Clinical Medicine: Endocrinology and Diabetes

REVIEW

The Impact of Obesity on Adverse Cardiovascular Outcomes in the General Population and in Patients with Type 2 Diabetes

Jayne Palmer[1], Anupama Kalsekar[2], Kristina Boye[2] and Gordon Goodall[1]

[1]IMS Health, Gewerbestrasse 25, CH-4123, Switzerland. Tel: +41 61 38307 58, Fax: +41 61 383 07 59. [2]Eli Lilly and Co, Indianapolis, USA.

Abstract

Objectives: There is an established causal link between obesity and cardiovascular outcomes. The aim of this review was to determine whether an independent relationship exists between anthropometric measurements of weight (typically body mass index [BMI]) and cardiovascular outcomes (e.g. angina, myocardial infarction, congestive heart failure, stroke, and mortality due to cardiovascular disease) in the general population and in patients with type 2 diabetes.

Methods: A review of the medical literature published between 1988 and May 2008 was conducted using the PubMed, EMBASE, Cochrane and Center for Review and Dissemination databases. Studies longer than 12 months, with ≥500 adult subjects and published in English were included.

Results: In studies conducted in general populations there was an overall trend towards increased risk for adverse cardiovascular outcomes with increasing BMI. The nature and strength of this relationship varied according to the measurement used (e.g. BMI, waist circumference, waist-to-hip ratio) and the population studied, with notable differences observed in Asian/Asia-Pacific compared with European or North American-based studies. However, data from diabetes-specific populations are limited.

Conclusions: In general, the degree of being overweight or obese was associated with an elevated risk of adverse cardiovascular events and mortality. Although inextricable links exist between obesity, type 2 diabetes and cardiovascular disease in the general population, the extent to which findings can be extrapolated to a diabetes-specific population is limited.

Keywords: obesity, body mass index, type 2 diabetes, cardiovascular disease

Clinical Medicine: Endocrinology and Diabetes 2009:2 43–69

This article is available from http://www.la-press.com.

Introduction

Type 2 diabetes and obesity both represent significant, and growing, global public health problems. Recent estimates suggest that in the region of 900 million to 1.6 billion adults worldwide are classified as overweight (body mass index [BMI] $\geq$ 25 kg/m^2) and that approximately 400 million adults are obese (BMI $\geq$ 30 kg/m^2).[1,2] Moreover, by the year 2015 the World Health Organization (WHO) project that these figures will rise to approximately 2.3 billion overweight and 700 million obese adults[1] and by 2030 (assuming current secular trends continue) Kelly et al estimate the global prevalence of overweight and obesity will be 2.16 billion and 1.12 billion, respectively.[2] The estimated prevalence of diabetes is equally alarming; Wild et al[3] estimated a global prevalence of 171 million in 2000 rising to 366 million in 2030, with the number of diabetes-related deaths projected to increase by more than 50% over the next 10 years.[1] Notably, the projections of Wild et al,[3] assume no increase in the prevalence of obesity and may therefore represent a conservative scenario.

Type 2 diabetes and obesity were once generally considered to be health problems that existed almost exclusively within high-income Westernized countries. However, the burden of diabetes and obesity is increasing at an alarming rate in many low- and middle-income countries and it is estimated that by 2025 three quarters of all people with diabetes will reside in developing countries.[4] Moreover, type 2 diabetes and obesity share a number of common etiological factors and a large part of the ever increasing burden of both conditions has been attributed to a shift towards an increased intake of energy dense foods with a high fat and sugar content combined with increasingly sedentary lifestyles.[1] A number of studies have shown that obesity is an independent risk factor for the development of type 2 diabetes[5–8] and in the US an estimated 60%–80% of diabetes patients are classified as abdominally obese.[9] Additionally, type 2 diabetes is an established risk factor for cardiovascular disease and it is estimated that individuals with diabetes are 2–6 times more likely to die from cardiovascular causes compared with those without diabetes.[10] Given the intricate nature of the association between obesity and cardiovascular disease and type 2 diabetes it is generally assumed that obesity should be associated with an elevated risk of cardiovascular disease in patients with type 2 diabetes. However, there is a general paucity of data from long-term longitudinal studies that examine the link between anthropometric measurements of overweight/obesity and cardiovascular events specifically within type 2 diabetes populations. We performed a literature review with the primary objective of elucidating whether BMI or other anthropometric measurements of body weight and adiposity are independent risk factors for cardiovascular events in patients with type 2 diabetes. However, owing to the lack of data from diabetes-specific populations the review also examined studies conducted in general populations, where studies were examined to ascertain whether diabetes was adjusted for as a covariate.

Methods

A literature search was performed in May 2008 to identify English language articles published within the last 20 years relating to the association between obesity and cardiovascular outcomes. Specifically, studies reporting results in terms of clinically relevant endpoints rather than association between risk factors were sought. Searches were performed using PubMed, MEDLINE, EMBASE, the Cochrane database, and the Center for Review and Dissemination databases. We included observational, prospective and retrospective longitudinal studies performed in adults (both single sex and mixed sex studies as well as studies performed in populations with pre-existing cardiovascular conditions were included); pooled- and meta-analyses were also included. Additionally, studies were required to have in excess of 500 patients and if reference to a follow-up period was made in the article this was required to be longer than 12 months. In addition to the online literature searches, reference sections of retrieved articles were examined in order to identify additional relevant articles. Article titles and abstracts were initially reviewed followed by full-text review where necessary. Owing to the overlapping nature of cardiovascular endpoints used, for example, coronary heart disease (CHD) and myocardial infarction (MI); where CHD was often specifically defined as non-fatal MI or death from CHD, and also to avoid potential misinterpretation of findings, studies were classified and are discussed according to endpoints as presented in the articles.

Results

The literature review identified a total of 51 studies that were examined in detail (Table 1). Endpoints assessed in these studies included incidence of MI (n = 9), angina (n = 1) ischemic heart disease (IHD; n = 2), incidence of and mortality from CHD (n = 11), heart failure and outcomes in patients with existing heart failure (n = 4) and overall incidence/prevalence of cardiovascular disease and mortality due to cardiovascular disease (n = 20).

Myocardial infarction and ischemic heart disease

Overall, a total of eight studies reported here examined the relationship between overweight/obesity and the incidence of MI, IHD or angina[11–17] (one study investigated the link between obesity and age at incidence of MI).[18] In addition, five studies investigated the relationship between obesity and endpoints including recurrent MI, overall mortality and CHD mortality in patients with previous MI.[19–23] All studies reported here that examined the link between overweight/obesity and MI, angina or IHD used BMI as an index of obesity; however, a substantial proportion of studies also used other indices of obesity including waist-to-hip ratio (WHR), waist circumference (WC) and visceral adipose tissue area.

Overall, there was a general trend towards a positive association between increased BMI and elevated risk for MI, although in some studies the strength of the association was such that it was not statistically significant. In a study of over 20,000 men enrolled in the Physician's Health Study Rexrode et al[11] reported a significant association between increasing BMI, by quintile, and the risk of MI (Table 1). Men in the highest BMI quintile (≥27.6 kg/m^2) had a relative risk (RR) for MI of 2.52 compared with men with a BMI < 22.8 kg/m^2. The association between BMI and risk for MI was apparent (and statistically significant) following adjustment for risk factors including smoking, history of MI, alcohol consumption, physical activity and WHR quintile. However, these data were not adjusted for diabetes and Rexrode et al[24] note that the men enrolled in the Physician's Health Study were generally healthier and had lower rates of obesity compared with the general population, which in turn, limits the interpretation of these results in a general population.

A graded association between increased BMI and the risk of MI was also observed in a large case-control study conducted by Yusuf et al[13] although this association became non-significant following adjustment for other risk factors including activity, alcohol use, diet, smoking, history of hypertension and history of diabetes. However, the authors reported a significant association between increased WHR and elevated risk for MI that remained following adjustment for other risk factors. Further, not only do these findings suggest that WHR may be a better predictor for MI risk compared with BMI, Yusuf et al also postulate that the reliance on BMI as a anthropometric measure may lead to an underestimation of the global burden of obesity, particularly in the Middle East and South and Southeast Asia.[13]

In a study of 2,503 elderly men and women Nicklas et al[12] observed a non-significant relationship between a 4.90 kg/m^2 increase in BMI and risk of MI, although in women a significant relationship was evident between visceral adipose tissue area and the risk of MI. Interestingly, using data collected from the Framingham Heart Study Wilson et al[17] reported that overweight women had a lower risk of MI compared with normal weight women (BMI 18.5–24.9 kg/m^2) but obese women had an elevated relative risk RR (95% confidence interval [CI]) of 1.46 (0.94–2.28) compared with normal weight women (following adjustment for risk factors including diabetes, smoking, hypertension and hypercholesterolemia). In men, Wilson et al[17] reported a lower risk of MI for obese men compared with overweight men (although both categories had an elevated risk for MI compared with men with a BMI in the normal range). In the same study the authors also investigated the risk for angina and reported an increased risk for angina with increasing BMI (following multivariate adjustment, including for diabetes) in both men and women. In common with many investigators, Wilson et al excluded underweight (BMI <18.5 kg/m^2) subjects from their analysis—stating that this group typically contains a high proportion of heavy smokers, and subjects with severe chronic disease or malignancies.

Newton and LaCroix[19] examined the rate of reinfarction following first MI in women and reported a 5% increase in the risk of reinfarction per unit increase in BMI, although this association was attenuated, but not eliminated, following adjustment for

Table 1. Summary findings of studies examining the relationship between anthropometric indices of obesity and cardiovascular endpoints.

