

The Prospective Urban Rural Epidemiology (PURE) study: Examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries

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Background Marked changes in the prevalence of noncommunicable diseases such as obesity, diabetes, and cardiovascular disease have occurred in developed and developing countries in recent decades. The overarching aim of the study is to examine the relationship of societal influences on human lifestyle behaviors, cardiovascular risk factors, and incidence of chronic noncommunicable diseases.

Methods The Prospective Urban Rural Epidemiology (PURE) study is a large-scale epidemiological study that plans to recruit approximately 140,000 individuals residing in >600 communities in 17 low-, middle-, and high-income countries around the world. Individual data collection includes medical history, lifestyle behaviors (physical activity and dietary profile), blood collection and storage for biochemistry and future genetic analysis, electrocardiogram, and anthropometric measures. In addition, detailed information is being collected with respect to 4 environmental domains of interest—the built environment, nutrition and associated food policy, psychosocial/socioeconomic factors, and tobacco environment. A minimum follow-up of 10 years is currently planned.

Results This report describes the design, justification, and methodology of the PURE study.

The PURE study has been recruiting since 2002 and has enrolled 139,506 individuals by March 31, 2009.

Conclusions The PURE study builds on the work and experience gained through conduct of the INTERHEART study. Its design and extensive data collection are geared toward addressing major questions on causation and development of the underlying determinants of cardiovascular disease in populations at varying stages of epidemiologic transition. (Am Heart J 2009;158:1-7.e1.)

For most populations, the last century has witnessed dramatic improvements in health; life expectancy has increased from a global average of 46 years in 1950 to 66 years in 1998.¹ During the 20th century, developed countries (early industrializers) experienced rapid declines in deaths from infections and childhood diseases and marked increases in chronic noncommunicable diseases such as obesity, diabetes, and cardiovascular disease (CVD), the latter peaking around 1960 to 1980.^{1,2}

The health transition in developed countries was associated with industrialization, mechanization, urbanization, and economic development,^{2,3} and these changes were accompanied by improved living standards and infrastructure, water and sanitation, economic growth, nutrition, and mechanization. More recently, the epidemic of chronic diseases has shifted from high-income countries (HIC) to developing countries as they industrialize (late industrializers). Cardiovascular disease is the leading cause of morbidity and premature mortality worldwide, and it is expected that by 2020, >80% of global CVD will be in low- and middle-income countries (LIC and MIC),⁴ with the bulk being in countries that are undergoing rapid industrialization and urbanization. Simultaneously, CVD is expected to continue to be a leading disease burden in HIC. Therefore, the control of CVD is an important goal for the prevention of premature death in all countries in the 21st century. Although research thus far has established many of the factors that differentiate the risks of individuals to develop CVD, the factors that increase the

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levels of cardiovascular risk factors (CVRFs) in a community or differentiate the risk of communities to develop more CVD is less well understood.

The INTERHEART study involving 15,152 individuals with first acute myocardial infarction (MI) matched to 14,820 individuals without CVD, from urban centers in 52 countries, found that 9 *individual-level* risk factors (smoking, ApoB/ApoA-1 ratio, hypertension, diabetes, abdominal obesity, psychosocial factors, lack of daily fruits and vegetables, physical inactivity, and lack of alcohol consumption) were associated with >90% of the population attributable risk of MI globally and that 99% of MI cases had at least 1 risk factor.⁵ These findings indicate that these risk factors are ubiquitous worldwide and that these risk factors explain why certain individuals develop CVD whereas others are relatively protected. INTERHEART however does not explain why the levels of CVRFs vary across regions. The increase in CVD in MIC and LIC is partially explained by the increased proportion of older subjects, but also likely to be caused by increasing population levels of risk factors as a result of changing societal factors.

The *urban transition* is one of the most dramatic shifts in environment that most populations have experienced in the last century. The proportion of individuals living in urban settings has markedly increased. In 1970, the proportion of the world's population living in urban areas was 37%, and by 2025, it is projected to be 61%. In HIC, this is projected to increase from 68% to 84%, and in MIC and LIC, from 13% to 44%.⁶ Although urbanization has increased worldwide, the associated societal and health impact is heterogeneous. In HIC, urbanization is accompanied by economic growth, development of infrastructure, and increased spending on social services, education, and health care. In LIC and MIC, rapid urbanization may occur without adequate infrastructure, creating urban slums and greater socioeconomic disparity.⁷

