SF 424 R&R and PHS-398 Specific

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PI: POTTER, JOHN D	Title: Consortium study of modifiable causes of death in Asians	
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John Potter Ph.D.	Fred Hutchinson Cancer Research Center	PD/PI
Wei Zheng PhD	Vanderbilt University	MPI

PROJECT SUMMARY/ABSTRACT

Asians constitute over 60% of the world's population. Over the past few decades, the burden of chronic diseases, particularly cardiovascular disease (CVD) and cancer, has increased substantially in Asian countries as a consequence of adverse lifestyle changes, including reduced physical activity, increased prevalence of obesity, cigarette smoking, and heavy alcohol consumption. Although each of the above modifiable factors has been linked to premature death, the overall impact of these factors on total and cause-specific mortality is unclear, particularly in the Asian populations. In 2008, we proposed, and have now successfully completed, the first analysis project in the Asia Cohort Consortium (ACC): to quantify the association between body mass index (BMI) and both total and cause-specific mortality by pooling and harmonizing data from over one million subjects across 18 cohort studies being conducted in Asian countries. In this application, we propose to expand the BMI pooling project to address study questions related to central obesity and other modifiable causes of death in Asians. We propose the following specific aims: 1) To evaluate the association between central obesity, as measured by waist-to-hip ratio (WHR), and both total and cause-specific mortality; and 2) To quantify the impact of major modifiable lifestyle factors, including high BMI, high WHR, cigarette smoking, and excessive alcohol drinking on both total and cause-specific mortality. Our consortium addresses the NCI objective to "expand the capacity of centers, networks, and consortia," and the goal to "create and sustain infrastructures that facilitate research collaboration" as outlined in the NCI Plans and Priorities. We anticipate that the analysis within the ACC will be a major step toward improving understanding of the causes and mechanisms of cancers and will enhance the collaboration within the consortium for further pooled analyses. The proposed study will generate substantial data that are valuable to inform policies and programs aimed at tackling the emerging epidemic of chronic diseases and to reduce premature death in Asian countries.

PROJECT NARRATIVE

Although obesity (including central obesity), cigarette smoking, and excessive alcohol consumption are each known to increase mortality, the overall impact of these modifiable factors on mortality is unclear, particularly in the Asian population. The proposed study, with its large sample size and strong methodology, will allow us to investigate, systematically, these important questions. The results from this study will have important public health implications in disease prevention.

FACILITIES & OTHER RESOURCES

The Fred Hutchinson Cancer Research Center (FHCRC), formed in 1973, is one of the world's leading cancer research centers. Home of three Nobel Laureates, the Hutchinson Center is an independent, nonprofit research institution dedicated to the development and advancement of biomedical research. Its organizational mission is the elimination of cancer, HIV/AIDS, and other diseases as causes of human suffering and death. In 2002, the Hutchinson Center took the lead role in forming the Fred Hutchinson/University of Washington Cancer Consortium, a research collaboration comprising Fred Hutchinson Cancer Research Center, the University of Washington (UW), Seattle Children's, and the Seattle Cancer Care Alliance (SCCA). While the participating institutions remain independent, the Consortium combines their strengths to accelerate research progress in the fight against cancer and build premier research programs across the disciplines of basic, clinical and public health sciences. The Consortium is one of 41 National Cancer Institute-designated comprehensive cancer research centers nationwide. In addition, the Hutchinson Center enjoys productive industry collaborations that enhance its ability to achieve advances in cancer research and treatment. The Hutchinson Center is organized into the four scientific divisions of Basic Sciences, Clinical Research, Public Health Sciences, and Human Biology; and the divisions of Administration and Development. On May 1, 2007, Fred Hutchinson Cancer Research Center announced the creation of the Vaccine and Infectious Disease Institute (VIDI) to develop and implement prevention strategies for globally important infectious diseases, including HIV, malaria, and the viruses and bacteria that can result in cancer. VIDI builds on the Center's international stature in the prevention of global infectious diseases, especially HIV, but also including human papilloma virus, malaria, Epstein-Barr virus, and other microbes. It is made up of three disciplines: population sciences, infectious disease sciences, and immunology and vaccine development; VIDI faculty working in the population sciences are PHS faculty members.

Division of Public Health Sciences

The Center's Program in Epidemiology and Biostatistics, established in 1975, became the Division of Public Health Sciences (PHS) in 1983. Research in the PHS Division studies cancer in populations, focusing on determining causes of cancer, helping to identify and assess effective screening and treatment methods, developing prevention strategies that reduce the risk of cancer, and developing research strategies to assist people to change behaviors toward healthier lifestyles. This prevention-oriented research also extends to other diseases, including HIV/AIDS, cardiovascular disease, diabetes, and fractures. The specific experience and expertise of the Division includes (1) the conduct of research in methodology for the design and analysis of rigorous follow-up studies, (2) the provision of statistical services needed for ensuring well-designed and properly conducted and analyzed clinical trials, (3) the evaluation of measures intended to reduce the incidence and impact of cancer, and (4) the design and conduct of epidemiological, cancer therapy, and cancer prevention trials. PHS is composed of six programs – Biostatistics and Biomathematics, Cancer Biology, Cancer Prevention, Computational Biology, Epidemiology, and Molecular Diagnostics.

PHS is the largest of the Hutchinson Center's four scientific Divisions, with over 680 faculty and staff working on over 400 grants and contracts supported by $69 million in annual direct funding. Division human resources include 121 member-track and joint faculty investigators assisted by 46 doctoral level staff scientists. Division faculty are supported by highly skilled technical staff, including 48 technical developers, 42 master level statisticians, 59 post-doctoral fellows, and 72 pre-doctoral graduate students. Through the Division's affiliation agreement with the UW, the SCCA, and Cancer Consortium, the Division and UW have formed the basis for strong research collaborations leveraging the talents of both institutions. The majority of Hutchinson Center senior faculty members maintain joint appointments at the UW in either the School of Public Health and Community Medicine or the School of Medicine.

The Cancer Prevention Program (CPP) at the Hutchinson Center is the oldest such program in the nation, and one of the largest in the world, with more than a million people around the globe participating in studies aimed at reducing cancer incidence and mortality and improving quality of life. Many of these studies are also relevant to the control of other chronic diseases. The CPP

consists of 54 member-track faculty (regular and joint) and staff scientists from diverse disciplines, 41 students and post-doctoral trainees, and 250 staff members. The 2008 research base totaled more than $27 million in direct funding, with 180 continuing grants and contracts. Cancer Prevention continues its interdisciplinary goals to address research questions that relate to cancer etiology and risk factors, including the identification of genetic, biologic, nutritional, and behavioral characteristics; to conduct clinic and community-based intervention studies in targeted populations in order to identify ways to reduce morbidity and mortality from cancer and other chronic diseases; to develop and test screening and surveillance methods that can be readily translated into clinical practice; to assess the outcomes of these maneuvers; and to train students and post-doctoral fellows in prevention research methods through formal grant-supported training programs. Close relationships to the UW and to specialized clinics at the SCCA have enhanced research and service opportunities of the Cancer Prevention Program.

Laboratory:
N/A - Laboratory facilities will not be required for the conduct of this research.

Clinical:
N/A - Clinical facilities will not be required for the conduct of this research.

Animal:
N/A - Animal facilities will not be required for the conduct of this research. The FHCRC maintains a fully accredited animal care facility for those projects engaged in animal studies.