References	Study details	Main endpoints	Summary of main findings
Ajani et al[46]	Cohort study in 85,078 male physicians aged 40 to 84 years in the US with no history of myocardial infarction, angina pectoris, stroke, transient ischemic attack, cancer, liver disease, or renal disease were enrolled. Examined relationship between BMI and mortality with 5 years of follow-up.	All cause mortality and cardiovascular mortality	In multivariate adjusted analysis of the total cohort U/J-shaped relationship was evident between increasing BMI and mortality. Multivariate RR for cardiovascular mortality in male physicians aged 40–84 years: BMI $<$ 20 = 1.50 BMI 20–22.4 = 0.86 BMI 22.5–24.9 = 1.00 (reference) BMI 25.0–27.4 = 1.16 BMI 27.5–29.9 = 1.24 BMI $\geq$ 30 = 1.92 Data adjusted for age, alcohol intake and physical activity.
Asia Pacific Cohort Studies Collaboration[14]	Pooled analysis of six cohort studies in a total of 45,988 men and women in the Asia Pacific region. Assessment of association of ischemic heart disease with obesity with a mean of 6 years of follow-up.	IHD and stroke	A 1 SD increase in indices of obesity (BMI, WC, WHR and hip circumference) was associated with an increased risk for IHD. A 1 SD increase in index was associated with the following increases in risk (95% CI) for IHD: BMI = 17% (7%–27%) WC = 27% (14%–40%) Hip circumference = 10% (1%–20%) WHR = 36% (21%–52%)
§Bender et al[27]	Analysis from a prospective cohort study of 6,192 obese men and women (BMI $\geq$ 25) aged 18 to 75 years referred to an obesity clinic in Germany. Assessing causes of death in obesity with a median of 14.8 years of follow-up.	All cause mortality and mortality from predefined diseases including CVD and diabetes	Obesity was associated with increased risk of death from CVD and diabetes in men and women Standardized mortality ratios (95% CI), compared with the German Population, for men (BMI $\geq$ 25) CV disease = 2.21 (1.91–2.54) Cardiac dysrhythmias and heart failure = 15.57 (10.58–22.10) Standardized mortality ratios (95% CI) for women (BMI $\geq$ 25) CV disease = 1.62 (1.45–1.82) Cardiac dysrhythmias and heart failure = 8.81 (6.45–11.75)
§Bibbins-Domingo et al[26]	Prospective cohort study investigating heart failure in 2,391 post-menopausal women ($<$79 years) in the US with established coronary disease. Assessing link between BMI and heart failure with 6.3 years of follow-up.	Incident heart failure defined by hospital admission or death from heart failure	Women with diabetes and also women with a BMI $>$ 35 kg/m^2 were at a significantly elevated risk for heart failure. Adjusted HRs (95% CI) for development of heart failure: Diabetes = 3.1 (2.3–4.2; P $<$ 0.001) BMI 25–30 = 1.2 (0.8–2.7; P = 0.34) BMI 30–35 = 1.2 (0.8–2.0; P = 0.34) BMI $>$ 35 = 1.9 (1.1–3.0; P = 0.01)

Calling et al[69]	Study in 26,942 men and women aged 45 to 73 in Sweden with no history of CVD. Assessment of body fat of CVD incidence and mortality with a mean of 7 years follow-up.	Incidence of coronary events, ischemic stroke and CVD mortality	Percentage body fat was a risk factor for coronary events, ischemic stroke and cardiovascular disease mortality. For men risk of coronary events and CVD increased with % body fat. RR (95% CI) of coronary events for highest quartile of % body fat = 1.37 (1.07–1.74) in men and 2.28 (1.50–3.46) in women compared with lowest quartile. Significant association between % bodyfat, stroke and incidence of coronary events in women.
Canoy et al[37]	Study of 25,408 men and women aged 45 to 79 years. Examining association between BMI and CHD with a mean of 9.1 years of follow-up.	CHD	BMI predictive of CHD, but risk estimates attenuated if fat distribution, biological mediating factors, and prevalent disease were considered. Indices of abdominal obesity were more consistently and strongly predictive of CHD than BMI HR (95% CI) for CHD for top versus bottom quintile: WHR = 1.55 (1.28–1.73) for men and 1.91 (1.44–2.54) for women. Significant trend for increased CHD with BMI in men ($P < 0.001$) and women ($P < 0.001$); significant trend for increased CHD with increasing WC in men ($P = 0.027$) and women ($P \leq 0.001$).
Curb and Marcus[32]	Prospective study of 8,006 Japanese-American men in Hawaii, examining relationship between body fat, stroke and CHD with 20 years of follow-up.	Stroke and CHD	BMI (and other indices of obesity) were predictors for CHD and remained predictive for CHD following multivariate adjustment. RR for developing CHD by BMI quintile: Q1(mean BMI = 19.6) = 1.0 Q2 (mean BMI = 22.1) = 1.2 Q3 (mean BMI = 23.7) = 1.3 Q4 (mean BMI = 25.4) = 1.4 Q5 (mean BMI = 28.2) = 1.6
§Curtis et al[29]	Study of 7,767 men and women with heart failure in the US and Canada. Assessing link between BMI and outcomes in patients with heart failure with 3 years of follow-up.	Mortality (all cause, cardiovascular and due to heart failure), hospitalization (all cause and for worsening heart failure)	Overweight and obesity associated with lower relative risk for overall mortality and lower mortality due to heart failure and hospitalization due to worsening heart failure Adjusted RRs (95% CI) for adverse outcomes: CV death: Underweight = 0.88 (0.65–1.19) Healthy = 1.00 Overweight = 0.86 (0.78–0.95) Obese = 0.82 (0.72–0.94) Death from worsening heart failure: Underweight = 0.86 (0.56–1.32) Healthy = 1.00 Overweight = 0.79 (0.68–0.92) Obese = 0.82 (0.66–1.01)

(*Continued*)

Table 1. (*Continued*)

References	Study details	Main endpoints	Summary of main findings
Czernichow et al[70]	Prospective study in 3,430 men in France. Investigated relationship between the hypertriglyceridemic waist (combined increase in plasma triglycerides and waist circumference) phenotype with 7.5 years of follow-up.	CVD	The phenotype of hypertriglyceridemic waist was associated with risk for CVD. Using low WC/low triglycerides as the reference category, RR (95% CI) for CVD was: 0.72 (0.17–3.05) for high triglycerides/low WC, 1.22 (0.76–1.95) for high WC/low triglycerides and 2.13 (1.21–3.76) for the hypertriglyceridemic waist group; 1 SD increase in BMI associated with an RR of a CVD event of 1.41 (1.23–1.63).
§Dagenais et al[42]	Analysis in 8,802 men and women aged >55 years from Europe and North and South America enrolled in the Heart Outcomes and Prevention (HOPE) study. Assessing prognostic impact of BMI and adiposity in patients with established CVD with 4.5 years of follow-up.	Death due to CVD, MI, stroke, hospitalization for congestive heart failure, and all cause mortality.	Increased BMI was significantly associated with increased risk for MI and congestive heart failure but not stroke, death due to cardiovascular disease or all cause mortality. Obesity (in particular defined by measures of abdominal adiposity) worsens prognosis in patients with established CVD. Adjusted RR (95% CI) for CVD death by tertile: Low BMI = 1.00 Mid BMI = 1.01 (0.84–1.23) High BMI = 1.04 (0.86–1.27) Adjusted RR (95% CI) for MI by tertile: Low BMI = 1.00 Mid BMI = 1.06 (0.91–1.24) High BMI = 1.20 (1.03–1.41) Adjusted RR (95% CI) for heart failure by tertile: Low BMI = 1.00 Mid BMI = 1.06 (0.79–1.42) High BMI = 1.29 (0.96–1.72)
De Koning et al[71]	Meta-regression analysis of 15 prospective cohort studies and randomized controlled trials in 258,114 patients. Assessing CVD risk and abdominal obesity (WC and WHR).	CVD events	Increases in WC and WHR were significantly associated with the risk of incident CVD events Multivariate RR for CVD event: For every 1 cm increase in WC, RR = 1.02 (1.01–1.03); For every 1U increase in WHR, RR = 1.05 (1.04–1.07).
Domanski et al[49]	Post-hoc analysis of a randomized controlled trial in 8,290 men and women aged >50 years in Canada, Italy, Puerto Rico and the United States with stable CAD. Assessing BMI and a composite endpoint of major adverse coronary event (cardiovascular death, non-fatal MI, coronary revascularization, or stroke) with up to 7 years of follow-up (median of 4.8 years).	Major adverse coronary event (cardiovascular death, non-fatal MI, coronary revascularization or stroke)	A significant link between obesity and major adverse coronary event was found in men but not women (J-shaped associated between BMI and major adverse coronary event in men). Adjusted HR (95% CI) for major adverse coronary event in men = 1.28 (1.13–1.46; $P < 0.01$) for BMI $\geq$ 30 vs. BMI $<$ 30: Adjusted HR (95% CI) for major adverse coronary event in women = 0.96 (0.70–1.31; $P = 0.77$) for BMI $\geq$ 30 vs. BMI $<$ 30.

Field et al[7]	Pooled retrospective analysis in 123,750 men and women in the US enrolled in the Nurse's Health study and the Health Professionals Follow-up Study. Examined impact of weight on common chronic diseases with 10 years of follow-up.	Chronic disease incidence including diabetes, gallstones, hypertension, high cholesterol, colon cancer, heart disease and stroke	Increased risk for developing diabetes, hypertension, heart disease, colon cancer and stroke (men only) with increased BMI in both men and women 10 years adjusted OR (95% CI) for heart disease: Men: BMI $<$ 25 = 1.00 BMI 25–29.9 = 1.5 (1.4–1.7) BMI 30–34.9 = 2.0 (1.7–2.3) BMI $\geq$ 35 = 2.2 (1.5–3.1) Women: BMI $<$ 25 = 1.00 BMI 25–29.9 = 1.4 (1.2–1.5) BMI 30–34.9 = 1.5 (1.3–1.7) BMI $\geq$ 35 = 1.5 (1.3–1.8)
§Galal et al[52]	Retrospective study of 5,950 men and women in the Netherlands with known or suspected CAD. Assessing relationship between BMI and outcomes in patients with CAD with 6 years of follow-up.	Total mortality and cardiac death/acute MI	Underweight patients with known or suspected CAD had an increased risk for cardiac death/MI. Overweight and obese patients had a lower risk for cardiac death/MI compared with patients in the normal BMI category. Multivariate HR (95% CI) for cardiac mortality: Underweight = 2.1 (1.5–3.1) Normal weight = 1.00 Overweight = 0.8 (0.7–0.9) Obese = 0.8 (0.6–0.9) Incidences of cardiac death/MI in underweight, normal, overweight and obese patients were 33%, 26%, 17%, and 14%, respectively.
§Harris et al[72]	Longitudinal study (NHANES I) of 1,581 men and women in the US with no history of CHD at baseline Examining relationship between current and previous BMI and CHD with a mean of 3.9 years of follow-up.	Incidence of CHD	Heavier weight (measured by BMI) in late middle age was a found to be a risk factor for coronary heart disease in late life RR (95% CI) of CHD in late life by current and former BMI and weight change: Past BMI: Lowest tertile =1.0 Middle tertile = 1.2 (0.9–1.7) Highest tertile = 1.5 (1.1–2.2) Current BMI:Lowest tertile = 1.0 Middle tertile = 1.0 (0.7–1.4) Highest tertile = 1.1 (0.8–1.5) Weight change of –10 to +10% = 1.0 Weight change $\geq$10% = 1.1 (0.6–1.8)

(*Continued*)

Table 1. (*Continued*)

