Supplementary Online Content

Zheng Y, Manson JE, Yuan C, et al. Associations of weight gain from early to middle adulthood with major health outcomes later in life. *JAMA*. doi:10.1001/jama.2017.7092

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Ascertainment of outcomes

Type 2 diabetes

Participants with self-reported diagnoses of diabetes on the main questionnaire were mailed a supplementary questionnaire regarding symptoms, diagnostic tests, and hypoglycemic therapy.[1] We used the National Diabetes Data Group criteria [2] for defining cases before 1998. For cases diagnosed after 1998, we used the American Diabetes Association criteria.[3] The validity of the self-reported questionnaire was verified by reviewing medical records in a subsample, and the diagnosis of type 2 diabetes was confirmed in 98% of the cases in women and 97% of the cases in men.[4,5] Only clinically confirmed diabetes cases were considered as the outcome.

Hypertension

The baseline and follow-up biennial questionnaires asked participants to report whether a clinician had made a new diagnosis of hypertension during the preceding 2 years. Among a sample of women participating in the NHS who reported a diagnosis of hypertension and participated in the validation study, all had blood pressure greater than 140/90 mm Hg.[6] In an age-stratified sample of 161 participants in NHS who lived in Boston-area and did not report hypertension, none had a blood pressure greater than 160/95 mmHg and 6.8 % had values between 140/90 and 160/95 mmHg. This confirms a low rate of false negative reporting. Self-reported blood pressure and hypertension are also strong predictors of coronary heart disease in the NHS study.[6]

Cardiovascular disease

We included coronary heart disease (CHD) and stroke in our composite end point of CVD, which was identified primarily through a review of medical records. We requested permission to review medical records when a participant reported a nonfatal CHD or stroke. We also sought medical records for deceased participants, whose deaths were identified by families and postal officials and through the National Death Index. Physicians blinded to the participant questionnaire reports reviewed all medical records. Nonfatal CHD was confirmed using the criteria of the World Health Organization, specifically, on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations. Stroke was confirmed by medical records according to the criteria of the National Survey of Stroke, requiring evidence of a neurologic deficit with a sudden or rapid onset that persisted for >24 h or until death. All strokes since 1976 were reviewed by a neurologist and classified according to the criteria used in the Perth Community Stroke Study by stroke subtype and/or etiology: subarachnoid hemorrhage, intraparenchymal hemorrhage, ischemic stroke (thrombotic or embolic), or stroke of unknown causes. Fatal CHD was defined as fatal myocardial infarction if this was confirmed by hospital records or autopsy, or if CHD was listed as the cause of death on the certificate and this was the underlying and only plausible cause, and evidence of previous CHD was available.[7] Fatal strokes were coded using the same criteria as for nonfatal cases, but autopsy evidence was also accepted as was a death certificate listing the cause of death as stroke.

Cancer

In both cohorts, self-reported diagnoses of cancer were obtained on biennial questionnaires, and participants who reported a cancer diagnosis were asked for

permission to acquire their medical records and pathologic reports. A study physician, blinded to exposure information, reviewed medical records to confirm cancer diagnosis and to extract relevant information, such as histology, grade, and sub-location.[8] The outcomes of interest in this study include total cancer and specific cancers that have been related to obesity with probable or convincing evidence in the most recent WCRF/AICR reviews, including cancers of the esophagus (adenocarcinoma only), colorectum, pancreas, kidney, breast (after menopause), endometrium, ovaries, prostate (advanced only), liver, and gallbladder. Because of the small number of cases, liver and gallbladder cancers were not examined individually but included in the obesity-related cancer analysis. Because only advanced prostate cancer was related to obesity in the WCRF/AICR review,[9] we only included advanced prostate cancer cases (defined as those that had spread outside the prostate [stage T3b/T4, N1, or M1] or lethal tumors) in our cancer analyses.

Cholelithiasis

We included unremoved gallstones and cholecystectomy in cholelithiasis. In NHS, biennial questionnaires were used to assess the occurrence and date of cholecystectomy. Previously, we randomly selected 50 nurses who self-reported cholecystectomy, and 43 who agreed to requests for additional information reiterated their earlier report. Cholecystectomy was confirmed in all 36 nurses for whom medical records were available.[10] HPFS, at baseline and in each biennial follow-up questionnaire, participants reported whether they had cholecystectomy or had received a diagnosis of gallstones from a physician. The participants were also asked whether their cholelithiasis was symptomatic and whether the diagnosis had been confirmed by radiography or

ultrasonography. To verify self-reports of cholelithiasis including symptomatic unremoved gallstones and cholecystectomy, we previously reviewed a random sample of 441 medical records of men who reported having cholelithiasis or cholecystectomy; of these, 99% (all but 5) confirmed the diagnosis.[11]

Severe osteoarthritis requiring hip replacement

The NHS questionnaires since 1996 asked whether and when the participants were diagnosed as osteoarthritis. The NHS questionnaires before 1996 and the HPFS questionnaires requested the same information about "other arthritis (other than rheumatoid arthritis)". In consideration that osteoarthritis is most common form of arthritis especially among the elder population, and the outcomes of interest here were incident cases after 55 years, we assumed that the self-reported cases of other arthritis can represent self-reported osteoarthritis in the current study. We used 1) self-reported total hip replacement (used as a surrogate for hip osteoarthritis) and 2) self-reported osteoarthritis (or other arthritis) as a surrogate for clinically severe osteoarthritis. The cases of osteoarthritis requiring hip replacement in our study met the above two criteria at the same time.

