each altitude level, except at 2890 m, when compared with the national prevalence in Nepal. Overall, HA residents who were men, older, with high household income, living a modern lifestyle, and who were overweight or obese were significantly more likely to be hypertensive after adjusting for the potential confounders. Ethnicity categorised as Tibetan or Khas-Arya was not associated with HT (or being on anti-hypertensive medication).

5.3 Electrocardiography recordings

This section describes ECG recordings taken at each level of altitude. As described in detail in the methods section (Chapter 4, section 4.4.3), ECG recordings were reviewed by a cardiologist and categorized as abnormal, borderline or normal. ECG reports are described in these categories in relation to socio-demographic, lifestyle, and clinical characteristics. Logistic regression was used to estimate the association between an abnormal (or borderline abnormal) ECG and altitude in univariate and multivariate models.

5.3.1 Electrocardiographic analysis

Arrhythmias: Three participants had *isolated ectopic beats* on their 12-lead ECGs: one atrial, one junctional and one ventricular. Four participants had clear evidence of *pre-excitation* of the ventricles (Wolff-Parkinson-White syndrome). Four participants showed prolonged AV (atrioventricular) nodal conduction (first degree AV block) with PR intervals varying between 205 msec and 286 msec (normal up to 200 msec). One participant had left bundle branch block (LBBB) and six had right bundle branch block (RBBB) (three each complete and incomplete). Two participants, a man and a woman, had prolonged QT intervals: 470 msec and 490 msec.

Morphological abnormalities: Two participants had tall peaked P waves, suggesting right atrial hypertrophy. Three participants showed extreme axis deviation (arm lead electrode positions all verified as correct) with QRS axes between +185^o and +237^o suggesting possible congenital abnormalities and/or pulmonary hypertension. Twenty-six other participants showed right axis deviation (RAD), with QRS axes between 92^o and 143^o, of which two had right ventricular hypertrophy (RVH). Four others had left axis deviation (LAD), with QRS axes between -34^o and -85^o. No participant had Q waves to suggest past Q-wave MI. Thirteen had inverted T waves outside the accepted normal leads (III, aVR, V1); nine of these were of doubtful significance as they were in the antero-septal precordial leads V1to V4. Two had inverted T waves in inferior leads (II, III and aVF) and two in aVL alone. Seventeen participants met Sokolow-Lyon criteria for left ventricular hypertrophy (LVH), with the largest S in V1 or V2 plus the largest R in V5 or V6 greater than 3.5mV, but only one of these met the stricter definition of Romhilt and Estes (six points); three others were borderline (four points). Two additional participants had downsloping ST segments with no other cause but suggestive of hypertrophy, one with four points on the Romhilt-Estes scoring system but negative using Sokolow-Lyon criteria.

The key findings of ECG recordings are presented in Table 5.26.

Table 5.26: Key findings of electrocardiographic recordings

ECG recordings	**Mustang (N)* N= 243**	**Humla (N)* N=242**	**Total (N) N=485**
Arrhythmias			
Ectopics	0	3	3
Wolff-Parkinson-White	2	2	4
Atrioventricular block	4	0	4
Left bundle branch block	0	1	1
Right bundle branch block	5	1	6
Long QT	2	0	2
Morphological abnormalities			
Right atrial hypertrophy	0	2	2
Right ventricular hypertrophy	0	2	2
Extreme axis deviation	3	0	3
Right axis deviation	8	18	26
Left axis deviation	2	2	4
Inverted T wave	7	6	13
Left ventricular hypertrophy	13	4	17

*Participants could have more than one abnormalities

None of the participants showed a definite electrocardiographic evidence of CHD. Overall 27/485, 5.6% (95% CI 3.7 to 8.0), of the participants gave a self-report of a history of CHD confirmed by a medical doctor. The prevalence of CHD by sex was 17/212 (8.0%) in men and 10/273 (3.7%) in women, Chi-square (1 df) 4.3, P=0.04. Altogether 95/485, 19.6% (95% CI 16.1 to 23.4), of the participants had an abnormal (or borderline abnormal) ECG. The main categories of abnormality were: RAD in 26/485, 5.4% (95% CI 3.5 to 7.7); and LVH by voltage criteria in 17/485, 3.5% (95% CI 2 to 5.5). Of the 26 participants with

RAD, 16 (61.5%) were men and 13 (50%) were from the age group 30 to 39 years. Among 17 participants with LVH, 11 (64.7%) were women, 12 (70.6%) were aged 50 years or over, and 11 (70.6%) were hypertensive or on anti-hypertensive treatment.

Participants living in the Mustang district at altitudes of 2800 m, 3270 m and 3620 m mostly had abnormalities on the left side of the heart. Humla participants at 2890 m mostly had abnormalities on the right side of the heart. However, the differences in proportions were not statistically significant. For example, Mustang participants had 15/243 (6.2%) ECG findings of LVH, LAD, or LBBB compared to 7/242 (2.9%) Humla participants: proportion difference (95% CI), 3.3% (-0.39 to 6.9), P=0.08. In Humla, 21/242 (8.7%) ECG reports had RAD, RBBB, or right atrial hypertrophy compared to 13/243 (5.3%) in the Mustang participants: proportion difference (95% CI), 3.4% (-1.1 to 7.9), P=0.14.

Table 5.27 shows the proportion of abnormal (or borderline abnormal) ECGs by altitude level. More than a quarter of the participants at 3270 m and 3620 m had an abnormal (or borderline abnormal) ECG, almost twice as high as those living at 2800 m and 2890 m. The proportion of abnormal (or borderline abnormal) ECGs was similar for similar level altitudes: 2800 m and 2890 m. After adjustment for age and sex, the odds ratio (95% CI) for abnormal (or borderline abnormal) ECG at 2890 m compared to 2800 m was 1.38 (0.73 to 2.43), P=0.34. There was no association between the participants' lifestyle (urban versus rural) and probability for abnormal (or borderline abnormal) ECG, with an estimate of the age and sex adjusted odds ratio (95% CI) of 0.85 (0.52 to 1.34), P=0.49.

Table 5.27: Abnormal or borderline abnormal electrocardiogram by altitude

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variable	**N/N (%)**			
Abnormal or borderline ECG	42/242 (17.4)	22/139 (15.8)	18/60 (30.0)	13/44 (29.5)

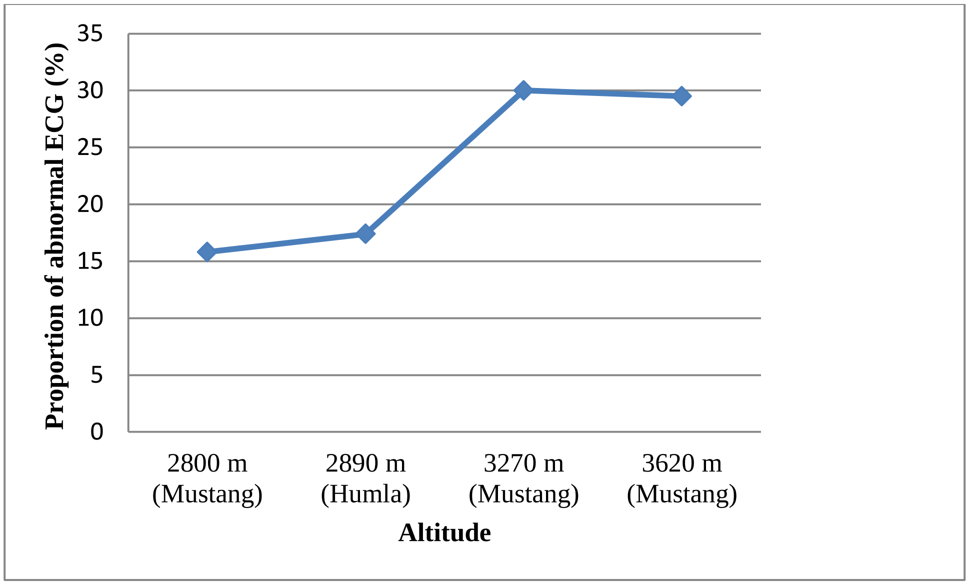

Figure 5.8: The line graph of abnormal or borderline abnormal electrocardiogram by altitude level

Figure 5.8 shows the line graph of the proportion of abnormal or borderline abnormal ECGs by altitude level. The proportions of abnormal (or borderline abnormal) ECGs by socio-economic and demographic characteristics at each altitude level are shown in Table 5.28. Participants in older age groups, men, and those with high self-reported household income, were more likely to have abnormal (or borderline abnormal) ECGs at all altitude levels. Among those with abnormal (or borderline abnormal) ECGs, there was no distinct pattern in self-reported types of occupation and completed levels of education by altitude levels. The sex adjusted odds ratio (95% CI) for abnormal or borderline abnormal ECG was 1.21 (1.02 to 1.44), P=0.02 per decade older age. Men had more than two-fold higher odds for presence of abnormal (or borderline) ECGs compared to women, age adjusted odds ratio (95% CI) of 2.10 (1.33 to 3.34), P=0.001. When compared with participants with self-reported annual household income of less than NRS 200,000, the age and sex adjusted odds ratio (95% CI) for abnormal (or borderline abnormal) ECGs was 0.78 (0.43 to 1.42), P=0.42 for those with annual household income of between NRS 200,000 and 400,000; and 1.08 (0.64 to 1.83), P=0.76 for those with greater than NRS 400,000.

Table 5.28: The proportion of abnormal or borderline abnormal electrocardiogram by socio-economic and demographic characteristics at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Abnormal ECG	**N=42**	**N=22**	**N=18**	**N=13**
Variables		**N/N (%)**		
Age group (years)				
30–39	16/100 (16.0)	3/40 (7.5)	1/6 (16.7)	6/16 (37.5)
40–49	11/68 (16.2)	4/33 (12.1)	5/16 (31.2)	2/10 (20.0)
50–59	12/49 (24.5)	7/29 (24.1)	3/14 (21.4)	2/6 (33.3)
≥60	3/25 (12.0)	8/22 (21.6)	9/24 (37.5)	3/12 (25.0)
Sex				
Male	25/99 (25.2)	11/65 (16.9)	10/29 (34.5)	10/19 (52.6)
Female	17/143 (11.9)	11/74 (14.9)	8/31 (25.8)	3/25 (12.0)
Education				
No formal education / illiterate	26/162 (16.0)	12/56 (21.4)	10/41 (24.4)	8/29 (27.6)
Less than primary level	1/18 (5.6)	5/39 (12.8)	8/18 (44.4)	1/6(16.7)
Primary level completed	3/19 (15.8)	1/21 (4.8)	0/0 (0)	2/4 (50.0)
Secondary level completed or more	12/43 (27.9)	4/23 (17.4)	0/1 (0)	2/5 (40.0)
Occupation				
Govt or non-govt employee	9/39 (23.1)	3/22 (13.6)	0/1 (0)	4/7 (57.1)
Self-employed	7/21 (33.3)	11/75 (14.7)	2/5 (40.0)	5/14 (35.7)
Agriculture/daily waged labour	20/129 (15.5)	5/30 (16.7)	10/39 (25.6)	3/21 (14.3)
Unemployed/retired/ homemaker	6/53 (11.3)	3/12 (25.0)	6/15 (40.0)	1/2 (50.0)
Household income (per year)				
<NRS 200,000	23/131 (17.6)	6/32 (18.7)	6/22 (27.3)	2/6 (33.3)
NRS 200,000 to 400,000	5/55 (9.1)	7/34 (20.6)	6/22 (27.3)	4/17 (23.5)

NRS >400,000	14/56 (25.0)	9/73 (12.3)	6/16 (37.5)	7/21 (33.3)
Marital Status				
Unmarried/divorced/ widowed	1/8 (12.5)	4/16 (25.0)	1/9 (11.1)	0/7 (0)
Currently married	41/234 (17.5)	18/123 (14.6)	17/51 (33.3)	13/37 (35.1)

•1 NZ $ = NRS 77 (as of 6th December 2016)

Table 5.29 shows the proportion of abnormal (or borderline abnormal) ECGs by ethnicity at each altitude level. Tibetan participants had a lower prevalence of abnormal (or borderline) ECGs at each level of altitude compared to Khas-Aryas. The age and sex adjusted odds ratio (95% CI) for abnormal (or borderline abnormal) ECG was 0.66 (0.40 to 1.08), P=0.10 for participants with Tibetan ethnicity compared to Khas-Aryas.

Table 5.29: The proportion of abnormal or borderline abnormal electrocardiogram by ethnicity at each altitude level

	Humla		**Mustang**		**Total**
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**	
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**	
Abnormal ECG	**N=42**	**N=22**	**N=18**	**N=13**	**N=95**
Variables			**N/N (%)**		
Tibetan	11/79 (13.9)	16/115 (13.9)	16/57 (28.1)	9/37 (24.3)	52/288 (18.1)
Khas-Arya	31/163 (19.0)	6/24 (25.0)	2/3 (66.7)	4/7 (57.1)	43/197 (21.8)

• Tibetan = Thakali and Tibetan Gurung in Mustang and Lama in Humla, Khas-Arya= Dalit, Brahmin and Chhetri in both Mustang and Humla.

As shown in Table 5.30, the proportions of abnormal (or borderline abnormal) ECGs were higher at 3270 m and 3620 m for most of the smoking and tobacco-related variables. Those reporting a habit of tobacco use or higher alcohol consumption in the past 30 days had a higher prevalence of abnormal (or borderline abnormal) ECGs.

Overall, the odds ratio adjusted for age and sex (95% CI) for abnormal (or borderline abnormal) ECG was 0.75 (0.43 to 1.34), P=0.34 for current smokers compared to non-smokers, and 0.77 (0.48 to 1.24), P=0.29 for current drinkers compared to non-drinkers.

Table 5.30: Abnormal or borderline abnormal electrocardiogram by self-reported tobacco and alcohol related characteristics at each altitude level

	Humla	**Mustang**		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**N/N (%)**			
Smoking status				
Current smoker	14/96 (14.6)	3/13 (23.1)	1/2 (50.0)	2/4 (50.0)
Past smoker	10/29 (34.5)	3/20 (15.0)	5/11 (45.4)	3/7 (42.9)
Current smokeless tobacco user	4/27 (14.8)	9/39 (23.1)	6/19 (31.6)	5/11 (45.4)
Past smokeless tobacco user	2/6 (33.3)	1/11 (9.1)	6/14 (42.9)	2/4 (50.0)
Alcohol status				
Current drinker	17/117 (14.5)	10/72 (13.9)	13/39 (33.3)	9/20 (45.0)
Ever a drinker	32/190 (16.8)	19/120 (15.8)	18/58 (31.0)	13/40 (32.5)
Hazardous drinker	4/22 (18.2)	4/21 (19.0)	10/22 (45.4)	6/8 (75.0)
	Mean (SD)			
Standard drink unit of alcohol in past 30 days	71.9 (116.7) N=17	99.0 (107.3) N=10	122.5 (62.2) N=13	98.8 (64.5) N=9

•Current drinker: participants who drank alcohol in the past 30 days •Hazardous drinker: participants drinking ≥21 (males) or ≥14 (females) standard drink units of alcohol per week

Participants with an abnormal (or borderline abnormal) ECG were physically less active and more sedentary than those with normal findings (data not shown). Table 5.31 describes self-reported physical activity among the participants with abnormal (or borderline abnormal) ECGs. There was no consistent trend by altitude level for vigorous and moderate physical activity and walk time, but participants with abnormal (or borderline abnormal) ECGs were more sedentary with increasing levels of altitude.

Table 5.31: Self-reported physical activity related characteristics among participants with abnormal (or borderline abnormal) electrocardiogram at each altitude level

	Humla	Mustang		
Altitude	**2890 m**	**2800 m**	**3270 m**	**3620 m**
	(Rural)	**(Urban)**	**(Rural)**	**(Urban)**
Variables	**Mean (SD)**			
Vigorous physical activity / week (hour)	38.7 (22.0) N=25	6.1 (9.6) N=22	3.3 (4.6) N=18	6.2 (15.4) N=13
Moderate physical activity / week (hour)	12.6 (8.0) N=30	15.3 (13.5) N=22	13.7 (12.0) N=18	11.8 (10.8) N=13
Walk time / day (min)	81.7 (50.9) N=42	40.7 (27.1) N=22	84.7 (105.6) N=18	61.5 (34.4) N=13
Sedentary time / day (hour)	2.9 (2.2) N=42	4.0 (2.0) N=22	4.6 (2.9) N=18	4.3 (1.9) N=13

•Vigorous physical activity: activity (like carrying heavy loads, digging) causing large increases in breathing or heart rate for at least 10 minutes continuously • Moderate physical activity: activity (such as brisk walking, cleaning, washing clothes by hand) causing small increases in breathing or heart rate

As shown in Figure 5.9, the proportion of abnormal or borderline abnormal ECGs consistently increased with increasing levels of altitude in overweight or obese participants and those with central obesity. The age and sex adjusted odds ratio (95% CI) for abnormal (or borderline abnormal) ECG was 3.08 (0.83 to 11.35), P=0.09, per 1000 m elevation among overweight or obese participants, and 4.3 (1.1 to 16.6), P=0.04 among centrally obese participants.

Figure 5.10 compares the proportions of HT, high TC/HDL ratio and diabetes among those with abnormal (or borderline abnormal) ECGs by altitude level. Among those with abnormal (or borderline abnormal) ECGs, the proportion of participants with HT or on medication was markedly high at all altitude levels except at 2890 m.

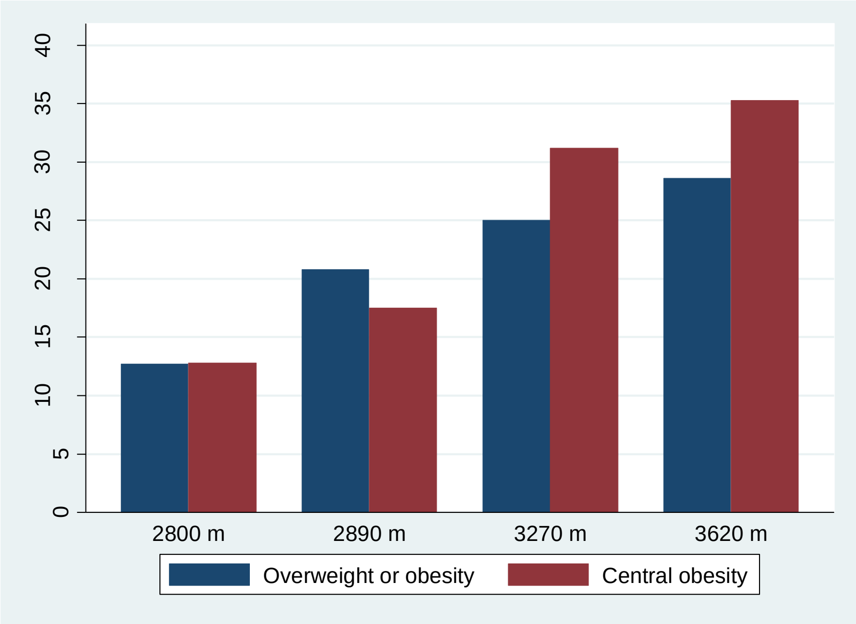

Figure 5.9: The proportions of abnormal or borderline abnormal electrocardiogram among the participants with overweight or obesity and central obesity

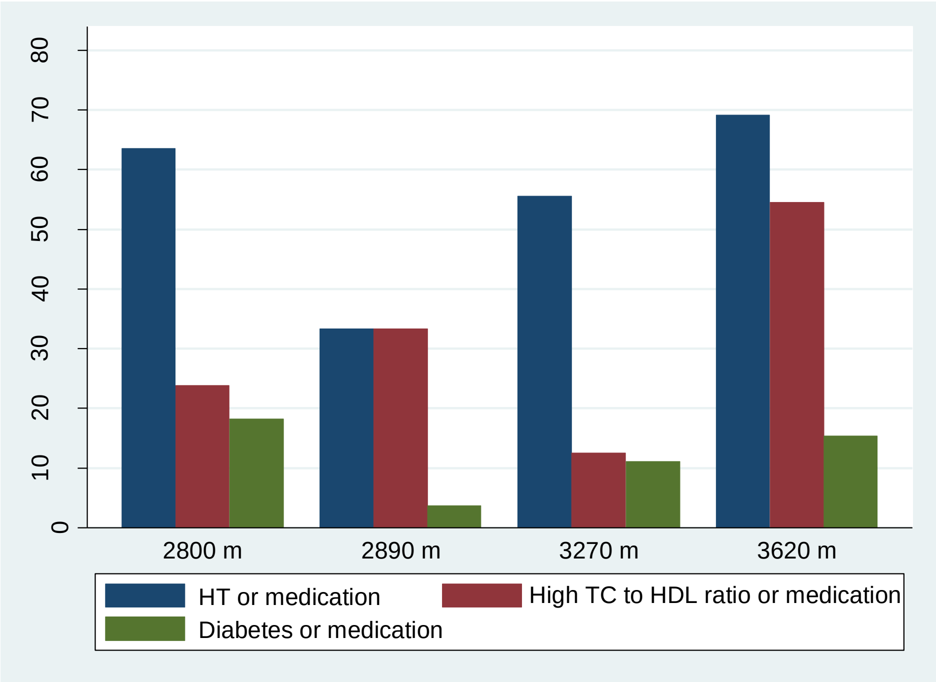

Figure 5.10: Comparison of hypertension, high TC/HDL ratio, and diabetes in participants with abnormal or borderline abnormal ECG by altitude level

BP, lipids and blood sugar levels among the participants with abnormal (or borderline abnormal) and normal ECGs are given in Table 5.32. Mean TC, TG, and HbA1c were higher and HDL levels lower among participants with abnormal (or borderline) ECGs compared to those with normal ECGs at every altitude level, with the exception of TC at 3270 m and TG at 2890 m.

Among those with an abnormal (or borderline abnormal) ECG there was no distinct ECG pattern by the levels of altitude. However, most of the abnormal values were measured at the highest altitude of 3620 m. Mean HDL cholesterol was lower than the abnormal cut-point of <1.3 mmol/L mostly for women. Women with low HDL had nearly three-fold higher odds for presence of abnormal or borderline abnormal ECG compared to women with normal HDL: age adjusted odds ratio (95% CI) of 2.83 (1.07 to 7.49), P=0.04.

Table 5.32: Blood pressure, lipids and blood sugar-related characteristics in participants with an abnormal (or borderline abnormal) and normal electrocardiogram by altitude level

	Humla		Mustang					
Altitude	**2890 m**		**2800 m**		**3270 m**		**3620 m**	
	(Rural)		**(Urban)**		**(Rural)**		**(Urban)**	
ECG status	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**	**Abnormal**	**Normal**
Variables	**Mean (SD)**							
Systolic BP (mmHg)	120.1(19.4)	116.5(18.1)	138.3(20.7)	123.2(17.5)	133.7 (22.4)	121.2(18.7)	146.1 (26.7)	125.5(19.5)
	N=42	N=200	N=22	N=117	N=18	N=42	N=13	N=31
Diastolic BP (mmHg)	86.3 (14.4)	83.2 (11.6)	91.2 (13.2)	85.1 (11.2)	87.1 (12.1)	82.3 (12.7)	98.1 (17.1)	85.5 (12.7)
	N=42	N=200	N=22	N=117	N=18	N=42	N=13	N=31
TC (mmol/L)	4.2 (1.2)	4.1 (0.9)	4.8 (0.8)	4.4 (0.9)	4.2 (0.7)	4.3 (0.9)	5.0 (1.4)	4.3 (0.9)
	N=25	N=137	N=22	N=116	N=16	N=39	N=12	N=26
TG (mmol/L)	1.6 (0.9)	1.7 (0.8)	2.2 (1.0)	1.9 (0.9)	1.8 (1.4)	1.4 (0.6)	2.6 (1.7)	2.2 (1.4)
	N=25	N=137	N=22	N=114	N=16	N=39	N=12	N=26
HDL men (mmol/L)	0.9 (0.1)	1.0 (0.3)	1.0 (0.4)	1.1 (0.6)	1.1 (0.2)	1.2 (0.2)	1.0 (0.3)	1.0 (0.2)
	N=14	N=42	N=11	N=51	N=10	N=15	N=10	N=7
HDL women (mmol/L)	1.0 (0.1)	1.0 (0.3)	1.0 (0.2)	1.2 (0.5)	1.0 (0.1)	1.4 (0.3)	1.1 (0.1)	1.3 (0.3)
	N=13	N=95	N=11	N=63	N=8	N=22	N=3	N=19
HbA1c (mmol/mol)	39.0 (4.9)	37.8 (4.9)	40.4 (12.4)	38.2 (10.0)	40.5 (6.9)	37.0 (4.3)	40.8 (10.5)	38.6 (8.0)
	N=27	N=138	N=22	N=115	N=18	N=42	N=13	N=31

5.3.2 Electrocardiographic abnormalities and altitude

Logistic regression models were used to estimate associations between the probability of an abnormal ECG and altitude. For these models altitude is treated as a continuous variable. There were four values of altitude (2800 m, 2890 m, 3270 m, and 3620 m). Both univariate and multivariate logistic regression models were used, firstly for the univariate association between ECG recordings and altitude, and secondly for the multivariate association adjusting for potential confounding variables. Systolic blood pressure, TC to HDL ratio, HbA1c, current smoking status, age and sex were considered potential confounders. The assumption of linearity between logarithm of the odds of abnormal (or borderline abnormal) ECG and explanatory variables were satisfactorily met.

In the univariate model there was a strong evidence of relationship between the probability of an abnormal (or borderline) ECGs and altitude: likelihood ratio (LR) Chi-square (1 df) 7.20, P=0.007. Table 5.33 shows the estimates of the odds ratio for an abnormal (or borderline abnormal) ECG by altitude.

Table 5.33: Estimates of the odds ratio for an abnormal or borderline abnormal electrocardiogram by altitude in a univariate logistic model

Variable	Odds ratio (95% CI)	P value
Altitude (per 1000 m higher)	3.16 (1.39 to 7.18)	0.006

There was also a moderate association between the probability of abnormal (or borderline abnormal) ECG and altitude when adjusted for potential confounding variables in a multivariate logistic model (Table 5.34). The odds ratio (95% CI) was 2.83 (1.07 to 7.45), P=0.03 per 1000 m elevation of altitude. The multivariate logistic model as a whole had LR Chi-square (7 df) 34.7, P<0.01. Among the confounding variables higher SBP was strongly associated with abnormal (or borderline abnormal) ECG.

