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Risk factors for the metabolic syndrome in contemporary China

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Introduction

Until the 18th century levels of economic development were fairly similar in Europe, India and China.\(^1\) Thereafter Europe and North America experienced the industrial revolution and sustained, but fairly gradual, economic growth. In contrast, industrialization and associated economic growth did not take place in China until well into the second half of the 20th century.\(^1\) Some improvements in living standards due to more equitable distribution may have taken place after the establishment of the People’s Republic of China in 1949, followed by some limited economic growth which accelerated at the end of the 1970s.\(^1\) As a result, China, like other developing countries, is currently experiencing a more rapid and compressed epidemiologic and nutritional transition than that described by Omran even in the accelerated model, with many changes taking place simultaneously. The population health implications of this rapid and compressed transition are not necessarily the same as the implications of a gradual transition. Some experiences in China today may be more akin to experiences in western populations at the start of the industrial revolution, for which the historical record is almost completely absent, whilst observations from a developed country setting may not translate directly to contemporary China. Nevertheless, these related transitions in China over the last half century encompass the expected changes: a sharp decline in infectious diseases evident by 1980;\(^3\) increased life expectancy from 39 in 1949 to 69 by 1995;\(^2\) dramatically lower fertility, increased availability of food\(^3\) and reduced physical activity. As predicted these changes have recently resulted in increased rates of “man made and degenerative diseases”, such as Type 2 diabetes and cardiovascular diseases. Diabetes prevalence in China has risen from about 1% in people aged ≥30 years in 1980,\(^4\) to levels more similar to Europe and North America, i.e. 5.5% in the 35 to 74 years age group by 2001,\(^5\) although rates are higher (about 10%) in some developed Chinese populations, e.g. in Singapore.\(^6\) Cardiovascular diseases are now the leading causes of death in China,\(^7\) although the profile of cardiovascular disease in China is different from that in Europe and North America, with more cerebrovascular disease, more hemorrhagic strokes and less coronary heart disease;\(^8\),\(^9\) more akin to the pattern historically seen some Western countries.\(^9\),\(^10\)

The prevalence of a constellation of risk factors for diabetes and atherosclerotic cardiovascular disease, the metabolic syndrome, provides a useful sentinel for the epidemic of man-made and degenerative diseases emerging in China. The metabolic syndrome is usually characterized by central obesity, hypertension, hyperglycemia, raised triglycerides and reduced HDL-cholesterol with the International Diabetes Federation (IDF) stipulating that the presence of central obesity and at least two other abnormalities constitute the metabolic syndrome whilst the National Cholesterol Education Program- Adult Treatment Panel III (NCEP-ATPIII) stipulates that the presence of any three (or more) is sufficient.\(^11\) The World Health Organization definition also includes insulin resistance, and so is less used. The cut-offs for each criteria have been reviewed and revised with ethnic specific criteria introduced for waist circumference. Currently the thresholds for central obesity are waist circumference ≥80 cm (females) or 90 cm (males) in Chinese, for hypertension are systolic and/or diastolic blood pressures ≥130/85 mm Hg or relevant
treatment, for hyperglycemia are fasting plasma glucose ≥5.6 mmol/L (IDF) or ≥6.1 mmol/L (NVEP-ATPIII) or treatment of type 2 diabetes), for triglycerides are fasting plasma triglycerides ≥1.7 mmol/L or specific treatment) and for reduced HDL-cholesterol are fasting HDL-cholesterol <1.03 (males) or 1.29 mmol (females) or specific treatment). In western populations, presence of the metabolic syndrome is consistently associated with excess risk of diabetes (190%), of cardiovascular diseases (53%) and of cardiovascular mortality (between 65% and 90%). Despite differences in prevalence similar findings would be expected in Chinese, and have been seen in Hong Kong Chinese men, although in Beijing the metabolic syndrome was better at predicting diabetes. Thus, the metabolic syndrome is not always a more useful predictor of diabetes or cardiovascular disease than its individual risk factors alone, or their summation into long-standing risk scores, such as the Framingham score. Hence, the status of the metabolic syndrome as a simple clinical tool for identifying and potentially treating at risk individuals is controversial, with some arguing that it has no clinical utility beyond its constituent parts, and others arguing that it helps promote a more holistic approach to tackling the common underlying risk factors. As a result a wider concept of cardiometabolic risk, including other measures such as C-reactive protein, fibrinogen, plasminogen activator inhibitor-1 and apolipoprotein B, is emerging. However, as yet there is no clearly operationalized definition of a cardiometabolic risk syndrome, so this review focuses on the metabolic syndrome.

