Body Mass Index and Risk of Cardiovascular Disease, Cancer and All-cause Mortality

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ABSTRACT

Objectives: To determine the dose-response relationship between body mass index (BMI) and cause-specific mortality among Canadian adults.

Methods: The sample includes 10,522 adults 18-74 years of age who participated in the Canadian Heart Health Surveys (1986-1995). Participants were divided into 5 BMI categories (<18.5, 18.5-24.9, 25-29.9, 30-34.9, and ≥35 kg/m^2). Multivariate-adjusted (age, sex, exam year, smoking status, alcohol consumption and education) hazard ratios for all-cause, cardiovascular disease (CVD) and cancer mortality were estimated using Cox proportional hazards regression.

Results: There were 1,149 deaths (402 CVD; 412 cancer) over an average of 13.9 years (range 0.5 to 19.1 years), and the analyses are based on 145,865 person-years. The hazard ratios (95% CI) across successive BMI categories for all-cause mortality were 1.25 (0.83-1.90), 1.00 (reference), 1.06 (0.92-1.22), 1.27 (1.07-1.51) and 1.65 (1.29-2.10). The corresponding hazard ratios for CVD mortality were 1.30 (0.60-2.83), 1.00 (reference), 1.57 (1.22-2.01), 1.72 (1.27-2.33) and 2.09 (1.35-3.22); and for cancer, the hazard ratios were 1.02 (0.48-2.21), 1.00 (reference), 1.14 (0.90-1.44), 1.34 (1.01-1.78) and 1.82 (1.22-2.71). There were significant linear trends across BMI categories for all-cause (p=0.0001), CVD (p<0.0001) and cancer mortality (p=0.003).

Conclusions: The results demonstrate significant relationships between BMI and mortality from all causes, CVD and cancer. The increased risk of all-cause, CVD and cancer mortality associated with an elevated BMI was significant at levels above 30 kg/m^2; however, overweight individuals (BMI 25-29.9 kg/m^2) also had an approximately 60% higher risk of CVD mortality.

Key words: Obesity; overweight; death; cohort studies; longitudinal studies

La traduction du résumé se trouve à la fin de l'article.

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Several cohort studies have demonstrated a J- or U-shaped relationship between body mass index (BMI) and mortality, such that mortality rates are higher in people with low and high BMI compared to those of normal weight.[1,2] These studies contributed evidence for the development of clinical thresholds for overweight and obesity.[3-5] Although there is little disagreement that extreme levels of BMI confer an increased risk of mortality, there is controversy about the risk associated with having a BMI in the overweight (25-29.9 kg/m^2) range.[6] For example, studies from the U.S. National Health and Nutrition Examination Surveys (NHANES) reported that mortality rates were not increased in people classified as overweight, compared to normal weight people.[7,8]

Several cohort studies from different countries have recently examined the dose-response relationship between BMI and mortality, and the results generally support a J-shaped association.[9-12] Although the specific shape of the curve differs across studies, there is always a point at which elevated BMI is associated with an increased risk of mortality. Given that there are limited data on this issue for Canada,[13-15] the purpose of this study was to determine the dose-response relationship between BMI and mortality among Canadian adults.

METHODS

Participants and study design

The sample includes 10,522 adults 18-74 years of age who participated in the Canadian Heart Health Surveys (CHHS), a series of provincial surveys on CVD risk factors.[16] Potential participants were identified in medical insurance registries and randomly sampled within 6 age-by-sex strata using a 2-stage probability design that selected approximately 2,000 participants per province. The CHHS were conducted in all provinces between 1986 and 1992,[16] followed by a second survey in Nova Scotia in 1995 (Nova Scotia Health Survey).[17] However, not all provinces participated in this mortality

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Conflict of Interest: None to declare.

