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Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians

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Abstract:

Background
Most studies that have evaluated the association of body mass index (BMI) with total and cause-specific mortality were conducted in populations of European origin.
Methods
Pooled analyses were conducted to evaluate the BMI-mortality association in over 1.1 million persons recruited in 19 cohorts in Asia, including approximately 120,700 deaths after a mean follow-up of 9.2 years. Cox regression models were used to adjust for confounding factors.

	Results In East Asians, including Chinese, Japanese, and Koreans, the lowest risk of death was found among persons with a BMI range of 22.6-27.5 kg/m.2 The risk was elevated with either higher or lower BMI level: up to 1.5-fold among those with a BMI ≥ 35.0 kg/m2 and 2.8-fold among those with a BMI < 15 kg/m2. A similar U-shaped association was found for mortality due to cancer, cardiovascular diseases, and other causes. In Indians/Bangladeshis, elevated risks, for total and other-cause mortality, were found among individuals with a BMI of <20 kg/m2, compared to those with a BMI of 22.6-25.0 kg/m2, whereas no excess risk for total or cause-specific mortality was associated with a high BMI. Conclusions Underweight was associated with a substantially increased risk of death in all Asian populations. The excess risk of death associated with high BMI, however, was found in East Asians but not in Indians/Bangladeshis. These results should be considered in designing weight reduction programs in some Asian populations in which under-nutrition and other causes of underweight are major health problems.

TWeek – Zheng OA (10-10679)

“Body Mass Index and Mortality in Over 1 Million Asian Persons”

This study presents pooled analyses of BMI-mortality associations in over 1.1 million people from 19 cohorts in Asia after a mean follow-up of 9.2 years. Underweight was associated with a substantially increased risk of death in all Asian populations. However, the excess risk of death associated with high BMI was observed in East Asians but not in Indians and Bangladeshis.

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Body Mass Index and Mortality in Over 1 Million Asian Persons

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ABSTRACT

Background

Most studies that have evaluated the association of body mass index (BMI) with total and cause-specific mortality were conducted in populations of European origin.

Methods

Pooled analyses were conducted to evaluate the BMI-mortality association in over 1.1 million persons recruited in 19 cohorts in Asia, including approximately 120,700 deaths after a mean follow-up of 9.2 years. Cox regression models were used to adjust for confounding factors.

Results

In East Asians, including Chinese, Japanese, and Koreans, the lowest risk of death was found among persons with a BMI range of 22.6-27.5 kg/m.^{2}

The risk was elevated with either higher or lower BMI level: up to 1.5-fold among those with a BMI $\geq$ 35.0 kg/m^2 and 2.8-fold among those with a BMI < 15 kg/m^2. A similar U-shaped association was found for mortality due to cancer, cardiovascular diseases, and other causes. In Indians/Bangladeshis, elevated risks, for total and other-cause mortality, were found among individuals with a BMI of $\leq$20 kg/m^2, compared to those with a BMI of 22.6-25.0 kg/m^2, whereas no excess risk for total or cause-specific mortality was associated with a high BMI.

Conclusions

Underweight was associated with a substantially increased risk of death in all Asian populations. The excess risk of death associated with high BMI, however, was found in East Asians but not in Indians/Bangladeshis.

Over the past few decades, there has been a dramatic increase in the prevalence of obesity in many countries. The World Health Organization estimates that more than one billion adults are overweight worldwide; of these, at least 300 million are obese (1). A large number of epidemiologic studies have evaluated the associations between body weight and, more often, body mass index (BMI, kg/m^2) and a wide range of health outcomes. Obesity is associated with multiple chronic diseases, including type 2 diabetes, hypertension, coronary heart disease, stroke, and several cancers (2). Uncertainties, however, remain regarding the dose-response relationship between BMI and overall mortality, particularly for Asians who account for over 60% of the world population, as most of the studies have been conducted in populations of European origin.

The definitions of overweight (BMI>25) and obese (BMI>30) are based essentially on criteria derived from studies conducted in populations of European origin. The validity of these criteria in Asian populations has yet to be determined. It has been suggested that the associations of BMI with body composition and health outcomes may differ in Asian and European populations (3). Studies have shown that, for a given BMI, Asians generally have a higher percentage of body fat than Europeans (3). Asian populations have also been found to have an elevated risk of type 2 diabetes, hypertension, and hyperlipidemia at a relatively low level of BMI (3). Based on these observations, lower BMI cut points have been proposed to define overweight (BMI > 23.0) and obesity (BMI > 25.0) for Asian populations (3). However, a recent consensus statement from the WHO concludes that the available data are not sufficient to support Asian-specific cut points to define overweight and obesity (3). The optimal weight range associated with minimal mortality in Asian populations remains controversial.

To address these unresolved issues, we evaluated the relationship between BMI and mortality endpoints using data from 19 cohort studies, involving more than one million participants, as part of the Asia Cohort Consortium (ACC). This pooling project, with its large sample size, not only provides the opportunity to address carefully the methodologic challenges that cannot be handled adequately in any single study, but also enables the evaluation of the associations by major Asian ethnicities.