The epidemic of the metabolic syndrome in China is recent, although exactly when it arose is difficult to assess, because of the lack of trend data. Nevertheless, prevalence of the metabolic syndrome in China is approaching levels seen in western countries, although comparisons are hampered by the use of ad-hoc samples and differing definitions. In nationally representative samples, from similar time periods (around 2000), using the same definition of the metabolic syndrome with internationally recommended ethnically appropriate criteria for central obesity, prevalence of the metabolic syndrome in USA men and women aged ≥30 years was about 40% and 44% respectively compared with 18% and 29% in Chinese men and women aged 35-74 years, with higher rates in urban areas and the north. However, higher prevalence in Chinese women compared with men is at variance with the higher rate of premature coronary heart disease in men than women, and may be the result of using a poor proxy of central obesity in men.

The metabolic syndrome can be seen as both a convenient shorthand for identifying people at higher risk of diabetes and cardiovascular diseases who should receive integrated management, and a form of metabolic dysregulation, with a common underlying pathophysiological abnormality. Initially insulin resistance or hyperinsulimia was seen as the underlying abnormality, because empirically most people with the metabolic syndrome had one of these. However, the role of insulin resistance is disputed because there is little evidence that reducing insulin resistance improves any component of the metabolic syndrome apart from glucose intolerance, with the causal role of insulin resistance in hypertension perhaps being least clear. More recently, abdominal obesity has been seen as the underlying abnormality, because visceral
adipose tissue is a source of factors, such as free fatty acids or tumor necrosis factor-alpha, that impair insulin action in skeletal muscle. However, abdominal obesity does not appear to be a necessary condition for IHD in the Chinese men with the metabolic syndrome.\textsuperscript{26} Currently, there are three potential etiologies for the metabolic syndrome, i.e. insulin resistance, central obesity and other factors, including inflammation. The longitudinal studies which might help distinguish these etiological pathways have yet to be carried out. Instead, statistical techniques, such as factor analysis, have been applied to the biological parameters defining the metabolic syndrome to determine the number of underlying constructs, which may potentially correspond to the underlying pathophysiological abnormalities. Most studies, including studies in Chinese, have identified several factors\textsuperscript{27,28} potentially indicating a number of distinct underlying abnormalities, although a recent study found only one factor\textsuperscript{29} potentially indicating that the metabolic syndrome is a distinct entity with a single underlying factor that influences expression of all the features of the metabolic syndrome. However, this finding could also have been the result of the small number of biological parameters used in the factor analysis. Such uncertainty about the pathogenesis of the metabolic syndrome makes it difficult to identify causal mechanisms and risk factors from a physiological perspective and hence to identify the relative importance of current environment, population genetics and influences over the life course.

**Macro-environment**

Increased availability of food in China since the establishment of the People’ Republic of China in 1949 has been successful in reducing under-nutrition and hunger, despite some periods of great hardship in the late 1950s and 1960s during the Great Leap Forward and the Cultural Revolution. Food availability has increased markedly in China, particularly since 1962,\textsuperscript{1} with the largest increases in cereal consumption and sugar before about 1985,\textsuperscript{2} followed more recently by increases in consumption of vegetable oil, edible oil and animal source foods,\textsuperscript{2} although more recently (i.e. from 1982 to 2002) average daily calorie intake has stabilised.\textsuperscript{30} Long-term trends in physical activity in China are less well-documented. However since 1949 there has been increasing urbanization, such that the proportion of the population living in urban areas increased from 10.6% in 1949 to 36.2% in 2000,\textsuperscript{31} with corresponding reductions in occupational physical activity, which can be a key contributor to energy balance. Reductions in potentially beneficial commuting physical activity would be expected from the increasing number of vehicles in China since 1949;\textsuperscript{32} where vehicle ownership is associated with weight gain.\textsuperscript{33} Many domestic changes associated with economic development, such as labor saving devices, television and even a more comfortable ambient temperature may have also contribute to reduced energy expenditure.\textsuperscript{34} Given, the historically recent transition in China from relatively short lives dominated by manual labor, there may be less of a tradition and culture of leisure exercise or sporting participation, and there has been a shorter period of historic time in which to build-up the relevant infrastructure of recreational facilities. Undeniably an imbalance of energy intake to energy expenditure in a more obesogenic environment requiring less physical activity is a proximal determinant of the recent increase in the metabolic syndrome in China. Positive energy imbalance results in weight gain;
even in the very lean small increases in weight are associated with hypertension, hyperglycemia, dyslipidemia. Moreover, reduced energy intake and/or increased energy output have been shown to improve metabolic profile in several trials.\textsuperscript{35,36,37} However, energy imbalance is only one facet of macro-environmental change towards a more obesogenic environment driven by socio-economic development. With increasing wealth there are many other changes which may impact the risk of the metabolic syndrome, such as greater availability of and access to a wider range of foods, cigarettes and alcohol. Moreover, all of these changes take place within a social context whose structure may impact the level of risk and which groups are at greatest risk.

