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Journal of Clinical Epidemiology 59 (2006) 1064–1071

Journal of Clinical Epidemiology

Causes of death in obesity: Relevant increase in cardiovascular but not in all-cancer mortality

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Accepted 17 January 2006

Abstract

Background and Objective: To assess the relation between body mass index (BMI) and the risk of death from various causes in a prospective cohort study.

Methods: In 6,192 obese patients (BMI ⩾25kg/m^2) with mean BMI 36.6 kg/m^2 (SD 6.1) and mean age 40.4 years (SD 12.9) who had been referred to the obesity clinic of the Heinrich-Heine-University Düsseldorf, Germany, between 1961 and 1994, there were 1,058 deaths from all causes during a median follow-up time of 14.8 years. We calculated standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) for death from predefined groups of diseases by using Germany as reference population.

Results: In both sexes, risk of death from cardiovascular diseases (men: SMR = 2.2, CI 1.9–2.5; women: SMR = 1.6, CI 1.5–1.8), from diabetes (men: SMR = 5.4, CI 3.2–8.7; women: SMR = 3.5, CI 2.6–4.8), and in men from digestive diseases (SMR = 1.6, CI 1.01–2.3) was significantly increased. In contrast to other studies, an association between obesity and all-cancer mortality could not be found. Only in morbidly obese women (BMI ⩾40 kg/m^2), all-cancer mortality was significantly increased (SMR = 1.5, CI 1.1–1.9).

Conclusion: Obesity is associated with increased risk of death from cardiovascular diseases and diabetes in both sexes, and from diseases of the digestive system in men.

Keywords: Body mass index; Excess mortality; Cause of death; ICD codes; Morbid obesity; Obesity

1. Introduction

Several prospective cohort studies have confirmed that obesity is associated with excess mortality, although there are still conflicting results regarding the dose–response relation between body mass index (BMI) and mortality [1–4]. Main causes of death described to be associated with obesity are cardiovascular diseases, diabetes, and cancer. However, there are only few epidemiologic studies presenting data for extreme BMI classes [5].

In the Framingham Study, obesity was an independent risk factor for cardiovascular disease and mortality [6]. Subsequently, the independent influence of obesity on the occurrence of cardiovascular disease and cardiovascular mortality has been confirmed in numerous cohort studies [7–16] and a recent meta-analysis [17]. However, there are still scarce data to quantify the association between BMI and cardiovascular mortality in morbid obesity (BMI ⩾40 kg/m^2) [18]. In most studies, the largest cut-point used to describe high grades of obesity lies between 30 and 35 kg/m^2. Therefore, most studies provide no specific information for the group of morbidly obese subjects with BMI higher than 40 kg/m^2.

Whereas diabetes is clearly associated with cardiovascular disease and obesity [19], data for cancer mortality in overweight people are scarce or inconsistent, especially in higher BMI groups. In several cohort studies no association

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0895-4356/06/$ – see front matter
doi: 10.1016/j.jclinepi.2006.01.006

between BMI and cancer mortality was found [11,13,20,21]. On the other hand, a large number of case–control and cohort studies reported an increased risk of death from all cancers and from cancers at multiple specific sites. The cohort study conducted by the American Cancer Society indicated excess mortality from cancers of the colon and rectum, prostate, uterine corpus, uterine cervix, gallbladder, and the female breast [22]. In a Swedish population-based case–control study associations between BMI and risk for esophageal and gastric cardia adenocarcinoma were found [23]. Results of the National Health and Nutrition Examination Survey [24] and the Cancer Prevention Study II [25] strongly supported the finding that excess body weight is a risk factor for colon cancer among men and women. A large Swedish cohort study of hospitalized obese patients indicated risk elevations for cancers of the small intestine, colon, gallbladder, pancreas, larynx, renal parenchyma, bladder, cervix uteri, endometrium, ovary, brain, connective tissue, and for lymphomas [26]. Additionally, an association of obesity with risk of female breast, prostate, and pancreas cancer was found, which was modified by age [26]. The Malmö Diet and Cancer Study supported the hypothesis that obesity is positively associated with risk of breast cancer in postmenopausal women [27]. In a recent report of the Cancer Prevention Study II, increased risks with increasing BMI were reported in both men and women for death due to cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas, and kidney, as well as for death due to non-Hodgkin's lymphoma and multiple myeloma [28]. Significantly increased death rates with increasing BMI were also found for cancers of the stomach and prostate in men and for cancers of the breast, uterus, cervix, and ovary in women [28]. A population-based case–control study conducted in Canada provided further evidence that obesity increases the risk for cancer of the kidney, colon, postmenopausal breast, pancreas, ovary, and prostate, as well as for non-Hodgkin's lymphoma, leukemia, and multiple myeloma [29]. However, in a recent meta-analysis based upon person-level data from 26 observational studies, a small nonsignificant protective effect of overweight (BMI between 25 and 30 kg/m^2) on cancer mortality was found compared to normal weight (BMI between 18.5 and 25 kg/m^2) in both sexes [17]. Small risk elevations for cancer mortality were found for obese persons (BMI $\geqslant$30 kg/m^2) compared to persons with normal weight (BMI between 18.5 and 25 kg/m^2), which were statistically significant in women but not in men [17].