Table 5.34: Estimates of the odds ratio for abnormal or borderline abnormal electrocardiogram by altitude in a multivariate logistic model and associations for confounding variables

Variables and Comparison	Odds ratio (95% CI)	P value
Altitude (per 1000 m higher)	2.83 (1.07 to 7.45)	0.03
Systolic blood pressure (per 10 mmHg higher)	1.25 (1.08 to 1.44)	0.002
TC to HDL ratio (per unit ratio higher)	0.93 (0.75 to 1.15)	0.49
HbA1c (per mmol/mol higher)	1.02 (0.99 to 1.05)	0.49
Smoke tobacco (yes compared to no)	1.69 (0.97 to 2.94)	0.06
Age (per decade older)	1.14 (0.91 to 1.43)	0.24
Sex (men compared to women)	1.69 (0.97 to 2.94)	0.06

The multivariate models had 99 missing data points for the confounding variables TC to HDL ratio and HbA1c. There were no statistically significant differences between ECG reports (abnormal or normal) and data status (missing or not missing): TC to HDL ratio, LR Chi-square (1 df) 1.05, P=0.31; HbA1c, LR Chi-square (1 df) 0.02, P=0.88.

A separate multivariate logistic model including the interaction term for the effect of sex on the association between altitude and the presence of abnormal (or borderline abnormal) ECG, adjusting for the potential confounding variables, showed a moderate evidence of effect modification by sex (P=0.04). The odds ratio (95% CI) was 7.92 (1.97 to 31.88), P=0.004 for men and 1.02 (0.24 to 4.29), P=0.98 for women for the presence of abnormal (or borderline) ECG, per 1000 m higher altitude. Another interaction analysis to examine the effect of residential settings (urban or rural) on the association between altitude and the probability of having abnormal ECG (or borderline abnormal) showed no significant association, the difference in odds ratio between urban and rural participants was 0.4 (95% CI -0.03 to 5.9) per 1000 m elevation of altitude, P=0.51.

In summary, none of the participants showed definite electrocardiographic evidence of CHD. However, logistic regression models suggest moderate evidence of an association between the probability of participants having an abnormal (or borderline abnormal) ECG and altitude. This association was particularly strong for men. Higher SBP was significantly associated with the presence of abnormal or borderline abnormal ECG.

The proportion of abnormal (or borderline abnormal) ECGs was almost twice as high at altitudes of 3270 m and 3620 m compared to 2800 m and 2890 m. RAD and LVH were the most common types of ECG abnormality. The proportion of participants with an abnormal (or borderline abnormal) ECG increased with increasing altitudes for participants who were overweight, obese, or had central obesity. Participants with an abnormal (or borderline abnormal) ECG were significantly more likely to be sedentary with increasing altitudes.

There was no statistically significant relationship between the types of lifestyle (urban or rural) and ethnicity (Tibetan or Khas-Arya) and the probability of having an abnormal (or borderline abnormal) ECG. Low HDL was associated with an abnormal (or borderline abnormal) ECG among women.

6 Discussion

This chapter first discusses the limitations of the present study and then concentrates on three key topic areas of this thesis i) cardiovascular disease (CVD) ii) blood pressure (BP), and iii) other CVD risk factors (lipid profile, diabetes and tobacco use). Where possible the results within these topic areas are compared with similar data from other high altitude (HA) areas of Nepal and other HA areas of the world, and with low altitude (LA) areas of Nepal and South Asia. Each section describes the main results in context, new findings, strengths and weaknesses, and areas for future research. Finally, overall conclusions are presented.

6.1 General limitations

A number of limitations relevant to the interpretation of the results are common across the three topic areas. These are: confounding and effect modification, lack of robust local administrative health datasets, the sampling process, reliance on self-report in an area of poor health literacy, that other literature uses cut-points for estimation of prevalence and incidence, and the cross-sectional design.

An important aspect of this thesis is whether there is a relationship between CVD, BP, and/or or other CVD risk factors, and increasing altitude of usual residence. Multiple potential confounding and effect modification factors could explain an apparent relationship between the three topic areas and altitude. These include ancestry, cultural-related lifestyle practices, socio-economic status, and residential settings (rural versus urban). As discussed in the literature review section, there are known differences in physiological responses to HA hypoxia and lifestyle practices (mainly the intake of dietary salt and alcohol, and use of tobacco) between those HA populations with Tibetan ancestry and other populations with a shorter history of living at HA, for example Khas-Aryas. The socio-economic status of the participants varied between different sampled areas included in the present study. Participants living in urban areas (2800 metre (m) and 3620 m) were relatively well off, but those in rural areas (2890 m and 3270 m) were poor. These differences are accounted for where relevant data were available, but clearly the potential inter-relationships between altitude of residence, ethnicity, socio-economic, and cultural factors are complex.

A lack of robust local administrative data sets means that key data that are usually available in more developed and wealthier countries, such as robust death certification, health surveys, accessible electronic or paper-based clinical records, and academic publications on important health conditions are not available for remote regions of Nepal. Therefore, it is difficult to triangulate the findings from the data gathered from this current study's pragmatic cross-sectional survey design with other forms of information. This means that any biases resulting from personal recollections of those surveyed, that is, recall bias, and the results of simple physical examination and testing, are difficult to assess.

The sampling process for this study had to be adapted to suit the available sampling frames and the logistical challenges of administering the research procedures in rural Nepal. As described in the methodology section, the sampling technique used was convenience-based cluster sampling. Although this technique meant that some observations may have been correlated within sampling units it was not feasible to weight this appropriately because of an absence of detailed knowledge of sampling frame factors such as socio-economic status, combined with the problem of sparsely populated areas. Furthermore, the study areas comprised both urban and rural settings, diverse ethnic populations and varying lifestyle practices, making it difficulties to use proper conventional weighting schemes in the analysis phase. The analysis strategy chosen assumed a simple random sample and this meant that the precision of estimates of associations might be too narrow. Due to the moderate sample size, there might be the possibility of type II error meaning that not rejecting the null associations when it should be.

The present study relied on participants 'self-report' to gather information about personal and family history of CVD and its risk factors, current and past medication, socio-demography, and lifestyle practices. The population surveyed had generally low health literacy based on a low level of overall education. At least 40% of participants at all altitude levels were illiterate or had no formal education. In addition, the self-reporting process could have led to various manifestations of information bias such as recall bias and social-desirability bias. This implies that there may be systematic discrepancies between self-report and actual behaviour, particularly for lifestyle practices such as smoking and alcohol intake due to under-reporting, which might also confound or bias the identified associations.

The literature review showed one limitation of the existing literature: that most publications defined CVD risk factors using dichotomous cut-off values, despite many CVD risk factors having a graded continuous relationship with actual risk. In order to compare the results of the current study with existing literature, these specific thresholds needed to be used, meaning an inevitable risk of loss of information, especially where values are closer to thresholds, and there are some discrepancies in threshold values between studies.

The cross-sectional design of the study also has other limitations with reference to inference about causality. One of these limitations is the uncertainty, already alluded to above with respect to recall bias, about when things occurred in relation to current reports. Odds ratios in the cross-sectional studies could be biased away from true measure of effect if prevalence is high. This could be relevant to the hypertension (HT) related odds ratios in this thesis. Another limitation is that individuals who could potentially have been part of the sampling frame may have moved away from the area or died after developing the conditions that were of interest, meaning that the sampling frame may only have contacted healthy individuals. This poses the risk of 'healthy survivor bias' or 'healthy individual effect' because, in the absence of quality health care, people with CVD, myocardial infarction (MI), or stroke might have moved to LA for treatment or died, so reported prevalence might not reflect true incidence. On the other hand, it is also likely that healthy young populations of study areas may have internally migrated to city areas or emigrated to other countries for job, education or for other reasons. Thus, this 'migration effect' could have missed eligible young and healthy individuals in the survey.

6.2 Cardiovascular disease

Main results in context

In the present study, none of the participants showed definite electrocardiographic evidence of coronary heart disease (CHD) as indicated by pathological Q wave infarction. However, 5.6% of the participants self-reported a personal history of CHD. Although few population-based studies have been done on CHD in HA populations living at 2500 m or more worldwide, the majority of available reports suggest a low incidence of MI in people living at HA (Ashouri et al., 1993; Alberto Hurtado, 1960; Ramos et al., 1967). These were all hospital-based studies, carried out and published a few decades ago. Nonetheless, this finding is consistent with a recent systematic analysis of the burden of disease in Chinese provinces reporting that the age-standardized mortality rate from CHD in men in Tibet, mean altitude of 4500 m above sea level, was significantly lower compared with those living at lower altitudes, although this difference was not seen in women (Zhou et al., 2016). Various biological (Cai et al., 2003; Ding et al., 2005; Essop, 2007; Sasaki et al., 2002; Semenza, 2006) and environmental-related (J. D. Anderson & Honigman, 2011; Burtscher, 2014) plausible explanations have been suggested for potential cardio-protection from living at HA.

The finding of a low prevalence of CHD in the present study, defined by the presence of pathological Q waves or self-report of a medical history of CHD, is similar to reports of CHD based on electrocardiogram (ECG) recordings or documented personal history at LA in Nepal of 5.7% (Vaidya et al., 2009). A systematic review of global studies of CHD prevalence (ECG recordings or documented personal history) in adults estimated the prevalence of CHD in Asia was 5.8%, between 5.6% and 5.9% in rural China, between 1.4% to 4.6% in rural areas of India, 3.4% in rural areas of Bangladesh, and 5.1% in urban Pakistan (Zhu, Wang, Zhu, Zhou, & Wang, 2015).

Caution should be taken when considering the CHD prevalence of the present study because it is based on self-report of personal history alone, as no participants had any objective evidence of CHD such as pathological Q waves on an ECG. Validity of the self-report of a medical history is questionable in both developed (Kehoe, Wu, Leske, &

Chylack, 1994) and developing (Vellakkal et al., 2013) countries. One study reported that for CHD the sensitivity of the self-report was low at 57% (Kehoe et al., 1994). In the context of the present study, there is an additional risk of inaccurate recall of personal history of CHD due to the poor literacy of the participants.

6.2.1 Major electrocardiographic abnormalities and patterns

In the present study, right axis deviation (RAD) was the most common ECG abnormality. This is a possible early indication of pulmonary HT or right ventricular hypertrophy (RVH). A large body of evidence also suggests RAD is the most common feature of HA residents, particularly among Andeans. A review reports that RAD could be up to four times higher in HA residents compared to sea-level residents (Windsor, Rodway, & Montgomery, 2010). A number of studies have reported a positive association between RAD and pulmonary artery pressure (Raynaud et al., 1981; Windsor et al., 2010). In the present study, pulmonary artery pressure was not measured; however, the prevalence of RAD was significantly higher in Humla participants (Khas-Aryas) compared to Mustang participants (Tibetan ancestry). Other studies also report higher prevalence of RAD in Andeans compared to Tibetan population samples (Jackson, 1975). Tibetan HA residents are known to be genetically adapted to the hypoxic pulmonary vasoconstriction (M. Gupta et al., 1992). In addition, morphological differences between these populations may be relevant to this difference, for example, the shorter stature of Tibetans compared to Khas-Aryas.

The present study identified that abnormal (or borderline abnormal) ECG recordings occurred on the left side of the heart amongst Tibetan-dominant areas (Mustang district), and on the right side among the Khas-Arya dominant area (Humla district). The ECG abnormalities suggesting right heart abnormalities may reflect increased pulmonary vascular resistance. Right-sided ECG abnormalities have previously been reported to occur more frequently among HA residents where the populations are likely to be less well adapted to hypoxia, such as Andeans or North Americans (Pryor et al., 1965; Rotta & Lopez, 1959), but with a lower prevalence in those with a high degree of adaptation, such as Tibetans (Groves et al., 1993). This phenomenon could apply to the findings of the present study. As discussed in the introduction chapter, contrasting cardiopulmonary responses to HA exposure have been reported among the largest HA populations: Tibetans, Andeans and Aymaras (Abdias Hurtado et al., 2012).

The prevalence of some ECG abnormalities in the present study was lower than in other studies of HA natives. For example, HA studies with ECG recordings frequently report a high prevalence of RVH and right bundle branch block (RBBB) in both Tibetan (Halperin et al., 1998) and Andean (Rotta & Lopez, 1959) HA populations. These occurred infrequently in the present study, with a prevalence of 0.4% for RVH and 1.2% for RBBB. However, this is similar to the findings of an Indian study of Tibetan-related participants (Kaushal et al., 1995). Studies reporting higher prevalence of RVH and RBBB were carried out at higher altitude levels than the present study. These higher altitudes may cause a greater decline in inspired oxygen level, leading to significant rise in pulmonary vascular resistance and resulting in greater strain on the right side of the heart.

A review of the English language literature in this thesis (Chapter 2, section 2.5) about the prevalence of ECG abnormalities identified no studies reporting an association of ECG abnormalities with altitude at different levels above 2500 m. Thus, it is difficult to compare the present study's finding of a moderate association between abnormal (or borderline abnormal) ECG and altitude with other studies. One study comparing RAD at different levels of HA in participants with a variety of ethnic backgrounds reported increasing deviation of frontal plane QRS with increasing levels of altitude (Raynaud et al., 1981).

6.2.2 Predictors of an abnormal (or borderline abnormal) electrocardiogram

In the present study, higher systolic blood pressure (SBP) was strongly associated with an increased probability of an abnormal (or borderline abnormal) ECG. There is a well-documented association between SBP and CVD (Banach et al., 2014; Lim et al., 2012; Prospective Studies Collaboration, 2002) so this association is unsurprising in the present study. High BP can also lead to left ventricular hypertrophy (LVH), which produces changes in the ECG that overlap with those caused by CHD. Among those with an abnormal (or borderline abnormal) ECG in the present study at least 50% at three altitude levels had HT or were on treatment for HT.

In the present study, there was a strong evidence of an association between altitude and the probability of having an abnormal (or borderline) ECG in men but not in women after controlling for confounding factors such as SBP, smoking tobacco, total cholesterol (TC) to high-density lipoprotein-cholesterol (HDL) ratio, glycated hemoglobin (HbA1c), and age. HA men may also have more of some other confounding factors that were not measured in the present study.

6.2.3 Other important observations

Consistent with well-established evidence of the association between obesity and CVD (Hubert et al., 1983; Kramer et al., 2013), in the present study obese and centrally obese participants were significantly more likely to have an abnormal (or borderline abnormal) ECG compared to those whose body mass index (BMI) and waist circumference (WC) were in the normal range. Furthermore, the proportion of abnormal (or borderline abnormal) ECGs in obese and centrally obese participants consistently increased with increasing altitude levels. Living at HA may exacerbate lifestyle-related risk such as high alcohol intake and sedentary behaviour due to cold temperatures and physical hardship (Littman, 1970; Schinder & Ruder, 1989).

6.2.4 Cerebrovascular disease

The present study found a positive stroke history, or stroke symptoms by positive self-report for at least one criterion of the Questionnaire for Verifying Stroke Free Status (QVSFS), among 6.7% of the participants. The QVSFS was chosen to investigate stroke-related risk because it is a widely accepted validated tool and is appropriate in settings like the present study where neuroimaging facilities are not available. In the present study 2.1% of participants self-reported that a physician had previously diagnosed them as having had a stroke. This is significantly higher than reported in most other studies carried out in LA residents using QVSFS (Fitzpatrick et al., 2012) or other prevalence estimates in South Asia (Dhamija & Dhamija, 1998). No previous studies carried out in HA populations have reported using the QVSFS. However, the high prevalence of self-reported stroke is consistent with past studies in Tibetans that have identified a disproportionately higher prevalence of HT and stroke compared to LA residents (G. Xu et al., 2013; Zhou et al., 2016). A significant proportion of the present study's participants had Tibetan ancestry and/or follow similar lifestyle and cultural practices as Tibetans. The apparently high prevalence of self-reported history of stroke may be related to the high prevalence of HT, which is a potent risk factor for all types of stroke (O'Donnell et al., 2010).

Accuracy of self-reported medical history of stroke is contestable even in developed countries (Cristina, Williams, Parkinson, Sibbritt, & Byles, 2016). With the poor literacy rate of the participants in the present study and possible lack of capability to understand the complex nature of stroke, misclassification and recall biases are possible.

Although a positive history of stroke was relatively high in the present study compared to most available studies at LA, the prevalence of positive stroke symptoms was lower than in LA studies using QVSFS (Farah et al., 2015; Fitzpatrick et al., 2012; V. J. Howard et al., 2006) or another stroke questionnaire (Toole et al., 1996). One possible reason may be the lower minimum age for participation in the present study (30 years or over), which in other studies was usually 40 years or over.

6.2.5 New findings

This is the first study to report the prevalence of CHD (based on ECG or self-report) and history of stroke or suggestive symptoms in HA residents of Nepal. While the prevalence of CHD in the present study was comparable to that of LA residents in Nepal, South Asia or China, the prevalence of a stroke history was higher than in most of the available studies in LA populations.

6.2.6 Strengths and weaknesses

The present study estimates prevalence of CHD (based on ECG or self-report) and a history of stroke and stroke symptoms in HA areas of Nepal where ECG and neuroimaging facilities are not routinely available. The use of ECG is a well-validated method of assessing the prevalence of CHD at a population level because of the strong prognostic value of major ECG findings on CVD and CHD mortality (De Bacquer, De Backer, Kornitzer, & Blackburn, 1998). This is also the first study in Nepal that administered the QVSFS. This may encourage other researchers to use that instrument for population-based screening and for clinicians working in rural settings to identify patients with the risk of stroke. Self-report of one or more positive symptoms from the QVSFS was significantly associated with the hazard ratio of 1.36 (95% confidence interval (CI) 1.08 to 1.72) for future incidence of stroke (Kleindorfer et al., 2011).

Very few population-based studies have been done on CVD prevalence in HA (≥2500 m) areas worldwide and in LA areas in Nepal in particular with which to compare data in the present study. We could not measure pulmonary artery pressure either directly or indirectly (e.g., by echocardiography) or hematocrit level, which could also explain the findings about the prevalence of CHD and stroke. All ECG reports were examined by one cardiologist, which may introduce bias, although interpretation was standard. Study participants were exposed to in-door air pollution to some extent, for example by using solid biomass fuels for cooking or heating purpose. Although improved cook-stoves (which significantly minimize in-door air pollution) is common in the study areas, they still use wood or coal inside the house for heating purpose. We could not assess the impact of in-door air pollution on CVD. In-door air pollution may increase the risk of pulmonary HT, right heart failure (Bloomfield et al., 2012) and can trigger CVD related mortality and non-fatal events (Brook et al., 2010). Stroke-like symptoms may arise from other conditions, for example migraine, seizure, cataract, and further examinations to rule out any other possibilities were not possible. In addition, the QVSFS has been reported to have high sensitivity but a moderate level of specificity (Jones et al., 2001). One possible confounding factor of 'healthy individual effect' as discussed in the general limitations section above (6.1) may be underestimating the reported prevalence of CHD and history and symptoms of stroke.

6.2.7 Areas for future research

The findings of the present study indicate a relatively higher risk of stroke at HA but CHD prevalence appears comparable to that in LA areas. A greater risk of stroke and related morbidities at HA is reported in several studies, particularly in Tibetan-related populations (G. Xu et al., 2013; H.-T. Zhang et al., 2015). However, such evidence for HA residents of other ethnicities is sparse, for example in the Andeans of South America, Amharics of Ethiopia, and Khas-Aryas of Nepal. Although the majority of past published work has findings consistent with a protective effect on CHD from permanent living at HA, there are few studies on comparable populations living at HA and LA. More research on the relationship between HA, ethnicity and CVD may clarify relationships and potential for interventions.

6.3 Blood pressure

Main results in context

The present study found a moderate association between SBP and altitude. Although point estimate for the association between diastolic blood pressure (DBP) with increasing altitude levels was consistent with a positive association, confidence interval for the estimate of association was wide. This study did not identify any association between HT (or use of anti-hypertensive medication) and ethnicity; however, those with Tibetan ancestry had a higher prevalence than Khas-Aryas. In multivariate models older age, increased body weight, and increased self-reported alcohol intake amount were associated with increased SBP and DBP. This study found an unexpected and inverse association between self-reported salt intake and SBP after adjusting for potential confounding variables.

A systematic review and meta-analysis developed from this thesis (Chapter 3, section 3.1) and published in a peer-reviewed journal reported a weak association between SBP, DBP and altitude in populations of Tibetan origin but in non-Tibetan populations both SBP and DBP tended to decrease with residence at higher altitude, although there were wide confidence intervals (N. Aryal, Weatherall, Bhatta, & Mann, 2016). Another systematic review including studies conducted in Tibet reported a 2% increment in the prevalence of HT for every 100 m increment in altitude (Mingji et al., 2015). These findings are consistent with findings in the present study where, although participants were from both Tibetan and Khas-Arya ethnicities, the geographical location of the study districts border on the Tibetan side of China and Khas-Aryas have consequently acquired Tibetan lifestyle practices, mainly drinking tea made with salty butter and high amounts of alcohol. This may well contribute to the association between SBP and altitude regardless of ethnicity. Nonetheless, the association between altitude and BP was found even after controlling for alcohol and salt intake, which may indicate that the HA environment itself is an additional independent factor in determining the high prevalence of HT although there may also be an underlying genetic risk (Gesang et al., 2002; Kumar et al., 2003).

Although the present study's finding of multivariate adjusted associations between BP and age, alcohol intake, and body weight is consistent with past research the inverse relationship between self-reported daily salt consumption and SBP is not (Elliott et al., 1996; Rose et al., 1988). High consumption of salt as a traditional dietary habit has been identified as one of the key factors for high BP in HA Tibetan populations (Sehgal et al., 1968; Sun, 1986). In addition, a randomized controlled trial of a low-sodium/high-potassium salt substitute showed a dramatic decline in BP among Tibetan HA populations (X. Zhao et al., 2014). The method used in the present study of self-report to calculate salt consumption may not have been an accurate reflection of actual salt consumption. Participants were asked about the mean amount of salt consumed by their family in a month, which was then divided by the number of family members sharing the kitchen for the main meal to estimate individual salt intake. This could have systematically led to underestimation of salt intake in those with the highest salt intake.

The prevalence of HT (or those on anti-hypertensive medication) in participants in the present study is higher than in other studies carried out in HA populations in Nepal using a similar definition (Koju et al., 2015; S. Shrestha et al., 2012; Smith, 1999). Two possible explanations for this difference are the different ages of the study samples and a cohort effect. The minimum age to participate in the present study was 30 years, whereas other studies usually included participants from the age of 18 years or over. HT may be increasing in prevalence with the passage of time for reasons other than ethnicity or altitude. However, in the present study, the prevalence of HT (or those on anti-hypertensive medication) in the Mustang district (Tibetans), is close to that reported in HA studies carried out on Tibetans living in Tibet or in India (Tripathy & Gupta, 2007; X. Zhao et al., 2012; X. Zheng et al., 2012). In the present study the prevalence of HT (or being on anti-hypertensive medication) in Mustang was higher than the national prevalence for the population aged 30 years or over (36.8%) (K. K. Aryal et al., 2014), but was lower in the Humla district with its dominant Khas-Arya population.

In the present study the prevalence of raised BP was high, but actual diagnosis and treatment of HT was very poor. Nearly two-thirds of participants who had raised BP were diagnosed with HT for the first time during the study. This highlights a huge unmet need for HT identification and management in these study areas. Only 3.3% of the study participants were on anti-hypertensive medication. This is substantially fewer compared to other HA settings where the prevalence of treatment is reported to be between 24.3% (X. Zheng et al., 2012) and 59.1% (Sherpa et al., 2013) in other parts of Tibet. A combination of factors such as lack of education and awareness and poor access to health care services in HA settings may contribute to this situation of undiagnosed and untreated HT.

6.3.1 New findings

This is the first study to report the relationship between BP and altitude at four different altitude levels above or equal to 2500 m. The present study also found that the non-Tibetan HA population of study areas has acquired Tibetan lifestyle habits (mainly high consumption of salty butter tea and alcohol), which may increase the risk of HT in the future.

6.3.2 Strengths and weaknesses

The main strength of the present study for the relationship between BP and HA is that information was collected at different altitude levels and from ethnically diverse samples. In an attempt to minimise BP measurement bias, recordings were carried out three times for each participant, a minimum of 10 minutes apart and the mean was used as the final reported BP. Also, if readings differed by more than 10 units, a fourth reading was taken and the lowest three readings were considered as the final mean. An electronic aneroid sphygmomanometer (Omron HEM-7221) well validated to operate at HA was used.

Weaknesses include that possible factors associated with BP were measured by self-report for alcohol intake, smoking status, salt intake, and current treatment for HT. Under-reporting of alcohol use in population surveys is very common because of such factors as social-desirability bias (Davis, Thake, & Vilhena, 2010) and recall bias (Stockwell et al., 2004). Similarly, there is good evidence that dietary salt intake by self-report is under-estimated compared to when using more objective measures (De Keyzer et al., 2015). Also, in the present study information on the amount of salt consumed during home cooking was requested and other sources such as salt included in processed foods was not taken into account. Although home cooking contributes to around two-thirds of total dietary salt in Asian settings (C. A. Anderson et al., 2010), the given estimates could be still under-reported. As mentioned above (6.2.6), study participants were likely to get exposed with in-door pollution and there is increasing evidence that chronic exposure to in-door air pollution is associated with higher BP (M.-S. Lee et al., 2012; Painschab et al., 2013). The present study could not examine this relationship.

6.3.3 Areas for future research

There is very limited research about BP among the non-Tibetan HA populations in Nepal. More data and analysis of these populations will help to better understand the HA and BP relationship. Comparisons of HA populations with homogeneous counterparts who later migrated to LA may also provide important insights into this relationship. The established association between salt intake and BP in general and known evidence of high intake of salt by some HA populations warrants further investigation. In HA settings of Nepal, no studies have collected information on salt intake by measuring urinary sodium excretion levels, which would yield the most definitive data. Recent findings suggest that a single fasting urine test with some correction (using the Kawasaki formula) is a valid method of measuring sodium excretion at a population level (Han et al., 2015). This could be a simple and reliable method to adopt in HA settings. Also, low-sodium/high-potassium salt substitute intervention, which was proved to be effective in reducing BP in other HA settings (X. Zhao et al., 2014), could also be tested in HA populations of Nepal. Finally, more exploration is required into the reasons behind the extremely high proportion of undiagnosed and untreated hypertensive populations in HA areas of Nepal.

6.4 Other cardiovascular disease risk factors

This section discusses the results of three key Framingham risk factors for CVD: lipid profile, diabetes, and tobacco use; and risk prediction for major cardiovascular events. Of other Framingham risk factors, BP has been discussed above and age has been discussed throughout the chapter.

6.4.1 Lipid Profile

Main results in context

In the present study, the prevalence of high TC and low HDL are lower, but the prevalence of raised triglyceride (TG) is higher when compared with the national prevalence in Nepal for the population aged greater than or equal to 30 years (K. K. Aryal et al., 2014). There were no consistent trends in lipid components in relation to altitude and ethnicity. In other studies of lipids in HA settings, TC and TG are usually lower than the present study, and HDL higher.