**Dietary composition**

Over and above energy imbalance, two facets of dietary composition closely linked to the clinical manifestations of the metabolic syndrome have been extensively investigated, i.e. dietary fat and glycemic index. Observational studies of diet are difficult to interpret, due to the practical difficulty of obtaining accurate and comprehensive records of dietary intakes, potentially compounded by under reporting of total energy intake and of foods considered to be unhealthy,\textsuperscript{38,39} although such biases in dietary reporting may be less of a problem in China, where notably accurate reports of energy intake have been obtained.\textsuperscript{40} Randomized control trials are expensive, rare, short-term, generally emphasis aspects of western diets, such as the consumption of olive oil or low-fat dairy products, and often include a variety of dietary changes, so it is difficult to know which are the key items that might translate into a different setting with different dietary patterns. Nevertheless, there is a clear consensus that diets with a higher proportion of saturated fats are harmful,\textsuperscript{41} and may be associated with the development of the metabolic syndrome,\textsuperscript{42} which can be reversed by reducing the proportion of saturated fats.\textsuperscript{43} Replacement of saturated fats with other fats may be more beneficial than replacement with simple carbohydrates, because diets with a high glycemic index may increase the risk of developing type 2 diabetes.\textsuperscript{44} Human trials suggest that diets low in carbohydrates or high in complex carbohydrates are associated with a healthier metabolic profile.\textsuperscript{36} It has also been suggested, based on ecological evidence, that a traditional Chinese diet, low in fat and protein, results in a higher (and hence protective) metabolic rate.\textsuperscript{45}

In the Chinese context, where most cooking oil is mono-unsaturated (peanut or rapeseed) or polyunsaturated (corn and soybean),\textsuperscript{46} the most significant change in dietary composition is probably an increase in the proportion of animal source foods, either from meat or dairy products, and possibly an increase in more highly processed foods. Animal source foods have long been regarded as a useful source of protein and trace elements. Epidemiological studies suggest a high meat intake may be associated with the metabolic syndrome,\textsuperscript{47} although in the Shanghai Women’s cohort higher intake of unprocessed meat protected against the development of diabetes.\textsuperscript{48} However there was no dose-response and the analysis was adjusted for total calories and vegetables, which could mean that higher meat intake was a proxy for lower rice intake, and protective for that reason. To date there is little evidence that milk or dairy produce intake
increases metabolic risk,\textsuperscript{49} despite, inevitably weak, ecological evidence to the contrary.\textsuperscript{50} However, almost all the evidence comes from populations where dairy products are a normal part of the diet and the comparisons are between levels of dairy intake, whereas the relevant comparison for China is between those who do and do not use dairy products. Moreover, due to genetic differences the sustained ability to digest the milk sugar lactose throughout adulthood (i.e. lactase persistence) is uncommon in China\textsuperscript{51} and could moderate the effect of dairy products. Overall changes in dietary composition taking place in China may have both positive and negative effects on the metabolic syndrome, positive through increasing dietary variety and possibly placing less emphasis on rice and whilst potentially negative through higher intakes of meat, saturated fats or processed foods.