Table 1. Descriptive Characteristics of the Sample of 10,522 Canadian Adults in the Canadian Heart Health Surveys Follow-up Study by Sex and Vital Status

	Men		Women	
	Survivors	**Decedents**	**Survivors**	**Decedents**
N	4503	707	4870	442
Follow-up Time (y)*	14.4 (2.9)	8.7 (4.2)	14.5 (2.8)	9.3 (4.3)
Age (y)	40.7 (15.9)	63.8 (11.4)	41.3 (16.0)	64.5 (10.9)
BMI (kg/m^2)	26.5 (4.4)	27.2 (4.5)	25.4 (5.3)	27.6 (6.1)
BMI Category (%)				
<18.5 kg/m^2	1.0	1.1	3.8	3.6
18.5-24.9 kg/m^2	38.4	29.1	51.7	31.9
25-29.9 kg/m^2	42.7	45.8	26.9	33.9
30-34.9 kg/m^2	14.0	19.4	11.6	19.2
≥35 kg/m^2	3.9	4.5	6.1	11.3
Smoking Status (%)				
Non-smoker	28.8	12.7	40.1	40.5
Former smoker	38.8	56.3	31.2	29.9
Current smoker	32.5	31.0	28.7	29.6
Alcohol Consumption (%)				
Never drink	1.6	1.4	3.9	11.5
Former drinker	10.0	17.5	11.3	22.6
Current drinker	77.6	67.6	73.8	55.2
Unknown	10.8	13.4	11.0	10.6
Education (%)				
Elementary school or less	3.3	9.2	2.3	9.7
Some secondary school	28.5	53.5	27.3	49.3
Secondary school completed	49.1	28.2	54.4	32.1
University degree completed	19.2	9.2	16.1	8.8

* y=years

study. The results reported here are from Manitoba (n=2,228), Saskatchewan (n=1,712), Alberta (n=1,980), British Columbia (n=1,259) and Nova Scotia (n=3,343; 2 surveys). Of the original 13,118 participants, the sample was reduced after eliminating deaths that occurred within six months of the survey (n=39), those over age 75 or who were missing information on education (n=470), and those who were missing BMI (n=2,087).

Exposure assessment

Height and weight were measured using a standard physician's scale, and the BMI was calculated and divided into 5 categories (<18.5, 18.5-24.9, 25-29.9, 30-34.9, and ≥35 kg/m^2).[5] Information on covariates was collected by questionnaire, and included smoking status, alcohol consumption and education. Smoking was coded as non-smoker, former smoker or current smoker, and alcohol consumption was coded as never, former, current drinker, or unknown. Educational attainment was classified as: elementary school or less, some secondary school, secondary school completed, university degree completed, or unknown.

Ascertainment of mortality

Mortality status was determined by linking to the Canadian Mortality Database (CMDB) at Statistics Canada.[18] The CMDB is regularly updated by death registrations supplied by every province and territory. Record linkage was performed using computerized probabilistic matching, and the potential for deaths to be missed using this approach is small (3-7%).[19,20] The present analysis includes all deaths that occurred between six months after the completion of CHHS data collection and December 31, 2004. Although reverse causation cannot be ruled out, deaths occurring within the first six months after data collection were not included in order to attempt to account for the existence of pre-existing disease. The linked file was received from Statistics Canada in April, 2010. There were 1,149 deaths (402 CVD and 412 cancer) over an average of 13.9 years (range 0.5 to 19.1 years) of follow-up, and the analyses are based on 145,865 person-years. Underlying cause of death was determined by using the International Classification of Diseases (ICD) code, revision in effect (ICD-9 through 1999 or ICD-10 from 2000), for deaths identified. The ICD codes were used to identify deaths from CVD (ICD-9: 390-448; ICD-10: I00-I78) and from cancer (ICD-9: 140-239; ICD-10: C00-D48). Ethics approval for the linkage to the CMDB was obtained from the Institutional Review Boards of all participating institutions.