Computer:
Computing Systems and Environment

FHCRC Information Technology (FHCRC IT) - FHCRC IT provides support for a complex heterogeneous computing environment. A pair of firewalls protects the Hutchinson Center network from the Internet. There are over 5000 nodes consisting of computers, VoIP phones, printers and servers that are connected to a high-availability CISCO network. The Hutchinson Center is connected to the Internet through a T-3 (45 Mb/s) circuit and also has a Gigabit connection to the Pacific Northwest GigaPop Network (PNWGP). The Center-wide Information technology environment fosters collaboration between colleagues within the Hutchinson Center, with Consortium partners and with institutions around the world. The Hutchinson Center supports both LINUX and Microsoft Exchange e-mail services. Fax and photocopier services are also available throughout the Center. This environment serves the needs of the proposed project well.

Research Computing Support (RCS) - RCS facilitates data-intensive research efforts for the Hutchinson Center and the Consortium by providing specialized computing hardware, software, storage and training for researchers. RCS collects research data generated by various Shared Resources at the Hutchinson Center and provides researchers with centralized data storage, data analysis tools, and archival backup services. The main RCS system is a Sun/Hitachi storage area network with over 150 terabytes of storage. RCS stores Solexa, MassSpec and other different instrument data operated in Shared Resources. Research data is further protected through off-site archival tape backup. RCS currently operates IBM Blade Centers for the Center's high performance computer cluster. RCS also provides support for over 60 applications that are made available to the entire Center. The Hutchinson Center continues to provide significant support for this resource, which is critical to ensure adequate support for the growing data management and analytical needs of the Center's scientific community.

PHS Divisional Information Technology (PHS-IT) – PHS-IT provides services that include cross-platform desktop and server support for 800 users. PHS IT maintains a Network Appliance cluster which provides high performance storage for the Division. The current raw capacity of the Netapp is 35.2 Terabytes. PHS IT also provides support for web/content management servers, developmental servers, virtual servers, terminal servers, database servers and high performance Linux compute Clusters. PHS IT also

supports two external SharePoint Portals for collaboration with external users. The Hutchinson Center network allows computer workstations continuous 24/7 access to PHS IT resources. PHS servers are backed-up daily for disaster recovery purposes. The primary desktop configuration in PHS is Windows XP Professional with Microsoft Office. Statistical applications that are used here are SAS, SPSS, STATA, SPLUS and MATLAB. The PHS Desktop IT also supports a variety of graphics packages on both PC and Macintosh platforms, which are used by desktop publishing personnel in the preparation of complex, high-quality materials.

Office:

Office Facilities

Office space and furnishings are available within the Cancer Prevention Program, which is allocated 61,475 net square feet in the Robert M. Arnold PHS Building, a state-of-the-art facility. Core program facilities available are located on Levels D and 1-5, and include offices for scientists, research associates and research support staff. In addition, research projects within the PHS Division can make use of specialized spaces for conferences, telephone and in-person interviewing, exercise studies, feeding studies and medical examination functions. The on-line Event Management System allows for scheduling appropriately-sized conference rooms and support services, including individualized room set-up, computerized projection, video conference connections, and catering for meetings held within the Arnold Building and across the Day Campus. The relocation of the PHS Division in 2004 marked the final stage in bringing all of the Hutchinson Center's scientific divisions together on the Robert W. Day Campus, in the South Lake Union area of Seattle. PHS researchers now benefit from greater access to the Consortium shared resources and other Hutchinson Center scientific divisions and facilities, as well as increased interactions with colleagues in PHS Laboratories (now closely located on Level 5 of the Arnold Building).

Other:

Arnold Library Shared Resource

The Arnold Library is a state-of-the-art, well-integrated library service at the Hutchinson Center with the primary purpose of providing high quality, responsive and up-to-date services in support of the Center's research, education and patient care programs. As such, it is one of the essential components of the information infrastructure that supports and facilitates biomedical inquiry and scientific progress for investigators at the Hutchinson Center. This centralized resource provides access to journals (print collections and online databases), monographs, bibliographic information, and extensive electronic resources in basic and public health sciences and biomedical research. Services range from intra-library loan/document delivery to assisting authors by depositing their papers in Pub Med Central, in compliance with NIH Public Access Policy.

Vanderbilt University Resources

LABORATORY: N/A

CLINICAL: N/A

ANIMAL: N/A

COMPUTER:

APCC is on Vanderbilt's MSP (Managed Support Program) plan. All of the software is downloaded from a central server to the PC via a NAL (Novell Application Launcher) window. NCS (Network Computing Services keeps all of the applications updated by upgrading the programs at the server level, instead of upgrading each PC individually. NCS maintains all of the "core build" applications (MS Windows, MS Office, Lotus Notes, Netscape, Epic, Medipac, Virus Checker, etc.) to the latest versions, any fixes or patches they may need, and their software licensing. Specialized Applications: If there is a need for any specialized applications, they will be loaded onto the server and delivered via a NAL window along with the "core build" applications. When the specialized programs need to be upgraded, NCS will get the software and upgrade it. The computer centers support university and Cancer Center research with a comprehensive and unified set of computing services, including hardware and software. The center staff is available for consultation/assistance with programming and/or analysis. Numerous software packages including major statistical packages such as SAS, GLIM, and SSCP are supported by the computer centers and will be available for the analysis of data collected from this study.

Computer resources for shared resource facilities are described in the Other section.

OFFICE:

The Vanderbilt-Ingram Cancer Center and the Vanderbilt Epidemiology Center will provide adequate office space for investigators and their associated staff. The lab collaborators also have adequate office space for this study.

OTHER:

The Biostatistics Shared Resource at the Vanderbilt-Ingram Cancer Center, directed by Dr. Yu Shyr, contains an Ethernet network with Windows XP, 2000, NT 4.0 and UNIX workstations. Network printers available include a Hewlett Packard LaserJet 4050 printer and a Xerox/Tektronix Phaser750N color printer. Four Intel Pentium 4 3.0 GHz, four Intel Pentium 4 1.7 GHz, two Pentium III 550 and one Sun Ultra 10 workstation are on this network. Each computer also has Hewlett Packard LaserJet 4 Plus and 4L printers attached for local use. These eleven computers contain 300 gigabytes or more of storage capacity which are backed up nightly by a Hewlett Packard Surestore DLT 40 tape backup system. All campus wide servers are attachable from these computers via the network. In addition, the equipment for the resource includes: a database file-server, a Hewlett Packard Scanjet 4500 document scanner and corresponding software for document and data input, two Xerox copiers, and a fax machine. The computer connections between the Head and Neck Cancer SPORE investigators and Biostatistics Core are attained via the Vanderbilt Medical campus Novell network using the Internet Packet eXchange (IPX) protocol.

Software available in the Cancer Center Biostatistics Shared Resource includes statistical packages such as S-PLUS, SAS, SPSS, STATA, Resampling Stats, EGRET, EPICURE, nQuery, EaSt, and PASS. Conversion of statistical data is accomplished by using DBMS/Copy or Open Database Connectivity Drivers and the accompanying software packages. Other software includes Mathematica for mathematical equations, DeltaGraph for producing high quality statistical graphs, Python which is an interpreted, interactive, object-oriented programming language and Ox which is an object-oriented matrix language with a comprehensive mathematical and statistical function library. There is also a full line of integrated Microsoft products such as Microsoft Visual C++, Microsoft Access, Excel, Word, and PowerPoint. These products support data sharing and object sharing to increase productivity.

Advanced Computing Center for Research and Education. The purpose of the Advanced Computing Center for Research and Education (ACCRE) is to provide high-performance computing support to computational studies across campus. The Advanced Computing Center for Research and Education (ACCRE) is built and operated by Vanderbilt faculty. ACCRE offers computing resources flexible enough to enable high performance computing applications in a wide variety of research and education areas. All ACCRE hardware resources are housed in the University's secure data center and administered by a team of ACCRE system administrators. In addition to the high performance computing system (described in detail below), ACCRE has several terabytes of disk space and a robotic tape storage system. The "/home" directories of all users are backed-up daily. Vanderbilt University is an Internet2 member and a participant in the Abilene network.

