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An update on cardiovascular disease epidemiology in South East Asia. Rationale and design of the LIFE course study in CARdiovascular disease Epidemiology (LIFECARE)

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Summary The burden of cardiovascular disease (CVD) is likely to increase dramatically in Asia over the next several decades. In this paper, we review the existing data on CVD epidemiology in Asia, with a focus on the INTERHEART study and the Asia Pacific Cohort Studies Collaboration. Existing data suggests that much of CVD may be preventable through reduction in the levels of well-established CVD risk factors and that these findings are likely to be relevant to Asian populations. However, these studies have several important limitations. These include a lack of longitudinal studies with collection of repeated measures of CVD risk factors and the environmental factors that may result in the age-related increase in the levels of these risk factors. As such, the natural history of the development of CVD risk factors such as obesity, diabetes, hypertension and dyslipidemia in Asia, and their relationship in terms of duration and timing of exposure to various environmental influences is currently unknown. In addition, there is a paucity of data related to psychosocial factors that may be involved in the pathogenesis of CVD, either directly or through effects on other CVD risk factors. Finally, little data is available with regards to the impact of CVD and its attendant risk factors on health related quality of life and health care utilization. This information is crucial for the design and evaluation of evidence based programs for primary prevention. We have designed a LIFE Course Study in CARdiovascular disease Epidemiology (LIFECARE) involving 12,000 individuals in four South East Asian countries to address these data needs.

Introduction

Socio-economic development, accompanied by rapid urbanization, has resulted in an epidemiologic transition in the burden of diseases, from those associated with infection and malnutrition to those associated with non-communicable chronic diseases. Cardiovascular diseases (CVD) represent some of the major causes of morbidity and mortality in developed countries today [1]. In developing countries, this transition is still in progress and many populations in Asia can be expected to experience a doubling of the burden of CVD over the next several decades [2].

The INTERHEART study

The INTERHEART study [3] was a standardized case-control study of acute myocardial infarction (MI) in 52 countries, representing every inhabited continent, involving 15,152 cases and 14,820 controls. It was found that nine risk factors for CVD explained over 90% of the population attributable risk for myocardial infarction in both men and women, in most of the geographical regions studied. These risk factors were cigarette smoking, hypertension, diabetes, obesity, blood lipids, exercise, alcohol ingestion, consumption of fruits and vegetables and psychosocial factors. Although some regional and ethnic variations in the risk associated with each factor were observed, most of the risk factors with larger effect sizes showed consistent associations across regions.

Despite the impressive breadth of its coverage, and its influential results, INTERHEART used a study design, which is susceptible to bias error [4]. One particular issue is that of establishing whether the proposed cause, such as smoking, really did precede the disease, MI. To this extent, the INTERHEART results might be regarded as hypothesis generating rather than definitively quantifying associations. Furthermore, although INTERHEART included significant numbers of individuals from China and Hong Kong, the rest of South East Asia and Japan were represented by only 969 and 1199 cases and controls, respectively. Given the diversity of the populations in South East Asia, this number is too small to establish reliable estimates of relative risks in this most populous region of the world.

The Asia Pacific Cohort Studies Collaboration (APCSC)

In an effort to address some of the limitations of earlier studies in Asia, the Asia Pacific Cohort Studies Collaboration was set up in 1999 to investigate the associations of major cardiovascular risk factors with stroke (fatal and non-fatal, ischaemic and haemorrhagic), coronary heart disease (CHD)

(fatal and non-fatal) and total cardiovascular disease (CVD) [5]. Secondary outcomes were all-cause mortality and non-cardiovascular causes of death. Studies from Australia and New Zealand were included to provide a ''Western'' comparison group, but are not mentioned further here. Studies were eligible for inclusion if based in the region, used a prospective cohort study design and had at least 5000 person-years of follow-up. The prospective design is important for establishing that the outcome came after the risk factor was measured. Individuals within studies were included when their date of birth (or age), sex and blood pressure were recorded at baseline and when their vital status was known at the end of follow-up and, for those that died, their age (or date) at death was known. Cohorts selected on the basis of a positive disease history, or diagnosis, were ineligible. Studies were identified by searches of electronic databases, from abstracts and proceedings of meetings and from personal knowledge.

