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# No Interaction of Body Mass Index and Smoking on Diabetes Mellitus Risk in Elderly Women

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## Abstract

**Objective—**We sought to assess the interaction of smoking and BMI on diabetes risk.

**Methods—**We analyzed data from a community-based prospective cohort of 41,836 women from Iowa who completed a baseline survey in 1986 and five subsequent surveys through 2004. The final analysis included 36,839 participants.

**Results—**At baseline (1986), there were 66% never smokers, 20% former smokers, and 14% current smokers. Subjects represented 40% normal weight, 38% overweight, and 22% obese individuals. Compared to normal weight women, the hazard ratio (HR) for diabetes was increased in overweight (HR 1.96; 95% CI 1.75–2.19) and obese subjects (HR 3.58; 95% CI 3.19–4.02). The hazard ratio for diabetes increased in a dose-dependent manner with smoking intensity. Compared to never smokers, former smokers had a higher risk for diabetes (HR 1.22; 95% CI 1.11–1.34). Among current smokers, the hazard ratio for diabetes was 1.21 (95% CI 0.95–1.53) for 1–19 pack-year smokers, 1.33 (95% CI 1.12–1.57) for 20–39 pack-year smokers, and 1.45 (95% CI 1.23–1.71) for ≥40 pack-year smokers. Similar trends were observed when the results were stratified by BMI. A test of interaction between BMI and smoking on diabetes risk was not statistically significant.

**Conclusions—**Our findings suggest that smoking increases diabetes risk through a BMI-independent mechanism.

### Keywords

Diabetes mellitus; smoking cessation; obesity; epidemiology

## Introduction

Cigarette smoking, overweight, and obesity constitute significant modifiable risk factors for cardiovascular disease and subsequent mortality.(Gregg et al., 2005, Thom et al., 2006) From 1997–2001, smoking contributed to 137,979 annual deaths in the United States from cardiovascular disease.(Centers for Disease Control and, 2005) Cigarette smoking and overweight are also risk factors for diabetes, the fourth leading cause of mortality in the United States.(Heron, 2007, Willi et al., 2007, Mokdad et al., 2003)

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Cigarette smokers typically weigh less than non-smokers.(Flegal et al., 1995) However, smokers frequently use cigarettes to control their weight,(Klesges et al., 1997) and weight gain after smoking cessation is associated with smoking relapse.(Borrelli and Mermelstein, 1998) Consequently, overweight and obese smokers may possess a heightened risk for diabetes if smoking and BMI act synergistically to increase the risk for diabetes.(Mokdad et al., 2003)

The Nurses Health Study observed a higher relative risk for diabetes mellitus among female smokers with a BMI >29.(Rimm et al., 1993) Other findings suggest that BMI does not modify the association between smoking and diabetes.(Will et al., 2001) Determination of an interaction between smoking and BMI on diabetes risk may enhance understanding of the risk for diabetes among overweight and obese smokers and improve counseling of smokers on their diabetes risk.

This study uses population-based survey data from the Iowa Women's Health Study (IWHS) to assess the BMI-stratified impact of smoking on the risk for diabetes mellitus in a cohort of elderly women. We hypothesized that cigarette smoking contributes to diabetes risk independent of BMI.

## Methods

The Iowa Women's Health Study (IWHS) is a prospective cohort study of 41,836 women aged 55–69 years at enrollment in 1986. Details of the cohort characteristics have been described previously.(Folsom et al., 1990) In 1986, a 16-page questionnaire was mailed to 99,286 randomly selected women and returned by 41,836 women (41.9% response rate). Follow-up questionnaires (response rates) were mailed in 1987 (91%), 1989 (90%), 1992 (83%), 1997 (79%) and 2004 (69%). The cohort was followed for mortality through annual linkage to the Iowa certificate files, supplemented by linkage to the National Death Index. We estimate <1% loss to follow-up for mortality.

