Lifetime adiposity and risk of pancreatic cancer in the NIH-AARP Diet and Health Study cohort[1–3]

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ABSTRACT

Background: The association of excess body weight across a lifetime with pancreatic cancer has not been examined extensively.

Objective: We determined the association for body mass index (BMI) at different ages and adiposity duration and gain with incident pancreatic adenocarcinoma in the NIH-AARP Diet and Health Study cohort.

Design: Participants aged 50–71 y completed questionnaires at baseline (1995–1996) and 6 months later that queried height and weight history. We calculated HRs and 95% CIs by using Cox proportional hazards models adjusted for age, smoking, sex, and intakes of energy and total fat.

Results: Over an average follow-up of 10.5 y, 1206 and 2122 pancreatic cancer cases were identified in the subcohort who completed the second questionnaire (n = 273,975) and the baseline cohort (n = 501,698), respectively. Compared with normal weight, overweight or obesity at ages 18, 35, 50, or >50 y (baseline BMI) was significantly associated with pancreatic cancer, with HRs ranging from 1.15 to 1.53. A longer duration of BMI (in kg/m^2) >25.0 was significantly associated with pancreatic cancer (overall HR per 10-y increment of duration: 1.06; 95% CI: 1.02, 1.09), with individuals who reported diabetes having the greatest risk (HR per 10-y increment of duration: 1.18; 95% CI: 1.05, 1.32; P-interaction = 0.01) and rates. A substantial gain in adiposity (>10 kg/m^2) after age 50 y was significantly associated with increased pancreatic cancer risk. The etiologic fraction of pancreatic cancer explained by adiposity at any age was 14% overall and 21% in never smokers.

Conclusion: Overweight and obesity at any age are associated with increased pancreatic cancer. *Am J Clin Nutr* 2013;98:1057–65.

INTRODUCTION

Cigarette smoking, diabetes mellitus, and obesity are among the few consistent and modifiable risk factors for pancreatic cancer (1–4). Although overweight and obesity at an older age are positively associated with pancreatic cancer in many studies, the association between adiposity at younger ages and across a lifetime and risk of pancreatic cancer has not been examined extensively, particularly in prospective studies (5). We conducted an analysis in a large cohort, the NIH-AARP Diet and Health Study, to examine BMI at different ages (18, 35, 50, and >50 y), adiposity duration, and weight change during a lifetime in relation to incident pancreas adenocarcinoma. To the best of our knowledge, this is the first prospective study to examine adiposity across multiple times in life (namely, early adulthood, midlife, and older age), BMI change, as well as adiposity duration as risk factors for pancreatic cancer.

SUBJECTS AND METHODS

Study population

The NIH-AARP Diet and Health Study is a large prospective study in AARP members established in 1995–1996 (6). Self-administered questionnaires eliciting information on demographic characteristics, dietary intake over the previous 12 mo, and numerous health-related factors, including current weight and height, were mailed to AARP members aged 50–71 y, who resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, GA, and Detroit, MI). The questionnaire was returned and satisfactorily completed by 566,402 members (6). Six months after the baseline questionnaire was sent, baseline respondents were sent a second risk factor questionnaire that queried information on height at age 18 y and weight at ages 18, 35, and 50 y (6). In total, 334,906 participants completed the second questionnaire. The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and informed consent was obtained from all participants.

We excluded subjects who had questionnaires completed by proxy respondents (n = 15,760), who had prevalent cancers as determined by the cancer registry data (n = 8587), who had missing height or weight (n = 13,240), and who were missing smoking data (n = 19,338). Among those who completed the second questionnaire, we further excluded participants with missing BMI at different ages (n = 37,076). Our final subcohort for analyses with complete BMI data at ages 18, 35, and 50 y consisted of 273,975 individuals (165,135 men, 108,840 women).

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For analyses of baseline BMI at ages >50 y in Tables 2 and 3 only, we used the larger baseline cohort but excluded participants censored during the first year of follow-up (n = 6650 total) to avoid the influence of subclinical disease on current weight and in those <51 y old (n = 1126). Our final baseline analytic cohort consisted of 501,698 individuals (296,448 men, 205,250 women).

Cohort follow-up and case ascertainment

Cancer cases were identified by linking cohort members to cancer registries covering the 8 states, as well as Arizona, Texas, and Nevada, and to the US National Death Index from 1995 through 2006 (7). The vital status of cohort participants was also ascertained by linkage to the Social Security Administration Death Master File. For these analyses, our outcome of interest was incident adenocarcinoma of the exocrine pancreas [*International Classification of Diseases for Oncology, Third Edition* (code C250–C259)]. Our case definition excluded pancreatic endocrine tumors, sarcomas, and lymphomas (histology types, 8150, 8151, 8153, 8155, 8240).