References	Study details	Main endpoints	Summary of main findings
Harris et al[33]	Longitudinal observational study in 5,201 (4800 patients included) men and women aged ≥65 years in the US. Examining the link between weight and weight change and CVD.	CVD and CAD	Heavier weight was associated with increased cardiovascular disease and CVD risk factors OR for CVD and CAD for patients in the heaviest quartile versus the lowest weight quartile (based on current weight): Women: CAD = 1.33; CVD = 1.08 Men: CAD = 0.96; CVD = 1.00 For weight loss of ≥10% since age 50: Women: CAD = 1.18; CVD = 1.30 Men CAD = 1.69, CVD = 1.89 For weight gain ≥10% since age 50: Women: CAD = 1.01; CVD = 0.87 Men: CAD = 1.26; CVD = 1.21
Hodge et al[53]	Population-based study of 3,861 men and women from Nauru and Fiji. Examined association between obesity and mortality and BMI with 10 years of follow-up.	All cause mortality and cardiovascular mortality	Little evidence to suggest that obesity was linked to overall or cardiovascular mortality (inverse relationship between BMI and mortality found in some sub-groups) Adjusted HR (95% CI) for cardiovascular mortality: Nauru men: BMI < 29.0 = 1.8 (0.6–5.1) BMI 29.0–32.5 = 1.6 (0.5–4.5) BMI 32.6 –36.3 = 1.7 (0.6 –5.1) BMI ≥ 36.4 = 1.0 Nauru women: BMI < 29.5 = 0.2 (0–0.9) BMI 29.5–34.4 = 0.5 (0.2–1.4) BMI 34.5–39.4 = 0.5 (0.2–1.5) BMI ≥ 39.5 = 1.0 Fiji Melanesian men: BMI < 23.3 = 0.5 (0.2–1.1) BMI 23.3–25.2 = 0.7(0.3–1.4) BMI 25.3–27.8 = 0.9 (0.4–1.7) BMI ≥ 27.9 = 1.0 Fiji Melanesian women: BMI < 23.7 = 3.1 (1.1–8.7) BMI 23.7–27.0 = 1.2 (0.4–3.8) BMI 27.1–30.8 = 2.4 (0.9–6.5) BMI ≥ 30.9 = 1.0 Fiji Indian men: BMI < 19.7 = 0.4 (0.1–1.4) BMI 19.7–22.2 = 0.9 (0.4–2.5) MI 22.3–25.1 = 1.4 (0.7–2.7) BMI ≥ 25.1 = 1.0 Fiji Indian women: BMI < 19.6 = 1.6 (0.5–5.3)

			BMI 19.6–23.1 = 1.3 (0.4–3.9) BMI 23.1–27.2 = 0.7 (0.3–2.0) BMI ≥ 27.2 = 1.0 Data adjusted for diabetes, smoking and age.
Janiszewski et al[41]	Analysis of NHANES cross-sectional study in 5,882 men and women aged ≥18 years living in the US. Investigating relationship between waist circumference and diabetes and CVD risk.	Diabetes and CVD	Increased WC and BMI were predictive for diabetes but not CVD after adjustment for age, race, smoking, and metabolic risk factors Multivariate OR (95% CI) of CVD: Low BMI = 1.00 Medium BMI = 1.26 (0.81–1.99) High BMI = 1.58 (0.88–2.23) Low WC = 1.00 Medium WC = 0.97 (0.62–1.50) High WC = 0.80 (0.43–1.52) Data shown adjusted for age, sex, race, smoking, metabolic risk factors, and BMI or WC.
§Jee et al[16]	Prospective study of 133,740 men and women aged 35 to 59 years in South Korea. Examining link between BMI and IHD with 9 years of follow-up.	Incidence of IHD and acute MI	Increased BMI was associated with an increased hazard ratio for IHD (using a reference group of BMI 18–19 kg/m^2; no evidence of a J-shaped relationship at lower BMI values). Increased risk for acute MI with increased BMI. After multivariate adjustment, 14% (95% CI: 12%–16%) increased risk of incident IHD per unit of increase in BMI. Adjusted RR (95% CI) for IHD: BMI 18–<19 = 1.00 BMI 19–<20 = 1.13 (0.71–1.80) BMI 20–<21 = 1.11 (0.72–1.72) BMI 21–<22 = 1.26 (0.82–1.92) BMI 22–<23 = 1.25 (1.82–1.90) BMI 23–<24 = 1.62 (1.07–2.45) BMI 24–<25 = 1.58 (1.04–2.40) BMI 25–<26 = 1.82 (1.20–2.78) BMI 26–<27 = 1.91 (1.24–2.95) BMI 27–<28 = 2.30 (1.47–3.58) BMI 28–<29 = 2.26 (1.40–3.66) BMI 29–<30 = 2.36 (1.36–4.86) BMI ≥ 30 = 2.75 (1.55–4.86)
Kannel et al[44]	Prospective study of 5,209 men and women aged 35 to 70 years in the US. Examining relationship between regional obesity and CVD with 24 years of follow-up.	CHD, CVD and all cause mortality	Increases in measures of obesity including BMI were associated with increased risk for CVD Ratio (Q5/Q1) 20 year age adjusted rates for CVD by adiposity measure: Weight/height: men = 1.4; women = 1.4 Subcapsular skinfold/BMI: men = 1.3; women = 1.7 Subcapsular skinfold/triceps skinfold = men = 1.5; women = 1.7

(*Continued*)

Table 1. (*Continued*)

Reference	Study details	Main endpoints	Summary of main findings
			Subcapsular skinfold: men = 1.4; women = 1.7 BMI: men = 1.5; women = 1.7 All $P < 0.05$; CVD = coronary disease, stroke, cardiac failure and peripheral artery disease.
Katzmarzyk et al[50]	Observational cohort study in 19,173 men aged 20 to 83 years in the US with no history of CHD, stroke or cancer at baseline. Endpoints were all-cause and CVD mortality	All cause mortality and CVD mortality	Healthy overweight and obese men and overweight and obese men with metabolic syndrome had elevated risk for mortality due to CVD RR (95% CI) for CVD mortality: Healthy overweight = 1.27 (0.83–1.94) Overweight with metabolic syndrome = 1.80 (1.10–2.97) Healthy obese = 2.70 (1.40–5.19) Obese with metabolic syndrome = 2.83 (1.70–4.72) Risk relative to healthy normal weight men. Data adjusted for age, alcohol consumption, and CVD but not cardiorespiratory fitness (data became non-significant after adjustment for cardiorespiratory fitness).
§Kenchaiah et al[25]	Prospective study of 5,881 men and women aged >30 participating in the Framingham Heart Study in the US. Assessing the association between obesity and heart failure with 14 years of follow-up.	Incidence of heart failure	Increasing BMI was associated with a graded increase in the risk of heart failure in both men and women when considered as a continuous and categorical variable. After adjustment for risk factors, there was an increased risk of heart failure of 5% for men and 7% percent for women for each 1 unit increase in BMI (covariates defined at baseline). Multivariate RR (95% CI) for heart failure (covariates defined at baseline): Women: BMI 18.5–24.9 = 1.00 BMI 25.0–29.9 = 1.50 (1.12–2.02; P = 0.007) BMI ≥ 30 = 2.12 (1.51–2.97; $P < 0.001$) Men: BMI 18.5–24.9 =1.00 BMI 25.0–29.9 = 1.20 (0.87–1.64; P = 0.27) BMI ≥ 30 = 1.90 (1.30–2.79; P = 0.001)
§Kim et al[34]	Longitudinal study of 5,209 men and women enrolled in the Framingham Heart Study, in the US. Examining link between BMI and conicity index and CHD with 24 years of follow up.	Incidence of CHD	Increasing BMI was associated with a graded increase in the risk for CHD in both men and women (BMI was found to be a better predictor for risk of CHD compared with conicity index). RR (95% CI) of CHD incidence by BMI quartile: Males: BMI < 23.8 = 1.00 BMI 23.8–<25.9 = 1.28 (1.0–1.65) BMI 25.9–<28.16 = 1.45 (1.13–1.86) BMI ≥ 28.16 = 1.53 (1.19–1.96) P = 0.0007

			Females: BMI < 22.34 = 1.00 BMI 22.34–<24.6 = 1.18 (0.87–1.59) BMI 24.6–<27.61 = 1.19 (0.89–1.61) BMI ≥ 27.61 = 1.56 (1.16–2.08) P = 0.0029
Kip et al[51]	Cohort study of 780 women aged 21 to 86 years in the US with suspected myocardial ischemia. Assessing link between obesity, metabolic syndrome and cardiovascular risk with 3.5 years of follow-up.	3-year risk of death and 3-year risk of major adverse coronary event	In women with suspected myocardial ischemia metabolic syndrome is predictive of cardiovascular risk but BMI measurement alone is not 3-year multivariate HR (95% CI) for major adverse coronary event: Normal BMI and normal metabolic = 1.00 Normal BMI and dysmetabolic = 2.21 (0.81–5.59; P = 0.13) Overweight and normal metabolic = 0.76 (0.23–2.56; P = 0.66) Overweight and dysmetabolic = 1.88 (0.81–4.23; P = 0.14) Obese and normal metabolic = 0.74 (0.19–2.84; P = 0.66) Obese and dysmetabolic = 2.04 (0.93–4.48; P = 0.08). Dysmetabolic indicates diabetes or metabolic syndrome
§Kragelund et al[21]	6,676 consecutive patients with acute MI, participating in the Danish Trandolapril Cardiac Evaluation (TRACE) study. Survival status was determined after 8–10 years. WHR was divided in quartiles and the lowest quartile was used as reference.	All cause mortality	In patients with acute MI there was a trend towards an inverse relationship between overall mortality and obesity results suggest that abdominal adiposity (WHR) may be a predictor of risk of mortality in men with acute MI Multivariate RR (95% CI) for mortality: Men: Underweight = 1.28 (0.87–1.89) Normal = 1.0 Overweight = 0.93 (0.84–1.02) Obese = 0.99 (0.85–1.14) Women: Underweight = 1.44 (1.15–1.79) Normal = 1.0 Overweight = 0.78 (0.68–0.90) Obese = 0.90 (0.74–1.10)
§Lakka et al[45]	Population-based study in 1,346 men aged 42 to 60 years in Finland with no history of CVD or cancer at baseline. Examining link between obesity and acute coronary events with a mean of 10.6 years of follow-up.	Acute coronary events	Increased WHR, WC and BMI when considered as continuous variables were associated with a significantly increased risk of coronary events. Increase in risk (%) (95% CI) in acute coronary events for a 1SD increase in obesity index: WHR = 21.3 (5.0–40.2; P = 0.009) WC = 24.2 (5.3–46.5; P = 0.010) BMI = 22.6 (4.4–44.1; P = 0.013) Data adjusted for age, years of examination, family history of CHD, adulthood socioeconomic status, smoking, and maximal oxygen uptake (risk reduced, and non-significant for WC and BMI when adjusted for diabetes; data not presented here).

