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Orang Asli Health and Lifeways Project (OA HeLP): a cross-sectional cohort study protocol

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ABSTRACT

Introduction Non-communicable disease (NCD) risk is influenced by environmental factors that are highly variable worldwide, yet prior research has focused mainly on high-income countries where most people are exposed to relatively homogeneous and static environments. Understanding the scope and complexity of environmental influences on NCD risk around the globe requires more data from people living in diverse and changing environments. Our project will investigate the prevalence and environmental causes of NCDs among the indigenous peoples of Peninsular Malaysia, known collectively as the Orang Asli, who are currently undergoing varying degrees of lifestyle and sociocultural changes that are predicted to increase vulnerability to NCDs, particularly metabolic disorders and musculoskeletal degenerative diseases.

Methods and analysis Biospecimen sampling and screening for a suite of NCDs (eg, cardiovascular disease, type II diabetes, osteoarthritis and osteoporosis), combined with detailed ethnographic work to assess key lifestyle and sociocultural variables (eg, diet, physical activity and wealth), will take place in Orang Asli communities spanning a gradient from remote, traditional villages to acculturated, market-integrated urban areas. Analyses will first test for relationships between environmental variables, NCD risk factors and NCD occurrence to investigate how environmental changes are affecting NCD susceptibility among the Orang Asli. Second, we will examine potential molecular and physiological mechanisms (eg, epigenetics and systemic inflammation) that mediate environmental effects on health. Third, we will identify intrinsic (eg, age and sex) and extrinsic (eg, early-life experiences) factors that predispose certain people to NCDs in the face of environmental change to better understand which Orang Asli are at greatest risk of NCDs.

Ethics and dissemination Approval was obtained from multiple ethical review boards including the Malaysian Ministry of Health. This study follows established principles for ethical biomedical research among vulnerable indigenous communities, including fostering collaboration, building cultural competency, enhancing transparency, supporting capacity building and disseminating research findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study integrates methods and theory from anthropology and epidemiology to examine risk of non-communicable diseases (NCDs) among the indigenous peoples of Peninsular Malaysia, known as the Orang Asli.
⇒ The study will be the first to collect detailed data on lifestyle and sociocultural factors potentially influencing NCD risk among the Orang Asli, including dietary and physical activity patterns.
⇒ Multiple NCDs and biomarkers of NCD risk to be studied have not been investigated previously among the Orang Asli, such as those related to musculoskeletal degeneration.
⇒ Study sample composition will depend on the willingness of Orang Asli communities and individuals to participate, which may lead to some selection bias.
⇒ Some data collected will be based on retrospective reporting and thus liable to measurement error.

INTRODUCTION

People today are getting sick and dying from a variety of non-communicable diseases (NCDs) that were much less prevalent among earlier generations. As recently as 100 years ago, the primary causes of morbidity and mortality in high-income countries (HICs) such as the USA were infectious diseases and malnutrition.[1] In contrast, the greatest threats today are posed by NCDs that include metabolic disorders such as obesity, cardiovascular disease and type II diabetes, musculoskeletal conditions such as osteoarthritis, back pain and osteoporosis-related bone fractures, and neurological illnesses such as Alzheimer's disease and other dementias.[2] In recent decades, there have also been dramatic increases in the incidence and burden of NCDs in low-income and middle-income countries (LMICs).[3] Rates of obesity and related diseases, for example, are currently rising fastest in Asia and Latin

America,[4–6] and evidence suggests that even rural and subsistence-based societies in these regions are increasingly susceptible to NCDs.[6–10] Such increases in NCDs are not necessarily associated with the same reductions in infectious diseases observed in HICs, leading to a 'double burden of disease'.[11 12] The escalating NCD pandemic is thus among the largest and most urgent global health concerns today.

NCD susceptibility is known to be influenced by intrinsic factors such as age, sex and genetic variation, yet the rapid increase of NCDs within a few generations indicates that recent environmental changes strongly contribute to disease pathogenesis. Many NCDs thus appear to fit the definition of 'mismatch diseases', disorders caused by human bodies being inadequately or imperfectly adapted to novel features of modern environments.[13 14] Nevertheless, explicitly testing the mismatch hypothesis, and more generally, identifying environmental factors responsible for the global NCD pandemic, has been challenging for three main reasons.

First, because most research to date has focused on HICs, the range of environments experienced by study participants is relatively static and homogenous.[15] For example, essentially all people in HICs consume some amount of highly processed foods and rely regularly on labor-saving technologies. Thus, we are unable to test how the full spectrum of environmental variation—ranging from minimal exposure to full exposure—predicts NCD risk within a single population, which could be important for revealing nonlinear relationships as well as for increasing statistical power. Furthermore, people in HICs tend to experience similar environments throughout their lifetimes, making it difficult to disentangle the effects of exposures that occur in early life versus adulthood. Given the growing appreciation that early-life conditions shape later life health and NCD risk,[16 17] identifying study systems with more dynamic, within-lifetime variation is a major priority.