BMI exposure variables

We calculated BMI by using weight (kg) divided by height (m) squared. BMI at age 18 y was computed by using height at age 18 y, whereas BMI at the older ages was computed by using baseline height at ages 50–71 y. BMI (in kg/m^2) categories at ages 18, 35, 50, and >50 y were consistent with the WHO obesity classifications of <18.5 (underweight), 18.5 to <25 (normal), 25 to <30 (overweight), 30 to <35 (moderate obesity), and ≥35 (severe obesity) (8). We used normal BMI (18.5 to <25.0) as the referent category for our most of our analyses. Because the majority of participants reported lower weights at ages 18 and 35 y, we separated BMI in the normal weight and overweight ranges by using finer categories within the WHO categories. Within each age category, continuous BMI was per 5-kg/m^2 unit increase excluding individuals with a BMI <18.5. The HRs for BMI gain and BMI loss were determined in separate analyses. BMI change was calculated as the difference between reported BMI at different ages. We calculated duration in years of being overweight (BMI >25) by using linear interpolation methods to assign years between consecutive BMI measures, with BMI <25 being assigned zero. Weighted cumulative overweight years (OWY; similar to pack-years) considers the degree of overweight over time and was calculated by multiplying the duration (y) of high BMI by the difference (in BMI units) above normal BMI (≥25.0) for each age-specific BMI. A continuous duration of BMI ≥25 was per 10-y increment and cumulative OWY was per 100 OWY units. Quintiles for years overweight and cumulative OWY were based on the distribution of the cohort who ever had overweight, with a separate category for never overweight.

Statistical analysis

For the baseline cohort, cases and person-years were accrued from 1 y after the date of receipt of the baseline questionnaire until the earliest of the following dates: December 2006, diagnosis of pancreatic cancer, death, or moving out of the registry area. For the subcohort, cases and person-years were accrued from the date of receipt of the second questionnaire until the same exit dates specified above. Cox proportional hazard models, with age as the time metric, were used to generate HRs and 95% CIs. Trends were calculated by using the median value of each category. Potential confounding variables were included in the model if their inclusion changed the risk estimate for the BMI variable ≥10% or if they were putative risk factors for pancreatic cancer. The dietary variables were energy, adjusted by using the density method. Variables included in the final multivariable models were smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), total fat (g · 1000 kcal^{-1} · d^{-1}) and energy intake (kcal/d), and sex. Self-reported diabetes (yes or no), a putative pancreatic cancer risk factor, is potentially on the causal pathway between BMI and pancreatic cancer and either changed slightly (<10%) or did not change risk estimates; therefore, it was not included in our final models. We also evaluated our primary associations by using proportional subdistribution hazard models for survival data (10, 11).

We used 3-knot splines to model nonlinear relations between BMI change in the different ages and pancreatic cancer risk. We assessed a priori interactions in stratified analyses by sex, smoking status (never, quit >10 y ago, and recent/current smoker), diabetes, and follow-up time; and tested for significance by using cross-product terms composed of median trend variables or continuous BMI and the categorical modifying variable. Because there was no significant interaction by sex (P-interaction > 0.05), we present most of our results with men and women combined.

Absolute incidence rates for pancreatic cancer standardized within 5-y age categories to the age distribution of the NIH-AARP population adjusted by sex were calculated for adiposity duration. We calculated the adjusted population attributable risk and 95% CI to estimate the percentage of pancreatic cancer cases that would have been eliminated if participants never achieved overweight and/or obesity at any age, assuming a causal relation between overweight/obesity and pancreatic cancer by using the methods described by Spiegelman et al (9).

All statistical analyses were performed by using Statistical Analysis Systems software (version 8.2; SAS Institute), and P values for statistical tests were 2-tailed. Results were considered significant if the associated P value was ≤0.05.

RESULTS

During 11.2 y of follow-up (median: 10.5 y), 1359 men and 763 women with incident pancreatic cancer were identified in the baseline cohort; 787 of these men and 419 of these women had also completed the second questionnaire that ascertained information on BMI at different ages. The pancreatic cancer incidence rates for men and women in the baseline cohort were 51.6 (95% CI: 48.8, 54.3) and 41.7 (95% CI: 38.7, 44.7) cases per 100,000 person-years, respectively; corresponding rates in the subcohort were 50.4 (95% CI: 46.9, 54.0) and 41.2 (95% CI: 37.2, 45.1) cases per 100,000 person-years.

The selected characteristics of cohort participants by duration of adiposity in the subcohort who completed the second questionnaire are shown in **Table 1**. Those who were ever overweight or obese were less likely to be college graduates, never or current smokers, physically active, and nondiabetic; they also had higher intakes of total and saturated fat and red meat. Those with the longest duration of overweight or obesity were more often men who had

TABLE 1
Selected characteristics of the AARP cohort according to lifetime BMI and onset of overweight or obesity[1]