(*Continued*)

Table 1. (*Continued*)

Reference	Study details	Main endpoints	Summary of main findings
§Leander et al[20]	Study in 1,635 men and women aged 45 to 70 years in Sweden surviving at least 28 days after first MI. Examining risk factors for recurrent MI with 6 to 9 years of follow-up.	Recurrent MI/fatal CHD	Central obesity (as measured by WHR) was associated with an increased risk for recurrent MI/fatal CHD in men but not in women. HR (95% CI) for recurrent MI/fatal CHD was 1.4 (1.0–2.0) in men and 0.8 (0.4–1.8) in women.
Lissin et al[28]	Analysis of 522 men in the US with a history of heart failure. Assessing prognostic value of BMI in men with heart failure with 6 years of follow-up.	Time to death	Inverse relationship between BMI and mortality suggesting that increased BMI is associated with improved survival in patients with heart failure. In multivariate analysis BMI was independently and significantly associated with time to death, HR = 1.5 (95% CI: 1.2–1.9), but patients with higher BMI at lower risk of death.
§Mann et al[40]	Data from the NHANES study used (n = 10,582), participants were adults aged 35 to 74 years, patients were classed as diabetics or non-diabetics based on a physician diagnosis of diabetes.	CHD mortality	Increased BMI was a significant risk factor for CHD mortality in both diabetics and non-diabetics Multivariate HR (95% CI) for CHD mortality: Non-diabetics: Lean: 1.0 Overweight: 0.83 (0.65–1.05) Obese: 1.44 (1.12–1.84) Diabetics. Lean: 2.2 (1.21–4.01) Overweight: 2.34 (1.42–3.84) Obese: 3.32 (1.87–5.91) Data adjusted for age, race, smoking, hypertension, serum cholesterol, education, alcohol and physical activity.
Manson et al[43]	Cohort study in 115,195 women aged 30 to 55 years in the US with no history of CVD or cancer at baseline. Examined relationship between mortality and BMI with 16 years of follow-up.	Overall mortality and mortality due to CVD	J-shaped relationship between BMI and overall mortality and increased BMI was associated with increased risk for cardiovascular mortality. Multivariate RR for cardiovascular mortality among never smokers: BMI $<$ 19 = 1.0 (Reference) BMI 19.0–21.9 = 1.0 BMI 22.0–24.9 = 1.2 (approx) BMI 25.0–26.9 = 1.6 (approx) BMI 27.0–28.9 = 1.9 (approx) BMI 29.0–31.9 = 7.1 BMI $>$ 32 = 7.7
McGee et al[73]	Meta analysis of 26 studies in a total of 388,622 men and women. Examining relationship between BMI and mortality, studies ranging from 3 to 30 years of follow-up.	CHD mortality and mortality due to CVD	Increased BMI was associated with a graded increase in the risk for CHD and cardiovascular mortality in both men and women. RR (95% CI) for CHD mortality versus normal weight:

			Overweight male = 1.16 (1.09–1.24) Overweight female = 1.10 (1.00–1.20) Obese male = 1.51 (1.36–1.67) Obese female = 1.62 (1.46–1.81) RR (95% CI) for CVD mortality versus normal weight: Overweight male = 1.10 (1.03–1.16) Overweight female = 1.03 (0.95–1.12) Obese male = 1.45 (1.33–1.59) Obese female = 1.53 (1.38–1.69)
Megnien et al[74]	Prospective study of 712 men and women aged 30 to 74 years in France. Examined predictive value of WHR on cardiovascular risk events.	CHD, MI, stroke, total CVD and mortality	Increased abdominal adiposity (assessed by WHR) is predictive of the risk of CHD. Rate (%) CHD death, MI, stroke and death (all $P < 0.01$) increased with increasing WHR quintile in men and women. For subjects in the highest WHR quintile, the proportion exceeding a 15% risk of developing a coronary event over the next 10 years was >2-fold (OR 2.60 CI 1.09–6.54) versus the lowest WHR quintile; corresponding OR (95% CI) for highest versus lowest BMI quintile was 2.03 (0.91–4.56).
Ness et al[23]	Study in 2,033 men with a history of recent MI in the UK. Examined CHD mortality in men with recent MI.	All cause mortality and CHD mortality	In men with recent MI a reverse-J shaped association was evident between BMI and overall and CHD mortality Multivariate HR (95% CI) CHD mortality: BMI 15–24 = 1.00 BMI 24–26 = 0.71 (0.58–0.87) BMI 26–28 = 0.64 (0.52–0.79) BMI 28–45 = 0.76 (0.62–0.93) Data adjusted for history of MI, angina, hypertension, treatment, smoking, diet and height.
Newton and LaCroix[19]	Retrospective cohort study of 691 women (mean age 66.2 years) in the US surviving first MI. Examining link between reinfarction and BMI.	Reinfarctions and deaths	Increased BMI was associated with an increase in risk for reinfarction in women surviving first MI. For each 1-unit increase in BMI, RR (95% CI) of reinfarction increased by 5%: RR = 1.05 (1.02–1.08). RR was not affected by smoking but attenuated after adjustment for diabetes and hypertension: RR = 1.03 (1.00–1.07).
§Nicklas et al[12]	Prospective study of 2,503 men and women aged 70 to 79 years in the US. Examined association between visceral adiposity and MI with a mean of 4.6 years of follow-up.	Incident MI	Increased BMI was associated with an increased risk for MI in women but not in men. Increases in WC, visceral adipose tissue area or visceral adipose tissue/fat mass were associated with increased risk of incident MI in men and women.

(*Continued*)

Table 1. (*Continued*)

References	Study details	Main endpoints	Summary of main findings
			Multivariate HR (95% CI) for incident MI by obesity index: BMI per 4.90 kg/m^2 increase: women = 1.15 (0.88–1.51); men = 1.00 (0.75–1.35) Waist circumference (per 13.37 cm increase): women = 1.13 (0.85–1.51); men = 0.87 (0.67–1.12) Visceral adipose tissue area (per 66.23 cm^2 increase): women = 1.67 (1.28–2.17); men = 1.05 (0.83–1.31) Visceral adipose tissue/fat mass (per 2.17 increase): women = 1.67 (1.20–2.31); men = 1.08 (0.86–1.37) Adjusted for age, race, education, smoking, COPD and for women hormone replacement therapy.
Ni Mhurchu et al[15]	Meta-analysis of 33 prospective cohort studies in 310,283 men and women in the Asia-Pacific region. Assessment of link between BMI and cardiovascular mortality and morbidity.	IHD, ischemic stroke, hemorrhagic stroke	A direct and continuous relationship was observed between increasing BMI and risk for IHD. In the age groups $<$60, 60 to 69, and $\geq$70 years, a 2-unit lower BMI was associated with an RR (95% CI) for IHD of 21% (17%–24%), 10% (5%–14%), and 6% (3%–9%) lower IHD risk, respectively (adjustment for SBP attenuated the association by approximately one third).
§Prineas et al[75]	Cohort study in 32,898 women aged 55 to 69 years. Examined association between central adiposity and fatal coronary artery disease with 4 years of follow-up.	Coronary death	Increased abdominal adiposity (assessed by WHR) was independently linked with coronary death (no independent association between BMI and coronary death). RR for coronary death was 1.3 for middle and 2.8 for highest WHR tertile versus lowest tertile ($P < 0.001$). Data adjusted for age, body mass, smoking, activity, estrogen use, marital status, and alcohol use. RR after adjustment for diabetes and hypertension 1.2 for middle and 2.0 for highest tertile versus lowest ($P = 0.03$).
§Rea et al[22]	Population-based study in 2,541 men and women aged 30 to 79 years in the US. Assessing impact of BMI on recurrent coronary events following first acute MI with a median follow-up of 3 years.	Recurrent coronary events	In survivors of MI obese patients were at higher risk for recurrent coronary events compared with patients with a normal BMI (moderately overweight patients [BMI 25–27.4 kg/m^2; without hypertension or diabetes] had a lower risk of recurrent coronary events compared with patients in the normal BMI range). RR of recurrent coronary events following acute MI in patients without diabetes or hypertension (n = 1,234): BMI 16–24.9 = 1.00 BMI 25–29.9 = 0.84 BMI 30–48 = 1.66

			In patients with diabetes, but without hypertension (n = 193): BMI 16–24.9 = 1.58 BMI 25–29.9 = 1.72 BMI 30–48 = 1.91 Data adjusted for age, sex, smoking, physical activity, congestive heart failure, cholesterol and aspirin use.
Rexrode et al[11]	Prospective study of 22,071 healthy men aged 40 to 84 years in the US. Examining association between heart disease and adiposity in men with a mean of 3.9 years of follow-up (in 16,164 men with anthropometric measurements and no history of CHD, stroke or cancer at baseline).	CHD and MI	Increased BMI in men was associated with a graded increase in risk for MI and CHD. Modest association between abdominal adiposity (WHR and WC) and risk for CHD in middle-aged and older men (did not remain an independent risk factor after adjustment for BMI). RR (95% CI) for MI and CHD: By WHR quintile: Q1 = 1.00 for MI and CHD Q2 = 0.93 (0.58 –1.50) for MI; 0.97 (0.72–1.31) for CHD Q3 = 0.64 (0.39–1.08) for MI; 0.99 (0.73–1.34) for CHD Q4 = 0.97 (0.61–1.53) for MI; 1.20 (0.90–1.60) for CHD Q5 = 0.99 (0.62–1.56) for MI; 1.23 (0.92–1.66) for CHD By WC quintile: Q1 = 1.00 for MI and CHD Q2 = 0.71 (0.40–1.24) for MI; 0.90 (0.65–1.24) for CHD Q3 = 0.92 (0.54–1.59) for MI; 1.10 (0.80–1.51) for CHD Q4 = 1.15 (0.66–2.03) for MI; 0.94 (0.66–1.32) for CHD Q5 = 1.10 (0.61–2.00) for MI; 1.06 (0.74–1.53) for CHD By BMI quintile: Q1 = 1.00 for MI and CHD Q2 = 1.34 (0.81–2.21) for MI; 1.31 (0.97–1.75) for CHD Q3 = 1.34 (0.81–2.19) for MI; 1.23 (0.91–1.67) for CHD Q4 = 1.93 (1.19–3.13) for MI; 1.62 (1.21–2.16) for CHD Q5 = 2.48 (1.54–4.01) for MI; 1.73 (1.29–2.32) for CHD Data adjusted for age, aspirin use, vitamin use, smoking parental history of MI, physical activity, alcohol consumption and BMI/WHR.
§Rexrode et al[24]	Prospective cohort study in 44,702 women aged 40 to 65 in the US with no history of stroke, CHD or cancer. Examining association between CHD and abdominal adiposity with 8 years of follow-up.	CHD (non fatal MI or CHD death)	Independent association between increased abdominal adiposity (WC and WHR) and risk for CHD in middle-aged women. Multivariate RR (95% CI) for CHD by WHR category: <0.72 = 1.00 0.72–<0.76 = 1.50 (0.84–2.70) 0.76–<0.80 = 2.02 (1.15–3.55) 0.80–<0.84 = 2.02 (1.14–3.59) 0.80–<0.88 = 2.28 (1.25–4.15) ≥0.88 = 2.43 (1.32–4.48; P = 0.003) RR (95% CI) for CHD by weight circumference (cm) <71.1 = 1.00

(*Continued*)

Table 1. (*Continued*)