In NHS, we mailed a supplementary questionnaire to all participants who reported a hip replacement, which asked about the date of surgery, the diagnosis of osteoarthritis, and other conditions (e.g., major hip trauma, fracture, congenital dysplasia, osteonecrosis, or inflammatory arthritis) that led to hip replacement. Primary hip osteoarthritis was defined as hip replacement, without the presence of these other conditions. The questionnaire was validated by reviewing preoperative radiographs from randomly selected women, of whom 100 reported primary osteoarthritis and 50 reported other

reasons for hip replacement. The response rate was 56% (n=84) after three mailings, and 60 radiographs were interpretable. Two radiologists who were blinded to diagnosis reviewed the radiographs. Ninety three percent (41/44) of women who reported primary osteoarthritis had this diagnosis confirmed by radiographs, 80% (35/44) had a radiographic severity of grade 3 or higher on the Kellgren-Lawrence scale, and only 7% (3/44) had radiographic evidence of other diagnoses (either osteonecrosis or congenital hip dysplasia). Of 16 women who reported secondary osteoarthritis (e.g., due to congenital hip dysplasia, osteonecrosis or inflammatory arthritis), the diagnosis was confirmed by radiograph in 13 (81%). Thus, self-reported hip replacement and a report of hip osteoarthritis identified clinically important primary hip osteoarthritis reliably and with minimal misclassification. The detailed information was described in one previous study.[12]

Cataract extraction

Participants were asked if they had a cataract extraction starting in 1984 for the NHS and in 1988 for the HPFS and, if so, when they were diagnosed and for permission to review medical records. We then contacted the ophthalmologist who performed the surgery and, when available, the patient's optometrist or other health care provider who had ophthalmologic records to confirm the dates of initial diagnosis and extraction and to determine any known cause of the cataract. From the records, we obtained the participant's best corrected visual acuity in both eyes prior to surgery and the location of the lens opacity in each eye. All of the ophthalmologists who responded to the questionnaire confirmed the extraction and 86% of the confirmed dates of extraction were within 6 months of the participants' reports. The details were described in a previous

study.[13] In the current analysis, we used cataract extraction as our endpoint, to minimum the misclassification of non-cases as cases and to decrease the chance for variation in the threshold for diagnosis of disease.

Mortality

Deaths were reported by next of kin and the postal system and through records of the National Death Index. Physicians reviewed death certificates and hospital or pathology reports to classify individual causes of death and were unaware of participants' reported questionnaire results.[14] Using all sources combined, we estimated that follow-up for death was over 98% complete.

Healthy aging

The basic definition of successful aging has been described in detail in previous publications.[15,16] In the current analysis, the successful aging health outcome summarizes survival until 2010, plus health information from three domains including chronic diseases, cognitive function, and physical function.

We used self-reported of major chronic diseases (including cancer, diabetes, CHD, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis) to define the history of chronic diseases. Our previous investigations have shown that the self-report of chronic diseases is highly accurate in both cohorts.

We measured cognitive function by the questions of subjective cognitive decline (SCD) in mailed or online questionnaires administered to the NHS and HPFS participants around 2012. The SCD scores were based on 6 yes/no questions: Do you have more trouble than usual remembering recent events? Do you have more trouble than usual remembering a short list of items, such as a shopping list? Do you have trouble remembering things from one second to the next? Do you have any difficulty in understanding things or following spoken instructions? Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory? Do you have trouble finding your way around familiar streets? The SCD score ranged between 0 and 6. Thus far, no single and standardized definition of SCD exists, and these above questions have been used in previous studies of subjective memory complaints and validated against objective measures of memory loss.[17] Additionally, subjective memory complaints have been associated with the presence of various mid and late-stage biological markers of Alzheimer's disease, including amyloid plaques, neurofibrillary tangles and grey matter atrophy.[18-20]

Physical function was assessed using the Medical Outcomes Study Short-Form Health Survey (SF-36). The SF-36 is a 36-item questionnaire that measures eight health concepts, and was embedded in the 1992, 1996, and 2000 NHS follow-up questionnaires, and in the 1996 and 2008 HPFS follow-up questionnaires. The validity and reproducibility of the SF-36 and its components have been previously established.[21]

Among the participants who had the above available assessments (the assessments of three domains) and survived to year 2010, we defined successful aging as meeting all of the following criteria: (1) no history of cancer (except non-melanoma skin cancer),

diabetes, CHD, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis; (2) no cognitive decline (SCD score=0); and (3) no physical limitations (no limitations on moderate activities, and no more than moderate limitations on more demanding physical performance measures from the SF-36). Since the majority of cognitive assessments occurred in 2010-2012, we considered chronic disease history as of the year 2010. Participants who survived to year 2010, but did not meet the remaining criteria were defined as usual agers.

Composite major chronic disease

Following previous publications on risk of chronic disease,[22,23] we included incident cardiovascular disease (including coronary heart disease, stroke), type 2 diabetes, cancer, and nontraumatic death in our composite major chronic disease endpoint. Heart disease, cancer, stroke and diabetes are the first, second, fifth, and seventh leading causes of death in the United States, respectively.[24] When a participant reported an incident event, we requested permission to review medical records, which were reviewed by study investigators blinded to the participant's risk factor status. The details of the definition and measurement of individual outcomes were reported before[23] and also described in the above paragraphs.