		Quintile of no. of years of overweight or obesity [BMI (in kg/m^2) >25]				
Characteristics	Never overweight[2] (*n* = 83,268)	>0 and <10.1 y (*n* = 38,141)	≥10.1 and <18.9 y (*n* = 38,142)	≥18.9 and <27.8 y (*n* = 38,141)	≥27.8 and <37.3 y (*n* = 38,140)	>37.3 (*n* = 38,143)
No. of years overweight	0 ± 0.02	5.0 ± 0.03	14.5 ± 0.03	23.3 ± 0.03	32.6 ± 0.03	43.6 ± 0.02
Age (y)	62.3 ± 0.02	61.2 ± 0.03	61.4 ± 0.03	62.0 ± 0.03	61.8 ± 0.03	64.2 ± 0.03
Sex (% male)	47.0	55.5	57.3	66.0	73.6	77.9
White (%)	94.3	93.9	92.5	92.7	93.5	94.3
College graduate (%)	46.5	42.9	39.2	39.3	41.2	42.0
Smoking history (%)						
Never smoker	40.3	34.0	34.3	34.6	35.4	35.0
Former smoker	45.1	54.3	55.4	56.1	55.3	56.6
Current smoker	14.6	11.7	10.3	9.3	9.3	8.4
Self-reported diabetes (%)	2.9	4.2	6.5	10.7	14.5	18.7
BMI (kg/m^2)						
Age 18 y	19.8 ± 0.007	20.2 ± 0.01	20.6 ± 0.01	21.1 ± 0.01	22.5 ± 0.02	25.5 ± 0.02
Age 35 y	21.1 ± 0.008	21.9 ± 0.01	22.8 ± 0.01	24.3 ± 0.01	26.9 ± 0.02	29.1 ± 0.02
Age 50 y	21.9 ± 0.008	23.3 ± 0.02	25.7 ± 0.01	27.5 ± 0.02	29.2 ± 0.02	30.5 ± 0.02
Baseline	22.5 ± 0.007	25.9 ± 0.01	28.0 ± 0.02	29.1 ± 0.02	30.4 ± 0.03	31.5 ± 0.03
Change: 18 y to baseline	2.7 ± 0.009	5.7 ± 0.02	7.4 ± 0.03	8.0 ± 0.03	7.9 ± 0.03	6.0 ± 0.03
Cumulative OWY	0 ± 0	20.3 ± 0.24	167 ± 0.76	446 ± 0.75	745 ± 1.1	1152 ± 1.5
Physical activity[3] (MET-h/wk)	44.2 ± 0.08	40.9 ± 0.12	38.4 ± 0.12	37.8 ± 0.12	37.6 ± 0.12	37.9 ± 0.12
Daily dietary intake[4]						
Fat (g/1000 kcal)	32.1 ± 0.03	33.3 ± 0.04	33.7 ± 0.04	34.0 ± 0.04	34.3 ± 0.04	34.2 ± 0.04
Saturated fat (g/1000 kcal)	9.9 ± 0.01	10.4 ± 0.02	10.5 ± 0.02	10.6 ± 0.02	10.7 ± 0.02	10.6 ± 0.02
Energy (kcal)						
Men	2005 ± 4.7	2024 ± 5.7	2053 ± 6.0	2057 ± 6.0	2071 ± 6.3	1998 ± 5.9
Women	1538 ± 3.1	1554 ± 5.8	1591 ± 6.3	1617 ± 6.6	1636 ± 6.9	1622 ± 7.2
Red meat (g/1000 kcal)						
Men	32.6 ± 0.10	37.0 ± 0.13	38.6 ± 0.14	39.6 ± 0.14	40.1 ± 0.14	39.4 ± 0.14
Women	25.9 ± 0.08	25.7 ± 0.16	30.9 ± 0.17	31.4 ± 0.17	32.2 ± 0.18	32.3 ± 0.18
Alcohol use: >3 drinks/d (%)						
Men	11.3	11.9	12.3	11.5	11.0	9.7
Women	3.5	3.4	2.9	2.7	2.2	1.4

[1] Values are means ± SDs or proportions; *n* = 273,977. Generalized linear models were used to estimate means and SEs for continuous variables and frequencies for proportions within each BMI category. MET-h, metabolic equivalent task hours; OWY, overweight years.
[2] Never overweight and ever underweight category includes participants who ever reported BMI <18.5 and never reported BMI >25.0.
[3] Metabolic equivalent during the past 10 y: *n* = 162,508 men and *n* = 106,912 women with complete physical activity data.
[4] Dietary variables adjusted for energy except for alcohol.

a higher proportion of diabetes, a higher baseline BMI, and who represented a lower proportion of current smokers and heavy drinkers.

Risk associated with BMI at ages 18, 35, 50, and >50 y

Increasing BMI at age 18 y was associated with a significantly greater pancreatic cancer risk compared with those with a BMI of 18.5–22.4 (**Table 2**). This association was not attenuated after additional adjustment for baseline BMI. Compared with those with a BMI of 18.5–22.4, those who were overweight or obese at age 35 had a significant and elevated pancreatic cancer risk. Compared with participants with a normal BMI within each age-specific stratum, those who were obese at age 50 y and those who were severely obese at ages >50 y also showed significantly increased pancreatic cancer risk with significant trends. Our results were similar when we used proportional subdistribution hazard models for survival data (10, 11).

The overall HRs per 5-unit increase in BMI were significantly associated with pancreatic cancer for each age stratum (**Table 3**). The association for BMI at age 18 y was strongest among those who reported diabetes at baseline compared with those without diabetes. The association for BMI at ages >50 y was stronger among never smokers compared with former and current smokers. There were no other significant interactions by sex, smoking status, or diabetes.

Risk associated with gain or loss in BMI over time

A 3-knot spline was used to model the nonlinear relation between BMI change in the different ages and risk of pancreatic cancer. The test for nonlinearity reached significance for BMI change between age 50 y and baseline ($P = 0.0001$), such that compared with no BMI change (zero), we observed significant positive associations for BMI gain >10 or any weight loss (**Figure 1**). None of the other differences in BMI between ages were significantly associated with pancreatic cancer.