Responses to the initial survey defined baseline cigarette smoking habits including smoking status (current, former, or never), age at initiation, intensity (average number of cigarettes per day), and duration (years). Smoking status was defined according to the following question on the baseline questionnaire: "Have you ever smoked cigarettes on a regular basis, that is, more than 100 cigarettes in your entire life?" To those who responded in the affirmative, we asked: "Do you smoke cigarettes now?" We defined former smokers as those who answered "yes" to the first question and "no" to the second. Current smokers were those who answered "yes" to both questions. For participants who smoked, the questionnaire asked about cigarettes smoked daily and number of years smoked. Cumulative pack-years smoked at baseline was the average number of cigarette packs smoked per day multiplied by the total number of years smoked. Self-reported height and weight at baseline were used to calculate body mass index (BMI), defined as weight (kg) divided by height ($m^2$). BMI categories were defined according to federal guidelines: underweight (BMI <18.5), normal weight (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0).(Expert Panel on the Identification, 1998) Diabetes status was defined based on an affirmative response to the question: "Have you ever been told by a doctor that you have sugar diabetes (diabetes mellitus)?" Diabetes status was collected at baseline and with each follow-up questionnaire.

Nutrient data was obtained from a 127-item food frequency questionnaire. Waist and hip circumferences were obtained by having a friend use a tape measure (included with the survey) and take the measurements in duplicate. Both types of data have been shown to be valid and reliable in this study population.(Kushi et al., 1988, Munger et al., 1992)

Exclusions included women who carried a baseline diagnosis of diabetes or had previously used medications to treat diabetes (N=2880), had an underweight baseline BMI <18.5 (N=443),

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did not return any follow-up questionnaires (N=1189), did not answer smoking questions on the baseline questionnaire (N=808), or initially reported diabetes on the first follow-up survey but provided a diagnosis date that preceded the baseline enrollment date (N=5). The main analysis excluded women with an underweight BMI due to a higher likelihood of poor health. We included them in a sensitivity analysis. Exclusions were not mutually exclusive. The main analysis included 36,839 participants.

Data were descriptively summarized using frequencies and percentages for categorical variables and means and standard deviations (SD) for continuous variables. Person-time at risk was calculated from baseline to the date of the last completed follow-up survey for women who did not report a diagnosis of diabetes. Among women who reported a diabetes diagnosis, person-time was calculated as the sum of the known disease-free period plus the midpoint between the date of questionnaire at which diabetes was first reported and the date of the previous questionnaire. A previous report from this cohort used similar methods to calculate diabetes cases.(Meyer et al., 2000)

Hazard ratios (HR's) and 95% confidence intervals were calculated using Cox proportional hazards regression analysis. Time to diagnosis was modeled as a function of age rather than length of follow-up time, since age better predicts diabetes risk than follow-up time.(Korn et al., 1997) We assessed the effect of smoking on incidence of diabetes both overall and by strata defined by BMI. We defined smoking status at baseline as never, former, or current, and we stratified current smokers by pack-years smoked, resulting in a five-level smoking variable. For all analyses, we modeled never smokers as the referent group. We fit two sets of regression models: (1) age-adjusted and (2) multivariate adjusted for waist-to-hip ratio, marital status, educational status, physical activity, hypertension, use of hormone replacements, vitamin supplement use, and dietary and nutrient consumption estimated from the food-frequency questionnaire (intake of calories, fat, cholesterol, carbohydrates, fruit and vegetables, red meat, whole grains, vitamin E, dairy products, and alcohol). We examined whether BMI modified the smoking-diabetes association using standard tests of interaction. The interaction p-value was based on the five-category smoking variable and three-category BMI variable as defined above. All statistical tests were two-sided, and all analyses were carried out using the SAS (SAS Institute, Inc., Cary, NC) and Splus (Insightful, Inc., Seattle, WA) software systems.