Tobacco and alcohol
Economic growth in China has enabled other changes in lifestyle, such as more widespread use of cigarettes and alcohol. The average number of manufactured cigarettes per man went up 15 times between 1952 and 1996 in China, from one to 15 cigarettes per man; although smoking is rare amongst Chinese women.\textsuperscript{52} Similarly, per adult pure alcohol consumption in China increased from 1.03 liters in 1970 to 5.17 liters in 1996.\textsuperscript{53} Again, use of alcohol is rare in Chinese women, both in China\textsuperscript{53} and in more developed Chinese settings, such as Hong Kong. Despite, the rise and fall of the smoking epidemic seen in developed western countries in men followed by women, there are as yet little indication of a female smoking epidemic emerging in developed Chinese settings, such as Hong Kong.\textsuperscript{54} Smoking is a well established risk factor for cardiovascular diseases and diabetes, and as would be expected has been shown to be associated with the development of the metabolic syndrome.\textsuperscript{55} The role of alcohol is more controversial, with a U or J shaped association between alcohol use and cardiometabolic risk often observed, such that moderate, but not heavy, alcohol use may appear protective. Patterns of alcohol use may change with ill-health making cross-sectional studies open to reverse causality. Prospective studies have the advantage of temporal sequence, potentially reducing reverse causality. Few studies have examined the prospective association of alcohol use with the metabolic syndrome, with somewhat mixed results. However, moderate alcohol use has been found associated with lower mortality from ischemic heart disease (IHD),\textsuperscript{56} ischemic stroke\textsuperscript{57} and diabetes\textsuperscript{58} but not hemorrhagic stroke.\textsuperscript{57} However in observational studies it is difficult to discern whether the effect of alcohol is due to alcohol or other attributes of moderate alcohol users. Both of the prospective studies to date examining the impact of alcohol use on mortality in Chinese found moderate use protective against CHD\textsuperscript{59} or cardiovascular disease,\textsuperscript{60} although one also found similar benefits of alcohol for accidents,\textsuperscript{59} suggesting perhaps a systematic difference between moderate alcohol users and non-uses. More limited, but possibly more reliable, evidence largely from randomized control trials suggests that alcohol increases blood pressure,\textsuperscript{61} has no effect on insulin sensitivity,\textsuperscript{62} but improves lipid profile (triglycerides and HDL-cholesterol).\textsuperscript{62,63} These differing effects of alcohol on various aspects of the metabolic syndrome suggest that overall moderate alcohol use might be having a largely neutral effect on the metabolic
syndrome in men, but due to the low levels use it is unlikely to be playing a role in the increase in the metabolic syndrome in women.

Social context
The differing use of tobacco and alcohol by men and women in contemporary China clearly indicates the impact of cultural context on lifestyle; these are but one example, which operates within the broader context of the impact of social structure on health. There are most likely others. For example, it is quite possible that within a culture with, until recently, high levels of food insecurity, adiposity is seen as projecting a socially desirable image of wealth and success. However, with the progress of the epidemiologic transition metabolic risk often become concentrated amongst the less advantaged. First, the less advantaged may have poorer access to all aspects of preventative health, including a healthy diet and recreational facilities. Second, there may be social patterning of shared values and culture, and hence the acceptability of a more or less health conscious lifestyle. Third, the physiological consequences of the stress generated by lower absolute or relative social position may increase metabolic risk, whilst a more socially cohesive society may be protective. Currently in China, with its recent epidemiological transition, lower social position is not consistently associated with poorer metabolic health, particularly in men. However, as elsewhere low social position could become a more important social determinant of metabolic health in China as the epidemiological transition progresses. Hence the need for population wide, possibly regulatory, public health interventions, most clearly illustrated in global tobacco control policies, but also recently extending beyond food safety in nutrition, such as action on trans-fats.

Genetics and Epigenetics
The epidemic of the metabolic syndrome in China has emerged over about 20 years, during which time the genetic make-up of the population is unlikely to have changed. Undoubtedly, genetic differences may make some individuals or populations more susceptible. Family and twin studies have shown a heritable contribution to the metabolic syndrome. However, its complexity and the lack of a clear aetiological framework make the identification of candidate genes based on functionality difficult. As yet, genes responsible for the metabolic syndrome have not been unequivocally identified, although various possibilities have been identified. There has been greater success in identifying genes associated with specific components, such as the FTO (fat-mass and obesity-associated) gene however the FTO risk variant may be less common in Chinese populations, where its role has been questioned. Genetic analysis can be unreliable and prone to the false positive findings because of the very large number of possible associations considered.