Risk associated with duration of being overweight and cumulative OWY

A longer duration of overweight was associated with greater pancreatic cancer risk (**Table 4**), particularly among those who reported diabetes at baseline (**Table 5**). For every 10 y of having

TABLE 2
HRs and 95% CIs of BMI history for men and women at ages 18, 35, 50, and >50 y[1]

				Multivariable HR (95% CI)	
	Cases	Age-adjusted HR (95% CI)	Multivariable HR (95% CI)	Additionally adjusted for baseline BMI	BMI (kg/m^2) ≥25
	n/*person-years*				
BMI (in kg/m^2) at 18 y[2]					
<18.5	188/380,405	1.08 (0.92, 1.27)	1.08 (0.92, 1.27)	1.10 (0.93, 1.29)	1.08 (0.92, 1.27)
≥18.5 and <22.5	652/1,429,772	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
≥22.5 and <25.0	216/442,799	1.10 (0.95, 1.29)	1.07 (0.92, 1.25)	1.05 (0.90, 1.23)	1.07 (0.92, 1.25)
≥25.0 and <27.5	91/185,345	1.16 (0.93, 1.45)	1.11 (0.89, 1.39)	1.08 (0.86, 1.35)	1.25 (1.04, 1.49)
≥27.5	59/90,518	1.62 (1.24, 2.12)	1.56 (1.19, 2.03)	1.52 (1.16, 2.00)	
P-trend		0.0009	0.005	0.01	0.02
BMI at 35 y[2]					
<18.5	34/75,215	1.06 (0.75, 1.50)	1.04 (0.73, 1.48)		1.04 (0.73, 1.48)
≥18.5 and <22.5	405/926,741	1.00 (referent)	1.00 (referent)		1.00 (referent)
≥22.5 and <25.0	350/730,737	1.10 (0.95, 1.27)	1.08 (0.94, 1.25)		1.08 (0.94, 1.25)
≥25.0 and <30.0	346/659,859	1.26 (1.09, 1.46)	1.22 (1.05, 1.41)		1.24 (1.08, 1.43)
≥30.0	71/136,267	1.40 (1.09, 1.81)	1.37 (1.06, 1.79)		
P-trend		0.0002	0.001		0.002
BMI at 50 y[2]					
<18.5	27/47,626	1.27 (0.86, 1.87)	1.26 (0.85, 1.85)		1.26 (0.85, 1.85)
≥18.5 and <25.0	532/1,171,086	1.00 (referent)	1.00 (referent)		1.00 (referent)
≥25.0 and <30.0	499/988,218	1.17 (1.03, 1.32)	1.13 (1.00, 1.29)		1.15 (1.02, 1.30)
≥30.0	148/321,888	1.24 (1.03, 1.49)	1.22 (1.02, 1.47)		
P-trend		0.004	0.01		0.02
BMI at baseline: >50 y[3]					
<18.5	25/44,834	1.25 (0.84, 1.87)	1.18 (0.79, 1.75)		1.16 (0.78, 1.73)
≥18.5 and <25.0	689/1,528,071	1.00 (referent)	1.00 (referent)		1.00 (referent)
≥25.0 and <30.0	934/1,876,406	1.07 (0.97, 1.18)	1.09 (0.98, 1.20)		1.12 (1.02, 1.23)
≥30.0 and <35.0	340/691,319	1.12 (0.98, 1.27)	1.14 (1.00, 1.30)		
≥35.0	134/273,965	1.24 (1.03, 1.50)	1.29 (1.07, 1.55)		
P-trend		0.04	0.01		0.01

[1] Cox proportional hazard models were used to calculate HRs with age as the time metric. *P*-trend values were based on a median value of BMI within each category and exclude participants with a BMI <18.5 for each respective age group. Multivariable HRs were additionally adjusted for smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), energy (continuous), energy-adjusted total fat (continuous), and sex.

[2] Subcohort of 273,977 participants and 1206 pancreatic cancer cases for models at ages 18, 35, and 50 y.

[3] BMI at >50 y based on a baseline cohort of 501,702 participants and 2122 pancreatic cancer cases and excludes participants who were censored during the first year of follow-up.

a BMI ≥25, pancreatic cancer risk increased 6% overall and 18% among those diagnosed with diabetes but not as strongly among participants without diabetes (*P*-interaction = 0.01). Participants with diabetes and the longest duration of adiposity also had the highest incidence rate for pancreatic cancer (incidence rate per 100,000 person-years: 85.8; 95% CI: 61.9, 109.7) compared with those with less duration of adiposity or without diabetes. A similar pattern was observed for cumulative OWY. Among those with ≥4 y of follow-up (n = 825 cases), a significant 2-fold increased risk remained among participants with diabetes and the longest duration of adiposity, whereas no significant associations were observed among those with adiposity without diabetes (*see* Supplemental Table S1 under "Supplemental data" in the online issue). In contrast, for the cases that occurred during the first 4 y of follow-up (n = 381 cases), significantly increased (~50%) risks were observed only among nondiabetic participants with shorter duration of overweight or obesity and cumulative adiposity (Supplemental Table S1). Our results were similar when we used proportional subdistribution hazard models for survival data (*see* Supplemental Tables S2–S4 under "Supplemental data" in the online issue) (10, 11).