## Results

We based the results on a maximum of 18 years and 487,013 person-years of follow-up. Mean follow-up was 13.2 years. Our cohort included 36,839 women with a mean baseline age of 62 years. Baseline smoking status included 24,265 (66%) never smokers, 7,271 (20%) former smokers, and 5,303 (14%) current smokers. A total of 14,899 women (40%) were of normal weight, 13,836 (38%) were overweight, and 8,104 (22%) were obese. During a maximum of 18 years and 487,013 person-years of follow-up, we detected 3,281 incident cases of diabetes mellitus (6.74 cases/1,000 person-years).

Overweight and obese individuals demonstrated higher mean waist-to-hip ratios, red meat consumption, and cholesterol intake. They were more likely to report low educational levels, low physical activity, less vitamin E consumption, and the presence of hypertension (Table 1). Normal, overweight, and obese subjects showed similarities with respect to other variables.

Across all BMI levels, current smokers tended to consume fewer carbohydrates, more alcohol, fewer servings of whole grains, and fewer fruits and vegetables than former smokers. A similar trend existed between former and never smokers. Within BMI categories, current smokers also tended to have higher waist-to-hip ratios, less education, and higher rates of physical inactivity (Table 1).

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As expected, BMI showed a strong association with diabetes risk. After multivariate adjustment, and compared to normal weight women, overweight subjects possessed a nearly two-fold risk of diabetes (HR 1.96, 95% CI 1.75–2.19). Obese individuals had a more than three-fold risk of diabetes (HR 3.58, 95% CI 3.19–4.02).

A strong, positive association existed between smoking status and diabetes incidence regardless of BMI. Multivariate analyses found former smokers 22% (HR 1.22, 95% CI 1.11–1.34) and current smokers 35% (HR 1.35, 95% CI 1.20–1.51) more likely to develop diabetes than never smokers. Current smokers demonstrated a dose-dependent increased risk for diabetes based on baseline smoking intensity: HR 1.21 (95% CI 0.95–1.53) for 1–19 pack-years; HR 1.33 (95% CI 1.12–1.57) for 20–39 pack-years; HR 1.45 (95% CI 1.23–1.71) for ≥40 pack-years, compared to never smokers.

Table 2 presents the age- and multivariate-adjusted hazard ratios for diabetes based on smoking status across normal, overweight, and obese BMI strata. Across all BMI strata in both the age- and multivariate-adjusted models, a trend of increased diabetes risk existed when comparing from never smokers to current, heavier smokers. Dose-response trends were consistent in the normal and obese BMI strata. In general, the heaviest current smokers (20–39 and ≥40 pack-years) demonstrated a higher HR for incident diabetes, although results were not always statistically significant. Former smokers displayed an increased HR for incident diabetes if they were obese (multivariate-adjusted HR 1.34, 95% CI 1.18–1.53).

A test for the interaction between smoking and baseline BMI on the risk for diabetes was not statistically significant (p=0.30). The test for interaction and hazard ratios for diabetes suggest that the relationship between cigarette smoking and diabetes incidence does not differ in BMI categories. However, the results should be viewed with a certain level of caution due to lower power to detect modest interactions.

Primary analyses excluded 443 women with BMI <18.5 $kg/m^2$. A series of sensitivity analyses grouped these women with those in the normal BMI group. Results (not shown) were similar to those in Table 2.

## Discussion

In this study, current smoking increased the risk for incident diabetes mellitus in a large cohort of elderly women in a dose-dependent fashion. No statistically significant interaction existed between smoking and BMI on diabetes risk. All results were similar after adjusting for multiple demographic and lifestyle variables.