Second, environmental conditions—including lifestyle and sociocultural factors such as physical activity patterns, diet and food processing, technology usage, degree of market integration, social organisation and stratification, gender relations, and divisions of labour—are highly variable among populations worldwide, so it is unlikely that findings from the Global North can be extrapolated to the rest of the world.[3 6] Moreover, evidence suggests that both the types and impacts of environmental factors underlying NCD susceptibility may differ between populations. In the USA, for example, the environmental shifts believed to be most responsible for current high levels of obesity and associated NCDs are major declines in physical activity and greater consumption of energy-dense processed foods and drinks.[18–20] Yet, outside of HICs, prevalence of metabolic NCDs is increasing even among societies in which most people are rarely able to avoid regular physical activity and/or have relatively little to moderate access to processed market foods.[8–10] Also, people in many such societies have been documented to have a heightened sensitivity to obesity-related diseases for a given body mass index (BMI) compared with people in HICs,[21 22] likely due to the extremely rapid rate of environmental changes occurring in LMICs.[23–25] Ultimately, understanding the diversity and complexity of environmental influences on NCD risk worldwide, as well as preventing further increases in NCDs on a global scale, requires more data from people living in diverse environments.[15]

Third, previous attempts to understand the ultimate causes of NCDs through the lens of the mismatch hypothesis have relied on study designs that are not well suited for rigorously testing the idea. In particular, many studies have sought to test the mismatch hypothesis by comparing NCD prevalence and risk factors between HICs and small-scale, subsistence-based societies (eg, hunter-gatherers, horticulturalists and pastoralists), which arguably have lifestyles that are more 'matched' to their recent evolutionary history. These studies have repeatedly found low levels of NCDs such as obesity, cardiovascular disease and type II diabetes in subsistence-based groups relative to HICs.[26–28] This study design, however, confounds genetic background and recent evolutionary history with current lifestyle, limiting our ability to distinguish genetic versus environmental effects. A more robust study design would be to compare health between individuals engaging in traditional lifeways versus individuals from the same general genetic background living an industrial or post-industrial lifestyle. Such data are required for understanding how past selection regimes affect current NCD susceptibility.

Here, we present a research programme that investigates the prevalence, underlying environmental causes and evolutionary explanations for NCDs among the indigenous peoples of Peninsular Malaysia, known collectively as the Orang Asli. The Orang Asli (meaning 'original people' in Malay) occupy a relatively small geographical area but are exposed to a wide range of environmental conditions. Traditionally, the Orang Asli live in relatively small, remote forest camps and villages and subsist on some combination of hunting, fishing, wild food collection, horticulture and trade of forest products.[29 30] Today, however, no Orang Asli communities are completely isolated from outside economic and cultural influences due to the rapid expansion of industries, governmental regulation, the market economy and urban areas across Malaysia over the last half-century.[31–38] As a result, Orang Asli groups have been experiencing varying types and degrees of environmental change (eg, ecological degradation, acculturation, market integration and urbanisation) that are occurring rapidly and within the span of an individual lifetime. At one extreme, some Orang Asli communities remain relatively isolated and continue to adhere largely to traditional lifestyles, but at the other extreme, some communities are now bound by urban areas, highly acculturated, and fully integrated into the market economy. Not surprisingly, while historical data suggest that NCDs were once rare among the Orang

Asli,[39–44] recent work indicates that NCDs are a growing problem, especially in the more urbanised, acculturated and market-integrated communities.[45–49] Infectious diseases also continue to be major health threats for the Orang Asli.[50–53]

Our project—called the Orang Asli Health and Lifeways Project (OA HeLP)—is a collaboration between anthropologists, biomedical researchers, clinicians and study communities that aims to better understand how and why environmental changes are occurring among the Orang Asli and how such changes are affecting individuals' susceptibility to NCDs. Presently, our focus is on metabolic disorders (obesity, cardiovascular disease and type II diabetes) and musculoskeletal degenerative diseases (osteoarthritis and osteoporosis), though research on additional types of NCDs is expected in the future. Specifically, the primary goals of the project are as follows: (1) conduct ethnographic fieldwork in Orang Asli communities to collect data on rapidly changing environmental variables including lifestyle and sociocultural conditions; (2) conduct biomedical screening to collect anthropometric, imaging, molecular and physiological data pertaining to general health, NCD risk and NCD diagnosis; (3) test for relationships between environmental variables, NCD risk factors and NCD occurrence to investigate how environmental changes are affecting NCD vulnerability among the Orang Asli; (4) understand the molecular and physiological mechanisms (eg, epigenetics and systemic inflammation) that mediate environmental effects on health and (5) identify intrinsic (eg, age and sex) and extrinsic (eg, early-life experiences) factors that predispose certain people to NCDs in the face of environmental change, in order to understand which Orang Asli individuals are at greatest risk of NCDs. More broadly, this project aims to provide insights useful for understanding the rising prevalence and burden of NCDs in other populations and regions of the world.