The proportion of our population ever having a BMI >25.0 was 70%, and the HR for ever having a BMI >25.0 was 1.25 (95% CI: 1.08, 1.41). The population attributable risk for being ever overweight or obese at any age was 14% (95% CI: 0.05, 0.22) overall, 21% (95% CI: 0.06, 0.34) among never smokers, 18% (95% CI: 0.03, 0.32) among former smokers who quit >10 y before baseline, 1% (95% CI: 0.14, 0.16) among recent smokers, 45% (95% CI: 0.05, 0.73) among those who reported baseline diabetes, and 10% (95% CI: 0.01, 0.19) among nonpatients with diabetes.

DISCUSSION

In this large cohort of middle-aged and older adults, excess body weight (BMI >25) at any age was positively associated with pancreatic cancer. Longer adiposity duration and cumulative duration that considered the degree of excess body fat were significantly associated with pancreatic cancer, with individuals having diabetes and longer adiposity experiencing the highest risk and rates. The etiologic fraction of pancreatic cancer explained by overweight or obesity at any age in our population

TABLE 3
HRs and 95% CIs for pancreatic cancer per 5-unit increase in BMI (kg/m^2) at ages 18, 35, and 50 y overall and by sex, diabetes, and smoking history[1]

	BMI (kg/m^2) at different ages			
Characteristics	18 y	35 y	50 y	>50 y[2]
All participants				
No. of cases	1018	1172	1179	2097
HR	1.11 (1.01, 1.21)	1.09 (1.01, 1.18)	1.10 (1.03, 1.17)	1.05 (1.01, 1.09)
Sex				
Male				
No. of cases	673	768	776	1355
HR	1.10 (0.97, 1.24)	1.12 (1.01, 1.23)	1.15 (1.06, 1.27)	1.10 (1.04, 1.17)
Female				
No. of cases	345	404	403	742
HR	1.12 (0.98, 1.27)	1.05 (0.93, 1.20)	1.03 (0.93, 1.15)	1.02 (0.96, 1.08)
History of diabetes				
No diabetes				
No. of cases	890	1030	1036	1821
HR	1.05 (0.94, 1.18)	1.05 (0.96, 1.15)	1.08 (1.00, 1.17)	1.03 (0.99, 1.08)
Diabetes				
No. of cases	128	142	143	276
HR	1.20 (1.02, 1.42)	1.10 (0.93, 1.31)	1.00 (0.84, 1.19)	1.04 (0.93, 1.16)
Smoking status				
Never				
No. of cases	293	347	349	627
HR	1.09 (0.92, 1.30)	1.06 (0.92, 1.23)	1.08 (0.96, 1.22)	1.11 (1.05, 1.17)[3]
Former				
No. of cases	399	466	469	796
HR	1.14 (1.00, 1.30)	1.11 (0.98, 1.25)	1.17 (1.06, 1.30)	1.06 (0.99, 1.14)
Current and recent quitter				
No. of cases	326	359	361	674
HR	1.07 (0.91, 1.27)	1.10 (0.97, 1.26)	1.01 (0.88, 1.15)	0.97 (0.89, 1.05)

[1] All analyses were based on a subcohort of 273,975 participants and pancreatic cancer cases except for the association between baseline BMI at ages >50 y. Cox proportional hazards models used age as the time metric and adjusted for smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), energy (continuous), energy-adjusted total fat (continuous), and sex (in sex-combined models). HRs based on BMI per 5-kg/m^2 increase exclude subjects with a BMI <18.5 for each respective age (18, 35, ≤50, >50 y).

[2] Significant interaction for BMI at age >50 y and smoking (P-interaction = 0.01). No other significant interaction by sex, diabetes history, or smoking for all BMI age categories (P-interaction > 0.05).

[3] BMI at ages >50 y based on a baseline cohort of 501,698 participants and excludes participants who were censored during the first year of follow-up.

was 14% overall, 18% in former smokers, and 21% in never smokers. BMI gain of >10 or any loss between the ages of 50 y and baseline was significantly associated with increased pancreatic cancer risk. Therefore, excess body mass represents an important potentially modifiable risk factor that, if prevented, could substantially decrease the burden of pancreatic cancer.

To our knowledge, this is the first prospective study to examine adiposity across multiple times in life, namely early adulthood, midlife, and older age, thus allowing us to calculate cumulative duration of overweight/obesity. We are also unaware of previous prospective studies that reported etiologic fractions for lifetime overweight/obesity and pancreatic cancer. Our results confirm the positive associations between excess weight in early adulthood and pancreatic cancer observed in some previous studies. Nine studies, 5 case-control (5, 12–15) and 4 prospective (16–19), have examined BMI during adolescence or early adulthood and risk of pancreatic cancer, with 5 showing significant positive associations (5, 12, 15, 18, 19). One of these was a pooled analysis of 14 cohorts that examined BMI in early adulthood (age 18 or 21 y) and showed a significant 20% increased risk per 5-unit increase in BMI (19). Another was a multicenter case-control study which reported that high compared with low BMI at ages 20 and 40 y and both ages was significantly associated with a 36%, 57%, and 86% elevated pancreatic cancer risk, respectively (15). Within a cohort of 720,000 Israeli men with BMIs measured at ages 16 and 19 y, adolescent overweight as defined by a BMI >85th percentile of the US-CDC adolescence reference distribution showed a significant 2-fold pancreatic cancer risk (18). Neither of these later 2 studies determined associations between BMI and pancreatic cancer at older ages.