Considered at a population level, currently, non-European ethnic groups appear more prone to central adiposity and hence its metabolic consequences. Neel’s ‘thrifty genotype’ hypothesis suggested that over human history famines had selected for genes enabling efficient food storage, i.e. the ‘thrifty genotype’,
which by postulating different selection pressures by ethnic group also explains differences between populations of European descent and others. However, the evidence that these famines took place, that they preferentially increased mortality in thinner people of reproductive age or differed between ethnic groups is increasingly being questioned.\footnote{75} As yet no relevant genes for the thrifty genotype have been clearly identified. Alternatively, the recent re-discovery of non-Mendelian heritable changes in gene expression driven by the environment in previous generations, i.e. epigenetics, suggests yet another pathway by which population history may leave an imprint on population health and also result in differences between individuals. Epigenetic mechanisms evolved to maximize maternal-offspring co-adaptations, which in species where the offspring continue to acquire resources from their parents in early life, would include parental regulation of post-natal as well as pre-natal growth.\footnote{76} Epigenetic effects can extend over generations. Epigenetically determined growth regulation during the growth phases of greatest dependence (infancy and childhood) would ensure the offspring’s demands did not outstrip the mother’s resources. There is some very limited empirical evidence of epigenetic constraints on linear growth during infancy and childhood (i.e. of the legs) in Chinese populations with a short history of economic development.\footnote{77} Impacts on long-term health have not been investigated, although there are potential physiological pathways that might generate a transitory epidemic of diabetes and associated metabolic disease for the first few generations to experience sustained economic development. Better living conditions in the current generation coupled with epigenetic constraints on infant and childhood linear growth resulting from limited living conditions in earlier generations, would be expected to result in more pubertal linear growth,\footnote{78} as has been seen in the current generation of southern Chinese compared with earlier generations.\footnote{79} Relatively or absolutely more pubertal linear growth is consistently associated with diabetes and/or insulin resistance,\footnote{79-81} probably due to alterations to the GH/IGF-1 axis,\footnote{80} whose effects might be exacerbated by lack of compensating muscle mass from longer legs. However, living in economically developed conditions over generations would reduce epigenetic constraints on early linear growth and correspondingly reduce relative pubertal linear growth and risk of diabetes. Whether transient epidemics of diabetes have previously occurred in other groups undergoing rapid economic development is lost in the mists of time. Nevertheless, something similar may have occurred following the Jewish exodus from Russia in the late 19th century to the north-eastern US cities, where in the early 20th century Jews were transiently more prone to diabetes.\footnote{82} Thus the current epidemic of diabetes in developing or recently developed populations such as Chinese may partially be a ‘first few generations through’ effect generated by rapid environmental change causing disproportionate growth against a background of epigenetic constraint on infant and childhood growth. Such a theory would provide an alternative conceptualization of ethnic differences in susceptibility to diabetes and the metabolic syndrome as the product of differences in population wide experiences of economic development over historical time, however as yet it is speculative.

\textbf{Life course influences}
Life course influences on health have long been recognized, but their prominence has varied with academic discipline and time. In the last 20 years, Barker’s work, coupled with the difficulty of modifying adult behavior has re-ignited interest in the developmental origins of health and disease. Despite two decades of intensive research the developmental origins of metabolic disease remain controversial with the underlying physiological pathways only beginning to be elucidated. Much attention has been focused on Barker’s fetal origins hypothesis, which interpreted the original empirical observations of associations between low birth weight and adult metabolic disease, as a fetal exposure, despite intervening exposures. Moreover, the effects of low birth weight on adult health are relatively small; for example in the well-established association between birth weight and blood pressure, results from meta-analysis suggest that a very large increase in birth weight of one kilogram would reduce adult systolic blood pressure by less than 1 mm Hg. Evidence from experiments designed to test the fetal origins hypothesis has highlighted the role of nutritionally driven post-natal growth as a possible missing link in the observed relation between birth weight and adult metabolic disease. Currently, the original ‘fetal origins’ hypothesis has been subsumed within a broader theoretical framework emphasizing the role of ‘mismatch’ between fetal and later life environments. In addition, the alternative interpretation of a key role for ‘accelerated’ growth has gained more prominence. Moreover, although fetal and infant life are undoubtedly critical windows of development with very rapid growth, others have highlighted the role of cumulative exposures throughout life and perhaps especially childhood, whilst yet others have recently drawn attention to another hitherto overlooked phase of rapid growth, i.e. puberty.

The “mismatch” theory suggests that the fetus uses environmental cues to make a predictive adaptive response which ‘tunes’ its phenotype for the expected environment, but which may result in increased metabolic risk for babies who subsequently encounter more plentiful conditions. This theory is intuitively appealing and specifically relevant to countries undergoing very rapid economic transition, such as China, where large differences in living conditions between generations, and a mother’s relatively poor growth environment, ‘constitution’ and ‘build’ might condition her offspring for “thriftiness” and hence result in increased metabolic risk in subsequent living conditions with a more plentiful food supply and sedentary lifestyle. Although, this theory is under-pinned by a large body of evidence concerning birth weight and metabolic disease or its consequences, effects are relatively small, and specific evidence that a greater degree of mismatch between fetal and adult environment generates metabolic disease is sparse, partly because the theory is hard to operationalize and investigate in the developing populations most likely to experience mismatch.