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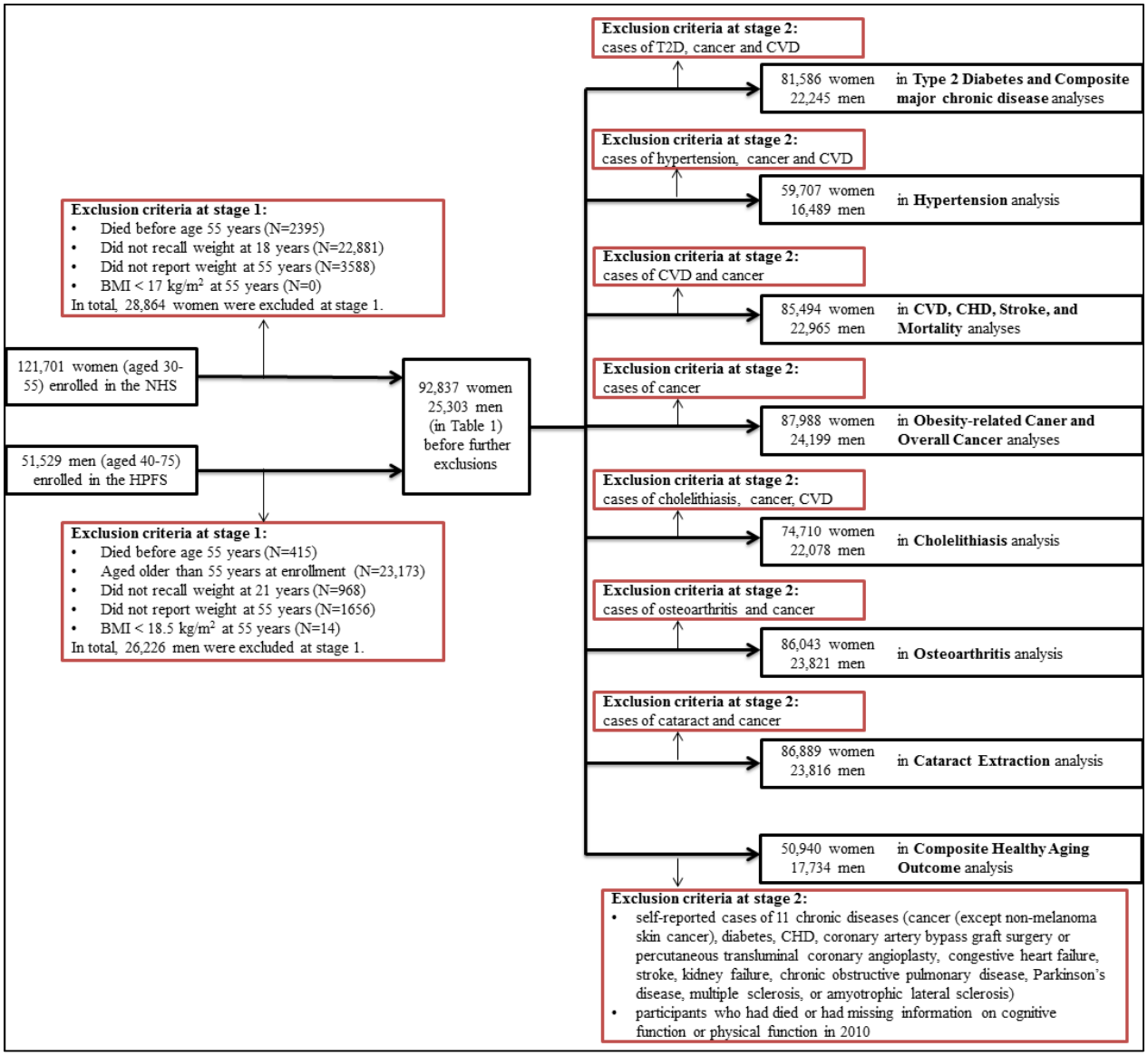
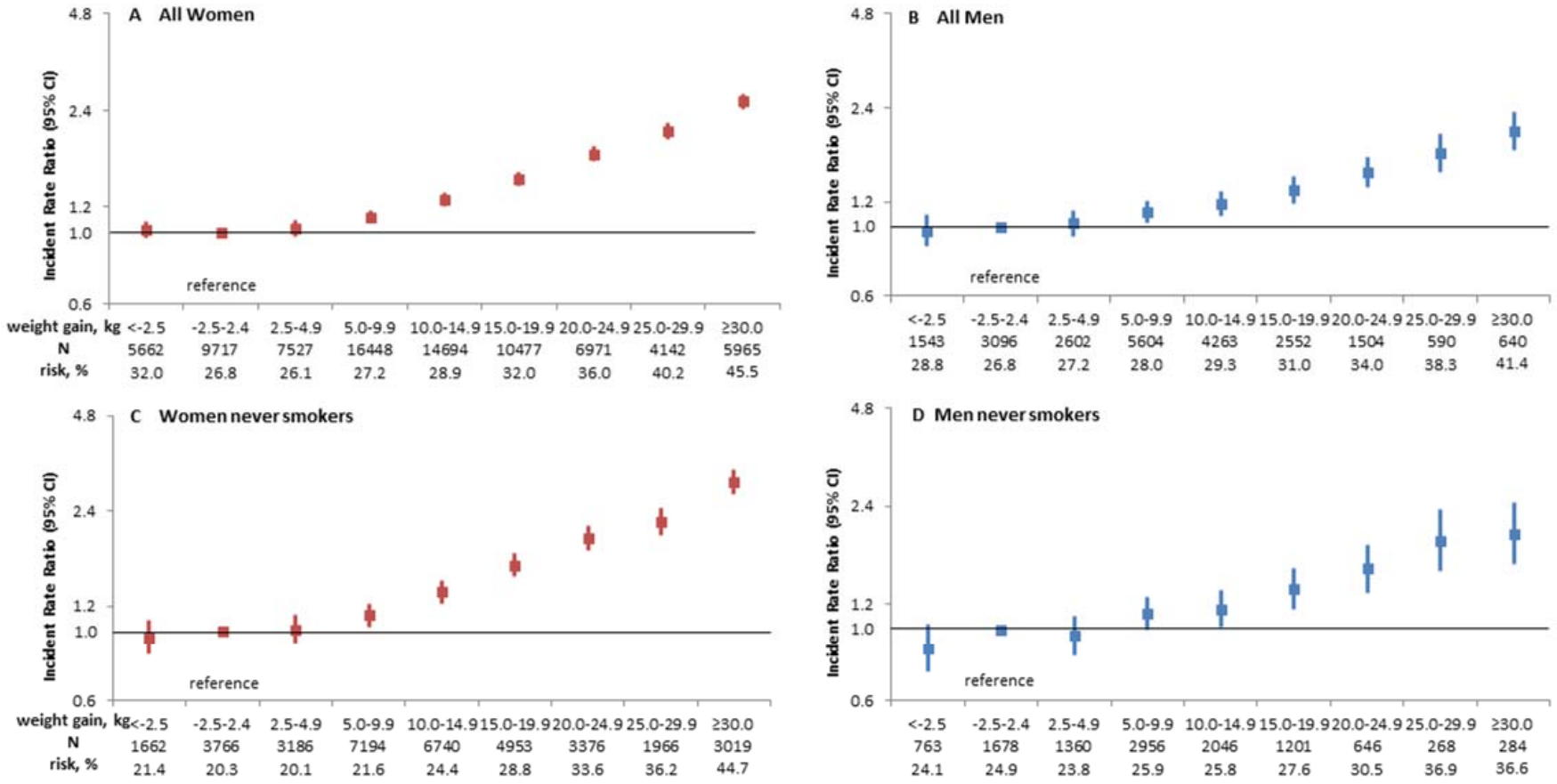
eFigure 1. Analysis population and exclusion criteria of specific health outcomes



Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, the Health Professionals Follow-up Study; NHS, the Nurses' Health Study.

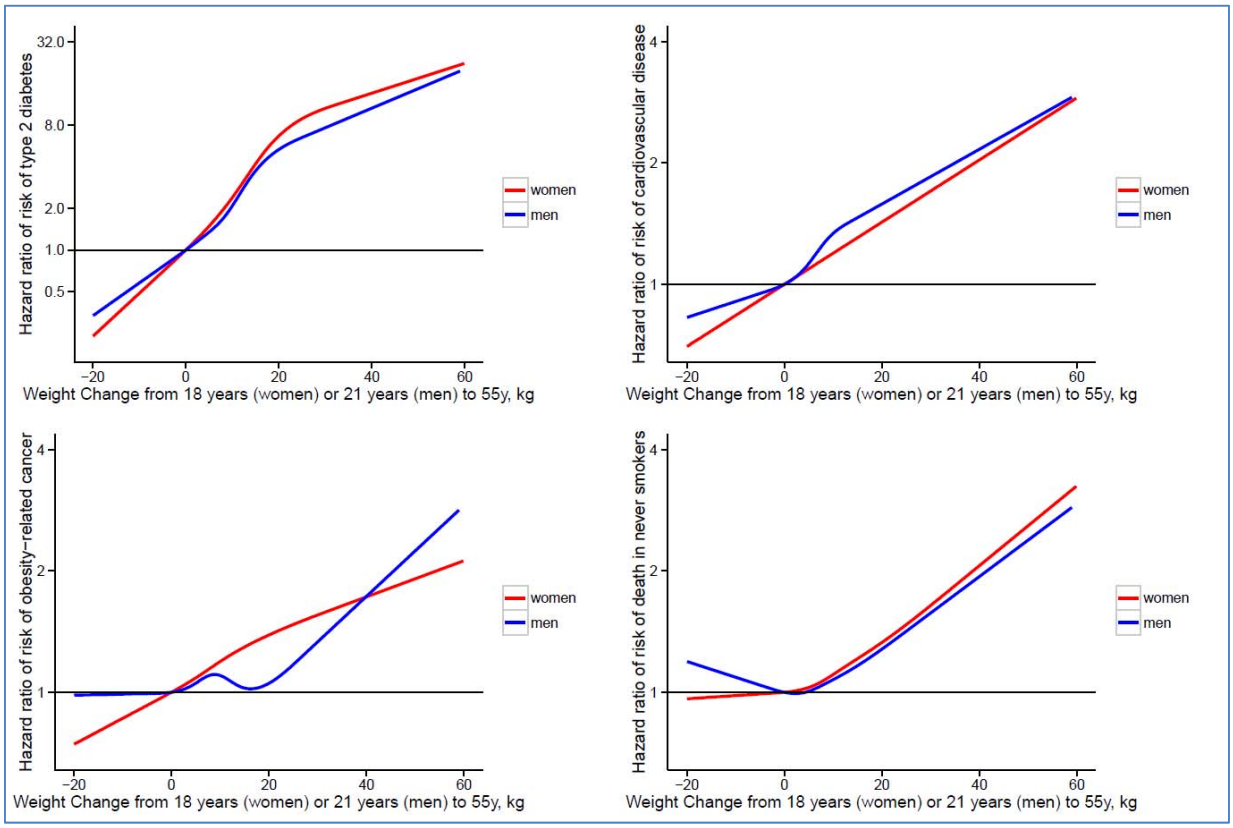
eFigure 2. Association of early to middle adulthood weight gain with the risk of composite major chronic disease from age of 55 to 75 years[a]



Major chronic disease is a composite outcome consisted of the incident cases of type 2 diabetes, cardiovascular disease, cancer, and non-traumatic death.
Among the overall 81,603 women, 25,339 developed at least one of the major chronic diseases, including 12,026 cases of cancer, 6192 of type 2 diabetes, 3249 of cardiovascular disease, and 3872 of non-traumatic death. Among the overall 22,394 men, 6585 developed at least one of four major chronic diseases, including 3492 cases of cancer, 1279 of type 2 diabetes, 924 of cardiovascular disease, and 890 of non-traumatic death.

[a] After adjustment for age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1–0.4, 0.5–1.9, 2–7, or ≥8 g/d; men: 0–4, 5–9, 10–14, 15–29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of diabetes, cardiovascular disease and cancer, and weight at 18 years in women and 21 years in men.