Our results are consistent with previous studies examining the risk of diabetes based on smoking status in women. Analysis of data on 434,637 women collected from 1959–1972 in the Cancer Prevention Study I (CPS-I) observed an increased risk for diabetes among women smoking >1 pack per day.(Will et al., 2001) Body weight did not modify the association between smoking and diabetes among men and women. However, this study was not specifically designed to measure such an association, and the authors did not report the test of for an interaction between BMI and smoking status.(Will et al., 2001)

The Nurses Health Study observed a multivariate-adjusted relative risk of diabetes of 1.42 (95% CI 1.18–1.72) among women smoking ≥25 cigarettes daily compared to non-smokers over 12 years of follow-up. The relative risk for diabetes among women with a BMI ≤29 smoking ≥25 cigarettes daily was not significantly elevated when compared to non-smokers (1.23, 95% CI 0.87–1.74). However, among those with a BMI >29, the relative risk increased to 1.40 (95% CI 1.11–1.75).(Rimm et al., 1993) At 16-years of follow-up, the Nurses Health Study reported a multivariate-adjusted relative risk of diabetes mellitus of 1.39 (95% CI 1.02–

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1.88) for normal weight and 1.40 (95% CI 1.14–1.71) for overweight current smokers smoking ≥15 cigarettes daily. Among obese individuals, they observed a significantly elevated multivariate-adjusted relative risk among former (1.24, 95% CI 1.12–1.39), light (1–14 cigarettes daily) current smokers (1.47, 95% CI 1.17–1.85), and heavy (≥15 cigarettes daily) current smokers (1.31, 95% CI 1.10–1.56).(Hu et al., 2001) These results compare similarly to our multivariate-adjusted hazard ratios across respective BMI strata. While the results are similar, the Nurses Health Study included only working women in health professions.(Rimm et al., 1995, Hu et al., 2001) The similarity of our data from the IWHS cohort makes the association of smoking with diabetes risk applicable to a more general population of older females.

A recent meta-analysis of 25 studies representing 1.2 million participants and 45,844 incident cases of diabetes found a pooled relative risk for diabetes of 1.44 (95% CI 1.31–1.58) for current smokers compared to non-smokers. Of the 7 studies reporting gender-specific data for women, the pooled relative risk for diabetes among current smokers (not corrected for BMI) was 1.25 (95% CI 1.03–1.46) compared to non-smokers. Regardless of BMI and gender, the pooled relative risk for diabetes among former smokers was 1.23 (95% CI 1.14–1.33).(Willi et al., 2007) In contrast to our findings, this meta-analysis reported a modest effect modification of BMI on the risk for diabetes among smokers. The relative risk for smokers with a BMI ≥25 was 1.57 (95% CI 1.35–1.82), while those with a BMI <25 had a relative risk of 1.34 (95% CI 1.13–1.58).(Willi et al., 2007) However, this stratification included both men and women across only two levels of BMI and two levels of current smoking intensity.

Our results align with previous studies to support the well-documented association between cigarette smoking and diabetes risk in women.(Willi et al., 2007, Foy et al., 2005, Will et al., 2001, Hu et al., 2001, Rimm et al., 1993) While smoking impacts BMI, our findings suggest a BMI-independent mechanism through which smoking elevates diabetes risk. Our study also adjusts for more potential confounding variables than most previous studies. For example, among other large studies specifically examining the risk for diabetes mellitus in women based on smoking status, the Nurses Health Study did not adjust for diet or physical activity.(Hu et al., 2001) The CPS-I study adjusted for education, diet components, physical activity, and alcohol, but did not consider calorie intake or marital status in their model.(Will et al., 2001) The Insulin Resistance Atherosclerosis Study accounted for abdominal obesity and alcohol consumption but not physical activity, diet components, education, or marital status.(Foy et al., 2005)

Proposed mechanisms to explain the observed relationship between smoking and diabetes include decreased insulin sensitivity, abdominal obesity, endothelial dysfunction, and antiestrogenic effects of smoking in women.(Eliasson, 2003, Celermajer et al., 1993, Khaw et al., 1988, Simon et al., 1997) Smoking has been shown to acutely provoke hyperglycemia, elevated insulin levels, and hypertension.(Frati et al., 1996, Facchini et al., 1992) However, others imply an insulin-independent mechanism through which smoking may mediate diabetes risk.(Godsland et al., 1992, Wareham et al., 1996) Our results imply that effect modification of BMI on the smoking-mediated risk for diabetes mellitus may be less important than previous data suggest.(Rimm et al., 1993)

The major strength of this study is the large, prospective cohort design with long-term follow-up. This allowed us to conduct multivariate analyses adjusted for 17 anthropometric, demographic, medical, and dietary variables potentially associated with incidence of diabetes.

