Published by Oxford University Press on behalf of the International Epidemiological Association
© The Author 2005; all rights reserved. Advance Access publication 28 October 2005

International Journal of Epidemiology 2006;**35:**141–150
doi:10.1093/ije/dyi215

Body mass index and mortality from ischaemic heart disease in a lean population: 10 year prospective study of 220 000 adult men

Zhengming Chen,[1]* Gonghuan Yang,[2,3] Maigeng Zhou,[2] Margaret Smith,[1] Alison Offer,[1] Jieming Ma,[2,3] Lijun Wang,[2,3] Hongchao Pan,[1] Gary Whitlock,[1] Rory Collins,[1] Shiru Niu[2] and Richard Peto[1]

Accepted 15 July 2005

Background Increased body mass index (BMI) is known to be related to ischaemic heart disease (IHD) in populations where many are overweight (BMI $\geqslant$ 25 kg/m^2) or obese (BMI $\geqslant$ 30). Substantial uncertainty remains, however, about the relationship between BMI and IHD in populations with lower BMI levels.

Methods We examined the data from a population-based, prospective cohort study of 222 000 Chinese men aged 40–79. Relative and absolute risks of death from IHD by baseline BMI were calculated, standardized for age, smoking, and other potential confounding factors.

Results The mean baseline BMI was 21.7 kg/m^2, and 1942 IHD deaths were recorded during 10 years of follow-up (6.5% of all such deaths). Among men without prior vascular diseases at baseline, there was a J-shaped association between BMI and IHD mortality. Above 20 kg/m^2 there was a positive association of BMI with risk, with each 2 kg/m^2 higher in usual BMI associated with 12% (95% CI 6–19%, 2P = 0.0001) higher IHD mortality. Below this BMI range, however, the association appeared to be reversed, with risk ratios of 1.00, 1.09, and 1.15, respectively, for men with BMI 20–21.9, 18–19.9, and $<$18 kg/m^2. The excess IHD risk observed at low BMI levels persisted after restricting analysis to never smokers or excluding the first 3 years of follow-up, and became about twice as great after allowing for blood pressure.

Conclusions Lower BMI is associated with lower IHD risk among people in the so-called normal range of BMI values (20–25 kg/m^2), but below that range the association may well be reversed.

Keywords Body mass index, IHD, cohort study, epidemiology

Introduction

In populations, such as those in Europe and North America in which overweight and obesity is common, many prospective observational studies have investigated the associations between body fatness and the risk of ischaemic heart disease (IHD). For these investigations, body mass index [BMI: weight in kilogrammes divided by the square of height in metres, (kg/m^2)] has generally been used as an indirect but useful measure of adiposity, even though additional information is provided by other indices (such as waist and hip circumference, or subscapular skinfold thickness). Most of these studies[1–11] are consistent in demonstrating a strong positive association between BMI and the risk of IHD, at least among individuals with BMI $>$ 20 kg/m^2 at the start of the follow-up. Even within this range, however, questions remain about the magnitude of the risk associated with BMI in various different circumstances (e.g. at different ages, in different populations, and at different levels of other risk factors).[12] Moreover, below this range, there is substantial uncertainty about not only the strength but also the direction of the relationship. For, in Western populations,

[1] Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Radcliffe Infirmary, University of Oxford, UK.

[2] Disease Surveillance Points, Chinese Center for Disease Control, Beijing, PRC.

[3] Centre for Chronic Disease and Behaviour Risk Factors Surveillance, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, Beijing, PRC.

* Corresponding author. Clinical Trial Service Unit & Epidemiological Studies Unit, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK. E-mail: zhengming.chen@ctsu.ox.ac.uk

the proportion of apparently healthy adults who have BMI < 20 kg/m^2 is relatively small, and the Western studies did not separately record enough events at these lower levels of BMI to determine the shape of the association reliably.[1,4–6,10,11] To address these issues, large prospective studies involving at least a few thousand events are needed in leaner populations.[13,14] We report a prospective study of the association between BMI and IHD mortality in a nationally representative cohort of >220 000 Chinese men with mean BMI 21.7 kg/m^2 when the study started in 1990–91, whose mortality has been followed-up for 10 years.

Subjects and methods

Baseline survey

The study design, field survey methods, and participants have been described elsewhere.[15] Briefly, 45 areas throughout China were chosen at random from the 145 nationally representative Disease Surveillance Points (DSP) for a large national prospective study of the correlates of adult mortality. The Chinese DSP system, which covers ~1% of the population, was established during the 1980s by the Chinese Centre for Disease Control and Prevention (CDC: formerly the Chinese Academy of Preventive Medicine) to provide mortality statistics on both communicable and non-communicable disease for the entire country.[16,17] A typical surveillance point covers a defined population of ~50 000–100 000 residents in 4–8 geographically defined units (urban street committees or groups of rural villages). During 1990–91, all men aged >40 years in two or three randomly selected units from each of the 45 selected DSP sites were invited to participate in the survey. About 80% of those invited did participate, and the present report is of 10 year follow-up to January 1, 2002 among the 222 246 men aged 40–79 at the start of the study.

Health screening clinics were set up in each of the study areas, and all study participants were interviewed by trained health workers using a standardized questionnaire. Information obtained at the initial baseline survey included education, occupation, smoking habits, alcohol consumption, tea drinking, current and previous exposure to indoor air pollution (particularly by coal smoke), diet, and medical history. Height, weight, blood pressure, and peak expiratory flow rate were also measured for all participants. The primary factor of interest for the present analysis is BMI, for which data were available for all but 154 study participants (Table 1). After the baseline survey, no systematic information about weight changes was collected.

Annual follow-up for cause-specific mortality

Vital status was monitored on a regular basis by local DSP staff using official death certificates and local residential records. Causes of death were sought chiefly from official death certificates, supplemented (if necessary) by review of selected medical records. The underlying cause of each death was coded centrally, blinded to baseline information, by trained staff in the central DSP office, using the ninth revision of the World Health Organization International Classification of Disease (ICD-9). Nearly all adult deaths in the study areas involved some form of medical attention, and their underlying causes were then certified by a doctor. In rare situations (<5%) when death had occurred at home without prior medical attention, a special investigation with standard procedures was conducted by local DSP staff to determine the probable cause from the symptoms or signs described by the family members.[16,17] To minimize under-reporting of deaths and identify those who had permanently moved out of the study area, active confirmation of vital status for each study participant was also carried out separately once a year through local street committees or the administrators of individual villages.