References	Study details	Main endpoints	Summary of main findings
			71.1–<76.2 = 1.24 (0.75–2.07) 76.2–<81.3 = 2.21 (1.33–3.69) 81.3–<86.4 = 2.20 (1.26–3.85) 86.4–<91.4 = 1.80 (0.97–3.36) 91.4–<96.5 = 1.86 (0.93–3.69) ≥96.5 = 2.32 (1.16–4.63) (P = 0.03) Data adjusted for age, BMI, smoking, parental history of myocardial infarction, alcohol, menopausal status, hormone replacement therapy, oral contraceptive use, aspirin intake, saturated fat intake (g/d), antioxidant score and biological mediators including diabetes.
Rogers et al[48]	Population-based cross-sectional study of 647,015 men and women in the US. Examining relationship between obesity, circulatory disease, diabetes-specific and all cause mortality.	Overall mortality and mortality due to diabetes and circulatory disease	U-shaped relationship between BMI and overall mortality and a J-shaped relationship between obesity and mortality from circulatory diseases. Increased risk of diabetes mortality with increased BMI. Multivariate HR for death from circulatory diseases: BMI ≥ 40 = 2.04* BMI 35–<40 = 1.61* BMI 30–<35 = 1.20* BMI 25–<30 = 0.98 BMI 18.5–<25 = 1 (Ref) BMI < 18.5 = 1.53*, (*P < 0.05) Data adjusted for age, gender, marital status, income, employment status, education and geographical area.
Suwaidi et al[18]	Study involving 906 consecutive male and female patients with acute MI in the US.	Age at occurrence of MI, hospital morbidity and mortality	Overweight and obese patients were significantly younger at first MI compared with patients with normal BMI. Overweight (BMI 25–30) and obese (BMI > 30) patients with acute MI were a mean of 3.6 years (95% CI; 1.9–5.4) and 8.2 years (95% CI; 6.2–10.1) younger, respectively versus normal weight patients with acute myocardial infarction (P < 0.001 for both). No relationship between BMI and hospital morbidity and mortality was observed.
Tanko et al[76]	Community-based study in 557 post-menopausal women aged 48 to 76 years in Denmark. Assessing relationship between enlarged waist (> 88 cm) and elevated triglycerides (≥1.45 mmol/L) and metabolic syndrome) with a mean of 8.5 years of follow-up.	All cause and cardiovascular mortality	Women with enlarged waist (≥88 cm) and elevated triglycerides and women with metabolic syndrome were at significantly higher risk for fatal cardiovascular events; Relationship persisted after the exclusion of women with prevalent diabetes Composite RR (95% CI) for cardiovascular mortality:

			All women: Composite metabolic syndrome = 3.2 (1.5–6.5; P < 0.001) Composite enlarged weight and elevated triglycerides = 4.7 (2.2–9.8; P < 0.001) Women without diabetes: Composite metabolic syndrome = 2.5 (1.1–5.5; P <0.05) Composite enlarged weight and elevated triglycerides = 4.2 (1.9–9.3; P < 0.001) Data adjusted for age, smoking and LDL cholesterol.
§Wang et al[77]	Prospective, community-based observational study of 5,282 men and women aged >35 years in the US with no history of atrial fibrillation. Assessing association between BMI and new onset atrial fibrillation with a mean of 13.7 years of follow-up.	Development of new onset atrial fibrillation	Obesity was associated with increased risk for new onset atrial fibrillation—excess risk thought to be mediated by left atrial dilatation. 4% increase in atrial fibrillation risk per unit increase BMI observed in men (P = 0.02) and women (P = 0.009). Multivariate adjusted HRs (95% CI) for atrial fibrillation associated with obesity were: Men = 1.52 (1.09–2.13; P = 0.02) Women = 1.46 (1.03–2.07; P = 0.03) After adjustment for echocardiographic left atrial diameter and clinical risk factors adjusted HR (95% CI) per 1-unit increase in BMI were: Men = 1.00 (0.97–1.04; P = 0.84) Women = 0.99 (0.96–1.02; P = 0.56).
Welborn et al[78]	Cross-sectional study of 9,206 men and women aged 20 to 69 years in urban areas of Australia. Assessment of link between WHR and cardiovascular death.	Mortality due to CVD and CHD	WHR ratio was an independent risk factor for death from cardiovascular disease and CHD (WHR was more predictive of risk than WC, which in turn was more predictive than BMI). Multivariate CVD mortality HR (95% CI) for 1 SD above the mean value: WHR men = 1.60 (1.27–2.02; P < 0.0001) WHR women = 1.59 (1.16–2.17; P < 0.01)
Whitlock et al[36]	Systematic review of 46 prospective cohort studies investigating the association between CHD risk and BMI.	CHD	Two-thirds of studies reported a positive or J-shaped association between BMI and CHD risk. In studies with >500 patients the mean increase in CHD risk per 2 unit increase in BMI was 14%.
§Widlansky et al[47]	Analysis of 5,010 men in the US with a history of prior MI or stroke. Examined relationship between BMI and cardiovascular mortality with a mean of 5 years of follow-up.	Total mortality and cardiovascular mortality	Elevated BMI not strongly associated with total or cardiovascular mortality, men with a BMI < 22 kg/m^2 had a small increase in risk for total and cardiovascular mortality RR (95% CI) for cardiovascular mortality: BMI < 22 = 1.40 (1.01–1.92) BMI 22.0–24.9 = 1.00 BMI 25.0–29.9 = 0.91 (0.70–1.18) BMI ≥ 30 = 1.02 (0.62–1.68) Data adjusted for age, aspirin, vitamin use, ascorbic acid, alcohol consumption, exercise, diabetes, hypertension and cholesterol.

(*Continued*)

Table 1. (*Continued*)

References	Study details	Main endpoints	Summary of main findings
Willett et al[31]	Prospective cohort study of 115,818 women aged 30 to 55 years in the US without a history of previous CHD. Examined influence of weight and weight change on incidence of coronary heart disease with 14 years of follow up. CHD defined as nonfatal MI or fatal CHD.	CHD (non fatal MI or fatal CHD)	Elevated previous BMI and weight gain in follow-up period associated with increased risk for CHD. RR (95% CI) of CHD: By BMI in 1976 BMI $<$ 21 = 1.00 BMI 21–22.9 = 1.19 (0.98–1.44) BMI 23–24.9 = 1.46 (1.20–1.77) BMI 25–28.9 = 2.06 (1.72–2.48) BMI $\geq$ 29 = 3.56 (2.96–4.29) RR (95% CI) by weight change (kg) Loss $\geq$ 20 = 1.09 (0.53–2.21) Loss 11–19.9 = 1.15 (0.77–1.71) Loss 5–10.9 = 0.78 (0.57–1.06) Loss 4.9 to gain 4.9 = 1.00 Gain 5.0–7.9 = 1.25 (1.01–1.55) Gain 8–10.9 = 1.65 (1.33–2.05) Gain 11–19 = 1.92 (1.61–2.29) Gain $\geq$ 20 = 2.65 (2.17–3.22) Data adjusted for age, smoking, menopausal status, postmenopausal hormone use, and parental history of MI before 60 years of age.
§Wilson et al[17]	Longitudinal study of 5,209 men and women aged 35 to 75 years enrolled in the Framingham Heart Study in the US. Examined relationship between overweight, obesity and cardiovascular risk with 44 years of follow-up.	Angina, MI, CHD, total CVD and death from CVD	Overweight was associated with increased risk for angina, MI and cardiovascular events. RR multivariate adjustment (95% CI; men/women) for the development of new: Angina: Overweight: men = 1.47 (1.12–1.92); women = 1.42 (1.08–1.86) Obese: men = 1.81 (1.28–2.55); women = 1.63 (1.18–2.25) MI: Overweight: men = 1.26 (0.98–1.61); women = 0.91 (0.61–1.36) Obese: men = 1.17 (0.82–1.67); women = 1.46 (0.94–2.28) Total CVD: Overweight: men = 1.24 (1.07–1.44); women = 1.13 (0.96–1.33) Obese: men = 1.38 (1.12–1.69); women = 1.38 (1.14 –1.68) CVD death: Overweight: men = 1.05 (0.74–1.48); women = 0.77 (0.50–1.18) Obese: men = 0.98 (0.59–1.63); women = 1.56 (1.00–2.43) Data adjusted for age, smoking, hypertension, diabetes and hypercholesterolemia.

§Yusuf et al[13]	Standardized case-control study in 27,097 men and women with first MI in 52 countries. Assessing association between obesity and risk of MI in an ethnically diverse population.	MI	A modest and graded association was reported between BMI and MI, which was reduced after adjustment for WHR and non-significant after adjustment for other risk factors; WHR was more strongly associated with risk for MI compared with BMI. OR (95% CI) for MI for a 1 SD increase in obesity index: BMI = 1·10 (1·07–1·13) WC = 1·19 (1·16–1·22) WHR = 1·37 (1·34–1·41) Data adjusted for age, sex and region.
§Zhang et al[38]	Population based, prospective cohort study in 67,334 women aged 40 to 70 years in China with no history of CHD, stroke or cancer at baseline. Examining anthropometric predictors of CHD in women with a mean of 2.5 years of follow-up.	Incidence of CHD (non-fatal MI or CHD death)	Increased WHR was associated with increased CHD women of all ages; BMI was more strongly related to CHD risk in younger women. RR (95% CI) multivariate adjustment of CHD (including non-fatal MI and CHD death) by BMI: BMI $<$ 22.2 = 1.00 BMI 22.2–$<$25.0 = 2.5 (1.2–5.1) BMI $\geq$ 25 = 2.4 (1.2–5.0; P for trend = 0.03) WC (cm): WC $<$ 73.0 = 1.00 WC 73.0–$<$80.0 = 2.0 (0.8–4.8) WC $\geq$ 80 = 3.1 (1.4–7.2; P for trend = 0.003) For WHR (cm/cm): WHR $<$ 0.784 = 1.0 WHR 0.784–$<$0.828 = 1.5 (0.7–3.5) WHR $\geq$ 0.828 = 3.0 (1.4–6.3; P for trend = 0.001) Data adjusted for age, smoking, alcohol, education, menopausal status, exercise, hormone replacement use and diet.

Note: §Denotes studies either conducted in diabetes patients or adjusting for diabetes.
Abbreviations: BMI, body mass index; CAD, coronary artery disease; CHD coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; SD, standard deviation; WC, waist circumference; WHR, waist-to-hip ratio.

diabetes and hypertension. Rea et al[22] investigated the risk for recurrent coronary events following first MI. They found that moderately overweight (BMI 25.0–27.4 kg/m^2) subjects had a lower relative risk for recurrent coronary events compared with subjects with a normal BMI (16–24.9 kg/m^2) but risk increased in a stepwise fashion in severely overweight subjects (27.5–29.9 kg/m^2) and those with class I and class II obesity (30–34.9 kg/m^2 and ≥35 kg/m^2, respectively).[22] Further, the authors postulate that approximately 43% of this excess risk could be attributed to clinical measurements of diabetes, hypertension and dyslipidemia.[22] Additionally, Kragelund et al[21] observed a non-significant relationship between obesity and mortality in patients with previous acute MI, although overweight and obese men and women had numerically lower RRs and underweight men and women had a numerically higher RR for mortality compared with their normal weight counterparts. In addition, Ness et al[23] reported a reverse J-shaped association between BMI and CHD mortality in men with a recent history of MI.