Our study possesses several limitations. First, the cohort consists of a homogenous white, elderly, female population, impacting the ability to generalize our findings. Second, we based our results on self-reported data, including height, weight, smoking status, and diabetes status.

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Incident diabetes was not based on biological confirmation. However, previous studies demonstrated self-report as a valid method for detecting diabetes diagnoses and smoking status. (Midthjell et al., 1992, Kenkel et al., 2003) Another large study showed a <1 kg difference in reported and measured weights in women ≥60 years old.(Kuczmarski et al., 2001) Other large studies examining smoking and/or BMI as risk factors for diabetes mellitus have also been self-reported.(Rimm et al., 1993, Hu et al., 2001, Simon et al., 1997, Manson et al., 2000) Previous studies have supported the reliability and validity of our food frequency questionnaire (Munger et al., 1992) and measurement of waist and hip circumferences. (Kushi et al., 1988) Third, our study only analyzed smoking status and BMI at baseline. It could not account for changes in status during follow-up that could lead to misclassification of exposure. Fourth, the baseline prevalence of smoking in our study (14%) at the time of the first IWHS survey (1986) was lower than the national smoking prevalence (30.1% in 1985).(Centers for Disease Control and, 2007) However, this difference would not impact the internal validity of our results. Fifth, although this analysis adjusted for a large number of factors, the possibility of residual or unmeasured confounding exists. Sixth, although a relatively small portion of the cohort (N=1,189) did not return any follow-up questionnaires, their exclusion introduces the possibility of selection bias. Finally, our study's large sample size allowed us to examine the association of diabetes and smoking status within strata defined by BMI. Even with this large sample size, statistical power to detect effect modification remains modest. We were, however, unlikely to have missed detecting large effects.

Our results allow clinicians to counsel their female patients that smoking acts independently of body weight to increase diabetes mellitus risk. The independent smoking-associated risk for diabetes may add to the diabetes risk associated with weight gain commonly following smoking cessation. This supports the need for clinician-directed weight control following smoking cessation.

While these data show no interaction between smoking and BMI on the risk for diabetes in women, the role of other potential interactions on diabetes risk with smoking remains unclear. Future studies must address other potential mediators such as physical activity, dietary components, alcohol consumption, or socioeconomic status. Evaluating diabetes incidence through physician-report or biological measures would also provide more credence to previous associations.

## Conclusion

Our results clearly support other findings that smokers possess a higher risk for diabetes mellitus. We provide well-adjusted data with no observed statistically-significant interaction between BMI and smoking on diabetes risk, implicating a BMI-independent mechanism for smoking-mediated diabetes risk.

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**Table 1**

Baseline characteristics stratified by smoking and BMI, Iowa Women's Health Study, 1986–2004