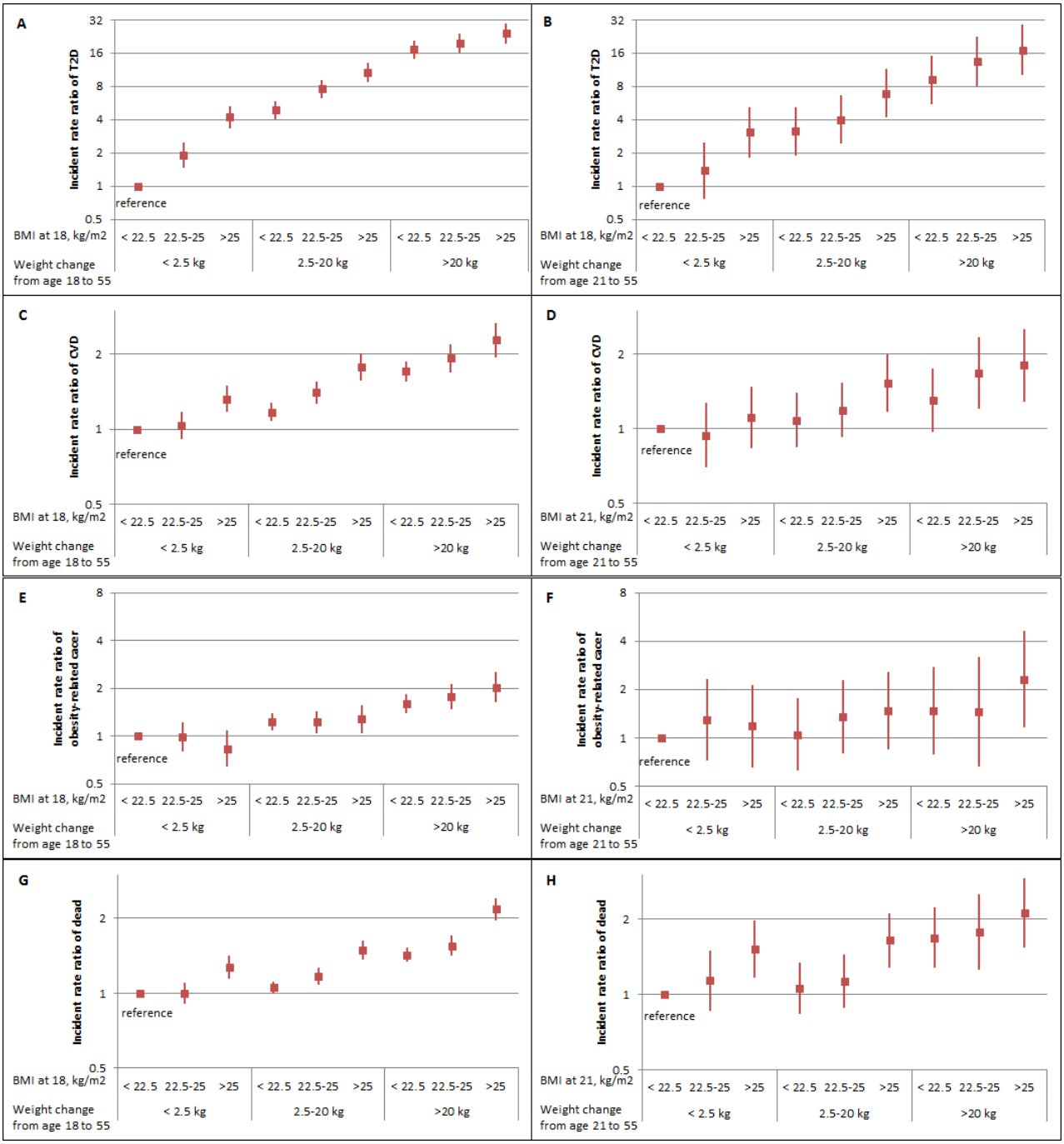
eFigure 3. Non-parametric restricted cubic splines of early to middle adulthood weight change (per kg) and major health outcomes



In consideration of the software availability and the general comparability between Cox regression and Poisson regression for survival analysis, restricted cubic splines of Cox proportional hazards regression models were used to examine non-parametrically the (possibly non-linear) relation between weight change and the incidence rate of major health outcomes.

The linear associations of weight change with risk for type 2 diabetes, cardiovascular disease, obesity-related cancer, and mortality in never smokers were significant in women and men (all p-value for linear relation <.001); and the non-linear associations of weight change were significant with risk for type 2 diabetes in women and men, and with risk of death in women never smokers (p-value for non-linear relation <.001).