METHODS AND ANALYSES

Study population and setting

The population of Peninsular Malaysia is multiethnic, with the majority people being ethnically Malay and predominantly Muslim, and with large minorities of Malaysian people of Chinese and Indian ancestry. The Orang Asli comprise less than 1% of the population (approximately 210 000 people) and include at least 19 distinct ethnolinguistic groups, which are typically divided into three broad categories (figure 1): the Semang (traditionally, speakers of northern Aslian languages and primarily nomadic hunter-gatherers), Senoi (traditionally, speakers of central Aslian languages and primarily horticulturalists) and Aboriginal Malay (traditionally, speakers of Melanesian language dialects and practitioners of mixed subsistence and cash crop economies).[29 30] The genetic history of the Orang Asli is complex and an area of active study. The three broad groups (Semang, Senoi and Aboriginal Malay) are genetically distinguishable, though

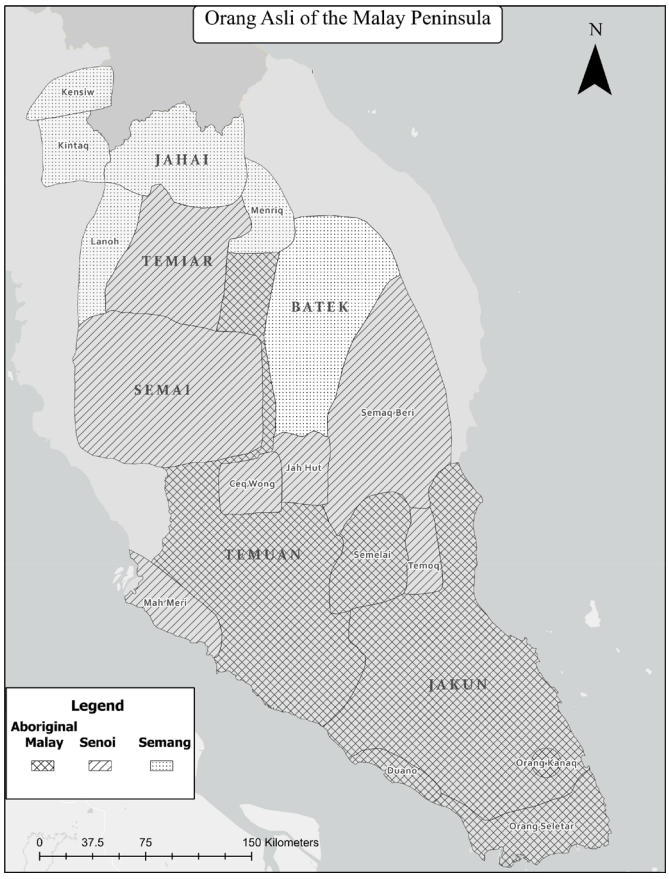

Figure 1 Map of Peninsular Malaysia showing the approximate locations of Orang Asli groups.

they are generally more similar to one another than they are to other surrounding Asian populations.[54] Currently, our project is focused on six particular ethnolinguistic groups—the Batek, Jahai, Semai, Temiar, Temuan and Jakun—which represent two examples each of Semang, Senoi and Aboriginal Malay peoples, respectively. Additional groups are expected to be added to the study in the future. Study communities are located in different areas of Peninsular Malaysia and span a gradient from remote, traditional camps and villages to acculturated, market-integrated urban areas (figure 2).

Among the environmental changes experienced by the Orang Asli over the last half-century, two trends deserve special mention because their effects on lifestyles and sociocultural conditions have been pronounced. First, a key component of efforts to accelerate growth of the national market economy has been the expansion of industries focused on plantation agriculture (particularly oil palm and rubber) and natural resource extraction (particularly timber, tin and petroleum).[55–57] As a result, Malaysia has experienced rapid, marked deforestation,[58–60] which has fragmented and altered large fractions of the lands traditionally occupied by the Orang Asli and has had broad negative impacts on biodiversity and water, soil and air quality.[61–65] Dispossessed of the land and resource base necessary for traditional subsistence strategies (most Orang Asli do not hold official title to

Figure 2 Orang Asli study communities span a gradient from (A) remote, traditional camps and villages to (B) acculturated, market-integrated urban areas.

their traditional lands), many communities have shifted their livelihoods to include wage labour, often in the very industries responsible for their land and resource dispossession.[33] Second, a long-standing objective of the Malaysian government has been to promote the assimilation of the Orang Asli into mainstream Malaysian society and the integration of Orang Asli economies with the national market economy.[30–32] To this end, government programmes have been established to resettle and regroup the Orang Asli into consolidated communities with modern facilities including administrative centres, schools, shops, clinics, houses and roadways.[33] In addition, community members are typically provided some form of income-generating activity (eg, oil palm or rubber). Ultimately, due to these two trends, many Orang Asli currently live in highly acculturated, market-integrated contexts.[33 35–37] Variation exists, however, in how long people have lived in such contexts, with some people having transitioned only recently and others having lived in such contexts for their entire lives.