In this article, a prospective investigation of the causes of death in a large cohort of obese patients is presented. We considered main groups of death causes such as all cancers, all cardiovascular diseases, all digestive diseases and all external causes, as well as individual cancer sites and individual diseases such as diabetes. This cohort has been used previously to examine the association between obesity and all-cause mortality [30], the effect of age on this association [31], and the relation of body weight and blood pressure to all-cause mortality [32]. The analysis presented in this article provides detailed information on the causes of death in obesity, which has not yet been available in former studies, especially for the group of morbidly obese patients.

2. Methods

2.1. Subjects and data

The Düsseldorf Obesity Mortality Study is a prospective cohort study of 6,192 obese patients (1,591 men, 4,601 women), who had been referred to the obesity clinic of the Heinrich-Heine-University of Düsseldorf, Germany, between 1961 and 1994. A detailed description of the design and data collection can be found elsewhere [30]. Inclusion criteria were an age at entry between 18 and 75 years and a BMI $\geqslant$25kg/m^2. Height and weight were measured with the patients wearing light clothes (shirts and trousers or skirts) and no shoes. After 1972, all patients signed an agreement that data may be used for scientific purposes, provided that anonymity is warranted in published material.

2.2. Mortality follow-up and causes of death

Vital status was ascertained from municipal residents' registries. Up to 1994/1995, 1,058 (17.1%) patients died (397 men, 679 women). In the first follow-up in 1980, death certificates of the deceased patients could be obtained from local health authorities. However, after 1982, access to the death certificates was not available due to the prevailing state law of North Rhine Westphalia (NRW). Recently, it has become possible in Germany to obtain the causes of death directly from regional statistical offices [33]. Through the State Office for Data Processing and Statistics (LDS) NRW, individual causes of death according to the *International Classification of Diseases* (ICD) for persons deceased in NRW after 1975 could be retrieved. Those deaths for which a death certificate but no ICD code was available (n = 37) were coded by trained codification staff from the Statistical State Office Saarland. The combination of the information from the local health authorities and the LDS resulted in 998 (94.3%) known causes of death. Codes for the underlying causes of death corresponding to the ICD revision in use at the time of death were applied (7th Revision for deaths occurring between 1961 and 1967, 8th Revision for deaths between 1968 and 1978, 9th Revision for deaths from 1979 onwards). Groups of death causes were defined by taking the three different ICD revisions into account. In a former analysis, we presented standardized mortality ratios (SMRs) for all-cause mortality by using the population of NRW as reference [30]. In this article, we used the population of Germany as reference because rates of cause-specific mortality data are available in quite more detail for Germany as a whole than for NRW alone. National reference rates of Germany were obtained from the

World Health Organization (WHO) mortality database and from the National German Statistical Office.

2.3. Statistical analysis

The BMI at baseline was categorized into approximate quartiles as follows: group 1: 25 to <32, group 2: 32 to <36, group 3: 36 to <40, group 4: ⩾40 kg/m^2 (morbid obesity). Person-years were calculated from the date of entry into the cohort (date of the first visit in the obesity clinic) until death or the latest date with known vital status (usually between 1994 and 1995, latest date 31.12.1995). We calculated SMRs [34] for predefined causes of deaths separately for men and women. Significance tests for the SMRs were calculated by using Byar's approximation to the exact Poisson test [34]. Exact confidence intervals (CIs) for the SMRs were calculated by means of the Poisson distribution. Trends in the SMRs across BMI groups were investigated by means of the Poisson trend test [34]. For statistical computations SAS Version 8.02 (SAS Institute Inc., Cary, NC) and the program PAMCOMP [35] were used.