In particular, other HA studies report markedly higher prevalence of high TC (≥200 mg/dL or ≥5.2 mmol/L) compared to the present study (Málaga et al., 2010; Mohanna et al., 2006; Sherpa et al., 2011). Only one study in Nepal reported TC in a HA setting and identified a prevalence of high TC of 14.1% in study participants aged 15 years or older living in mountainous areas (K. K. Aryal et al., 2015). This is consistent with the present study's overall prevalence of elevated TC of 17.3%. The expectation was that the prevalence of TC would be high in those with Tibetan ancestry because of traditional diets with large amounts of oil, butter and meat products (Stevens, 1996). There is strong evidence that plasma TC level is highly genetically dependent and heritability is estimated to be around 40% to 60% (Y. Lu et al., 2010). This may partly explain the reason for the relatively low prevalence of a high TC in the present study compared to other most HA studies.

The present study's high TC prevalence is slightly lower compared to the studies carried out in LA areas of other South Asian countries using similar definitions (Guptha et al., 2014; Kinra et al., 2010). This may be because of the hypoxia and cold temperature-induced increments in plasma catecholamines (Moncloa, Gómez, & Hurtado, 1965) and subsequent metabolic effects on lipolysis (Okuda, Yanagi, & Fujii, 1966). The present study also identified a higher prevalence of a high TG level compared with other LA populations. This is likely to be related to high consumption of alcohol and carbohydrates (Klop et al., 2013; Parks, 2001). In addition, alteration in hepatic lipid oxidation in hypoxia induced by HA may also increase TG levels (Muratsubaki et al., 2003).

In the present study more than half of the men and two-thirds of women had low HDL. This finding, despite being higher than the results from other HA settings (Baracco et al., 2007; Mohanna et al., 2006; Sherpa et al., 2011; Sherpa et al., 2013), is lower than the national prevalence in Nepal for the population aged 30 years or over (K. K. Aryal et al., 2014) and closer to the studies conducted in LA areas of South Asia (N. Aryal & Wasti). Nearly half of the participants in the present study were current drinkers of alcohol and studies report a positive association between alcohol intake and HDL (Sung, Kim, & Reaven, 2007; Wakabayashi & Araki, 2010). The apparently low HDL in the present study compared to that in Nepal may be confounded by alcohol intake. There is also strong evidence of low HDL in South Asians (Karthikeyan et al., 2009; L. Zhang et al., 2010). Factors such as a low level of physical activity, low consumption of fruit and vegetables, other dietary habits (Joshi et al., 2007), and genetic predisposition (Dodani, Dong, Zhu, & George, 2008) are possible contributory factors to the high prevalence of low HDL in South Asian populations.

Although most of the South American HA studies report a slightly higher prevalence of high TG and lower prevalence of low HDL compared to the present study (Baracco et al., 2007; Gonzales & Tapia, 2013; Málaga et al., 2010; Mohanna et al., 2006), Tibetan studies show a markedly lower prevalence of high TG and low HDL (Sherpa et al., 2011; Sherpa et al., 2013). The known ethnic differences in lipid components (Anand et al., 2000; Chandalia, Mohan, Adams-Huet, Deepa, & Abate, 2008) may be the reason for the differences seen in different HA populations.

Urban dwellers (2800 m and 3620 m) have higher levels of TC and TG compared to rural dwellers (2890 m and 3270 m) even in similar ethnic populations. This suggests lifestyle practices are more important in determining lipid component levels than altitude and ethnicity. Previous studies in Tibet also indicate desirable patterns of plasma lipid components in rural residents (Sherpa et al., 2013) compared to the urban population (Sherpa et al., 2011).

6.4.1.1 New findings

This is the first study to report the prevalence of abnormal lipid components of Nepalese people living at different levels of HA. Just one previous study reported TC levels in mountainous regions but without specifying particular altitudes (K. K. Aryal et al., 2015). The present study found a low prevalence of high TC at HA compared to other reports both at HA and in South Asian LA populations.

6.4.1.2 Strengths and weaknesses

The main strength of this study with respect to lipid profile measurement was the use of a robust measurement system at HA. Quality control testing, as per the manufacturing company's instructions, was carried out. An instrument failure at 2890 m reduced the sample size and precision of mean measurements in this group. This survey used non-fasting blood samples for determination of a lipid profile. Fasting is not routinely recommended for lipid profile test. However, evidence shows a minor increase in TG levels after habitual meal, although clinically not significant (Nordestgaard et al., 2016). The present study might have over-reported TG levels in some participants with lipid profile measurements after meal.

6.4.1.3 Areas for future research

A low prevalence of raised TC levels in the present study compared to other HA areas warrants further research in other HA populations in Nepal. More data are needed from diverse ethnic groups. The major HA populations of Nepal are of Tibetan ancestry with traditional dietary habits of consuming high amounts of oil, butter, cheese, and meat products and these may raise TC levels. Detail information on use of these dietary components may help to assess this relationship. This study has also corroborated previous reports of high TG levels in HA population. Further research could focus on effective intervention to reduce TG levels and concomitant metabolic risk in HA populations.

Little research has been published on the specific impact of HA on lipid components. For example, an association has been reported between vitamin D levels and favourable lipid profiles (Challoumas, 2014). HA populations have a high level of vitamin D because of high ultraviolet B (UVB) light exposure (J. D. Anderson & Honigman, 2011). Some studies also report a positive association between hemoglobin and lipid components at HA (Gonzales & Tapia, 2013) and LA (Kawamoto et al., 2011). Since some HA populations, particularly those with a short ancestral history of living at HA, have high hemoglobin levels, this relationship may be worth assessing further to explore whether hemoglobin level *per se* is the determinant of abnormal lipid components in HA population.

6.4.2 Diabetes

Main results in context

There was no consistent pattern of blood glucose levels or prevalence of diabetes in relation to altitude and ethnicity in the present study. However, the prevalence of diabetes was higher in urban areas (2800 m and 3620 m) than in rural areas (2890 m and 3270 m). The prevalence of pre-diabetes was high in rural areas. Diabetes was more likely in men than in women but this difference was not statistically significant at any altitude level.

In the present study the prevalence of diabetes was 3.3% (3270 m) and 3.5% (2890 m) in rural settings, and 10.6% (2800 m) and 13.6% (3620 m) in urban settings. This is higher than past estimates for the Nepalese population, particularly those in rural areas (Gyawali et al., 2015; International Diabetes Federation, 2015), and also higher than that reported in mountainous regions of Nepal (K. K. Aryal et al., 2015). Although differences in definitions and the inclusion of only participants aged 30 years or over may partly explain the difference when compared with other estimates, the increasing risk of diabetes in HA populations in the present study was unsurprisingly accompanied by a higher rate of pre-diabetes. The prevalence of pre-diabetes was higher than the national estimate of 10.3% (Gyawali et al., 2015) at all altitude levels in the present study, particularly so in rural settings (2890 m and 3270 m) where at least one-third of the participants were pre-diabetics.

There may be both physiological and environmental reasons for the high prevalence of diabetes and pre-diabetes in rural populations in the present study compared to the national estimates for rural populations in Nepal. While moderate drinking has been found to have protective effects on blood glucose levels, evidence is strong on the relationship between heavy drinking and the risk of diabetes (Baliunas et al., 2009; A. A. Howard, Arnsten, & Gourevitch, 2004). A significant proportion of rural dwellers in the present study were hazardous drinkers (men drinking ≥21 standard drinking unit (SDU) and women drinking ≥14 SDU of alcohol per week); for example, 56.4% participants at 3270 m were hazardous drinkers. This may account for the very high prevalence of pre-diabetes in rural dwellers in the present study.

The present study's findings on diabetes prevalence in urban HA areas (2800 m and 3620 m) is higher than the reports from other urban HA settings (W. Chen et al., 2011; López de Guimaraes, Chiriboga García, Gonzáles Crisóstomo, & Vega Mejía, 2007; Okumiya et al., 2016; Schargrodsky et al., 2008). However, there is significant variability in the prevalence of diabetes in other rural HA settings (Málaga et al., 2010; Negi et al., 2012; Ojeda et al., 2014; Okumiya et al., 2016). The higher prevalence of diabetes in the urban HA areas in the present study compared to other HA settings may be due to high economic status and obesity. Urban areas studied are popular tourist destinations, for both religious and adventure travelling, and local people are mostly self-employed, mainly in shops and hospitality-related jobs. Thakali is the particular dominant Tibetan-related ethnic group in these areas and this group has the highest human development index (HDI) in Nepal (Government of Nepal & United Nations Development Programme, 2014). A positive association between income level and risk of diabetes is well established in the South Asian setting (Deepa, Anjana, Manjula, Narayan, & Mohan, 2011). In the present study urban participants had a considerably higher prevalence of overweight or obesity, 56.6% at 2800 m and 47.7% at 3620 m. Obesity is the most significant risk associated with type 2 diabetes (Field et al., 2001), which is mediated by insulin resistance (Boden & Chen, 1995). One study in Eastern Nepal reported higher BMI, urban residency, and high socio-economic status as the risk factors for diabetes (Mehta et al., 2011), which seems to apply in the present study as well.

The finding of a higher prevalence of diabetes in men compared to women is similar to most studies carried out in other HA settings (W. Chen et al., 2011; Gonzales & Tapia, 2013; S. Xu et al., 2015). This trend is observed worldwide as well. According to a recent estimate, in 2014, the prevalence of diabetes in men was 9% compared to 7.9% in women (NCD Risk Factor Collaboration, 2016). Although the prominent risk factor of obesity is more prevalent in women than in men globally, differences in biology, culture, nutritional uptake, lifestyle habits and environmental factors are likely to contribute to the higher risk of diabetes in men (Kautzky-Willer, Harreiter, & Pacini, 2016).

In the present study 44% of diabetics were newly diagnosed, which is close to the global rate of 46.5% for undiagnosed diabetes in adults (International Diabetes Federation, 2015).

However, this prevalence of undiagnosed diabetes is far lower than the International Diabetes Federation (IDF) estimates of 62.1% in both urban and rural areas of Nepal (International Diabetes Federation, 2015). This may be partly due to the easily available self-monitoring blood glucose testing devices and purchasing capacity of study participants, particularly those located in urban areas.

6.4.2.1 New findings

This is the first study in Nepal to report the prevalence of diabetes in HA areas of Nepal at specified levels of altitude. One previous study reported on diabetes prevalence in mountainous regions without mentioning the altitude levels (K. K. Aryal et al., 2015) and it is likely that it included study areas located at less than 2500 m.

Although the existing literature from HA populations has usually reported a lower prevalence of diabetes compared to the general population, this study is one of the very few which has found a higher prevalence in HA urban populations.

6.4.2.2 Strengths and weaknesses

The present study measured HbA1c levels using technology that is validated to perform well at HA. Quality control guidelines were strictly followed to ensure accuracy. Lipid profiles and HbA1c were measured using the same instrument and as mentioned in the lipid profile section, the machine had technical problems at 2890 m, which may minimize the precision of estimates for this group because of the reduced sample size.

6.4.2.3 Areas for future research

More evidence on the risk of diabetes and its risk factors among different ethnic HA populations in Nepal and at different levels of altitude may lead to appropriate health interventions. Particularly, future research should prioritize the role of alcohol and other lifestyle habits play in diabetes risk in Nepalese HA populations. This is equally important in HA residents of other countries. Recently some evidence has emerged of a strong association between polycythemia and glucose intolerance (Okumiya et al., 2016). Some HA populations, particularly those who are ancestrally less adapted to HA environments, tend to have high levels of erythrocytes or hemoglobin (Beall, 2007). The present study did not measure these and exploring these relationships may contribute to the current small amount of evidence on hemoglobin-blood glucose association in HA populations.

6.4.3 Tobacco use

The present study found that the patterns of tobacco use varied with ethnicity rather than with altitude and residential settings (urban or rural). Compared with the national prevalence, the Mustang district with predominantly Tibetan populations (2800 m, 3270 m, and 3620 m) had a significantly lower prevalence of current smokers. The prevalence was higher in the Humla district (2890 m) where the majority were of Khas-Arya ethnicity. This pattern was reversed for current smokeless tobacco users. Men were more likely to be both smokers and smokeless tobacco users.

In the present study, between 3.3% and 10.3% of the participants self-reported being current smokers in three different altitudes of Tibetan-dominant Mustang but this rate was markedly higher (38.6%) in Khas-Aryas who dominated in the Humla district. A low prevalence of current smokers among Tibetan-related populations in the present study compared to nationally (K. K. Aryal et al., 2014) and South East Asia region (World Health Organization, 2014b) may be attributed to the influence of cultural norms and practices. Unlike alcohol use, the preference for smoking is lower in traditional Tibetan culture. This tendency has also been observed among residents of the Appalachian Mountains in the US (Meyer et al., 2008). Other studies carried out in Tibetan (Sherpa et al., 2013; Sherpa et al., 2010) and Andean HA populations (Gonzales & Tapia, 2013; Jaillard et al., 1995) also report a low prevalence of smoking.

There was a much higher rate of current smoking among dominant Khas-Arya populations in Humla in both genders than nationally (K. K. Aryal et al., 2014) and regionally (World Health Organization, 2014b). In this population at 2890 m, 49.5% men and 31.1% women self-reported current smoking with the vast majority being daily smokers. The main reason for this high prevalence may be the familial and societal acceptance of tobacco smoking as most of them recalled being inspired to smoke by senior family members or peers. In addition, locally made and cheaply available *bidis* (unprocessed tobacco wrapped in leaves) are also popular in villages. A high rate of smoking has been reported in a few other South Asian HA populations as well (Shah, Arif, et al., 2001). Lack of tobacco control initiatives and poor awareness levels of smoking related risks could also be reasons for higher rates of tobacco smoking in the Nepalese rural population. One recent study among women in a LA rural area of Nepal reported a 43.6% prevalence of being a current smoker (Khatri et al., 2015).

Cultural influences on tobacco use are reflected in the prevalence of the use of smokeless tobacco as well. While smoked tobacco is not preferred behaviour in Tibetan culture, use of smokeless tobacco is very common. Nose-snuffing of ground tobacco leaves is the most popular form of smokeless tobacco use in traditional Tibetan practice. Other common forms of smokeless tobacco are commercially or non-commercially manufactured chewing tobacco. In the present study, between 25% and 31.1% of participants from the Tibetan-dominant Mustang district self-reported being current smokeless tobacco users, whereas the rate was just 10.9% for Khas-Aryas who dominate in the Humla district. The prevalence of current users of smokeless tobacco in Mustang (Tibetans) was slightly higher than the national prevalence of 23.2% (men 39.1% and women 7.7%) for the age group 30 years or over (K. K. Aryal et al., 2014).

The present study found a high prevalence of current smoking or use of smokeless tobacco in men compared to women. Globally, smoking prevalence is at least five times higher in men (37%) than in women (7%) (World Health Organization, 2014b). However, in the present study this difference was much wider in the Tibetan-related populations of Mustang but smaller in Khas-Aryas in Humla. It is rare to find tobacco smoking among Tibetan women. However, Tibetan men, being more exposed to the outer world, show a greater tendency to smoke. Among Tibetan-related populations in the present study, none of the women at 3270 m and 3620 m self-reported current smoking and the rate was 2.3% at 2800 m. About one-third of female participants in Humla were current smokers. A very low prevalence of smoking in Tibetan women, as in the present study, has been reported in several other HA studies (Sherpa et al., 2013; X. Zhao et al., 2012).

6.4.3.1 New findings

This study reports that half of the men and one-third of the women in the Humla population at 2890 m were current smokers. This is the highest documented prevalence of current smokers in HA populations. This study also found that tobacco use did not correlate with levels of HA.

6.4.3.2 Strengths and weaknesses

The main strength of this study regarding tobacco use is that other related information was collected from those who self-reported being a current smoker or used smokeless tobacco. For example, for current smokers, data was gathered on the age of starting smoking, years of smoking, number of cigarettes smoked per day, and any previous attempts to stop smoking. This helped to confirm self-reported smoking behaviour. However, it was difficult to confirm whether the past smokers and past smokeless tobacco users really had stopped using tobacco or whether use had recurred. This is important to note because a number of participants self-reported having recently quit using tobacco. A growing bias against the social desirability of smoking may have led to underestimates of current tobacco use. The prevalence of nose-snuffing of ground tobacco leaves in Tibetan-related participants should be interpreted cautiously because only a few participants reported using it daily. Most reported using it while suffering from the common cold or during social gatherings.

6.4.3.3 Areas for future research

The present study shows that while Tibetan-related HA populations have a cultural bias against smoking tobacco, other HA residents may have exceptionally high rates. More information is required on tobacco use of HA populations in Nepal, particularly in Khas-Aryas. There is no reliable information on determinants or triggers of tobacco use in Nepal's HA populations. It is important to examine this because HA populations are different from LA residents in many ways; for example, environmental and working conditions are different. The government of Nepal introduced a stringent Tobacco Control Act in 2011 but there is no evidence on how effective it is in remote HA settings. Future research on its impact in HA areas and barriers to successful enforcement may significantly help health policy planners in Nepal.

6.4.4 Risk prediction for major cardiovascular events

In the present study, 3.9% of the participants were estimated to have a high risk (probability equal to or greater than 20%) of fatal or non-fatal cardiovascular events (MI or stroke) within the next 10 years according to the World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction chart for South-East Asia sub-region D. The reported prevalence of CHD in the present study is in line with this. This is also similar to the report from the WHO-led study in a LA area of Nepal using the same risk prediction chart, which estimated the probability of high risk of future major cardiovascular events in 3.3% of the population aged 40 years or older (Mendis et al., 2011).

6.5 Overall conclusion

The sample of HA residents in the present study had a similar prevalence of CHD and future risk of major CVD events but a higher prevalence of a history of stroke, compared to the LA populations. Men were more likely than women to have a raised risk of abnormal ECG and lipid components, HT, diabetes, and being a smoker. The only exception was the prevalence of low HDL, which was higher in women.

Cardiovascular risk profiles of HA populations may depend on altitude, ethnicity, cultural lifestyle practices, and residential setting (urban or rural). Altitude *per se* could be an important additional risk factor because of the relationship between HA levels and higher SBP, and increased prevalence of an abnormal (or borderline abnormal) ECG. Differences in ECG abnormality patterns in Tibetan and Khas-Arya populations may reflect different ancestry-related physiological responses to the low oxygen environment and the varying patterns of CVD-related risk in HA populations. Other important findings are: HT particularly in Tibetan-related populations, high current smoking rates in Khas-Aryas, and a high prevalence of pre-diabetes in all study samples. This indicates that ethnicity associated lifestyle practices are likely to be an important determinant of CVD health for HA residents and that HA populations are passing through a phase of epidemiological transition from lower to higher risk for CVD.

To conclude, despite having a similar risk of CHD as the LA populations, some CVD risk factors (particularly HT) and consequent risk of stroke may be higher in specific HA populations. The main factors that should be considered for assessment and management of cardiovascular risk in HA populations are altitude, ethnicity and associated cultural lifestyle practices (such as salt and alcohol intake, smoking habit), and residential settings (mainly differences in physical activity and fruit and vegetable consumption between urban and rural participants).

7 References

Abusuev, S., Khachurov, D., & Akhmedkhanov, A. (1992). Epidemiologic aspects of diabetes mellitus in Dagestan. *Problemy Endokrinologii, 39*(1), 21-24.

Aceituno-Madera, P., Buendía-Eisman, A., Olmo, F., Jiménez-Moleón, J., & Serrano-Ortega, S. (2011). Melanoma, altitud y radiación UVB (Melanoma, altitude, and UV-B radiation). *Actas Dermo-Sifiliograficas, 102*(3), 199-205.

Akhtar, M., Bandopadhaya, P., Chatterjee, P., & Krishnamurti, S. (1978). Electrocardiographic changes under moderate hypoxia. *Indian Heart Journal, 31*(6), 353-358.

Al-Huthi, M. A., Raja'a, Y. A., Al-Noami, M., & Rahman, A. R. A. (2006). Prevalence of coronary risk factors, clinical presentation, and complications in acute coronary syndrome patients living at high vs low altitudes in Yemen. *Medscape General Medicine, 8*(4), 28.

Al Tahan, A., Buchur, J., El Khwsky, F., Ogunniyi, A., Al-Rajeh, S., Larbi, E., . . . Bamgboye, E. (1998). Risk factors of stroke at high and low altitude areas in Saudi Arabia. *Archives of Medical Research, 29*(2), 173-177.

Alberti, G., Zimmet, P., & Shaw, J. (2006). Metabolic syndrome—a new world-wide definition. A consensus statement from the international diabetes federation. *Diabetic Medicine, 23*(5), 469-480.

Ambrose, J. A., & Barua, R. S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease : an update. *Journal of the American College of Cardiology, 43*(10), 1731-1737.

American Diabetes Association. (2016). Classification and diagnosis of diabetes. *Diabetes Care, 39*(Supplement 1), S13-S22.

Anand, S. S., Yusuf, S., Vuksan, V., Devanesen, S., Teo, K. K., Montague, P. A., . . . Gerstein, H. (2000). Differences in risk factors, atherosclerosis, and cardiovascular disease between ethnic groups in Canada: the Study of Health Assessment and Risk in Ethnic groups (SHARE). *The Lancet, 356*(9226), 279-284.

Anderson, C. A., Appel, L. J., Okuda, N., Brown, I. J., Chan, Q., Zhao, L., . . . Curb, J. D. (2010). Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP study. *Journal of the American Dietetic Association, 110*(5), 736-745.

Anderson, J. D., & Honigman, B. (2011). The effect of altitude-induced hypoxia on heart disease: do acute, intermittent, and chronic exposures provide cardioprotection? *High Altitude Medicine & Biology, 12*(1), 45-55.

Arestegui, A. H., Fuquay, R., Sirota, J., Swenson, E. R., Schoene, R. B., Jefferson, J. A., . . . Johnson, R. J. (2011). High altitude renal syndrome (HARS). *Journal of the American Society of Nephrology, 22*(11), 1963-1968.

Arias-Stella, J. (1966). Morphological patterns : mechanism of pulmonary arterial hypertension *Life at high altitudes* (pp. 9-12). Washington DC: Pan American Health Organisation.

Arias-Stelalnad, J., & Topilsky, M. (1971). *Anatomy of the coronary circulation at high altitude.* Paper presented at the Ciba Foundation Symposium-High Altitude Physiology: Cardiac and Respiratory Aspects.

Aryal, K. K., Mehata, S., Neupane, S., Vaidya, A., Dhimal, M., Dhakal, P., . . . Paulin, F. H. (2015). The burden and determinants of non communicable diseases risk factors in Nepal: findings from a nationwide STEPS survey. *PloS One, 10*(8), e0134834.

Aryal, K. K., Neupane, S., Mehata, S., Vaidya, A., Singh, S., Paulin, F., . . . Lohani, G. R. (2014). Non communicable diseases risk factors: STEPS Survey Nepal 2013. Kathmandu, Nepal: Nepal Health Research Council.

Aryal, N., & Wasti, S. P. (2016). The prevalence of metabolic syndrome in South Asia: a systematic review. *International Journal of Diabetes in Developing Countries, 36*(3), 255-262.

Aryal, N., Weatherall, M., Bhatta, Y. K. D., & Mann, S. (2016). Blood pressure and hypertension in adults permanently living at high altitude : a systematic review and meta-analysis. *High Altitude Medicine & Biology, 17*(3), 185-193.

Ashouri, K., Ahmed, M., Kardash, M., Sharif, A., Abdalsattar, M., & al Ghozeim, A. (1993). Acute myocardial infarction at high altitude: the experience in Asir Region, southern Saudi Arabia. *Ethnicity and Disease, 4*(1), 82-86.

Asia Pacific Cohort Studies Collaboration. (2003). Blood pressure and cardiovascular disease in the Asia Pacific region. *Journal of Hypertension, 21*, 707-716.

Baibas, N., Trichopoulou, A., Voridis, E., & Trichopoulos, D. (2005). Residence in mountainous compared with lowland areas in relation to total and coronary mortality. A study in rural Greece. *Journal of Epidemiology and Community Health, 59*(4), 274-278.

Baker, P. T. (1969). Human adaptation to high altitude. *Science, 163*(3872), 1149-1156.

Baliunas, D. O., Taylor, B. J., Irving, H., Roerecke, M., Patra, J., Mohapatra, S., & Rehm, J. (2009). Alcohol as a risk factor for type 2 diabetes : a systematic review and meta-analysis. *Diabetes Care, 32*(11), 2123-2132.

Banach, M., Bromfield, S., Howard, G., Howard, V. J., Zanchetti, A., Aronow, W. S., . . . Muntner, P. (2014). Association of systolic blood pressure levels with cardiovascular events and all-cause mortality among older adults taking antihypertensive medication. *International Journal of Cardiology, 176*(1), 219-226.

Baracco, R., Mohanna, S., & Seclén, S. (2007). A comparison of the prevalence of metabolic syndrome and its components in high and low altitude populations in Peru. *Metabolic Syndrome and Related Disorders, 5*(1), 55-62.

Barker, D. J., Osmond, C., Forsén, T. J., Kajantie, E., & Eriksson, J. G. (2005). Trajectories of growth among children who have coronary events as adults. *New England Journal of Medicine, 353*(17), 1802-1809.

Barson, J. R., Karatayev, O., Chang, G.-Q., Johnson, D. F., Bocarsly, M. E., Hoebel, B. G., & Leibowitz, S. F. (2009). Positive relationship between dietary fat, ethanol intake, triglycerides, and hypothalamic peptides: counteraction by lipid-lowering drugs. *Alcohol, 43*(6), 433-441.

Basnyat, B., Ogilvie, R., White, A., O'Brien, B., Hackett, P., & Roach, R. (2001). High-altitude illness. *New England Journal of Medicine, 345*(17), 1279-1271.

Bassett, M., Gimenez, M., Romaguera, D., & Sammán, N. (2013). Nutritional status and food intake of populations from high altitude regions of the Northwest of Argentia. *Archivos Latinoamericanos de Nutrición, 63*(2), 114-124.

Beagley, J., Guariguata, L., Weil, C., & Motala, A. A. (2014). Global estimates of undiagnosed diabetes in adults. *Diabetes Research and Clinical Practice, 103*(2), 150-160.

Beall, C. M. (2007). Two routes to functional adaptation: Tibetan and Andean high-altitude natives. *Proceedings of the National Academy of Sciences of the United States of America, 104*(Suppl 1), 8655-8660.

Beall, C. M., Cavalleri, G. L., Deng, L., Elston, R. C., Gao, Y., Knight, J., . . . McCormack, M. (2010). Natural selection on EPAS1 (HIF2α) associated with low hemoglobin concentration in Tibetan highlanders. *Proceedings of the National Academy of Sciences of the United States of America, 107*(25), 11459-11464.