Notwithstanding the strength of industry, government and other forces, many Orang Asli continue to adhere largely to traditional lifestyles, although on lands that are threatened or degraded relative to those occupied by earlier generations. The most averse to change have been Semang groups (eg, Batek and Jahai), which traditionally practice a hunter-gatherer lifestyle.[31 34 66] Because of the traditionally nomadic, egalitarian and autonomous nature of these groups,[66–68] most have resisted sedentarisation and the authority of industry, government and other entities.[31 66] Consequently, there still exist remote communities that rely heavily on the availability of natural resources.

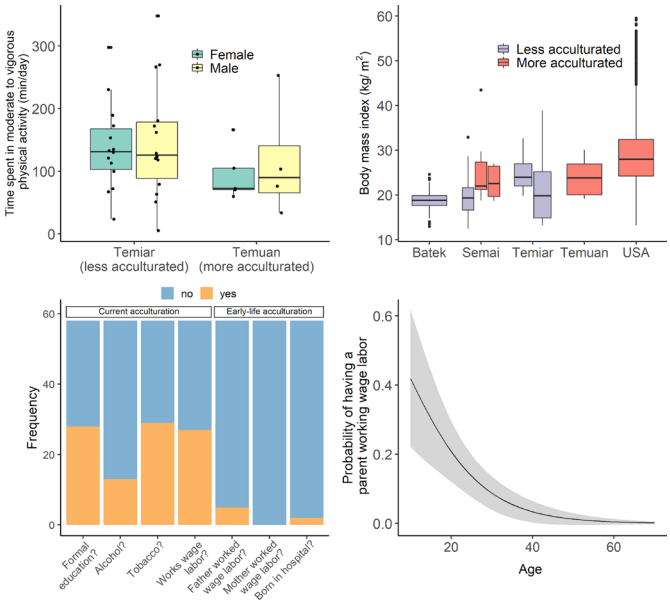

Figure 3 Pilot data showing lifestyle/sociocultural variation and recent lifestyle/sociocultural change among the Orang Asli. (Top left) Physical activity was measured among study participants (n=37) using Axivity accelerometers worn for approximately 5 days, and data were processed with the *GGIR* package in R software to summarise minutes per day spent in moderate-to-vigorous physical activities (MVPA) using 1 min epochs and standard cutoffs. Non-wear time was classified for 15 min blocks based on the SD (<13 mg) and value range (<50 mg) of acceleration in the surrounding 60 min window, and invalid data were imputed by the average at similar time points using different days of the week to calculate summary metrics. Less-acculturated Temiar spend more time per day in MVPA than more-acculturated Temuan. (Top right) Boxplots showing that body mass index among study participants (n=251) is generally higher in more-acculturated Orang Asli communities, though still generally lower than in the USA (USA data are from the National Health and Nutrition Examination Survey, 2009–2010). (Bottom left) Lifestyle/sociocultural questionnaires administered among study participants (n=58) demonstrate recent lifestyle/sociocultural shifts among the Orang Asli (eg, the large difference between the frequency of individuals working wage labour now versus their mothers and fathers when they were young). (Bottom right) The predicted probability (mean±CI) of having a parent who performed wage labour decreases with age (binomial generalised linear model: p=0.03, n=56 study participants), suggesting cohort effects in early-life environmental conditions. Age is reported in years.

Study design

Our current project uses a cross-sectional cohort design[69] that will be implemented over at least 5 years. Participant recruitment has begun, and pilot data have been collected to confirm lifestyle/sociocultural variation and recent lifestyle/sociocultural changes among the Orang Asli (figure 3). The project will be fully operational by the end of 2022.

Research in Orang Asli communities will occur in two phases meant to assess lifestyle/sociocultural conditions and NCD susceptibility, respectively. In the first phase, ethnographic fieldwork will be carried out by anthropologists aided by community members to conduct interviews, administer questionnaires, construct demographic profiles and collect data on key lifestyle and sociocultural variables, as well as physical activity. Depending on the size of the community, this phase will take 1–3 weeks to complete. In the second phase, biomedical researchers will join anthropologists to carry out biomedical screening to collect anthropometric, imaging, molecular and physiological data pertaining to general health, NCD risk and NCD diagnosis, particularly metabolic and

musculoskeletal NCDs. In each community, this phase will take 1–7 days to complete.