For each identified study, the principal investigators were invited to supply individual participant data to the study secretariat. This was to include a raft of commonly-accepted CVD risk factors, both at baseline and (if available) repeated values from subsequent evaluations at intervals during the follow-up period. These repeat observations were used to correct continuous associations for regression dilution error. Data on the timing and cause of death were also requested, as well as (where available) information on non-fatal CVD events.

In all, APCSC has data from 513,000 Asians. It includes 35 studies from Asia: 16 from mainland China, 12 from Japan, two from Taiwan and from Singapore and one each from Hong Kong, South Korea and Thailand. The extent of the data provided varied greatly from study-to-study, such as in the number of risk factors measured, how often (if at all) these were remeasured and the length of follow-up.

Fig. 1 gives an example of some key results produced from APCSC data [6]. This shows that increasing systolic blood pressure is an important risk factor for mortality from both haemorrhagic and ischaemic stroke and CHD in Asia [7], with some attenuation of relative risk, taking these three outcomes in this order. Diabetes [8] and smoking [9] are also important risk factors for all three of these outcomes. Increasing total cholesterol (TC) is a significant (i.e. the 95% confidence interval crosses the line of unity; $p < 0.05$) risk factor for CHD death, and almost significant for ischaemic stroke, but as TC increases the risk of haemorrhagic stroke death decreases significantly [10]. Increasing body mass index increases the risk of coronary death significantly, but there is no definitive evidence for it having an effect on death due to stroke [11]. For increasing triglycerides, there is a suggestion of an increased risk of all three types of cardiovascular death, but without achieving significance [12]. The uncertainty in estimates of relative risk (hazard ratio), measured by the widths of the confidence limits, is affected by differences in the amount of data that were available in APCSC — greatest for SBP and least for triglycerides.

Many of the conclusions that may be drawn from Fig. 1 are just what would be expected from the classical studies done in the West, such as Framingham, but showing that Western associations are also important in Asia is crucial to motivating local health promotion and treatment initiatives. Furthermore, precise quantification of associations allows for an Asian risk prediction score to be constructed, so as to quantify individual risk [13]. But APCSC has also shown evidence for associations that might otherwise have been missed — the inverse association between TC and haemorrhagic stroke in Fig. 1 being an example. This is possible to see only in a large database from a region where haemorrhagic stroke is relatively common and TC levels vary from very low to high.

Life course studies

In simple terms, life course studies follow a group of people over time to discover what happens to them. The longitudinal nature of these studies has a number of advantages. Because information is collected prospectively before the outcome of interest occurs, life course studies avoid recall bias and other errors that can arise from trying to remember events that occurred many years earlier. Often life course studies are the only way to obtain accurate information about events and circumstances earlier in the life of study participants. Life course studies can also reliably establish the temporal sequence between exposure and disease, which is not possible in cross-sectional or case-control studies. This allows us to assess whether the association between exposure and disease is causal, since exposure must antedate the onset of disease for a causal association, as was mentioned in the preceding section on the APCSC.

In addition, a life course understanding of chronic disease explicitly recognizes the importance of ''time and timing'' for understanding the development of multifactorial disorders [14—16]. The 'time' aspect of life course theory relates to