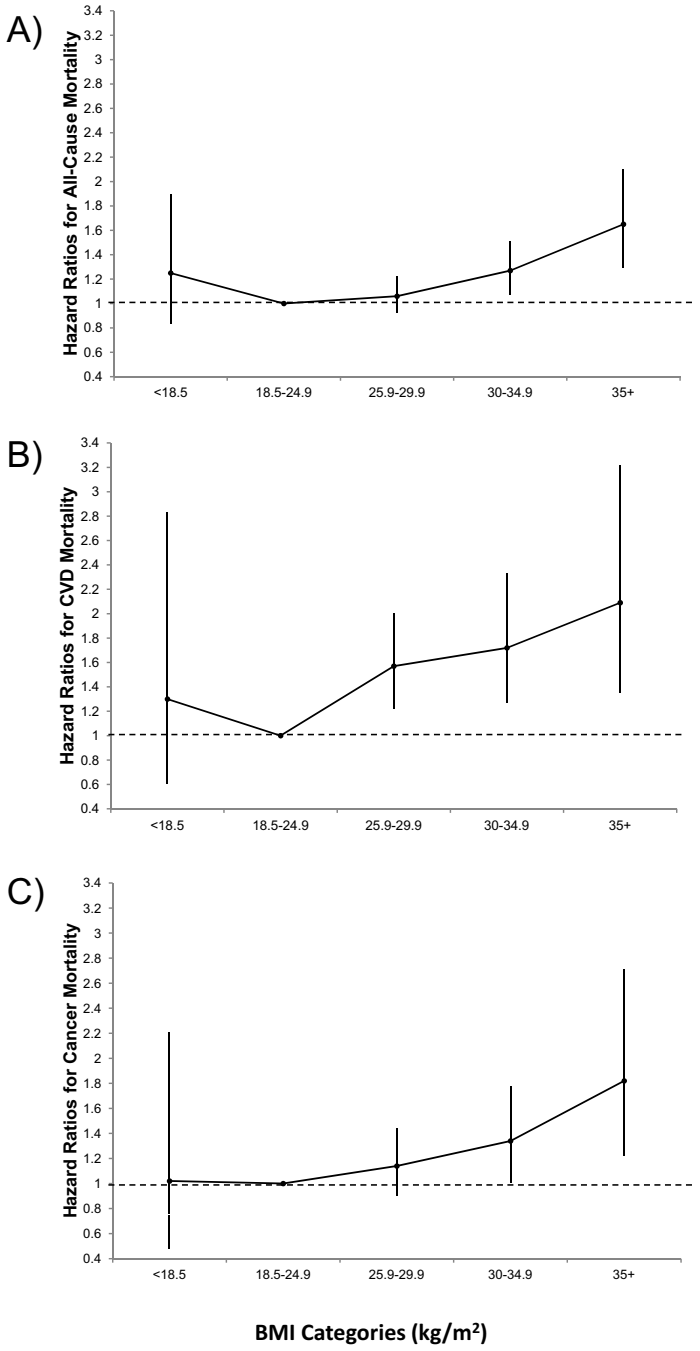
Statistical analysis

All analyses were conducted using SAS version 9.2 (Cary, NC). Mortality rates were computed across baseline BMI categories, and hazard ratios were computed using Cox proportional hazards regression models. Both age-adjusted and multivariable-adjusted (age, sex, exam year, smoking status, alcohol consumption and education) hazard ratios were estimated. Age and exam year were included as continuous variables, and other covariates were included as categorical variables as described above. Since 10.9% of the sample was missing information on alcohol consumption, missing values were multiply-imputed (MI) (5 imputations) under missing at random (MAR) assumptions and using the MI procedure.[21] Results from the proportional hazards regressions across the five imputed datasets were averaged, and the standard errors were adjusted appropriately, using the MIANALYZE procedure. Results were also compared with those from complete-case analyses, and no differences were noted in the estimated effects. All analyses were first conducted on the total sample of men and women, followed by stratification by sex.

RESULTS

At baseline, 54% of the sample was overweight or obese, and 30.5% were current smokers. The descriptive characteristics of the sample are provided in Table 1. Decedents were older ($p<0.0001$) and also had a higher mean BMI ($p<0.0001$) than survivors at baseline. Figure 1 presents the association between baseline BMI and mortality

Figure 1. Hazard ratios across baseline categories of BMI for A) all-cause, B) cardiovascular disease (CVD), and C) cancer mortality among 10,522 men and women in the Canadian Heart Health Surveys Follow-up Study



All models included age, exam year, smoking status, alcohol consumption and education as covariates. Error bars represent 95% confidence intervals.

from all causes, CVD and cancer in men and women. A J-shaped relationship is apparent for total and CVD mortality, where the lowest risk of mortality is seen in normal-weight participants at baseline, and increasing risk is evident across successively higher categories of BMI.