Biomedical screening will be conducted in partnership with mobile clinics organised by the Federation of Private Medical Practitioners' Associations of Malaysia (FPMPAM). The FPMPAM is the national body representing doctors in private practice in Malaysia. Among other programmes, the FPMPAM organises mobile clinics that travel to Orang Asli communities throughout Peninsular Malaysia to perform routine physical examinations, provide primary care and medicines, and arrange for transport to a hospital when necessary (a programme known as Drs4All, led by SKWC). These mobile clinics play a critical role in providing health care to the Orang Asli because many communities are located far from clinics and hospitals, and even in communities that have clinics, the clinics tend to be understaffed and lack supplies and medicines.[50]

There are multiple benefits to scheduling biomedical screening to coincide with mobile clinic visits. First, the overall safety and comfort of the participants will be enhanced by having physicians nearby. Second, based on many positive prior interactions between Orang Asli communities and the mobile clinics, community members trust the medical expertise of members of the mobile clinics, whom they can consult if they have any questions or concerns about participating in biomedical screening. Third, biomedical researchers will be collecting specimens and data that could be useful to physicians in diagnosing medical conditions. Fourth, if a chronic condition is diagnosed through our research, we can work with FPMPAM physicians to ensure that the affected individuals have access to routine care, since FPMPAM clinics regularly travel to the same communities.

Study sample and recruitment

All people ≥18 years old who self-identify as ethnically Orang Asli are eligible to participate in the study. However, people <40 years old, as well as pregnant woman, will be excluded from radiographic musculoskeletal imaging (see below). Participation in the study will not affect whether people are able to receive care from the mobile clinics.

The following formula was used to estimate the target sample sizes for the study:

$$n = \frac{Z^2 * P * (1-P)}{d^2}$$

where n is sample size, Z is the statistic corresponding to level of confidence, P is expected prevalence, and d is precision/margin of error.[70] We assumed standard parameters for Z (specifically, a 99% confidence level) and a prevalence of 0.5 (the recommended value for diseases whose prevalence is not known a priori, and therefore, the value that captures the largest range of possibilities). Based on these parameter values, we will aim for a sample size of 1000 people, approximately half women and half men, to achieve a <5% margin of error when estimating the prevalence of any given NCD. We will try to sample approximately equal numbers of individuals across ethnolinguistic groups, ages and the lifestyle/sociocultural gradient.

Orang Asli communities that are willing to be included in the project have been identified through existing relationships developed over many years of prior work by multiple members of our team. Our process of recruitment at the community level involves two general steps, which are then followed by the individual-level consent process. First, permission to conduct research is sought from community leaders. Traditionally, the existence of 'leaders' varies across Orang Asli groups, but today most communities have individuals who maintain official titles of *penghulu* or *tok batin* assigned by the government that indicate a leadership role. In more egalitarian communities, initial meetings are held with an advisory committee of community members. Second, researchers and community leaders hold public meetings to discuss the project, including research questions and goals, methods and procedures, participant inclusion and exclusion criteria, and participant compensation.

Study procedures: ethnographic fieldwork

Interviews and questionnaires

Interviews will be conducted, and questionnaires administered, to construct demographic profiles and collect data on key lifestyle and sociocultural domains. In terms of 'environmental' effects, we are primarily interested in capturing variation related to rapid lifestyle and sociocultural changes that have taken place in Malaysia over the last half-century. Our questionnaires in this area will cover five primary domains: subsistence practices and market integration, location and environmental surroundings, diet and food processing, access to education and modern technology, and relational wealth (presence of family or other human support). Questions will be administered across domains to assess both current adult and early-life lifestyle and sociocultural conditions. Because childhood is not associated with a specific age among many Orang Asli, but rather degree of independence from one's parents, questions about early life will be specified as 'when you were young' with interviewers explaining that this pertains to the time when their parents took care of them. Queries about recent engagement in particular activities will be individually scaled to reflect appropriate time depth. For example, a question about engagement in wage labour will ask about activities within the past month, whereas questions about diet will focus on consumption in the past week.

Adult and early-life questionnaire results will be summarised to create composite indices of adult and early-life conditions that span a gradient from 'traditional' to 'non-traditional.' First, continuous quantitative variables will be binarised based on meaningful cutoffs (eg, highest level of education summarised as 'did or did not complete primary school') or converted to a scale between 0 and 1 to facilitate consolidation. Second, outcomes will be summed to produce composite scores

that represent different phenomena based on variable subsets of questions. Composite indices of lifestyle and sociocultural conditions will be generated separately for both adult and early-life periods. These summary measures will serve as predictor variables in downstream modelling.