3. Results

The 6,192 patients (1591 men, 4601 women) were followed up for a maximum time of 34 years with a mean of 14.3 years (SD 8.2, median 14.8 years). The range for BMI was 25.0 to 74.4 kg/m^2 (mean 36.6, SD 6.1 kg/m^2) and for age 18 to 75 years (mean 40.4, SD 12.9 years). Up to 1994/1995, 1,058 (17.1%) patients died (379 men, 679 women). For 998 deceased patients (94.3% of 1058) the ICD code was available. The total number of observed patient years was 88,646 (men: 22,269, women: 66,377). A descriptive analysis of the patients' baseline characteristics is shown in Table 1. A more detailed descriptive analysis is presented elsewhere [30–32]. The estimated cause-specific SMRs with exact 95% confidence intervals are shown in Table 2.

Cardiovascular disease (501 deaths, 50% of 998 patients with known death cause) represented the main cause of death, followed by cancer (211 deaths, 21%), diabetes (61 deaths, 6.1%), and diseases of the digestive system (57 deaths, 5.7%). Risk of death from cardiovascular disease (men: SMR = 2.2, 95% CI 1.9–2.5; women: SMR = 1.6, 95% CI 1.5–1.8), from diabetes (men: SMR = 5.4, 95% CI 3.2–8.7; women: SMR = 3.5, 95% CI 2.6–4.8), and from diseases of the digestive system in males (men: SMR = 1.6, 95% CI 1.0–2.3; women: SMR = 1.2, 95% CI 0.8–1.7) was significantly increased compared to the population of Germany. Naturally, the highest excess risk was found for death from obesity (ICD-9 code 278; men: SMR = 33.7, 95% CI 16.2–62.0; women: SMR = 10.3, 95% CI 5.0–19.0). In contrast to other studies, an overall association between obesity and cancer mortality could not be found. The only specific cancer sites showing a significantly increased mortality were colon cancer in both sexes (men: SMR = 5.4, 95% CI 2.3–10.5; women: SMR = 2.5, 95% CI 1.3–4.3) and uterine corpus cancer in women (SMR = 2.1, 95% CI 1.04–3.7). There was no significantly increased risk of death due to breast cancer in women (SMR = 1.0, 95% CI 0.7–1.4). In both sexes, risk of death from external causes was lower than in the German population, although the result was not statistically significant (men: SMR = 0.8, 95% CI 0.4–1.3; women: SMR = 0.8, 95% CI 0.5–1.2). The number of deaths due to symptoms, senility and ill-defined conditions was significantly higher than in the population of Germany (men: SMR = 2.4, 95% CI 1.3–4.0; women: SMR = 3.2, 95% CI 2.2–4.6).

To investigate the effect of increasing BMI, the leading causes of deaths were also analyzed separately according to

Table 1
Baseline characteristics according to BMI among 6192 obese patients in Germany, 1961–1994