Our study and most other prospective studies showed positive associations between middle-aged and older adult BMI and pancreatic cancer, with the risk being stronger among nonsmokers (19). One case-control study found that significant increases in risk associated with increasing BMI during early adulthood and middle age diminished and became nonsignificant for BMI at ages >40 y, particularly among women and never smokers (5). It is possible that these differing results may be explained by biases related to recalling older adult weight after being diagnosed with

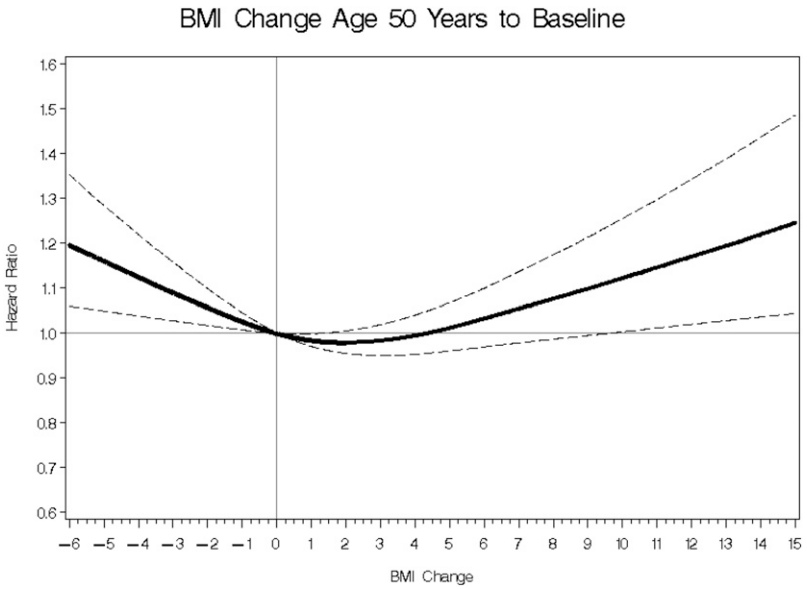

FIGURE 1. BMI (in kg/m^2) change between age 50 y and baseline and pancreatic cancer risk. The figure shows a 3-knot spline of the nonlinear relation for BMI change and risk of pancreatic cancer adjusted for smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), energy (continuous), energy-adjusted total fat (continuous), and sex. The solid line represents the OR, and the dashed lines represent 95% CIs. The test for nonlinearity reached significance ($P = 0.0001$), such that compared with no change in BMI (referent zero), any BMI loss or BMI gain >10 was significantly associated with greater pancreatic cancer risk.

pancreatic cancer or reverse causation in the case-control study because pancreatic cancer is most often diagnosed at advanced stages and is preceded by significant weight loss.

We observed a nonlinear association with BMI change between age 50 y and baseline, such that any weight loss and substantial gain in adiposity during older ages was significantly

TABLE 4
Incidence rates, HRs, and 95% CIs of duration of overweight or obesity across a lifetime[1]

	Cases	Incidence rate (95% CI)[2]	HR (95% CI)[3]
	n/*person-years*		
Years overweight[4]			
Never overweight	317/774,273	37.5 (33.3, 41.7)	1.00 (referent)
>0 and <10.1 y	156/354,539	44.0 (37.1, 50.9)	1.16 (0.96, 1.41)
≥10.1 and <18.9 y	170/354,362	47.5 (40.3, 54.6)	1.25 (1.04, 1.51)
≥18.9 and <27.8 y	162/352,253	42.1 (35.4, 48.8)	1.14 (0.94, 1.38)
≥27.8 and <37.3 y	186/350,058	50.0 (42.2, 57.8)	1.32 (1.10, 1.59)
≥37.3 y	215/343,333	49.0 (40.6, 57.4)	1.31 (1.09, 1.56)
P-trend[5]			0.002
Continuous, per 10 y	1206/2,528,844		1.06 (1.02, 1.09)
Cumulative OWY[4]			
Never overweight	317/774,273	37.5 (33.3, 41.7)	1.00 (referent)
>0 and <24 OWY	186/353,197	52.7 (45.1, 60.2)	1.23 (1.03, 1.48)
≥24 and <415 OWY	130/355,857	46.7 (37.6, 55.9)	1.14 (0.93, 1.40)
≥415 and <663 OWY	195/350,578	52.1 (44.5, 59.9)	1.23 (1.03, 1.48)
≥663 and <949 OWY	163/351,861	50.6 (42.0, 59.1)	1.20 (0.99, 1.46)
≥949 OWY	215/343,072	57.5 (49.1, 65.8)	1.35 (1.13, 1.62)
P-trend[5]			0.006
Continuous, per 100 units OWY	1206/2,528,844	48.4 (45.4, 51.3)	1.02 (1.01, 1.03)

[1] All analyses were limited to the subcohort of 273,977 participants and 1206 pancreatic cancer cases. OWY, overweight years.