Statistical analysis

Since it is often difficult to assign reliably underlying causes to deaths at older ages, all analyses are restricted to deaths occurring between ages 40 and 79, with censoring when men reached 80 years of age (or moved away from the original study area). In case pre-existing vascular disease had caused weight loss, thereby producing a spurious inverse association between BMI and IHD mortality, study participants who reported a history of heart disease or stroke at baseline were excluded from the main analyses. But, because obesity can cause hypertension or diabetes that then predisposes to IHD, these latter conditions (including medication for hypertension) were not used to exclude participants from the main analyses.

A stratified Cox proportional hazards model was used with BMI as the exposure variable and IHD death as the outcome.[18] The analyses were stratified by individual area and by age at risk, and were adjusted simultaneously for smoking (current/former/never) and alcohol drinking in most weeks (yes/no). All study participants were divided into six categories of baseline BMI (with cut-points at 18, 20, 22, 24, and 26 kg/m^2) and the hazard ratios for IHD mortality, which are referred to as risk ratios (RRs), were calculated for each category. The 95% confidence interval (CI) for each log RR was estimated using the 'floating absolute risk' method, which facilitates many different comparisons and tests for trend between different BMI categories, rather than

Table 1 Prevalences of underweight, overweight, and obesity among men aged 40–79 at 1990 baseline, classified according to WHO criteria of BMI levels

Age at baseline	No. of men[a]	Mean BMI (kg/m^2)	% Underweight (BMI $<$ 18.5)	% Normal (18.5 $\leqslant$ BMI $<$ 25)	% Overweight (BMI $\geqslant$ 25)
40–49	83 716	22.0	5.5	83.5	11.0
50–59	70 070	21.8	8.4	79.7	11.9
60–69	47 768	21.5	12.8	76.1	11.1
70–79	20 533	21.0	18.8	72.0	9.2
All men	222 092	21.7	9.2	79.7	11.1

[a] An additional 154 men were excluded from the analysis because of unknown (152) or extreme (2) BMI values (<10 or >50 kg/m^2) at the baseline survey.

just the pairwise comparisons between one arbitrarily chosen reference category and each of the other BMI categories considered singly.[19]

To allow for regression dilution bias,[20] the estimated RRs for each of the six baseline BMI categories (along with their 95% CIs) are plotted not against the mean baseline values in each category but against estimates of the mean usual values of these variables for each category. In the present study, it was not possible to estimate the mean usual values of BMI directly from the data as repeat measurements of weight and height were not available. Instead, it was assumed that the correlation between repeated measurements (i.e. the regression dilution ratio[20]) for each category would be similar to that seen in other studies, and a usual value was derived from the Prospective Studies Collaboration (PSC).[21] Weight and height are, however, easy to measure reliably and tend not to fluctuate substantially over a period of just a few years (the correlation between BMI measurements ~5 years apart being 0.90 in the PSC), so the effects of our correction for this bias were only marginal. In addition to the semi-parametric analyses described above that plotted disease risk against estimated mean usual BMI in each category, RRs were also calculated by fitting an inverse-variance-weighted regression line through the log RRs for selected BMI categories.

Results

After an average of 10 years of follow-up, 30 040 (13.5%) men had died between the ages of 40 and 79, and 13 832 men had survived to age 80, while 23 834 (10.7%) were known to have been lost to follow-up before age 80 (~1% per annum), mainly because of the demolition of entire residential areas for redevelopment. Those who were lost to follow-up were slightly younger than those who were not (53.1 vs 54.5 years), but had similar age-standardized mean BMI (21.9 vs 21.7 kg/m^2), systolic blood pressure (SBP) (123.4 vs 124.2 mm Hg), and prevalence of ever smoking (73.6% vs 73.3%) or of self-reported poor health status (7.2% vs 7.3%). Of the deaths recorded, 10 264 (34%) were attributed to cardiovascular disease (ICD-9 390–459 or 798), including 1942 (6.5%) from IHD (ICD-9 410–414) and 6435 (21.4%) from stroke (ICD-9 430–438). In urban areas the proportion of deaths attributed to IHD was 10.5% (676 deaths), compared with 5.4% (1266 deaths) in rural areas. Of the IHD deaths, 247 deaths occurred among men who had reported a history of heart disease or of stroke at the baseline survey, and are therefore excluded from the main analyses.

Relationship of baseline BMI with other key variables

The overall mean (SD) BMI was 21.7 (2.7) kg/m^2, decreasing slightly with increasing age (Table 1), and it was significantly higher among urban men (23.1) than among rural men (21.2) after adjustment for age. By standard WHO criteria,[22] 79.7% had weight within the desirable range (18.5–25 kg/m^2), whereas 11.1% were 'overweight' (10.3% with BMI = 25–30 kg/m^2 plus 0.8% with BMI > 30 kg/m^2) and 9.2% 'underweight' (BMI < 18.5 kg/m^2).

Table 2 shows the relationship of BMI with certain other variables among all men aged 40–79 at baseline, after standardizing for age (mean 54.3 years) and area. BMI was only slightly negatively related to height, whereas it was strongly positively related to body weight. For every 2 kg/m^2 higher BMI, the SBP was on average ~3 mm Hg higher. Men with higher BMI tended to be better educated and to have a higher peak expiratory flow rate, with higher proportions consuming alcohol, green tea, meat, fish, and fruit (but not milk). Although smoking was more prevalent among men with low BMI, no apparent association was found among smokers between BMI and the mean amount smoked per day (which means that the dose of tobacco per kg body weight was inversely related to BMI). Participants with lower BMI (especially those with BMI <18 kg/m^2) were more likely to report poor general health, but those with higher BMI were more likely to report diabetes, hypertension, heart disease, and stroke.