		BMI			
BMI group	Total n = 6,192	25 to < 32 n = 1,438	32 to < 36 n = 1,860	36 to < 40 n = 1,347	⩾40 n = 1,535
Men	n = 1,591	n = 315	n = 548	n = 376	n = 345
BMI (kg/m^2)	36.6 (5.9)	30.1 (1.4)	34.0 (1.1)	37.8 (1.1)	45.5 (5.2)
Weight (kg)	112.7 (20.3)	92.8 (8.5)	104.8 (9.4)	116.2 (10.1)	139.6 (19.6)
Height (cm)	175.3 (7.1)	175.3 (6.9)	175.4 (7.4)	175.1 (7.0)	175.2 (7.0)
Age (years)	39.7 (13.2)	41.5 (13.1)	40.4 (13.8)	38.9 (13.9)	37.7 (11.3)
Systolic blood pressure (mmHg)	161.4 (26.9)	153.1 (24.2)	158.9 (25.2)	162.1 (27.0)	172.2 (28.5)
Diastolic blood pressure (mmHg)	100.8 (17.3)	95.3 (15.1)	99.1 (16.7)	101.7 (16.2)	107.5 (18.9)
Diabetes	304 (22%)	65 (24%)	105 (22%)	65 (20%)	66 (21%)
Women	n = 4,601	n = 1,123	n = 1,312	n = 971	n = 1,190
BMI (kg/m^2)	36.6 (6.2)	29.7 (1.6)	34.0 (1.2)	37.9 (1.2)	45.0 (4.6)
Weight (kg)	97.1 (17.3)	80.2 (7.4)	90.4 (7.9)	100.2 (8.7)	117.8 (14.7)
Height (cm)	162.8 (6.7)	164.2 (6.5)	162.9 (6.6)	162.5 (6.7)	161.8 (6.7)
Age (year)	40.7 (12.8)	39.0 (12.6)	40.8 (13.3)	41.4 (12.9)	41.5 (12.2)
Systolic blood pressure (mmHg)	158.4 (28.3)	148.7 (23.6)	155.5 (25.9)	159.8 (27.5)	169.8 (31.5)
Diastolic blood pressure (mmHg)	97.8 (15.9)	92.1 (13.4)	96.2 (14.5)	98.8 (14.9)	104.2 (17.9)
Diabetes	602 (15%)	95 (10%)	161 (14%)	129 (15%)	217 (20%)

Values are mean (SD) or numbers (%).
BMI was missing for n = 12, blood pressure for n = 260, and diabetes for n = 678 patients.

Table 2
SMRs with 95% confidence intervals for predefined groups of ICD codes among 6,192 obese patients in Germany, 1961–1994

		Men			Women		
Causes of death	ICD-9 Codes	No.	SMR	95% CI	No.	SMR	95% CI
All causes	001–999	379	1.73	1.56–1.92	679	1.46	1.35–1.57
Infectious diseases	001–139	0	0	0–1.87	3	0.89	0.18–2.59
All cancers	140–208	55	0.92	0.69–1.20	156	1.03	0.88–1.21
Buccal cavity and pharynx	140–149	1	0.44	0.01–2.44	0	0	0–2.83
Esophagus	150	2	1.10	0.13–3.97	0	0	0–3.49
Stomach	151	2	0.35	0.04–1.28	8	0.70	0.30–1.38
Colon	153	8	5.35	2.31–10.53	13	2.51	1.34–4.30
Rectum	154	2	0.80	0.10–2.88	3	0.48	0.10–1.40
Liver and gallbladder	155–156	2	1.45	0.18–5.22	9	1.37	0.63–2.60
Pancreas	157	3	1.07	0.22–3.12	5	0.73	0.24–1.70
Larynx	161	2	1.98	0.24–7.16	0	0	0–14.29
Lung	162	8	0.56	0.24–1.10	13	1.46	0.76–2.49
Skin	172–173	0	0	0–4.78	2	1.10	0.13–3.97
Breast	174–175	1	12.80	0.32–71.31	31	0.98	0.67–1.39
Cervix uteri	180	—	—	—	6	1.09	0.40–2.38
Corpus uteri	179, 181–182	—	—	—	11	2.09	1.04–3.74
Ovary	183	—	—	—	14	1.25	0.68–2.10
Prostate	185	3	0.80	0.16–2.32	—	—	—
Testis	186	1	3.64	0.09–20.26	—	—	—
Bladder	188	2	1.04	0.13–3.76	3	1.49	0.31–4.35
Kidney	189	3	1.43	0.29–4.18	5	1.39	0.45–3.24
Brain and nervous system	191–192	1	0.74	0.02–4.11	5	1.52	0.49–3.55
Endocrine	193–194	0	0	0–13.71	1	0.86	0.02–4.77
All lymphoma	200–202	2	0.59	0.07–2.12	6	0.72	0.27–1.57
Multiple myeloma	203	0	0	0–7.50	3	2.13	0.44–6.24
All leukemia	204–208	1	0.57	0.01–3.20	8	1.84	0.79–3.62
All other cancers	Rest of 140–208	11	—	—	10	—	—
Unspecified neoplasms	230–239	0	0	0–2.50	1	0.26	0.01–1.44
Diabetes mellitus	250	17	5.40	3.15–8.65	44	3.54	2.57–4.76
Obesity (since 1968)	278	10	33.72	16.17–62.01	10	10.32	4.95–18.98
Cardiovascular diseases	390–459	194	2.21	1.91–2.54	307	1.62	1.45–1.82
Hypertension	401–405	11	5.23	2.61–9.36	12	1.50	0.78–2.63
Coronary heart disease	410–414	104	2.18	1.78–2.64	125	1.75	1.46–2.09
Acute myocardial infarction (since 1968)	410	64	1.84	1.42–2.35	86	1.97	1.58–2.44
Cardiac dysrhythmias and heart failure	426–428	31	15.57	10.58–22.10	46	8.81	6.45–11.75
Cerebrovascular diseases	430–438	23	1.39	0.88–2.08	74	1.43	1.12–1.80
Nonmalignant respiratory diseases	460–519	10	0.79	0.38–1.45	20	1.05	0.64–1.62
Pneumonia	480–486	1	0.37	0.01–2.04	8	1.27	0.55–2.50
Chronic bronchitis	490–493	5	0.69	0.22–1.61	10	1.12	0.54–2.06
Diseases of the digestive system	520–579	25	1.56	1.01–2.30	32	1.19	0.81–1.68
Gastrointestinal hemorrhage	531–533	1	0.78	0.02–4.36	0	0	0–1.93
Liver cirrhosis	571	14	1.37	0.75–2.29	15	1.14	0.64–1.88
Diseases of the genitourinary system	580–629	3	1.26	0.26–3.69	9	1.36	0.62–2.59
External causes	E800–E999	14	0.75	0.41–1.26	18	0.76	0.45–1.20
Transport accidents	E800–E848	3	0.54	0.11–1.57	4	0.77	0.21–1.96
Suicides	E950–E959	6	0.79	0.29–1.72	7	0.69	0.28–1.72
Homicides	E960–E969	0	0	0–10.42	1	1.53	0.04–8.56
All other external causes	Rest of E800–E999	5	—	—	6	—	—
Symptoms, senility, and ill-defined	780–799	14	2.38	1.30–3.99	33	3.24	2.23–4.55
All other causes	Rest of 001–999	9	—	—	14	—	—
No ICD code available		28			32		