[2] Sex-adjusted, age-standardized incidence rates per 100,000 person-years.

[3] Cox proportional hazard models were used to calculate HRs with age as the time metric. Adjusted for smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), energy (continuous), energy-adjusted total fat (continuous), and sex.

[4] Quintiles for years overweight and cumulative OWY were based on the distribution of the cohort who ever had overweight with a separate category for never overweight. Weighted cumulative OWY (similar to pack-years) are based on the degree of overweight over time.

[5] Based on the median of each category.

TABLE 5
Incidence rates, HRs, and 95% CIs of duration of overweight or obesity across a lifetime by history of diabetes[1]

	Cases		Incidence rate (95% CI)[2]		HR (95% CI)[3]	
	No diabetes	Diabetes	No diabetes	Diabetes	No diabetes	Diabetes
	n/*person-years*					
Years overweight[4]						
Never overweight	308/752,914	9/21,358	38.6 (34.3, 42.9)	38.8 (9.9, 67.6)	1.00 (referent)	0.88 (0.45, 1.71)
>0 and <10.1 y	148/340,307	8/14,231	45.0 (37.5, 52.5)	43.0 (10.5, 75.4)	1.15 (0.95, 1.40)	1.31 (0.65, 2.64)
≥10.1 and <18.9 y	157/332,470	13/21,892	46.9 (39.4, 54.4)	63.6 (27.5, 99.7)	1.24 (1.02, 1.50)	1.43 (0.82, 2.49)
≥18.9 and <27.8 y	142/316,371	20/35,882	42.1 (34.8, 49.5)	47.6 (25.5, 69.8)	1.12 (0.92, 1.37)	1.32 (0.84, 2.07)
≥27.8 and <37.3 y	157/301,682	29/48,377	49.1 (40.2, 58.1)	52.5 (31.1, 73.9)	1.29 (1.06, 1.57)	1.48 (101, 2.17)
≥37.3 y	150/283,341	65/59,993	39.2 (30.7, 47.7)	85.8 (61.9, 109.7)	1.10 (0.90, 1.34)	2.27 (1.73, 2.98)
P-trend[5]					0.14	0.003
Continuous, per 10 y	1062/2,327,086	144/201,733	48.4 (45.4, 51.3)	71.4 (59.7, 83.1)	1.03 (0.99, 1.07)	1.18 (1.05, 1.32)
Cumulative OWY[4]						
Never overweight	308/752,914	9/21,358	38.6 (34.3, 42.9)	38.8 (9.9, 67.6)	1.00 (referent)	0.88 (0.46, 1.72)
>0 and <24 OWY	175/337,176	11/16,004	46.5 (39.4, 53.6)	53.5 (17.3, 89.6)	1.22 (1.01, 1.47)	1.44 (0.79, 2.63)
≥24 and <415 OWY	120/334,241	10/21,616	42.2 (34.0, 50.4)	46.8 (16.9, 76.7)	1.13 (0.91, 1.40)	1.44 (0.79, 2.63)
≥415 and <663 OWY	172/315,450	23/35,128	45.3 (37.4, 53.3)	57.6 (31.3, 83.9)	1.21 (1.00, 1.46)	1.39 (0.91, 2.12)
≥663 and <949 OWY	135/306,953	28/44,908	44.4 (35.2, 53.5)	56.2 (32.2, 80.2)	1.14 (0.93, 1.40)	1.60 (1.08, 2.36)
≥949 OWY	152/280,352	63/62,720	42.1 (33.6, 50.6)	82.3 (59.5, 105.2)	1.17 (0.96, 1.42)	2.18 (1.65, 2.87)
P-trend[5]					0.31	0.003
Continuous, per 100 units OWY	1062/2,327,086	144/201,733	48.4 (45.4, 51.3)	71.4 (59.7, 83.1)	1.01 (0.99, 1.02)	1.03 (1.01, 1.07)

[1] All analyses were limited to the subcohort of 273,977 participants and 1206 pancreatic cancer cases. OWY, overweight years.

[2] Sex-adjusted, age-standardized incidence rates per 100,000 person-years.

[3] Cox proportional hazard models were used to calculate HRs with age as the time metric. Adjusted for smoking (never, quit ≥10 y ago, quit 5–9 y ago, quit 1–4 y ago, quit <1 y ago, or current and smokes ≤20 or >20 cigarettes/d), energy (continuous), energy-adjusted total fat (continuous), and sex (in sex-combined models). Duration of overweight by diabetes, *P*-interaction = 0.01. Cumulative overweight by diabetes, *P*-interaction = 0.02.

[4] Quintiles for years overweight and cumulative OWY were based on the distribution of the cohort who ever had overweight with a separate category for never overweight. Weighted cumulative OWY (similar to pack-years) are based on the degree of overweight over time.