The urban transition is also accompanied by transitions in the environment that impact on behaviors such as diet, physical activity, and smoking. For example, changes in diet have been attributed to economic growth,⁸ leading to changes in food production, food policies affecting the relative cost, availability and consumption of different food types,⁹ and to media¹⁰ and industry influences.¹¹ Changes in physical activity have been attributed to mechanization at work and home, changes in transportation (eg, increased motor vehicle ownership), and changes in the built environment (eg, increased urban sprawl and poor connectivity in residential areas). Smoking is also influenced by environmental factors such as tobacco control policy and the degree of social acceptability of smoking.^{12,13}

To better understand the impact of social and environmental transition on health, large prospective studies of people who live in a wide variety of communities exposed

to a diverse range of political, sociocultural, and socioeconomic factors are needed. The variable rates and patterns of health transitions occurring in countries at heterogeneous states of development provide a unique opportunity to examine the relationships of the changing characteristics of communities to the changes in the rates and types of cardiovascular and other chronic diseases. Within this context, the PURE study was designed to collect data on social, environmental, behavioral, biological, and genetic factors that contribute to the development of CVD in a large-scale international cohort of communities.

Objectives

The framework of the PURE study is based on the assumption that the 'causal' pathways for the development of CVD involve influences at multiple levels. Characteristics of countries (eg, policy and economic environment) influence the characteristics of communities (eg, built environment, nutrition environment, and sociocultural factors), and households (eg, family structure, income, housing). These in turn influence individual lifestyle behaviors (physical activity, diet, psychosocial behavior) modified by the individual's attitudes, culture, and awareness of healthy behaviors. Adverse changes in these health behaviors lead to the development of biological risk factors (eg, blood pressure, diabetes, obesity) and ultimately the development of CVD (Figure 1).

The 2 main objectives of PURE are the following:

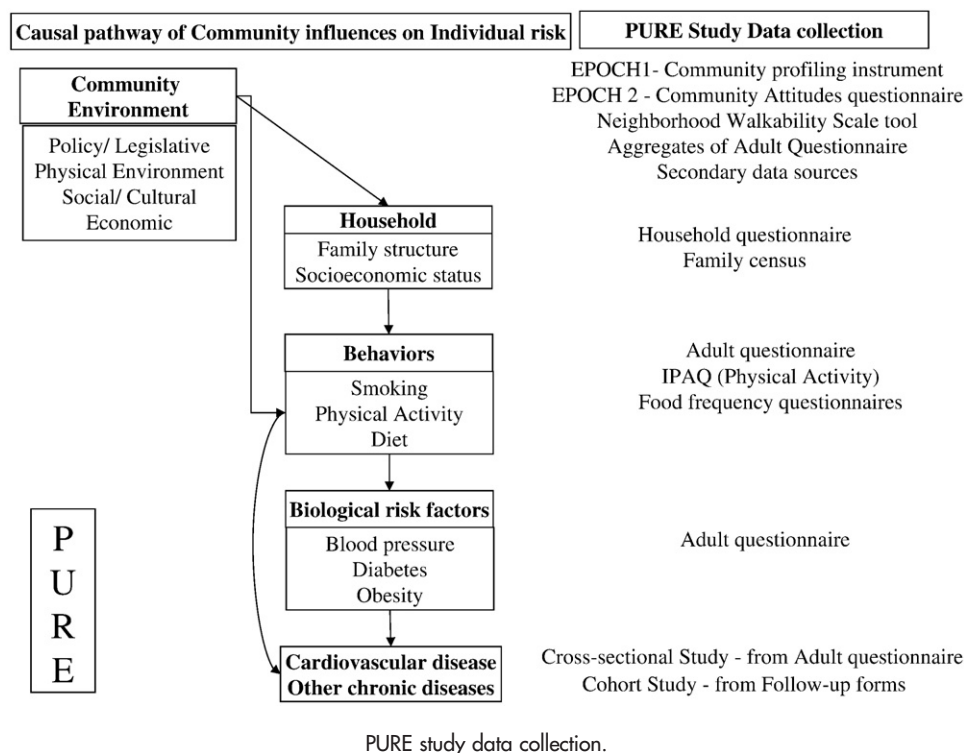
1. To examine the relationship between societal influences and prevalence of risk factors and chronic noncommunicable diseases measured at baseline—cross sectional component of study. Societal determinants are measured by an index of measures from each of the 4 domains of interest: built environment, food and nutrition policy, psychosocial/socioeconomic factors, and tobacco.
2. To examine the relationship between societal determinants and incidence of chronic noncommunicable disease events and on changes in rates of selected risk factors (eg, smoking)—cohort component of study.

