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Author(s)	He, Y; Lam, TH; Jiang, B; Li, LS; Sun, DL; Wu, L; Liu, M; Yang, SS; Wang, YY; Tobias, DK; Sun, Q; Hu, FB
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Changes in body mass index before and during economic development and subsequent risk of cardiovascular disease and total mortality: a 35-year follow-up study in China

Running title: BMI and mortality in China

Yao He, MD, PhD^{1,2,3*}, Tai Hing Lam, MD⁴, Bin Jiang, MD, PhD⁵, Lan Sun Li, MD⁶, Dong Ling Sun, MD, PhD¹, Lei Wu, MPH^{1,3}, Miao Liu, MPH^{1,3}, Shan Shan Yang, MPH^{1,3}, Yi Yan Wang, MB^{1,3}, Deirdre K. Tobias, ScD⁷, Qi Sun, MD, PhD⁷, Frank B. Hu, MD, PhD^{7*}

Author Affiliations:

¹ Institute of Geriatrics, ²State Key Laboratory of Kidney Disease, ³Beijing Key Laboratory of Aging and Geriatrics, ⁵Department of Chinese Traditional Medicine and Acupuncture and Chinese PLA General Hospital, Beijing, China;

⁴ School of Public Health and Department of Community Medicine, The University of Hong Kong, China;

⁶ Department of Cardiology, 4th Military Medical University, Xi'an, China;

⁷ Departments of Nutrition and Epidemiology, Harvard School of Public Health, Boston Massachusetts

*Corresponding authors. Dr. Yao He, Institute of Geriatrics, Chinese PLA General Hospital, 28 Fuxing Road, Beijing 100853, China (Tel: 86-10-66876411; Fax: 86-10-68219351; E-mail: yhe301@x263.net) and Dr. Frank Hu, Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA (Tel: 6174320113; Fax: 6174322435; E-mail: frank.hu@channing.harvard.edu)

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Abbreviations

USA = United States of America

WHO = World Health Organization

BMI = body mass index

CVD = Cardiovascular disease

CHD = Coronary heart disease

HR = Hazard Ratio

95% CI = 95% confidence interval

SD = Standard deviation

Abstract

OBJECTIVE—It is unclear whether changes in body mass index (BMI) during rapid economic development influence subsequent mortality.

RESEARCH DESIGN AND METHODS— We analyze whether BMI in 1976 and 1994, and changes in BMI during 1976-1994 predict cardiovascular disease (CVD) and all-cause mortality in a 35-year follow-up cohort of 1,696 Chinese (1,124 men and 572 women, aged 35-65 years) in Xi'an, China. Participants were categorized as underweight ($<18.5 \text{ kg/m}^2$), normal weight ($18.5\text{-}24.9 \text{ kg/m}^2$), and overweight ($\geq 25.0 \text{ kg/m}^2$).

RESULTS—During 51,611 person years of follow-up, we identified 655 deaths from all-causes and 234 from CVD. From 1976-1994, the prevalence of overweight rose from 9.2% to 27.8%. With each unit increment in 1976 BMI, multivariate hazard ratios (HRs) (95% CI) were 0.78 (0.72-0.84) for CVD and 0.91(0.87-0.95) for all-cause mortality. In contrast, corresponding HRs were 1.14 (1.08-1.19) and 1.05 (1.01-1.08) in 1994 BMI. The HRs for each unit increment in BMI change from 1976-1994 were 1.35 (1.25-1.41) for CVD and 1.09 (1.05-1.13) for all-cause. Compared to participants with stable normal weight in 1976 and 1994, HRs of all-cause mortality for those who had normal weight in 1976 but became overweight in 1994 and for those who were persistently overweight during 1976-1994 were 1.42 (1.12-1.80) and 1.80 (1.04-3.14), respectively.

CONCLUSIONS—Gaining weight with increased BMI at middle age in Chinese during economic development was associated with elevated risks of all-cause and

CVD mortality. Higher BMI measured before development was associated with lower mortality risk, whereas BMI measured afterwards was associated with increased mortality.