Age- and multivariate-adjusted hazard ratios for mortality are presented for men and women in Table 2. The association between BMI and all-cause mortality was not significant in men, but there were significant associations with CVD and cancer mortality. Both overweight and obese men had an elevated risk of CVD mortality, with a significant linear trend across categories; however, the risk for cancer mortality did not become significant until a BMI ≥35 kg/m^2. There was no apparent elevated risk of mortality in underweight men.

There were significant linear trends across BMI categories for mortality rates from all causes, CVD and cancer in women (Table 2). The excess mortality risk did not become significant until the obese category (BMI 30-34.9 kg/m^2), as overweight women did not have a significantly elevated risk. In contrast to men, there appears to be an elevated risk of mortality in underweight women; however, due to the small number of cases, this association was only significant for all-cause mortality.

DISCUSSION

The results demonstrate significant relationships between BMI and mortality from all causes, CVD and cancer. The increased risks of all-cause and cancer mortality were evident in the obese; however, the risk of CVD mortality was also elevated in overweight men (BMI 25-29.9 kg/m^2). Flegal et al.[7] reported an increased risk of all-cause mortality in underweight and obese participants, but a lower risk among overweight participants, compared to the normal weight category, respectively, in the NHANES. In a subsequent analysis of cause-specific mortality, there was no association between overweight and cancer and CVD mortality; however, being obese was associated with an increased risk of CVD mortality.[8]

Several studies have been published examining the dose-response relationship between BMI and mortality using large cohorts. There was a J-shaped relationship between BMI and all-cause mortality among 1.2 million Korean adults.[10] The lowest risk of death was among participants with a BMI of 23-24.9 kg/m^2. Whereas the risk of all-cause mortality was higher among underweight compared to normal-weight subjects, the relationship between BMI and CVD mortality increased steadily with increasing BMI.[10] Likewise, the relationship between BMI and all-cause mortality was J-shaped in a cohort of 1.46 million White adults from the National Cancer Institute Cohort Consortium, with the lowest risk among participants with a BMI of 22.5-24.9 kg/m^2.[9] The shape of the association was similar for CVD death; however, the magnitude of the hazard ratios was greater at every BMI above 22.4-24.9 kg/m^2 than for mortality from cancer and other causes.[9] A recent study that followed 1.14 million Asians from 19 cohorts found that participants with a BMI below 15 kg/m^2 had an elevated risk of mortality; however, the risks associated with an elevated BMI differed by population. East Indians had an elevated risk of death with higher BMI, but populations from Bangladesh and India did not.[12] Overall, the lowest risk of death among the Asian cohort was in participants with a BMI of 22.6-27.5 kg/m^2. A study of 184,697 Austrian adults found a U-shaped relationship between BMI and mortality, with elevated risks in the low BMI (<18.5 kg/m^2) and high BMI (≥35 kg/m^2) groups, relative to the reference (22.5-24.9 kg/m^2).[11] The increased risk associated with a high BMI was largely driven by CVD, and to a lesser extent cancer mortality. The lowest risk of all-cause mortality in the present study was among normal-weight adults (BMI 18.5-24.9 kg/m^2), which is in the range of the nadirs reported in these previous studies.

There have been only limited attempts to assess the mortality risk associated with overweight and obesity in Canadians. A study

Table 2. Relative Risks of All-cause, Cardiovascular Disease, and Cancer Mortality Associated With Body Mass Index in 10,522 Men and Women From the Canadian Heart Health Surveys Follow-up Study