METHODS

Eligible cohorts for the BMI Pooling Project were identified through a systematic literature search in early 2008, followed by a survey that was sent to the investigators of each cohort to further determine study eligibility. Nineteen cohorts were included in the pooling project. With the exception of the Taiwan CVDFACTS cohort, all other cohorts had accrued at least five years of follow-up and had recruited a minimum of at least 10,000 participants with baseline BMI data. All participating cohorts were required to have baseline data on BMI, age, sex, and cigarette smoking, plus follow-up data on all-cause mortality. Additional data were collected on selected baseline morbid conditions and cause-specific mortality. Individual data from participating cohorts were collected and harmonized for statistical analysis. This study was approved by ethics committees for all participating studies and the Fred Hutchinson Cancer Research Center.

A total of 1,155,676 participants were included in the 19 participating cohorts. Excluded from the analysis were participants with missing data on age (n=2), BMI (n= 13,780), and vital status (n=7). In addition, we excluded those with age<18 (n=14), with BMI>50 (n=174) and with invalid or missing survival time (n=105). After these exclusions, 1,141,609 participants remained (535,199 men and 606,410 women). The association between BMI and mortality was examined using Cox proportional hazards regression models, employing a categorical representation of BMI as the predictor variable. To define BMI groups for the analysis, we utilized pre-determined levels of 25 (overweight) and 30 (obesity) as cut-off points. With 2.5-unit increments per group between 15 and 35, along with the lowest (≤15.0) and highest (>35.0) BMI groups, ten BMI levels were established: ≤15.0, 15.1-17.5, … 32.6-35.0, and >35.0. Using the BMI range 22.6-24.5 as the reference, hazard ratios (HR) and 95% confidence intervals (CI) were estimated for the other BMI ranges, after adjusting for potential confounders, including baseline age, sex, education, urban/rural resident, and marital status. We adjusted for additional variables in some analyses — cigarette smoking and known baseline morbid conditions (cancer, coronary heart disease [CHD], stroke, diabetes, and hypertension). Analyses were conducted separately for Indian/Bangladeshi, and East Asians (Chinese, Japanese, and Koreans), as there are significant heterogeneities between these two populations. Pre-specified stratified analyses were performed by smoking status and sex to evaluate the consistency of the associations. Some analyses were conducted among lifetime nonsmokers to eliminate the potential confounding effect of cigarette smoking on the association between BMI and mortality outcomes. To minimize the influence of possible "reverse causation" (morbid conditions causing low BMI) due to the presence of terminal diseases at baseline in some participants, we excluded the first three years of follow-up and restricted some analyses to those who did not have CHD, stroke, and/or cancer at baseline or to lifetime nonsmokers without these morbid conditions at baseline. Ages at entry and exit were used to define the time variable in the Cox models.

In the models, the effect of BMI on mortality was assumed to be cohort-specific. For each cohort, we assumed that the log hazard ratio for BMI has a fixed-effect component that is common to all cohorts within each of the three major Asian populations and a random effect that is cohort-specific. The random effects for the log hazard ratios were assumed to be normally distributed, with mean zero; that is, we assumed that $\hat{\beta}_{ij}$, the estimated log hazard ratio for the j-th BMI level in the ith cohort, has distribution $\hat{\beta}_{ij} \sim N(\beta_j, \hat{\sigma}_{ij}^2 + \tau_j^2)$ where $\hat{\sigma}_{ij}^2$ is within-study variance of $\hat{\beta}_{ij}$ as estimated from the Cox regression model (4;5). Parameters β_j and 95% CIs were estimated in the meta-analysis. Cox model estimation for each cohort was performed using the PHREG procedure in SAS version 9.2. Meta-analysis estimation was performed using the SAS MIXED procedure.

RESULTS

More than 1.14 million participants from 19 cohorts were included in the analysis (Table 1). Overall, the mean BMI for the study population was 22.9 (SD=3.6; range: 19.8 - 23.7). Nearly 34% of study subjects were ever smokers. Over a mean follow-up of 9.2 years, approximately 120,700 cohort members died. Approximately one-third of deaths were due to each of the following causes: cardiovascular diseases (CVD) (35.7%), cancer (29.9%), and other causes (34.3%). Considerable variation, however, existed across the cohorts.

Compared to those with a BMI of 22.6 to 25.0, adjusted HRs for total mortality were elevated among groups with lower BMI in both Asian groups (Table 2). Subjects in the lowest BMI group (<15.0) had an approximately 2- to 2.8-fold elevated risk. Compared with the reference group, HRs for total mortality were elevated with an increasing BMI in East Asians, but not in Indians/Bangladeshis. In general, the magnitude of the association was similar in ever smokers and lifetime nonsmokers. Results for men and women are similar to those shown in Table 2 (Supplementary Tables S1, S2).