Association of BMI with IHD

Table 3 shows the relationship between measured BMI at baseline and the subsequent age-standardized mortality rate from IHD among participants without a prior history of vascular disease reported at baseline. The overall age-standardized IHD mortality rate was 7.7 per 10 000 person years (by contrast with 17.0 among men with pre-existing vascular disease), and there appeared to be a J-shaped association between BMI and IHD mortality (*P*-value for test of non-linearity across all six groups was 0.017), with a measured BMI in the range 20–21.9 kg/m^2 associated with the lowest risk after adjustment for age, locality, smoking, and alcohol drinking. Above this range, IHD mortality increases steadily with increasing BMI, with RRs of 1.12, 1.29, and 1.44, respectively, in the upper three BMI groups (*P*-value for trend between four groups <0.0001). Figure 1 indicates that the percentage difference in risk associated with a given absolute difference in usual BMI was similar across all levels of BMI > 20–21.9 kg/m^2, with each 2 kg/m^2 higher in usual BMI associated with a 12% (95% CI 6–19%, 2P = 0.0001) higher IHD mortality.

After adjustment for SBP in the Cox regression, each 2 kg/m^2 higher baseline BMI was associated with an 8% (95% CI 2–14%, 2P = 0.013) higher IHD mortality. However, the self-correlation of repeat measurements of SBP is expected to be much lower than the self-correlation of repeat measurements of BMI. In this population, each 3 mm Hg higher baseline SBP was associated with ~3.5% (95% CI 2–5%) higher IHD mortality (data available). If the self-correlation of repeat measurements of SBP was about one-half, then the relationship of usual SBP to risk would be about twice as steep as the relationship of a single measurement of SBP to risk.[20] Hence, a 3 mm Hg higher 'usual' SBP would be associated with ~7% (95% CI 4–10%) higher IHD mortality. Using this assumed relationship between risk and 'usual' SBP to adjust for blood pressure, the IHD RRs in the BMI range above 20–21.9 kg/m^2 were not significantly different from unity (Table 3).

This 7% increase in risk per 3 mm Hg higher usual SBP is somewhat weaker than that seen in largely European and North American populations (10% higher risk for every 3 mm Hg higher usual SBP),[23] suggesting that there may still be some underestimation of the relevance of usual blood pressure to the relationship between BMI and IHD.

Among men with baseline BMI < 20 kg/m^2, lower BMI was still associated with lower SBP (as well as diastolic BP) but not with lower IHD mortality—indeed, the association with IHD appeared to be reversed. Although the relative risk of death for BMI < 20 kg/m^2 was not significantly greater than that for BMI

Table 2 Characteristics of the participants by BMI category, all men aged 40–79 at baseline

Baseline characteristics[a]	BMI (kg/m^2) group at baseline						
	Total (222 092)	<18 (13 429)	18–19.9 (44 924)	20–21.9 (70 991)	22–23.9 (53 237)	24–25.9 (23 944)	≥26 (15 567)
Age (years)[a]	54.3	59.8	55.7	53.6	53.0	53.5	55.0
% Urban locality[a]	27.5	19.9	16.2	18.9	29.7	50.9	68.8
BMI (kg/m^2)	21.7	17.1	19.2	21.0	22.9	24.8	27.8
Height (m)	1.65	1.66	1.65	1.65	1.64	1.64	1.63
Weight (kg)	59.0	47.4	52.5	57.1	61.7	66.7	74.7
SBP (mm Hg)	124.1	119.1	121.2	123.2	125.0	127.6	133.0
DBP (mm Hg)	78.8	75.7	76.9	78.1	79.4	81.3	84.5
Peak flow (l/min)	395	355	380	396	405	410	412
≥6 year education (%)	33.0	32.7	31.2	32.1	33.6	35.9	36.7
Ever smoked (%)	73.3	78.5	76.9	74.8	71.1	68.9	65.8
Current smoker (%)	66.9	71.9	71.4	69.3	64.9	60.9	55.3
Tobacco per Smoker (g/day)	20.8	20.6	21.1	21.1	20.7	20.2	19.8
Alcohol drinking (%)	33.5	30.7	31.8	33.7	34.2	35.2	34.7
Green tea drinking (%)	31.5	31.0	30.6	30.6	31.2	34.0	36.7
Daily fresh vegetable (%)	94.8	94.3	94.4	94.8	95.0	95.0	94.9
Daily meat intake (%)	24.7	23.6	23.1	23.6	25.2	27.4	28.8
Daily fruit intake (%)	8.4	7.4	7.4	8.2	8.4	9.4	11.3
Weekly fish intake (%)	24.5	23.6	23.6	24.1	24.7	26.0	27.0
Weekly milk drinking (%)	8.2	9.4	8.8	8.3	8.4	7.7	4.6
Diabetes (%)[b]	0.5	0.5	0.4	0.4	0.5	0.9	1.3
Hypertension (%)[b]	4.9	2.2	3.1	3.5	4.6	8.0	15.4
Prior heart disease (%)[b]	3.8	4.2	3.6	3.4	3.4	4.6	6.9
Prior stroke (%)[b]	0.8	0.7	0.7	0.7	0.8	1.0	1.5
Self-rated poor health status (%)	7.3	14.9	8.8	6.8	5.5	5.9	6.8

[a] Except for mean age and urban locality, all other variables were adjusted for individual area and age by 5 year age group by direct standardization to the study population.

[b] Based on the self-reported prior history of hospital diagnosis. Those with prior heart disease or stroke are excluded from subsequent analyses.