The ACCRE high performance computing system (schematic shown below) consists of 924 x86 processors (756 2.0 GHz Xeon and Opteron processors plus 168 1.8 GHz Opteron processors) running under 32-bit Linux and 668 PowerPC processors (2.2 GHz IBM JS20 Blades) running the SuSe Linux 64-bit operating system. Each processor has at least 1 GB of memory, a 40 GB disk drive, and dual Gigabit copper Ethernet ports. Over one-third of the systems also have Myrinet networking. Each node is monitored via Nagios. The disk servers and gateways are equipped with external gigabit Ethernet connections. All machines see the same disk which holds the user "/home" directories. Resource management, scheduling of jobs, and tracking usage is handled by the Moab/Torque schedulers. These utilities include an "advance reservation" system that allows a block of nodes to be reserved for pre-specified periods of time (e.g., a class or lab session) for educational purposes.

IBMs General Parallel File System (GPFS) is used for user "/home" directories and scratch space and can sustain 10 Gb/s to the cluster. The internal network design is a classic tree with a Foundry BigIron RX-16 at the root providing 1.54 Tb/s of available bandwidth (3.84 Tb/s total switch capacity) to the cluster. All of the disk servers and management nodes are connected to the top level. A collection of compute nodes, typically 20, are connected to a small local gigabit switch with a 1 Gb uplink to the RX-16.

ACCRE's suite of computing resources also has one high-memory 16-processor (1.5 GHz Itanium2) SGI Altix with 6MB cache per processor and a total of 32GB memory.

EQUIPMENT

Standard office equipment (photocopiers, facsimile machines, typewriters, paper shredders, etc.) is available to all investigators and staff within Cancer Prevention at Fred Hutchinson Cancer Research Center and at Vanderbilt University. All offices are equipped with touch-tone telephones (with voice mail) and Ethernet connections – allowing access for FHCRC staff to the CP LAN, FHCRC WAN, and Internet.

FOREIGN JUSTIFICATION

Dr. John D. Potter has been designated the lead PI for this project. Dr. Potter is based in New Zealand and works remotely for the Fred Hutchinson Cancer Research Center. He remains a Full Member and is also a Senior Advisor. For this project, Dr. Potter will communicate with the Coordinating Center staff via email, telephone and web conferencing. No funds will be sent to a foreign institution.

This project will involve data originating from seven countries or national economies identified in this application. Please see Section C *Preliminary Studies* of the Research Designs and Methods portion of this application for a list of participating cohort studies and countries involved in the first phase of the project. We do not recognize the transfer of data from its country of origin to the ACC Coordinating Center as an activity of this grant.

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OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix: Dr.

* First Name: John

Middle Name: D.

* Last Name: Potter

Suffix: Ph.D.

* New Investigator? [X] No [ ] Yes

Degrees: MBBS PhD

2. Human Subjects

Clinical Trial? [X] No [ ] Yes

* Agency-Defined Phase III Clinical Trial? [ ] No [ ] Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

Prefix: Mr.

* First Name: Mark

Middle Name:

* Last Name: Boyer

Suffix:

* Phone Number: 206-667-4868

Fax Number: 206-667-6221

Email: gmail@fhcrc.org

* Title: Director, Office of Sponsored Research

* Street 1: PO Box 19024

* Street 2: J6-500

* City: Seattle

County/Parish: King

* State: WA: Washington

* Country: USA: UNITED STATES

*Zip/Postal Code: 98109

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4. Human Embryonic Stem Cells

* Does the proposed project involve human embryonic stem cells? ☒ No ☐ Yes

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

[X] New [ ] Resubmission [ ] Renewal [ ] Continuation [ ] Revision

SPECIFIC AIMS

(**Please note**: the bibliography with the references listed throughout this section in the original grant application was omitted in order to decrease the file size.)

The Asia Cohort Consortium (ACC) was established in 2004 to promote collaborative research into the causes of cancer and other chronic diseases. In 2008, we proposed, and have now successfully completed, the first analysis project in the consortium: to quantify the association between body mass index (BMI) and both total and cause-specific mortality by pooling and harmonizing data from over one million subjects across 18 cohort studies being conducted in Asian countries (See Section C). In this application, we propose to expand the BMI pooling project to address study questions related to obesity and other modifiable causes of death in Asians. We propose the following specific aims:

1) To quantify the impact of major modifiable lifestyle factors, including high BMI, cigarette smoking, and excessive alcohol drinking, on both total and cause-specific mortality in all 18 cohorts included in the BMI pooling project. We anticipate that these risk factors explain a large fraction of deaths in most Asian populations.

2) To evaluate the association between central obesity, as measured by waist-to-hip ratio (WHR), and both total and cause-specific mortality in five cohorts (approximately 172,600 subjects) that collected WHR information at baseline. We hypothesize that central obesity is a strong, independent predictor for mortality even among a generally non-obese Asian population.

3) To evaluate the value of adding WHR to the model that includes BMI, cigarette smoking, and excessive alcohol drinking in predicting total and cause-specific mortality.

Although obesity, cigarette smoking, and excessive alcohol consumption are each known to increase the risk of multiple chronic diseases, the overall impact of these modifiable factors on mortality is unclear, particularly in the Asian population. Virtually all large cohort studies that have evaluated the association of central obesity with disease risk or mortality have been conducted in Europe and North America, where the prevalence of obesity is high. The impact of central obesity on mortality burden is unclear in Asians, a generally non-obese population. Considerable measurement errors exist to capture central obesity in studies conducted in the U.S. where a large proportion of subjects have a high BMI, limiting the ability of these studies to quantify the effect of central obesity. This study will provide an exceptional opportunity to evaluate the association of central obesity with health outcomes in the absence of high BMI. The proposed study, with its large sample size and strong methodology, will allow us to investigate, systematically, these important questions. The results from this study will have important public health implications in disease prevention not only for Asians, including Asian Americans, but also in other populations.

Background and Significance

Asians constitute over 60% of the world's population. Over the past few decades, the burden of chronic diseases, particularly cardiovascular disease (CVD) and cancer, has increased substantially in Asian countries as a consequence of adverse lifestyle changes, including reduced physical activity, increased prevalence of obesity, cigarette smoking, and heavy alcohol consumption (1-8). In 2005, chronic diseases were estimated to account for 80% of total deaths in China and 53% of total deaths in India (2, 4). According to the World Health Organization, China will lose $558 billion between 2005-2015 in foregone national income due to heart disease, stroke, and diabetes (9). Clearly, cancer and other chronic diseases have increasingly become a serious and costly public health problem in many Asian countries. Although numerous studies have investigated the effects of modifiable lifestyle-related factors on chronic disease morbidity and mortality in Western populations (10-17), relatively few studies have addressed the health impact of these factors in Asians. Such information, however, is urgently needed to inform policies and programs aimed at tackling the emerging epidemic of chronic diseases and to reduce premature death in Asian countries. In this application, we propose to conduct pooled analyses in the Asia Cohort Consortium to systematically evaluate and quantify the impact of central obesity and other major lifestyle-related risk factors on total and cause-specific mortality, particularly cancer mortality, in Asians.