Methods

The PURE study aims to recruit 150,000 adults initially aged 35 to 70 years from communities in low-, middle-, and high-income regions of the world representing various levels of development and encompassing great sociocultural diversity (Figure 2). Recruitment commenced in 2003 and is expected to be complete by March 2009.

The Prospective Urban Rural Epidemiology (PURE) study is an investigator-led study that is funded through a variety of sources including the Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, grants from several pharma-

Figure 1



ceutical companies, and grants from various governmental granting bodies in different countries. These are detailed in Appendix A (available online).

Selection of countries

The choice and number of countries selected in PURE reflects a balance between involving a large number of communities in countries at different economic levels, with substantial heterogeneity in social and economic circumstances and policies, and the feasibility of centers to successfully achieve long-term follow-up. Thus, PURE includes sites in which investigators are committed to collecting good-quality data for a low-budget study over the planned 10-year follow-up period and did not aim for a strict proportionate sampling of the entire world. The countries involved in the PURE study include 4 LIC: Zimbabwe, Bangladesh, India, and Pakistan; 10 MIC: South Africa, Brazil, Argentina, Colombia, Chile, Poland, China, Malaysia, Iran, and Turkey; and 3 HIC: Canada, Sweden, and UAE (Table I).

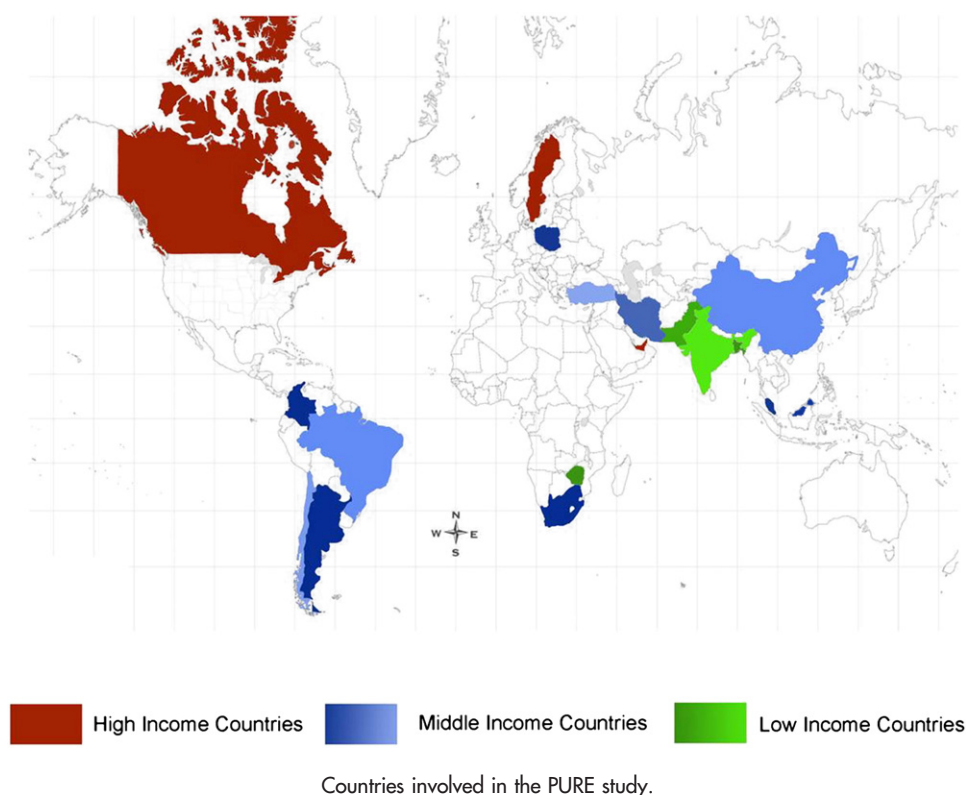
Selection of communities

Within each country, urban and rural communities have been selected based on broad guidelines (Table II). A common definition for “community” that is applicable globally is difficult to establish.¹⁴ In PURE, the community is defined as a group of people who have common characteristics and reside in a defined geographic area. A city or large town is not usually considered to be a single community, rather communities from low-, middle-, and high-income areas are selected from section of the city and the community area defined according to a geographical measure (eg, a set of contiguous postal code areas or a group

