How did the study come about?
The basis of this cohort, comprising over 88% of all ethnic Chinese births during April and May of 1997 in Hong Kong, is a large, prospective, population-representative study far-sightedly initiated as the ‘Infant health and lifestyle survey’ by Professor Tai-Hing Lam of the University of Hong Kong and by Dr Gloria Tam of the Government Department of Health. The study was initially designed to examine the effect of primarily second-hand smoke exposure and secondarily breastfeeding on infant health and health-care utilization in the first 18 months of life.1

The initial study lasted for 18 months, and generated local evidence concerning the detrimental effect of second-hand smoke exposure in utero and in early life on infant health.1,2 This local evidence made an important contribution to tobacco control in Hong Kong, including the provision of evidence for the total ban on smoking in indoor workplaces and many public places in Hong Kong since 2007.

With the increasing awareness of both inter-generational influences on health, and the value of evidence from non-Western contexts, the study was resurrected and reconceived in 2005 by Professor Gabriel Leung and Dr C Mary Schooling with a focus on life course epidemiology in a non-Western society. The associated fieldwork was facilitated by Drs Shirley Leung and Kwok-Hang Mak of the Department of Health. One of the motivating forces was the simultaneous realization that patterns of non-communicable chronic diseases are different from those usually seen in the West.3–5

Contemporaneous determinants of the non-communicable chronic diseases (NCDs), which become more common with economic development, such as unhealthy diet, low physical activity and all their corresponding consequences, have been extensively examined and undoubtedly play the same role in non-Western populations as elsewhere. However, diet and physical activity do not explain why the pattern of NCDs is different in this region. As has long been suggested, non-Western populations may simply be genetically more vulnerable to diabetes6,7 and perhaps to haemorrhagic stroke as well as less vulnerable to IHD and hormonally related cancers, although few candidate genes have yet been found.8 In developed Western settings, poor early life and/or pre-natal environments have increasingly been recognized as relevant to IHD,8 cardiovascular and metabolic diseases,9–18 with underlying mechanisms potentially driven by non-Mendelian inheritance.19,20 Nevertheless, these theories with cardiovascular diseases (CVD) and diabetes as a composite group are difficult to relate to disparate secular and geo-ethnic trends,21–24 or to non-Western settings where the evidence appears less compelling.25,26 Understandably perhaps, because of the lack of relevance to long-term developed populations, the socio-biology of macro-economics on inter-generational growth, development and NCDs has not received nearly as much attention.

Given the very recent history of rapid economic development in this region, this gap raises the question as to the biological consequences of a hitherto overlooked aspect of economic development, i.e. up-regulation of the major axes controlling growth,39 so obviously embodied in greater height and earlier
sexual maturation over generations of economic development.\textsuperscript{40,41} Despite observed positive associations within, but not necessarily across, populations of height with health,\textsuperscript{27,28,35,42} it is becoming increasingly clear from animal experiments that down- rather than up-regulation of the somatotropic axis increases life-span,\textsuperscript{43,44} with potentially inter-generational effects.\textsuperscript{39,45,46} Although effects on growth and development have rarely been explicitly investigated. However, higher levels of growth hormone, particularly in boys,\textsuperscript{47,48} would be expected to advance puberty and possibly to increase cardiovascular risk,\textsuperscript{43,44} unless offset by other benefits. Earlier puberty is usually associated with increased CVD risk in both sexes,\textsuperscript{49} although whether the association is always monotonic is unclear.\textsuperscript{50,51} In contrast, pubertal sex steroids have well-known, well-documented effects, including greater life long muscle mass,\textsuperscript{52,53} but sexually dimorphic effects on fat patterning,\textsuperscript{54} lipids\textsuperscript{55–57} and immune responsiveness,\textsuperscript{58–60} detrimental among men but sometimes protective among women.\textsuperscript{54–60}

How up-regulation of these axes over generations might affect health with economic development cannot easily be answered in long-term developing populations, where these changes have already taken place over the past 200 years since the Industrial Revolution. However, that does not negate the relevance to developing or rapidly developed countries, or to often neglected minorities in and migrants to developed countries.\textsuperscript{61} Specifically, we would suggest that growing up in a less developed environment, with greater exposure to infections and more limited nutrition, would increase vulnerability to diabetes for both sexes,\textsuperscript{62,63} and to IHD among women, while reducing vulnerability to hormonally related cancers for both sexes and to IHD among men.\textsuperscript{64} Whether, this also relates to the long life expectancy sometimes seen in such populations remains to be determined. As such, this conceptual framework provides a mechanism for secular trends in patterns of NCDs with economic development as well as being consistent with patterns of disease often observed in migrants from less to more developed locations.\textsuperscript{65–75} Moreover, in developed countries, there is manifest evidence of the pleiotropic consequences of this single exposure of pubertal sex steroids, such as the stronger associations of IHD, central obesity, lipids and pro-inflammatory states with diabetes among women than men.\textsuperscript{76–78} Thus, in this cohort, we are focusing on the health effects of up-regulation over generations of the major axes controlling growth, because it may be relevant to both the changes in health with economic development and the aetiology of patterns of disease in long-term developed populations.\textsuperscript{39}