Impact of Modifiable Lifestyle Risk Factors on Mortality

Cigarette smoking, excessive alcohol consumption, and obesity are among the major modifiable lifestyle-related factors that have been suggested to contribute to the growing burden of chronic diseases and premature deaths in many parts of worlds, including Asia (5, 7, 18-25). Cigarette smoking is one of the leading preventable causes of morbidity and mortality worldwide (18, 23-24, 26). Smoking increases the risk of CVD, many types of cancer, chronic obstructive pulmonary disease, and other serious illness (26-29). In 2005, an estimated 673,000 adult deaths were attributable to smoking in China (23). Smoking is predicted to cause approximately 450 million adult deaths worldwide between 2000 and 2050 (26). Although light to moderate alcohol intake has been linked to a reduced risk of CVD, high intake has been shown to increase the risk of hypertension, type 2 diabetes, hemorrhagic stroke, liver disease, and several types of cancer (25, 30-36). Heavy alcohol consumption also confers an increased risk of mortality (37-38). Obesity is emerging rapidly as a major public health threat in many countries as a consequence of urbanization (5, 19, 39). Obesity is a well known risk factor for numerous chronic conditions, including metabolic syndrome, type 2 diabetes, CVD, and certain cancers, and is a major cause of premature death (40-43). It has been suggested that obesity due to physical inactivity or poor diet may soon overtake smoking as the leading preventable cause of death in the United States (28).

Many lifestyle behaviors are intercorrelated. In recent years, there has been a growing interest in studying the health effects of combinations of lifestyle-related factors (10-11, 13-16, 43-44). The Nurses' Health Study has shown that a combination of five lifestyle factors, including smoking, physical inactivity, BMI, diet, and alcohol consumption, accounted for 82% of coronary heart disease cases, 91% of diabetes cases, and 55% of total deaths in the cohort (10-11, 15). In the EPIC Norfolk study, a combination of four lifestyle behaviors, including smoking, physical inactivity, alcohol intake, and diet, was found to predict more than a 2-fold difference in stroke incidence and 4-fold difference in total mortality (13, 16). In addition, a recent analysis of data from the EPIC Potsdam study indicated that adherence to four healthy lifestyle practices, namely: not smoking, engaging in regular physical activity, maintaining a BMI of less than 30, and eating healthier food, was associated with a nearly 80% reduced risk of developing major chronic diseases, including diabetes, myocardial infarction, stroke, and cancer (14). These findings provide strong evidence that many chronic diseases and premature deaths are largely preventable by targeting a limited number of lifestyle-related risk factors. It remains unknown, however, whether these findings, which are based on studies in Western populations, can be extended to non-Western populations, e.g., Asians, given the substantial differences among populations in the prevalence of various lifestyle risk factors and sociodemographic factors. This proposed study will provide important insights into the impact of several key modifiable lifestyle factors, considered individually and in combination, on all-cause and cause-specific mortality in Asians.

Abdominal Adiposity, Central Obesity, and Mortality

Obesity, a well established risk factor for CVD, type 2 diabetes, several forms of cancer, and many other medical conditions (40, 45-47), has also been shown to increase the risk of premature death (43, 48-49). The adverse effects of obesity are known to be closely related to the distribution of body fat (50). Central (intra-abdominal) obesity, a key feature of the metabolic syndrome (50-51), has been associated with elevated levels of C-reactive protein, tumor necrosis factor-α, interleukin-6, plasminogen activator inhibit 1, and reduced levels of adiponectin, all of which may be involved in the pathogenesis of many obesity-related diseases (50-53). It is believed that central obesity may be more detrimental to health than general obesity, although exactly how specific distribution of adipose tissue interacts with total adipose load is not clear.

A growing number of epidemiologic studies have investigated the effect of abdominal adiposity in disease risk and mortality (45, 54-57). The results from these studies, although not entirely consistent, have shown, in general, that increased abdominal adiposity is associated with an increase in mortality and risk of several major chronic diseases, independent of overall adiposity. It has also been suggested that measures of abdominal adiposity, such as waist-to-hip ratio (WHR), may be better markers than body

mass index (BMI), a measure of overall adiposity, in predicting certain obesity-related disease risk and mortality (45, 54-57). The INTERHEART study, involving 12,461 cases of myocardial infarction in 52 countries, reported that WHR, in comparison with BMI and other anthropometric measures, best predicted the risk of myocardial infarction across all age and ethnic groups (45). Only a small group of Asians, however, was included in this study. WHR also appeared to be a more robust predictor of mortality than BMI in several large cohort studies, including the Iowa Women's Health Study, the Nurses' Health Study, and the EPIC study (54-57).

Our current understanding of the effects of abdominal adiposity on mortality is derived largely from studies conducted in Western populations, where overweight and obesity are highly prevalent. The association between abdominal adiposity and mortality in relatively lean populations remains unclear. Obesity, although showing worrying trends, historically has been relatively uncommon in Asians (58). However, studies have shown that for a given amount of total body fat, Asian populations are more prone to abdominal and visceral fat accumulation than white or European populations (51, 59). It has also been shown that Asian populations are more likely to develop insulin resistance, type 2 diabetes, hypertension, and dyslipidemia at a relatively lower level of BMI than their Western counterparts (39, 51, 59-62). In the INTERHEART study, abdominal obesity was associated with a population attributable risk (PAR) for myocardial infarction of 58% in Southeast Asia and Japan, an estimate that was comparable to that observed for North America (PAR=59.5%), although the level of BMI was substantially lower in Asians than Caucasians (63). These findings underscore the particular importance of quantifying the impact of abdominal adiposity on mortality in Asian populations who are apparently lean, yet may have an elevated risk because of a high degree of abdominal adiposity. The Asia Cohort Consortium provides a unique opportunity to address this issue.

Over the past few years, a number of models have been proposed to predict the risk of diseases outcomes. Such models are helpful in identifying high risk individuals for disease prevention. To our knowledge, no study has thus far include WHR in the prediction models for mortality outcomes, as information on WHR is not typically obtained in large cohort studies. Given that WHR has been shown repeatedly to be a strong predictor of mortality independent of BMI, it is conceivable that WHR may improve risk prediction in models that include traditional predictors. With data from over 172,600 subjects in this proposed pooled analysis, the proposed study will provide exceptional opportunities to evaluate, for the first time, the combined effects of central obesity with other lifestyle-related factors on mortality and the value of a model incorporating both WHR and traditional variables in predicting mortality outcomes.

Preliminary Studies

First proposed in 2004, the Asia Cohort Consortium (ACC) is an international body of investigators committed to the study of genetics, environmental exposure, and the etiology of disease in Asian populations. ACC investigators represent Bangladesh, mainland China, India, Japan, Korea, Malaysia, Singapore, Taiwan, the U.S., and other economies. The mission of the ACC is two-fold: (1) to serve as a platform for cross-cohort collaborative projects and combined analysis; and (2) to act as an incubator for new cohorts. The ACC is currently chaired by Dr. John Potter, Fred Hutchinson Cancer Research Center, and Dr. Daehee Kang, Seoul National University. The ACC Coordinating Center (CC), located at the Fred Hutchinson Cancer Research Center (FHCRC), Seattle, USA, was established in 2007 and is responsible for facilitating collaborative research activities.

In 2008, we proposed to evaluate and quantify the association of BMI with total and cause-specific mortality. A working group was established for the study, which is co-led by Drs. Wei Zheng and Paolo Boffetta. A literature search was conducted to identify cohorts that had been established to study Asians, each with a sample size of ≥ 8,000 subjects at baseline and ≥ 500 deaths during a follow-up period of ≥ 3 years. Eligibility for study participation was further determined through a survey to the PIs of all identified cohorts. Eighteen cohorts that met the study eligibility were invited to participate in the pooling project with a combined sample size of over a million subjects (112,963 deaths) (See Table C1). Individual data were collected from all participating cohorts and harmonized at the coordinating center at FHCRC. We

have recently completed data analyses for this pooling project and are in the process of preparing a manuscript for publication. This study, the largest and most comprehensive analysis of its kind, has not only quantified the association of BMI with total and cause-specific mortality in Asians, but also laid a solid foundation for future collaborative projects in the ACC.