the BMI groups. The estimated SMRs for the BMI groups with exact 95% confidence intervals are shown in Tables 3 and 4.

A statistically significant trend in the SMRs across BMI groups was observed in men for all causes ($P < .001$), cardiovascular diseases ($P < .001$), coronary heart disease ($P = .001$), cardiac dysrhythmias and heart failure ($P < .001$), and diseases of the digestive system ($P = .018$). In women, there was a significant trend for all causes ($P < .001$), all cancers ($P = .023$), uterine cancer ($P = .008$), diabetes ($P < .001$), cardiovascular diseases ($P < .001$), coronary heart disease ($P < .001$), cardiac dysrhythmias and heart failure ($P < .001$), and cerebrovascular diseases ($P < .001$). The significant trend for all cancers in females is based only on an increased risk of morbidly obese (BMI $\geqslant$40 kg/m^2) women (SMR = 1.5, 95% CI 1.1–1.9). The nonsignificant trend test for diabetes in men is probably due to low power. In morbidly obese men, only one death due to diabetes was observed. In an analysis based upon three BMI groups by collapsing groups 3 and 4, an estimated SMR of 9.55 (95% CI 4.58–17.57) for the highest BMI group was obtained, resulting in a significant trend test ($P = .019$).

4. Discussion

In this large cohort of obese patients, the main findings were increased mortality risks for cardiovascular and digestive diseases as well as for diabetes, whereas the all-cancer mortality risk was not increased. The colon and uterine corpus were the only cancer sites with elevated mortality among cohort members, although a clear dose–response relationship with BMI was only seen for uterine corpus cancer. Both cancers have previously been reported to be associated with obesity [22,24–26,28,36]. Obesity and the associated high energy intake may affect colon carcinogenesis by various mechanisms, including slow colonic transit leading to increased exposure to carcinogens, development of adenoma or—in animal experiments—aberrant crypts [37,38]. Recent studies indicate that insulin and insulin-like growth factors [39,40] as well as leptin [41] might play a role in the pathogenesis of colon cancer. Uterine cancer carcinogenesis is likely to be associated with altered endogenous hormone metabolism, in particular with regard to estrogens [42]. These considerations would also apply to breast cancer carcinogenesis. We did not, however, observe any increases in breast cancer mortality in the cohort. As the association between BMI and breast cancer varies by menopausal status [43], this may be explained by the large proportion of young women in our cohort. About 85% of the women were younger than 55 years at baseline. Among women older than 55 years, only five deaths due to breast cancer were observed. Similarly, no mortality increases were found for other cancer sites previously postulated as obesity-associated, such as the esophagus, stomach, and rectum. This may partially be explained by the small number of specific cancer deaths which limits the power of our study. However, the upper limits of the confidence interval, for example, for stomach cancer among both men and women, indicate only very slight potential risk increases.