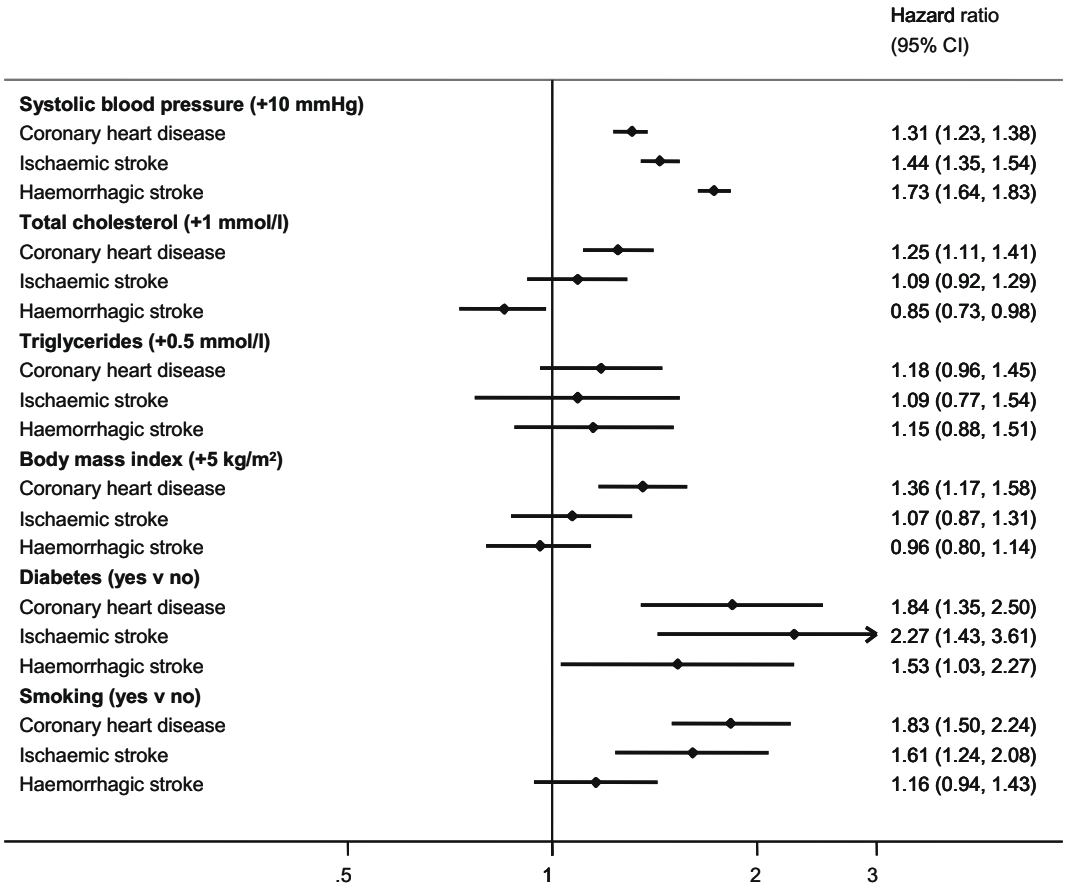

Figure 1 Hazard ratios with 95% confidence intervals (CIs) for death from coronary heart disease, ischaemic stroke and haemorrhagic stroke in Asian cohorts from the Asia Pacific Cohort Studies Collaboration. Results are from Cox regression models, stratified by study and sex. Hazard ratios for systolic blood pressure (SBP), total cholesterol (TC), body mass index (BMI) and smoking are adjusted for each other and for age; hazard ratios for diabetes and triglycerides are adjusted for SBP, TC, BMI, smoking and age. Continuous relationships are adjusted for regression dilution error.

the emphasis on the accumulation of lifetime exposures in determining disease outcomes. In other words, it is the total burden of risk exposure accruing over time that is the key determinant of a person's health, not simply proximal events. The 'timing' aspect posits that there are certain critical and sensitive developmental periods in life (e.g. adolescence, young adult hood, early childhood) during which people are especially sensitive to risk exposures, with risk effects associated with these exposures magnified during this period. As such, it is important to determine not only the magnitude or duration of exposure to a particular risk factor, but also the period in a person's life at which he or she is exposed to the risk factor. This requires repeated measurement of disease and exposures.

Importantly, analytic strategies, based on propensity scores [17], are now available to quantify ''treatment" effects in observational life course designs when randomized controlled trials are not a viable option for hypothesis testing (e.g. ethical constraints prevent random allocation to toxic psychosocial or physical exposures). Such methods are designed to recreate the desirable features of experimental designs by creating balance between exposed (''treatment") vs. non-exposed (''control") groups that have formed naturally over the life course and have been applied, for example, to examine the importance of exposure of adolescents to drugs and alcohol [18].

Limitations of the Asia Pacific Cohort Studies Collaboration

Despite its success, APCSC has some important drawbacks. Most obvious is the lack of a common core protocol for the studies involved, since their recruitment into APCSC was retrospective. Thus definitions, assay methods and means of ascertain-

ing outcomes all vary between studies and reduces our ability to directly compare data between populations. In this manuscript, we highlight several other limitations that we believe to be important which will need to be addressed in order to facilitate evidence based disease prevention.