To evaluate possible influence due to reverse causation, we performed analyses that excluded subjects with a baseline diagnosis of CHD, stroke, and/or cancer (Table 3). These exclusions had minimal impact on the point estimate of HRs for the association between BMI and total mortality. Excluding two more years of follow-up (from the first three years to the first five years) slightly attenuated the positive association with low BMI but had no impact on the results for high-BMI groups. Following the exclusion of smokers, the elevated risk associated with lower BMI was attenuated, whereas the positive association with higher BMI was slightly strengthened in East Asians. No positive association of total mortality with high BMI was seen in the Indian/Bangladeshi group in all analyses regardless of the types of exclusions. These results indicate that any possible reverse causation was adequately addressed in analyses conducted among lifetime nonsmokers, after excluding deaths that occurred within the first three years of follow-up, an approach that was used in all main analyses in this study.

As with the findings for total mortality, a U-shaped association was found between BMI and mortality from CVD, cancer, and other causes in East Asians but not in Indians/Bangladeshis (Fig. 1). In fact, no elevated risk in the high-BMI groups was seen for any of the three cause-specific mortality outcomes in Indians/Bangladeshis. The positive association of low BMI was strongest for other-cause mortality. Results of stratified analyses by smoking status are, in general, consistent with the pattern shown in Fig, 1, although point estimates for some BMI categories were not statistically significant, due to small sample size (Supplementary Tables S3, S4).

The strikingly positive association between low BMI and other-cause mortality was primarily caused by deaths due to respiratory diseases (Fig, 2). After excluding respiratory-disease deaths, the positive association with low BMI was substantially reduced. The association between BMI and respiratory-disease mortality was similar in smokers and non-smokers (Supplementary Fig. 1). It is possible that the observed strong association between low BMI and respiratory diseases mortality could be explained, in part, by reverse causation since respiratory disease can lead to weight loss long before clinical diagnosis.

DISCUSSION

In this pooled analysis of approximately 850,000 East Asians, both low and high BMI were associated with an increased risk of total and cause-specific mortality in this population, resulting in an overall U-shaped association. Analyses of data from over 287,000 Indians/Bangladeshis, however, showed that an elevated risk of death was seen only among those with low BMI. This large pooled analysis provides not only reliable estimates of the overall impact of BMI on total and cause-specific mortality in Asians, but also unique opportunities for a careful evaluation of the association between low BMI and mortality endpoints that could not be adequately investigated in most previous studies, which were conducted in populations of European origin.

The findings among the East Asian populations are, in general, consistent with those of another recent pooled analysis from the Prospective Studies Collaboration (PSC), involving 900,000 participants from 57 prospective studies, mostly from Western Europe and North America (6). Only 8% of the PSC populations were Asians (Japanese). In our analysis of data from Indians and Bangladeshis, however, a virtually inverse association between BMI and total mortality was found. Even among East Asians, the shape of the curve of the association was quite different between the PSC and the current analysis, as were the values of the hazard ratios (higher at the low-BMI end in Asians, higher at the high-BMI end in the largely European population). Over the past 10 years, several large cohort studies have also evaluated the association of BMI with mortality, again mostly in populations of European origin (6;7-10). Although different groupings were used, these studies, in general, have found that the lowest mortality was associated with a BMI in the range of 23 to 27, regardless of study population. The finding that the same optimal weight range is associated with the lowest mortality both in the current study of East Asians and in previous studies in populations of European origins, argues strongly against the use of ethnic-specific BMI cutoff points to define overweight and obesity.

In a longitudinal analysis of approximately 1.2 million Koreans, Jee et al. reported a J-shaped association between BMI and total mortality (9). The BMI associated with the lowest overall mortality was 21.5 to 27.9 in the Korean study, similar to those found in our study for East Asians (Supplementary Tables S5, S6, S7). The magnitudes of the associations for some analyses, however, differ between the Korean study and the current study. Extensive exclusions were made in the Korean study; thus, subjects with a baseline diagnosis of CHD, cancer, liver diseases, diabetes, stroke, and respiratory diseases were not included in the Korean study. Most other cohort studies do not use such extensive exclusions in their analysis, nor did we in the present study. Because only about 16,000 Koreans were included in our analysis, the East Asian group in our study consists primarily of Chinese and Japanese. Therefore, differences in population characteristics across these populations also could contribute to inconsistencies in the findings.

Although mortality is the most critical measure of the health consequences of excess adiposity, epidemiologic studies examining the relationship between body weight and mortality are fraught with methodologic challenges (11;12). The most important of these is the problem of reverse causation, in which weight loss resulting from illness can distort the relationship between leanness and health. An additional concern is confounding, mainly by smoking tobacco, as smokers often have a lower body mass than nonsmokers. To address these problems, multiple studies have conducted analyses among nonsmokers and people who report no serious underlying illness at the time of enrollment or by excluding from analyses the early years of follow-up (13-16). However, a J- or U-shaped relation between BMI and mortality persisted after addressing major methodologic issues in the current analysis, the PSC project, and the Korean insurance cohort, as well as some other large cohort studies (6;7-10).