Table 3 Number of deaths at ages 40–79 years, and age-standardized mortality rates from IHD, and adjusted RRs by baseline BMI category, for men without prior history of vascular diseases at baseline

Baseline BMI group (kg/m^2)	Estimated 'usual' BMI (kg/m^2)	No. IHD deaths	Mean age at death	Annual IHD mortality rate (1/10 000)	RR[a] (95% CI)	Mean SBP (mm Hg)	RR adjusted for mean SBP[b]
<18	17.5	118	69.7	9.4	1.15 (0.95–1.38)	118.9	1.27 (1.05–1.52)
18–19.9	19.4	337	67.3	6.7	1.09 (0.97–1.22)	120.9	1.15 (1.02–1.29)
20–21.9	21.1	474	66.4	7.1	1.00 (0.91–1.10)	122.9	1.00 (0.91–1.10)
22–23.9	22.9	406	65.0	8.2	1.12 (1.01–1.24)	124.6	1.07 (0.98–1.19)
24–25.9	24.7	203	65.8	9.4	1.29 (1.12–1.49)	127.2	1.16 (1.00–1.34)
≥26	27.5	157	65.5	10.8	1.44 (1.21–1.70)	132.4	1.15 (0.96–1.37)
Test for heterogeneity:					χ^2_5=19 (P = 0.002)		
Test for trend for groups 3–6:					χ^2_1 = 18 (P < 0.0001)		
RR for 2 kg/m^2 higher BMI above 20–22 kg/m^2 [c]					1.12 (1.06–1.19)		

[a] Estimated in a Cox proportional hazards model with covariates corresponding to smoking (current/former/never) and regular alcohol drinking (yes/no). All analyses were stratified by age at baseline and study areas.

[b] Assuming an RR of 1.07 per 3 mm Hg higher in usual SBP.

[c] Estimated from results for groups 3–6 only.

20–21.9 kg/m^2, it was significantly above a linear trend line through all BMI groups ($P = 0.017$ for non-linearity test), with relative risks of 1.09 (0.97–1.22) and 1.15 (0.95–1.38), respectively, for BMI 18–19.9 and BMI < 18 kg/m^2 (Table 3; Figure 1).

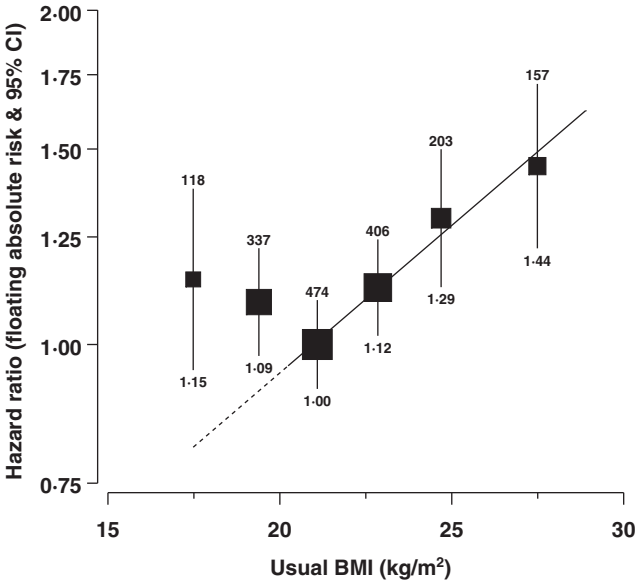

Figure 1 IHD hazard ratios vs usual BMI among men aged 40–79 with no history of cardiovascular disease at baseline. The hazard ratios are plotted on floating absolute scales, and each closed square has an area inversely proportional to the effective variance of the log of the hazard ratio and has a vertical solid line that represents the 95% CI. For BMI, the regression lines ignore the two left-hand points (i.e. those at BMI < 20 kg/m^2)

After allowing for usual SBP, the excess risk associated with BMI < 20 kg/m^2 was significant: 1.15 (1.02–1.29) and 1.27 (1.05–1.52; Table 3), respectively. To exclude the possibility that higher risk among individuals with BMI < 20 kg/m^2 could be a consequence of undiagnosed vascular disease (even though participants with a prior history of diagnosed vascular disease were excluded from the analyses), further analyses were carried out after excluding the first 3 years of follow-up, but the same pattern was still observed (Figure 2a). Likewise, exclusion of men with medication for hypertension or self-reported poor general health status at baseline did not materially alter the excess risk of IHD observed among men with BMI <20 kg/m^2, nor did further adjustment for the frequencies of meat, fish, fruit, and vegetable intake (data not shown).

In the present study, smoking was associated with a lower BMI and this was adjusted for in all the standard analyses (current/former/never). The amount smoked per smoker was largely unrelated to BMI (Table 2), so further adjustment for amount smoked made no material difference to the estimated RR. Likewise, a further analysis restricted to those men who reported never having smoked indicated a similar excess risk of IHD among those with BMI < 20 kg/m^2, though the CIs were wider owing to the relatively small number of IHD cases involved (Figure 2b).

About 13% of the men had a prior history of chronic obstructive pulmonary disease (COPD) at baseline. Those individuals had a lower baseline value of BMI and a much higher risk of subsequent death from COPD, which includes pulmonary heart disease. To limit the possible effects of any misclassification of pulmonary heart disease (which is relatively prevalent at the low end of the BMI distribution) as IHD, further analyses were conducted after excluding men with prior COPD