	Body Mass Index (kg/m²)					
	<18.0	18-24.9	25-29.9	30-34.9	≥35.0	P for Trend
Men						
N	55	1933	2246	768	208	
Person-years of follow-up	790	27,115	30,576	9997	2689	
All-cause mortality						
Deaths	8	206	324	137	32	
Age-adjusted hazard ratio (95% CI)	1.02 (0.50-2.06)	1.00	0.96 (0.80-1.14)	1.15 (0.93-1.43)	1.28 (0.88-1.86)	0.12
Multivariate-adjusted hazard ratio (95% CI)*	0.84 (0.41-1.72)	1.00	0.99 (0.83-1.18)	1.16 (0.94-1.45)	1.41 (0.97-2.05)	0.05
Cardiovascular disease mortality						
Deaths	2	53	138	52	12	
Age-adjusted hazard ratio (95% CI)	0.95 (0.23-3.90)	1.00	1.56 (1.13-2.14)	1.68 (1.15-2.46)	1.92 (1.03-3.60)	0.003
Multivariate-adjusted hazard ratio (95% CI)*	0.77 (0.19-3.22)	1.00	1.61 (1.17-2.22)	1.71 (1.16-2.51)	2.16 (1.14-4.18)	0.001
Cancer mortality						
Deaths	2	72	117	47	15	
Age-adjusted hazard ratio (95% CI)	0.73 (0.18-2.99)	1.00	0.98 (0.73-1.32)	1.13 (0.78-1.63)	1.72 (0.99-3.00)	0.12
Multivariate-adjusted hazard ratio (95% CI)*	0.56 (0.16-2.19)	1.00	1.04 (0.77-1.39)	1.16 (0.82-1.64)	2.02 (1.14-3.55)	0.04
Women						
N	200	2657	1459	650	346	
Person-years of follow-up	2907	38,305	20,298	8642	4549	
All-cause mortality						
Deaths	16	141	150	85	50	
Age-adjusted hazard ratio (95% CI)	1.98 (1.18-3.32)	1.00	1.12 (0.89-1.42)	1.38 (1.05-1.81)	1.90 (1.38-2.63)	0.002
Multivariate-adjusted hazard ratio (95% CI)*	1.80 (1.07-3.03)	1.00	1.16 (0.92-1.46)	1.47 (1.12-1.93)	1.85 (1.33-2.56)	0.0008
Cardiovascular disease mortality						
Deaths	5	40	55	30	15	
Age-adjusted hazard ratio (95% CI)	2.11 (0.83-5.34)	1.00	1.36 (0.90-2.04)	1.60 (0.99-2.56)	1.91 (1.05-3.45)	0.04
Multivariate-adjusted hazard ratio (95% CI)*	1.87 (0.73-4.79)	1.00	1.44 (0.95-2.16)	1.78 (1.10-2.88)	1.86 (1.02-3.39)	0.02
Cancer mortality						
Deaths	5	49	57	32	16	
Age-adjusted hazard ratio (95% CI)	1.73 (0.69-4.35)	1.00	1.32 (0.90-1.94)	1.61 (1.02-2.52)	1.81 (1.03-3.20)	0.03
Multivariate-adjusted hazard ratio (95% CI)*	1.57 (0.62-3.97)	1.00	1.36 (0.92-2.00)	1.70 (1.08-2.68)	1.80 (1.02-3.18)	0.02

* Multivariate models included age, exam year, smoking status, alcohol consumption and education as covariates.

of adults from the 1981 Canada Fitness Survey showed only a slightly elevated risk of all-cause mortality in overweight participants (HR = 1.16; 95% CI: 0.96-1.39), whereas the risk increased substantially among participants with a BMI ≥35 kg/m² (HR = 2.96; 1.39-6.29).[14] An analysis of women from the Canadian Breast Screening Study found increased risks of all-cause mortality at a BMI 25-27.9 kg/m² (HR = 1.28; 1.24-1.32) and 28-29.9 kg/m² (HR = 1.34; 1.29-1.39), relative to a BMI 18.5-21.9 kg/m², and the risks increased linearly across levels of BMI.[13] More recently, an analysis from the National Population Health Survey found a lower risk of all-cause mortality among overweight participants (HR = 0.83; 0.72-0.96), and the risk did not become significant until a BMI ≥35 kg/m² (HR = 1.36; 1.00-1.85).[15] Our results support these previous Canadian studies and suggest only a minimally increased risk of all-cause mortality associated with being overweight. To our knowledge, none of the previous Canadian studies have examined associations with cause-specific mortality, and the present study suggests that overweight individuals may have a significantly elevated risk of CVD mortality, particularly in men.