Table C1: Characteristics of Participating Cohorts in the Asia Cohort Consortium BMI Project

Cohort	No of subjects	Study entry	Years of follow-up[a]	Age at entry[a]	BMI [a]	No of deaths
India (Mumbai)	146,820	1991-1997	5.2	50.8	22.3 (4.2)	13,001
Bangladesh	11,744	2000-2002	6.6	37.1	19.8 (3.2)	404
China (Mainland)						
CHEFS	154,737	1990-1992	7.2	55.4	22.6 (3.7)	17,687
SCS	18,100	1986-1989	16.3	55.3	22.2 (3.0)	4983
SMHS	61,501	2001-2006	3.1	54.9	23.7 (3.1)	956
SWHS	74,934	1996-2000	8.6	52.1	24.0 (3.4)	2908
Taiwan						
CBCSP	23,818	1991-1992	15.2	47.3	24.0 (3.4)	2768
CVDFACTS	5160	1990-1993	14.9	47.1	23.7 (3.5)	841
Singapore	63,242	1993-1999	11.5	56.5	23.1 (3.3)	10,689
Japan						
3 Pref Aichi	33,513	1985	11.5	56.4	22.1 (3.0)	6216
Ibaraki	98,165	1993-1994	11.5	58.8	23.5 (3.2)	11,185
JACC	86,671	1998-1990	12.7	57.6	22.8 (3.0)	12,888
JPHC1	43,096	1990-1992	14.4	49.6	23.6 (3.0)	3441
JPHC2	56,572	1992-1995	11.5	54.3	23.5 (3.1)	5501
3 Pref Miyagi	31,316	1984	11.5	57.3	23.2 (3.4)	6607
Miyagi	47,604	1990	12.8	52.1	23.6 (3.0)	3815
Ohsaki	51,213	1995	9.9	60.5	23.5 (3.2)	7771
Korea (KMCC)	16,013	1993-2004	6.5	55.6	23.7 (3.3)	1302
Total	1,024,219	1984-2006	9.5	54.5	23.5 (3.5)	112,963

[a] Mean (SD) for BMI and mean for other variables.

Provided in Table C2 are main results from the BMI pooled analysis. A U-shaped association was observed between BMI and mortality. Subjects with a BMI in the range of 22.5 – 24.9 had the lowest total mortality. The ideal weight differed slightly for cause-specific mortality. In general, these findings are similar to those observed in the Western population and provide no support of using population-specific BMI cut-off points to define overweight and obesity. The results from the study also suggest that BMI may not explain the excess risk of insulin resistance observed in Asians. In other words, BMI does not capture sufficient information to define insulin resistance and obesity-related health outcomes in Asians. We hypothesize that WHR may be a better predictor than BMI for insulin-resistance and obesity-related health outcomes. The study proposed in this application will address this important question.

Table C2: Hazard ratios (HR) for the association of BMI with total and cause-specific mortality in the ACC[a,b]

Body mass index (BMI) at baseline	<15.0	15.0-	17.5-	20.0-	22.5-[c]	25.0-	27.5-	30.0-	32.5-	35.0-
CVD										
All Subjects	1.92	1.44	1.24	1.09	1.00	0.99[d]	1.10	1.23	1.55	1.45
Healthy non-smokers	1.83	1.33	1.06[d]	0.98[d]	1.00	1.01[d]	1.15	1.27	1.65	1.77
Cancer										
All Subjects	2.22	1.31	1.10[d]	0.99[d]	1.00	1.05	1.17	1.47	1.69	1.81
Healthy non-smokers	3.01	1.50	1.13[d]	1.02[d]	1.00	1.04[d]	1.14	1.51	1.53	2.29
Other Causes										
All Subjects	3.66	2.51	1.55	1.16	1.00	1.00[d]	1.10	1.21	1.61	1.96
Healthy non-smokers	3.81	2.41	1.38	1.08[d]	1.00	0.96[d]	1.10[d]	1.33	2.16	1.97
Total Mortality										
All Subjects	2.64	1.74	1.29	1.07	1.00	1.01[d]	1.13	1.28	1.59	1.61
Healthy non-smokers[e]	2.43	1.73	1.20	1.02[d]	1.00	1.02[d]	1.16	1.30	1.65	1.93

[a] Individuals with less than three years of follow-up were excluded.
[b] Meta-analysis estimates of left-truncated Cox proportional hazard ratios with age as time variable and adjusted for age, gender, and education.
[c] Reference group.
[d] 95% confidence interval include 1.0.
[e] Lifetime non-smokers with no diagnosis of CVD and cancer at baseline.

Provided below are brief descriptions of cohorts that participated in the BMI pooling project:

CardioVascular Disease risk FACtor Two-township Study (CVDFACTS) (P.I.: Wen-Harn Pan, Taiwan): This study recruited participants from 1990-1993. In all, 5160 men and women, aged 18 and above, were recruited from Chu-Don, a Hakka community in northwest Taiwan and from Pu-Tze, a Fukien community in southern Taiwan. Five villages in each of the two townships were selected randomly from those with greater than 1000 people or with a population density greater than 200 per square kilometer. Follow-up is every 3 years. Death-certificate data are obtained from the Department of Health in Taiwan.

China National Hypertension Survey Epidemiology Follow-up Study (CHEF) (P.I.: Jiang He, China): Baseline risk factors were carefully collected during the 1991 China National Hypertension Survey. A follow-up study was conducted during 1999-2000; it included in-person interviews to ascertain disease status and vital information for all study participants and a review of hospital records and death certificates for cardiovascular and renal events. The follow-up proportion was 95% over a period of 8 years. The CHEF study will provide unique and important information for developing national prevention strategies to reduce the societal burden of cardiovascular and renal disease in China.

Health Effects of Arsenic Longitudinal Study (P.I.: Habibul Ahsan, Bangladesh): This cohort includes approximately 20,000 men and women. For each cohort member, active follow-up is through biennial in-person visits by trained study physicians who do detailed clinical and diagnostic work-ups for the detection of study outcomes. This is supplemented by biannual in-person visits by village health workers and passive follow-up through study clinics dedicated exclusively to providing health care to the cohort members.

Ibaraki Prefectural Health Study (P.I.: Fujiko Irie, Japan): A total of 33,336 men and 64,272 women, 40 to 79 years of age, with no history of stroke or coronary heart disease, completed a baseline risk factor survey in 1993 under the auspices of the Ibaraki Prefectural Health Study. Systematic mortality surveillance was performed through 2003, and 264 intra-parenchymal hemorrhage deaths were identified. Participants are followed up every 2 years and deaths are certified through systematic review of death certificates and resident registrations.

Japan Collaborative Cohort Study (JACC) (P.I.: Akiko Tamakoshi, Japan): The study has contributions from 45 areas of the country and now covers 86,682 participants, enrolled at various centers located from Hokkaido in the North to Kyushu in the South. To collect epidemiologic information at baseline, a self-administered questionnaire was used. Follow-up is current to 2003 in the majority of cases and a total of 12,888 deaths were registered; the five most common sites of cancer development are lung, stomach, liver, pancreas, and colon in men, and the stomach, lung, pancreas, colon and liver in women.

The Community-Based Cancer Screening Project (P.I.: Chien-Jen Chen, Taiwan): This project was established in 1991. The study includes 23,820 male and female subjects aged 30-65 from seven townships in Taiwan, with a mean of 15.2 years of follow-up. Follow-up includes structured questionnaires administered by trained staff and computerized linkage of cancer-registration and death-certification systems to ascertain cancer incidence and death.