Apart from examining the effect of socio-economic development on health from a novel perspective, i.e. a non-Western, developing population perspective, our cohort also represents a community with a different way of life and a different confounding structure. These differences encompass lifestyle, values and ways of thought.\textsuperscript{79} For example, few Chinese women in Hong Kong smoke or drink.\textsuperscript{80} Dairy products are not a typical part of the southern Chinese diet, which includes more seafood. In common with many Asian populations, there is a strong emphasis on academic success and commitment to hard work, with the teacher seen as responsible for the student’s learning throughout education. There is also a strong family orientation. Currently, there is also a less clear social patterning of factors such as birth weight\textsuperscript{81} or IHD.\textsuperscript{82} Thus, our birth cohort from Hong Kong provides a unique opportunity to confirm or refute empirically derived hypotheses from Western populations as causal or otherwise.

\section*{Where is the study area?}

Our study is set in Hong Kong, located in the ‘factory of the world’ on the Pearl River Delta in southern China, as shown in Figure 1. Hong Kong is one of the most densely populated urban areas in the world. Currently, Hong Kong has a higher gross domestic product per head than Western Europe.\textsuperscript{83} Hong Kong has a mixed health-care economy with universally accessible high-quality health care. There is population coverage in health-care services in the public sector, with means tested, nominal copayments at the point of care. About 30% of outpatient services are in the public sector, whereas the other 70% is fee for service in the private sector. About 90% of total bed days are provided by public sector hospitals and the rest by private hospitals. Currently, there are 9 years of free, compulsory primary and junior secondary education, with a further 3 years of free secondary education or vocational training available. Hong Kong also has a progressively increasing level of inequality.\textsuperscript{84} Since the repatriation of Hong Kong from its former colonial status to China in 1997, Hong Kong has been a separately administered region of China, in the mode of ‘one country, two systems’. The Hong Kong population is 95% Chinese, mainly southern Chinese originating from the neighbouring Guangdong province.

Hong Kong has one of the first populations to experience very rapid economic transition from pre- to post-industrial living conditions over a lifetime, i.e. in the past 70 years. The Hong Kong population was mainly formed in the mid-20th century by an influx after World War II of largely young people from Guangdong province looking for work\textsuperscript{85,86} in relatively developed Hong Kong,\textsuperscript{83,87,88} as compared with pre-industrial China.\textsuperscript{83,88–90} Hong Kong had traditionally had an open border with China and a transient population of migrant workers.\textsuperscript{86} However, with the establishment of the People’s Republic of China in 1949 and the outbreak of the Cold War, Hong Kong acquired a settled population,\textsuperscript{86} augmented by occasional influxes in the 1950s and early 1960s.\textsuperscript{86}
Rapid development to a post-industrial economy then took place. As a result, most older people in Hong Kong were born into very limited conditions in Guangdong province in China, and experienced a sudden ‘step-change’ in living conditions in the mid-20th century, whereas children today in Hong Kong represent the first generation of Chinese to grow up in a post-industrial Chinese setting. This recent history of rapid transition provides a unique opportunity to examine the inter-generational influences of growth and maturation on health, which is unrivalled anywhere in the world. In contrast, Japan and the southeast Asian Chinese diaspora (notably Singaporean Chinese) both have had longer and more gradual histories of economic development. Moreover, although the Hong Kong population has different lifetime and inter-generational experiences from those prevalent in the more commonly studied long-term developed Western populations, experiences in Hong Kong are much more likely to have relevance to the rest of the global population, where a similarly rapid transition is taking place. Thus, a birth cohort from Hong Kong may provide unique insights and presage events elsewhere.

What does the study cover—and how has this changed?