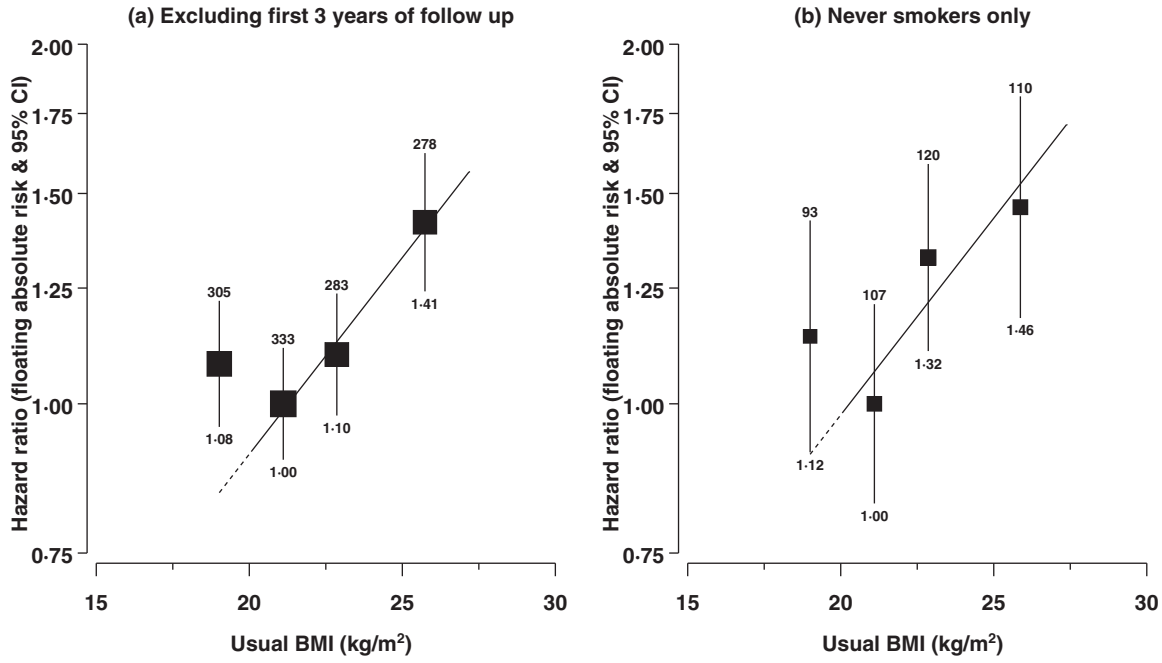

Figure 2 IHD hazard ratios vs usual BMI among men aged 40–79 with no history of cardiovascular disease at baseline, (a) excluding those who died during the first 3 years of follow-up, and (b) in never smokers. Conventions as in Figure 1. For both (a) and (b), those in the lowest and highest two categories were combined, so each figure has four groups with similar number of deaths

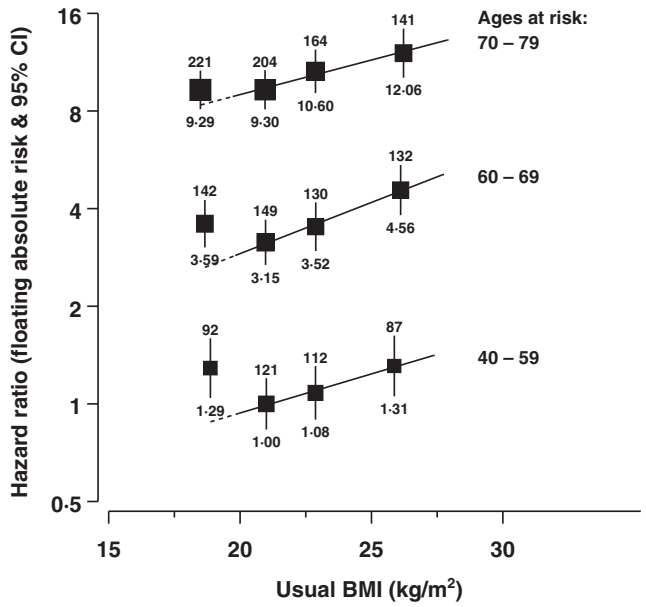

Figure 3 IHD hazard ratios at different age groups vs usual BMI among men with no history of cardiovascular disease at baseline. Conventions same as in Figure 1

and adjusting for peak flow rate. Again, however, the apparent excess risk of IHD among those with BMI of < 20 kg/m^2 remained almost unchanged (data not shown).

Associations of BMI with IHD risk in different categories of men

Figure 3 shows the associations of BMI with risk of IHD death separately for three age (at risk) groups. Among men with BMI >20 kg/m^2, there was a positive relationship between BMI and IHD risk in all three age groups. In Figure 4, the proportional effects associated with a 2 kg/m^2 difference in BMI appeared to be stronger at younger ages, although non-significantly (trend $\chi^2_1 = 2.7$; $P = 0.1$), which perhaps reflects the stronger relationship between blood pressure and IHD risk at younger ages.[23] Similarly, the excess risk of IHD death among men with BMI < 20 kg/m^2 appeared to be more pronounced at younger ages (29, 13, and 0%, respectively, for men aged 40–59, 60–69, and 70–79; $P = 0.2$ for trend), and would become more so after allowing for usual blood pressure.

Figure 4 also shows the strength of the association by locality of residence (urban/rural), smoking, alcohol drinking, and height among men with BMI > 20 kg/m^2. There was little evidence that the association of IHD death with BMI was significantly modified by any of these variables, although the statistical power to detect potentially important modifications is limited.

Discussion

This is by far the largest prospective study in China of the association between BMI and mortality from IHD, and it involves a nationally representative population of men. In this study, only 11% of the men were overweight or obese at baseline, by contrast with more than half in the USA or UK at these ages,[24,25] and throughout the range of BMI levels that were studied BMI was strongly positively related to blood pressure.

Direct association among people with BMI $>$ 20–22 kg/m^2

Among men without known history of vascular disease at baseline, there was a direct and positive association between BMI and IHD mortality that continued down to a BMI of ~20–21.9 kg/m^2. Among men with a BMI above this range, a 2 kg/m^2 higher in usual BMI corresponded on average to 12% higher IHD mortality. These effects, though moderate, appeared to be largely independent of age, smoking, and alcohol drinking, and were similar in urban and rural areas.

It has been suggested that East Asian populations may experience adiposity-related adverse health outcomes at lower BMI levels than Western populations, but these were based largely on cross-sectional or small prospective study data.[26,27] The results of this prospective study for men with BMI $>$ 20–21.9 kg/m^2 are largely compatible with those from large prospective studies in Western populations.[1–11] They are also consistent with results from other Chinese populations,[13,14] although none of those studies was nationally representative and, even collectively, they involved far fewer cases of IHD than the present study. In a meta-analysis of prospective studies from the Asia Pacific region,[28] involving just over 2000 non-fatal or fatal IHD (but including only ~200 IHD cases from 11 relatively small studies in China), the mean baseline BMI was ~24 kg/m^2 and it was positively associated with the risk of IHD (independently of age, smoking, and alcohol), with each 2 kg/m^2 higher BMI again being associated with ~12% (95% CI 10–14%) higher IHD risk. In the present study, as well as in these other studies, higher BMI was associated with higher IHD risk not only for people who would conventionally be regarded as overweight but also for many people in the so-called normal range of BMI values (20–25 kg/m^2).[22]

There continues to be some uncertainty as to how much of these adverse effects of BMI on IHD risk can be accounted for by its adverse effects on blood pressure, blood lipids, and diabetes.[29–34] In the present study blood lipids were not measured, but about half of the adverse effect of BMI on IHD in the range >20 kg/m^2 could be accounted for by its adverse effect on blood pressure. Other studies have found that BMI is also associated with adverse changes in LDL and HDL cholesterol (and, perhaps less importantly in this population, diabetes) that have not been allowed for in the present analyses. Consequently, the adverse association of higher BMI with IHD risk in the range >20 kg/m^2 can probably be largely or wholly explained by its adverse associations with blood pressure, blood lipids, and diabetes.