Measurements of physical activity

Accelerometry will be used to objectively measure physical activity, which is a risk factor for NDCs including obesity, cardiovascular disease, type II diabetes, osteoarthritis and osteoporosis.[71–75] Participants will be given Axivity accelerometers and asked to wear them for 5–14 days.[76] These waterproof units weigh little (11 g), thus causing no inconvenience to the participant. Accelerometry data will then be processed to quantify variables such as step counts and time spent in moderate-to-vigorous physical activities, as well as potentially gait characteristics (eg, step length and voluntary walking speed), locomotor stability and postural behaviours (eg, knee-bending activities).[76–78]

Study procedures: biomedical screening

Anthropometry

Anthropometric data will be collected to measure BMI and adiposity and diagnose obesity, which are risk factors for NDCs including cardiovascular disease, type II diabetes and osteoarthritis.[79–82] Standing height will be measured with a stadiometer.[83] Body weight and body fat percentage will be measured with a digital bioelectrical impedance scale. Waist circumference will be measured with a tape measure.[83]

Blood pressure

A stethoscope and arm cuff will be used to measure resting blood pressure and diagnose hypertension, which is a risk factor for many NCDs including cardiovascular disease and osteoarthritis.[74 84] Participants will be resting in a seated position for at least 5 min before measurement, and three measurements will be taken 1 min apart.

Blood samples

Venous blood samples (approximately 15 mL) will be collected to assess biomarkers of lipid and glucose metabolism and chronic low-grade systemic inflammation, which are documented risk factors for NDCs including cardiovascular disease, type II diabetes and osteoarthritis.[74 85–88] Approximately 1 mL of blood will be used with multiple point-of-care devices including: (1) a CardioCheck Plus Analyzer to measure levels of blood lipids and glucose and to diagnose dyslipidaemia; (2) a HemoCue WBC DIFF system to measure white cell counts and (3) A1CNow+ tests to measure percentage of glycated haemoglobin levels and diagnose type II diabetes.

Approximately 1 mL of blood will be preserved on (1) Whatman 903 Protein Saver Cards and (2) Whatman FTA Cards. The remaining sample will be processed to (1) isolate and store plasma to study circulating biomarkers of inflammation (eg, C-reactive protein and IL-6) and (2) isolate and store peripheral blood mononuclear cells to study genome-wide gene expression and DNA methylation levels. All collected blood samples will be stored long term at the Universiti Malaya in the laboratory of YALL, and in-country facilities and vendors will be used whenever possible to generate biomarker data.

Fecal and urine samples

Faecal samples will be collected to analyse the gut microbiome and intestinal parasites, which are known mediators of chronic low-grade systemic inflammation and hence potentially NCDs including cardiovascular disease, type II diabetes and osteoarthritis.[89–91] Urine samples will be collected to analyse biomarkers of bone and cartilage turnover (eg, crosslinked C- (CTX) and N- (NTX) telopeptides of type I collagen).[92 93] Participants will be given two opaque disposable plastic cups with lids in the evening and asked to collect the next day's first faeces and urination and return them to the biomedical team.

Bone ultrasound

Quantitative ultrasonography of the radius and tibia will be conducted with a portable MiniOmni probe to assess risk of osteoporosis.[94] The probe will be placed at the medial aspect of the distal one-third of the radius of the non-dominant arm and at the anteromedial aspect of the midshaft tibia of the left leg. The speed of sound (SOS) of the ultrasound wave will be measured, which is related to bone quantity and density.[95]

Hand photos

A digital photo of the dorsum of both hands will be collected to diagnose osteoarthritis in the hand joints.[96] The participant will relax their hands and place them palm down on a plastic grid pad, with fingers apart and thumbs angled approximately 30°.

Knee x-rays

Among people aged 40 years and older, we will collect knee radiographs to diagnose knee osteoarthritis. These will be collected using a portable MinXray Impact digital x-ray system, along with a SynaFlexer frame to standardise the positioning of participants' knees in fixed-flexion view.[97] The overall effective dose for each knee x-ray will be approximately 0.001 milliSieverts, which is equivalent to roughly 3 hours of natural background radiation.[98]

Precautions related to SARS-CoV-2

During the fieldwork, several steps will be taken to minimise risk of transmission of SARS-CoV-2. All researchers will be fully vaccinated and tested for SARS-CoV-2 shortly before entering any study community. Team members will immediately withdraw from research activities should they receive a positive test result or experience symptoms consistent with SARS-CoV-2. In study communities, encounters between researchers and study participants will occur outdoors or in open-air structures. Before and after data collection, all equipment will be sanitised. During the data collection, researchers will wear disposable masks, and participants will be given masks to wear if

they wish to. If a participant displays symptoms consistent with SARS-CoV-2, they will be offered free transport to a nearby health care facility where they can receive free testing and any necessary treatment for SARS-CoV-2. We will also integrate SARS-CoV-2 public health education into our visits to communities, with researchers explaining how transmission works, precautions that should be taken to avoid transmission, and what to do if someone starts experiencing symptoms.