The initial study collected parent or carer reported information on second-hand smoke exposure, breastfeeding and health service utilization shortly after birth, at 3, 9 and 18 months as well as birth characteristics and family socio-demographics. When the study was resurrected in 2005 with a broader life course perspective, we went back and retrieved all the infant and early childhood growth measurements for the cohort, as well as obtaining information that allowed us to link to routinely collected information on child growth, child development, lifetime hospital use and vital status. The public provision of popular services for infants and children in Hong Kong has enabled the acquisition of high quality, comprehensive, routine data on these topics by various government bodies. Hong Kong is a very small place facilitating high levels of standardization within government and high levels of cooperation between academia and government. Thus, we have been able to put the infrastructure informally in place for ongoing passive follow-up through ad hoc extracts, after obtaining relevant ethical approval, of routine data from government bodies, such as the Department of Health, which provides annual health checks for school children via the Student Health Service (SHS), and the Hospital Authority (HA).

In order to obtain a better understanding of the child’s family’s experience over generations and a broader perspective on the child’s life, we instituted a programme in 2007 to re-establish direct contact with the birth cohort families. This programme lasted 2 years, and included a press conference, a television programme, direct mailings, indirect mailings via all the schools in Hong Kong and, if necessary, repeated telephone calls. We have also instituted an
active cohort maintenance program, including regular mailing of birthday cards, seasonal greetings cards and newsletters, which facilitates keeping contact details up to date. We have also instituted a regular programme of postal surveys. The first, in 2008–09, focused on family history and current lifestyle. The second, in 2010, focused on the general well-being of the child and their family. We piloted in-person follow-up in the first half of 2010. Figure 2 provides a summary of the study structure and gives the current numbers in the study.

Who is in the sample?
The sampling frame of this study consisted of all infants born in April and May 1997 brought to one of the then 49 Maternal and Child Health Centres (MCHC) of the Department of Health for their first postnatal visit. Parents or carers of all newborns in Hong Kong are encouraged shortly after birth to attend the MCHC, which provides free-of-charge preventive care and immunizations. For the index year, 92% of infants born in Hong Kong visited the MCHC at least once. Families who did not attend the MCHC most likely represent groups we did not intend to recruit to this Chinese birth cohort, i.e. transient westerners, ethnic minorities or migrants who returned to China shortly after the birth. It is also possible that a few of the very rich or the very disadvantaged also did not attend the MCHC. The study recruited 8327 mother–infant pairs, which corresponded to 88% of all births during the recruitment period. The study initially used a self-administered questionnaire in Chinese, which again excluded the small non-Chinese population.

What has been measured?
Table 1 provides a summary of the information that has been assembled to date about the cohort members at different ages. Our cohort has detailed information on early environmental exposures, particularly second-hand smoke, as well as several measures of socio-economic position of the family and the neighbourhood. It also has detailed information on birth characteristics, and regular clinical measurements of infant and child anthropometrics, which has enabled the consideration of growth as trajectories at different stages rather than as the change between two points. It also has repeated clinical measurements of outcomes in childhood and early adolescence, such as pubertal stage and blood pressure, which obviates potential problems with self-reported pubertal stages. Moreover, it is possible to distinguish between the determinants and consequences of age at pubertal onset as compared with the determinants and consequences of different tempi and intensities of pubertal progression in girls and boys.

Bearing in mind our unique location, we have also collected information specific to our socio-historical setting. In our setting, factors such as lower use of dairy products, child care by servants and sustained out of school study time are relatively common and well accepted. In our historical setting, parents and grandparents may have grown up in a totally different environment with very limited nutrition, no running water and little education as well as experiencing social re-assortment on migration, all of which may have an impact down the generations.

What is attrition like?
Of the 8327 participants originally recruited, 113 have permanently withdrawn or migrated and 281 cannot be traced, probably because of migration. Of the remaining 7933 original cohort members who are alive, living in Hong Kong and not permanently withdrawn, contact has been re-established with 7381 (93%), as shown in Figure 2. We are continuing our efforts to contact the remaining children originally recruited to the study.

Figure 2 Hong Kong’s ‘Children of 1997’ birth cohort study outline
Table 1 Hong Kong’s ‘Children of 1997’ birth cohort—data