| **BMI** | **18.5–24.9** | | | **25–29.9** | | | **≥30** | | |
|---|---|---|---|---|---|---|---|---|---|
| **Smoking status** | **Never** | **Former** | **Current** | **Never** | **Former** | **Current** | **Never** | **Former** | **Current** |
| | **N=9054** | **N=2965** | **N=2880** | **N=9392** | **N=2710** | **N=1734** | **N=5819** | **N=1596** | **N=689** |
| Risk Factors | Mean (SD) | | | | | | | | |
| Age (years) | 62.3 (4.3) | 62.0 (4.2) | 61.4 (4.2 ) | 62.5 (4.2) | 61.9 (4.2) | 61.3 (4.2) | 62.4 (4.2) | 61.9 (4.2) | 61.2 (4.0) |
| Waist-to-hip ratio | 0.795 (0.071) | 0.799 (0.072) | 0.814 (0.080) | 0.841 (0.079) | 0.845 (0.080) | 0.866 (0.094) | 0.880 (0.078) | 0.887 (0.084) | 0.898 (0.086) |
| BMI | 22.8 (1.5) | 22.7 (1.5) | 22.3 (1.7) | 27.2 (1.4) | 27.2 (1.4) | 27.1 (1.4) | 33.9 (3.9) | 34.5 (4.5) | 33.7 (3.9) |
| Total Calories (kcal/day) | 1804 (644) | 1725 (659) | 1783 (887) | 1805 (706) | 1759 (780) | 1772 (779) | 1828 (752) | 1779 (739) | 1781 (778) |
| Total fat (g/day) | 67.2 (28.3) | 63.8 (29.5) | 69.4 (39.3) | 68.3 (30.6) | 66.3 (34.6) | 69.2 (33.0) | 70.4 (33.3) | 68.9 (32.6) | 71.9 (34.2) |
| Carbohydrates (g/day) | 227 (87) | 209 (87) | 205 (107) | 223 (92) | 211 (98) | 204 (102) | 223 (93) | 212 (94) | 201 (96) |
| Alcohol (g/day) | 2.6 (6.6) | 7.6 (12.6) | 10.1 (16.5) | 2.2 (6.2) | 5.6 (10.6) | 8.1 (14.8) | 1.4 (5.3) | 3.8 (9.1) | 6.0 (14.0) |
| Fruit/Vegetables (g/day) | 562 (311) | 548 (326) | 453 (298) | 565 (335) | 541 (331) | 482 (512) | 571 (397) | 542 (356) | 461 (338) |
| Red Meat (g/day) | 85.4 (63.2) | 76.2 (66.2) | 88.2 (78.2) | 92.3 (71.3) | 83.6 (78.5) | 92.7 (68.2) | 98.1 (87.3) | 88.6 (77.1) | 100.0 (71.1) |
| Whole Grains (servings/wk) | 12.3 (9.5) | 11.8 (9.4) | 9.1 (8.6) | 11.5 (8.9) | 11.6 (9.3) | 9.2 (8.4) | 10.7 (8.8) | 10.6 (9.0) | 9.1 (9.0) |
| Cholesterol (mg/day) | 262 (134) | 244 (123) | 269 (166) | 276 (142) | 264 (168) | 280 (154) | 293 (179) | 278 (151) | 294 (173) |
| Vitamin E (mg/day) | 73.2 (155.7) | 73.0 (159.6) | 65.2 (146.7) | 67.1 (148.3) | 68.0 (145.1) | 58.7 (148.3) | 63.0 (144.8) | 62.3 (144.6) | 57.0 (137.9) |
| Dairy (servings/wk) | 26.5 (15.7) | 26.1 (18.1) | 28.9 (20.1) | 26.4 (16.1) | 26.2 (15.6) | 27.5 (19.9) | 26.8 (15.7) | 27.8 (17.2) | 27.3 (18.6) |
| | Number (%) | | | | | | | | |
| Married | 7004 (78) | 2279 (77) | 1944 (68) | 7574 (81) | 2094 (78) | 1222 (71) | 4506 (78) | 1179 (74) | 461 (67) |
| White race | 8892 (99) | 2921 (99) | 2831 (99) | 9222 (99) | 2662 (99) | 1694 (99) | 5678 (99) | 1552 (98) | 669 (99) |
| > High School Education | 3945 (44) | 1465 (50) | 1147 (40) | 3598 (38) | 1168 (43) | 605 (35) | 1956 (34) | 585 (37) | 199 (29) |
| Low Physical Activity | 3444 (39) | 1038 (36) | 1623 (57) | 4013 (44) | 1158 (43) | 1040 (61) | 3165 (56) | 943 (60) | 486 (71) |
| Hypertension | 2142 (24) | 784 (27) | 744 (26) | 3413 (37) | 992 (37) | 568 (33) | 3032 (53) | 807 (51) | 331 (48) |
| Hormone replacement therapy | | | | | | | | | |
| Never | 5416 (60) | 1615 (55) | 1679 (59) | 5843 (63) | 1496 (55) | 1018 (59) | 3926 (68) | 950 (60) | 420 (61) |
| Current | 1159 (13) | 458 (16) | 337 (12) | 1037 (11) | 353 (13) | 174 (10) | 452 (8) | 127 (8) | 38 (6) |
| Former | 2437 (27) | 882 (30) | 854 (30) | 2463 (26) | 853 (32) | 536 (31) | 1411 (24) | 514 (32) | 229 (33) |
| Vitamin Supplement Use | 6168 (68) | 2054 (69) | 1763 (61) | 6039 (64) | 1792 (66) | 967 (58) | 3386 (58) | 954 (60) | 389 (57) |