In contrast, the accelerated growth hypothesis stresses the role of over-nutrition in early infancy as a critical window. For example the first few weeks of life may be a critical time for setting regulation of appetite and satiety, susceptible to disruption by over-feeding. The theory is supported by experimental evidence in mainly premature babies. Observational evidence from many settings, including in Chinese, also shows
that more rapid infant growth is associated with higher childhood body mass index (BMI),\textsuperscript{88,89} such that Chinese boys who gained weight rapidly between birth and 3 months (equivalent to going from the 25\textsuperscript{th} to the 50\textsuperscript{th} centile or similar on a growth chart) approximately doubled their risk of being overweight or obese at 7 years, whilst Chinese girls with similarly rapid growth increased their risk by almost 50\%.\textsuperscript{89} Childhood BMI is in turn associated with cardiovascular risk in adult life.\textsuperscript{90} Moreover, evidence from both developed settings and China shows that a marker of more rapid growth from infancy through childhood, i.e. earlier sexual maturity, is associated with increased metabolic risk,\textsuperscript{91,92} although inevitably there is more evidence for girls than boys, because of the relative ease of collecting proxies of sexual maturation in girls than boys. In one large recent study from China, older women with menarche before the age of 12.5 years had 49\% higher odds of the metabolic syndrome than women with menarche at 14.5 years or older.\textsuperscript{92} If ‘accelerated’ growth is a risk factor, the increasingly plentiful conditions in China since 1949, as shown by increases in height\textsuperscript{93} and decreases in the age of menarche,\textsuperscript{94} may have already contributed to an immutable increase in the risk of the metabolic syndrome.

Theories concerning the role of cumulative disadvantage stem from the observation that childhood deprivation and its proxies, such as shorter legs or shorter height, are associated with diseases for which the metabolic syndrome may be a sentinel.\textsuperscript{81,95} Almost all the evidence on this topic comes from long-term industrialized populations. More limited evidence from other locations with more recent histories of economic development suggest that the association between poor childhood conditions and stroke may be universal,\textsuperscript{96} whilst the association between poor childhood conditions and the metabolic syndrome or its proxies is less clear\textsuperscript{79,96} especially for obesity in men.\textsuperscript{99} Given that the mechanism responsible for the association between poor childhood conditions and later metabolic risk has not been clearly specified, this theory does not shed any light on why these epidemiologic stage specific findings are occurring. In contrast, a recent, biologically based theory proposes that dietary-driven levels of sex-steroids at puberty permanently increase sexual dimorphism in body shape and lipids with opposite effects by sex, but has less effect on diabetes risk, because its pre-cursors are more strongly related to another hypothalamic-pituitary-endocrine axis, i.e. growth hormone.\textsuperscript{97} This theory implies that growing up in poor conditions should be associated with central obesity and dyslipidemia in women, but conversely growing up in better conditions should be associated with central obesity and dyslipidemia in men, consistent with some recent studies from China.\textsuperscript{69,97} This theory is consistent with the observed emergence of an epidemic of coronary heart disease, but not diabetes, in western men with economic development.\textsuperscript{9,98} However, although the theory does no more than state the implications over historical time of known biological processes it is not congruent with the ‘common soil’ hypothesis.

Distinguishing between these theories and correctly identifying the critical period (if any) and the nature of the exposure (under or over) nutrition is critically important to developing potentially vital public health interventions for the generations growing up in China today and their offspring. Currently, given the
epidemic of childhood obesity also emerging in China,\textsuperscript{99} and the likely tracking of risk factors into adulthood\textsuperscript{100} it would appear that early life might be a key target of intervention. It is thus vital to clarify the role of growth and nutrition from conception onwards on all aspects of metabolic risk in a developing country context, so as to take account of any differences arising from epidemiological stage or population history.

**Conclusion**
Currently there is an epidemic of metabolic disease in China, undoubtedly fuelled by the greater availability of more palatable foods and decreases in physical activity facilitated by recent economic development. Chinese people may be genetically more susceptible to the metabolic consequences of an obesogenic environment, or they may be conditioned by their history of very recent development to be both psychologically and physiology more vulnerable, because of cultural norms, lifetime experiences and the inter-generational transmission of risk via epigenetic processes. Identifying the relative importance and mutability of epigenetic processes, influences over the life course and current environment is key to developing effective public health interventions during the current ‘demographic window’ before the costs of metabolic disease become overwhelming.
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