Marked strengths of this study include the large population-based sample of men and women with measured BMI followed prospectively for an average of 13.9 years, and the reliable link to the CMDB to determine causes of death. However, the sample sizes were relatively small for some subgroups (such as underweight men), resulting in wider confidence limits for the estimates of RR and these estimates should be interpreted with caution. Unfortunately, information on changes in BMI over the follow-up period is not available; having this information would have refined the analysis. It would have been preferred to stratify the analysis by smoking status; however, the sample size was not sufficient for this. Previous studies have demonstrated that the relationship between BMI and mortality is similar in smokers and non-smokers; however, it tends to be stronger in non-smokers.[9,10]

This study adds important new information on the risks associated with being overweight. Although the risk of all-cause and cancer mortality was only significantly elevated among obese individuals, those in the overweight range had an increased risk of CVD mortality, particularly in men. This finding has significant implications for public health. Further research is required to understand the full range of short-term and long-term health risks associated with overweight versus obesity. However, based on self-reported data from the 2010 Canadian Community Health Survey, the prevalence of overweight and obesity is approximately 52.3%, and the prevalence of overweight *per se* (BMI 25-29.9 kg/m²) is 34.2%,[22] which represents a substantial proportion of the at-risk population. Thus, based on the results of this study, a significant proportion of the general Canadian population is at elevated risk for premature mortality from cardiovascular disease, cancer and all causes.

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RÉSUMÉ

Objectif : Déterminer la relation dose-réponse entre l'indice de masse corporelle (IMC) et la mortalité par cause chez les Canadiens d'âge adulte.

Méthode : Notre échantillon comprenait 10 522 adultes de 18 à 74 ans ayant participé aux Enquêtes sur la santé cardiovasculaire des Canadiens (1986-1995). Les participants ont été divisés en cinq catégories d'IMC (<18,5, 18,5-24,9, 25-29,9, 30-34,9 et ≥35 kg/m^2). À l'aide du modèle de régression à effet proportionnel de Cox, nous avons estimé des coefficients de danger ajustés selon plusieurs variables (âge, sexe, année d'examen, usage du tabac, consommation d'alcool et niveau d'instruction) pour la mortalité toutes causes confondues, la mortalité par maladie cardiovasculaire (MCV) et la mortalité par cancer.

Résultats : Il y a eu 1 149 décès (402 par MCV; 412 par cancer) sur une moyenne de 13,9 ans (intervalle de 0,5 à 19,1 ans), et les analyses sont basées sur 145 865 personnes-années. Les coefficients de danger (IC de 95 %) par catégorie successive d'IMC pour la mortalité toutes causes confondues étaient de 1,25 (0,83-1,90), 1,00 (référence), 1,06 (0,92-1,22), 1,27 (1,07-1,51) et 1,65 (1,29-2,10). Les coefficients de danger correspondants pour la mortalité par MCV étaient de 1,30 (0,60-2,83), 1,00 (référence), 1,57 (1,22-2,01), 1,72 (1,27-2,33) et 2,09 (1,35-3,22); pour le cancer, ils étaient de 1,02 (0,48-2,21), 1,00 (référence), 1,14 (0,90-1,44), 1,34 (1,01-1,78) et 1,82 (1,22-2,71). Nous avons relevé des tendances linéaires significatives d'une catégorie d'IMC à l'autre pour la mortalité toutes causes confondues (p=0,0001), la mortalité par MCV (p<0,0001) et la mortalité par cancer (p=0,003).

Conclusion : Ces résultats font état de relations significatives entre l'IMC et la mortalité toutes causes confondues, par MCV et par cancer. Dans les trois cas, le risque accru de mortalité associé à un IMC élevé était significatif à plus de 30 kg/m^2; cependant, les sujets en surpoids (IMC 25-29,9 kg/m^2) avaient aussi un risque plus élevé d'environ 60 % de mourir d'une MCV.

Mots clés : obésité; surpoids; mort; études de cohortes; études longitudinales