

Introduction to the Singapore Chinese Health Study (SCHS)

The Singapore Chinese Health Study is a large-scale research study in the National University of Singapore (Current PI: Prof Woon-Puay Koh), and has been supported by grants from the National Cancer Institute, USA since 1993. The main objective of this Cohort is to build a stable cohort for long-term study of dietary, genetic and environmental determinants of cancer and other chronic diseases in Singapore.

The study was established between April 1993 and December 1998 through the recruitment of a residential cohort of 63,257 Chinese men (n=27,959) and women (n=35,298), who were aged 45–74 years and resided in public housing estates, where 86% of Singapore residential population resided at the time of recruitment. At recruitment, each study subject was interviewed in person by a trained interviewer using a structured questionnaire, which focused on history of tobacco and alcohol use, current diet, current physical activity, menstrual and reproductive history in women, medical history, and family history of cancer. Current diet was assessed using a validated 165-item, semi-quantitative food frequency questionnaire. Developed as part of the SCHS, a Singapore Food Composition Table based on raw and cooked foods lists the contents of roughly 100 nutritive/non-nutritive ingredients in close to 900 foods and dishes in the Singapore Chinese diet, and allowed for the computation of personal intake of 96 dietary ingredients in study subjects.

Beginning in April 1994, a 3% random sample of subjects were re-contacted for donation of blood/buccal cells and spot urine specimens. In January 2001, the accrual of biospecimens was extended to include all consenting cohort enrollees. Hitherto, biospecimens have been collected from about 32,800 subjects (28,439 blood samples; 4,438 buccal cells; and 31,201 urine samples), representing a consent rate of about 60%. Between July 1999 and June 2004, the team also re-contacted, by telephone, all study subjects to update their use of tobacco and alcohol, medical history, and for women, their menopausal status and possible use of replacement hormones. A total of 52,325 subjects were re-contacted successfully, representing 83% of the original cohort. The cohort has also been passively followed for mortality and morbidity through regular record linkage with the population-based Singapore Cancer Registry, the Hospital Discharge Summary Database and the Singapore Registry of Births and Deaths through collaboration with the Ministry of Health. The Ministry of Health in Singapore regards the Study as a significant undertaking in the field of epidemiology locally, and is actively collaborating with and supporting the Study.

Between July 2006 and May 2010, the team once again successfully re-contacted 39,528 surviving subjects to update selected lifestyle exposure and medical histories. Between July 2014 and March 2016, 17,100 surviving subjects were re-contacted to collect information on various aspects of health related to ageing. Functional assessments will be measured in specific domains including:

1. Physical ability (subcohort)
 - a. Using the modified Timed Get-Up-and-Go Test (mTUG), which is a reliable and valid test for quantifying lower extremity physical mobility in elderly
 - b. Measuring grip strength using portable handgrip dynamometer to quantify upper extremity physical strength in elderly
2. Cognitive ability, using a combination of the Chinese Frontal Assessment Battery (FAB) and Mini-Mental State Examination (MMSE)
3. Emotional state, using the Geriatric Depression Scale and Geriatric Anxiety Inventory
4. Functional ability, using EQ-5D, Lawton Instrumental Activities of Daily Living Scale

Table 1 summarizes key features of the SCHS

Eligibility criteria:	Chinese, housing estate residents, ages 45-74 years
Recruitment period:	April 1993 to December 1998
Cohort size:	Total of 63,257, with 35,298 women and 27,959 men
Baseline data:	In-person interview, focus on current diet using a validated 165-item food frequency questionnaire, smoking, alcohol, physical activity, medical history, menstrual and reproductive history from women
Follow-up:	Disease Registry, death certificates, address/phone updates via linkage
Follow-up I (1999 – 2004)	Total of ~55,000 subjects. Telephone and in-person interviews to update smoking, drinking, tea, coffee, exercise, medical history and for women, menstrual history
Biospecimen Subcohort:	Blood or buccal cells, and urine collected from consenting subjects between 1999 and 2004. A total of 32,575 subjects contributed biospecimens, representing 51% of the cohort.
Follow-up II (2006-2010)	Total of about 39,000 subjects. Second update on selected lifestyle factors and medical history.
Follow-up III (2014- 2016)	Total of 17,100 subjects re-contacted. Ageing outcomes such as cognition, quality of life and activities of daily living.