Three studies included in this review examined the link between BMI and IHD. Jee et al,[16] Ni Mhurchu et al[15] and the Asia Pacific Cohort Studies Collaboration[14] all reported an increased risk for IHD with increased BMI. Notably, all three of these studies/pooled analyses were performed in Asian or Asian-Pacific populations. Jee et al[16] used a reference group with a BMI of 18–<19 kg/m^2 and reported an elevated risk for IHD in subjects with a BMI above 19 kg/m^2. These results are reflective of the fact that overweight and obesity are defined by lower BMI thresholds in Asian populations compared with European and North American populations.

Heart failure

The relationship between obesity and heart failure appears to be complex; obesity is reported to be an independent risk factor for the development of heart failure,[25] yet conversely, in patients with established heart failure, obesity appears to be associated with a survival advantage. Although a number of hypotheses exist, the mechanism underlying this "obesity paradox" has yet to be fully elucidated. Kenchaiah et al[25] investigated the relationship between BMI and heart failure in participants of the Framingham Heart Study (both as a continuous and categorical variable; Table 1) over a follow-up period of up to 14 years. They observed a graded association between increased BMI and the risk of developing heart failure in both men and women (following adjustment for age, smoking status, alcohol intake, total serum cholesterol, valve disease, hypertension, left ventricular hypertrophy, MI and diabetes). Notably, the authors suggest that elevated BMI may predispose certain individuals to heart failure owing to the causal link between elevated BMI and atherogenic traits such as hypertension and type 2 diabetes, which are themselves risk factors for the development of heart failure. Additionally, they discuss the reported links between increased BMI and left-ventricular remodeling, which may be attributable to a number of factors including increased hemodynamic load, neurohormonal activation and oxidative stress.

Bibbins-Domingo et al[26] examined potential risk factors for the development of heart failure in postmenopausal women with established coronary disease; diabetes was found to be an independent risk factor for heart failure in this population but overweight (BMI 25–30 kg/m^2) or class I obesity (BMI 30–35 kg/m^2) were not. Only a BMI of >35 kg/m^2 was found to be an independent risk factor for the development of heart failure in this group of women.[26] However, Bender et al[27] examined the risk for mortality due to heart failure or cardiac dysrhythmias in obese patients and reported a massively elevated risk for mortality in men and women with a BMI ≥ 25 kg/m^2 (standardized mortality ratio [95% confidence interval] was 15.57 [10.58–22.10] for men and 8.81 [6.45–11.75] for women compared with the population of Germany).

As stated above, obesity may be a risk factor for the development of heart failure but conversely it appears to be indicative of a more favorable prognosis in terms of overall survival in patients with established heart failure. For example, an inverse correlation between increased BMI and overall mortality was observed by Lissin et al in a group of male US veterans with established heart failure.[28] This "obesity paradox" has also been observed in terms of cardiovascular mortality, for example, Curtis et al[29] observed higher RRs for death from cardiovascular causes and death from worsening heart failure in patients with a normal BMI (18.5–24.9 kg/m^2) compared with both underweight (BMI < 18.5 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese

(BMI ≥ 30 kg/m^2) patients. Although diabetes is an established independent risk factor for heart failure and a number of studies performed multivariate adjustment that included diabetes there was a notable paucity of data investigating whether the obesity paradox also exists in overweight or obese patients with concomitant type 2 diabetes and heart failure. Nevertheless, potential explanations for the obesity paradox observed in patients with heart failure include the hypothesis that a proportion of overweight or obese patients who present with cardinal signs and symptoms of heart failure such as dyspnea, leg and ankle edema and basilar pulmonary crepitations may be diagnosed with heart failure without actually having heart failure.[25,30] Alternate hypotheses to explain this paradox include the postulate that the increased risk for mortality in patients with a lower BMI may be due to the deleterious effects of cardiac cachexia and muscle wasting associated with advanced heart failure rather than a beneficial effect of increased BMI *per se*.[29] However, in the study by Curtis et al[29] underweight subjects (BMI < 18.5 kg/m^2) also had a lower hazard ratio (HR; 95% CI) for death due to worsening heart failure 0.86 (0.56–1.32) compared with subjects in the normal BMI range (18.5–24.9 kg/m^2).

Coronary heart disease

In terms of the relationship between obesity and CHD, an overall trend towards an increased risk of CHD incidence (or mortality due to CHD) with increasing BMI was evident (Table 1).[31–36] However, a systematic review performed by Whitlock et al[36] and the results of Canoy et al[37] provide some evidence of a J-shaped relationship between BMI and CHD with Canoy and colleagues reporting that individuals in the lowest BMI quintile had an elevated risk for CHD compared with those in the second-lowest quintile. Interestingly, the same authors also investigated the relationship between WHR and WC and risk for CHD and concluded that indices of abdominal adiposity more predictive of the risk of CHD compared with BMI.

Overweight and obesity are commonly defined as a BMI of 25–29.9 kg/m^2 and >30 kg/m^2, respectively. However, these classifications are not appropriate for all populations, as illustrated by the findings of Zhang et al[38] who investigated the relationship between BMI and CHD (including non-fatal MI and CHD death) in 67,334 Chinese women. It was reported here that women with a BMI over 22.2 kg/m^2 had a more than twofold increase in the RR for CHD compared with those with a BMI below 22.2 kg/m^2. These findings suggest that the detrimental health consequences of obesity, in terms of CHD risk, generally commence at a lower BMI threshold in this population compared with predominantly North American or European populations. Furthermore, the findings of Zhang et al[38] are concordant with the findings of studies that investigated the relationship between BMI and IHD in Asian populations.[14–16] The differences in the relationship between increased BMI and negative health consequences that exist between Asian populations and North American and European populations are such that the WHO now define overweight as a BMI of 23–25 kg/m^2 and obesity as a BMI of ≥25 kg/m^2 in Asian populations.[39]

Only one study identified during the course of the literature review reported here explicitly examined the relationship between obesity and CHD mortality in a subgroup of patients with diabetes (CHD defined as International Classification of Diseases 9 [ICD-9] codes 410–414). Mann et al[40] reported that for obese non-diabetics the RR (95% CI) for CHD mortality was 1.44 (1.12–1.84) compared with non-diabetic individuals in the normal BMI range (<25 kg/m^2). Unexpectedly, Mann et al observed that overweight non-diabetics had a lower relative risk for CHD mortality compared with non-diabetics in the normal BMI range. For subjects with diabetes the RRs for CHD mortality for each BMI category (lean, overweight and obesity) were more than twofold greater than the RR for the corresponding BMI category for non-diabetics (following adjustment for age, race, smoking, hypertension, serum cholesterol, education level, alcohol consumption and physical activity). In subjects with diabetes there was also a trend for increased risk due to CHD mortality with increasing BMI; indeed in comparison with lean non-diabetics, obese subjects with diabetes had a relative risk (95% CI) of CHD mortality of 3.32 (1.87–5.91).[40]

Cardiovascular disease

A large number of studies have investigated the link between increased BMI and clinical endpoints that have been placed under an umbrella term such as cardiovascular disease, circulatory disease or major adverse coronary events (Table 1). A substantial proportion

of these studies reported a trend (both significant or non-significant) towards an increased risk in incidence, or mortality due to cardiovascular disease or coronary events with increasing BMI.[27,35,41–45] However, as with other clinical endpoints examined here, a J-shaped, U-shaped or inconsistent relationship between BMI and the risk for cardiovascular disease or mortality due to cardiovascular disease was reported in some studies.[17,36,46–48] This suggests that patients with low BMI may also have an elevated risk of incidence, or mortality, due to cardiovascular disease compared with individuals with a normal BMI. For example, in a study of over 80,000 US physicians aged 40–84 years Ajani et al[46] reported that men with a BMI < 20 kg/m^2 had a higher RR of cardiovascular mortality compared with men with a BMI of 22.5–24.9 kg/m^2 (1.50 for BMI < 20 kg/m^2 versus 1.00 for BMI of 22.5–24.9 kg/m^2; adjusted for smoking, age, alcohol intake and physical activity). They also reported a trend for an increased risk of cardiovascular mortality with increasing BMI in men in BMI categories above 25 kg/m^2. A gender-effect was also noted by some investigators, for example Domanski et al[49] reported that in subjects with established coronary artery disease, obesity (BMI ≥ 30 kg/m^2 versus BMI < 30 kg/m^2) was associated with an increased risk for a composite endpoint of major adverse coronary event in men but not in women. However, in a large prospective study of over 115,000 women enrolled in the Nurses' Health Study Manson et al[43] reported a trend for an increased age-adjusted RR for mortality due to cardiovascular disease with increasing BMI (in women who were never smokers). Notably, for those women with a BMI over 29 kg/m^2 the RR of death from cardiovascular disease was sevenfold greater compared with women with a BMI in the range of 19–21.9 kg/m^2. Wilson et al[17] examined the association between BMI and cardiovascular disease and mortality in men and women enrolled in the Framingham Heart Study. It was noted that the risk for total cardiovascular disease increased with increasing BMI in both men and women. However, in terms of the RR of death due to cardiovascular causes overweight women and obese men had a lower risk for death than subjects in the reference category.

In a meta-analysis of 26 studies McGee et al[35] reported a trend for an increased risk of cardiovascular disease with increasing BMI; however, the magnitude of the increased risk was less than that observed by other studies such as the study by Manson et al.[43] McGee et al also reported a RR for cardiovascular mortality of approximately 1.5 in both obese men and women.[35] Moreover, the authors make an interesting point that whilst the relationship between obesity and traditional risk factors for cardiovascular disease such as type 2 diabetes and hypertension is well established the role of non-traditional factors such as homocysteinemia and levels of lipoprotein A are less well characterized.

A number of investigators have considered the effect of overweight/obesity in combination with the metabolic syndrome on clinical outcomes. Katzmarzyk et al[50] compared the risk of mortality due to cardiovascular disease in "healthy" overweight and obese men with that of overweight and obese men with metabolic syndrome. In both healthy men and those with metabolic syndrome the risk of mortality due to cardiovascular disease increased with increasing BMI. However, the increase in risk was higher for overweight and obese men with metabolic syndrome compared with healthy men in the corresponding BMI group. Kip et al[51] also observed an elevated risk for major adverse coronary event with increasing BMI in dysmetabolic women with myocardial ischemia but not in women classified as metabolically normal.