Beall, C. M., Decker, M. J., Brittenham, G. M., Kushner, I., Gebremedhin, A., & Strohl, K. P. (2002). An Ethiopian pattern of human adaptation to high-altitude hypoxia. *Proceedings of the National Academy of Sciences of the United States of America, 99*(26), 17215-17218.

Beall, C. M., Gebremedhin, A., Brittenham, G. M., Decker, M. J., & Shamebo, M. (1997). Blood pressure variation among Ethiopians on the Simien Plateau. *Annals of Human Biology, 24*(4), 333-342.

Beall, C. M., Laskowski, D., Strohl, K. P., Soria, R., Villena, M., Vargas, E., . . . Erzurum, S. C. (2001). Pulmonary nitric oxide in mountain dwellers. *Nature, 414*(6862), 411-412.

Beall, C. M., Strohl, K. P., Blangero, J., Williams-Blangero, S., Almasy, L. A., Decker, M. J., . . . Villena, M. (1997). Ventilation and hypoxic ventilatory response of Tibetan and Aymara high altitude natives. *American Journal of Physical Anthropology, 104*(4), 427-447.

Bennett, C. L., Silver, S. M., Djulbegovic, B., Samaras, A. T., Blau, C. A., Gleason, K. J., . . . McKoy, J. M. (2008). Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *Journal of the American Medical Association, 299*(8), 914-924.

Benowitz, N. L. (2003). Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. *Progress in Cardiovascular Diseases, 46*(1), 91-111.

Bert, P. (1878). *La pression barométrique: recherches de physiologie expérimentale*: Masson.

Berti, P. R., Fallu, C., & Cruz Agudo, Y. (2014). A systematic review of the nutritional adequacy of the diet in the Central Andes. *Revista Panamericana de Salud Publica, 36*(5), 314-323.

Berti, P. R., Jones, A. D., Cruz, Y., Larrea, S., Borja, R., & Sherwood, S. (2010). Assessment and characterization of the diet of an isolated population in the Bolivian Andes. *American Journal of Human Biology, 22*(6), 741-749.

Bhandari, G. P., Angdembe, M. R., Dhimal, M., Neupane, S., & Bhusal, C. (2014). State of non-communicable diseases in Nepal. *BMC Public Health, 14*(23). doi:10.1186/1471-2458-14-23

Bhandari, S., Sayami, J. T., Thapa, P., Sayami, M., Kandel, B. P., & Banjara, M. R. (2016). Dietary intake patterns and nutritional status of women of reproductive age in Nepal: findings from a health survey. *Archives of Public Health, 74*(2). doi:10.1186/s13690-016-0114-3

Bigham, A. W., Mao, X., Mei, R., Brutsaert, T., Wilson, M. J., Julian, C. G., . . . Shriver, M. D. (2009). Identifying positive selection candidate loci for high-altitude adaptation in Andean populations. *Human Genomics, 4*(2), 79-90.

Bloomfield, G. S., Lagat, D. K., Akwanalo, O. C., Carter, E. J., Lugogo, N., Vedanthan, R., . . . Sherman, C. B. (2012). Conditions that predispose to pulmonary hypertension and right heart failure in persons exposed to household air pollution in LMIC. *Global Heart, 7*(3), 249-259.

Boden, G. (2011). Obesity, insulin resistance and free fatty acids. *Current Opinion in Endocrinology, Diabetes, and Obesity, 18*(2), 139-143.

Boden, G., & Chen, X. (1995). Effects of fat on glucose uptake and utilization in patients with non-insulin-dependent diabetes. *Journal of Clinical Investigation, 96*(3), 1261-1268.

Bolinder, G., & de Faire, U. (1998). Ambulatory 24-h blood pressure monitoring in healthy, middle-aged smokeless tobacco users, smokers, and nontobacco users. *American Journal of Hypertension, 11*(10), 1153-1163.

Booth, G. L., Kapral, M. K., Fung, K., & Tu, J. V. (2006). Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *The Lancet, 368*(9529), 29-36.

Borgi, L., Rimm, E. B., Willett, W. C., & Forman, J. P. (2016). Potato intake and incidence of hypertension: results from three prospective US cohort studies. *The British Medical Journal, 353*, i2351.

Brahmachari, H. D., Malhotra, M. S., Joseph, S., & Krishnan, U. R. (1973). Glucose tolerance at high altitude in man. *Indian Journal of Medical Research, 61*(3), 411-415.

Braun, B. (2008). Effects of high altitude on substrate use and metabolic economy: cause and effect? *Medicine and Science in Sports and Exercise, 40*(8), 1495-1500.

Brenner, B. M., Garcia, D. L., & Anderson, S. (1988). Glomeruli and blood pressure less of one, more the other? *American Journal of Hypertension, 1*(4), 335-347.

Brito, J., Siqués, P., Leon-Velarde, F., De La Cruz, J. J., López, V., & Herruzo, R. (2007). Chronic intermittent hypoxia at high altitude exposure for over 12 years: assessment of hematological, cardiovascular, and renal effects. *High Altitude Medicine & Biology, 8*(3), 236-244.

Brook, R. D., Rajagopalan, S., Pope, C. A., 3rd, Brook, J. R., Bhatnagar, A., Diez-Roux, A. V., . . . Kaufman, J. D. (2010). Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation, 121*(21), 2331-2378.

Brubaker, P. L. (2005). Adventure travel and type 1 diabetes: the complicating effects of high altitude. *Diabetes Care, 28*(10), 2563-2572.

Burton, A. C. (1975). Cancer and altitude. Does intracellular pH regulate cell division? *European Journal of Cancer (1965), 11*(5), 365-371.

Burtscher, M. (2014). Effects of living at higher altitudes on mortality: a narrative review. *Aging and Disease, 5*(4), 274-280.

Burtscher, M., Mairer, K., Wille, M., & Broessner, G. (2011). Risk factors for high-altitude headache in mountaineers. *Cephalalgia, 31*(6), 706-711.

Caballero, A., Torres-Duque, C. A., Jaramillo, C., Bolívar, F., Sanabria, F., Osorio, P., . . . Maldonado, D. (2008). Prevalence of COPD in five Colombian cities situated at low, medium, and high altitude (PREPOCOL study). *Chest, 133*(2), 343-349.

Caceres Pilares, J., Rojas Bravo, M. L., Caceres Espinoza, L., & Ortiz Martinez, J. d. C. (2004). Total cholesterol and it´ s fractions in adults of 30 to 39 years, according to gender and sub-groups of age. *Situa, 13*(2), 12-19.

Cai, Z., Manalo, D. J., Wei, G., Rodriguez, E. R., Fox-Talbot, K., Lu, H., . . . Semenza, G. L. (2003). Hearts from rodents exposed to intermittent hypoxia or erythropoietin are protected against ischemia-reperfusion injury. *Circulation, 108*(1), 79-85.

Cao, J., Zhao, Y., Liu, J., Xirao, R., Danzeng, S., Daji, D., & Yan, Y. (2003). Brick tea fluoride as a main source of adult fluorosis. *Food and Chemical Toxicology, 41*(4), 535-542.

Central Bureau of Statistics. (2012). *Nepal in Figures*. Kathmandu, Nepal: Government of Nepal, National Planning Commission Secretariat.

Challoumas, D. (2014). Vitamin D supplementation and lipid profile: what does the best available evidence show? *Atherosclerosis, 235*(1), 130-139.

Chandalia, M., Mohan, V., Adams-Huet, B., Deepa, R., & Abate, N. (2008). Ethnic difference in sex gap in high-density lipoprotein cholesterol between Asian Indians and Whites. *Journal of Investigative Medicine, 56*(3), 574-580.

Chang, H.-Y., Yeh, W.-T., Chang, Y.-H., Tsai, K.-S., & Pan, W.-H. (2002). Prevalence of dyslipidemia and mean blood lipid values in Taiwan: results from the Nutrition and Health Survey in Taiwan (NAHSIT, 1993-1996). *Chinese Journal of Physiology, 45*(4), 187-198.

Chen, H.-W., Chu, N.-F., Chen, H.-H., & Yeh, M.-L. (2014). The smoking behaviors of indigenous Taiwanese: individual and family/community factors of influence. *Journal of Nursing Research, 22*(1), 12-19.

Chen, Q. H., Liu, F. Y., Wang, X. Q., Qi, G. R., Liu, P. F., Jin, X. H., . . . Qi, S. G. (2009). A cross-sectional study of congenital heart disease among children aged from 4 to 18 years at different altitudes in Qinghai province, China. *Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi, 30*(12), 1248-1251.

Chen, R., & Tunstall-Pedoe, H. (2005). Socioeconomic deprivation and waist circumference in men and women: The Scottish MONICA surveys 1989–1995. *European Journal of Epidemiology, 20*(2), 141-147.

Chen, W., Liu, Q., Wang, H., Chen, W., Johnson, R. J., Dong, X., . . . Luo, N. (2011). Prevalence and risk factors of chronic kidney disease: a population study in the Tibetan population. *Nephrology Dialysis Transplantation, 26*(5), 1592-1599.

Chhetri, D., Parajuli, P., & Subba, G. (2005). Antidiabetic plants used by Sikkim and Darjeeling Himalayan tribes, India. *Journal of Ethnopharmacology, 99*(2), 199-202.

Chhetri, M., & Chapman, R. (2009). Prevalence and determinants of diabetes among the elderly population in the Kathmandu Valley of Nepal. *Nepal Medical College Journal, 11*(1), 34-38.

Cho, K., Tian, M., Lan, Y., Zhao, X., & Yan, L. L. (2013). Validation of the Omron HEM-7201 upper arm blood pressure monitor, for self-measurement in a high-altitude environment, according to the European Society of Hypertension International Protocol revision 2010. *Journal of Human Hypertension, 27*(8), 487-491.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., . . . Wright, J. T. (2003). Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension, 42*(6), 1206-1252.

Clegg, E., Jeffries, D., & Harrison, G. A. (1976). Determinants of blood pressure at high and low altitudes in Ethiopia. *Proceedings of the Royal Society of London-Biological Sciences, 194*(1114), 63-82.

Cogill, B. (2003). *Anthropometric indicators measurement guide*. Washington DC: Food and Nutrition Technical Assistance Project, Academy for Educational Development.

Cossio-Bolaños, M., Campos, R. G., Andruske, C. L., Flores, A. V., Luarte-Rocha, C., Olivares, P. R., . . . de Arruda, M. (2015). Physical growth, biological age, and nutritional transitions of adolescents living at moderate altitudes in Peru. *International Journal of Environmental Research and Public Health, 12*(10), 12082-12094.

Cote, T. R., Stroup, D. F., Dwyer, D. M., Horan, J. M., & Peterson, D. E. (1993). Chronic obstructive pulmonary disease mortality; a role for altitude. *Chest, 103*(4), 1194-1197.

Cristina, T. J. N., Williams, J. A. S., Parkinson, L., Sibbritt, D. W., & Byles, J. E. (2016). Identification of diabetes, heart disease, hypertension and stroke in mid-and older-aged women: comparing self-report and administrative hospital data records. *Geriatrics & Gerontology International, 16*(1), 95-102.

Dang, S., Yan, H., & Yamamoto, S. (2008). High altitude and early childhood growth retardation: new evidence from Tibet. *European Journal of Clinical Nutrition, 62*(3), 342-348.

Dang, S., Yan, H., Yamamoto, S., Wang, X., & Zeng, L. (2004). Poor nutritional status of younger Tibetan children living at high altitudes. *European Journal of Clinical Nutrition, 58*(6), 938-946.

Dasgupta, D., Prasher, B., Vaidya, N., Ahluwalia, S., Sharma, P., Puri, D., & Mehrotra, A. (1982). Blood pressure in a community at high altitude (3000m) at Pooh (North India). *Journal of Epidemiology and Community Health, 36*(4), 251-255.

Davis, C. G., Thake, J., & Vilhena, N. (2010). Social desirability biases in self-reported alcohol consumption and harms. *Addictive Behaviors, 35*(4), 302-311.

De Bacquer, D., De Backer, G., Kornitzer, M., & Blackburn, H. (1998). Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. *Heart, 80*(6), 570-577.

De Keyzer, W., Dofková, M., Lillegaard, I. T. L., De Maeyer, M., Andersen, L. F., Ruprich, J., . . . Huybrechts, I. (2015). Reporting accuracy of population dietary sodium intake using duplicate 24 h dietary recalls and a salt questionnaire. *British Journal of Nutrition, 113*(3), 488-497.

De Mendoza, S., Nucete, H., Ineichen, E., Salazar, E., Zerpa, A., & Glueck, C. (1978). Lipids and lipoproteins in subjects at 1,000 and 3,500 meter altitudes. *Archives of Environmental Health, 34*(5), 308-311.

de Mol, P., de Vries, S. T., de Koning, E. J., Gans, R. O., Tack, C. J., & Bilo, H. J. (2011). Increased insulin requirements during exercise at very high altitude in type 1 diabetes. *Diabetes Care, 34*(3), 591-595.

Deepa, M., Anjana, R. M., Manjula, D., Narayan, K. M. V., & Mohan, V. (2011). Convergence of prevalence rates of diabetes and cardiometabolic risk factors in middle and low income groups in urban India: 10-Year follow-up of the chennai urban population study. *Journal of Diabetes Science and Technology, 5*(4), 918-927.

Deng, B., Luo, T., Huang, Y., Shen, T., & Ma, J. (2012). Prevalence and determinants of hyperlipidemia in moderate altitude areas of the Yunnan-Kweichow plateau in Southwestern China. *High Altitude Medicine & Biology, 13*(1), 13-21.

Devkota, K. C., Thapa Magar, S. B., & Malla, S. (2006). Retrospective analysis of stroke and its risk factors at Nepal Medical College Teaching Hospital. *Nepal Medical College Journal, 8*(4), 269-275.

Dhamija, R., & Dhamija, S. (1998). Prevalence of stroke in rural community-an overview of Indian experience. *The Journal of the Association of Physicians of India, 46*(4), 351-354.

Dhital, R. (2001). Alcohol and young people in Nepal. *The Globe, 4*, 21-25.

Ding, H.-l., Zhu, H.-f., Dong, J.-w., Zhu, W.-z., Yang, W.-w., Yang, H.-t., & Zhou, Z.-n. (2005). Inducible nitric oxide synthase contributes to intermittent hypoxia against ischemia/reperfusion injury. *Acta Pharmacologica Sinica, 26*(3), 315-322.

Dodani, S., Dong, Y., Zhu, H., & George, V. (2008). Can novel Apo AI polymorphisms be responsible for low HDL in South Asian immigrants? *Indian Journal of Human Genetics, 14*(1), 9-15.

Dulal, R. K., & Karki, S. (2009). Disease management programme for diabetes mellitus in Nepal. *Journal of Nepal Medical Association, 48*(176), 1261-1270.

Eagle, S. (2000). The language situation in Nepal. In R. B. Baldauf & R. B. Kaplan (Eds.), *Language Planning in Nepal, Taiwan, and Sweden* (Vol. 20). Clevedon, UK: Multilingual Matters Ltd.

Eldwood, P., Beswick, A., O'Brien, J. R., Renaud, S., Fifield, R., Limb, E., & Bainton, D. (1993). Temperature and risk factors for ischaemic heart disease in the Caerphilly prospective study. *British Heart Journal, 70*(6), 520-523.

Elliott, P., Stamler, J., Nichols, R., Dyer, A. R., Stamler, R., Kesteloot, H., & Marmot, M. (1996). Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. *The British Medical Journal, 312*(7041), 1249-1253.

Ervasti, O., Juopperi, K., Kettunen, P., Remes, J., Rintamäki, H., Latvala, J., . . . Hassi, J. (2004). The occurrence of frostbite and its risk factors in young men. *International Journal of Circumpolar Health, 63*(1), 71-80.

Esparza-Romero, J., Valencia, M. E., Martinez, M. E., Ravussin, E., Schulz, L. O., & Bennett, P. H. (2010). Differences in insulin resistance in Mexican and US Pima Indians with normal glucose tolerance. *Journal of Clinical Endocrinology and Metabolism, 95*(11), E358-E362.

Essop, M. F. (2007). Cardiac metabolic adaptations in response to chronic hypoxia. *Journal of Physiology, 584*(3), 715-726.

Ezzati, M., Henley, S. J., Thun, M. J., & Lopez, A. D. (2005). Role of smoking in global and regional cardiovascular mortality. *Circulation, 112*(4), 489-497.

Ezzati, M., Horwitz, M. E., Thomas, D. S., Friedman, A. B., Roach, R., Clark, T., . . . Honigman, B. (2012). Altitude, life expectancy and mortality from ischaemic heart disease, stroke, COPD and cancers: national population-based analysis of US counties. *Journal of Epidemiology and Community Health, 66*(7), e17-e17.

Faeh, D., Gutzwiller, F., & Bopp, M. (2009). Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. *Circulation, 120*(6), 495-501.

Faeh, D., Moser, A., Panczak, R., Bopp, M., Röösli, M., Spoerri, A., . . . Künzli, N. (2016). Independent at heart: persistent association of altitude with ischaemic heart disease mortality after consideration of climate, topography and built environment. *Journal of Epidemiology and Community Health*. doi:10.1136/jech-2015-206210

Fang, J., Zhuo-Ga, C., Zhao, Y., Kong, F., Si, Y., Liu, M., & Zhou, D. (2011). Characteristics of stroke in Tibet Autonomous Region in China: a hospital-based study of acute stroke. *European Neurology, 66*(3), 151-158.

Farah, R., Zeidan, R. K., Chahine, M. N., Asmar, R., Chahine, R., Salameh, P., & Hosseini, H. (2015). Prevalence of stroke symptoms among stroke-free residents: first national data from Lebanon. *International Journal of Stroke, 10*(A100), 83-88.

Ferezou, J., Richalet, J., Coste, T., & Rathat, C. (1988). Changes in plasma lipids and lipoprotein cholesterol during a high altitude mountaineering expedition (4800 m). *European Journal of Applied Physiology and Occupational Physiology, 57*(6), 740-745.

Ferroni, M. A. (1982). Food habits and the apparent nature and extent of dietary nutritional deficiencies in the Peruvian Andes. *Archivos Latinoamericanos de Nutrición, 32*(4), 850-866.

Field, A. E., Coakley, E. H., Must, A., Spadano, J. L., Laird, N., Dietz, W. H., . . . Colditz, G. A. (2001). Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Archives of Internal Medicine, 161*(13), 1581-1586.

Fiori, G., Facchini, F., Pettener, D., Rimondi, A., Battistini, N., & Bedogni, G. (2000). Relationships between blood pressure, anthropometric characteristics and blood lipids in high-and low-altitude populations from Central Asia. *Annals of Human Biology, 27*(1), 19-28.

Fitzpatrick, A. L., Van Ngo, Q., Ly, K. A., Ton, T. G., Longstreth, W., Vo, T. T., . . . Tirschwell, D. L. (2012). Symptoms and risk factors for stroke in a community-based observational sample in Viet Nam. *Journal of Epidemiology and Global Health, 2*(3), 155-163.

Foerster, M., Marques-Vidal, P., Gmel, G., Daeppen, J.-B., Cornuz, J., Hayoz, D., . . . Vollenweider, P. (2009). Alcohol drinking and cardiovascular risk in a population with high mean alcohol consumption. *American Journal of Cardiology, 103*(3), 361-368.

Foody, J. M. (2006). Low-density lipoprotein cholesterol and coronary artery disease: clinical evidence and clinical implications. In J. M. Foody (Ed.), *Preventive cardiology : Insights into the prevention and treatment of cardiovascular disease* (Second ed., pp. 49-79). Totowa, New Jersey: Humana Press Inc.

Ford, E. S., Merritt, R. K., Heath, G. W., Powell, K. E., Washburn, R. A., Kriska, A., & Haile, G. (1991). Physical activity behaviors in lower and higher socioeconomic status populations. *American Journal of Epidemiology, 133*(12), 1246-1256.

Freminet, A., Megas, P., & Puceat, M. (1990). Depressed gluconeogenesis and ureogenesis in isolated hepatocytes after intermittent hypoxia in rats. *International Journal of Biochemistry, 22*(11), 1307-1313.

Fujimaki, T., Matsutani, M., Asai, A., Kohno, T., & Koike, M. (1986). Cerebral venous thrombosis due to high-altitude polycythemia: case report. *Journal of Neurosurgery, 64*(1), 148-150.

Furberg, C. D., Psaty, B. M., & Soliman, E. Z. (2010). Blood pressure and cardiovascular disease. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 165-178). Chichester, U.K.: Wiley-Blackwell Publishing.

Gagnon, D. R., Zhang, T.-J., Brand, F. N., & Kannel, W. B. (1994). Hematocrit and the risk of cardiovascular disease—the Framingham study: a 34-year follow-up. *American Heart Journal, 127*(3), 674-682.

Gaillard, S., Dellasanta, P., Loutan, L., & Kayser, B. (2004). Awareness, prevalence, medication use, and risk factors of acute mountain sickness in tourists trekking around the Annapurnas in Nepal: a 12-year follow-up. *High Altitude Medicine & Biology, 5*(4), 410-419.

Galan, H. L., Rigano, S., Radaelli, T., Cetin, I., Bozzo, M., Chyu, J., . . . Ferrazzi, E. (2001). Reduction of subcutaneous mass, but not lean mass, in normal fetuses in Denver, Colorado. *American Journal of Obstetrics and Gynecology, 185*(4), 839-844.

Garmendia, F., Arroyo, J., & Muro, M. (1970). Glicemia del nativo normal de altura. *Archivos del Instituto de Biología Andina, 3*, 209-216.

Gellner, D. N. (2016). *The idea of Nepal*. Kathmandu: Social Science Baha.

Gerstein, H. C., & Punthakee, Z. (2010). Dysglycemia and the risk of cardiovascular events. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 179-189): Blackwell Publishing.

Gerstein, H. C., Santaguida, P., Raina, P., Morrison, K. M., Balion, C., Hunt, D., . . . Booker, L. (2007). Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Research and Clinical Practice, 78*(3), 305-312.

Gesang, L., Liu, G., Cen, W., Qiu, C., Zhuoma, C., Zhuang, L., . . . Chan, Y. (2002). Angiotensin-converting enzyme gene polymorphism and its association with essential hypertension in a Tibetan population. *Hypertension Research, 25*(3), 481-485.

Ghafoorunissa. (1994). Dietary lipids and heart disease - the Indian context. *National Medical Journal of India, 7*, 270-275.

Gilbert, D. L. (1983a). The first documented description of mountain sickness: the Andean or Pariacaca story. *Respiration Physiology, 52*(3), 327-347.

Gilbert, D. L. (1983b). The first documented report of mountain sickness: the China or Headache Mountain story. *Respiration Physiology, 52*(3), 315-326.

Gonzales, G. F. (2001). Metabolismo en las grandes alturas. *Acta Andina, 9*(1-2), 31-42.

Gonzales, G. F., Rubio, J., & Gasco, M. (2013). Chronic mountain sickness score was related with health status score but not with hemoglobin levels at high altitudes. *Respiratory Physiology & Neurobiology, 188*(2), 152-160.

Gonzales, G. F., & Tapia, V. (2013). Association of high altitude-induced hypoxemia to lipid profile and glycemia in men and women living at 4100m in the Peruvian Central Andes. *Endocrinología y Nutrición (English Edition), 60*(2), 79-86.

Gonzales, G. F., Tapia, V., & Carrillo, C. E. (2008). Stillbirth rates in Peruvian populations at high altitude. *International Journal of Gynecology & Obstetrics, 100*(3), 221-227.

Gorer, G. (1938). *Himalayan village: an account of The Lepchas of Sikkim*. London, England: Michael Joseph.

Government of Nepal & United Nations Development Programme. (2014). *Nepal human development report 2014 : beyond geography, unlocking human potential*. Retrieved from Kathmandu, Nepal: http://hdr.undp.org/sites/default/files/nepal_nhdr_2014-final.pdf

Graham, T., & Baulk, K. (1980). Effect of alcohol ingestion on man's thermoregulatory responses during cold water immersion. *Aviation, Space, and Environmental Medicine, 51*(2), 155-159.

Green, R., Sutherland, J., Dangour, A. D., Shankar, B., & Webb, P. (2016). Global dietary quality, undernutrition and non-communicable disease: a longitudinal modelling study. *BMJ Open, 6*(1), e009331.

Groves, B. M., Droma, T., Sutton, J. R., McCullough, R. G., McCullough, R. E., Zhuang, J., . . . Moore, L. G. (1993). Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. *Journal of Applied Physiology, 74*(1), 312-318.

Grundy, S. M. (1997). What is the desirable ratio of saturated, polyunsaturated, and monounsaturated fatty acids in the diet? *The American Journal of Clinical Nutrition, 66*(4), 988S-990S.

Grundy, S. M., Becker, D., Clark, L., Cooper, R., Denke, M., Howard, J., . . . McBride, P. (2002). Detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Circulation, 106*(25), 3143-3421.

Guo, W., Lanzi, G., Luobu, O., Ma, X., Zhen, P., Ji, Y., . . . Zhuoma, B. (2008). An epidemiological survey of alcohol use disorders in a Tibetan population. *Psychiatry Research, 159*(1), 56-66.

Gupta, M., Rao, K., Anand, I., Banerjee, A., & Boparai, M. (1992). Lack of smooth muscle in the small pulmonary arteries of the native Ladakhi. *American Review of Respiratory Disease, 145*, 1201-1204.

Gupta, R., Misra, A., Pais, P., Rastogi, P., & Gupta, V. (2006). Correlation of regional cardiovascular disease mortality in India with lifestyle and nutritional factors. *International Journal of Cardiology, 108*(3), 291-300.

Guptha, S., Gupta, R., Deedwania, P., Bhansali, A., Maheshwari, A., Gupta, A., . . . Achari, V. (2014). Cholesterol lipoproteins and prevalence of dyslipidemias in urban Asian Indians: a cross sectional study. *Indian Heart Journal, 66*(3), 280-288.

Gyawali, B., Sharma, R., Neupane, D., Mishra, S. R., van Teijlingen, E., & Kallestrup, P. (2015). Prevalence of type 2 diabetes in Nepal: a systematic review and meta-analysis from 2000 to 2014. *Global health action, 8*(1), 29088. doi:10.3402/gha.v8.29088.

Hall, J. E. (2000). Pathophysiology of obesity hypertension. *Current Hypertension Reports, 2*, 139-147.

Halperin, B. D., Sun, S., Zhuang, J., Droma, T., & Moore, L. G. (1998). ECG observations in Tibetan and Han residents of Lhasa. *Journal of Electrocardiology, 31*(3), 237-243.

Haman, F., Péronnet, F., Kenny, G. P., Massicotte, D., Lavoie, C., & Weber, J. M. (2005). Partitioning oxidative fuels during cold exposure in humans: muscle glycogen becomes dominant as shivering intensifies. *The Journal of Physiology, 566*(1), 247-256.