of streets or a village). The primary sampling unit for rural areas in many countries is the village. The reason for inclusion of both urban and rural communities is that for many countries, urban and rural environments exhibit distinct characteristics in social and physical environment, and hence, by sampling both, we ensure considerable variation in societal factors across PURE communities. The number of communities selected in each country varies, with the aim to recruit communities with substantial heterogeneity in social and economic circumstances balanced against the capacity of local investigators to maintain follow-up. In some countries (eg, India, China, Canada, and Colombia), communities from several states/provinces have been included to capture regional diversity, in policy, socioeconomic status, culture, and physical environment. In other countries (eg, Iran, Poland, Sweden, and Zimbabwe), fewer communities have been selected.

Selections of households and individuals

Within each community, sampling has been designed to achieve a broadly representative sample of that community of adults aged between 35 and 70 years. Choice of the sampling frame within each center is based on both “representativeness” and feasibility of long-term follow-up, following broad study guidelines. Once a community has been identified, where possible, common and standardized approaches have been applied to the enumeration of households, identification of individuals, recruitment procedures, and data collection. The method of approaching households may differ between regions. For example, in rural areas of India and China, a community announcement is made to the village through contact of a community leader, followed by in-person door-to-door

Figure 2

visits of all households. In contrast in Canada, initial contact is by mail followed by telephone inviting members of the households to a central clinic. For each approach, at least 3 attempts at contact are made. Households are eligible if at least 1 member of the household is between the ages of 35 and 70 years and the household members intend to continue living in their current home for a further 4 years. All individuals within these households between 35 and 70 years providing written informed consent are enrolled. When a household refuses to participate, demographics and simple self-report risk factor data are recorded in a nonresponder form.

Data collection

Data collection occurs at 4 levels in the PURE study: national, community, household, and individual (Figure 1).

National level data collection at baseline and then every 3 years involves the collection of data on policy and economic indicators that influence health. Information is collated from similar sources for each country where possible, that is, World Bank reports, National Census, and Survey data.

Community level data involves the collection of social and environmental factors that influence health using several instruments: (1) The Environmental Profile of a Community's Health (EPOCH) Instrument, (2) The Neighbourhood Walkability Scale, and (3) Aggregate data from individual or household questionnaires for certain factors.

The EPOCH Instrument is a 2-part tool that has been developed by the Population Health Research Institute (PHRI, Hamilton, Ontario, Canada) in collaboration with investigators at the

London School of Hygiene and Tropical Medicine to characterize the built, nutrition, social, and tobacco environments of communities. Measures selected for inclusion in EPOCH is based on an extensive literature review.¹³ EPOCH part 1 is a direct observation tool in which trained researchers appraise each of the communities, following a standardized protocol. This involves walking around the community visiting specified locations and recording observations. The researcher starts the appraisal at a central location within the community's main service area and follows a preplanned walk on which defined aspects of the community environment are assessed. For example, relevant to the tobacco environment, observations include the presence of no smoking signs, tobacco promotion, visibility of cigarette displays, and cost and availability of tobacco. EPOCH part 2 is a brief interviewer-administered survey of community awareness, attitudes, and social norms administered to a subsample of PURE participants. It examines awareness and attitudes toward policies, implementation of policies, and social acceptability of certain behaviors such as smoking/alcohol consumption.

The *Neighbourhood Walkability Scale questionnaire* is administered to a household representative and collects information on individual perceptions of neighborhood walkability.¹⁵ It includes measures of land use mix, access to services, neighborhood aesthetics, traffic safety, crime safety, and neighborhood satisfaction.

In addition, questions contained in the individual and household questionnaires will be aggregated to describe the community environment, for example, perceptions of the influence of media on food choices, perceptions of the influence of food costs on diet, and questions on food security.^{16,17} Social factors,

Table I. Participating countries and target recruitment goals

World Bank income classification*		Urban communities	Urban individuals	Rural communities	Rural	Total
HIC	Canada	44	5500	21	4500	11 000
	Sweden	3	3500	3	1500	5000
	UAE	1	1000	2	1000	2000
Upper-middle-income countries	Argentina	14	2500	14	2500	5000
	Brazil	22	2500	42	2500	5000
	Chile	6	2500	9	2500	5000
	Malaysia	61	5000	26	5000	10 000
	Poland	1	1000	3	1000	2000
	South Africa	4	1000	4	1000	2000
	Turkey	29	1000	12	1000	2000
Lower-middle-income countries	China	100	25 000	117	25 000	60 000
	Colombia	30	2500	10	2500	5000
	Iran	9	2500	7	2500	5000
	Bangladesh	30	2500	26	2500	5000
LIC	India	31	15 000	60	15 000	30 000
	Pakistan	3	1000	3	1000	2000
	Zimbabwe	2	500	2	500	1000

* <http://web.worldbank.org>.