The findings of some investigators suggest that the obesity paradox may not be limited to patients with heart failure. In a retrospective study of 5,950 men and women with known or suspected coronary artery disease Galal et al[52] reported that the hazard ratio (HR) for cardiac death or death from acute MI in underweight patients (BMI < 18.5 kg/m^2) was more than double that for subjects in the normal BMI range (18.5–24.9 kg/m^2). In comparison, overweight (BMI 25–29.9 kg/m^2) and obese (BMI ≥ 30 kg/m^2) subjects had a lower HR for cardiac death compared with subjects in the normal BMI range (following multivariate adjustment).[52] In a study conducted in Micronesian Naurans and Melanesian and Indian Fijians Hodge et al[53] reported that there was little evidence to suggest that obesity is a risk factor for cardiovascular disease in these populations, although curiously there was an inverse correlation between overall mortality and obesity in some diabetic subgroups analyzed. Nauru is known to have among

the highest prevalence of diabetes in the world, which makes the observations of Hodge et al all the more pertinent. However, it is possible that BMI may not be the most appropriate measure of obesity in this population. A study by Rush et al[54] compared percentage body fat and BMI in women from New Zealand and Polynesia; they found that at a given percentage body fat Polynesian women typically had a BMI approximately 3–4 units higher than New Zealand women.

Discussion

The initial aim of this review was to examine the link between BMI and adverse cardiovascular endpoints specifically in patients with type 2 diabetes. However, until recently there has been a notable paucity of data from this particular group. A recent study by Eeg-Olofsson et al[55] examined the association between BMI at baseline (as a continuous variable) and first-incident fatal or non-fatal CHD, stroke and cardiovascular disease in 13,087 patients with type 2 diabetes enrolled in the Swedish National Diabetes Register. It was reported that there was a significant relationship between BMI and CHD, stroke and cardiovascular disease (adjusted for age, gender, duration of diabetes, type of hypoglycemic treatment, smoking and significant interaction variables) and we discuss the findings of Eeg-Olofsson et al in the context of this review in detail below.

The underlying trend emerging from studies conducted in general populations and included in this review was, perhaps unsurprisingly, that overweight and obese subjects are at an elevated risk for cardiovascular disease or mortality due to cardiovascular causes compared with subjects with a normal BMI. The results from a number of studies also suggest that underweight patients are at an elevated risk for cardiovascular disease or mortality due to cardiovascular disease compared with their normal weight counterparts. However, when attempting to draw conclusions with regards to overall trends it should firstly be noted that a formal meta-analysis was not performed here and that the heterogeneity of the clinical endpoints, sample populations and methods used complicates the ability to directly compare trends across studies. Additionally, some studies with lengthy follow-up periods excluded the first few years of follow-up in order to reduce confounding from the presence of sub-clinical disease at baseline. In comparison, a number of the studies included here were performed in groups in which established cardiovascular disease (or heart failure or previous MI) were a prerequisite for inclusion.

It is apparent that there are a number of underlying pathophysiological changes that are associated with obesity, which may contribute towards the elevated risk for adverse cardiovascular outcomes. Individuals who are defined as being overweight or obese commonly have a greater proportion of adipose tissue than individuals with a normal BMI. Adipose tissue represents an important endocrine organ and consequently overweight and obese individuals frequently have elevated levels of a number of adipocytokines such as leptin and resistin as well as elevated levels of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Together, the elevated levels of these cytokines combined with the effects of the dysregulation of downstream targets may contribute towards pathophysiological processes that are frequently manifest in the form of cardiovascular disease as well as other comorbid conditions. Serum leptin levels have been shown to be directly correlated with percentage body fat[56] and increased leptin levels are independently associated with cardiovascular disease and insulin resistance as well as the generation of reactive oxygen species in endothelial cells.[57] The role of resistin, another adipocytokine that is frequently found in elevated levels in obese subjects, is less well characterized but speculation exists that resistin may represent a key component of the mechanistic link between obesity and the development of insulin resistance and type 2 diabetes and cardiovascular disease.[58] In contrast, the secretion of the adipocytokine adiponectin is reduced in both obese individuals and in those with type 2 diabetes compared with healthy age-matched controls.[59] Adiponectin has been linked to MI and cardiovascular risk; in a study of 18,000 men increased circulating levels of adiponectin were linked with a decreased risk of MI.[59] Further, in men with type 2 diabetes increased levels of circulating adiponectin were associated with decreased cardiovascular risk.[59] An inverse correlation has also been observed between circulating levels of adiponectin and a number of cardiovascular risk factors including hypertension, and C-reactive protein (CRP) levels.

Adiponectin is also thought to play an important role in a number of steps involved in the development of atherosclerosis as well as vascular and cardiac remodeling processes.[60]

There are a number of difficulties in interpreting the data relating anthropometric measurements to cardiovascular risk. The observation that a proportion of the studies included here reported a J-shaped or U-shaped relationship between BMI and adverse cardiovascular endpoints, suggests that underweight patients are also at an elevated risk for cardiovascular disease. As a number of studies either did not include underweight patients or grouped them into the same BMI category as normal weight subjects it is possible that there may be a general underestimation of the detrimental effects of being underweight in terms of cardiovascular disease. Although again, the effects of cachexia due to aging or the presence of comorbid conditions such as chronic obstructive pulmonary disease may be a contributing factor in terms of the elevated risks often observed in underweight patients. These conclusions are then seemingly countered, however, by the "obesity paradox" observed in patients with heart failure and with other preexisting cardiovascular conditions. As discussed earlier, it is possible the deleterious effects of muscle wasting associated with advanced disease or the misdiagnosis of obese patients with signs and symptoms consistent with a differential diagnosis of heart failure may be contributing factors in this paradox but these facts are difficult to reconcile with each other. Interestingly, the obesity paradox appears not to be limited to cardiovascular diseases as increased BMI has also been associated with improved overall survival in patients on maintenance hemodialysis[61] and in patients that have undergone percutaneous coronary intervention.[62]

In this review we have investigated the link between BMI and adverse cardiovascular outcomes and although other indices of obesity such as WC and WHR exist, BMI appears to be the most commonly used, possibly due at least in part to its simplicity. However, as an index of obesity BMI is associated with certain obvious caveats that may lead to erroneous conclusions being drawn from studies. Firstly, BMI does not account for body disposition and is therefore prone to overestimating "fatness" in groups such as athletes and underestimating "fatness" in groups in which sarcopenic obesity may be prevalent, such as the elderly. The agreement in terms of the correlation between different indices of obesity and clinical endpoints is also variable and there is a widely held belief that fat distribution rather than absolute amount may be a more important prognostic indicator.[12,37,63] In terms of predicting the risk for type 2 diabetes both BMI and measures of central adiposity including WC and WHR are strong independent predictors for the development of the disease.[64–66] Additionally, weight gain in adult life is also thought to be an important factor in the risk for developing type 2 diabetes.[64] Another important limitation associated with defining overweight and obesity in terms of BMI is its applicability in Asian populations. In Asian populations the detrimental health effects associated with being overweight or obese commence at a lower BMI compared with European or North American populations. Consequently, in Asian populations a threshold value of 23–25 kg/m^2 is commonly applied for the overweight category and ≥25 kg/m^2 for obesity, in line a report published by the WHO in 2000.[39] The need for anthropometric measurements and thresholds appropriate to the population under investigation is underscored by the findings of numerous studies. For example, data from a study by Lear et al[67] suggests that at a given BMI percentage body fat is approximately four percent greater in South Asians compared with Europeans. Such observations may potentially have implications for the treatment of types with agents such as the thiazolidinedione, which are associated with weight gain due to expansion of the subcutaneous fat depot (and edema in some patients), whereas the proportion of visceral adipose tissue remains stable (or even decreases). However, the long-term implications of the use of thiazolidinediones in terms of cardiovascular risk remain largely unknown.

The link between increasing BMI and cardiovascular disease has been the subject of extensive investigation, as has the link between increasing BMI and the risk for developing type 2 diabetes. The paucity of published data investigating the relationship between elevated BMI and the risk of cardiovascular disease, MI, heart failure and other endpoints specifically in patients with type 2 diabetes is therefore surprising. This relationship was however the subject of a recent study by Eeg-Olofsson et al[55] where, in an observational

study of over 13,000 individuals in the Swedish National Diabetes Register, it was shown that a five unit increase in BMI at baseline was associated with a 15% increase in the risk of CHD, an 11% increase in the risk if stroke and a 13% increase in the risk of cardiovascular disease. Additionally, the authors estimated that the impact of elevated BMI on HbA1c, blood pressure, hyperlipidemia and microalbuminuria was responsible for 40% of the increased risk in terms of CHD and 46% for CVD; they also speculated that the effect of BMI on endothelia dysfunction and low grade inflammation may also be important in the development of cardiovascular disease in overweight and obese patients with diabetes. Moreover, Eeg-Olofsson et al also investigated the impact of weight change during the study on the risk for CHD reporting that a one unit increase in BMI was associated with a 13% increase in the risk for fatal or non-fatal CHD. In terms of the limitations of this study Eeg-Olofsson and colleagues acknowledge that due to lack of data they were unable to adjust for blood lipid values. Additionally, this study was observational in nature and therefore associated with the inherent limitation of this type of study design.

The answers sought for in this review may well be answered by the Look AHEAD (Action for HEAlth in Diabetes) study[68] which is currently ongoing and will examine cardiovascular disease risks and overall mortality in 5,145 obese diabetes patients. Individuals enrolled in this investigation were randomized to either lifestyle intervention or diabetes support and education and will receive 11.5 years of follow up with an anticipated delivery of results by 2012. The Look AHEAD study will also examine the long-term consequences of intentional weight loss and weight gain in this population, a variable that is frequently overlooked in the context of clinical trials and/or epidemiological studies. Although there are data that report the short-term benefits of weight loss in patients with type 2 diabetes, there are little data that examine the long-term implications of weight loss, but the results of the Look AHEAD trial will hopefully address this.

In summary, there is an established causal link between elevated BMI and the increased risk of cardiovascular diseases in general populations, although an obesity paradox in terms of overall survival has been noted in patients with pre-existing cardiovascular conditions and heart failure. Recent evidence from an observational study suggests that overweight and obesity are also independent risk factors for the development of cardiovascular disease in patients with type 2 diabetes.

Acknowledgements

This study was funded by Eli Lilly and company.

GG and JSP are current or former employees of IMS Health who have received consultancy fees from Eli Lilly and company; KB and AK are employees and shareholders of Eli Lilly and Company.

Grant Supporters

This study was supported by funding from Eli Lilly.