Han, W., Sun, N., Chen, Y., Wang, H., Xi, Y., & Ma, Z. (2015). Validation of the spot urine in evaluating 24-hour sodium excretion in Chinese hypertension patients. *American Journal of Hypertension, 28*, 1368-1375.

Hanaoka, M., Droma, Y., Basnyat, B., Ito, M., Kobayashi, N., Katsuyama, Y., . . . Ota, M. (2012). Genetic variants in EPAS1 contribute to adaptation to high-altitude hypoxia in Sherpas. *PloS One, 7*(12), e50566. doi:10.1371/journal.pone.0050566

Hance, A., Robin, E., Simon, L., Alexander, S., Herzenberg, L., & Theodore, J. (1980). Regulation of glycolytic enzyme activity during chronic hypoxia by changes in rate-limiting enzyme content. Use of monoclonal antibodies to quantitate changes in pyruvate kinase content. *Journal of Clinical Investigation, 66*(6), 1258-1264.

Hanna, J. M. (1974). Coca leaf use in southern Peru: some biosocial aspects. *American Anthropologist*, *76*(2), 281-296.

Hansen, J. C., Gilman, A. P., & Odland, J. Ø. (2010). Is thermogenesis a significant causal factor in preventing the “globesity” epidemic? *Medical Hypotheses, 75*(2), 250-256.

Harris, N. S., Crawford, P. B., Yangzom, Y., Pinzo, L., Gyaltsen, P., & Hudes, M. (2001). Nutritional and health status of Tibetan children living at high altitudes. *New England Journal of Medicine, 344*(5), 341-347.

Hashmi, M., Rashid, M., Haleem, A., Bokhari, S., & Hussain, T. (1998). Frostbite: epidemiology at high altitude in the Karakoram mountains. *Annals of the Royal College of Surgeons of England, 80*(2), 91-95.

Hayes, D. P. (2010). Cancer protection related to solar ultraviolet radiation, altitude and vitamin D. *Medical Hypotheses, 75*(4), 378-382.

He, J., Tell, G. S., Tang, Y. C., Mo, P. S., & He, G. Q. (1991). Effect of migration on blood pressure: The Yi people study. *Epidemiology, 2*(2), 88-97.

Health Promotion Agency New Zealand. (2015). What's a standard drink ? Retrieved from http://alcohol.org.nz/help-advice/standard-drinks/whats-a-standard-drink

Hernandez-Hernandez, R., Silva, H., Velasco, M., Pellegrini, F., Macchia, A., Escobedo, J., . . . Pramparo, P. (2010). Hypertension in seven Latin American cities: The cardiovascular risk factor multiple evaluation in Latin America (CARMELA) study. *Journal of Hypertension, 28*(1), 24-34.

Hessien, M. (2013). Improved glycemic control in moderate altitude type II diabetic residents. *High Altitude Medicine & Biology, 14*(1), 27-30.

Higgins, J. P., Tuttle, T., & Higgins, J. A. (2010). Altitude and the heart: is going high safe for your cardiac patient? *American Heart Journal, 159*(1), 25-32.

Hill, J. O., & Wyatt, H. R. (2013). The myth of healthy obesity. *Annals of Internal Medicine, 159*(11), 789-790.

Holden, J., Stone, C., Clark, C., Brown, W., Nickles, R., Stanley, C., & Hochachka, P. (1995). Enhanced cardiac metabolism of plasma glucose in high-altitude natives: adaptation against chronic hypoxia. *Journal of Applied Physiology, 79*(1), 222-228.

Holick, M. F., Chen, T. C., Lu, Z., & Sauter, E. (2007). Vitamin D and skin physiology: A D-lightful story. *Journal of Bone and Mineral Research, 22*(S2), V28-V33.

Honigman, B., Theis, M. K., Koziol-McLain, J., Roach, R., Yip, R., Houston, C., & Moore, L. G. (1993). Acute mountain sickness in a general tourist population at moderate altitudes. *Annals of Internal Medicine, 118*(8), 587-592.

Howard, A. A., Arnsten, J. H., & Gourevitch, M. N. (2004). Effect of alcohol consumption on diabetes mellitus: a systematic review. *Annals of Internal Medicine, 140*(3), 211-219.

Howard, V. J., McClure, L. A., Meschia, J. F., Pulley, L., Orr, S. C., & Friday, G. H. (2006). High prevalence of stroke symptoms among persons without a diagnosis of stroke or transient ischemic attack in a general population: the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. *Archives of Internal Medicine, 166*(18), 1952-1958.

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation, 67*(5), 968-977.

Huerta-Sánchez, E., DeGiorgio, M., Pagani, L., Tarekegn, A., Ekong, R., Antao, T., . . . Robbins, P. A. (2013). Genetic signatures reveal high-altitude adaptation in a set of Ethiopian populations. *Molecular Biology and Evolution, 30*(8), 1877-1888.

Huicho, L., Trelles, M., Gonzales, F., Mendoza, W., & Miranda, J. (2009). Mortality profiles in a country facing epidemiological transition: an analysis of registered data. *BMC Public Health, 9*(47). doi:10.1186/1471-2458-9-47

Hurtado, A. (1960). Some clinical aspects of life at high altitudes. *Annals of Internal Medicine, 53*(2), 247-258.

Hurtado, A., Escudero, E., Pando, J., Sharma, S., & Johnson, R. J. (2012). Cardiovascular and renal effects of chronic exposure to high altitude. *Nephrology, Dialysis, Transplantation, 27*(suppl 4), iv11-iv16.

International Diabetes Federation. (2015). IDF Diabetes Atlas (7th Edition). Retrieved 28th September, 2016, from International Diabetes Federation http://www.diabetesatlas.org/key-messages.html

Jackson, F. (1975). *Hypoxia and the heart.* Paper presented at the Mountain Medicine and Physiology. Proceedings of a Symposium sponsored by the Alpine Club.

Jaillard, A. S., Hommel, M., & Mazetti, P. (1995). Prevalence of stroke at high altitude (3380 m) in Cuzco, a town of Peru: a population-based study. *Stroke, 26*(4), 562-568.

Jansen, G. F., & Basnyat, B. (2011). Brain blood flow in Andean and Himalayan high-altitude populations: evidence of different traits for the same environmental constraint. *Journal of Cerebral Blood Flow and Metabolism, 31*(2), 706-714.

Jayawardena, R., Ranasinghe, P., Byrne, N. M., Soares, M. J., Katulanda, P., & Hills, A. P. (2012). Prevalence and trends of the diabetes epidemic in South Asia: a systematic review and meta-analysis. *BMC Public Health, 12*(380). doi:10.1186/1471-2458-12-380

Jensen, G. M., & Moore, L. G. (1997). The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *American Journal of Public Health, 87*(6), 1003-1007.

Jha, P., Mony, P., Moore, J., & Zatonski, W. (2010). Avoidance of worldwide vascular deaths and total deaths from smoking. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 111-124): Blackwell Publishing.

Jha, S. K., Anand, A. C., Sharma, V., Kumar, N., & Adya, C. M. (2002). Stroke at high altitude: Indian experience. *High Altitude Medicine & Biology, 3*(1), 21-27.

Jin, X., Chen, Q., Tong, Y., Zhu, C., Qu, Y., Zhao, G., & Cai, J. (2008). Study on the epidemiology of congenital heart disease in Tibetan ethnic children aged from 4 to 18 living at different altitudes in Qinghai province. *Zhonghua liu xing bing xue za zhi= Zhonghua liuxingbingxue zazhi, 29*(4), 317-320.

Johnson, R. J., Kang, D.-H., Feig, D., Kivlighn, S., Kanellis, J., Watanabe, S., . . . Mazzali, M. (2003). Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension, 41*(6), 1183-1190.

Joint WHO/FAO Expert Consultation on Diet, & Nutrition and the Prevention of Chronic Diseases. (2002). *Diet, nutrition and the prevention of chronic diseases* (916). Retrieved from

Geneva, Switzerland: http://www.who.int/dietphysicalactivity/publications/trs916/download/en/

Jones, W. J., Williams, L. S., & Meschia, J. F. (2001). Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke, 32*(10), 2232-2236.

Joshi, P., Islam, S., Pais, P., Reddy, S., Dorairaj, P., Kazmi, K., . . . Yusuf, S. (2007). Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. *Journal of the American Medical Association, 297*(3), 286-294.

Jourdanet, D. (1875). *Influence de la Pression de l'Air sur la Vie de l'Homme. Climats d'Altitude et Climats de Montagne*: Masson.

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature, 444*(7121), 840-846.

Kanteres, F., Lachenmeier, D. W., & Rehm, J. (2009). Alcohol in Mayan Guatemala: consumption, distribution, production and composition of cuxa. *Addiction, 104*(5), 752-759.

Kapoor, S. C. (1984). Changes in electrocardiogram among temporary residents at high altitude. *Defence Science Journal, 34*(4), 389-395.

Kappelle, P., Gansevoort, R., Hillege, J., Wolffenbuttel, B., & Dullaart, R. (2011). Apolipoprotein B/A-I and total cholesterol/high-density lipoprotein cholesterol ratios both predict cardiovascular events in the general population independently of nonlipid risk factors, albuminuria and C-reactive protein. *Journal of Internal Medicine, 269*(2), 232-242.

Karki, D. B., Neupane, A., Pradhan, B., & Magar, A. (2003). Lipid levels in Nepalese population. *Kathmandu University Medical Journal, 2*(4), 349-353.

Karliner, J. S., Sarnquist, F. F., Graber, D. J., Peters, R. M., & West, J. B. (1985). The electrocardiogram at extreme altitude: experience on Mt. Everest. *American Heart Journal, 109*(3), 505-513.

Karthikeyan, G., Teo, K. K., Islam, S., McQueen, M. J., Pais, P., Wang, X., . . . Pandey, M. (2009). Lipid profile, plasma apolipoproteins, and risk of a first myocardial infarction among Asians: an analysis from the INTERHEART Study. *Journal of the American College of Cardiology, 53*(3), 244-253.

Kaushal, S., DasGupta, D., Prashar, B., & Bhardwaj, A. (1995). Electrocardiographic manifestations of healthy residents of a tribal Himalayan village. *Journal of the Association of Physicians of India, 43*(1), 15-16.

Kautzky-Willer, A., Harreiter, J., & Pacini, G. (2016). Sex and gender differences in risk, pathophysiology and complications of type 2 diabetes mellitus. *Endocrine Reviews, 37*(3), 278-316.

Kawamoto, R., Tabara, Y., Kohara, K., Miki, T., Kusunoki, T., Takayama, S., & Abe, M. (2011). Hemoglobin is associated with serum high molecular weight adiponectin in Japanese community-dwelling persons. *Journal of Atherosclerosis and Thrombosis, 18*(3), 182-189.

Kayser, B., & Verges, S. (2013). Hypoxia, energy balance and obesity: from pathophysiological mechanisms to new treatment strategies. *Obesity Reviews, 14*(7), 579-592.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. *The Lancet, 365*(9455), 217-223.

Kehoe, R., Wu, S.-Y., Leske, M. C., & Chylack, L. T. (1994). Comparing self-reported and physician-reported medical history. *American Journal of Epidemiology, 139*(8), 813-818.

Khalid, M. E. (1995). Anthropometric comparison between high-and low-altitude Saudi Arabians. *Annals of Human Biology, 22*(5), 459-465.

Khalid, M. E. (2007). The prevalence of abdominal obesity and its associated risk factors in married, non-pregnant women born and living in high altitude, southwestern, Saudi Arabia. *Saudi Medical Journal, 28*(12), 1875-1880.

Khalid, M. E. (2008). Is high-altitude environment a risk factor for childhood overweight and obesity in Saudi Arabia? *Wilderness and Environmental Medicine, 19*(3), 157-163.

Khalid, M. E., & Adzaku, F. K. (1995). The effect of altitude on blood pressure in the Assir Province of Saudi Arabia. *Wilderness and Environmental Medicine, 6*(4), 401-406.

Khan, K. S., Ter Riet, G., Glanville, J., Sowden, A. J., & Kleijnen, J. (2001). *Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews* (4). Retrieved from York (UK): https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf

Khanal, V., Adhikari, M., & Karki, S. (2013). Social determinants of tobacco consumption among Nepalese men: findings from Nepal Demographic and Health Survey 2011. *Harm Reduction Journal, 10*(40). doi:10.1186/1477-7517-10-40

Khatri, R. B., Mishra, S. R., & Khanal, V. (2015). Tobacco use among rural Nepalese women: cross-sectional community based study. *Indian Journal of Cancer, 52*(4), 699-704.

Khoo, A.-L., Chai, L. Y., Koenen, H. J., Kullberg, B.-J., Joosten, I., van der Ven, A. J., & Netea, M. G. (2011). 1, 25-dihydroxyvitamin D3 modulates cytokine production induced by Candida albicans: impact of seasonal variation of immune responses. *Journal of Infectious Diseases, 203*(1), 122-130.

Kinnunen, T. I., & Neupane, S. (2014). Prevalence of overweight among women of childbearing age in Nepal: trends from 2001 to 2011 and associations with socio-demographic factors. *Maternal and Child Health Journal, 18*(8), 1846-1853.

Kinra, S., Bowen, L. J., Lyngdoh, T., Prabhakaran, D., Reddy, K. S., Ramakrishnan, L., . . . Kurpad, A. V. (2010). Sociodemographic patterning of non-communicable disease risk factors in rural India: a cross sectional study. *The British Medical Journal, 341:c4974*. doi:http://dx.doi.org/10.1136/bmj.c4974

Klatsky, A. (2015). Alcohol and cardiovascular diseases: where do we stand today? *Journal of Internal Medicine, 278*(3), 238-250.

Kleindorfer, D., Judd, S., Howard, V. J., McClure, L., Safford, M. M., Cushman, M., . . . Howard, G. (2011). Self-reported stroke symptoms without a prior diagnosis of stroke or transient ischemic attack: a powerful new risk factor for stroke. *Stroke, 42*(11), 3122-3126.

Klop, B., do Rego, A. T., & Cabezas, M. C. (2013). Alcohol and plasma triglycerides. *Current Opinion in Lipidology, 24*(4), 321-326.

Koirala, M., Khatri, R., Khanal, V., & Amatya, A. (2015). Prevalence and factors associated with childhood overweight/obesity of private school children in Nepal. *Obesity Research & Clinical Practice, 9*(3), 220-227.

Koju, R., Manandhar, K., Risal, A., Steiner, T. J., Holen, A., & Linde, M. (2015). Undertreated hypertension and its implications for public health in Nepal: nationwide population-based survey. *Kathmandu University Medical Journal, 13*(1), 3-7.

Kramer, C. K., Zinman, B., & Retnakaran, R. (2013). Are metabolically healthy overweight and obesity benign conditions? A systematic review and meta-analysis. *Annals of Internal Medicine, 159*(11), 758-769.

Kris-Etherton, P., Daniels, S. R., Eckel, R. H., Engler, M., Howard, B. V., Krauss, R. M., . . . Stampfer, M. (2001). Summary of the scientific conference on dietary fatty acids and cardiovascular health conference: summary from the nutrition committee of the American Heart Association. *Circulation, 103*(7), 1034-1039.

Kumar, R., Pasha, M. Q., Khan, A. P., Gupta, V., Grover, S., Norboo, T., . . . Brahamchari, S. (2003). Association of high-altitude systemic hypertension with the deletion allele-of the angiotensin-converting enzyme (ACE) gene. *International Journal of Biometeorology, 48*(1), 10-14.

Ladell, W. (1964). Terrestrial animals in humid heat: man. In D. Dill, E. Adolph, & C. Wilber (Eds.), *Handbook of physiology, section 4, Adaptation to the environment* (pp. 625-659). Washington, DC: American Physiological Society.

Laniado-Laborin, R., Rendón, A., & Bauerle, O. (2011). Chronic obstructive pulmonary disease case finding in Mexico in an at-risk population. *International Journal of Tuberculosis and Lung Disease, 15*(6), 818-823.

Lankford, H. V., & Swenson, E. R. (2014). Dilated hearts at high altitude: words from on high. *High Altitude Medicine & Biology, 15*(4), 511-519.

Law, M. (2010). Lipids and cardiovascular disease. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 138-146): Blackwell Publishing.

Law, M. R., Frost, C. D., & Wald, N. J. (1991). By how much does dietary salt reduction lower blood pressure? III-Analysis of data from trials of salt reduction. *The British Medical Journal, 302*(6780), 819-824.

Lee, K. (2012). Gender-specific relationships between alcohol drinking patterns and metabolic syndrome: the Korea National Health and Nutrition Examination Survey 2008. *Public Health Nutrition, 15*(10), 1917-1924.

Lee, M.-S., Hang, J.-q., Zhang, F.-y., Dai, H.-l., Su, L., & Christiani, D. C. (2012). In-home solid fuel use and cardiovascular disease: a cross-sectional analysis of the Shanghai Putuo study. *Environmental Health, 11*(1), 18.

Lee, W.-C., Chen, J.-J., Ho, H.-Y., Hou, C.-W., Liang, M.-P., Shen, Y.-W., & Kuo, C.-H. (2003). Short-term altitude mountain living improves glycemic control. *High Altitude Medicine & Biology, 4*(1), 81-91.

León-Velarde, F., Maggiorini, M., Reeves, J. T., Aldashev, A., Asmus, I., Bernardi, L., . . . Moore, L. G. (2005). Consensus statement on chronic and subacute high altitude diseases. *High Altitude Medicine & Biology, 6*(2), 147-157.

León-Velarde, F., Sanchez, J., Bigard, A. X., Brunet, A., Lesty, C., & C., M.-C. (1993). High altitude tissue adaptation in Andean coots: capillarity, fibre area, fibre type and enzymatic activities of skeletal muscle. *Journal of Comparative Physiology B, 163*(1), 52-58.

León-Velarde, F., Villafuerte, F. C., & Richalet, J.-P. (2010). Chronic mountain sickness and the heart. *Progress in Cardiovascular Diseases, 52*(6), 540-549.

Leonard, W. R. (1989). Nutritional determinants of high-altitude growth in Nunoa, Peru. *American Journal of Physical Anthropology, 80*(3), 341-352.

Li, B., Baylink, D. J., Deb, C., Zannetti, C., Rajaallah, F., Xing, W., . . . Qin, X. (2013). 1, 25-Dihydroxyvitamin D3 suppresses TLR8 expression and TLR8-mediated inflammatory responses in monocytes in vitro and experimental autoimmune encephalomyelitis in vivo. *PloS One, 8*(3), e58808. doi:10.1371/journal.pone.0058808

Li, S.-Q., & Zhang, Q. H. (2001). Advances in the development of functional foods from buckwheat. *Critical Reviews in Food Science and Nutrition, 41*(6), 451-464.

Li, S., Zheng, B., Wang, H., Zheng, J., Cai, Z., Long, R., . . . Peng, H. (2006). The clinical characteristics of acute severe high-altitude diseases in indigenous Tibetans. *Chinese Journal of Tuberculosis and Respiratory Diseases, 29*(12), 835-836.

Lichtenstein, A. H., Appel, L. J., Brands, M., Carnethon, M., Daniels, S., Franch, H. A., . . . Howard, B. (2006). Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association nutrition committee. *Circulation, 114*(1), 82-96.

Lim, S. S., Vos, T., Flaxman, A. D., Danaei, G., Shibuya, K., Adair-Rohani, H., . . . Memish, Z. A. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *The Lancet, 380*(9859), 2224-2260.

Lindgärde, F., Ercilla, M. B., Correa, L. R., & Ahrén, B. (2004). Body adiposity, insulin, and leptin in subgroups of Peruvian Amerindians. *High Altitude Medicine & Biology, 5*(1), 27-31.

Lindgärde, F., & Liljekvist, R. (1984). Failure of long-term acclimatization in smokers moving to high altitude. *Acta Medica Scandinavica, 216*(3), 317-322.

Littman, G. (1970). Alcoholism, illness, and social pathology among American Indians in transition. *American Journal of Public Health and the Nations Health, 60*(9), 1769-1787.

Liu, L., Ding, Y., Huang, Z., He, B., Sun, S., Zhao, G., . . . Ikeda, K. (2001). Ethnic and environmental differences in various markers of dietary intake and blood pressure among Chinese Han and three other minority peoples of China: results from the WHO Cardiovascular Diseases and Alimentary Comparison (CARDIAC) Study. *Hypertension Research, 24*(3), 315-322.

López de Guimaraes, D., Chiriboga García, M. R., Gonzáles Crisóstomo, G. P., & Vega Mejía, V. C. (2007). Prevalencia de algunos factores de riesgo cardiovascular en dos poblaciones de Huaraz (3 100 m sobre el nivel del mar). *Acta Médica Peruana, 24*(1), 18-21.

Lossio, J. (2006). *Life at high-altitudes: Medical historical debates (Andean region, 1890-1960).* (PhD), University of Manchester, U.K.

Lozano, R., & Monge, C. (1965). Renal function in high-altitude natives and in natives with chronic mountain sickness. *Journal of Applied Physiology, 20*(5), 1026-1027.

Lu, C. J. (1993). Experimental report of Fagopyrum tartaricum on lowering the blood sugar level and lipid level. *Journal of Food Science (Chinese), 3,* 45-46.

Lu, Y., Feskens, E. J. M., Boer, J. M. A., Imholz, S., Verschuren, W. M. M., Wijmenga, C., . . . Dollé, M. E. T. (2010). Exploring genetic determinants of plasma total cholesterol levels and their predictive value in a longitudinal study. *Atherosclerosis, 213*(1), 200-205.

Luis Enrique Macias Bustes, L. E., Cabrera Valentin, J. L., & Blas Posada, M. V. (2011, April). *Hypertension, smoking, diabetes and hypercholesterolemia in altitude.* Paper presented at the European Journal of Cardiovascular Prevention and Rehabilitation.

Luobu, G. (2012). The dynamic balance between adaptation and lesions of the cardiovascular system in Tibetans living at high altitude. In S. Sanders & F. Ming (Eds.), *Advances in high altitude medicine and hypoxic physiology in China* (pp. 33-34). Washington, D.C.: The American Association for the Advancement of Science.

Maccallini, G., Aranda, C., Molinari, C., Colque, G., Biancardi, D., Figueroa, M., . . . Oneto, A. (2012). High rates of dyslipidaemia among indigenous argentinean children living at high altitudes. *International Journal of Clinical Practice, 66*(10), 1015-1015.

Mahajan, S., Kashyap, R., Sood, B., Jaret, P., Mokta, J., Kaushik, N., & Prashar, B. (2004). Stroke at moderate altitude. *Journal of Association of Physicians of India, 52*, 699-702.

Makela, M., Barton, S. A., Schull, W. J., Weidman, W., & Rothhammer, F. (1978). The multinational Andean genetic and health program—IV. Altitude and the blood pressure of the Aymara. *Journal of Chronic Diseases, 31*(9), 587-603.

Málaga, G., Zevallos-Palacios, C., Lazo, M. d. l. Á., & Huayanay, C. (2010). High frequency of dyslipidemia and impaired fasting glycemia in a high altitude Peruvian population. *Revista Peruana de Medicina Experimental y Salud Publica, 27*(4), 557-561.

Malconian, M., Hultgren, H., Nitta, M., Anholm, J., Houston, C., & Fails, H. (1990). The sleep electrocardiogram at extreme altitudes (Operation Everest II). *American Journal of Cardiology, 65*(15), 1014-1020.

Mandal, C., Adak, D., Biswas, S., & Bharati, P. (2011). A study on BMI among the Bhotia of Uttaranchal, India. *Asian Pacific Journal of Tropical Disease, 1*(1), 55-58.

Marchi, K. C., Muniz, J. J., & Tirapelli, C. R. (2014). Hypertension and chronic ethanol consumption: What do we know after a century of study. *World Journal of Cardiology, 6*(5), 283-294.

Mark, A. L., Correia, M., Morgan, D. A., & et al. (1999). State-of-the-art-lecture: obesity induced hypertension: new concepts from emerging biology of obesity. *Hypertension, 33*, 537-541.

Martin, S., Diewold, R., & Cooper, K. (1977). Alcohol, respiration, skin and body temperature during cold water immersion. *Journal of Applied Physiology, 43*(2), 211-215.

Maskey, A., Sayami, A., & Pandey, M. (2003). Coronary artery disease: an emerging epidemic in Nepal. *Journal of Nepal Medical Association, 42*(146), 122-124.

Matsubayashi, K., Kimura, Y., Sakamoto, R., Wada, T., Ishimoto, Y., Hirosaki, M., . . . Kosaka, Y. (2009). Comprehensive geriatric assessment of elderly highlanders in Qinghai, China : activities of daily living, quality of life and metabolic syndrome. *Geriatrics & Gerontology International, 9*(4), 333-341.

McAllister, E. J., Dhurandhar, N. V., Keith, S. W., Aronne, L. J., Barger, J., Baskin, M., . . . Eisenmann, J. C. (2009). Ten putative contributors to the obesity epidemic. *Critical Reviews in Food Science and Nutrition, 49*(10), 868-913.

Meerson, F., Tverdokhlib, V., Nikonorov, A., Filippov, V., & Frolov, B. (1988). The role of suppression of cholesterol 7-hydroxylase activity of the liver in the development of atherogenic stress-induced dyslipoproteinemia. *Kardiologiia, 28*(9), 85-87.

Mehta, K. D., Karki, P., Lamsal, M., Paudel, I. S., Majhi, S., Das, B. K. L., . . . Baral, N. (2011). Hyperglycemia, glucose intolerance, hypertension and socioeconomic position in eastern Nepal. *Southeast Asian Journal of Tropical Medicine and Public Health, 42*(1), 197-207.

Meigs, J. B., Nathan, D. M., Wilson, P. W., Cupples, L. A., & Singer, D. E. (1998). Metabolic risk factors worsen continuously across the spectrum of nondiabetic glucose tolerance: the Framingham Offspring Study. *Annals of Internal Medicine, 128*(7), 524-533.

Mendis, S., Lindholm, L. H., Anderson, S. G., Alwan, A., Koju, R., Onwubere, B. J. C., . . . Heagerty, A. (2011). Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings. *Journal of Clinical Epidemiology, 64*(12), 1451-1462.

Mendis, S., Lindholm, L. H., Mancia, G., Whitworth, J., Alderman, M., Lim, S., & Heagerty, T. (2007). World Health Organization (WHO) and International Society of Hypertension (ISH) risk prediction charts: assessment of cardiovascular risk for prevention and control of cardiovascular disease in low and middle-income countries. *Journal of Hypertension, 25*(8), 1578-1582.

Menezes, A. M. B., Perez-Padilla, R., Jardim, J. B., Muiño, A., Lopez, M. V., Valdivia, G., . . . Victora, C. G. (2005). Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *The Lancet, 366*(9500), 1875-1881.