There is substantial evidence supporting the biologic plausibility of a positive association between excess adiposity and mortality. Obesity is a well established risk factor for numerous chronic diseases (2). Adipose tissue has been increasingly recognized as an active endocrine organ, capable of releasing a large number of cytokines and bioactive mediators that play important roles in the pathogenesis of many obesity-related diseases (17). In contrast, an increased risk of mortality associated with a low BMI observed in our analysis and other studies remains to be fully explained. Inadequate or incomplete control for confounding or reverse causation bias could explain some of the increased risk (18). Residual influence of reverse causation may remain in our study, particularly since we did not have information on baseline infection and chronic lung disease diagnosis, so those conditions could not be excluded in our data analysis. Low BMI can be an indicator of certain other chronic medical conditions that were not adequately controlled in the study, or an indicator of poor health or living conditions such as under-nutrition, that increase the risk of premature death (21). Several recent cohort studies have shown that, even among individuals with a low BMI, elevated waist-hip ratio or waist circumference (measures of abdominal adiposity) were associated with a statistically significant increased risk of mortality (10;19); this suggests that the observed excess mortality among individuals with a low BMI may be, in part, due to the abdominal adiposity that cannot be measured adequately using BMI (20).

We did not assess mortality risk in relation to abdominal obesity, which may be particularly important in Asian populations. The interval between BMI measurement and mortality outcome ascertainment for several participating cohorts in this consortium is relatively short, raising concern about the effects of subclinical or undiagnosed chronic diseases on the results. Self-reported BMI data were included in our analysis, although the pattern of association between BMI and total mortality was similar, regardless of the method for assessing BMI (Table S9). Social-economic status (SES) could confound the association between BMI and mortality since people with a high BMI are more likely to have a high SES in less well-developed countries (and thus better access to healthcare) than those with lower BMI. Although we adjusted for several SES indicators, such as education, a major measure of SES status, it is possible that residual confounding effects of SES remain, which could attenuate the positive association between high BMI and mortality outcomes.

In conclusion, this large pooled analysis revealed a U-shaped association between BMI and mortality in East Asians with a pattern broadly comparable to that of earlier studies conducted mostly in North American and European populations. In Indians and Bangladeshis, however, no elevated risk of total and cause-specific mortality was seen in high BMI groups. Overall, mortality in Asians, compared with Europeans, seems to be more strongly affected by low BMI and less by high BMI. Given the limitations of the current study using mortality as the outcome, additional studies are needed to quantify the association of BMI with disease incidence to better define BMI criteria for overweight and obesity in Asians.

Disclosure:

Dr. Gupta reports receiving consulting fees from the CDC Foundation for Global Adult Tobacco Survey. His institution, Healis - Sekhsaria Institute for Public Health, has received grants from the World Lung Foundation for advancing tobacco control in India and consulting fees from the Institute for Community Research for a project on smokeless tobacco use in an urban slum in Mumbai. No other potential conflict of interest relevant to this article was reported. Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Figure legends

Figure 1. Hazard ratios for the association between BMI and cause-specific mortality by ethnicity: the Asia Cohort Consortium BMI Project. Two figures are presented for each population (A and C for East Asians; B and D for Indians/Bangladeshis), one with and one without confidence interval bars. HRs were adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities and excluding subjects with less than three years of follow-up.

Figure 2. Hazard ratios (HR) for the association of BMI with mortality due to respiratory diseases or non-respiratory diseases, CVD, and cancer, the Asia Cohort Consortium BMI project. Two figures are presented for each population (A and C for East Asians; B and D for Indians/Bangladeshis), one with and one without confidence interval bars.

HRs were adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities and excluding subjects with less than three years of follow-up.

*Excluding deaths due to respiratory diseases, CVD, and cancer.

Table 1: Characteristics of Participating Cohorts in the Asia Cohort Consortium BMI Project