References

1. World Health Organization. Obesity and overweight: Fact sheet number 311. 2006. WHO: Geneva. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Last accessed July 22 2009.
2. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes (Lond)*. 2008;32:1431–7.
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27:1047–53.
4. Dagogo-Jack S. Primary prevention of type-2 diabetes in developing countries. *J Natl Med Assoc*. 2006;98:415–9.
5. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA*. 2003;289:76–9.
6. Kopelman P. Health risks associated with overweight and obesity. *Obes Rev*. 2007;8 Suppl 1:13–7.
7. Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med*. 2001;161:1581–6.
8. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA*. 1999;282:1523–9.
9. Lin SX, Pi-Sunyer EX. Prevalence of the metabolic syndrome among US middle-aged and older adults with and without diabetes—a preliminary analysis of the NHANES 1999–2002 data. *Ethn Dis*. 2007;17:35–9.
10. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383–93.
11. 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.
12. Nicklas BJ, Penninx BW, Cesari M, et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: the Health, Aging and Body Composition Study. *Am J Epidemiol*. 2004; 160:741–9.
13. Yusuf S, Hawken S, Ounpuu S, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet*. 2005;366:1640–9.
14. Central obesity and risk of cardiovascular disease in the Asia Pacific Region. *Asia Pac J Clin Nutr*. 2006;15:287–92.
15. Ni Mhurchu C, Rodgers A, Pan WH, Gu DF, Woodward M. Body mass index and cardiovascular disease in the Asia-Pacific Region: an overview of 33 cohorts involving 310 000 participants. *Int J Epidemiol*. 2004;33:751–8.
16. Jee SH, Pastor-Barriuso R, Appel LJ, Suh I, Miller ER, III, Guallar E. Body mass index and incident ischemic heart disease in South Korean men and women. *Am J Epidemiol*. 2005;162:42–8.

17. Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. *Arch Intern Med*. 2002;162:1867–72.
18. Suwaidi JA, Wright RS, Grill JP, et al. Obesity is associated with premature occurrence of acute myocardial infarction. *Clin Cardiol*. 2001;24:542–7.
19. Newton KM, LaCroix AZ. Association of body mass index with reinfarction and survival after first myocardial infarction in women. *Journal of Women's Health*. 1996;5:433–44.
20. Leander K, Wiman B, Hallqvist J, Andersson T, Ahlbom A, de FU. Primary risk factors influence risk of recurrent myocardial infarction/death from coronary heart disease: results from the Stockholm Heart Epidemiology Program (SHEEP). *Eur J Cardiovasc Prev Rehabil*. 2007;14:532–7.
21. Kragelund C, Hassager C, Hildebrandt P, Torp-Pedersen C, Kober L. Impact of obesity on long-term prognosis following acute myocardial infarction. *Int J Cardiol*. 2005;98:123–31.
22. Rea TD, Heckbert SR, Kaplan RC, et al. Body mass index and the risk of recurrent coronary events following acute myocardial infarction. *Am J Cardiol*. 2001;88:467–72.
23. Ness AR, Gunnell D, Hughes J, Elwood PC, Davey SG, 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;56:218–9.
24. Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998;280:1843–8.
25. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med*. 2002;347:305–13.
26. Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation*. 2004;110:1424–30.
27. Bender R, Zeeb H, Schwarz M, Jockel KH, Berger M. Causes of death in obesity: relevant increase in cardiovascular but not in all-cancer mortality. *J Clin Epidemiol*. 2006;59:1064–71.
28. Lissin LW, Gauri AJ, Froelicher VF, Ghayoumi A, Myers J, Giacommini J. The prognostic value of body mass index and standard exercise testing in male veterans with congestive heart failure. *J Card Fail*. 2002;8:206–15.
29. Curtis JP, Selter JG, Wang Y, et al. The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med*. 2005;165:55–61.
30. Habbu A, Lakkis NM, Dokainish H. The obesity paradox: fact or fiction? *Am J Cardiol*. 2006;98:944–8.
31. 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;273:461–5.
32. Curb JD, Marcus EB. Body fat, coronary heart disease, and stroke in Japanese men. *Am J Clin Nutr*. 1991;53:1612S–5.
33. Harris TB, Savage PJ, Tell GS, Haan M, Kumanyika S, Lynch JC. Carrying the burden of cardiovascular risk in old age: associations of weight and weight change with prevalent cardiovascular disease, risk factors, and health status in the Cardiovascular Health Study. *Am J Clin Nutr*. 1997; 66:837–44.
34. Kim KS, Owen WL, Williams D, ms-Campbell LL. A comparison between BMI and Conicity index on predicting coronary heart disease: the Framingham Heart Study. *Ann Epidemiol*. 2000;10:424–31.
35. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15:87–97.
36. Whitlock G, Lewington S, Mhurchu CN. Coronary heart disease and body mass index: a systematic review of the evidence from larger prospective cohort studies. *Semin Vasc Med*. 2002;2:369–81.
37. Canoy D, Boekholdt SM, Wareham N, et al. Body fat distribution and risk of coronary heart disease in men and women in the European Prospective Investigation Into Cancer and Nutrition in Norfolk cohort: a population-based prospective study. *Circulation*. 2007;116:2933–43.
38. Zhang X, Shu XO, Gao YT, et al. Anthropometric predictors of coronary heart disease in Chinese women. *Int J Obes Relat Metab Disord*. 2004;28:734–40.
39. The World Health Organization Asia-Pacific Region. The Asia-Pacific perspective: redefining obesity and its treatment. 2000. Available at: http://www.wpro.who.int/NR/rdonlyres/0A35147B-B1D5-45A6-9FF2-F7D86608A4DE/0/Redefiningobesity.pdf. Last accessed July 22 2009.
40. Mann DM, Lee J, Liao Y, Natarajan S. Independent effect and population impact of obesity on fatal coronary heart disease in adults. *Prev Med*. 2006;42:66–72.
41. Janiszewski PM, Janssen I, Ross R. Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors? *Diabetes Care*. 2007;30:3105–9.
42. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J*. 2005;149:54–60.
43. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med*. 1995;333:677–85.
44. Kannel WB, Cupples LA, Ramaswami R, Stokes J III, Kreger BE, Higgins M. Regional obesity and risk of cardiovascular disease; the Framingham Study. *J Clin Epidemiol*. 1991;44:183–90.
45. Lakka HM, Lakka TA, Tuomilehto J, Salonen JT. Abdominal obesity is associated with increased risk of acute coronary events in men. *Eur Heart J*. 2002;23:706–13.
46. Ajani UA, Lotufo PA, Gaziano JM, et al. Body mass index and mortality among US male physicians. *Ann Epidemiol*. 2004;14:731–9.
47. Widlansky ME, Sesso HD, Rexrode KM, Manson JE, Gaziano JM. Body mass index and total and cardiovascular mortality in men with a history of cardiovascular disease. *Arch Intern Med*. 2004;164:2326–32.
48. Rogers RG, Hummer RA, Krueger PM. The effect of obesity on overall, circulatory disease- and diabetes-specific mortality. *J Biosoc Sci*. 2003;35: 107–29.
49. Domanski MJ, Jablonski KA, Rice MM, Fowler SE, Braunwald E. Obesity and cardiovascular events in patients with established coronary disease. *Eur Heart J*. 2006;27:1416–22.
50. Katzmarzyk PT, Church TS, Janssen I, Ross R, Blair SN. Metabolic syndrome, obesity, and mortality: impact of cardiorespiratory fitness. *Diabetes Care*. 2005;28:391–7.
51. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE study). *Circulation*. 2004;109:706–13.
52. Galal W, van Domburg RT, Feringa HH, et al. Relation of body mass index to outcome in patients with known or suspected coronary artery disease. *Am J Cardiol*. 2007;99:1485–90.
53. Hodge AM, Dowse GK, Collins VR, Zimmet PZ. Mortality in Micronesian Nauruans and Melanesian and Indian Fijians is not associated with obesity. *Am J Epidemiol*. 1996;143:442–55.
54. Rush EC, Plank LD, Laulu MS, Robinson SM. Prediction of percentage body fat from anthropometric measurements: comparison of New Zealand European and Polynesian young women. *Am J Clin Nutr*. 1997; 66:2–7.
55. Eeg-Olofsson K, Cederholm J, Nilsson PM, et al. Risk of cardiovascular disease and mortality in overweight and obese patients with type 2 diabetes: an observational study in 13,087 patients. *Diabetologia*. 2009;52:65–73.
56. Considine RV, Sinha MK, Heiman ML, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med*. 1996;334:292–5.
57. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. *J Am Coll Cardiol*. 2008;52:1201–10.
58. Kusminski CM, McTernan PG, Kumar S. Role of resistin in obesity, insulin resistance and Type II diabetes. *Clin Sci (Lond)*. 2005;109:243–56.
59. Pischon T, Girman CJ, Hotamisligil GS, Rifai N, Hu FB, Rimm EB. Plasma adiponectin levels and risk of myocardial infarction in men. *JAMA*. 2004;291:1730–7.
60. Hopkins TA, Ouchi N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. *Cardiovasc Res*. 2007;74:11–8.
61. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr*. 2005;81:543–54.
62. Poludasu S, Cavusoglu E, Khan W, Marmur JD. Impact of body mass index on long-term all-cause mortality after percutaneous coronary intervention in African-Americans. *J Invasive Cardiol*. 2009;21:20–5.

63. Stevens J, McClain JE, Truesdale KP. Selection of measures in epidemiologic studies of the consequences of obesity. *Int J Obes (Lond)*. 2008;32 Suppl 3: S60–6.
64. Ioannidis I. The road from obesity to type 2 diabetes. *Angiology*. 2008;59:39S–43S.
65. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. *Am J Clin Nutr*. 2006;84:483–9.
66. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr*. 2005;81:555–63.
67. Lear SA, Humphries KH, Kohli S, Birmingham CL. The use of BMI and waist circumference as surrogates of body fat differs by ethnicity. *Obesity (Silver Spring)*. 2007;15:2817–24.
68. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity (Silver Spring)*. 2006;14:737–52.
69. Calling S, Hedblad B, Engstrom G, Berglund G, Janzon L. Effects of body fatness and physical activity on cardiovascular risk: risk prediction using the bioelectrical impedance method. *Scand J Public Health*. 2006;34:568–75.
70. Czernichow S, Bruckert E, Bertrais S, Galan P, Hercberg S, Oppert JM. Hypertriglyceridemic waist and 7.5-year prospective risk of cardiovascular disease in asymptomatic middle-aged men. *Int J Obes (Lond)*. 2007; 31:791–6.
71. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J*. 2007;28:850–6.
72. Harris TB, Launer LJ, Madans J, Feldman JJ. Cohort study of effect of being overweight and change in weight on risk of coronary heart disease in old age. *BMJ*. 1997;314:1791–4.
73. McGee DL. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15:87–97.
74. Megnien JL, Denarie N, Cocaul M, Simon A, Levenson J. Predictive value of waist-to-hip ratio on cardiovascular risk events. *Int J Obes Relat Metab Disord*. 1999;23:90–7.
75. Prineas RJ, Folsom AR, Kaye SA. Central adiposity and increased risk of coronary artery disease mortality in older women. *Ann Epidemiol*. 1993;3:35–41.
76. Tanko LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation*. 2005;111:1883–90.
77. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004;292:2471–7.
78. Welborn TA, Dhaliwal SS, Bennett SA. Waist-hip ratio is the dominant risk factor predicting cardiovascular death in Australia. *Med J Aust*. 2003;179:580–5.