The Japan Public Health Center-based Prospective Study (P.I.: Shoichiro Tsugane, Japan): The first cohort was established in 1990, followed by a second cohort in 1993. A total of 140,420 men and women, aged 40-59 were recruited for the study. Self-administered questionnaires and biologic samples were collected at baseline, and participants were followed up with additional surveys after five and ten years. Incidence of cancer and cardiovascular diseases, as well as information on death and migration, are captured annually.

The Korea Multi-center Cancer Cohort (P.I.: Keun-Young Yoo, Korea): During the period 19932004, 19,688 men and women over 18 years of age were recruited from four areas of Korea.

Interviews at the time of enrollment collected information on past histories, lifestyle factors, physical activity, reproductive factors, and in-brief diet and agricultural exposures. Biologic samples have been collected for a subset of the cohort. Follow-up includes record linkage with the national cancer registry, death-certificate system, and health-insurance databases.

The Linxian General Population Trial (P.I.: Ping Zhao and You Lin-Qiao, China): This cohort was originally established in 1985 as an interventional trial in Linxian, a high risk area for upper GI cancer. A total of 29,584 male and female residents of 4 communes aged 40-69, were recruited. Subjects were randomly assigned to one of eight treatment groups for a period of 5 years and 3 months. Monthly follow-up included biochemical assays and endoscopic and cytologic examinations. Samples of serum and tissue have been collected four times during the course of the study.

The Miyagi Cohort Study (P.I.: Ichiro Tsuji, Japan): This population-based cohort was established in 1990. Subjects were residents of fourteen municipalities in the Miyagi Prefecture aged 40-64. In total, 47,605 men and women were recruited to the study. Follow-up includes linkage with the local cancer registry and death certificates.

The Mumbai Cohort Study (P.I.: Prakash C. Gupta and Mangesh S. Pednekar, India): This prospective study was conducted with recruitment in two phases, between 1991-1994 and 1994-1996. At recruitment, cohort members were residents of Mumbai, India, 35 years of age and older. Approximately 150,000 subjects were interviewed for demographic, economic, and lifestyle variables. To ascertain vital status, an active house-to-house follow-up after an average 5.5 years was also conducted in two phases. Cause of death was obtained from the local death registry and linked to study participants using international classification of diseases 10th revision codes (ICD–10).

The Ohsaki National Health Insurance Cohort Study (P.I.: Ichiro Tsuji, Japan): This cohort was established in 1995. Subjects were National Health Insurance beneficiaries, aged 40-79, who received care at the Ohsaki Public Health Center. A total of 51,253 male and female subjects were recruited. The last follow-up was completed in December 2003. The study continues to conduct monthly reviews of death certificates and National Health Insurance files. Cancer incidence is obtained from the local cancer registry.

The Shanghai Cohort Study (P.I.: Jian-Min Yuan, China): Established in 1986, this study recruited a total of 18,244 men aged 45-64, residing in four communities of Shanghai, China. At recruitment, dietary and medical histories, as well as blood and urine specimens, were collected. The most recent, complete follow-up was conducted in 2008. The local cancer registry, vital statistics unit, and annual in-person visits are used to identify cancer occurrence, death, and other major health outcomes, including cardiovascular disease.

The Shanghai Men's Health Study (P.I.: Xiao-Ou Shu, China): This population-based cohort study includes 61,504 Chinese men aged 40-74, free of cancer at enrollment, and living in seven communities in urban Shanghai, China. Recruitment for the SMHS was initiated in April 2002 and completed in June 2006. Detailed information on dietary and other lifestyle factors was collected at baseline and is being updated with a follow-up survey using a validated questionnaire. At baseline, peripheral blood samples from 46,354 participants, and urine samples from 54,807 participants, were collected. Participants who did not donate a blood sample donated a buccal cell sample.

The Shanghai Women's Health Study (P.I.: Wei Zheng, China): This population-based cohort was established during 1997-2000. A total of 74,942 women, aged 40-70, in Shanghai were recruited; these cohort members have been followed up with a combination of record linkage and biennial interviews. Biologic samples were collected from 87.5% of the cohort. The most recent follow-up was completed in 2008. Deaths and cancer incidence are verified through the local cancer registry, vital-statistics unit, and in-person visits to cohort members.

The Singapore Chinese Health Study (P.I.: Jian-Min Yuan, China): The Singapore Chinese Health Study is a long-term, population-based cohort study focused on the role of diet and its interplay with genetic factors in cancer etiology. Established in 1993, the study recruited a total of 63,257 men and women, aged 4574. Upon recruitment, subjects were interviewed using a staff-administered questionnaire, which included a validated Food Frequency Questionnaire. Follow-up has included additional interviews and the collection of biologic samples for all consenting cohort members. The study conducts regular record linkages with local cancer and vital status registries.

Three Prefecture Cohort Study Aichi (P.I.: Hideo Tanaka, Japan): This cohort study conducted a baseline survey with self-administered questionnaire regarding lifestyle on the residents aged 40 years or older in both urban area (Chikusa-ku in Nagoya City) and rural area (Inuyama Area) in Aichi Prefecture between 1983 and 1985. A total of 15,738 male (10,044 from urban area) and 17,777 female (11,740 from urban area) without history of cardiovascular diseases or respiratory diseases were selected for the study subjects. The study subjects were followed up by linking to death certificate. The total observed person-years was 127,409 for male and 149,978 for female.

Three Prefecture Cohort Study Miyagi (P.I.: Hiroshi Satoh, Japan): The study areas of Three Prefecture Cohort Study Miyagi were six primary school sectors in a city and the whole areas of two towns, located in Miyagi Prefecture. In January 1984, a baseline survey was conducted on inhabitants aged 40 years and over using self-completion questionnaires, which included questions on lifestyle factors such as smoking, drinking and dietary habits, and reproductive history. Usable questionnaire were returned from 31,345 subjects (response rate = 94 %). The vital and residential status of the subjects from 1 January 1984 through 31 December 1998 was obtained by the use of the population registries for the three municipalities. The incidence of cancer was ascertained by means of computerized linkage with the records of the Miyagi Prefectural Cancer Registry through the end of 1992.

RESEARCH DESIGN AND METHODS

We propose to conduct pooled analysis in the Asia Cohort Consortium with data from approximately one million subjects recruited in 18 cohorts to quantify the impact of major lifestyle-related factors, including BMI, cigarette smoking, and excessive alcohol consumption on total and cause-specific mortality (Aim 1). Using data from five cohorts with approximately 172,600 subjects who were measured for waist and hip circumferences at baseline, we propose to evaluate the association of central obesity, as measured by WHR, with total and cause-specific mortality (Aim 2) and further quantify the added value of WHR in predicting mortality (Aim 3). Most of the data needed for these analyses have already been collected as part of the BMI pooling project completed recently by the same group of investigators. Mechanisms for interaction, study implementation, and data analysis are in place for the proposed study. Provided in this section are methodologies proposed for this study.

Data Pooling

As described previously, 18 cohorts have agreed to participate in this pooling project (see Table C1). Most of the data needed for the proposed pooling project have already been collected and harmonized as part of the BMI pooling project. Provided below in Table D1 is the list of major variables relevant to the proposed study.