Cohort	No of subjects	Study entry	Years of follow-up[a]	Age at entry[a]	BMI [a]	Female (%)	Ever smokers (%)	No of deaths	Cancer death (%)[c]	CVD death (%)[c]	Other death (%)[c]
India											
Mumbai [d]	146,820	1991-1997	5.2	50.8	22.3 (4.2)[b]	40.4	18.9	13,001	8.7	43.8	47.5
Trivandrum	129,097	1995-2002	7.5	49.5	21.8 (4.1) [b]	61.6	23.5	10,680	11.8	37.4	50.8
Bangladesh	11,452	2000-2002	6.6	37.1	19.8 (3.2)[b]	57.0	35.6	392	15.6	43.7	40.7
China (Mainland)											
CHEFS	154,737	1990-1992	7.2	55.4	22.6 (3.7)[b]	51.1	37.9	17,687	22.5	46.4	31.0
SCS [d]	18,100	1986-1989	16.3	55.3	22.2 (3.0)	0.0	57.3	4983	39.6	33.8	26.6
SMHS	61,379	2001-2006	3.1	54.9	23.7 (3.1)[b]	0.0	69.6	946	45.2	31.1	23.7
SWHS	74,873	1996-2000	8.6	52.1	24.0 (3.4)[b]	100.0	2.8	2895	46.4	27.6	26.0
Taiwan											
CBCSP	23,763	1991-1992	15.2	47.3	24.0 (3.4)[b]	49.7	28.9	2758	36.6	20.1	43.3
CVDFACTS	5129	1990-1993	14.9	47.0	23.7 (3.5)[b]	55.9	24.8	829	26.7	26.3	47.0
Singapore	63,242	1993-1999	11.5	56.5	23.1 (3.2)	55.8	30.6	10,689	36.4	34.7	28.9
Japan											
3 Pref Aichi [d]	32,210	1985	11.6	56.2	22.1 (3.0)	52.6	50.7	5764	32.9	34.8	32.4
Ibaraki	97,578	1993-1994	11.5	58.8	23.5 (3.2)[b]	65.8	30.3	10,980	NA[e]	NA	NA
JACC	86,671	1988-1990	12.7	57.6	22.8 (3.0)	58.2	38.6	12,888	36.8	31.0	32.2
JPHC1	42,771	1990-1992	14.4	49.6	23.6 (3.0)	52.2	40.3	3394	43.6	26.1	30.3
JPHC2	55,712	1992-1995	11.5	54.2	23.5 (3.1)	52.6	40.1	5357	44.5	24.9	30.7
3 Pref Miyagi	29,525	1984	11.6	56.9	23.2 (3.3)	55.0	43.1	5880	30.2	40.5	29.3
Miyagi	44,867	1990	12.8	52.0	23.6 (3.0)	52.1	49.5	3441	54.9	27.1	18.0
Ohsaki	47,670	1995	9.9	60.1	23.5 (3.1)	51.8	48.6	6892	35.9	32.9	31.2
Korea (KMCC) [d]	16,013	1993-2004	6.5	55.6	23.7 (3.3)[b]	60.3	36.4	1302	29.6	25.4	45.0
Total	1,141,609	1984-2006	9.2	53.9	22.9 (3.6)	53.1	33.5	120,758	29.9	35.7	34.3

[a] Mean (SD) for BMI and mean for other variables.
[b] BMI estimated using weight and height measured at enrollment. For other studies weight and height were self-reported.
[c] Excluding deaths with unknown causes.
[d] Data on CHD diagnosis at baseline were unavailable. Table S8 provides data for cohorts with and without baseline CHD data.
[e] NA, not available.

Table 2. Hazard ratios (HR) for the association between BMI and total mortality by major study populations: The Asia Cohort Consortium BMI Project

	Body mass index (BMI) at baseline									
	≤15.0	15.1-17.5	17.6-20.0	20.1-22.5	22.6-25.0	25.1-27.5	27.6-30.0	30.1-32.5	32.6-35.0	35.1-50.0
All subjects[a]										
East Asian										
No. of deaths	456	3795	13,547	21,200	21,391	11,009	4679	1623	484	283
HR (95% CI)[b]	2.76 (1.88,4.07)	1.84 (1.65,2.05)	1.35 (1.25,1.45)	1.09 (1.05,1.14)	1.00 (reference)	0.98 (0.95,1.01)	1.07 (1.02,1.12)	1.20 (1.10,1.32)	1.50 (1.31,1.71)	1.49 (1.31,1.69)
Indian & Bangladeshi										
No. of deaths	755	2412	3340	3196	2349	1269	537	233	64	57
HR (95% CI)[b]	2.14 (1.78,2.57)	1.59 (1.40,1.81)	1.26 (1.12,1.41)	1.09 (0.97,1.23)	1.00 (reference)	0.98 (0.84,1.13)	0.94 (0.77,1.16)	1.03 (0.77,1.39)	0.86 (0.50,1.49)	1.27 (0.71,2.26)
Ever smokers[a]										
East Asian										
No. of deaths	191	1990	7590	11,737	10,450	4733	1722	531	127	82
HR (95% CI)[b]	2.66 (1.62,4.37)	1.81 (1.61,2.04)	1.38 (1.28,1.49)	1.14 (1.09,1.18)	1.00 (reference)	0.97 (0.93,1.00)	1.01 (0.95,1.07)	1.18 (1.07,1.30)	1.44 (1.13,1.84)	1.60 (1.26,2.03)
Indian & Bangladeshi										
No. of deaths	267	1055	1277	1067	678	318	116	41	9	5
HR (95% CI)[b]	1.97 (1.43,2.72)	1.59 (1.28,1.98)	1.24 (1.01,1.53)	1.13 (0.92,1.40)	1.00 (reference)	0.99 (0.74,1.33)	0.99 (0.64,1.53)	1.16 (0.58,2.32)	NA	NA
Lifetime nonsmokers[a]										
East Asian										
No. of deaths	247	1618	5280	8366	9925	5704	2713	1017	325	179
HR (95% CI)[b]	2.43 (2.06,2.87)	1.72 (1.52,1.94)	1.23 (1.12,1.35)	1.02 (0.97,1.07)	1.00	1.00 (0.95,1.06)	1.11 (1.04,1.20)	1.27 (1.12,1.43)	1.51 (1.30,1.76)	1.56 (1.31,1.86)
Indian & Bangladeshi										
No. of deaths	488	1357	2063	2128	1671	951	421	192	55	52
HR (95% CI)[b]	2.15 (1.71,2.69)	1.54 (1.31,1.81)	1.24 (1.07,1.43)	1.07 (0.93,1.23)	1.00 (reference)	0.97 (0.82,1.16)	0.94 (0.74,1.19)	1.01 (0.73,1.41)	0.86 (0.48,1.55)	1.34 (0.73,2.46)

[a] Included in the analysis were all subjects / ever smokers / lifetime nonsmokers from India and Bangladesh (265,036 / 55,435 / 209,596) and East Asia (779,537 / 270,045 / 479,492)

[b] Adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities and excluding subjects with less than three years of follow-up.