Obesity is regarded as a risk factor for nonalcoholic fatty liver disease and nonalcoholic steatohepatitis due to higher insulin levels and insulin resistance, with a subsequently increased risk for developing liver cirrhosis and hepatocellular carcinoma [44]. Data on the risk for developing hepatocellular carcinoma in obesity are inconsistent. Significant increased liver cancer mortality has been found in some studies [28,45], whereas other large cohort studies could not find these associations [26,46]. We observed a small, nonsignificant increase in mortality for liver cirrhosis and hepatocellular carcinoma in men and women. This relatively small impact of obesity on liver mortality may be due to the fact that alcohol abuse and viral hepatitis currently still have the largest impact on the etiology and pathogenesis of liver cirrhosis.

Our study confirmed marked risk increases and a clear dose–response association with BMI for cardiovascular diseases among both obese men and women. Obese men had

Table 3
SMRs with 95% confidence intervals for main predefined groups of ICD codes according to BMI among 1591 obese men in Germany, 1961–1994

	BMI group			
Cause of death	25 to <32 kg/m^2	32 to <36 kg/m^2	36 to <40 kg/m^2	$\geqslant$40 kg/m^2
All causes**	1.32 (1.0–1.7)	1.37 (1.1–1.6)	2.02 (1.6–2.5)	3.04 (2.5–3.7)
All cancers	0.71 (0.3–1.3)	0.82 (0.5–1.3)	1.16 (0.6–2.0)	1.13 (0.5–2.1)
Colon	5.68 (0.7–20.5)	3.30 (0.4–11.9)	3.13 (0.1–17.4)	10.2 (1.2–36.8)
Diabetes mellitus	2.62 (0.3–9.5)	3.07 (0.8–7.9)	14.2 (6.5–27.0)	2.41 (0.1–13.5)
Cardiovascular diseases**	1.69 (1.2–2.3)	1.88 (1.5–2.4)	2.24 (1.6–3.1)	4.36 (3.2–5.8)
Hypertension	5.70 (1.2–16.7)	2.30 (0.3–8.3)	11.98 (3.9–28)	3.74 (0.1–20.8)
Coronary heart disease**	1.71 (1.1–2.7)	2.03 (1.4–2.8)	2.25 (1.4–3.5)	4.12 (2.7–6.0)
Cardiac dysrhythmias and heart failure**	10.99 (3.5–25.7)	18.86 (10.3–31.6)	3.84 (0.4–13.9)	53.56 (25.6–98.5)
Cerebrovascular diseases	1.15 (0.4–2.7)	1.28 (0.6–2.4)	1.25 (0.3–3.2)	2.81 (0.9–6.6)
Diseases of the digestive system*	0.84 (0.2–2.5)	1.12 (0.5–2.3)	2.10 (0.8–4.3)	2.94 (1.3–5.8)
External causes	0.79 (0.2–2.3)	0.72 (0.2–1.7)	0.71 (0.2–2.1)	0.83 (0.2–2.4)

Test for trend: **P<.001, *P<.05.