Meyer, M. G., Toborg, M. A., Denham, S. A., & Mande, M. J. (2008). Cultural perspectives concerning adolescent use of tobacco and alcohol in the Appalachian mountain region. *Journal of Rural Health, 24*(1), 67-74.

Miao, C.-Y., Zuberbuhler, J. S., & Zuberbuhler, J. R. (1988). Prevalence of congenital cardiac anomalies at high altitude. *Journal of the American College of Cardiology, 12*(1), 224-228.

Miller, S., Tudor, C., Nyima, Thorsten, V. R., Sonam, Droyoung, . . . Varner, M. W. (2007). Maternal and neonatal outcomes of hospital vaginal deliveries in Tibet. *International Journal of Gynecology and Obstetrics, 98*(3), 217-221.

Mingji, C., Onakpoya, I. J., Perera, R., Ward, A. M., & Heneghan, C. J. (2015). Relationship between altitude and the prevalence of hypertension in Tibet: a systematic review. *Heart*. doi:10.1136/heartjnl-2014-307158

Ministry of Health and Population, Government of Nepal, Society for Local Integrated Development Nepal (SOLID Nepal), & WHO. (2008). *WHO STEPS Surveillance: Non communicable disease risk factors survey*. Retrieved from Kathmandu, Nepal: http://www.who.int/chp/steps/Nepal_2007_STEPS_Report.pdf

Mishra, S. R., Neupane, D., Bhandari, P. M., Khanal, V., & Kallestrup, P. (2015). Burgeoning burden of non-communicable diseases in Nepal: a scoping review. *Globalization and Health, 11*(32). doi:10.1186/s12992-015-0119-7

Misra, A., Chowbey, P., Makkar, B., Vikram, N., Wasir, J., Chadha, D., . . . Gulati, S. (2009). Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. *The Journal of the Association of Physicians of India, 57*, 163-170.

Mitchell, R., Blane, D., & Bartley, M. (2002). Elevated risk of high blood pressure: climate and the inverse housing law. *International Journal of Epidemiology, 31*(4), 831-838.

Mohanna, S., Baracco, R., & Seclén, S. (2006). Lipid profile, waist circumference, and body mass index in a high altitude population. *High Altitude Medicine & Biology, 7*(3), 245-255.

Moncloa, F., Gómez, M., & Hurtado, A. (1965). Plasma catecholamines at high altitudes. *Journal of Applied Physiology, 20*(6), 1329-1331.

Moore, L. G., Armaza, V. F., Villena, M., & Vargas, E. (2002). Comparative aspects of high-altitude adaptation in human populations. In S. Lahiri, N. R. Prabhakar, & R. E. Forster (Eds.), *Oxygen sensing: molecule to man* (pp. 45-62): Springer.

Moore, L. G., Charles, S. M., & Julian, C. G. (2011). Humans at high altitude: hypoxia and fetal growth. *Respiratory Physiology & Neurobiology, 178*(1), 181-190.

Moore, L. G., Niermeyer, S., & Zamudio, S. (1998). Human adaptation to high altitude: regional and life-cycle perspectives. *American Journal of Physical Anthropology, 107*(S27), 25-64.

Mori, L. M., Seclén, S., Rosas, A., & Arias, A. (2015). *Perú lower diabetes prevalence above 3,000 m of altitude in Peru can be explained by wealth index, age and sex distribution: analysis of the Peruvian Demographic and Health Survey*. Paper presented at the 8th World Congress on Prevention of Diabetes and its Complications. , Cartagena, Columbia.

Mortimer Jr, E. A., Monson, R. R., & MacMahon, B. (1977). Reduction in mortality from coronary heart disease in men residing at high altitude. *New England Journal of Medicine, 296*(11), 581-585.

Mosihuzzaman, M., Nahar, N., Ali, L., Rokeya, B., Khan, A., & Nandi, R. (1993). Hypoglycemic effects of three plants from eastern Himalayan belt. *Diabetes Research, 26*(3), 127-138.

Mozaffarian, D. (2016). Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: a comprehensive review. *Circulation, 133*(2), 187-225.

Mozaffarian, D., Fahimi, S., Singh, G. M., Micha, R., Khatibzadeh, S., Engell, R. E., . . . Powles, J. (2014). Global sodium consumption and death from cardiovascular causes. *New England Journal of Medicine, 371*(7), 624-634.

Mukhopadhyay, B., Mukhopadhyay, S., & Majumder, P. P. (1996). Blood pressure profile of Lepchas of the Sikkim Himalayas: epidemiological study. *Human Biology, 68*(1), 131-145.

Muratsubaki, H., Enomoto, K., Ichijoh, Y., & Yamamoto, Y. (2003). Hypertriglyceridemia associated with decreased post-heparin plasma hepatic triglyceride lipase activity in hypoxic rats. *Archives of Physiology and Biochemistry, 111*(5), 449-454.

Murillo, F., Barton, S. A., Palomino, H., Lenart, V., & Schull, W. J. (1980). The Aymara of Western Bolivia: health and disease. *Bulletin of the Pan American Health Organization, 14*(1), 52-64.

Naeye, R. L. (1965). Children at high altitude: pulmonary and renal abnormalities. *Circulation Research, 16*(1), 33-38.

Napier, K. (2006). Obesity and coronary artery disease. In J. M. Foody (Ed.), *Preventive cardiology: insights into the prevention and treatment of cardiovascular disease* (Second ed., pp. 161-178). Totowa, New Jersey: Humana Press Inc.

National Heart Foundation of Australia. (2006). Position statement: carbohydrates, dietary fibre, glycaemic index/load and cardiovascular disease. Retrieved from www.heartfoundation.com.au

National Institute of Health. (1998). *NIH Clinical Guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report* (NIH publication no. : 98-4083). Retrieved from http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf

National working committee on children and women. (2001). *Report of the People's of China on the Development of Children in the 1990s.*

NCD Risk Factor Collaboration. (2016). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *The Lancet, 387*(10027), 1513-1530.

Negi, P. C., Bhardwaj, R., Kandoria, A., Asotra, S., Ganju, N., Marwaha, R., . . . Kanwar, A. (2012). Epidemiological study of hypertension in natives of Spiti Valley in Himalayas and impact of hypobaric hypoxemia; a cross-sectional study. *Journal of the Association of Physicians of India, 60*, 21-25.

Negi, P. C., Marwaha, R., Asotra, S., Kandoria, A., Ganju, N., Sharma, R., . . . Bhardwaj, R. (2014). Prevalence of high altitude pulmonary hypertension among the natives of Spiti Valley - a high altitude region in Himachal Pradesh, India. *High Altitude Medicine & Biology, 15*(4), 504-510.

Nepal Health Research Council. (2010). *Prevalence of non-communicable diseases in Nepal : Hospital based study*. Retrieved from Kathmandu, Nepal: http://nhrc.org.np:8080/nhrc/handle/123456789/70

Neupane, D., McLachlan, C. S., Sharma, R., Gyawali, B., Khanal, V., Mishra, S. R., . . . Kallestrup, P. (2014). Prevalence of hypertension in member countries of South Asian Association for Regional Cooperation (SAARC): systematic review and meta-analysis. *Medicine, 93*(13), e74. doi:10.1097/MD.0000000000000074

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., . . . Abera, S. F. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet, 384*(9945), 766-781.

Niaz, A., & Nayyar, S. (2003). Cerebrovascular stroke at high altitude. *Journal of the College of Physicians and Surgeons Pakistan, 13*(8), 446-448.

Niermeyer, S., Zamudio, S., & Moore, L. G. (2001). The people. In T. Hornbein & R. Schoene (Eds.), *High altitude: an exploration of human adaptation* (pp. 43-100). New York: CRC Press.

Norboo, T., Yahya, M., Bruce, N., Heady, J., & Ball, K. (1991). Domestic pollution and respiratory illness in a Himalayan village. *International Journal of Epidemiology, 20*(3), 749-757.

Nordestgaard, B. G., Langsted, A., Mora, S., Kolovou, G., Baum, H., Bruckert, E., . . . Borén, J. (2016). Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cut-points—a joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine. *European Heart Journal*, ehw152.

O'Donnell, M., Mente, A., Rangarajan, S., McQueen, M. J., Wang, X., Liu, L., . . . Devanath, A. (2014). Urinary sodium and potassium excretion, mortality, and cardiovascular events. *New England Journal of Medicine, 371*(7), 612-623.

O'Donnell, M., Xavier, D., Liu, L., Zhang, H., Chin, S. L., Rao-Melacini, P., . . . McQueen, M. J. (2010). Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *The Lancet, 376*(9735), 112-123.

O'Donnell, M., Yusuf, S., Mente, A., Gao, P., Mann, J. F., Teo, K., . . . Dans, A. (2011). Urinary sodium and potassium excretion and risk of cardiovascular events. *Journal of the American Medical Association, 306*(20), 2229-2238.

Ogden, C. L., Carroll, M. D., Kit, B. K., & Flegal, K. M. (2014). Prevalence of childhood and adult obesity in the United States, 2011-2012. *Journal of the American Medical Association, 311*(8), 806-814.

Ojeda, E., Blümel, J. E., Vallejo, M. S., & Lavín, P. (2014). Climacteric symptoms in Quechua and Mestizo women from the Andean region of Cusco, Peru: effects of altitude and ethnicity. *Maturitas, 77*(4), 356-360.

Okuda, H., Yanagi, I., & Fujii, S. (1966). The mechanism of in vitro stimulation of lipolysis by adrenaline. *The Journal of Biochemistry, 59*(5), 438-442.

Okumiya, K., Fukutomi, E., Kimura, Y., Ishimoto, Y., Chen, W. l., Ishikawa, M., . . . Otsuka, K. (2011). Strong association between polycythemia and glucose intolerance in older adults living at high altitudes in the Andes. *Journal of the American Geriatrics Society, 59*(10), 1971-1973.

Okumiya, K., Sakamoto, R., Ishimoto, Y., Kimura, Y., Fukutomi, E., Ishikawa, M., . . . Kato, E. (2016). Glucose intolerance associated with hypoxia in people living at high altitudes in the Tibetan highland. *BMJ Open, 6*(2), e009728. doi:10.1136/bmjopen-2015-009728

Okumiya, K., Sakamoto, R., Kimura, Y., Ishimoto, Y., Wada, T., Ishine, M., . . . Ge, R. L. (2010). Diabetes mellitus and hypertension in elderly highlanders in Asia. *Journal of the American Geriatrics Society, 58*(6), 1193-1195.

Oli, K. K., & Agrawal, J. P. (2001). Critical review of stroke. *Journal of Institute of Medicine, 23*, 68-71.

Ostadal, B., & Kolar, F. (2007). Cardiac adaptation to chronic high-altitude hypoxia: beneficial and adverse effects. *Respiratory Physiology & Neurobiology, 158*(2), 224-236.

Otsuka, K., Norboo, T., Otsuka, Y., Higuchi, H., Hayajiri, M., Narushima, C., . . . Wada, T. (2005). Effect of aging on blood pressure in Leh, Ladakh, a high-altitude (3524 m) community, by comparison with a Japanese town. *Biomedicine and Pharmacotherapy, 59*, S54-S57.

Oyarzun, P. J., Borja, R. M., Sherwood, S., & Parra, V. (2013). Making sense of agrobiodiversity, diet, and intensification of smallholder family farming in the highland Andes of Ecuador. *Ecology of Food and Nutrition, 52*(6), 515-541.

Padwal, R. S., & Sharma, A. M. (2010). Obesity. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 221-234): Blackwell Publishing.

Painschab, M. S., Davila-Roman, V. G., Gilman, R. H., Vasquez-Villar, A. D., Pollard, S. L., Wise, R. A., . . . Casas, J. P. (2013). Chronic exposure to biomass fuel is associated with increased carotid artery intima-media thickness and a higher prevalence of atherosclerotic plaque. *Heart, 99*(14), 984-991.

Pan American Health Organization. (1994). *Health conditions in the Americas. Scientific publication 549.* Washington DC: Pan American Health Organization.

Pan, W. H., Yeh, W. T., Chang, H. Y., Hwu, C. M., & Ho, L. T. (2003). Prevalence and awareness of diabetes and mean fasting glucose by age, sex, and region: results from the Nutrition and Health Survey in Taiwan, 1993–1996. *Diabetic Medicine, 20*(3), 182-185.

Pandey, M. R. (1970). Myocardial infarction in Nepal. *Indian Heart Journal, 22*, 73-82.

Pandey, M. R., Neupane, R. P., & Gautam, A. (1988). Epidemiological study of tobacco smoking behaviour among adults in a rural community of the hill region of Nepal with special reference to attitude and beliefs. *International Journal of Epidemiology, 17*(3), 535-541.

Papaetis, G. S., Papakyriakou, P., & Panagiotou, T. N. (2015). Central obesity, type 2 diabetes and insulin: exploring a pathway full of thorns. *Archives of Medical Science, 11*(3), 463-482.

Parajuli, V. J., Macdonald, S., & Jimba, M. (2015). Social–contextual factors associated with alcohol use among adolescents of traditional alcohol user and nonuser ethnic groups of Nepal. *Journal of Ethnicity in Substance Abuse, 14*(2), 151-165.

Paralikar, S. J. (2012). High altitude pulmonary edema-clinical features, pathophysiology, prevention and treatment. *Indian Journal of Occupational and Environmental Medicine, 16*(2), 59-62.

Parks, E. J. (2001). Effect of dietary carbohydrate on triglyceride metabolism in humans. *Journal of Nutrition, 131*(10), 2772S-2774S.

Pawson, I. G. (1977). Growth characteristics of populations of Tibetan origin in Nepal. *American Journal of Physical Anthropology, 47*(3), 473-482.

Pawson, I. G., & Huicho, L. (2010). Persistence of growth stunting in a Peruvian high altitude community, 1964–1999. *American Journal of Human Biology, 22*(3), 367-374.

Pawson, I. G., & Jest, C. (1978). The high-altitude areas of the world and their cultures. In P. T. Baker (Ed.), *The biology of high-altitude peoples* (pp. 17-45). London, New York, Melbourne: Cambridge University Press.

Pearce, J. L., Aguilar-Villalobos, M., Rathbun, S. L., & Naeher, L. P. (2009). Residential exposures to PM 2.5 and CO in Cusco, a high-altitude city in the Peruvian Andes: a pilot study. *Archives of Environmental & Occupational Health, 64*(4), 278-282.

Pei, T., Li, X., Tao, F., Xu, H., You, H., Zhou, L., . . . Gao, Y. (2012). Burden of disease resulting from chronic mountain sickness among young Chinese male immigrants in Tibet. *BMC Public Health, 12*(401). doi:10.1186/1471-2458-12-401

Peñaloza, D., & Arias-Stella, J. (2007). The heart and pulmonary circulation at high altitudes healthy highlanders and chronic mountain sickness. *Circulation, 115*(9), 1132-1146.

Peñaloza, D., & Echevarría, M. (1957). Electrocardiographic observations on ten subjects at sea level and during one year of residence at high altitudes. *American Heart Journal, 54*(6), 811-822.

Peñaloza, D., Gamboa, R., Dyer, J., Echevarría, M., & Marticorena, E. (1960). The influence of high altitudes on the electrical activity of the heart. I. Electrocardiographic and vectocardiographic observations in the newborn, infants, and children. *American Heart Journal, 59*(1), 111-128.

Pereira-Santos, M., Costa, P., Assis, A., & Santos, D. (2015). Obesity and vitamin D deficiency: a systematic review and meta-analysis. *Obesity Reviews, 16*(4), 341-349.

Peto, R., Boreham, J., & Lopez, A. D. (1996). *Mortality from smoking in developed countries*: Oxford University Press.

Peto, R., Boreham, J., Lopez, A. D., Thun, M., & Heath, C. (1992). Mortality from tobacco in developed countries: indirect estimation from national vital statistics. *The Lancet, 339*(8804), 1268-1278.

Piccinelli, M., Tessari, E., Bortolomasi, M., Piasere, O., Semenzin, M., Garzotto, N., & Tansella, M. (1997). Efficacy of the alcohol use disorders identification test as a screening tool for hazardous alcohol intake and related disorders in primary care: a validity study. *The British Medical Journal, 314*(7078), 420-425.

Picón-Reátegui, E. (1963). Intravenous glucose tolerance test at sea level and at high altitudes. *Journal of Clinical Endocrinology and Metabolism, 23*(12), 1256-1261.

Pipe, A. (2010). Tobacco and cardiovascular disease : achieving smoking cessation in cardiac patients. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based Cardiology* (3rd ed., pp. 125-137): Blackwell Publishing.

Ponce-Caballero, G., Loma-Rodriguez, F., Villegas, P., & Laura, G. (1976). Persistencia del conducto arterial hipertenso en la altura. *Anthropologie des Populations Andines. INSERM, 63*, 333-344.

Pradhan, B., Chappuis, F., Baral, D., Karki, P., Rijal, S., Hadengue, A., & Gache, P. (2012). The alcohol use disorders identification test (AUDIT): validation of a Nepali version for the detection of alcohol use disorders and hazardous drinking in medical settings. *Substance Abuse Treatment, Prevention, and Policy, 7*, 42. doi:10.1186/1747-597X-7-42

Prospective Studies Collaboration. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet, 360*(9349), 1903-1913.

Prospective Studies Collaboration. (2007). Blood cholesterol and vascular mortality by age, sex and blood pressure: a meta analysis of individual data from 61 prospective studies with 55000 vascular deaths. *The Lancet, 370*(9602), 1829-1839.

Pryor, R., Weaver, W. F., & Blount, S. G. (1965). Electrocardiographic observation of 493 residents living at high altitude (10,150 feet). *American Journal of Cardiology, 16*(4), 494-499.

Quintero, P., Milagro, F., Campion, J., & Martinez, J. (2010). Impact of oxygen availability on body weight management. *Medical Hypotheses, 74*(5), 901-907.

Rambal, C. (2012). Tibetan pride of place : or, why Nepal's Bhotiyas are not an ethnic group. In D. N. Gellner, J. Pfaff-Czarnecka, & J. Whelpton (Eds.), *Nationalism and ethnicity in a Hindu Kingdom : the politics of culture in contemporary Nepal* (pp. 379-414). New York: Taylor and Francis.

Ramos, A., Krüger, H., Muro, M., & Arias-Stella, J. (1967). Pathology of natives of high altitudes. Study of the causes of death in 300 autopsies. *Boletin de la Oficina Sanitaria Panamericana. Pan American Sanitary Bureau, 62*(6), 496-502.

Raynaud, J., Valeix, P., Drouet, L., Escourrou, P., & Durand, J. (1981). Electrocardiographic observations in high altitude residents of Nepal and Bolivia. *International Journal of Biometeorology, 25*(3), 205-217.

Reddy, K. S. (2010). Diet and cardiovascular disease. In S. Yusuf, J. A. Cairns, A. J. Camm, E. L. Fallen, & B. J. Gersh (Eds.), *Evidence-based cardiology* (3rd ed., pp. 304-327): Blackwell Publishing.

Regensteiner, J. G., & Moore, L. G. (1985). Migration of the elderly from high altitudes in Colorado. *Journal of the American Medical Association, 253*(21), 3124-3128.

Regmi, P. R., & Wyber, R. (2013). Prevention of rheumatic fever and heart disease: Nepalese experience. *Global Heart, 8*(3), 247-252.

Rehm, J., Baliunas, D., Borges, G. L., Graham, K., Irving, H., Kehoe, T., . . . Poznyak, V. (2010). The relation between different dimensions of alcohol consumption and burden of disease: an overview. *Addiction, 105*(5), 817-843.

Richalet, J.-P., Larmignat, P., Poitrine, E., Letournel, M., & Canouï-Poitrine, F. (2012). Physiological risk factors for severe high-altitude illness: a prospective cohort study. *American Journal of Respiratory and Critical Care Medicine, 185*(2), 192-198.

Rimm, E. B., Williams, P., Fosher, K., Criqui, M., & Stampfer, M. J. (1999). Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *The British Medical Journal, 319*(7224), 1523-1528.

Roberts, A., Butterfield, G., Cymerman, A., Reeves, J., Wolfel, E., & Brooks, G. (1996). Acclimatization to 4,300-m altitude decreases reliance on fat as a substrate. *Journal of Applied Physiology, 81*(4), 1762-1771.

Roeggla, G., Roeggla, H., Roeggla, M., Binder, M., & Laggner, A. N. (1995). Effect of alcohol on acute ventilatory adaptation to mild hypoxia at moderate altitude. *Annals of Internal Medicine, 122*(12), 925-927.

Roerecke, M., & Rehm, J. (2010). Irregular heavy drinking occasions and risk of ischemic heart disease: a systematic review and meta-analysis. *American Journal of Epidemiology, 171*(6), 633-644.

Romhilt, D. W., & Estes, E. H. (1968). A point-score system for the ECG diagnosis of left ventricular hypertrophy. *American Heart Journal, 75*(6), 752-758.

Ronksley, P. E., Brien, S. E., Turner, B. J., Mukamal, K. J., & Ghali, W. A. (2011). Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. *The British Medical Journal, 342*, d671. doi:10.1136/bmj.d671

Rose, G., Stamler, J., Stamler, R., Elliott, P., Marmot, M., Pyorala, K., . . . Sans, S. (1988). Intersalt: An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. *The British Medical Journal, 297*(6644), 319-328.

Rosenblum, J. L., Castro, V. M., Moore, C. E., & Kaplan, L. M. (2012). Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. *The American Journal of Clinical Nutrition, 95*(1), 101-108.

Rotta, A., & Lopez, A. (1959). Electrocardiographic patterns in man at high altitudes. *Circulation, 19*(5), 719-728.

Rudolph, G. (1992). In memory of Paul Bert (1833-1886) and the development of high altitude physiology in Switzerland. *Gesnerus, 50*, 79-95.

Ruhli, F. J., Henneberg, M., Schaer, D. J., Imhof, A., Schleiffenbaum, B., & Woitek, U. (2008). Determinants of inter-individual cholesterol level variation in an unbiased young male sample. *Swiss Medical Weekly, 138*(19-20), 286-291.

Ruidavets, J.-B., Ducimetière, P., Evans, A., Montaye, M., Haas, B., Bingham, A., . . . Kee, F. (2010). Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *The British Medical Journal, 341*, c6077. doi:http://dx.doi.org/10.1136/bmj.c6077

Ruiz, L., Figueroa, M., Horna, C., & Peñaloza, D. (1969). Occurrence of arterial hypertension and ischemic heart disease in high altitudes. *Archivos del Instituto de Cardiología de México, 39*(4), 476-489.

Ruiz, L., & Penaloza, D. (1977). Altitude and hypertension. *Mayo Clinic Proceedings, 52*(7), 442-445.

Santos, J. L. (2000). Plasma leptin and insulin levels in Aymara natives from Chile. *Annals of Human Biology, 27*(3), 271-279.

Santos, J. L., Pérez-Bravo, F., Carrasco, E., Calvillán, M., & Albala, C. (2001). Low prevalence of type 2 diabetes despite a high average body mass index in the Aymara natives from Chile. *Nutrition, 17*(4), 305-309.

Sarfo, F. S., Gebregziabher, M., Ovbiagele, B., Akinyemi, R., Owolabi, L., Obiako, R., . . . Melikam, S. (2016). Validation of the 8-item questionnaire for verifying stroke free status with and without pictograms in three West African languages. *eNeurologicalSci, 3*, 75-79.

Sasaki, H., Fukuda, S., Otani, H., Zhu, L., Yamaura, G., Engelman, R. M., . . . Maulik, N. (2002). Hypoxic preconditioning triggers myocardial angiogenesis: a novel approach to enhance contractile functional reserve in rat with myocardial infarction. *Journal of Molecular and Cellular Cardiology, 34*(3), 335-348.

Sawhney, R., Malhotra, A., & Singh, T. (1991). Glucoregulatory hormones in man at high altitude. *European Journal of Applied Physiology and Occupational Physiology, 62*(4), 286-291.

Schargrodsky, H., Hernández-Hernández, R., Champagne, B. M., Silva, H., Vinueza, R., Ayçaguer, L. C. S., . . . Pellegrini, F. (2008). CARMELA: assessment of cardiovascular risk in seven Latin American cities. *The American Journal of Medicine, 121*(1), 58-65.

Schinder, E., & Ruder, A. (1989). Epidemiology of coca and alcohol use among high-altitude miners in argentina. *American Journal of Industrial Medicine, 15*(5), 579-587.

Schneider, M., Bernasch, D., Weymann, J., Holle, R., & Bartsch, P. (2002). Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate. *Medicine and Science in Sports and Exercise, 34*(12), 1886-1891.

Schoutsen, B., De Jong, J. W., Harmsen, E., De Tombe, P. P., & Achterberg, P. W. (1983). Myocardial xanthine oxidase/dehydrogenase. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 762*(4), 519-524.

Sehgal, A., Krishan, I., Malhotra, R., & Gupta, H. (1968). Observations on the blood pressure of Tibetans. *Circulation, 37*(1), 36-44.

Semenza, G. L. (2006). Regulation of physiological responses to continuous and intermittent hypoxia by hypoxia-inducible factor 1. *Experimental Physiology, 91*(5), 803-806.

Shah, S. M. A., Arif, A. A., Delclos, G. L., Khan, A. R., & Khan, A. (2001). Prevalence and correlates of smoking on the roof of the world. *Tobacco Control, 10*, e1. doi:10.1136/tc.10.1.e1

Shah, S. M. A., Luby, S., Rahbar, M., Khan, A. W., & McCormick, J. B. (2001). Hypertension and its determinants among adults in high mountain villages of the Northern Areas of Pakistan. *Journal of Human Hypertension, 15*(2), 107-112.

Shah, S. M. A., Nanan, D., Rahbar, M. H., Rahim, M., & Nowshad, G. (2004). Assessing obesity and overweight in a high mountain Pakistani population. *Tropical Medicine and International Health, 9*(4), 526-532.

Shahid Gangalal National Heart Centre. (2008). *Annual report 2008*. Kathmandu, Nepal.

Sharma, A., & Khandelwal, S. (2000). Women with alcohol-related problems in Nepal. *Addiction, 95*(7), 1105-1106.

Sharma, S. C., Vijayan, G. P., Suri, M. L., & Seth, H. N. (1977). Platelet adhesiveness in young patients with ischaemic stroke. *Journal of Clinical Pathology, 30*(7), 649-652.

Sharma, S. K., Ghimire, A., Radhakrishnan, J., Thapa, L., Shrestha, N. R., Paudel, N., . . . Brodie, D. (2011). Prevalence of hypertension, obesity, diabetes, and metabolic syndrome in Nepal. *International Journal of Hypertension, 2011*. doi:10.4061/2011/821971

She, J., Yang, P., Hong, Q., & Bai, C. (2013). Lung cancer in China: challenges and interventions. *Chest, 143*(4), 1117-1126.