Keywords body mass index, weight change, mortality, cohort study, Chinese

Obesity is a major threat to public health in economically developed countries as well as developing nations.^{1,2} Over the past three decades, China has experienced rapid economic development and nutrition transition, and the prevalence of overweight and obesity in China has increased 2-3 times since the 1980s.²⁻⁴

Numerous epidemiological studies and meta-analyses have documented that obesity is a strong and independent risk factor for diabetes, cardiovascular disease (CVD) and all-cause mortality.^{5,6,7} The association between body mass index (BMI) and all-cause mortality showed J-shaped^{8,9} or U-shaped¹⁰⁻¹⁶ relationships in recent studies, including a recently pooled analysis of prospective data from the Asia Cohort Consortium⁷ and five cohort studies from mainland China.¹²⁻¹⁶ However, nearly all previous reports used a single measurement (i.e. baseline), ignoring the changes during rapid economic development of these countries.⁵⁻¹⁶ Some cohort studies have examined the association between weight or BMI change and subsequent mortality,¹⁷⁻²³ but the duration of follow-up was typically short (<10 years) and methodological biases are common, such as confounding by smoking and pre-existing diseases.^{16,20,24}

In a cohort in Xi'an, China, we measured baseline BMI in 1976 and again in 1994, and it provides a unique opportunity to examine BMI before and during economic development, and its change in relation to subsequent risk of CVD and all-cause mortality.

RESEARCH DESIGN AND METHODS

Participants

Our cohort has been previously described.²⁵ Briefly, from March to May 1976, we carried out a cross-sectional survey on risk factors and the prevalence of CVD in a machinery factory in Xi'an, a capital city in the central part of China. In total, we included 1,696 healthy employees without diagnosed CVD or cancer (1,124 men and 572 women) in the 1976 baseline cohort.

From January to March 1994, we carried out a follow-up survey of the participants in the 1976 cohort. Information was collected on the 1,535 surviving participants, while 154 participants had died during 1976-94, and 7 participants were lost to follow-up. A total of 184 participants (154 deaths, 7 lost to follow-up, and 23 patients diagnosed with cancer) were excluded from the 1994 dataset and yielded a 1994 follow-up cohort of 1,512 participants (976 men and 536 women)

(Supplementary figure 1).

Data collection

In 1976 and 1994, trained interviewers conducted face-to-face interviews on participants with a standardized questionnaire that included demographic factors (education, occupation, and marital status), medical history and family history of CVD, and lifestyle factors such as smoking and alcohol consumption. Leisure time physical activity was assessed in 1994 only.²⁶ Data were self-reported through questions about types of physical activity (e.g., running, tai chi, and playing balls) and overall frequency and duration, and was calculated a summary score then divided into low, moderate and high levels.

Trained nurses and physicians used a standard protocol for physical examination. Height was measured in meters (without shoes). Weight was measured in kilograms, without heavy clothing and 1 kg deducted for remaining garments. Fasting plasma concentrations of total cholesterol and triglycerides were assessed enzymatically with commercially available reagents.

The Ethics Committees of Chinese PLA General Hospital (EC0411-2001) and Faculty of Medicine at University of Hong Kong (EC1246-99) approved the study.

Exposure and covariables

Body mass index (BMI, kg/m^2) was calculated as weight in kilograms divided by the square of height in meters. For a dose-response analysis, BMI (kg/m^2) was grouped into four categories: <18.5 , $18.5\text{--}22.9$, $23.0\text{--}24.9$ and ≥ 25 .²⁷ BMI change (kg/m^2) from 1976-1994 was classified into five categories: <-1.00 , ± 1.00 , $1.01\text{--}2.00$, $2.01\text{--}3.00$ and >3.00 . Smoking status was categorized into never, current and former smokers. Former smokers were defined as those who had quit smoking for at least two years and ever-smokers as those who had smoked at least one cigarette daily for one year or more. Alcohol consumption was defined as drinking alcohol at least once weekly over the past two years.

Ascertainment of deaths

Two physicians from the factory hospital tracked and assessed vital status of all participants every three years. Payment of pensions and post-death welfare of all employees required a report to the personnel department with confirmation by the factory hospital; therefore, follow-up of deaths was 100% complete. We used death

certificates from hospitals or local police departments to identify causes of death.

Hospital records of deaths were reviewed by two physicians from the Medical University teaching hospital blinded to the exposure status of lifestyle factors of the participants, and coded according to ICD-9.

CVD included Coronary heart disease (CHD) and stroke, and were defined by WHO/MONICA criteria.²⁸ Myocardial infarction was diagnosed by a representative set of ECG, cardiac enzyme values and typical symptoms. Stroke was defined as events requiring hospitalization and over 85% of strokes were confirmed by CT and/or MRI.