Table 3. Hazard ratios (HR) for the association between BMI and total mortality in subgroup analyses designed to address reverse causation: The Asia Cohort Consortium BMI Project.

	All participants				Lifetime nonsmokers			
	Low BMI groups		High BMI groups		Low BMI groups		High BMI groups	
	Deaths [f]	HR (95% CI)[g]	Deaths [f]	HR (95% CI)[g]	Deaths [f]	HR (95% CI)[g]	Deaths [f]	HR (95% CI)[g]
East Asian, total	74226	1.18 (1.14,1.22)	47512	1.06 (1.04,1.08)	31543	1.13 (1.09,1.18)	24010	1.08 (1.05,1.10)
Excluding first 3 years of follow-up[a]	59933	1.18 (1.14,1.22)	39469	1.06 (1.04,1.08)	25189	1.13 (1.09,1.18)	19863	1.08 (1.05,1.10)
Subjects with CHD data at baseline[a]	49807	1.18 (1.14,1.23)	34666	1.05 (1.03,1.08)	21895	1.14 (1.09,1.19)	17999	1.08 (1.05,1.10)
Excluding subjects with baseline CHD[a,c]	46706	1.18 (1.14,1.23)	31832	1.06 (1.03,1.08)	20597	1.14 (1.09,1.19)	16531	1.08 (1.05,1.11)
Excluding subjects with severe comorbidity[a,d]	44115	1.18 (1.14,1.23)	29964	1.06 (1.03,1.08)	19425	1.13 (1.08,1.19)	15529	1.08 (1.05,1.11)
Subjects without any severe comorbidity[a,e]	27367	1.19 (1.13,1.25)	20162	1.06 (1.03,.109)	11012	1.13 (1.06,1.20)	9775	1.08 (1.04,1.12)
Excluding first 5 years of follow-up[b]	48187	1.16 (1.13,1.20)	32353	1.06 (1.04,1.08)	20078	1.12 (1.07,1.17)	16124	1.08 (1.05,1.11)
Subjects with CHD data at baseline[b]	39552	1.17 (1.12,1.22)	28177	1.06 (1.03,1.09)	17286	1.12 (1.07,1.17)	14528	1.08 (1.04,1.11)
Excluding subjects with baseline CHD[b,c]	37137	1.17 (1.13,1.22)	25916	1.06 (1.03,1.09)	16280	1.12 (1.07,1.17)	13362	1.08 (1.05,1.11)
Excluding subjects with severe comorbidity[b,d]	35173	1.17 (1.13,1.21)	24511	1.06 (1.03,1.09)	15380	1.12 (1.06,1.17)	12616	1.08 (1.05,1.12)
Subjects without any severe comorbidity[a,e]	23000	1.17 (1.12,1.23)	17010	1.06 (1.02,1.10)	9267	1.11 (1.04,1.18)	8209	1.08 (1.03,1.13)
Indian & Bangladeshi, total	18988	1.16 (1.12,1.21)	7295	1.00 (0.93,1.06)	12155	1.15 (1.09,1.21)	5392	1.00 (0.93,1.07)
Excluding first 3 years of follow-up[a]	11297	1.16 (1.12,1.21)	4509	1.00 (0.93,1.06)	7219	1.15 (1.09,1.21)	3342	1.00 (0.93,1.07)
Subjects with CHD data at baseline[a]	5876	1.17 (0.99,1.38)	1962	0.99 (0.73,1.33)	3410	1.17 (0.94,1.46)	1437	0.99 (0.71,1.39)
Excluding subjects with baseline CHD[a,c]	5733	1.17 (0.99,1.39)	1892	0.99 (0.73,1.34)	3349	1.17 (0.94,1.47)	1385	0.99 (0.71,1.39)
Excluding subjects with severe comorbidity[a,d]	5694	1.17 (0.99,1.39)	1871	0.99 (0.72,1.34)	3322	1.17 (0.94,1.47)	1369	0.99 (0.70,1.40)
Excluding first 5 years of follow-up[b]	5459	1.14 (1.08,1.21)	2154	0.98 (0.90,1.08)	3398	1.12 (1.04,1.21)	1599	1.00 (0.90,1.11)
Subjects with CHD data at baseline[b]	3611	1.15 (0.93,1.43)	1253	1.01 (0.70,1.47)	2082	1.16 (0.87,1.54)	904	1.03 (0.68,1.55)
Excluding subjects with baseline CHD[b,c]	3529	1.15 (0.93,1.43)	1216	1.01 (0.69,1.47)	2045	1.16 (0.87,1.55)	875	1.02 (0.67,1.55)
Excluding subjects with severe comorbidity[a,d]	3512	1.15 (0.93,1.43)	1206	1.00 (0.68,1.47)	2033	1.16 (0.87,1.55)	868	1.02 (0.67,1.55)