Longitudinal repeated measurements of risk factors

Although some studies in the APCSC included longitudinal repeated measurements of risk factors, this was unusual and rarely was there more than one repeat measure per person. Hence the life course of risk factor levels cannot be estimated with any reasonable validity. This has several implications. Firstly, we do not know the time of life when the increases in these risk factors occur, or whether there are critical periods in a person's life when the risk factor levels increase. As such, we cannot assess the duration of exposure to the risk factor and the effect that this might have on cardiovascular disease risk. If it is true, as hypothesized in life course theory (described in the preceding section), that cardiovascular disease is a consequence of the accumulated exposure to risk factors over time, then a single measurement, which does not consider the duration of exposure, would under-estimate the risk of CVD associated with that risk factor. Secondly, the pathogenesis of most of these risk factors has a significant environmental component. Diet, physical activity, psychosocial factors, cigarette smoking, alcohol intake, all have important effects on the risk of hypertension, dyslipidemia, obesity and diabetes mellitus. Amongst the CVD risk factors identified in the INTERHEART study, these environmental risk factors are the most imprecisely measured, in part due to difficulties in recall. In fact, the risk of myocardial infarction associated with these environmental factors showed the greatest regional and ethnic variation in the INTERHEART study [3]. Repeated measurements prior to the onset of disease, with attention to the 'time' and 'timing' of exposures could allow us better assessment of the risk associated with these environmental factors. Finally, the levels for most of the risk factors that the APCSC has shown to be important in Asia increase with increasing age. Single measurements of risk factors tell us nothing about the factors that drive the age-related increase. Thus, while the findings from the APCSC suggest that public health policies to prevent the uptake of smoking and promote quitting, restrict salt consumption, increase exercise and restrict the intake of fatty foods, by reducing obesity, dyslipidemia, hypertension and diabetes mellitus, are likely to have great consequence for CVD in Asia, the APCSC provides no information as to the specific measures that might be relevant to the various populations in Asia (which may be culturally and ethnically distinct), nor the actual impact that these changes might have on risk factor levels.

Prospective measurement of psychosocial factors

We believe that, of the environmental factors that have been implicated, psychosocial factors, which accounted for 32.5% of the population attributable risk in the INTERHEART study [3], deserve special mention. Only dyslipidemia and smoking had a higher population attributable risk. There is increasing interest in the role that psychosocial risk factors might play in the development of chronic physical disease from a life course perspective [19]. A key question that remains is whether psychosocial factors directly influence poor physical health outcomes, or whether they exert their influence by virtue of their relation to established risk factors (e.g. smoking, high cholesterol, obesity) [15]? Research is beginning to provide some insights into the nature, strength and direction of associations between various psychosocial factors early in life and cardiovascular risk in adulthood, while applying appropriate controls for (i) selection effects (ii) co-occurring (to the exposure) risk factors; (iii) mediating factors; and (iv) risk variables measured at the same time as the outcome [20]. These types of studies illustrate the value and promise of the life course approach for understanding how psychosocial pathways lead to both good and poor health, and ultimately may shed light on just how the psychosocial world ''gets under the skin" to cause physical disease [21,22].

To date, empirical work has been limited by several factors. First, the majority of research on the psychosocial correlates of physical health has been cross-sectional. In contrast, life course methods (i.e. prospective-longitudinal studies) and within-subject comparisons offer a stronger strategy for inferring developmental influences [23]. Second, and more generally, epidemiological studies whose primary focus is on physical health tend to have comparatively weak psychosocial data, and vice versa. Gold standard measurement of both psychosocial and physical health variables, collected prospectively and therefore uncontaminated by recall bias, is paramount.

Health related quality of life (HRQoL) and health care utilization

Data on health care utilization and HRQoL are not included in APCSC, yet these are now recognized as crucial indicators of the burden of CVD. The treatment of CVD, and its attendant risk factors, is expensive and consumes considerable health care resources. Diabetes and its associated co-morbidities such as hypertension increase both hospitalization [24—26] and the utilization of primary care services [27,28]. Furthermore the presence of multiple co-morbidities had an additive effect on health care utilization [29]. In particular, the concomitant presence of CVD increased the cost of treating a diabetic patient by 2—3-fold [30,31]. The patterns of health care utilization are ethnic and culturally specific. Even in North America, the patterns of health care utilization for patients with diabetes differ between Canada and the United States [32]. The impact that these disorders have on health care utilization is unknown in most countries in Asia, and forms an important aspect of the economic analysis required to adequately assess the cost vs. benefit of any interventional strategies to prevent CVD.