Statistical Analysis

We entered the data (double entry) using Epidata (3.1) and analyzed it with SPSS for Windows (20.0). A multivariable Cox proportional hazard regression model was used to calculate hazard ratios (HR) with 95% confidence intervals (95% CI) for the associations between BMI and risk of CVD and all-cause mortality. The date of death, the last date of known survival, or the last date of follow-up for those who were alive on that date (July 1, 2011) was used as the right censored date in the proportional hazards analysis as appropriate. Seven subjects (6 men and 1 woman) could not be traced after they were transferred away from the factory and their last day in the factory was considered as the censored date in the analysis of 1976 dataset. Covariates included age, marital status, occupation, education, smoking and alcohol drinking, change of smoking status in 1994 and physical activity in 1994.

We tested the interaction between BMI and gender; if not significant, men and

women were analyzed together with adjustment for gender. Blood pressure and plasma concentrations of triglycerides and total cholesterol were adjusted for separately to examine their potential mediation effects, rather than as confounders.²⁹ Several sensitivity analyses were conducted by excluding deaths occurring in the first 3 years of follow-up in the 1976 cohort or the 1994 cohort; excluding current smokers in 1976 or in 1994 and subjects with COPD diagnosed in 1994³⁰; and excluding participants whose height declined >3 cm from 1976 to 1994 for considering significant decrement in height after the age of 40 in both sexes that could reach a 2-4cm reduction in height over the life course, particularly in women^{31,32}. We also examined the relationship of weight change from 1976 to 1994 with subsequent mortality.

RESULTS—Of the 1,696 participants, there were 655 total deaths from 15 May 1976 through 1 July 2011, and 154 deaths in the time period from 1976 to 1994 and 501 deaths from 1 March 1994 through the end of follow-up. Among the 655 deaths, 234 (36%) were due to CVD (106 CHD and 128 stroke) and the number of total person-years of follow-up (1976-2011) was 51,611, and the mean duration of follow-up was 30.4 years. For analyses using 1512 survivors on BMI measured in 1994 and change of BMI from 1976-94, there were 478 deaths (193 of them were CVD) and 22,648 person-years over 14.8 years of follow-up.

Table 1 shows the general characteristics of subjects in 1976 and in 1994. In 1976, the mean (SD) age was 44.4 (6.1) years (range: 35 to 65 years). The

demographic characteristics in 1994 were similar at baseline in 1976, although blood pressure and lipids significantly increased. From 1976 to 1994, the prevalence of overweight (≥ 25 kg/m²) rose from 7.2% to 25.1% in men and from 13.1% to 32.6% in women over the same period.

During 1976 to 1994, the mean BMI (95% CI) was changed from 22.1 (22.0-22.2) to 23.1 (22.9-23.2) in male, 22.4 (22.2-22.6) to 23.6 (23.4-23.9) in female and 22.2 (22.1-22.3) to 23.2 (23.1-23.4) in total subjects. The distribution of mean BMI of total subjects in 1976 and 1994 is shown in **Figure 1**. The BMI at 1976 baseline correlated with BMI at 1994 follow-up but the correlation was not high (Pearson's coefficient = 0.57, $P < 0.001$).

Table 2 shows that higher BMI categories (23-24.9 and ≥ 25 kg/m²) in 1976 were associated with significantly lower risk of CVD and all-cause mortality in multivariate analyses compared to participants with a BMI of 18.5-22.9 kg/m². In 1994, however, being overweight (BMI ≥ 25) was associated with a significantly greater risk of CVD mortality (HR=2.15, 95%CI=1.53-3.03) and all-cause (1.27, 1.02-1.59) mortality compared to a BMI of 18.5-22.9 kg/m². Being underweight was associated with increased all-cause mortality for 1994 BMI (HR=1.43, 1.00-2.04).

Table 3 shows that compared to participants with relatively stable BMI (± 1.00 kg/m²), the HRs of CVD mortality across categories of BMI increments (1.00-2.00 units, 2.01-3.00 units, >3.00 units) were 1.36, 2.65, and 5.69 (p for trend < 0.001), respectively. These associations were slightly attenuated after adjustment for blood pressure, total cholesterol and triglycerides as intermediates. There was a significant

association between an increase ≥ 3 BMI units from 1976-1994 and all-cause mortality (HR=1.80, 1.39-2.34), and it was attenuated to 1.61 (1.23-2.10) after additional adjustments.

Table 4 shows the HRs of CVD and all-cause mortality according to BMI in 1976, BMI in 1994, and change in BMI modeled as a continuous variable. Because the association of BMI with mortality appeared to be reverse J-shaped in 1976 and U-shaped in 1994 (Table 2), participants with BMI < 18.5 kg/m² were excluded from the 1976 and 1994 BMI analyses. The multivariate HRs (95% CI) of mortality for each one unit increment of BMI in 1976 were 0.78 (0.72-0.84) for CVD and 0.91 (0.87-0.95) for all-cause mortality. In contrast, the corresponding HRs in 1994 were 1.14 (1.08-1.20) and 1.05 (1.01-1.08). From 1976 to 1994, each 1 kg/m² gain in BMI was associated with 35% (25%-41%) and 9% (5%-13%) increased risk of CVD and all-cause mortality, respectively.