Data analysis

Overview

Our primary goals for data analysis are as follows: (1) estimate the prevalence of metabolic and musculoskeletal NCDs among the Orang Asli; (2) test for relationships between environmental variables, NCD risk factors and NCD occurrence; (3) examine molecular and physiological mechanisms that mediate environmental effects on health and (4) identify intrinsic and extrinsic factors that predispose certain people to NCDs in the face of environmental exposures. Below, we provide an overview of the specific strategies we will use to achieve these goals.

Estimating NCD prevalence

Anthropometric, imaging and physiological data will be used to determine the presence or absence of the following NCDs in each participant: (1) overweight (25≤ BMI<30) and obesity (BMI≥30)[45]; (2) hypertension (blood pressure >130/80 mm Hg)[99]; (3) type II diabetes (percentage of glycated hemoglobin of 6.5% or higher) and pre-diabetes (percentage of glycated hemoglobin of 6.0–6.4%)[45]; (4) metabolic syndrome (diagnosed using of combination of data on waist circumference, blood pressure, and blood lipid and glucose levels)[48]; (5) knee and hand osteoarthritis (diagnosed from radiographs and photos by qualified experts)[95 100] and (6) elevated risk of osteoporosis (SOS T-score of −2.5 or below) and osteopaenia (SOS T-score between −1.0 and −2.5).[101] These data will be used to estimate the prevalence of each NCD, which will be compared with estimates from other studies including those from HICs.

Testing for environmental effects on NCD risk and occurrence

To assess the effects of environmental variables on NCD risk and occurrence, we will first derive several composite measures of lifestyle and sociocultural conditions from interviews and questionnaires, as described above. We will then use linear and generalised linear mixed models controlling for key covariates (eg, age and sex) to ask whether specific environmental variables or our composite indices predict continuous variables associated with NCD risk, as well as binary data on NCD occurrence (presence/absence). Community, household and month of data collection will be included as random effects, while demographic covariates and environmental predictors will be modelled as fixed effects. Continuous variables of interest include BMI, waist circumference, body fat percentage, blood pressure, blood lipid and glucose levels, systemic inflammation, gut microbiome composition, intestinal parasite load, levels of bone and cartilage turnover biomarkers, bone SOS values and physical activity. In addition to examining the effects of individual environmental variables and using composite measures to reduce the dimensionality of the interview data, we will also apply techniques that are well suited to infer complex relationships between multiple predictor variables and an outcome, such as random forests, lasso regression or structural equation modelling.

Examining the mechanistic basis of environmental effects on NCD risk and occurrence

Several candidate molecular and physiological mechanisms will be considered that are known to be environmentally responsive and involved in the aetiology of NCDs,[102–105] including: (1) genome-wide DNA methylation, an epigenetic gene regulatory mechanism; (2) C-reactive protein and IL-6, circulating biomarkers of systemic inflammation and (3) proportional and total counts of neutrophils, lymphocytes, basophils, eosinophils and monocytes, which provide information about immune function and current infection status. To assess the involvement of these and other candidate mechanisms in mediating environmental effects on NCD risk and occurrence, we will first ask whether any of our environmental variables (composite or individually, focusing on those that are identified as most predictive of NCD risk and occurrence) predict variation in our mechanistic variables (using methods appropriate for each data type).[06 107] Then, we will use formal mediation analyses[108 109] to assess causal relationships between environmental variables, mechanisms and NCD risk and occurrence, and to estimate the proportion of the total effect explained by a given mediator.

Examining interindividual variation in NCD risk and occurrence

In all likelihood, environmental effects on NCD risk and occurrence will vary among individuals. A goal of our project is to identify factors that predispose individuals toward susceptibility versus resilience in the face of environmental change. To this end, we will test the degree to which several intrinsic and extrinsic factors mediate environmental influences on NCD risk and occurrence, including age, sex and early-life experiences.[16 17] To do so, we will use linear and generalised linear mixed models to test for interaction effects for all environmental and NCD-related outcome variable combinations that were found to be significant in previous analyses. Analyses will control for multiple hypothesis testing using a Storey-Tibshirani false discovery rate approach,[110] and all code will be made publicly available on Github or Open Science Framework.