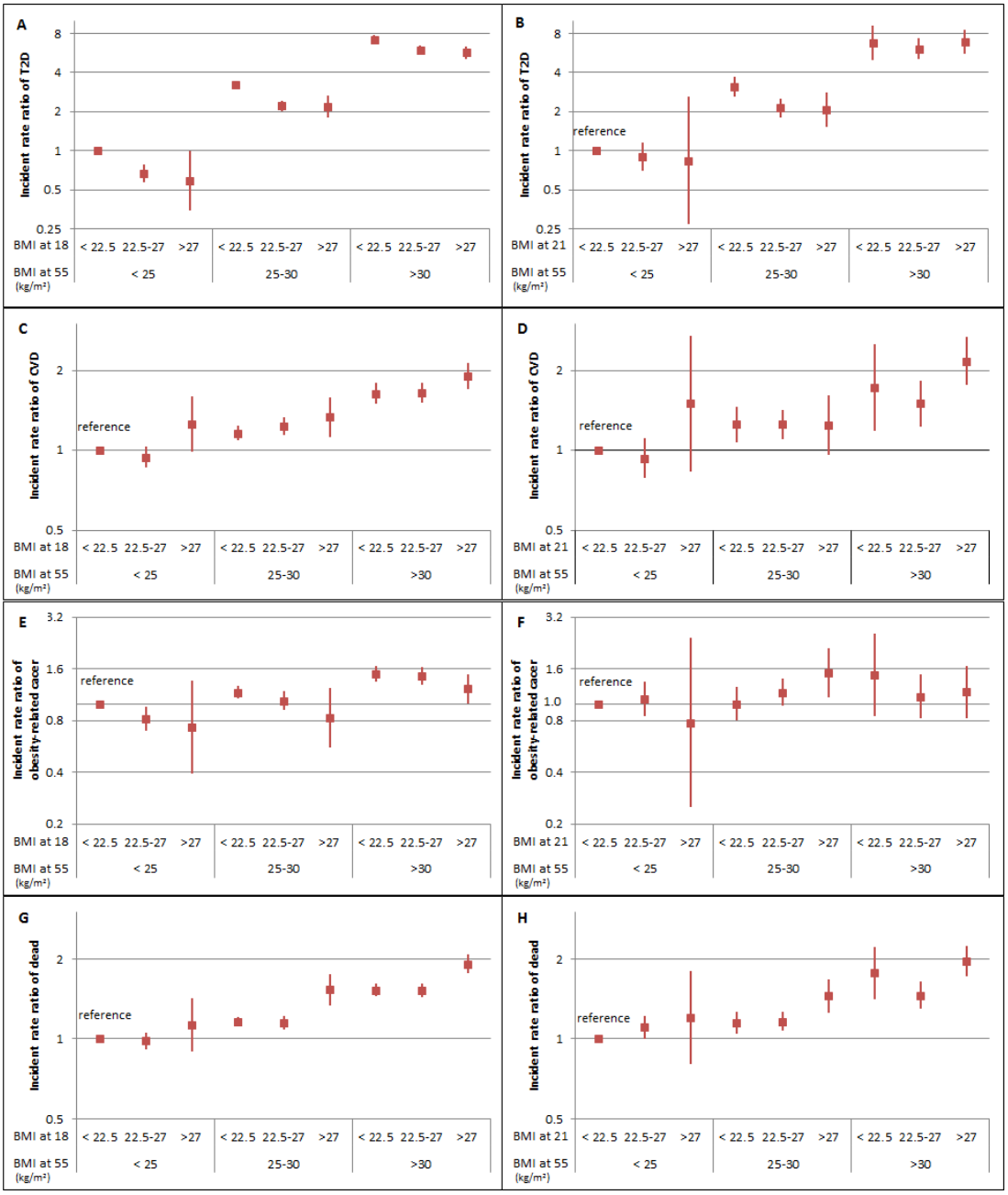
eFigure 4. Joint association of early to middle adulthood weight change and body mass index at early adulthood with risk of individual major health outcomes in women from the Nurses' Health Study (A, C, E, G) and men from the Health Professionals Follow-up Study (B, D, F, H)



After adjustment for age at cohort recruitment (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and

never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases. Analyses of obesity-related cancer and mortality were conducted among non-smokers only.

eFigure 5. Joint association of body mass index at early adulthood and that at middle adulthood with risk of major health outcomes in women from the Nurses' Health Study (A, C, E, G) and men from the Health Professionals Follow-up Study (B, D, F, H)



After adjustment for age at cohort recruitment (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4,

0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases. Analyses of obesity-related cancer and mortality were conducted among non-smokers only.

eTable 1. Association between early to middle adulthood weight gain and secondary health outcomes in the Nurses' Health Study and the Health Professionals Follow-Up Study