Sherpa, L. Y., Stigum, H., Chongsuvivatwong, V., Luobu, O., Thelle, D. S., Nafstad, P., & Bjertness, E. (2011). Lipid profile and its association with risk factors for coronary heart disease in the highlanders of Lhasa, Tibet. *High Altitude Medicine & Biology, 12*(1), 57-63.

Sherpa, L. Y., Stigum, H., Chongsuvivatwong, V., Nafstad, P., & Bjertness, E. (2013). Prevalence of metabolic syndrome and common metabolic components in high altitude farmers and herdsmen at 3700 m in Tibet. *High Altitude Medicine & Biology, 14*(1), 37-44.

Sherpa, L. Y., Stigum, H., Chongsuvivatwong, V., Thelle, D. S., & Bjertness, E. (2010). Obesity in Tibetans aged 30–70 living at different altitudes under the north and south faces of Mt. Everest. *International Journal of Environmental Research and Public Health, 7*(4), 1670-1680.

Sherpa, L. Y., Supamai, S., & Virasakdi, C. (2008). Impaired glucose regulation in a Sherpa indigenous population living in the Everest region of Nepal and in Kathmandu Valley. *High Altitude Medicine & Biology, 9*(3), 217-222.

Shrestha, A., Shah, D., Adhikari, S. K. K., Sapkota, S., & Regmi, P. (2011). Retrospective analysis of Stroke and its risk factors at Bir Hospital. *Post-Graduate Medical Journal of NAMS, 11*(2), 28-30.

Shrestha, S., Shrestha, A., Shrestha, S., & Bhattarai, D. (2012). Blood Pressure in Inhabitants of High Altitude of Western Nepal. *Journal of Nepal Medical Association, 52*(188), 154-158.

Shrestha, U., Singh, D., & Bhattarai, M. (2006). The prevalence of hypertension and diabetes defined by fasting and 2-h plasma glucose criteria in urban Nepal. *Diabetic Medicine, 23*(10), 1130-1135.

Simkhada, P., Poobalan, A., Simkhada, P. P., Amalraj, R., & Aucott, L. (2009). Knowledge, attitude, and prevalence of overweight and obesity among civil servants in Nepal. *Asia-Pacific Journal of Public Health, 23*, 507-517.

Simons, L. A. (1986). Interrelations of lipids and lipoproteins with coronary artery disease mortality in 19 countries. *American Journal of Cardiology, 57*(14), G5-G10.

Singh, I., & Chohan, I. (1973). Reversal of abnormal fibrinolytic activity, blood coagulation factors and platelet function in high-altitude pulmonary oedema with frusemide. *International Journal of Biometeorology, 17*(1), 73-81.

Sinnett, P., & Whyte, H. (1973). Epidemiological studies in a total highland population, Tukisenta, New Guinea: cardiovascular disease and relevant clinical, electrocardiographic, radiological and biochemical findings. *Journal of Chronic Diseases, 26*(5), 265-290.

Siqués, P., Brito, J., Leon-Velarde, F., Barrios, L., De La Cruz, J. J., López, V., & Herruzo, R. (2007). Hematological and lipid profile changes in sea-level natives after exposure to 3550-m altitude for 8 months. *High Altitude Medicine & Biology, 8*(4), 286-295.

Smith, C. (1999). Blood pressures of Sherpa men in modernizing Nepal. *American Journal of Human Biology, 11*(4), 469-479.

Smyth, A., Teo, K. K., Rangarajan, S., O'Donnell, M., Zhang, X., Rana, P., . . . Yusuf, S. (2015). Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: a prospective cohort study. *The Lancet, 386*(10007), 1945-1954.

Sokolow, M., & Lyon, T. P. (1949). The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *American Heart Journal, 37*(2), 161-186.

Solomon, C. G., & Manson, J. (1997). Obesity and mortality: a review of the epidemiologic data. *The American Journal of Clinical Nutrition, 66*(4), 1044S-1050S.

Sørensen, H. T., Sabroe, S., Rothman, K. J., Gillman, M., Fischer, P., & Sørensen, T. I. (1997). Relation between weight and length at birth and body mass index in young adulthood: cohort study. *The British Medical Journal, 315*(7116), 1137.

Srivastava, K. K., Kumria, M. M., Grover, S. K., Sridharan, K., & Malhotra, M. S. (1975). Glucose tolerance of lowlanders during prolonged stay at high altitude and among high altitude natives. *Aviation Space and Environmental Medicine, 46*(2), 144-146.

Stevens, S. F. (1996). *Claiming the high ground: Sherpas, subsistence, and environmental change in the highest Himalaya*: Motilal Banarsidass Publisher.

Stewart, C. P., Christian, P., Wu, L. S., LeClerq, S. C., Khatry, S. K., & West Jr, K. P. (2013). Prevalence and risk factors of elevated blood pressure, overweight, and dyslipidemia in adolescent and young adults in rural Nepal. *Metabolic Syndrome and Related Disorders, 11*(5), 319-328.

Stockwell, T., Donath, S., Cooper-Stanbury, M., Chikritzhs, T., Catalano, P., & Mateo, C. (2004). Under-reporting of alcohol consumption in household surveys: a comparison of quantity–frequency, graduated–frequency and recent recall. *Addiction, 99*(8), 1024-1033.

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., . . . Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Journal of the American Medical Association, 283*(15), 2008-2012.

Stuber, T., & Scherrer, U. (2010). Circulatory adaptation to long-term high altitude exposure in aymaras and Caucasians. *Progress in Cardiovascular Diseases, 52*(6), 534-539.

Sullivan, K. M., Mei, Z., Grummer-Strawn, L., & Parvanta, I. (2008). Haemoglobin adjustments to define anaemia. *Tropical Medicine and International Health, 13*(10), 1267-1271.

Sun, S. (1986). Epidemiology of hypertension on the Tibetan Plateau. *Human Biology, 58*(4), 507-515.

Sung, K.-C., Kim, S. H., & Reaven, G. M. (2007). Relationship among alcohol, body weight, and cardiovascular risk factors in 27,030 Korean men. *Diabetes Care, 30*(10), 2690-2694.

Superko, H. R. (1996). What can we learn about dense low density lipoprotein and lipoprotein particles from clinical trials? *Current Opinion in Lipidology, 7*(6), 363-368.

Sutton, J., & Garmendia, F. (1976). Hormonal variation during physical exertion at high altitude. *Archivos de Biología Andina, 7*(2), 83-93.

Swenson, E. R. (2013). Hypoxic pulmonary vasoconstriction. *High Altitude Medicine & Biology, 14*(2), 101-110.

Tag, H., Kalita, P., Dwivedi, P., Das, A., & Namsa, N. D. (2012). Herbal medicines used in the treatment of diabetes mellitus in Arunachal Himalaya, northeast, India. *Journal of Ethnopharmacology, 141*(3), 786-795.

Takhelmayum, R., Thanpari, C., Kumar, S., Singh, A., & Sinha, J. (2014). Lipid profile of population of central region of Nepal. *Mymensingh Medical Journal, 23*(3), 552-557.

Tin'kov, A. N., & Aksenov, V. A. (2002). Effects of intermittent hypobaric hypoxia on blood lipid concentrations in male coronary heart disease patients. *High Altitude Medicine & Biology, 3*(3), 277-282.

Tonstad, S., & Johnston, J. A. (2006). Cardiovascular risks associated with smoking: a review for clinicians. *European Journal of Cardiovascular Prevention and Rehabilitation, 13*(4), 507-514.

Toole, J. F., Lefkowitz, D. S., Chambless, L. E., Wijnberg, L., Paton, C. C., & Heiss, G. (1996). Self-reported transient ischemic attack and stroke symptoms: methods and baseline prevalence: the ARIC Study, 1987–1989. *American Journal of Epidemiology, 144*(9), 849-856.

Torres, J., Correa, P., Ferreccio, C., Hernandez-Suarez, G., Herrero, R., Cavazza-Porro, M., . . . Morgan, D. (2013). Gastric cancer incidence and mortality is associated with altitude in the mountainous regions of Pacific Latin America. *Cancer Causes and Control, 24*(2), 249-256.

Tripathy, V., & Gupta, R. (2007). Blood pressure variation among Tibetans at different altitudes. *Annals of Human Biology, 34*(4), 470-483.

Tyagi, R., Tungdim, M. G., Bhardwaj, S., & Kapoor, S. (2008). Age, altitude and gender differences in body dimensions. *Anthropologischer Anzeiger, 66*, 419-434.

Vaidya, A. (2011). Tackling cardiovascular health and disease in Nepal: epidemiology, strategies and implementation. *Heart Asia, 3*(1), 87-91.

Vaidya, A., Aryal, U. R., & Krettek, A. (2013). Cardiovascular health knowledge, attitude and practice/behaviour in an urbanising community of Nepal: a population-based cross-sectional study from Jhaukhel-Duwakot Health Demographic Surveillance Site. *BMJ Open, 3*(10), e002976. doi:10.1136/bmjopen-2013-002976

Vaidya, A., & Krettek, A. (2014). Physical activity level and its sociodemographic correlates in a peri-urban Nepalese population: a cross-sectional study from the Jhaukhel-Duwakot health demographic surveillance site. *International Journal of Behavioral Nutrition and Physical Activity, 11*, 39. doi:10.1186/1479-5868-11-39

Vaidya, A., Pathak, R. P., & Pandey, M. R. (2012). Prevalence of hypertension in Nepalese community triples in 25 years: a repeat cross-sectional study in rural Kathmandu. *Indian Heart Journal, 64*(2), 128-131.

Vaidya, A., Pokharel, P. K., Nagesh, S., Karki, P., Kumar, S., & Majhi, S. (2005). Association of obesity and physical activity in adult males of Dharan, Nepal. *Kathmandu University Medical Journal, 4*(2), 192-197.

Vaidya, A., Pokharel, P. K., Nagesh, S., Karki, P., Kumar, S., & Majhi, S. (2009). Prevalence of coronary heart disease in the urban adult males of eastern Nepal: a population-based analytical cross-sectional study. *Indian Heart Journal, 61*(4), 341-347.

Vallerand, A., & Jacobs, I. (1990). Influence of cold exposure on plasma triglyceride clearance in humans. *Metabolism: Clinical and Experimental, 39*(11), 1211-1218.

van den Bemd, G.-J., Pols, H. A., & van Leeuwen, J. P. (2000). Anti-tumor effects of 1, 25-dihydroxyvitamin D3 and vitamin D analogs. *Current Pharmaceutical Design, 6*(7), 717-732.

van Rooyen, J. M., Kruger, H. S., Huisman, H. W., Schutte, A. E., Malan, N. T., & Schutte, R. (2005). Early cardiovascular changes in 10 to 15 year old stunted children: the transition and health during urbanization in South Africa in children study. *Nutrition, 21*(7), 808-814.

Vats, P., Ray, K., Majumadar, D., Joseph, D. A., Bayen, S., Akunov, A., . . . Singh, S. B. (2013). Changes in cardiovascular functions, lipid profile, and body composition at high altitude in two different ethnic groups. *High Altitude Medicine & Biology, 14*(1), 45-52.

Vellakkal, S., Subramanian, S., Millett, C., Basu, S., Stuckler, D., & Ebrahim, S. (2013). Socioeconomic inequalities in non-communicable diseases prevalence in India: disparities between self-reported diagnoses and standardized measures. *PloS One, 8*(7), e68219. doi:0.1371/journal.pone.0068219

Villareal, D. T., Chode, S., Parimi, N., Sinacore, D. R., Hilton, T., Armamento-Villareal, R., . . . Shah, K. (2011). Weight loss, exercise, or both and physical function in obese older adults. *New England Journal of Medicine, 364*(13), 1218-1229.

Virues-Ortega, J., Hogan, A. M., Baya-Botti, A., Kirkham, F. J., Baldeweg, T., Mahillo-Fernandez, I., . . . Bucks, R. S. (2009). Survival and mortality in older adults living at high altitude in Bolivia: a preliminary report. *Journal of the American Geriatrics Society, 57*(10), 1955-1956.

Voors, A. W., & Johnson, W. D. (1979). Altitude and arteriosclerotic heart disease mortality in white residents of 99 of the 100 largest cities in the United States. *Journal of Chronic Diseases, 32*(1), 157-162.

Voss, J. D., Masuoka, P., Webber, B. J., Scher, A. I., & Atkinson, R. L. (2013). Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States. *International Journal of Obesity, 37*(10), 1407-1412.

Wakabayashi, I., & Araki, Y. (2010). Influences of gender and age on relationships between alcohol drinking and atherosclerotic risk factors. *Alcoholism: Clinical and Experimental Research, 34*(s1), S54-S60.

Wannamethee, S., Shaper, A., & Whincup, P. (2005). Alcohol and adiposity: effects of quantity and type of drink and time relation with meals. *International Journal of Obesity, 29*(12), 1436-1444.

Wasielewski, J. A., & Holloway, F. A. (2001). Alcohol's interactions with circadian rhythms. *Alcohol Research & Health, 25*, 94-100.

Weitz, C. A. (1982). Blood pressure at rest and during exercise among Sherpas and Tibetan migrants in Nepal. *Social Science and Medicine, 16*(2), 223-231.

West, J. B. (2002). Highest permanent human habitation. *High Altitude Medicine & Biology, 3*(4), 401-407.

West, J. B. (2003a). Acclimatization to high altitude: truths and misconceptions. *High Altitude Medicine & Biology, 4*(4), 401-402.

West, J. B. (2003b). Improving oxygenation at high altitude: acclimatization and O2 enrichment. *High Altitude Medicine & Biology, 4*(3), 389-398.

West, J. B. (2011). Exciting times in the study of permanent residents of high altitude. *High Altitude Medicine & Biology, 12*(1), 1-1.

Westman, E. C. (1995). Does smokeless tobacco cause hypertension? *Southern Medical Journal, 88*(7), 716-720.

Willey, J. Z., Xu, Q., Boden-Albala, B., Paik, M. C., Moon, Y. P., Sacco, R. L., & Elkind, M. S. (2009). Lipid profile components and risk of ischemic stroke: the Northern Manhattan Study (NOMAS). *Archives of Neurology, 66*(11), 1400-1406.

Williams, E. (1975). Mountaineering and the endocrine system. In C. Clarke, M. Ward, & E. Williams (Eds.), *Mountain medicine and physiology* (pp. 38): Alpine Club, London.

Windsor, J. S., Rodway, G. W., & Montgomery, H. E. (2010). A review of electrocardiography in the high altitude environment. *High Altitude Medicine & Biology, 11*(1), 51-60.

Woolcott, O. O., Ader, M., & Bergman, R. N. (2015). Glucose homeostasis during short-term and prolonged exposure to high altitudes. *Endocrine Reviews*, *36*(2), 149-173.

Woolcott, O. O., Castillo, O. A., Torres, J., Damas, L., & Florentini, E. (2002). Serum leptin levels in dwellers from high altitude lands. *High Altitude Medicine & Biology, 3*(2), 245-246.

World Health Organisation. (1995). *Physical status: the use and interpretation of anthropometry. Report of a WHO expert committee.* Retrieved from Geneva, Switzerland:

World Health Organization. (1995). *Physical status: the use of and interpretation of anthropometry, report of a WHO expert committee*. Retrieved from Geneva, Switzerland: http://apps.who.int/iris/handle/10665/37003

World Health Organization. (1997). *Tobacco or health : A global status report*. Retrieved from Geneva, Switzerland: http://apps.who.int/iris/handle/10665/41922

World Health Organization. (2000). *Obesity: preventing and managing the global epidemic* (894). Retrieved from Geneva, Switzerland: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/

World Health Organization. (2003). *Research report on NCD risk factors surveillance in Nepal, 2003*. Retrieved from Kathmandu, Nepal: http://nhrc.org.np:8080/nhrc/handle/123456789/524

World Health Organization. (2007a). *Prevention of cardiovascular disease: pocket guidelines for assessment and management of cardiovascular risk*. Retrieved from Geneva, Switzerland: http://www.who.int/cardiovascular_diseases/guidelines/Pocket_GL_information/en/

World Health Organization. (2007b). *WHO expert committee on problems related to alcohol consumption,* (0512-3054). Retrieved from Geneva, Switzerland: http://www.who.int/substance_abuse/expert_committee_alcohol/en/

World Health Organization. (2008). *Waist circumference and waist-hip ratio, report of a WHO expert consultation*. Retrieved from Geneva, Switzerland: http://apps.who.int/iris/bitstream/10665/44583/1/9789241501491_eng.pdf

World Health Organization. (2011). *Non-communicable diseases country profiles 2011*. Retrieved from Geneva, Switzerland: http://www.who.int/nmh/publications/ncd_profiles2011/en/

World Health Organization. (2014a). *Assessing national capacity for the prevention and control of noncommunicable diseases. Report of the 2013 global survey*. Retrieved from Geneva, Switzerland: http://www.who.int/chp/ncd_capacity/en/

World Health Organization. (2014b). *Global status report of noncommunicable disease 2014*. Retrieved from Geneva, Switzerland: http://www.who.int/nmh/publications/ncd-status-report-2014/en/

World Health Organization. (2014c). *Global status report on alcohol and health 2014*. Retrieved from Geneva, Switzerland: http://www.who.int/substance_abuse/publications/global_alcohol_report/en/

World Health Organization. (2015a). *Healthy diet*. Retrieved from Geneva, Switzerland: http://www.who.int/mediacentre/factsheets/fs394/en/

World Health Organization. (2015b). *Obesity and overweight* (311). Retrieved from Geneva, Switzerland: http://www.who.int/mediacentre/factsheets/fs311/en/

World Health Organization. (2015c). *Tobacco* (339). Retrieved from Geneva, Switzerland: http://www.who.int/mediacentre/factsheets/fs339/en/

World Health Organization : Joint WHO/FAO expert consultation. (2003). *Diet, nutrition and the prevention of chronic diseases*. Retrieved from Geneva, Switzerland: http://health.euroafrica.org/books/dietnutritionwho.pdf

Wright, S. M., & Aronne, L. J. (2012). Causes of obesity. *Abdominal Imaging, 37*(5), 730-732.

Wu, T.-Y. (2001). Take note of altitude gastrointestinal bleeding *Newsletter of International Society of Mountain Medicine* (Vol. 10, pp. 9-11).

Wu, T.-Y., Ding, S.-Q., Liu, J.-L., Jia, J.-H., Chai, Z.-C., Dai, R.-C., . . . Kayser, B. (2012). Smoking, acute mountain sickness and altitude acclimatisation: a cohort study. *Thorax, 67*(10), 914-919.

Wu, T.-Y., Ding, S. Q., Liu, J. L., Yu, M. T., Jia, J. H., Chai, Z. C., . . . Pan, L. (2007). Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. *High Altitude Medicine & Biology, 8*(2), 88-107.

Wu, T.-Y., & Kayser, B. (2006). High altitude adaptation in Tibetans. *High Altitude Medicine & Biology, 7*(3), 193-208.

Xie, G., He, R.-R., Feng, X., Yan, T., Lan, F., Wu, M.-Z., & Kurihara, H. (2009). The hypoglycemic effects of Camellia assamica var. kucha extract. *Bioscience, Biotechnology, and Biochemistry, 74*(2), 405-407.

Xing, G., Qualls, C., Huicho, L., River-Ch, M., Stobdan, T., Slessarev, M., . . . Norboo, A. (2008). Adaptation and mal-adaptation to ambient hypoxia; Andean, Ethiopian and Himalayan patterns. *PloS One, 3*(6), e2342. doi:10.1371/journal.pone.0002342

Xu, G., Ma, M., Liu, X., & Hankey, G. J. (2013). Is there a stroke belt in China and why? *Stroke, 44*(7), 1775-1783.

Xu, S., Jiayong, Z., Li, B., Zhu, H., Chang, H., Shi, W., . . . Wang, J. (2015). Prevalence and clustering of cardiovascular disease risk factors among Tibetan adults in China: a population-based study. *PloS One, 10*(6), e0129966. doi:10.1371/journal.pone.0129966

Yang, J., He, Z., Zhai, H., Yan, Z., Zhang, H., & Qin, F. (1987). A study of the pulmonary artery pressure in healthy people living at lowland and high altitude under exercise. *Chinese Journal of Cardiovascular Diseases, 15*, 39-41.

Yao, Y., Cheng, X., Wang, S., Wang, L., & Ren, G. (2012). Influence of altitudinal variation on the antioxidant and antidiabetic potential of Azuki bean (Vigna angularis). *International Journal of Food Sciences and Nutrition, 63*(1), 117-124.

Yeomans, M. R. (2010). Alcohol, appetite and energy balance: is alcohol intake a risk factor for obesity? *Physiology and Behavior, 100*(1), 82-89.

Yingzhong, Y., Droma, Y., Rili, G., & Kubo, K. (2006). Regulation of body weight by leptin, with special reference to hypoxia-induced regulation. *Internal Medicine, 45*(16), 941-946.

Yoda, T., Crawshaw, L. I., Saito, K., Nakamura, M., Nagashima, K., & Kanosue, K. (2008). Effects of alcohol on autonomic responses and thermal sensation during cold exposure in humans. *Alcohol, 42*(3), 207-212.

Youk, A. O., Buchanich, J. M., Fryzek, J., Cunningham, M., & Marsh, G. M. (2012). An ecological study of cancer mortality rates in high altitude counties of the United States. *High Altitude Medicine and Biology, 13*(2), 98-104.

Zhang, A. J., Rimando, A. M., Fish, W., Mentreddy, S. R., & Mathews, S. T. (2012). Serviceberry [Amelanchier alnifolia (Nutt.) Nutt. ex. M. Roem (Rosaceae)] leaf extract inhibits mammalian α-glucosidase activity and suppresses postprandial glycemic response in a mouse model of diet-induced obesity and hyperglycemia. *Journal of Ethnopharmacology, 143*(2), 481-487.

Zhang, H.-T., Gao, L., Ye, Y., Pang, Y., & Long, G. (2015). Association between local population's lifestyle and the morbidity of cerebral stroke in Ganzi Tibetan state: a cross-sectional study. *Chinese Journal of Evidence-based Medicine, 15*(1), 4-7.

Zhang, L., Qiao, Q., Tuomilehto, J., Janus, E. D., Lam, T. H., Ramachandran, A., . . . Nakagami, T. (2010). Distinct ethnic differences in lipid profiles across glucose categories. *The Journal of Clinical Endocrinology & Metabolism, 95*(4), 1793-1801.

Zhao, D. (1993). The epidemiology of coronary heart disease (CHD) in 16 provinces of China. Multi-province Cooperative Group of Cardiovascular Disease Surveillance (MONICA Project). *Zhonghua Liu Xing Bing Xue Za Zhi, 14*(1), 10-13.

Zhao, G., & Li, L. (1989). Analysis of the etiology and clinical characteristics of Tibetan cirrhosis in Tibet. *Chinese Journal of Internal Medicine, 28*(9), 529-531, 571-522.

Zhao, X., Li, S., Ba, S., He, F., Li, N., Ke, L., . . . Zhou, Y. (2012). Prevalence, awareness, treatment, and control of hypertension among herdsmen living at 4,300 m in Tibet. *American Journal of Hypertension, 25*(5), 583-589.

Zhao, X., Yin, X., Li, X., Yan, L. L., Lam, C. T., Li, S., . . . Luobu, G. (2014). Using a low-sodium, high-potassium salt substitute to reduce blood pressure among Tibetans with high blood pressure: a patient-blinded randomized controlled trial. *PloS One, 9*(10), e110131. doi:10.1371/journal.pone.0110131

Zheng, J.-Y., Tian, H.-T., Zhu, Z.-M., Li, B., Han, L., Jiang, S.-L., . . . Zhao, Z. (2013). Prevalence of symptomatic congenital heart disease in Tibetan school children. *American Journal of Cardiology, 112*(9), 1468-1470.

Zheng, X., Yao, D.-K., Zhuo-Ma, C.-R., Tang, J., Wang, T.-R., Zhang, H.-H., & Wang, L.-X. (2012). Prevalence, self-awareness, treatment, and control of hypertension in Lhasa, Tibet. *Clinical and Experimental Hypertension, 34*(5), 328-333.

Zhou, M., Wang, H., Zhu, J., Chen, W., Wang, L., Liu, S., . . . Yin, P. (2016). Cause-specific mortality for 240 causes in China during 1990–2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. *The Lancet, 387*(10015), 251-272.

Zhu, K.-F., Wang, Y.-M., Zhu, J.-Z., Zhou, Q.-Y., & Wang, N.-F. (2015). National prevalence of coronary heart disease and its relationship with human development index: a systematic review. *European Journal of Preventive Cardiology*. doi:10.1177/2047487315587402

Zuppinger, K., Teuscher, A., & Lüscher, R. (1975). Frequency of juvenile diabetes mellitus in the Canton Bern (Switzerland). *Schweizerische medizinische Wochenschrift*, *105*(38), 1218-1223.

Appendices

Appendix A: Modified WHO NCD STEPS Questionnaire

Appendix B: Questionnaire for Verifying Stroke Free Status

Appendix C: Participant Information Sheet

Appendix D: Participant Consent form

Appendix A: Modified WHO NCD STEPS Questionnaire

WHO STEPS Instrument

(Core and Expanded)

The WHO STEPwise approach to noncommunicable disease risk factor surveillance (STEPS)

WHO STEPS Instrument

for Noncommunicable Disease
Risk Factor Surveillance

<insert country/site name>

Survey Information

Location and Date	Response	Code
Participants ID	└─┴─┴─┴─┴─┴─┘	I1
Village	└─┴─┴─┘	I2
Village ward	└─┴─┴─┘	I3
Interviewer ID	└─┴─┴─┘	I4
Interview date		I5

CORE: Demographic Information		
Question	**Response**	**Code**
Sex (*Record Male / Female as observed*)	Male 1 Female 2	C1
What is your date of birth? *Don't Know 77 77 7777*	└─┴─┘ └─┴─┘ └─┴─┴─┴─┘ *If known, Go to C4* dd mm year	C2
How old are you?	Years └─┴─┘	C3
In total, how many years have you spent at school and in full-time study (excluding pre-school)?	Years └─┴─┘	C4

Step 1 Demographic Information

EXPANDED: Demographic Information		
What is the **highest level of education** you have completed? *[INSERT COUNTRY-SPECIFIC CATEGORIES]*	No formal schooling 1 Less than primary school 2 Primary school completed 3 Secondary school completed 4 High school completed 5 College/University completed 6 Post graduate degree 7	C5
What is your *[insert relevant ethnic group / racial group / cultural subgroup / others]* **background**?	Thakali 1 Tibetan Gurung 2 Dalit 3 Brahmin / Chhetri 4 Gurung/Magar 5 Other 6	C6

What is your **marital status**?	Never married 1 Currently married 2 Separated 3 Divorced 4 Widowed 5 Cohabitating 6 Refused 88	C7
Which of the following best describes your **main work** status over the past 12 months? *[INSERT COUNTRY-SPECIFIC CATEGORIES]* (*USE SHOWCARD)*	Government employee 1 Non-government employee 2 Self-employed 3 Agriculture 4 Student 5 Homemaker 6 Retired 7 Unemployed (able to work) 8 Unemployed (unable to work) 9 Refused 88	C8
How many people older than 15 years, including yourself, live in your household?	Number of people |__|__|	C9

EXPANDED: Demographic Information, Continued		
Question	**Response**	**Code**
If you don't know the amount, can you give an **estimate** of the annual household income if I read some options to you? Is it *[INSERT QUINTILE VALUES IN LOCAL CURRENCY]*	>1,00,000 NRS 1 1,00,000 to 2,00,000 NRS 2 2,00,000 to 4,00,000 NRS 3 >4,00,000 NRS 4	C10

Question	Response		Code
Where were you borned ?	Mustang OR Humla	1	C11
	Elsewhere	2	
For how long haveyou been living in Mustang OR Humla ?	For the life time 1 >10 years 2 5 to 10 years 3 >5 years 4		C12

Step 1 Behavioural Measurements

CORE: Tobacco Use

Now I am going to ask you some questions about tobacco use.