Table 4
SMRs with 95% confidence intervals for main predefined groups of ICD codes according to BMI among 4601 obese women in Germany, 1961–1994

	BMI group			
Cause of death	25 to <32 kg/m^2	32 to <36 kg/m^2	36 to <40 kg/m^2	⩾40 kg/m^2
All causes***	1.01 (0.8–1.2)	1.21 (1.0–1.4)	1.29 (1.1–1.5)	2.29 (2.1–2.6)
All cancers*	0.88 (0.6–1.3)	1.03 (0.8–1.4)	0.72 (0.5–1.1)	1.45 (1.1–1.9)
Colon	0 (0–3.7)	3.21 (1.0–7.5)	2.42 (0.5–7.1)	3.69 (1.2–8.6)
Breast	0.86 (0.3–1.9)	0.98 (0.5–1.8)	0.71 (0.2–1.7)	1.31 (0.7–2.4)
Corpus uteri**	0 (0–3.5)	0.64 (0.0–3.6)	3.29 (0.9–8.4)	4.29 (1.6–9.3)
Diabetes mellitus***	1.21 (0.3–3.5)	1.57 (0.6–3.4)	3.95 (2.0–6.9)	7.58 (4.8–11.4)
Cardiovascular diseases***	0.86 (0.6–1.2)	1.34 (1.1–1.7)	1.51 (1.2–1.9)	2.77 (2.3–3.3)
Hypertension	0 (0–2.3)	1.63 (0.4–4.2)	1.51 (0.3–4.4)	2.63 (0.9–6.1)
Coronary heart disease***	1.35 (0.8–2.1)	1.44 (0.98–2.1)	1.57 (1.1–2.3)	2.83 (2.1–3.8)
Cardiac dysrhythmias and heart failure***	2.13 (0.2–7.7)	8.09 (4.4–13.6)	7.28 (3.5–13.4)	17.19 (10.5–26.5)
Cerebrovascular diseases***	0.58 (0.2–1.3)	1.12 (0.7–1.8)	1.53 (0.9–2.4)	2.41 (1.6–3.5)
Diseases of the digestive system	0.53 (0.1–1.5)	1.13 (0.5–2.1)	1.44 (0.7–2.7)	1.59 (0.8–2.9)
External causes	0.76 (0.2–2.0)	0.87 (0.3–1.9)	0.37 (0.1–1.4)	0.99 (0.4–2.1)

Test for trend: ***$P < .001$, **$P < .01$, *$P < .05$.

a 16- and obese women had a ninefold risk increase for cardiac dysrhythmias and heart failure compared to the general population. These observations are in line with a recent study that found an increased risk of heart failure in obese patients [47]. In this study, heart failure was at least partially independent of the other risk factors associated with excessive body weight, and obesity alone was estimated to account for 11% of cases of heart failure in men and 14% of cases in women [47].

The high mortality from diabetes and from obesity has also been demonstrated before. However, the excess risks estimated here are in part lower than reported previously. For example, in the Health Professionals Study a relative risk of 3.9 was estimated for death due to cardiovascular disease among men with BMI ⩾30 kg/m^2 [21]. Our data show excess risks (SMRs) of 1.9, 2.2 and 4.4 in men for the BMI groups 32 to <36, 36 to <40, and ⩾40 kg/m^2, respectively. Thus, it is important to describe the dose–response relation between obesity and mortality risk over the whole BMI range.

The increases related to poorly defined causes of mortality (ICD-9 categories 780–799) are somewhat difficult to understand. For these frequently multimorbid patients, the diagnosing physicians may tend to more often omit a more thorough search for specific causes of death than for other patients.

One strength of our study is that more than one-fifth ($n = 345$) of all male patients and approximately one-fourth ($n = 1{,}190$) of the female cohort were morbidly obese (BMI ⩾40 kg/m^2). Only scarce mortality data have so far been available for this group of patients. A large cohort study conducted in Norway included 713 men and 6,050 women with BMI above 40 kg/m^2 [48]. However, in the Norwegian study, only all-cause mortality was examined and no information about the causes of death was available. In a report of the Cancer Prevention Study II, data on morbid obesity (BMI ⩾40 kg/m^2) were presented, but only for cancer mortality and not for other death causes [28]. Thus, our study adds detailed information about the causes of death in obesity, especially for the group of patients with morbid obesity. Our considered cohort of obese patients showed no relevantly increased all-cause mortality risk in the moderately obese subjects. Accordingly, it may be conjectured that our findings may carry over to the general population, when morbidly obese subjects are compared to those with normal weight.