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
Nurses' Health Study							
Coronary heart disease	No. cases	303	397	1137	1102	1018	
	Person-years	124266	218720	531134	537613	347511	
	Multivariable-adjusted incidence/100k person-years [a]	109.5 (96.4, 124.4)	109.8 (98.9, 121.9)	146.3 (136.9, 156.4)	156.4 (146.5, 166.9)	245.3 (229.8, 262)	
	Multivariable-adjusted ARD/100k person-years [a]	-0.2 (-15.8, 17.9)	0	36.5 (20.7, 54.3)	46.6 (29.4, 65.9)	135.6 (107.8, 167)	
	Age-adjusted IRR (95% CI) [b]	1.33 (1.14, 1.54)	1	1.22 (1.09, 1.37)	1.26 (1.12, 1.41)	2.04 (1.81, 2.29)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1 (0.86, 1.16)	1	1.33 (1.19, 1.49)	1.42 (1.27, 1.6)	2.23 (1.98, 2.52)	<.001
Stroke	No. cases	349	459	1229	1213	863	
	Person-years	124514	219145	531858	537808	348863	
	Multivariable-adjusted incidence/100k person-years [a]	168.1 (149.5, 189.1)	142.4 (129.3, 156.9)	169 (158.8, 179.9)	181.1 (170.5, 192.5)	223 (208, 239.1)	
	Multivariable-adjusted ARD/100k person-years [a]	25.7 (3.6, 51.2)	0	26.6 (9.5, 45.6)	38.7 (20.1, 59.5)	80.6 (56, 108.2)	
	Age-adjusted IRR (95% CI) [b]	1.32 (1.15, 1.52)	1	1.14 (1.03, 1.27)	1.2 (1.08, 1.34)	1.49 (1.33, 1.67)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1.18 (1.03, 1.36)	1	1.19 (1.07, 1.32)	1.27 (1.14, 1.42)	1.57 (1.39, 1.76)	<.001
Overall	No. cases	1339	2093	5054	5349	3735	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
cancer	Person-years	121166	209743	511817	520106	341436	
	Multivariable-adjusted incidence/100k person-years [a]	895.6 (845.7, 948.4)	892.2 (854, 932)	924 (898.1, 950.6)	1007 (980.4, 1035)	1127 (1091, 1164)	
	Multivariable-adjusted ARD/100k person-years [a]	3.4 (-56.2, 67.3)	0	31.8 (-13.6, 79.5)	115 (65.2, 167.3)	234.5 (174.4, 297.9)	
	Age-adjusted IRR (95% CI) [b]	1.1 (1.03, 1.18)	1	1 (0.95, 1.05)	1.06 (1, 1.11)	1.15 (1.09, 1.22)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1 (0.94, 1.08)	1	1.04 (0.98, 1.09)	1.13 (1.07, 1.19)	1.26 (1.2, 1.33)	<.001
Health Professionals Follow-Up Study							
Coronary heart disease	No. cases	78	152	435	447	195	
	Person-years	26053	52002	133787	109089	43696	
	Multivariable-adjusted incidence/100k person-years [a]	202.4(159.5,256.9)	240.1(203.3,283.5)	275.6(248.9,305.2)	351.6(318.3,388.3)	387.9(334.9,449.4)	
	Multivariable-adjusted ARD/100k person-years [a]	-37.7 (-86.6, 26.8)	0	35.5 (-11.6, 92.4)	111.5 (50.6, 185.2)	147.8 (70.3, 244.7)	
	Age-adjusted IRR (95% CI) [b]	1.02 (0.78, 1.34)	1	1.13 (0.94, 1.36)	1.46 (1.22, 1.76)	1.65 (1.33, 2.03)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.84 (0.64, 1.11)	1	1.15 (0.95, 1.38)	1.46 (1.21, 1.77)	1.62 (1.29, 2.02)	<.001
Stroke	No. cases	31	68	170	158	77	
	Person-years	26267	52452	135793	110947	44332	
	Multivariable-adjusted	85.4(58.3,	106(82.4,136.3)	105.3(89.5,123	123.9(105,146.	156.1(123.	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	incidence/100k person-years [a]	125.1)		.9)	2)	2,197.7)	
	Multivariable-adjusted ARD/100k person-years [a]	-20.6 (-50.5, 25.5)	0	-0.7 (-26.8, 34.1)	18 (-13.9, 60.9)	50.1 (4.6, 114.5)	
	Age-adjusted IRR (95% CI) [b]	0.91 (0.6, 1.39)	1	0.98 (0.74, 1.3)	1.15 (0.87, 1.53)	1.45 (1.05, 2)	0.004
	Multivariable-adjusted IRR (95% CI) [a]	0.81 (0.52, 1.24)	1	0.99 (0.75, 1.32)	1.17 (0.87, 1.57)	1.47 (1.04, 2.08)	0.002
Overall cancer [c]	No. cases	210	380	992	760	328	
	Person-years	25674	50920	130625	108525	44393	
	Multivariable-adjusted incidence/100k person-years [a]	669.1(579.5,772.6)	651.1(586.3,723.1)	672.8(629.6,719)	626.5(581.6,674.9)	673(602.5, 751.8)	
	Multivariable-adjusted ARD/100k person-years [a]	18 (-86.9, 142.5)	0	21.8 (-53.7, 106.8)	-24.5 (-98.7, 59.7)	21.9 (-73.4, 133)	
	Age-adjusted IRR (95% CI) [b]	1.09 (0.92, 1.29)	1	1.03 (0.92, 1.16)	0.97 (0.86, 1.1)	1.06 (0.91, 1.22)	0.71
	Multivariable-adjusted IRR (95% CI) [a]	1.03 (0.87, 1.22)	1	1.03 (0.92, 1.16)	0.96 (0.85, 1.09)	1.03 (0.89, 1.20)	0.78

Abbreviations: ARD, absolute rate difference; IRR, incident rate ratio.
a Multivariable-adjusted model included age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases and weight at young adulthood.
b Age-adjusted model included age at cohort recruitment (continuous).
c Overall cancer excluded non-advanced prostate cancer.

eTable 2. Association between middle life weight gain and overall and cause-specific mortality in the Nurses' Health Study and Health Professionals Follow-Up Study