[a] Excluding subjects with less than 3 years of follow-up
[b] Excluding subjects with less than 5 years of follow-up
[c] Excluding subjects with a prior diagnosis of coronary heart disease at baseline and restricted to cohorts that collected data on prior CHD diagnosis at baseline.
[d] Excluding subjects with a prior diagnosis of coronary heart disease, cancer, or stroke at baseline and restricted to cohorts that collected data on prior CHD diagnosis at baseline.
[e] Excluding subjects with a prior diagnosis of coronary heart disease, cancer, or stroke at baseline and restricted to cohorts that collected complete data on prior CHD, cancer, and stroke diagnosis at baseline. This analysis was not performed for the Indian & Bangladesh group since none of the cohorts in this population collected complete data on these comorbidity diagnoses at baseline.
[f] Deaths in the reference level are included in the proportional hazards model for both low and high BMI group analyses.
[g] HRs represent the incremental effect per BMI category from 22.6-25.0 to 20.1-22.5, 17.6-20.0, and 15.1-17.5 in the low BMI group analysis and 22.6-25.0 to 25.1-27.5, 27.6-30.0, 30.1-32.5, 32.6-35, and 35.1-50.0 in the high BMI group analysis. All models adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities.

Figure 1. Hazard ratios for the association between BMI and cause-specific mortality by ethnicity: the Asia Cohort Consortium BMI Project. Two figures are presented for each population (A and C for East Asians; B and D for Indians/Bangladeshis), one with and one without confidence interval bars. HRs were adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities and excluding subjects with less than three years of follow-up.