Possible IHD risk threshold at BMI of ~20–21.9 kg/m^2

There has been inconsistent evidence from previously published studies in Western populations as to whether there is a threshold of BMI below which lower levels of BMI are no longer associated with lower risks of IHD. Some studies have reported evidence of such a threshold,[1,5,6,10,35] with the reported thresholds ranging from as high as 27 kg/m^2 [10] to as low as 20 kg/m^2,[1,35] whereas others have reported no such threshold.[4,11] The fundamental problem with most previous studies has been the relatively small number of IHD cases at low BMI values (owing to the small number of participants with low BMI in Western populations),

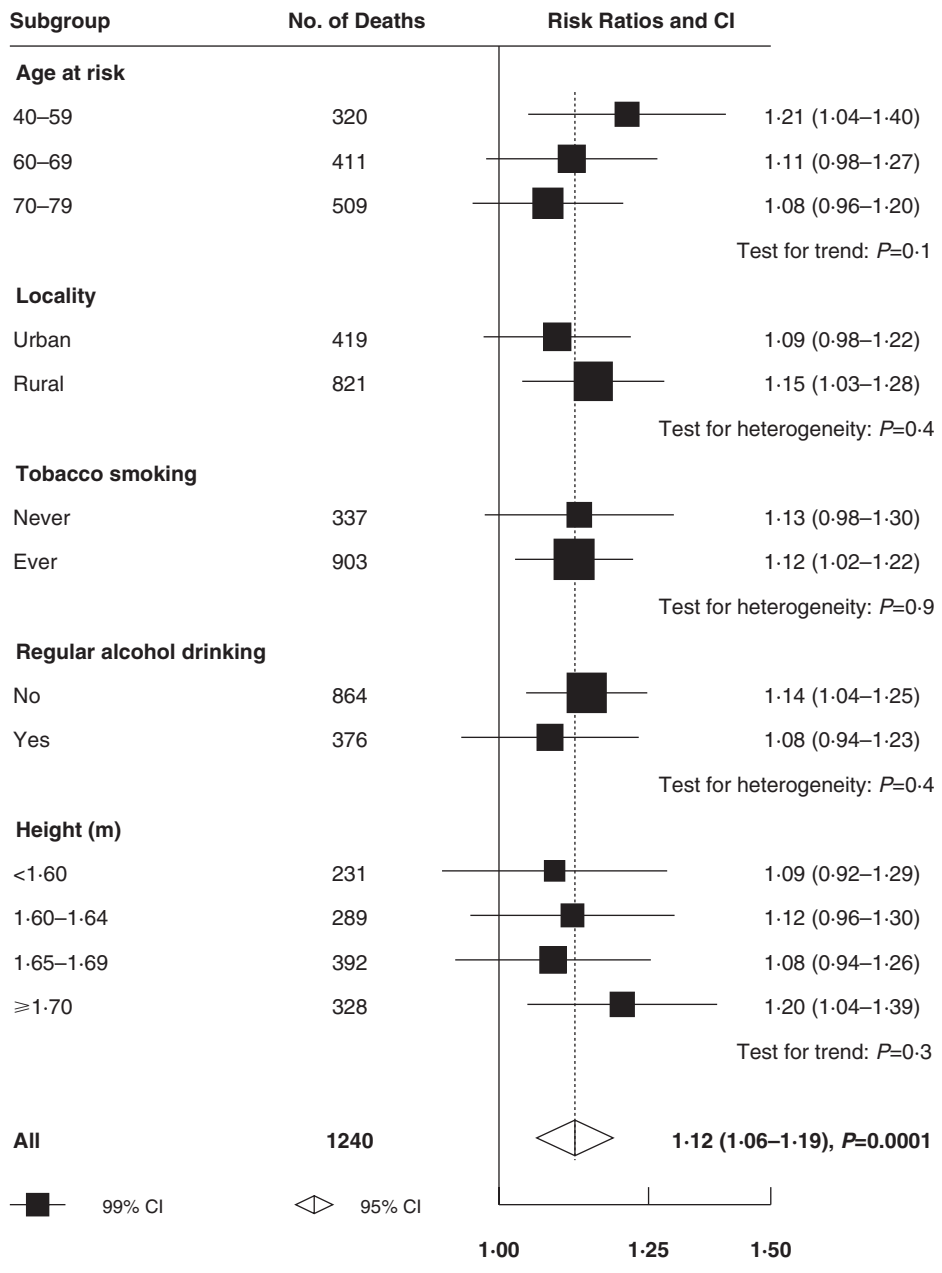

Figure 4 IHD rate ratio associated with a 2 kg/m^2 higher usual BMI among men with baseline BMI of at least 20 kg/m^2 and with no history of cardiovascular disease at baseline. Each closed square representing a rate ratio (RR) with the size of the area inversely proportional to the variance of the log RR. The dotted vertical line indicates the overall RR, and open diamonds indicates it and its 95% CI

so that the shape of the association at the low end of the BMI distribution was susceptible to large random fluctuations. The present study involves substantial number of IHD deaths among men whose BMI was <20 kg/m^2, thus providing statistically reliable evidence that the relationship does not continue linearly downwards and may even be reversed among those who are underweight.