HRQoL is defined as ''the physical, psychological and social domains of health, seen as distinct areas that are influenced by a person's experiences, beliefs, expectations and perceptions" [33]. The health perspective from a patient's point of view is increasingly being recognized as an important clinical outcome [33,34]. This perspective is especially important for patients undergoing therapy or treatment, who may experience significant reductions in HRQoL despite being adequately treated for a particular illness or disease [35]. For instance, it has been seen that patients with systemic lupus erythromatosus (SLE) may experience fatigue and poor physical and emotional functioning even if SLE is inactive [36]. This emphasis on patient's perceptions of health (which is measured by HRQoL) is thus important given that patient's functional status and perceptions of health often differ from physicians' assessment of the patient's health status. In the United States between the years 1993 and 2001, studies show a worsening trend for the HRQoL in most demographic group studies [37]. In recent years, HRQoL has become a focus for clinical research in which it is used as an outcome measure among people with chronic diseases [38]. In many chronic illnesses, it is difficult to find any linear association between a patient's improvement in disease symptoms and improvements in functional status. In such instances, HRQoL plays a significant role in assessing a patient's satisfaction with and functional response to a given treatment or therapy. At present little is known about the patient perspective on function as measured by HRQoL in Asia. The published literature on HRQoL in CVD in Asia is sparse, and has largely emphasized the cross-cultural validation of existing scales [39], development of new scales [40] or assessment of existing CVD in hospital based studies [41]. To the best of our knowledge, no population based studies assessing HRQoL in CVD exist.

The life course study in cardiovascular disease epidemiology (LIFECARE)

To address these limitations, we have designed a multi-center life course study to examine the link between environmental (psychosocial factors, exercise, smoking, alcohol intake), and CVD risk factors (obesity, diabetes mellitus, hypertension and dyslipidemia) and ultimately, their impact on health related quality of life and health care utilization in four countries in Asia.

The LIFECARE study will recruit four cohorts of 3000 subjects each (total 12,000 subjects) in four countries in South East Asia: Indonesia, Malaysia, the Philippines and Thailand. Each of these countries has experienced an increased burden of CVD and its risk factors. This has been most clearly documented in Thailand [42] and the Philippines [43]. Although each country has the independence to incorporate distinct aspects into their individual studies, each study site also follows a standardized core protocol that is described in this manuscript. This core protocol was jointly developed by the study advisory committee, which includes representative from each country-specific cohort. The study was initiated in 2008, and partially funded by Pfizer Inc. through an Investigator Initiated Research Grant.

The primary aims of the study are to:

(1) Identify factors that underlie changes in CVD risk factors over time in Asia.
   a. The CVD risk factors of interest include:
      i. Blood glucose.
      ii. Blood lipids.
      iii. Blood pressure.
      iv. Obesity.
   b. The exposures of interest include:
      i. Psychosocial factors (socio-economic status, psychological distress).
      ii. Lifestyle factors (exercise, alcohol intake, cigarette smoking, obesity).

(2) To determine the impact of CVD and its risk factors on:
   a. Health related quality of life.
   b. Health care utilization.

Secondary aims are to:

(1) To determine baseline epidemiologic data on prevalence of risk factors for CVD on a selected cohort including dyslipidaemia, diabetes, hypertension, obesity and smoking that are present within the cohort and compare them with those in other countries in the region.
(2) To create and maintain a bio-bank of specimens that could be used for future clinical epidemiology studies related to CVD, including studies of genetic and other biomarkers.

Methods for the LIFECARE study

Study population

The study populations will comprise individuals aged 18—50, with the youngest members giving us an opportunity to observe them prior to the onset of disease so that we can observe the changes over time. The populations will be mostly recruited from urban or semi-urban areas, which we anticipate will experience the greatest increase in CVD risk factors. In Indonesia, Malaysia and the Philippines, the studies will be population based and selected randomly from a defined geographical region. In Thailand, the study will comprise an occupational workforce with a history of long term employment of individuals. This approach has been extensively used in Thailand with great success for the study of CVD risk factors [44—49]. Although we recognize that some of the findings of this study will not necessarily be generalizable to the entire population in the countries involved (particularly in rural areas), we believe that this approach will provide valid data that will be useful to regions with the greatest population density and at the greatest risk for CVD.

Measurements

The initial plan is to study all subjects at baseline, followed by two additional cycles at intervals of 3—5 years. At each cycle, a core-set of measurements will be made.

Questionnaire

An interviewer-administered questionnaire will be used to collect data on demographics, socio-economic status, smoking habits, alcohol ingestion, physical activity, medical history (including diabetes, hypertension, dyslipidemia and CVD) and any medication use.