Table D1. Number of cohorts reporting specified variables in the ACC BMI pooling project

Variable Name	Variable Description	# of Cohorts*	No. of Subjects
BL_Yr	Baseline year (YYYY)	18	1,024,434
BL_Height	Height (cm)	18	1,013,569
BL_Weight	Weight (kg)	18	1,016,912
Vital_Status	Vital status (1:Alive, 2:Dead)	18	1,024,427
Time_Under_Surveillance	Days from BL to last contact	18	1,024,395
ICD_Code	ICD cause of death	17	96,029
BL_Age	Age at baseline	18	1,024,432
Gender	Gender (1:male, 2:female, 9:unknown/refused)	18	1,024,434
Smoke_Ever	Ever smoke? (0:No, 1:Yes, 9: unknown/refused)	18	988,588
Smoke_Current	Currently Smoke? (Same)	18	946,098
Smoke_PackYrs	Total pack-years	17	886,795
AlcoholUse_Ever	Ever drink alcohol? (0:No, 1:Yes, 9:unk/ref)	14	730,252
AlcoholUse_Current	Currently drink alcohol? (Same)	16	798,522
Alcohol_Intake	Alcohol consumption in grams/week	12	754,709
BL_Dx_Cancer	Diagnosed with cancer at BL? (0:No, 1:Yes, 9:unk/ref)	13	603,426
BL_Dx_CHD	Diagnosed with CHD at BL? (Same)	14	798,021
BL_Dx_Diabetes	Diagnosed with diabetes mellitus at BL? (Same)	17	843,092
BL_Dx_Hypertension	Diagnosed with hypertension at BL? (Same)	17	859,366
BL_Dx_Stroke	Diagnosed with stroke at BL? (Same)	12	734,894
BL_Menopause	Entered menopause at BL (Same)	1	323,324
BL_Waist	Waist circumference at BL (cm)	5	172,718
BL_Hip	Hip circumference at BL (cm)	5	172,686
BL_WaistHipRatio	Waist to hip ratio at BL	5	172,674

* Cohorts that have submitted data.

In addition to the variables listed above, the working group will scrutinize questionnaires collected from all participating studies in order to determine what additional variables are needed for the pooling project. Differences in the wording of questions and assumptions required for combining variables across studies will be recorded. Our, now, quite extensive experience in the BMI pooling project is that data on major risk factors (including tobacco, alcohol, and BMI) and most confounders are available and can be harmonized easily across essentially all participating cohorts. It will be more challenging to pool factors such as socio-economic status, which have been measured in different ways in the participating studies. In addition, outcome variables/causes of death will be abstracted and pooled, including date of exit (cause of death, date of death, last contact, and end of follow-up). Data pooling will follow a hierarchical

approach, with some studies excluded from some analyses, depending on availability of data or level of detail (e.g., smoking status vs. pack-years). All personal identifiers will be removed but study-specific ID numbers will be retained in order to facilitate all queries of the data from the FHCRC coordinating center back to the study PIs. We will ensure that ID numbers cannot be used to identify individuals, directly or indirectly. Data will be checked for illogical or missing values and queries sent to the centers for clarification. Data will be transferred to the ACC Coordinating Center at FHCRC for integration and analysis. The distribution of each variable will be explored to identify false and implausible values, e.g., values more than 3 standard deviations from the mean. Proposals will be developed to derive comparable exposure variables, based on our experience with the pooled analysis on BMI and overall mortality. In reality, most of the data needed for the proposed study have already been pooled and harmonized as part of the BMI pooling project.

Statistical Analysis and Power

Three primary aims are proposed for this study. Statistical methods to be used in the study involve the evaluation of associations of single (Aim 2 for WHR) or multiple variables (Aim 1) with mortality, quantification of the overall impact of multiple variables on mortality outcomes by estimating PAR (Aim 1), and evaluation of the performance of selected variables in risk prediction (Aim 3). Cox regression will be the primary tool for data analysis, supplemented by other methods that are specific for each aim. Statistical power for the study is extremely high, given the large sample size and the strong effect of risk factors to be evaluated in the study. As demonstrated in Table C2, most of the point estimates are statistically significant, even for RRs as low as 1.10. Therefore, issues related to statistical power will not be discussed in detail in this proposal. Provided below are statistical methods and data analysis strategies for each of the aims proposed for the study.

Aim 1: To quantify the impact of major lifestyle factors on mortality

Detailed analyses will be performed for each of the three risk factors (tobacco smoking, alcohol consumption, and BMI). The main effects of each factor will be assessed by estimating hazard ratios (HR) and 95% confidence intervals (95% CI) using Cox regression models that combine studies in an individual participant data (IPD) meta-analysis (64-68). The primary analysis will consist of a Cox model of IPD data stratified by cohort to account for possible differences between cohorts in the baseline hazard (64). The IPD data approach allows for models in which effects of predictors are assumed to be the same in all cohorts as well as models in which the effects of predictors are assumed to vary across cohorts. We will employ a likelihood ratio test to determine which model is appropriate and report statistics for the preferred model. Potential confounders for the basic model include only demographic factors such as age, sex, residence, ethnicity, and socio-economic status. Variables will be included in the model only if reported with fewer than 5% missing values. Data imputation will be done for variables if fewer than 5% of the data are missing.

Similar to the pooled analysis conducted for BMI, analyses will be conducted in this study to address possible reverse causation (morbidity affecting risk factor levels) and effects of confounders. We will analyze the data: 1) after excluding outcomes that occurred in the first three years of follow-up; and 2) among those without major baseline co-morbid conditions including cancer and CVD. We will also analyze data by years of follow-up, such as < 3 years, 3-5 years, 6-9 years, and 10+ years. These approaches worked well in the BMI pooling project to address reverse causation. Results will be presented to quantify the independent effect of each factor in a model that includes all three risk factors.

Two risk scores will be constructed. The first score will be constructed by simply counting the number of risk factors a subject has. The second score will use more detailed information from the analysis of each individual variable, incorporating the relative risk (RR) value of each variable corresponding to the level of exposure of the individual. The first score is simple and intuitive and can be easily explained to the public. The second score will provide a more precise estimate of the impact of these risk factors on mortality, although it may also suffer from data overfitting. Because not all cohorts have collected the detailed data needed for constructing the second score, the use of the two-score system will maximize the use of data available for the pooling project so that virtually all cohorts can be included in the analysis

deriving the first score, whereas a smaller number of cohorts will be included in the analysis to derive the second score.

Analyses will also be done stratifying by the presence of baseline co-morbidity. This would not only address issues related to possible reverse causation, but also evaluate the impact of lifestyle-related factors on mortality among those who have various baseline co-morbid conditions, both serious conditions (e.g. stroke, cancer, and CHD) and more moderate diseases (e.g. hypertension and type 2 diabetes). Answers to this question would have important implications toward reducing mortality in this growing group of individuals who live with various chronic diseases in Asian countries. Analyses will be conducted for total mortality, as well as for the following groups of chronic diseases: all cancers, tobacco-related cancers, cardiovascular diseases, myocardial infarction, stroke, chronic respiratory diseases. Sensitivity analyses will be conducted by excluding cohorts without medically certified causes of death. Also, stratified analysis by major populations will be conducted to evaluate the association for major ethnic groups.

To quantify public health impacts of modifiable lifestyle factors, we will estimate PARs and age-adjusted PARs for each of the variables or their combination on mortality outcomes. PARs will also be estimated by countries and gender separately to evaluate the impact of these factors for each population.

Aim 2: Pooled analysis of WHR with total and cause-specific mortality.

This analysis will be conducted among 172,600 subjects who were measured for waist and hip circumferences at baseline. These subjects were recruited from the following studies: CardioVascular Disease risk FACtor Two-township Study (CVDFACTS), Community-Based Cancer Screening Project (CBCSP), Korea Multi-center Cancer Cohort (Korea), Shanghai Men's Health Study, and Shanghai Women's Health Study. This will be one of the largest pooling projects to date that has included WHR in the evaluation of the combined effect of major lifestyle-related factors on mortality. Similar to the strategies described above for Aim 1, Cox regression will be used with adjustment for age, gender, and study sites. Additional adjustments will be made for risk factors, especially smoking, drinking, and BMI. Some of these risk factors may be in the causal
pathway between WHR and mortality. Thus, care will be taken to avoid over-adjustment. Results with and without adjustment for some of these variables will be presented to allow us and our readers to infer possible causation with different underlying assumptions. Additional analyses will be performed among never smokers and by age at WHR measurement, in order to understand the nature of the association. Analyses will be performed to address potential causality effects described above.