The main analyses were restricted to those without a prior history of vascular diseases and were adjusted for various other factors, so the observed excess risk of IHD death, in comparison with what would have been extrapolated from linear downwards of the relationship at higher BMI levels, is not accounted for by chance or by prior vascular disease affecting BMI at baseline. This apparent excess risk is not attributable to misclassification of COPD-related pulmonary heart disease, or to residual confounding by smoking. The excess risk of IHD death at BMI < 20 kg/m^2 given usual SBP is unexplained, and it would probably be even more extreme given not only usual blood pressure but also usual levels of blood lipids. It is, however, not necessarily causal.

Potential mechanisms for excess risk at BMI < 20 kg/m^2

The higher IHD risk associated with low BMI could represent a combination of various other factors. For example, a very low BMI in the absence of chronic illness may be a consequence of consuming a very restricted diet for a prolonged period of time, resulting not only in diminished fat stores but also in an inadequate supply of some important cardioprotective nutrients. In Western populations, individuals with extremely low body weight (such as patients with anorexia nervosa and bulimia, or those undergoing strict diet restriction) are at increased risk of several cardiovascular abnormalities, including reduction of ventricular mass, valvular dysfunction,[36] electrocardiographic changes,[37] and damage of the myocardial fibres.[38] Some chronic infections may also contribute to the development of IHD,[39–43] and individuals with extremely low body weight may have reduced immune function,[44,45] which might predispose them to increased risk of chronic infection. Moreover, severe loss of adipose tissue and its triglyceride storage capacity (as in lipodystrophy) can lead to insulin resistance, diabetes, hyperlipidaemia and fatty liver, which have the effects that are similar to some of those caused by obesity.[46] Finally, in Western studies of acute MI, patients with very low BMI have worse survival in hospital than those with a higher BMI.[47,48] If this was also the case in Chinese MI patients, then this might help explain the higher IHD mortality associated with very low BMI in this prospective study.

Implications

The present study involves large numbers of IHD deaths, so its findings are statistically reliable. The positive association between BMI and IHD death at BMI levels >20 kg/m^2 can largely or wholly be explained by the association of BMI with blood pressure and, most probably, blood lipids. But, although the association between BMI and blood pressure continues downwards at lower levels of BMI, the risk of IHD death does not continue down linearly—indeed, after adjustment for blood pressure, the risk is somewhat greater for those with BMI < 20 than for those with BMI = 20–21.9 kg/m^2. Further epidemiological studies with collection of blood samples, perhaps using additional measures of adiposity (such as waist circumference and bioelectrical impedance[49–51]), in low BMI populations may help elucidate mechanisms by which extremely low BMI increases the risk of IHD at given levels of blood pressure and blood lipids.

The present findings among those with BMI levels >20 kg/m^2 cannot be translated directly into public health conclusions about the relevance of elevated BMI to overall mortality in China, as IHD accounted for only 6.5% of all the deaths in this study, and some non-IHD causes of death are inversely related to BMI. The BMI values associated with minimum overall mortality may vary from population to population, depending on the particular BMI distributions and the background rates of mortality from IHD and other diseases.[52]

Acknowledgements

The original survey and subsequent follow-up were supported by the Chinese Ministry of Health; the UK Medical Research Council, British Heart Foundation and Cancer Research UK; the World Bank loan to China; and the Canadian International Development Research Centre. We thank Gonghao Wang and Xinzhou He for their collaboration in the initial survey, the China DSP staff for their continuing effort and cooperation with long-term follow-up of study participants, and Peilong Liu, Chunming Chen, Richard Bumgarner, and Don de Savigny for help getting funding for the initial survey.

KEY MESSAGES

- In this relatively lean male Chinese population, there is a positive and direct relationship between BMI and IHD mortality in the so-called normal range of BMI values (20–25 kg/m^2).
- About half of the adverse effect of BMI on IHD in the range >20 kg/m^2 could be accounted for by its adverse effect on blood pressure.
- For BMI < 20 kg/m^2, the association with IHD risk is reversed, which does not appeared to be caused by confounding or other bias, and became more extreme after allowing for blood pressure.
- As IHD accounted for only ~7% of all the deaths in the study, the present study findings cannot be translated directly into public health conclusions about the optimal levels of BMI in the population.

References

[1] Willett WC, Manson JE, Stampfer MJ *et al*. Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. *JAMA* 1995;**273:**461–65.

[2] Jarrett RJ, Shipley MJ, Rose G. Weight and mortality in the Whitehall Study. *Br Med J* 1982;**285:**535–37.

[3] Hubert HB, Feinleib M, McNamara PM, Castelli WB. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;**67:**968–77.

[4] Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. *Br Med J* 1997;**314:**1311–17.

[5] Seidell JC, Verschuren WM, van Leer EM, Kromhout D. Overweight, underweight and mortality. A prospective study of 48,287 men and women. *Arch Intern Med* 1996;**156:**958–63.

[6] Jousilahti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P. Body weight, cardiovascular risk factors and coronary mortality. 15-year follow-up of middle-aged men and women in eastern Finland. *Circulation* 1996;**93:**1372–79.

[7] Rimm EB, Stampfer MJ, Giovannucci E *et al*. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. *Am J Epidemiol* 1995;**141:**1117–27.

[8] Baik I, Ascherio A, Rimm EB *et al*. Adiposity and mortality in men. *Am J Epidemiol* 2000;**152:**264–71.

[9] Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. *Int J Obes Relat Metab Disord* 2001;**25:**1047–56.

[10] Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. A prospective population study. *Eur Heart J* 1999;**20:**269–77.

[11] Singh PN, Lindsted KD, Fraser GE. Body weight and mortality among adults who never smoked. *Am J Epidemiol* 1999;**150:**1152–64.

[12] Whitlock G, Lewington S, Mhurchu CN. Coronary heart disease and body mass index: A systematic review of the evidence from larger prospective cohort studies. *Seminars in Vascular Medicine*. 2002;**2:** 369–81.

[13] Yuan JM, Ross RK, Gao YT, Yu MC. Body weight and mortality: a prospective evaluation in a cohort of middle-aged men in Shanghai, China. *Int J Epidemiol* 1998;**27:**824–32.

[14] Zhou BF, Wu Y, Yang J, Li Y, Zhang HY, Zhao L. Overweight is an independent risk factor for cardiovascular disease in Chinese populations. *Obes Rev* 2002;**3:**147–56.