Table II. Guidelines for selection of countries, communities, households, and individuals recruited to PURE

Countries

1. HIC, MIC, and LIC, with the bulk of the recruitment from low- and middle-income regions.
2. Committed local investigators with experience in recruiting for population studies.

Communities

1. Select both urban and rural communities. Use the national definition of the country to determine urban and rural communities.
2. Select rural communities that are isolated (distance of >50 km or lack easy access to commuter transportation) from urban centers. However, consider ability to process bloods samples, eg, villages in rural developing countries should be within 45-min drive of an appropriate facility.
3. Define community to a geographical area, eg, using postal codes, catchment area of health service/clinics, census tracts, areas bordered by specific streets or natural borders such as a river bank.
4. Consider feasibility for long-term follow-up, eg, for urban communities, choose sites that have a stable population such as residential colonies related to specific work sites in developing countries. In rural areas, choose villages that have a stable population. Villages at greater distance from urban centers are less susceptible to large migration to urban centers.
5. Enlist a community organization to facilitate contact with the community, eg, in urban areas, large employers (government and private), insurance companies, clubs, religious organizations, clinic or hospital service regions. In rural areas, local authorities such as priests or community elders, hospital or clinic, village leader, or local politician.

Individual

1. Broadly representative sampling of adults 35 to 70 years within each community unit.
2. Consider feasibility for long-term follow-up when formulating community sampling framework, eg, small percentage random samples of large communities may be more difficult to follow-up because they are dispersed by distance. In rural areas of developing countries that are not connected by telephone, it may be better to sample entire community (ie, door-to-door systematic sampling).
3. The method of approach of households/individuals may differ between sites. In MIC and HIC, mail, followed up by phone contact may be the practical first means of contact. In LIC, direct household contact through household visits may be the most appropriate means of first contact.
4. Once recruited, all individuals are invited to a study clinic to complete standardized questionnaires and have a standardized set of measurements.

including social capital (trust), family structure, social networks, community club membership, levels of trust, and volunteerism are also measured in the questionnaire for individuals as are socioeconomic factors including income, employment/occupation, education, and wealth.

Data on PURE study families and households are collected in 2 questionnaires. The *Family Census Questionnaire* records demographic information (ie, number of individuals in the household, sex ratio, number of children, and other relatives), tobacco use, education, and major morbidities in all inhabitants of the household. The *Household Questionnaire* obtains information from the household head on house structure, amenities, access to water, and sanitation.

The *Adult Questionnaire* for adult participants collects data on the 9 INTERHEART risk factors (lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors [stress and symptoms of depression], consumption of fruits, and vegetables, consumption of alcohol, and regular physical activity). The physical examination includes 2 measures of resting blood pressure (sitting), anthropometric measures (weight, height, waist, and hip), spirometry (forced expiratory volume in 1 second, forced expiratory vital capacity), and electrocardiogram. A 10-mL fasting blood sample is collected from all consenting participants. Blood samples are centrifuged and transferred to centralized long-term storage in secure -70°C freezers or large -180°C liquid nitrogen tanks for future biochemical and genetic testing. In addition,

detailed information on physical activity and diet is collected using the International Physical Activity Questionnaire (IPAQ)¹⁸ (or regional questionnaires with comparable variables) and semiquantitative Food Frequency Questionnaires (FFQs). For some countries, existing validated FFQs have been used; however, for most countries, the project office has developed a country-specific FFQ that have been validated against 24-hour dietary recalls as reference methods.¹⁹ To enable comparability of all data and calculation of nutrient content, a master international nutrient database has been created primarily based on the United States Department of Agriculture (Washington, D.C.) food composition database, modified appropriately with reference to local food composition tables, and supplemented with recipes of locally eaten mixed dishes. This ensures that the units of measurement, method of selection of foods for testing, and assays used for nutrient estimation are consistent and as current as possible and yet have taken into account some local variations.²⁰ Food patterns will also be generated using the FFQ data following published established methods.²¹

Quality of data collection is maintained through the use of standardized protocols and centralized training. Key staff from each center attend an initial training session in each country/region (standardization across regions is provided by Project Office staff attending these training sessions) and in turn, train local staff using centrally created manuals and training videos. These staff are trained, tested on "mock" subjects, and certified. If the variation between the staff compared to the coordinator is unacceptable, the staff member is retrained.