<table>
<thead>
<tr>
<th>Topic</th>
<th>Source</th>
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<td><strong>Socio-economic position</strong></td>
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<td>Parental education</td>
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<td>Parental occupation</td>
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<td>Neighbourhood of residence</td>
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<td>Disease</td>
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<td>Maturation (maternal age of menarche)</td>
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<td>Economic transition</td>
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<td><strong>Prenatal exposures</strong></td>
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<tr>
<td>Maternal second-hand smoking</td>
<td>Self-report</td>
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<td>Gestational age</td>
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<td>Child (2, 3 years then annual from 6 years)</td>
<td>Clinically measured (from MCHC and SHS)</td>
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<td><strong>Type of child care</strong></td>
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<td>Diet (food frequency at 11 years)</td>
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<td>Physical activity at 11 years</td>
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<td>Clinically assessed (from HA)</td>
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<td>Lipids, glucose, hormones, immune function</td>
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<td>Epigenetic markers</td>
<td>Fat biopsy</td>
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<tr>
<td>Diet and physical activity</td>
<td>Diary</td>
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<sup>a</sup>Based on the hospital discharge record.
Passive follow-up via record linkage has low attrition, because most cohort members attend preventive services provided free by the Department of Health. Active follow-up via surveys has higher attrition likely because of the difficulty for parents in finding the time to complete a questionnaire. Given the very high number of cohort members currently contactable and living in the very compact geographical area of Hong Kong, we are confident that with a suitably designed programme we could achieve high follow-up for a comprehensive in-person follow-up planned for 2010–11. Here, we plan to examine the socio-biology of macroeconomics on inter-generational growth, development and non-communicable chronic diseases. Specifically, we will examine the impact of family history of economic development on pubertal hormones, their associations with muscle mass, metabolic parameters, fat patterning and immune function as well as investigating the underlying physiological mechanisms of non-Mendelian inheritance, such as epigenetics, as shown in Table 1.

What has been found?
The original study clearly demonstrated the costs and harms of second-hand smoke exposure,1–3 and that the effect may be reduced by smokers keeping at a distance (at least 3 m) from the baby.3 In a developed non-Western setting, with a comparatively low rate of breastfeeding,91 it showed that breastfeeding initiation was adversely impacted by caesarean delivery92 and parental smoking.93 Although breastfeeding protected against doctor consultations, it also increased health services use due to jaundice in the first 3 months of life in this genetically perhaps more vulnerable population.94 The study also highlighted the rising rate of caesarean deliveries, and that almost 50% of the deliveries in private hospitals were caesareans.95

More recently, based on our interest in growth, we have focused on the determinants and early consequences of different infant growth patterns. Despite our developed setting our cohort as toddlers were shorter, but not thinner, than the new WHO growth standards,96 which we have suggested may be because of inter-generational constraints on the somatotropic axis,97 perhaps determined by epigenetic influences.96,97 Consistent with most other studies, infants with lower gestational age and lower birth rank gained weight faster in infancy,98 as in our setting did infants from families with higher socio-economic position.99 As elsewhere, both birth weight and infant weight gain were positively associated with childhood body mass index,99 with little indication that infants with a rapid trajectory of weight gain had any complementary protection from serious infectious morbidity.100

We have also exploited our developed non-Western setting to clarify whether necessarily observational findings from long-term developed countries are biologically based or the artefactual results of contextual biases possibly extending over generations. In our setting, both breastfeeding and childhood body mass index are less strongly socially patterned than in many Western populations.101,102 Despite clear associations in infancy between breastfeeding and less infectious morbidity but more jaundice,99 breastfeeding was not associated with childhood body mass index101 or childhood infections,103 suggesting that the associations observed elsewhere may be non-causal.104 However, although in our setting second-hand smoke exposure had little effect on serious morbidity after 6 months of age,105 paternal smoking was associated with higher body mass index, but not shorter height, in childhood,106 suggesting that the association might be biological rather than entirely mediated by socio-economic position.

What are the main strengths and weaknesses of the study?
To our knowledge, this is the only active Chinese birth cohort. Other strengths of our study include the large sample size, the population-representative sample, the regular growth measurements, the unique population setting and history, the ethnic homogeneity, the clinically assessed pubertal status and the high follow-up obtained via record linkage. Moreover, in our very compact location access to other family members, such as grandparents, may be easier than elsewhere. The weaknesses of this study are that inferences will have to be made by comparison with other studies rather than within the cohort because of the ethnic homogeneity, we also do not have detailed information or bio-materials from before birth. Moreover, we are following the footsteps of several well-established long-running birth cohorts mainly from Western Europe. As such, there may be a primacy publication bias generated by prior publication of contextually specific findings which are inadvertently assumed to be universal.

Can I get hold of the data?
Currently, we do not have the resources to make our data open access. We are of course open to collaboration with interested groups.

Where can I find out more?
The data currently resides with the Life Course and Lifestyle Epidemiology Group in the School of Public Health in the Li Ka Shing Faculty of Medicine at The University of Hong Kong. Please visit our website at http://hku.hk/aprmay97/.
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