Question	Response			Code
Do you **currently** smoke any **tobacco** products, such as cigarettes, cigars or pipes? *(USE SHOWCARD)*	Yes	1		T1
	No	2	*If No, go to T8*	
Do you currently smoke tobacco products **daily**?	Yes	1		T2
	No	2		
How old were you when you **first started** smoking?	Age (years) Don't know 77	└─┴─┘	*If Known, go to T5a/T5aw*	T3
Do you remember how long ago it was? *(RECORD ONLY 1, NOT ALL 3)*	In Years	└─┴─┘	*If Known, go to T5a/T5aw*	T4a
	OR in Months	└─┴─┘	*If Known, go to T5a/T5aw*	T4b
	OR in Weeks	└─┴─┘		T4c
On average, **how many** of the following products do you smoke **each day/week?**		DAILY↓	WEEKLY↓	
	Manufactured cigarettes	└─┴─┴─┴─┘	└─┴─┴─┴─┘	T5a/T5aw

(IF LESS THAN DAILY, RECORD WEEKLY) *(RECORD FOR EACH TYPE, USE SHOWCARD)* *Don't Know 7777*	Hand-rolled cigarettes └─┴─┴─┴─┘ └─┴─┴─┴─┘	T5b/T5bw
	Other └─┴─┴─┴─┘ └─┴─┴─┴─┘ *If Other, go to T5other, else go to T6*	T5c/T5cw
	Other (please specify): └─┴─┴─┴─┴─┴─┘	T5other/ T5otherw
During the past 12 months, have you tried to **stop smoking**?	Yes 1 No 2	T6
During any visit to a doctor or other health worker in the past 12 months, were you advised to quit smoking tobacco?	Yes 1 *If T2=Yes, go to T12; if T2=No, go* No 2 *If T2=Yes, go to T12; if T2=No, go* No visit during the past 12 months 3 *If T2=Yes, go to T12; if T2=No, go to T9*	T7
In the past, did you **ever smoke** any tobacco products? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to T12*	T8
In the past, did you **ever** smoke **daily**?	Yes 1 *If T1=Yes, go to T12, else go to T10* No 2 *If T1=Yes, go to T12, else go*	T9

EXPANDED: Tobacco Use		
Question	**Response**	**Code**
How old were you when you **stopped** smoking?	Age (years) Don't Know 77 └─┴─┘ *If Known, go to T12*	T10
How **long ago** did you stop smoking? *(RECORD ONLY 1, NOT ALL 3)* *Don't Know 77*	Years ago └─┴─┘ *If Known, go to T12*	T11a
	OR Months ago └─┴─┘ *If Known, go to T12*	T11b
	OR Weeks ago └─┴─┘	T11c
Do you **currently use** any **smokeless tobacco** products such as *[snuff, chewing tobacco, betel]*? *(USE SHOWCARD)*	Yes 1 No 2 *If No, go to T15*	T12

Do you **currently use smokeless tobacco** products **daily?**	Yes 1 No 2 *If No, go to T14aw*	T13
How frequently do you use snuff by nose ?	1 = Daily, 2= 1-2 times a week 3=3-4 times a week, 4= Once a week 5= Rarely	T14a
Do you chew tobacco products daily ?	Yes = 1, No= 2	T14c
In the **past**, did you **ever use** smokeless tobacco products such as *[snuff, chewing tobacco, or betel]*?	Yes 1 No 2 *If No, go to T17*	T15
In the **past**, did you **ever use** smokeless tobacco products such as *[snuff, chewing tobacco, or betel]* **daily**?	Yes 1 No 2	T16
During the past 30 days, did someone smoke **in your home**?	Yes 1 No 2	T17
During the past 30 days, did someone smoke in closed areas **in your workplace** (in the building, in a work area or a specific office)?	Yes 1 No 2 Don't work in a closed area 3	T18
Total home and work smoking exposure days in a week		T19

CORE: Alcohol Consumption		
The next questions ask about the consumption of alcohol.		
Question	**Response**	**Code**
Have you **ever** consumed any alcohol such as beer, wine, spirits or *[add other local examples]*? *(USE SHOWCARD OR SHOW EXAMPLES)*	Yes 1 No 2 *If No, go to A16*	A1a
Have you consumed any alcohol within the **past 12 months**?	Yes 1 *If Yes, go to A4* No 2 If No, go to A16	A1b
During the past 12 months, **how frequently** have you had at least one standard alcoholic drink?	Daily 1 5-6 days per week 2 3-4 days per week 3 1-2 days per week 4 1-3 days per month 5	A2

(READ RESPONSES, USE SHOWCARD)	Less than once a month 6	
Have you consumed any alcohol within the **past 30 days**?	Yes 1 No 2 *If No, go to D1*	A3
During the past 30 days, on how many **occasions** did you have at least one standard alcoholic drink?	Number Don't know 77 └─┴─┘	A4
During the past 30 days, when you drank alcohol, how many **standard drinks on average** did you have during one drinking occasion? *(USE SHOWCARD)*	Number Don't know 77 └─┴─┘	A5
No. of standard drinks consumed in a month (A4 X A5)		A6
During the past 30 days, what was the **largest number** of standard drinks you had on a single occasion, counting all types of alcoholic drinks together?	Largest number └─┴─┘ Don't Know 77	A7
During the past 30 days, how many times did you have **four or more** standard drinks in a single drinking occasion?	Number of times Don't Know 77 └─┴─┘	A8

CORE: Diet		
The next questions ask about the fruits and vegetables that you usually eat. I have a nutrition card here that shows you some examples of local fruits and vegetables. Each picture represents the size of a serving. As you answer these questions please think of a typical week in the last year.		
Question	**Response**	**Code**
In a typical week, on how many days do you **eat fruit**? *(USE SHOWCARD)*	Number of days └─┴─┘ *If Zero days, go to* Don't Know 77 *D3*	D1
How many **servings** of fruit do you eat on **one** of those days? *(USE SHOWCARD)*	Number of servings Don't Know 77 └─┴─┘	D2
In a typical week, on how many days do you **eat vegetables**? *(USE SHOWCARD)*	Number of days └─┴─┘ *If Zero days, go to* Don't Know 77 *D5*	D3
How many **servings** of vegetables do you eat on one of those days? *(USE SHOWCARD)*	Number of servings └─┴─┘ Don't know 77	D4
Mean consumption of fruits and veg per day		D5
Average fruits and vegetables servings per day	≥5 servings per day 1 <5 servings per day 2	D6

EXPANDED: Diet		
What type of **oil or fat is most often** used for meal preparation in your household? *(USE SHOWCARD)* *(SELECT ONLY ONE)*	Vegetable oil 1 (Soybean or & Sunflower) Mustard 2 Ghee 3 Veg or mustard oil 4 *If Other, go to D5 other* None in particular 5 Other 6 Don't know 77	D7
	Other └─┴─┴─┴─┴─┴─┴─┘	D7other
On average, how much oil does your family consume per month (in litre) ?	Litre └─┴─┘ Don't know 77	D8
Individual consumption of oil per month by a family members (including children) (D8/no. of family members)		D9

Salt Questionnaire

Question	Response	Code
How often do you add salt during dining ?	a. Mostly 1 b. Occasionally (if salt level seems low) 2 c. Rarely 3 d. Never 4	DS1
How frequently do you eat processed food (like noodles, crisps, fast foods) which usually contains high amount of salt ?	a. Mostly 1 b. Occasionally 2 c. Never 3	DS2
In your opinion, how much amount of salt do you usually prefer ?	a. Very high 1 b. High 2 c. Medium 3 d. Low 4 e. Very low 5	DS3
Do you think consuming high amount of salt would affect your health ?	a. Yes 1 b. No 2	DS4
What type of salt do you mostly use at your home ?	a. Crystal salt 1 c. Iodized packet salt 2 d. Tibetan salt 3 e. Other 4	DS5
How much amount of salt does your family usually consume ? (kg/month)		DS6
Individual consumption of salt in your family member (gram/day) (DS6/no. of family members)		DS7

CORE: Physical Activity		
Next I am going to ask you about the time you spend doing different types of physical activity in a typical week. Please answer these questions even if you do not consider yourself to be a physically active person. Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. *[Insert other examples if needed].* In answering the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.		
Question	**Response**	**Code**
Work		
Does your work involve vigorous-intensity activity that causes large increases in breathing or heart rate like *[carrying or lifting heavy loads, digging or construction work]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 4*	P1
In a typical week, on how many days do you do vigorous-intensity activities as part of your work?	Number of days └─┘	P2
How much time do you spend doing vigorous-intensity activities at work on a typical day?	Hours : minutes └─┴─┘ : └─┴─┘ hrs mins	P3 (a-b)
Total time spent on vigorous physical activities in a typical week (hours) (P2 X P3)		P4
Does your work involve moderate-intensity activity, that causes small increases in breathing or heart rate such as brisk walking *[or carrying light loads]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 7*	P5
In a typical week, on how many days do you do moderate-intensity activities as part of your work?	Number of days └─┘	P6
How much time do you spend doing moderate-intensity activities at work on a typical day?	Hours : minutes └─┴─┘ : └─┴─┘ hrs mins	P7 (a-b)
Total time spent on moderate physical activities in a typical week (hours) (P6 X P7)		P8
Travel to and from places		
The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way you travel to and from places. For example to work, for shopping, to		

market, to place of worship. *[Insert other examples if needed]*		
Do you walk or use a bicycle *(pedal cycle)* for at least 10 minutes continuously to get to and from places?	Yes 1 No 2 *If No, go to P 10*	P9
In a typical week, on how many days do you walk or bicycle for at least 10 minutes continuously to get to and from places?	Number of days └─┘	P10
How much time do you spend walking or bicycling for travel on a typical day?	Hours : minutes └─┴─┘ : └─┴─┘ hrs mins	P11 (a-b)
Do you walk 30 minutes or more on a typical day ?	Yes 1 No 2	P12

CORE: Physical Activity, Continued		
Question	**Response**	**Code**
Recreational activities		
The next questions exclude the work and transport activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities (leisure), *[Insert relevant terms]*.		
Do you do any vigorous-intensity sports, fitness or recreational *(leisure)* activities that cause large increases in breathing or heart rate like *[running or football]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P 14*	P13
In a typical week, on how many days do you do vigorous-intensity sports, fitness or recreational *(leisure)* activities?	Number of days └─┘	P14
How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day?	Hours : minutes └─┴─┘ : └─┴─┘ hrs mins	P15 (a-b)
Do you do any moderate-intensity sports, fitness or recreational *(leisure)* activities that cause a small increase in breathing or heart rate such as brisk walking, *[cycling, swimming, volleyball]* for at least 10 minutes continuously?	Yes 1 No 2 *If No, go to P17*	P16
In a typical week, on how many days do you do moderate-intensity sports, fitness or recreational *(leisure)* activities?	Number of days └─┘	P17

How much time do you spend doing moderate-intensity sports, fitness or recreational *(leisure)* activities on a typical day?	Hours : minutes └─┴─┘ : └─┴─┘ hrs mins	P18 (a-b)

EXPANDED: Physical Activity		
Sedentary behaviour		
The following question is about sitting or reclining at work, at home, getting to and from places, or with friends including time spent sitting at a desk, sitting with friends, traveling in car, bus, train, reading, playing cards or watching television, but do not include time spent sleeping. *[INSERT EXAMPLES] (USE SHOWCARD)*		
How much time do you usually spend sitting or reclining on a typical day?	└─┴─┘ : └─┴─┘ hrs mins	P19 (a-b)

CORE: History of Raised Blood Pressure		
Question	**Response**	**Code**
Have you ever had your blood pressure measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to H6*	H1
Have you ever been told by a doctor or other health worker that you have raised blood pressure or hypertension?	Yes 1 No 2 *If No, go to H6*	H2a
Have you been told in the past 12 months?	Yes 1 No 2	H2b
In the past two weeks, have you taken any drugs (medication) for raised blood pressure prescribed by a doctor or other health worker?	Yes 1 No 2	H3
Have you ever seen a traditional healer for raised blood pressure or hypertension?	Yes 1 No 2	H4
Are you currently taking any herbal or traditional remedy for your raised blood pressure?	Yes 1 No 2	H5

CORE: History of Diabetes		
Have you ever had your blood sugar measured by a doctor or other health worker?	Yes 1 No 2 *If No, go to H12*	H6
Have you ever been told by a doctor or other health worker that you have raised blood sugar or diabetes?	Yes 1 No 2 *If No, go to H12*	H7a
Have you been told so in the past 12 months?	Yes 1 No 2	H7b
In the past two weeks, have you taken any drugs (medication) for diabetes prescribed by a doctor or other health worker?	Yes 1 No 2	H8
Are you currently taking insulin for diabetes prescribed by a doctor or other health worker?	Yes 1 No 2	H9
Have you ever seen a traditional healer for diabetes or raised blood sugar?	Yes 1 No 2	H10
Are you currently taking any herbal or traditional remedy for your diabetes?	Yes 1 No 2	H11

CORE: History of Cardiovascular Diseases		
Have you ever had a heart attack or chest pain from heart disease (angina) ?	Yes 1 No 2	H12
Do you have a family history of CVD ?	Yes 1 No 2	H13

CORE: Lifestyle Advice

1.1.1.1.1.1.1.1.1.1 During the past three years, has a doctor or other health worker advised you to do any of the following? *(RECORD FOR EACH)*

Quit using tobacco or don't start	Yes 1 No 2	H14a
Reduce salt in your diet	Yes 1 No 2	H14b
Eat at least five servings of fruit and/or vegetables each day	Yes 1 No 2	H14c
Reduce fat in your diet	Yes 1 No 2	H14d
Start or do more physical activity	Yes 1 No 2	H14e
Maintain a healthy body weight or lose weight	Yes 1 *If C1=1 go to M1* No 2 *If C1=1 go to M1*	H14f

Step 2 Physical Measurements

CORE: Blood Pressure		
Question	**Response**	**Code**
Interviewer ID	└─┴─┴─┘	M1
Device ID for blood pressure	└─┴─┴─┘	M2
Reading 1	Systolic (mmHg)	M3a
	Dystolic (mmHg)	M3b
	Heart rate (bpm)	M3c
Reading 2	Systolic (mmHg)	M4a
	Dystolic (mmHg)	M4b
	Heart rate (bpm)	M4c
Reading 3	Systolic (mmHg)	M5a
	Dystolic (mmHg)	M5b
	Heart rate (bpm)	M5c
Average systolic blood pressure		M6
Average diastolic blood pressure		M7
Average heart rate		M8
Hypertension any	Yes 1 No 2	M9
Hypertension any or currently on hypertensive medication	Yes 1 No 2	M10
Hypertension known for the first time (H2a=No, M9=Yes)	Yes 1 No 2	M11
Pre-hypertension (SBP:120-139 mmHg or DBP: 80 to 89 Hg)	Yes 1 No 2	M12
Stage I hypertension (SBP:140-159 mmHg or DBP: 90-99 mmHg)	Yes 1 No 2	M13
Stage II hypertension (SBP: ≥160 mmHg or DBP:≥100 mmHg)	Yes 1 No 2	M14
Isolated systolic hypertension (SBP:≥140 mmHg and DBP: <90 mmHg)	Yes 1 No 2	M15

CORE: Height and Weight		
For women : Are you pregnant ?	Yes 1 If yes go to B1 No 2	M16
Interviewer ID	└─┴─┴─┘	M17
Height	in meter (m)	M18
Weight	in Kilograms (kg)	M19
Body mass index	in Kg/m^2	M20
Obesity	1=<18.5 Kg/m^2 (underwt.), 2=18.5-24.9 Kg/m^2 (normal), 3=25-29.9 Kg/m^2 (preobese), 4=30-34.9 Kg/m^2 (obesity I), 5= 35-39.9 Kg/m^2 (obesity II), 6= ≥40 Kg/m^2 (obesity III)	M21
CORE: Waist and Hip Circumference		
Waist circumference	in Centimeters (cm)	M22
Hip circumference	in Centimeters (cm)	M23
Waist-hip ratio		M24
High Waist circumference (IDF criteria for South Asian)	1= Yes (>90 cm for male and >80 cm for female) 2=No	M25
Central adiposity (WHO recommendation of metabolic complications)	1 = Yes (if W-H ratio ≥0.90 for male and ≥0.85 for female) 2= No	M26

Step 3 Biochemical Measurements

CORE: Blood Glucose		
Question	**Response**	**Code**
Glycated hemoglobin (HbA1C) *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/mol └─┴─┴─┘ . └─┴─┴─┘	B1
Estimated average glucose (eAG)	mmol/mol └─┴─┴─┘ . └─┴─┴─┘	B2
Diabetes (HbA1C= ≥ 48 mmol/mol)	Yes 1 No 2	B3

Impaired glucose tolerance (HbA1c= ≥ 39 to 47 mmol/mol)	Yes 1 No 2	B4
Diabetes or currently on diabetes medication	Yes 1 No 2	B5
Diabetes known for the first time (H7a=No, B3 = Yes)	Yes 1 No 2	B6
CORE: Blood Lipids		
During the past two weeks, have you been treated for raised cholesterol with drugs (medication) prescribed by a doctor or other health worker?	Yes 1 No 2	B7
Total cholesterol *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/L └─┴─┴─┘.└─┘	B8
High levels of total cholesterol (≥5.2 mmol/L)	Yes 1 No 2	B9
Tryglyceride *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/L └─┴─┴─┘.└─┘	B10
High levels of tryglycerides (≥1.7 mmol/L)	Yes 1 No 2	B11
HDL cholesterol *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/L └─┴─┴─┘.└─┘	B12
Low levels of HDL cholesterol (<1.0 mmol/L for males and <1.3 mmol/L for females)	Yes 1 No 2	B13
LDL cholesterol *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/L └─┴─┴─┘.└─┘	B14
High levels of LDL cholesterol (≥3.4 mmol/L)	Yes 1 No 2	B15
Non-HDL cholesterol *[CHOOSE ACCORDINGLY: MMOL/L OR MG/DL]*	mmol/L └─┴─┴─┘.└─┘	B16
High levels of Non-HDL cholesterol (≥4.1 mmol/L)	Yes 1 No 2	B17
Total Cholesterol to HDL ratio		B18

High total cholesterol to HDL ratio (≥ 5)	Yes 1 No 2	B19
Dyslipidemia (Abnormal levels of at least one among TC, TG, HDL & LDL)	Yes 1 No 2	B20
Clustering of lipids (More than one abnormal levels of TC, TG, HDL & LDL)	1= >1, 2= 2 or more, 3= 3 or more, 4= All four, 5=None	B21

WHO/ISH Risk Prediction		
Question	**Response**	**Code**
10 year risk of fatal or non-fatal CVD event (combined risk of MI and stroke) (According to WHO/ISH risk prediction chart for WHO region SEAR D, only among the participants aged 40 years or more)	a. <10% 1 b. 10% to <20% 2 c. 20% to <30% 3 d. 30% to <40% 4 e. ≥40% 5 f. NA 6	R1

Appendix B: Questionnaire for Verifying Stroke Free Status

Question	Response	Code
Were you ever told by a physician that you had a stroke ?	a. Yes 1 b. No 2 c. Unknown 3	S1
Were you ever told by a physician that you had a TIA, ministroke, or transient ischemic attack ?	a. Yes 1 b. No 2 c. Unknown 3	S2
Have you ever had sudden painless weakness on one side of your body ?	a. Yes 1 b. No 2 c. Unknown 3	S3
Have you ever had sudden numbness or a dead feeling on one side of your body ?	a. Yes 1 b. No 2 c. Unknown 3	S4
Have you ever had sudden painless loss of vision in one or both eyes ?	a. Yes 1 b. No 2 c. Unknown 3	S5
Have you ever suddenly lost one half of your vision ?	a. Yes 1 b. No 2 c. Unknown 3	S6
Have you ever suddenly lost the ability to understand what people are saying ?	a. Yes 1 b. No 2 c. Unknown 3	S7
Have you ever suddenly lost the ability to express yourself verbally or in writing ?	a. Yes 1 b. No 2 c. Unknown 3	S8

Jones W J et al. Validating the Questionnaire for Verifying Stroke-Free Status (QVSFS) by neurological history and examination. *Stroke* 2001,32:2232-2236.

Appendix C: Participant Information Sheet

Study title:	Cardiovascular risk in high altitude people of Nepal	
Principal investigator:	**Associate Prof. Stewart Mann** **Department of Medicine** **University of Otago, Wellington**	Contact phone number: +64 4 918 6793

Thank you for showing an interest in this project. Please read this information sheet carefully. Take time to consider and, if you wish, talk with relatives or friends, before deciding whether or not to participate.

If you decide to participate we thank you. If you decide not to take part there will be no disadvantage to you and we thank you for considering our request.

Our team is conducting a study on factors related to cardiovascular diseases in people living at high altitude in Nepal. Cardiovascular diseases are diseases of the heart and blood vessels. The most common risk factors of cardiovascular diseases are high levels of blood pressure, cholesterols, diabetes, obesity, smoking, dietary habit, physical inactivity etc. It is not clearly known whether people living at high altitude in Nepal are at risk of cardiovascular disease, and further research is needed.

This study is sponsored by the University of Otago, New Zealand and has been supported by an independent cardiovascular research trust.

We are seeking participants from people living permanently at high altitude (>2400 metre), aged 30 years or above, and who speak and understand the Nepalese language. We are sorry that we are unable to include those with impairments in hearing and speaking, pregnant women, and those unable or unwilling to provide written or verbal consent.

If you agree, your participation in this study will involve you being asked some questions about your lifestyle, diet, medical conditions and history. Your height and weight, waist and hip measurements, and blood pressure will be measured. A very small sample of blood will be obtained from you once using a finger prick which may be briefly uncomfortable. A well-trained person will conduct this procedure. The sample will be put into a machine immediately and will provide the results of cholesterol and diabetes test within a turnaround time of 15 minutes. After processing, blood sample will be disposed of straight away. We will also record an ECG (electrocardiogram) which involves making recordings of the electrical activity of your heart from stickers attached lightly to your skin. This whole study process will take approximately 45 minutes.

It would be greatly appreciated if you could take part in this study. Your participation in this study is entirely voluntary and your responses will be kept strictly confidential and anonymous. You will not be paid any money to be part of this study, nor be asked to pay any money to take part. Your decision on whether or not to participate in this study will have no consequences for your future healthcare. If you agree to participate, you have the right to withdraw from this study at any point without giving any reasons. You will be requested to provide consent by signing a form with signature or thumb print or by giving witnessed oral consent.

Any questions?

If you have any questions now or in the future, please feel free to contact either:

Name Nirmal Aryal **Position** Student Investigator **Department** Medicine, University of Otago	Contact phone number: (To be confirmed)
Name Stewart Mann **Position** Principal Investigator **Department** Medicine, University of Otago	Contact phone number: +64 4 918 6793
Name .... **Position** Research Assistant **Department**	Contact phone number: ………………………………

This study has been approved by the University of Otago Human Ethics Committee (Health). If you have any concerns about the ethical conduct of the research you may contact the Committee through the Human Ethics Committee Administrator (phone +64 3 479 8256 or email gary.witte@otago.ac.nz). Any issues you raise will be treated in confidence and investigated and you will be informed of the outcome.

Appendix D: Participant Consent form

Cardiovascular risk in high altitude people of Nepal

Principal Investigator: Associate Prof. Stewart Mann, stewart.mann@otago.ac.nz

CONSENT FORM FOR PARTICIPANTS

Following signature and return to the research team this form will be stored in a secure place for ten years.

Name of participant:…………………………………………..

1. I have read the Information Sheet concerning this study and understand the aims of this research project.
2. I have had sufficient time to talk with other people of my choice about participating in the study.
3. I confirm that I meet the criteria for participation which are explained in the Information Sheet.
4. All my questions about the project have been answered to my satisfaction, and I understand that I am free to request further information at any stage.
5. I know that my participation in the project is entirely voluntary, and that I am free to withdraw from the project at any time without disadvantage. I also agree to inform my health practitioner that I am taking part in this study.
6. I know that as a participant I will have to provide bio-physical measurements, bio-chemical tests from finger-pricked blood sample and an ECG recording. I will also be asked about my medical condition and medical history.
7. I know that the questionnaire will mainly explore lifestyle and dietary information and that if the line of questioning develops in such a way that I feel hesitant or uncomfortable I may decline to answer any particular question(s) , and /or may withdraw from the project without disadvantage of any kind.
8. I understand the nature and size of the risks of discomfort or harm which are explained in the Information Sheet.

9. I know that when the project is completed all personal identifying information will be removed from the paper records and electronic files which represent the data from the project, and that these will be placed in secure storage and kept for at least ten years.
10. I understand that the results of the project may be published and be available in the University of Otago Library. I agree that any personal identifying information will remain confidential between myself and the researchers during the study. It will not appear in any spoken or written report of the study. However, I may agree for my named results being provided to my preferred health care provider.
11. I know that there is no remuneration offered for this study, and that no commercial use will be made of the data.
12. I understand that the blood samples will be disposed by the study team immediately after testing using the standard procedure.

Signature or thumb print of participant:	Date:

Signature or thumb print and name of witness:	Date:

Or verbal agreement to participate but unable to provide signature or thumb print ☐

I wish / do not wish (delete one) for my results to be provided to my usual health provider ………………………………..(name of provider)

Signature / thumb print …………………………

For the study researcher or independent witness: The above statement has been read to and understood by the participants. He / She has verbally agreed to each of the above statements and has agreed to participate in this study.

Name: ………………………

Signature: ………………….....

Date:…………………………