ETHICS

Procedures for this study have been reviewed and approved by the Medical Review and Ethics Committee of the Malaysian Ministry of Health (protocol ID:

NMRR-20-2214-55565), the Malaysian Department of Orang Asli Development (permit ID: JAKOA.PP.30.052 JLD 21 (98)) and the Institutional Review Boards of the University of New Mexico (protocol ID: 14420) and Vanderbilt University (protocol ID: 212175) in the USA. Informed consent will be obtained and documented for all study participants. All data obtained in the study will be kept confidential, securely protected and managed, and used only for research purposes. Throughout the project, we will follow established principles for ethical biomedical research among indigenous communities, including fostering collaboration, building cultural competency, being transparent about research practices, supporting capacity building and disseminating research findings.[111]

PARTICIPANT AND PUBLIC INVOLVEMENT

In 2020, we hosted a multiday public webinar series in collaboration with the Orang Asli Archive at Keene State College in the USA entitled 'Orang Asli Health and Well-Being.' The series brought together a large international group of anthropologists, biomedical researchers, clinicians, activists and members of the general public, including many Orang Asli, to identify the greatest health challenges faced by the Orang Asli today. There emerged a strong consensus that NCDs are a rapidly escalating problem and that lifestyle and sociocultural changes are almost certainly largely to blame. These conclusions were consistent with observations made by many of us through our work in different domains. One of us (IbMS) is Orang Asli and the Director of the Hospital Orang Asli, Gombak, a facility devoted exclusively to the care of Orang Asli that has experienced a growing number of patients with NCDs in recent years. Clinicians involved in the FPMPAM mobile clinics (SKWC and MTHS), as well as Malaysian biomedical researchers (YALL, RN and K-SN), have noted similar trends in the Orang Asli communities in which we work. Another author (CN) directs the Centre for Orang Asli Concerns, a human rights organisation that advocates for the Orang Asli, and through this work has received an increasing number of reports of concerns from Orang Asli about NCDs. Ultimately, it was insights gleaned from diverse perspectives in the webinar series, together with our own observations, that motivated the current aims, study design and methodology of OA HeLP.

We are committed to carrying out this project as a collaboration with the Orang Asli communities in which we work. This collaboration will take at least four forms. First, local community leaders and members will be consulted regarding all aspects of the research process including the questions and goals of the project, study procedures, participant compensation, data analysis and management, and results dissemination. During fieldwork, these consultations will occur with community leaders on a continuous basis and with community members during regular public meetings. During non-fieldwork periods, consultations will continue through non-research-related follow-up visits to study communities, email and text messaging, and videoconferencing. As a result of these consultations, we expect the scope of OA HeLP to eventually expand to include additional research questions and goals. We also expect our current questions and goals to be enhanced by the perspectives of community members, and that our protocol will warrant some adjustment to be better suited for certain communities. Second, in study communities, we will employ as many Orang Asli as possible to participate in conducting interviews, collecting data, translation, community relations and more. These individuals will be especially well positioned to provide input on the effectiveness and cultural appropriateness of our fieldwork as it occurs. Third, we aim to recruit and provide funding for Orang Asli students and researchers to join the OA HeLP team and use OA HeLP resources and infrastructure to pursue their own health-related research goals in study communities. Our project will also support medical training among Orang Asli from study communities through a programme organised by the FPMPAM, in which Orang Asli individuals receive funding to work at private clinics across Malaysia where they receive education in first aid and emergency medicine before returning to their communities where they then serve as medical 'first responders'. Fourth, all individuals in Orang Asli study communities who make substantial contributions to the research programme will be invited to be coauthors on scientific publications arising from the research.

PLAN FOR RESULTS DISSEMINATION

A critical part of OA HeLP is the communication of our findings to study communities. As results become available, they will be presented in layperson's terms at public meetings held in each study community, during which community members will be able to ask questions and provide their own perspectives on the findings. These meetings will provide important opportunities for developing interpretations of results that incorporate Orang Asli viewpoints. During meetings, we will discuss the prevalence of various NCDs and risk factors for those diseases, as well as the lifestyle and sociocultural factors that our research indicates are most closely associated with those NCDs. We will also discuss potential lifestyle adjustments that individuals could make to lower their vulnerability to NCDs. In addition, we will present our findings to the Malaysian Ministry of Health in written reports and in-person presentations. The Malaysian Ministry of Health oversees all government-run public health and prevention services for the Orang Asli. Thus, communicating our findings to the Malaysian Ministry of Health has the potential to improve health care among the Orang Asli by generating data that could be used to develop and provide more effective health services.

To publicise OA HeLP more broadly, we maintain a website (www.orangaslihealth.org) that summarises our progress and findings and provides photos from our fieldwork. The website also provides the questionnaires

and more detailed descriptions of the protocols used in the study. We will continue to organise and participate in public webinars and in-person seminars where we will present our findings in layperson's terms, which will be advertised through our universities, the FPMPAM, the Centre for Orang Asli Concerns, and various social media outlets. In addition to communicating results to study communities and the general public, our findings will be presented to the scientific community in peer-reviewed journal articles and at national and international scientific conferences. Whenever possible, we will publish in Open Access formats. On request, anonymised data will be made available to other researchers pending data-use agreements and approval from a review committee made up of ourselves and Orang Asli community leaders. We welcome researchers to contact us if they are interested in becoming involved in OA HeLP, particularly researchers in Malaysia who share our research interests and are committed to improving Orang Asli health.

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