[5] Based on the median of each category.

associated with greater pancreatic cancer risk; however, we observed no associations for BMI changes occurring at younger ages. Our finding with weight loss after age 50 y is consistent with the aforementioned weight loss that occurs during latent pancreatic cancer. Previous studies that examined change in weight or BMI across a lifetime have mostly shown no association (20). One pooled analysis of BMI change between early adulthood and older age reported a significant 40% increased risk among participants whose BMI decreased by >2 or increased by >10 compared with those with BMI changes of ±2 (19). In contrast, BMI change between ages 18 y and baseline was not associated with pancreatic cancer in our study. Our results suggest that weight gain later in life, closer to the time of pancreatic cancer diagnosis, may promote or stimulate pancreatic tumor growth more strongly than weight gain occurring earlier in life. Given the characteristics of the NIH-AARP study population, however, we are only able to evaluate associations for pancreatic cancer occurring at ages >50 y. Future studies should examine whether weight gain earlier in life is associated with pancreatic cancer occurring at younger ages (<50 y).

The pattern of pancreatic cancer associations that we observed for absolute and cumulative duration of adiposity, as well as recent weight gain, and pancreatic cancer might be explained by the growth-promoting effects of insulin. Overweight and obesity lead to insulin resistance and eventually diabetes (21). Biomarkers of insulin resistance have been associated with increased pancreatic cancer risk in prospective epidemiologic studies (2, 3, 22–25). Experimental studies have shown that insulin has mitogenic effects on pancreatic cancer cell lines (26) and peripheral insulin resistance promotes ductal pancreatic carcinogenesis in animals (27–31). Experimental and epidemiologic studies also suggest that administration of certain antidiabetic drugs such as metformin, an insulin sensitizer, decreases pancreatic cancer risk and progression, whereas insulin and insulin secretagogues increase risk (5, 21, 30, 32, 33). Alternatively, rodent studies have shown that circulating stromal and vascular progenitor cells derived from white adipose tissue are recruited by tumors and enhance tumor vascularization, growth, and progression (34–36). This might be relevant for pancreatic cancer given the proximity of the pancreas to visceral intraabdominal adipose tissue (34) and that intraabdominal body fat has been associated with pancreatic cancer (19, 37–39).

In the present study, baseline BMI appeared to be more clearly associated with pancreatic cancer among participants who were never smokers. Many studies have observed stronger positive associations with adult BMI among never smokers compared with smokers or the overall population (19, 41). Cigarette smoke contains a multitude of potential carcinogens that may contribute to pancreatic carcinogenesis. Therefore, it is possible that adiposity does not play a substantial role in the etiology of pancreatic cancer among older current smokers.

An important strength of our study is its large prospective design with detailed information about body weight at different ages collected on the same individuals, which was assessed before cancer diagnosis, thereby reducing the influence of reverse causation and differential biases. Seventy percent of our study population was ever overweight or obese, a proportion similar to that of the American population (41); this suggests that our cohort

is representative of the US population with respect to the prevalence of overweight and obesity.

Our study also has limitations. Our case definition included nonmicroscopically confirmed cancer, which could contribute to misclassification of case status and some attenuation of risk estimates (42). Measurement error related to self-reported height and weight could contribute to inaccurate associations, particularly because participants had to recall their weight from the distant past. However, others have shown that self-reported body weight can be recalled with fairly good accuracy and reproducibility (43–49). The misclassification of reported body weight, particularly among those who are overweight or obese (because this group tends to underreport true weight), would attenuate the associations. Because we tested many associations, it is possible that some of the significant associations that we observed may be due to chance. However, we had one primary hypothesis, namely overweight and obesity is associated with pancreatic cancer. In addition, our results for overweight and obesity and pancreatic cancer risk are consistent with those of other studies, particularly cohort studies (20).

In conclusion, we observed significant positive associations between overweight and obesity in early, middle, and older age and subsequent pancreatic cancer. Individuals with the longest duration of overweight and diabetes had the greatest risk and rates. Our results are relevant given the increasing rates of obesity, diabetes, and pancreatic cancer in the United States (42, 50), particularly among individuals who were overweight at younger ages. Maintaining a healthy weight and avoidance of adiposity might prevent pancreatic cancer.

Cancer incidence data from Arizona were collected by the Arizona Cancer Registry; from Georgia by the Georgia Center for Cancer Statistics; from California by the California Department of Health Services, Cancer Surveillance Section; from Michigan by the Michigan Cancer Surveillance Program; from Florida by the Florida Cancer Data System under contract to the Department of Health; from Louisiana by the Louisiana Tumor Registry; from New Jersey by the New Jersey State Cancer Registry; from North Carolina by the North Carolina Central Cancer Registry; from Pennsylvania by the Division of Health Statistics and Research, Pennsylvania Department of Health; and from Texas by the Texas Cancer Registry. The views expressed herein are solely those of the authors and do not necessarily reflect those of the cancer registries or contractors. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions. We are indebted to the participants of the NIH-AARP Diet and Health Study for their outstanding cooperation. We acknowledge Arthur Schatzkin, the visionary who founded the NIH-AARP Diet and Health Study, and the contributions of Barry Graubard for his assistance and discussions regarding the statistical analysis and splines.

The authors' responsibilities were as follows—RZS-S: conceived and designed the study, performed statistical analyses, drafted and revised the manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis; AH and RZS-S: acquired the data; RZS-S and CS: analyzed the data; RZS-S, CS, SM, and DTS: interpreted the data; and all authors: contributed substantive interpretation of and editorial comments on the manuscript drafts. None of the authors declared a conflict of interest.

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