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**Table 2**

Age and multivariate adjusted hazard ratios for diabetes mellitus by smoking history and BMI, Iowa Women's Health Study, 1986–2004

| | | Diabetes Incidence | | | |
|---|---|---|---|---|---|
| **BMI** | **Smoking status** | **Person Years** | **Events** | **Age-Adjusted HR (95% CI)[1]** | **Multivariate HR (95% CI)[1]** |
| 18.5–24.9[2] | Never | 128,725 | 285 | 1.00 (reference) | 1.00 (reference) |
| | Former | 40,327 | 95 | 1.09 (0.86–1.37) | 1.14 (0.89–1.46) |
| | Current | 34,190 | 103 | 1.51 (1.20–1.89) | 1.28 (0.99–1.64) |
| | 1–19 pack-years | 6,940 | 18 | 1.33 (0.82–2.14) | 1.13 (0.68–1.89) |
| | 20–39 pack-years | 15,412 | 43 | 1.39 (1.01–1.92) | 1.24 (0.88–1.75) |
| | ≥40 pack-years | 11,838 | 42 | 1.77 (1.28–2.45) | 1.40 (0.98–1.99) |
| 25–29.9[2] | Never | 129,641 | 848 | 1.00 (reference) | 1.00 (reference) |
| | Former | 35,793 | 221 | 0.98 (0.84–1.13) | 1.08 (0.92–1.26) |
| | Current | 20,217 | 162 | 1.34 (1.14–1.59) | 1.35 (1.13–1.62) |
| | 1–19 pack-years | 4,543 | 35 | 1.27 (0.91–1.78) | 1.46 (1.03–2.07) |
| | 20–39 pack-years | 8,430 | 60 | 1.21 (0.93–1.57) | 1.27 (0.97–1.66) |
| | ≥40 pack-years | 7,244 | 67 | 1.55 (1.20–1.98) | 1.38 (1.06–1.79) |
| ≥30[2] | Never | 72,486 | 1,082 | 1.00 (reference) | 1.00 (reference) |
| | Former | 18,621 | 348 | 1.26 (1.12–1.43) | 1.34 (1.18–1.53) |
| | Current | 7,014 | 137 | 1.34 (1.12–1.60) | 1.34 (1.11–1.62) |
| | 1–19 pack-years | 1,508 | 23 | 1.04 (0.69–1.57) | 0.93 (0.60–1.46) |
| | 20–39 pack-years | 2,889 | 58 | 1.38 (1.06–1.79) | 1.42 (1.08–1.87) |
| | ≥40 pack-years | 2,617 | 56 | 1.47 (1.12–1.93) | 1.49 (1.13–1.97) |

[1] Cox proportional hazards regression analysis.

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[2]Multivariate analyses adjust for waist-to-hip ratio, marital status, educational status, physical activity, hypertension, use of hormone replacements, vitamin supplement use, alcohol consumption, and intake of calories, fat, carbohydrates, fruit and vegetables, red meat, whole grains, cholesterol, vitamin E, and dairy products.