Compared to participants who maintained normal weight in both 1976 and 1994, those who changed from normal to overweight had highly elevated HRs of CVD (3.39, 2.38-4.83) and all-cause mortality (1.42, 1.12-1.80) (**Figure 2**). Those who maintained overweight at both time points had the highest risk of CVD (4.02, 1.49-10.85) and all-cause mortality (1.80, 1.04-3.14). The attributable fraction (AF)³³ for all-cause mortality in the group of persistent overweight during 1976-1994 and in the group with normal weight in 1976 and became overweight was 44.4% (3.8%-68.2%) and 29.6% (10.7%-44.4%), respectively.

Sensitivity analysis after excluding the deaths during the first 3 years (13 deaths

in 1976 cohort and 74 deaths in 1994 cohort) of follow-up did not substantially alter the results (**Supplementary table 1-2**). Similar results were obtained when current smokers and subjects with COPD diagnosed in 1994 were excluded from the analyses (**Supplementary table 3-6**). Also, after restricting the analysis to participants whose height declined ≤ 3 cm during 1976-1994, the results remained similar (**Supplementary table 7**). Instead of analyzing BMI changes, we also examined the relationship between weight change during 1976-1994 and subsequent mortality, and the results showed same pattern of BMI changes (**Supplementary table 8**).

CONCLUSIONS—The follow-up of our cohort spanned more than three decades, during a unique period of rapid and unprecedented economic development in China. Overall, BMI gain in middle and older aged Chinese was associated with a significantly elevated risk of CVD and all-cause mortality. Interestingly, BMI measured prior to and during economic development showed opposite associations with mortality risk; a higher BMI before development was associated with lower mortality risk, whereas an elevated BMI in the midst of economic development was associated with increased mortality. These findings provide first prospective evidence on the association of BMI at two times (before and during industrialization) and changes in BMI between these two times and subsequent risk of CVD and total mortality in China and developing countries.

Most evidence on the relationship between BMI and weight change and subsequent mortality was derived from Western nations^{17,18,20,21,34} or developed Asian

countries (e.g., Japan) where their baseline data were collected after economic development.^{20,23} Thus, these findings may not apply to developing countries, such as China. Moreover, results from previous studies have been inconsistent^{17-24, 34-36} and these discrepancies may be due to different degrees of reverse causation (weight loss due to pre-existing chronic diseases) or obesity paradox³⁰, varied economic and social developments in different populations^{19, 20} and other methodological issues.^{3,17-24}

China's economic reform began in 1978. Since then, in parallel with a rapid economic development and a nutrition transition, the prevalence of overweight and obesity has increased substantially.³⁷ Three nationally-representative surveys conducted in 1981, 1992 and 1998 among middle-aged men and women showed that the prevalence of overweight (by WHO criteria of $BMI \geq 25 \text{ kg/m}^2$) increased significantly from the early 1980s (9.9% in men and 14.6% in women) to the early 1990s (19.6% in men and 26.1% in women), and the late 1990's (23.5% for men and 28.5% for women).³ In our cohort, the prevalence of overweight increased from 9.2% to 27.8% between 1976 and 1994, which is broadly consistent with the national trend from multiple cross-sectional surveys,^{3,4} although the age distribution in our cohort changed over time.

Anthropometric measurements, such as BMI, are useful markers of the nutritional status for individuals and populations. In Western populations, obesity is typically correlated with lower educational levels and low socioeconomic status.^{37,38} In contrast, in less developed countries, low BMI is considered as a marker of under-nutrition, and

low socio-economical status (SES),^{38,39} while a higher BMI tends to be associated with higher SES and better nutritional status. This was especially true in less developed countries like China and India prior to the onset of economic development,³⁷ and this may explain the inverse association between BMI measured in 1976 and mortality risk observed in our cohort, and from a study conducted in rural India.¹⁹ Other studies from Asia also found a positive association between higher BMI and education, better living standards, and an inverse association with mortality.^{37,40}

Five prospective studies conducted in mainland China, three based on BMI measured in the 1980s¹²⁻¹⁴ and two in 1991,^{15,16} showed that both underweight and obesity were associated with increased mortality in the Chinese adult population. These results were similar to our findings based on BMI measured in 1994. The positive association between BMI and mortality in 1994 may reflect two observations. First, the prevalence of overweight and obesity had become more common in 1994, which increased our power to observe the association.^{2-4,37} Second, higher BMI in 1994 was probably more likely to reflect increased adiposity and its detrimental effects of body fatness on health outcomes.