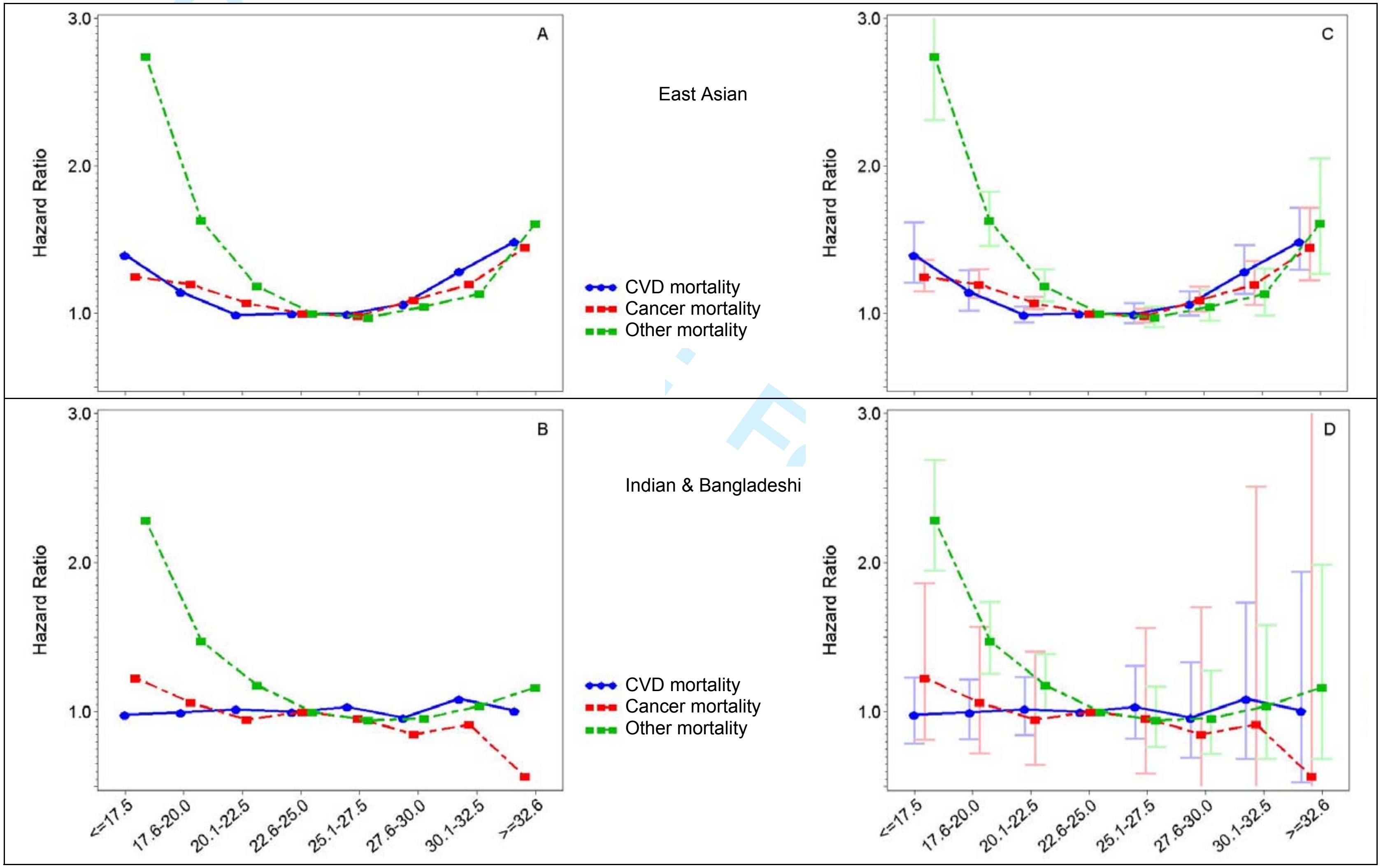
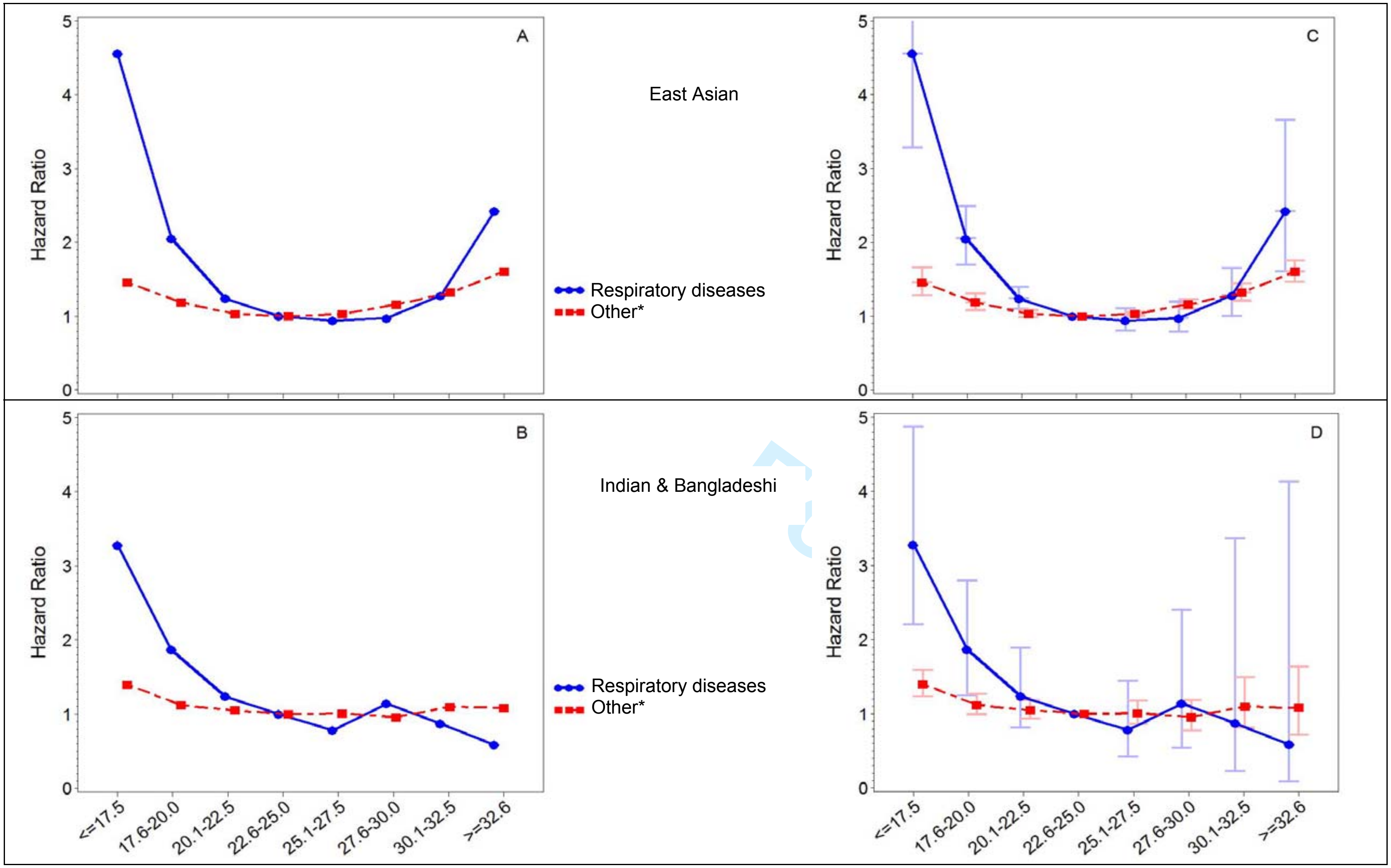


Figure 2. Hazard ratios (HR) for the association of BMI with mortality due to respiratory diseases or non-respiratory diseases, CVD, and cancer, the Asia Cohort Consortium BMI project. Two figures are presented for each population (A and C for East Asians; B and D for Indians/Bangladeshis), one with and one without confidence interval bars. HRs were adjusted for age, gender, education, urban/rural resident, marital status, and baseline comorbidities and excluding subjects with less than three years of follow-up.



*Excluding deaths due to respiratory diseases, CVD, and cancer.