All data are entered at each site electronically into a customized database programed with range and consistency checks and transmitted electronically to the Project Office in Hamilton where further quality control measures are implemented. All bloods are either shipped to the Central Research Laboratories in Hamilton (most countries) or national core laboratories (India and China) following standardized procedures.

Cohort follow-up

Annual contacts are made to document chronic noncommunicable disease events over the 10 years of planned follow-up. Detailed follow-up encounters at 3 and 6 years are planned to repeat measures of selected risk factors. Cause of death, in the absence of formal documentation, will be ascertained by a validated verbal autopsy method.²² Confirmatory evidence of morbid events will be obtained from collection of extra information on standardized event forms and collection of supporting medical documentation. These will be adjudicated using standardized definitions and without knowledge of the participant's residence.

Follow-up at 3 years will include additional questions on risk factors and repeat of some community data collection. Follow-up at 6 years will include in-person assessment of weight, waist-hip ratio, and blood pressure. At the 6-year follow-up, it is planned that a small sample of blood will be drawn to measure blood glucose and cholesterol. By excluding households that plan to move in the next 5 years and individuals <35 years who tend to be highly mobile, high follow-up rates are expected.

Analysis and power calculations

The contribution of each of the 4 societal domains on the Framingham Risk Score (FRS)²³ and its components and the

prevalence of CVD²⁴ at baseline will be analyzed using a multilevel generalized linear model, with hierarchical levels (individual, household, community, and country), adjusted for age and sex to account for imbalances across communities. A linear model will be used for continuous risk factors and FRS score and a logistic model for prevalence of CVD. The impact of each component of the 4 societal domains cannot be precisely calculated. However, power to detect differences in mean risk score or CVD prevalence when communities are categorized into thirds based on levels of the societal domains can be calculated. With 600 communities (average sample size of 225), we would have 90% power to detect differences of 0.74 points on the FRS assuming an intraclass correlation of 0.06 and a relative risk of 1.41 for prevalence of CVD assuming a baseline prevalence of 3% and intraclass correlation of 0.06. Because our power is high, imbalances in sample sizes per communities should not compromise study power significantly.

Strengths and weaknesses

PURE builds upon the knowledge generated from several previous national and international epidemiologic studies, which have considerably advanced knowledge.²⁵⁻²⁸ This global study will provide important and novel information on the societal causes of the major health burden due to obesity, diabetes, and CVD globally. Its size, scope (both societal and individual influences), and inclusion of communities from a diverse group of countries will enable us to examine which risk factors are universal and which have contextual variations in their impact on CVD. This avoids the limitations inherent in studying more homogeneous groups. Its focus on societal changes, affecting individual lifestyles and biologic markers (including genetic markers and their interaction with the environment), is novel and will provide new and valuable information that governments and international organizations could use to develop policies that could mitigate the adverse health effects of rapid societal changes. The PURE study will also set up a unique cohort for the examination of interactions between genes and environment. The data collection instruments have been carefully developed to characterize the environment and will be a useful resource for other researchers working in the countries involved in PURE. Although we have already faced challenges to the study, such as turmoil in Zimbabwe in 2007 to 2008 due to crippling levels of inflation making the study difficult, and are likely to face more challenges, these social upheavals themselves influence health, and by continuing to conduct the study in these settings, relevant information on the impact of interim social changes on health can be obtained. We recognize that under such circumstances, achieving good follow-up will be challenging.

Conclusions

The PURE study is unique in both its goals and scope. Currently, no similar study exists that addresses questions regarding the cause and development of CVRFs and disease within populations with comparable coverage, particularly of low and middle income countries. The PURE study is being conducted by a study team with experience in conducting international studies, and the data collection instruments have been developed from international epidemiological studies such as the

INTERHEART study. Recruitment of the ambitious 150,000 is nearly complete. Results of the baseline data will enable investigation of a variety of questions inclusive and beyond the primary objectives of this study. Further information can be obtained through emailing the project office pure@phri.ca.

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Appendix B. PURE project office staff, national coordinators, investigators and key staff

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