[15] Niu SR, Yang GH, Chen ZM *et al*. Emerging tobacco hazards in China: II. Early mortality results from a prospective study. *Br Med J* 1998;**317:**1423–24.

[16] Chinese Academy of Preventive Medicine. *Annual Report on Chinese Diseases Surveillance Points*. Beijing: Hua Xia Press, 1991.

[17] Yang GH, Murray CJL, Zhang Z. *Exploring Adult Mortality in China: Levels, Patterns and Causes*. Beijing: Hua Xia Press, 1991.

[18] Cox DR. Regression models and life-tables. *J R Stat Soc [Ser B]* 1972;**34:**187–220.

[19] Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med* 1991;**10:**1025–35.

[20] Clarke R, Shipley M, Lewington S *et al*. Underestimation of risk associations due to regression dilution in long-term follow-up of prospective studies. *Am J Epidemiol* 1999;**150:**341–53.

[21] Prospective Studies Collaboration. Collaborative overview ('meta-analysis') of prospective observational studies of the associations of usual blood pressure and usual cholesterol levels with common causes of death: protocol for the second cycle of the Prospective Studies Collaboration. *J Cardiovasc Risk* 1999;**6:**315–20.

[22] World Health Organisation. *Physical Status: The use and interpretation of anthropometry*. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;**854:**1–452.

[23] Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**360:** 1903–13.

[24] Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002;**288:**1723–27.

[25] Seidell JC. The epidemiology of obesity. In: Björntorp P (ed.) *International Textbook of Obesity*. Chichester, John Wiley, 2001, pp. 23–29.

[26] Deurenberg P, Deurenberg-Yap M, Curicci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes Rev* 2002;**3:**141–46.

[27] Ko GTC, Tang J, Chan JCN *et al*. Lower BMI cut-off value to define obesity in Hong Kong Chinese: an analysis based on body fat assessment by bioelectrical impedance. *Br J Nutr* 2001;**85:** 239–42.

[28] Asia Pacific Cohort Studies Collaboration. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *In J Epidemiol* 2004;**31:** 1–8.

[29] Cassano PA, Rosner B, Vokonas PS, Weiss ST. Obesity and body fat distribution in relation to the incidence of non-insulin-dependent diabetes mellitus: a prospective cohort study of men in the normative aging study. *Am J Epidemiol* 1992;**136:**1474–86.

[30] Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. *Am J Epidemiol* 1997;**146:**214–22.

[31] Stamler R, Stamler J, Riedlinger WF, Algera G, Roberts RH. Weight and blood pressure. Findings in hypertension screening of 1 million Americans. *JAMA* 1978;**240:**1607–10.

[32] Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;**97:**1837–47.

[33] McGill HC Jr, McMahan CA, Herderick EE *et al*. Obesity accelerates the progression of coronary atherosclerosis in youth. *Circulation* 2002;**105:**2712–18.

[34] Grundy SM. Obesity, metabolic syndrome and coronary atherosclerosis. *Circulation* 2002;**105:**2696–98.

[35] Thorogood M, Appleby PN, Key TJ, Mann J. Relation between body mass index and mortality in an unusually slim cohort. *J Epidemiol Community Health* 2003;**57:**130–33.

[36] de Simone G, Scalfi L, Galderisi M *et al*. Cardiac abnormalities in young women with anorexia nervosa. *Br Heart J* 1994;**7:**287–92.

[37] Swenne I. Heart risk associated with weight loss in anorexia nervosa and eating disorders: electrocardiographic changes during the early phase of refeeding. *Acta Paediatr* 2000;**89:**447–52.

[38] Garnett ES, Barnard DL, Ford J, Goodbody RA, Woodehouse MA. Gross fragmentation of cardiac myofibrils after therapeutic starvation for obesity. *Lancet* 1969;**1:**914–16.

[39] Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link. *Lancet* 1997;**350:**430–36.

[40] Shor A, Phillips JI. Chlamydia pneumoniae and atherosclerosis. *JAMA* 1999;**282:**2071–73.

[41] Epstein SE, Zhou YF, Zhu J. Infection and atherosclerosis: emerging mechanistic paradigms. *Circulation* 1999;**100:**e20–28.

[42] Zhu J, Nieto FJ, Horne BD, Anderson JL, Muhlestein JB, Epstein SE. Prospective study of pathogen burden and risk of myocardial infarction or death. *Circulation* 2001;**103:**45–51.

[43] Kiechl S, Egger G, Mayr M *et al*. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. *Circulation* 2001;**103:**1064–70.

[44] Marcos A, Varela P, Toro O *et al*. Interactions between nutrition and immunity in anorexia nervosa: A 1-y follow-up study. *Am J Clin Nutr* 1997;**66:**485S–490S.

[45] Field CJ, Gougeon R, Marliss EB. Changes in circulating leukocytes and mitogen responses during very-low-energy all-protein reducing diets. *Am J Clin Nutr* 1991;**54:**123–29.

[46] Garg A. Acquired and inherited lipodystrophies. *N Engl J Med* 2004;**350:**1220–34.

[47] Ness AR, Gunnell D, Hughes J, Elwood PC, Davey Smith G, Burr ML. Height, body mass index, and survival in men with coronary disease: follow up of the diet and reinfarction trial (DART). *J Epidemiol Community Health* 2002;**56:**218–19.

[48] Lee KL, Woodlief LH, Topol EJ *et al*. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results

from an international trial of 41,021 patients. *Circulation* 1995;**91:** 1659–68.

[49] Allison DB, Faith MS, Heo M, Kotler D. Hypothesis concerning the U-shaped relation between body mass index and mortality. *Am J Epidemiol* 1997;**146:**339–49.

[50] Prentice AM, Jebb SA. Beyond body mass index. *Obes Rev* 2001;**2:** 141–47.

[51] Jebb SA, Cole TJ, Doman D, Murgatroyd PR, Prentice AM. Evaluation of the novel Tanita body-fat analyser to measure body composition by comparison with a four-compartment model. *Br J Nutr* 2000;**83:** 115–22.

[52] Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. *N Engl J Med* 1999;**341:**1097–105.