Strengths of the SCHS

The SCHS represents one of the largest population-based cohorts in Southeast Asia with high quality prospective data on exposure and comprehensive capture of morbidity and mortality. One of the major strengths of the Study is its ability to examine potential disease-protective dietary factors that are rarely consumed among the well-studied occidental populations. Given the distinct genetic and lifestyle factors of the cohort members compared with other populations, the information obtained from the studies will not only help in a better understanding of the mechanisms of disease development, but should also aid in developing prevention strategies. The wide range of exposure on various foods such as soy, tea and vegetables among the Cohort's subjects also allows for an efficient examination of the effects of these dietary compounds on disease protection.

Another major strength of the SCHS is the completeness in follow-up of this long-term cohort. To date, less than 1% of study subjects are lost to follow-up. In addition, the Team has managed to devise an extremely cost-efficient method of tracking address and telephone changes, as well as deaths and disease occurrence in the study cohort with the full support of the Ministry of Health. In addition, being a cohort of middle-aged and elderly participants who have been followed up for a mean period of 15 years, the Cohort has accrued a significant incidence in diseases of public health concern including cancer of various sites, cardiovascular diseases such as acute myocardial infarctions and stroke, type 2 diabetes, neurological diseases such as Parkinson's Disease and cognitive impairment, chronic respiratory diseases such as adult-onset asthma and chronic obstructive pulmonary disease, hip fractures from osteoporosis, severe osteoarthritis, liver cirrhosis, gout, end stage renal disease and tuberculosis disease (latest outcome added).

The genetic homogeneity of the cohort members makes the SCHS especially suited to the series of gene x diet x disease studies. The Singapore Cohort is remarkably homogeneous in its genetic makeup. Cohort subjects were drawn from the two major dialect groups of Chinese in Singapore, the Hokkiens and the Cantonese, who originated from two contiguous prefectures in southern China. Until very recently (and thus, irrelevant to this cohort), marriage across dialect groups in Singapore was minimal.

The SCHS also stands out as a population-based cohort with a high rate of compliance. Cohort members represent 85% of eligible subjects solicited at baseline. Consent rate for the first follow-up interview (via telephone), conducted between July 1999 and December 2003, was over 90%. Consent rate for the donation of biospecimens (blood or buccal cells, and urine) was over 60%.

At present, over **200** papers have been published from this cohort, including several noteworthy and novel scientific contributions of reports in disease aetiology and prevention, including protective roles of fish, soy, cruciferous vegetables and tea against cancer, which have been presented in leading international conferences and top cancer journals. Sub-studies arising from this cohort have also been established in collaboration with other international research institutes and research groups in Europe, USA and China, and received prestigious NIH grants. All the previous work from the SCHS has hitherto received much scientific interest as evidenced by the publications in high impact journals. The team is confident that findings from the SCHS will continue to put Singapore on the world map of epidemiologic research.

Significant scientific contributions of this prospective Cohort amongst the 200-odd publications include:

- First reports of an association between polymorphic genes involved in the angiotensin II system, and breast cancer risk and possible interaction with green tea.
- First report of an inverse association between intake of marine n-3 fats and breast cancer risk that is modified by the GST genotypes. Study also provided the first positive link between dietary n-6 fats and breast cancer risk.
- First report of a protective effect of ITC on colorectal cancer, principally among individuals lacking both copies of GSTM1 and GSTT1.
- First reports of an inverse association between soy intake and prediagnostic markers of breast cancer risk, including high mammographic density, and breast cancer.
- First reports of an association between colorectal cancer and genotypes of the vitamin D receptor, the cyclooxygenase 2, the insulin-like growth factor 1 and PPARgamma 3 genes.
- First application of statistical modelling to correct for dietary measurement errors and residual confounding by smoking to demonstrate an unequivocal beneficial effect of dietary beta-cryptoxanthin on lung cancer risk.
- First report of an association between fibre (non-starch polysaccharide) intake from fruit and soy and symptoms of chronic bronchitis.

- First Asian prospective study of Parkinson's disease showing independent protective effect of caffeine and black tea.
- First Asian prospective study of diabetes mellitus demonstrating protective effect of coffee and possibly black tea.
- First study to show the use of a urinary cigarette-related biomarker (NNAL) for lung cancer risk.
- First prospective study to show gender-specific effect of soy on hip fracture risk.
- First prospective studies to look at dietary patterns in an Asian population with regards to colorectal cancer and breast cancer.
- First Asian study to look at combination of lifestyle and dietary factors on cardiovascular disease risk.