Aim 3: Evaluate the value of WHR and other lifestyle factors in risk prediction

This analysis will be built upon the work conducted in Aims 1 and 2 and limited to those whose data on WHR are available (~172,600 subjects). The basic model will include age, gender, cigarette smoking, alcohol consumption, and BMI. WHR will be added to this model to evaluate its added value in risk prediction for total mortality and cause-specific mortality. Analyses will be conducted separately for those with no baseline co-morbid conditions and those with severe baseline co-morbid conditions (cancer, CHD, and stroke) or more moderate co-morbid conditions (hypertension and diabetes). For the overall model, these co-morbid conditions will be included as predictors.

The discriminatory accuracy of each prediction model will be quantified by calculating the concordance statistic generalized to survival data (69), which examines the concordance probability that the predicted failure time for a person with event at time T is less than the predicted failure time for persons who survive past time T. The generalized C statistic is the proportion of concordant observations out of all possible pairings of events with other events and non-events. This generalized concordance statistic has interpretation much like the area under the curve of the receiver operating characteristic (ROC) curve obtained from logistic regression, but applicable to survival data. Bootstrap methods will be employed to compare the generalized C statistic for models with and without WHR.

Organization of the project

The project will be conducted primarily by an ad-hoc Working Group in collaboration with the PI of the participating study. Under the leadership of the Principal Investigators, a working group will be established similar to the one established for the ACC BMI pooling project. Telephone conferences will be organized to discuss the various stages. Data management and analysis will be conducted at the ACC Coordinating Center at FHCRC. Working Group meetings will be organized on the occasion of the biannual Consortium plenary meetings. Manuscripts will be prepared by the Working Group and circulated to the PIs for comment, editing, and approval, before submission.

Future directions of the collaboration

The ACC consortium utilizes the data collected in recently conducted medium-to-large cohort studies in Asian populations to overcome the sample-size limitation of individual studies. Pooling projects not only substantially increase power, but also provide opportunities to evaluate the consistency of associations. Furthermore, the project proposed here will evaluate the impact across a large geographic region, enhancing the value of data generated from the study. The establishment of the ACC and the preparation of the pooled dataset for analysis offer a great opportunity for further collaborative research projects. The ACC has longer-term plans for detailed pooled analyses of environmental, lifestyle, and genetic risk factors for multiple disease outcomes. The large sample size allows detailed analyses that cannot be undertaken in individual studies. Detailed results will be presented on the ACC webpage (www.asiacohort.org). This will be important for study-specific results, many of which cannot be reported in detail in the literature. Furthermore, this approach helps avoid selective reporting of positive results, and consequent publication bias. The ACC provides a flexible and dynamic means for pursuing new ideas and hypotheses of interest to its members.

Diet and physical activity are also major components of lifestyle, and there are many unique features of the Asian diet that deserve careful evaluation. These two lifestyle factors are more complicated to study than the factors selected for the current investigation. Part of the information on diet and physical activity is captured by adiposity measurements, such as BMI and WHR. Currently, the ACC dietary working group is actively planning the development of a Pan-Asian nutrition database and discussing a plan to conduct pooled analyses of dietary data. We will expand our study to include such dietary and physical activity data in the near future.

Timeline

It took about 18 months to complete the BMI pooling project, as it was time-consuming to identify study cohorts, evaluate cohort eligibility, and collect individual data. Now that most of these tasks have already been accomplished, the proposed study will be extremely efficient. We anticipate completing Aim1 in the first 6 months of the study. Data analysis for Aims 2 and 3 will have been completed by the 18th month of the study. All manuscripts will be prepared and submitted for publication before the end of the grant period.

PROTECTION OF HUMAN SUBJECTS

This study falls under category Exemption 4. Our research involves existing data, documents, and records, and the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. This application is to conduct secondary analysis of data already collected for cohort studies at fourteen institutions.

Risks to the subjects

Human subjects involvement and characteristics. Collected data from participating institutions will be sent to the Coordinating Center at Fred Hutchinson Cancer Research Center in an anonymous format. We will ensure that subjects cannot be identified directly or indirectly. The strategy at each participating institution has been to recruit healthy adult individuals of both sexes (some studies were restricted to individuals of one sex) and to follow up with them for cancer incidence or mortality. The pooled analysis will include approximately one million individuals.

Sources of materials. The source of research material is in the form of data. The data were collected at each institute for the purpose of the cohort studies. Our pooled analysis will make use of these existing data.

Potential risks. We do not foresee any physical, psychologic, social, legal or other risks to subjects, other than the unintentional release of participant data, protected against by strict confidentiality provisions.

Adequacy of protection against risks

Recruitment and informed consent. All studies have been approved by the relevant Institutional Review Boards (IRB). Subjects included in all participating cohorts have provided written informed consent which covers the objectives of the pooled analysis. The pooled analysis of BMI with mortality has already been approved by the IRB of FHCRC and by the IRBs of all participating institutions before beginning. An approval to expand the project will be obtained before launching the study.

Protection against risk. Risks to confidentiality are removed by ensuring that each data set sent to the Coordinating Center does not include personal identifiers.

Potential benefits of the proposed research to the subjects and others

No direct benefit for study subjects is anticipated. However, results from the study will have important public health implications in disease prevention.

Importance of the knowledge to be gained

The pooled analysis will provide valuable information on the role of major lifestyle factors on mortality. These results will have immediate public health and preventive relevance. Furthermore, it will provide a proof of principle of the feasibility of pooled projects within the Asia Cohort Consortium and will offer an opportunity for establishing collaboration between consortia of Asians.

INCLUSION OF WOMEN AND MINORITIES

Inclusion of women in the study

Women are included in the study. Data have already been collected from participants recruited in the parent studies of the project described in this application.

Inclusion of minorities in the study

All ethnic groups are included in the study. Because the study is conducted in Asia, the ethnic diversity does not reflect that of the United States. In particular, the number of subjects of European, African, and South American ancestry will be essentially nil. On the other hand, the study will provide information on populations from countries such as India, China, Taiwan and Japan, which represent the origin of important groups of immigrants to the United States.

TARGETED/PLANNED ENROLLMENT TABLE

Not applicable. Subjects have already been recruited by individual participating cohorts. No new subjects will be recruited for this study.

INCLUSION OF CHILDREN

All the cohort studies included in the pooled analysis are restricted to adults.

MULTIPLE PD/PI LEADERSHIP PLAN

Drs. John Potter and Wei Zheng will provide oversight of the entire Program and development and implementation of all policies, procedures and processes. In these roles, Drs. Potter and Zheng will be responsible for the implementation of the Scientific Agenda, the Leadership Plan and the specific aims and ensure that systems are in place to guarantee institutional compliance with US laws, DHHS and NIH policies including human research, data and facilities. Specifically, Dr. Potter will oversee the staff of the Coordinating Center and be responsible for all human research approvals. Dr. Zheng will be responsible for leading the Scientific Agenda, communicating with participating cohorts and will help direct the work of the statistical and data management team.

Dr. Potter will serve as contact PI for the full term of the grant and will assume fiscal and administrative management including maintaining communication among PIs and key personnel through monthly meetings. He will be responsible for communication with NIH and submission of annual reports. Publication authorship will be based on the relative scientific contributions of the PIs and key personnel.

RESOURCE SHARING PLAN(S)

We will publish our results in scientific journals in a timely manner and present results at scientific meetings. We will follow all relevant policies and practices of the individual studies and the Internal Review Boards of the study centers regarding human subjects and IRB privacy. NIH Intellectual Property guidelines will be followed, consistent with study-specific rules and procedures.