Assessment of psychosocial factors

Socio-economic status will be measured via (i) country-specific (i.e. culturally appropriate) metrics, augmented by (ii) standard questions about income, education, occupation.

The 10-item Kessler Psychological Distress Scale (K10) questionnaire will be used to assess anxiety and depression. It is a brief 10-item questionnaire designed to measure the level of distress and its severity associated with psychological symptoms in population surveys [50]. Using data from a large (n = 10,641) nationally representative household survey undertaken in Australia, Furukawa and colleagues found that the K10 outperformed the General Health Questionnaire (GHQ-12) in screening for the CIDI/DSM-IV mood and anxiety disorders [51]. The K10 questionnaire is currently being utilized in multiple countries (such as annual government health surveys in the US and Canada as well as in the World Health Organization World Mental Health Surveys) with an estimated combined sample of over 200,000 respondents. The careful construction and brevity of the K10 scale means that it is likely to become one of the more widely used mental health screening instruments in contemporary psychiatry. The same features of brevity, validity in multiple populations and widespread utilization internationally, were the same reasons for the selection of this instrument for use in this study. In addition, levels of stress experienced by participants will be measured using questionnaires from the INTERHEART study [52].

Assessment of health related quality of life

Health related quality of life with be assessed using a profile based measure (the Short Form 36 Health Survey (SF-36) and a utility-based measure (EQ-5D). Profile based measures provide information of a subject's HRQoL in a variety of domains (e.g. physical functioning), while preference based measures provide information on a subject's preference for a given health state, which is necessary for pharmacoeconomic studies including cost utility analysis.

Assessment of health care utilization

Utilization of health care will be assessed using a questionnaire developed by the study investigators which will collect data on any hospitalization or visits to outpatient clinics as well as the health care expenditure in the six months prior to participation in the study.

Translation and local validation of the questionnaires

Each site will carry out the translations locally, with appropriate forward and back-translations. The assessment of health related quality of life will be carried out using the official versions of the SF-36 and EQ-5D. Where appropriate, local validation of the instruments was carried out in a standardized manner, including both informal and cognitive debriefing, an assessment of test—retest reliability as well as tests of construct/criterion validity.

Assessment of CVD risk factors

All participants will have a clinic examination where we will measure anthropometry (weight, height, waist circumference, hip circumference) and blood pressure. Fasting blood specimens will be collected for measurement of blood glucose and lipids (total cholesterol, triglyceride and high density lipoprotein cholesterol). Low density lipoprotein cholesterol will be calculated using the Friedewald formula. Each country will use a local laboratory for the biochemical measurements. However, for each examination, 100 randomly selected samples will be analyzed at an accredited laboratory which participates in the Centers for Disease Control and Prevention-National Heart, Lung, and Blood Institute Lipid standardization program. This will allow us to calibrate the measurements across countries.

Study and data management

The principal investigator of the study (EST) chairs an advisory committee comprising the co-principal investigator (MW) and the principal investigators for each of the four countries: Indonesia (JA), Malaysia (KHS), the Philippines (RS) and Thailand (PS). Additional members provide advice, both in general and in specific areas such as HRQoL and health care utilization (JT, WHL) and psychosocial factors and life course epidemiology (RP). This committee oversees the development of the standard protocol which all countries will follow, the analytical plan and eventual communication of findings pertaining to more than one country. In each country, the principal investigator chairs a working committee which will conduct the study, collate and analyze local data in accordance with the standard protocol and analytical plan. The country-specific working committee will also be responsible for the communication of country-specific findings.

Conclusion

South East Asia is likely to see a large increase in the morbidity and mortality associated with CVD over the next several decades. Efforts to reduce the levels of common CVD risk factors have tremendous potential to reduce the burden that CVD poses for the individual and for society. However, several knowledge gaps exist that limit our ability to design and assess the potential efficacy of interventional programs. Specifically, the natural history for the development of diabetes mellitus, hypertension, obesity and dyslipidemia are largely unknown in relation to the timing of their development and also the factors that underlie their development. Several of these factors include modifiable environmental factors such as physical activity, smoking, alcohol ingestion and psychosocial factors. In addition, there is little or no information regarding the impact of CVD and its attendant risk factors on health related quality of life or health care utilization. We have designed a life course study in four South East Asian countries that will address these issues, and link environmental factors to the development of CVD risk factors and, ultimately, CVD, health related quality of life and health care utilization. This information is critical for the design and evaluation of evidence based programs for primary prevention.

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