We see the completeness of the mortality follow-up and of the specific causes of death as a further strength of the current study. The collected ICD codes are basically identical to the data entered into official mortality statistics in Germany. Systematic bias in the assignment of causes of death is therefore unlikely. Additionally, our study reveals advantages concerning duration and total costs of this new method of obtaining the causes of death directly from regional statistical offices in comparison to the traditional approach via the local health authorities [33]. This new way of obtaining information about the causes of death can be used in future cohort studies in Germany and may have a large impact on the success of cohort studies. As the storage time for death certificates is short in some Federal German states, causes of death cannot be obtained from the local health authorities if death occurred before storage deadline. This was the case for a large number of deceased patients in our study. Therefore, an adequate analysis of the causes of death would have been impossible without the information from the regional statistical office.

Several limitations of our study should be noted. Because all patients were recruited through the Düsseldorf obesity clinic, the cohort does not represent a random sample of all obese patients in Germany. It appears possible that obese persons with particular social or health-related characteristics were overrepresented in the cohort recruited via this highly specialized obesity clinic. However, it can be assumed that the referred obese patients have more health problems associated with obesity than the remaining population of obese people living in the same geographic area,

so that selection bias—if at all—induces an overestimation of the true excess risk. The cohort is of only moderate size, which limits the power of the study to precisely estimate mortality risks for some causes. BMI was measured only once at one age, for each subject. Thus, no conclusion can be drawn about the effect of changes in weight over time. No other anthropometric measures such as waist-to-hip ratio or percentage body fat were collected. Important confounders such as smoking, alcohol, medication use, physical activity, or menopausal, as well as social status, could not be analyzed for the total cohort. Another methodologic limitation concerns the accuracy of the diagnosis obtained from the death certificate. A validation study conducted in Germany based on a study population of 1.1 million inhabitants in different regions between October 1992 and April 1993 revealed a reasonable accuracy of the diagnoses on the level of the main ICD groups [49]. Overall, cancer diagnoses were more reliable and valid than diagnoses of the circulatory system. However, in most cases misclassification of diagnosis or exposure, that is, overweight in our situation, should be nondifferential resulting in underestimation of the SMR. This may not, however, apply to the diagnoses obesity and diabetes, resulting in a potential overestimation of excess risk for these causes of death.

In the context of the ongoing discussion about the obesity epidemic, detailed information on obesity-associated morbidity and mortality is necessary to define further research priorities and to target preventive clinical management more effectively including counseling messages for patients. Our article points to the importance of cardiovascular and metabolic causes of death for obese patients. Especially, the high number of morbidly obese patients included in our study may help to define the future role of surgery in the treatment of obesity. Weight reduction surgery is recommended only for morbidly obese patients (BMI $\geqslant$40 kg/m^2). Bariatric surgery is one of the fastest growing surgical procedures in the United States, with an increase of more than 400% between 1998 and 2002 [50]. Benefits and risks for the patient and costs of different methods of bariatric surgery have recently been analyzed [51–53], and need to be compared to the mortality risks of morbid obesity as described by our study.

The high risks for heart failure and cardiac dysrhythmias observed in the study indicate that early warning signs of heart disease such as electrophysiologic abnormalities may require particular attention in these patients. Also, preventive advice can build on the convincing demonstration of the major—particularly cardiovascular—health gains patients can expect when lower BMI values are achieved.

In conclusion, this study confirms the increased risk of obese subjects for causes of death due to diseases of the circulatory and digestive systems and certain cancers, especially colon cancer in both sexes and cancer of the uterine corpus in women. However, an overall increased risk of all cancers could not be found, except for morbidly obese women. When describing the association between obesity and cause-specific mortality, the dose–response relation between increasing BMI and risk of death should be considered, especially for cancer mortality. Based on our results, therapeutic approaches and preventive advice with the focus on lowering cardiovascular morbidity are more important than those focusing on cancer morbidity in obese patients.

Acknowledgments

We thank the State Office for Data Processing and Statistics of North Rhine Westphalia, Düsseldorf, for providing the individual causes of death according to the ICD for persons deceased after 1975, and the National German Statistical Office for providing national reference rates for death causes not available from the WHO. We thank H. Schubert-Engelhart, N. Suffner and S. Assmann for assistance, and R. Lenz-Tönjes (Bielefeld, Germany), H. Overmann (Düsseldorf, Germany), and T. Rotthoff (Düsseldorf, Germany) for cooperation in the context of this study. The advice of D. Bardehle (Bielefeld, Germany) in defining the groups of death causes is gratefully acknowledged.

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