In the present study, a gain of 1 kg/m² BMI from 1976 to 1994 was associated with a 35% increased risk for CVD and a 9% greater risk for all-cause mortality. These associations were stronger than those observed by analysing 1994 BMI data alone. Few studies have examined the association of BMI or weight change assessed in middle age with mortality risk. Several studies in the US and Europe showed that weight loss, but not weight gain, was associated with increased mortality from

all-causes and CVD.^{21,22} These paradoxical findings known as the “obesity paradox” was increasing in some studies and shown that those patients, especially elderly, with several chronic diseases (CHD, chronic heart failure, peripheral arterial disease, stroke, COPD, type 2 diabetes, etc) and elevated BMI may demonstrate lower all-cause and cardiovascular mortality compared with patients of normal weight.³⁰ Two Japanese studies showed that a large weight change, either loss or gain, was associated with an increased risk of mortality.^{20, 23}

Using stable and normal weight participants as the reference group, for all-cause mortality, we estimated an attributable fraction of 44% in the participants who were persistently overweight during 1976-94 and of 29.6% in normal weight participants in 1976 who had become overweight in 1994. These estimates could be translated into alarming public health messages, suggesting that if the relationships are causal, about half of those who were overweight during the entire follow-up would be killed prematurely by their persistent overweight (from diseases associated with or induced by persistent overweight) and one-third of the people who became overweight during 18 years of rapid economic development in China would be killed by diseases associated with weight gain.

Our findings should have global public health implications. Many developing countries undergoing economic development and nutrition transition carry a dual burden of disease with the coexistence of under and over nutrition.³⁵ The transition from under-nutrition to over-nutrition heralds an impending epidemic of obesity-related chronic diseases (such as CVD) and health outcomes, especially

mortality.⁴¹ Our findings may help explain the inconsistent relationships between BMI and mortality observed in different populations at various stages of economical development and nutrition transitions. A recent meta-analysis showed a reduced mortality in overweight and moderately obese group, but the results have been highly controversial. Some of the studies included in the meta-analysis were based on Asian populations but none considered different stage of economic developments.⁶ Clearly, more long-term studies with regular and multiple repeated measures of BMI and other indicators of obesity (such as waist circumference and waist to hip ratio) are needed to monitor changes in obesity status during the course of nutrition transitions in developing countries and their consequences on morbidity and mortality.

To our knowledge, this is the first and longest-running cohort study in China. Our follow-up rate was extremely high over 35 years, with only 0.4% of participants lost to follow-up. This study is unique in that two repeated measurements of BMI, an occupational cohort with related stable social characteristics before and during economic development, allowed us to examine the relationship between changes in BMI and subsequent mortality. Moreover, we adjusted for important confounding variables such as education, occupation, physical activity, alcohol drinking and change in smoking status. To minimize reverse causation or obesity paradox due to underlying diseases (such as COPD) and smoking, sensitivity analyses were also carried out and showed similar results.

This study has some limitations. First, we did not collect data on dietary factors; such information may have helped us better understand the role of nutrition transition

on changes in BMI during follow-up. Second, because our sample was derived from survivors of a cohort recruited 18 years earlier, some bias in estimating the relationship between 1994 BMI and subsequent mortality might have been introduced. However, the number of deaths that occurred between 1976 and 1994 was small (n=154). Third, our sample size was relatively small and thus we were not able to conduct subgroup analysis by age or other covariates. However, we had sufficient power to detect the associations between BMI as well as BMI change and mortality risk, partly due to the long duration of follow-up and nearly 100% follow-up rate. Finally, because all participants were Chinese, it is unclear whether the results can be generalized to other ethnic groups.

In summary, this long-term prospective study demonstrated that gaining weight with increased BMI at middle-aged and older Chinese during economic development was associated with an elevated risk of all-cause and CVD mortality. A higher BMI measured before economic development was associated with lower mortality risk, whereas higher BMI measured afterwards was associated with increased mortality. This study underscores the importance of preventing overweight and obesity in countries undergoing economic development.

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Author Contributions: YH, THL and FBH designed the study and analyzed the data. YH, BJ, LLS, DLS, LW, ML, SSY and YYW contributed to data collection and field operations. YH, BJ, DLS, QS and LW contributed to data analysis. YH, THL, DKT and FBH wrote the manuscript. YH and THL obtained the funding for the project. YH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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