		weight loss > 2.5kg	**-2.5kg ≤ weight change < 2.5kg**	**2.5kg ≤ weight gain < 10kg**	**10kg ≤ weight gain < 20kg**	**weight gain ≥ 20kg**	**P for trend**
Nurses' Health Study							
overall mortality	No. cases	2716	3701	8331	8021	5740	
	Person-years	126457	221939	540076	546068	354830	
	Multivariable-adjusted incidence/100k person-years [a]	1114 (1076, 1153)	1050 (1020, 1080)	1071 (1049, 1093)	1133 (1110, 1156)	1411 (1380, 1443)	
	Age-adjusted IRR (95% CI) [b]	1.27 (1.22, 1.32)	1	0.96 (0.93, 0.99)	0.99 (0.96, 1.02)	1.25 (1.21, 1.29)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1.06 (1.02, 1.1)	1	1.02 (0.99, 1.05)	1.08 (1.05, 1.11)	1.34 (1.3, 1.39)	<.001
overall mortality among never smokers	No. cases	528	1085	2956	3243	2655	
	Person-years	39231	88894	240739	259997	178126	
	Multivariable-adjusted incidence/100k person-years [a]	745.9(691.4, 804.6)	751(711.4, 792.7)	801.7(773, 831.5)	877.9(848.4, 908.4)	1144(1104, 1186)	
	Age-adjusted IRR (95% CI) [b]	1.12 (1.03, 1.21)	1	1.04 (0.99, 1.1)	1.15 (1.08, 1.21)	1.56 (1.47, 1.65)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.99 (0.91, 1.08)	1	1.07 (1.01, 1.13)	1.17 (1.1, 1.24)	1.52 (1.44, 1.62)	<.001
Cardiovascular mortality	No. cases	472	619	1456	1392	1253	
	Person-years	142865	241132	580239	583286	379532	
	Multivariable-adjusted incidence/100k person-years [a]	111.2 (99.9, 123.8)	117.2 (107.3, 128)	130 (122.2, 138.3)	141 (132.7, 149.8)	221.8 (208.6, 235.8)	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	Age-adjusted IRR (95% CI) [b]	1.26 (1.12, 1.42)	1	1.03 (0.94, 1.12)	1.09 (0.99, 1.19)	1.79 (1.63, 1.97)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.95 (0.84, 1.07)	1	1.11 (1.01, 1.22)	1.2 (1.09, 1.32)	1.89 (1.72, 2.09)	<.001
Cardiovascular mortality among never smokers	No. cases	82	186	498	567	592	
	Person-years	41642	93457	252637	273427	189458	
	Multivariable-adjusted incidence/100k person-years [a]	71.4(56.8, 89.7)	85.5(72.9, 100.3)	91.6(82, 102.2)	105.2(95, 116.6)	173.4(156.9, 191.6)	
	Age-adjusted IRR (95% CI) [b]	1.01 (0.78, 1.3)	1	1.04 (0.88, 1.22)	1.2 (1.02, 1.41)	2.13 (1.82, 2.5)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.83 (0.65, 1.08)	1	1.07 (0.91, 1.26)	1.23 (1.04, 1.45)	2.03 (1.72, 2.39)	<.001
Cancer mortality	No. cases	805	1110	2442	2404	1574	
	Person-years	138627	234894	567239	571194	375039	
	Multivariable-adjusted incidence/100k person-years [a]	339.9 (314.4, 367.4)	329.6 (309.9, 350.7)	328.6 (314.7, 343.1)	353.8 (339.3, 368.9)	394.6 (375.2, 415)	
	Age-adjusted IRR (95% CI) [b]	1.21 (1.11, 1.33)	1	0.93 (0.87, 1)	0.96 (0.9, 1.03)	1.04 (0.96, 1.12)	0.28
	Multivariable-adjusted IRR (95% CI) [a]	1.03 (0.94, 1.13)	1	1 (0.93, 1.07)	1.07 (1, 1.15)	1.2 (1.11, 1.29)	<.001
Cancer mortality among never smokers	No. cases	125	273	721	860	681	
	Person-years	41167	91958	248722	269181	187178	
	Multivariable-adjusted incidence/100k person-years	202.2(168, 243.2)	213.7(189, 241.7)	219.1(202, 237.6)	258.4(240.5, 277.6)	315.7(291.5, 341.9)	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	[a]						
	Age-adjusted IRR (95% CI) [b]	1.03 (0.83, 1.27)	1	1 (0.87, 1.15)	1.17 (1.02, 1.34)	1.45 (1.26, 1.67)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.95 (0.76, 1.17)	1	1.03 (0.89, 1.18)	1.21 (1.06, 1.38)	1.48 (1.28, 1.7)	<.001
Health Professionals Follow-Up Study							
overall mortality	No. cases	309	541	1305	1147	611	
	Person-years	26457	52873	136900	112106	44782	
	Multivariable-adjusted incidence/100k person-years [a]	746.2(667.7,834)	780.9(717.9,849.3)	748.5(707.8,791.6)	804.1(758.3,852.7)	1082(1001,1170)	
	Age-adjusted IRR (95% CI) [b]	1.14 (1, 1.3)	1	0.95 (0.86, 1.04)	1.06 (0.96, 1.17)	1.47 (1.33, 1.64)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.96 (0.84, 1.09)	1	0.96 (0.87, 1.05)	1.03 (0.93, 1.13)	1.39 (1.24, 1.55)	<.001
overall mortality among never smokers	No. cases	114	228	547	420	221	
	Person-years	13008	27964	70938	51971	19186	
	Multivariable-adjusted incidence/100k person-years [a]	538.8(446.4,650.3)	607.6(533.1,692.5)	598.3(547.4,653.8)	666.3(604.5,734.5)	952.2(837.2,1083)	
	Age-adjusted IRR (95% CI) [b]	1.07 (0.87, 1.31)	1	0.96 (0.83, 1.11)	1.07 (0.92, 1.24)	1.6 (1.35, 1.9)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.89 (0.72, 1.1)	1	0.98 (0.85, 1.14)	1.1 (0.94, 1.28)	1.57 (1.31, 1.87)	<.001
Cardiovascular mortality	No. cases	65	116	265	264	154	
	Person-years	27608	54747	141540	115614	46433	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	Multivariable-adjusted incidence/100k person-years [a]	112.1(86.2,145.8)	142.9(117.5,173.8)	137.7(120.8,157.1)	174.5(152.9,199)	260.3(219.8,308.1)	
	Age-adjusted IRR (95% CI) [b]	1.11 (0.82, 1.49)	1	0.9 (0.72, 1.11)	1.14 (0.92, 1.42)	1.73 (1.37, 2.2)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.78 (0.58, 1.06)	1	0.96 (0.77, 1.2)	1.22 (0.98, 1.53)	1.82 (1.42, 2.34)	<.001
Cardiovascular mortality among never smokers	No. cases	21	47	120	91	56	
	Person-years	13355	28743	72569	53026	19682	
	Multivariable-adjusted incidence/100k person-years [a]	68.4(43.2, 108.5)	101.5(74.5,138.2)	112.5(91.8,137.8)	127.2(101.7,158.9)	202.1(152, 268.7)	
	Age-adjusted IRR (95% CI) [b]	0.96 (0.58, 1.59)	1	1.03 (0.74, 1.44)	1.14 (0.81, 1.62)	2 (1.37, 2.93)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	0.67 (0.41, 1.12)	1	1.11 (0.79, 1.56)	1.25 (0.88, 1.79)	1.99 (1.33, 2.97)	<.001
Cancer mortality	No. cases	110	169	467	388	197	
	Person-years	27352	54355	139995	114604	46353	
	Multivariable-adjusted incidence/100k person-years [a]	281.6(230.5,344.1)	248.8(212.4,291.4)	266.9(242.1,294.3)	265.5(238.5,295.5)	329.8(284.4,382.5)	
	Age-adjusted IRR (95% CI) [b]	1.29 (1.02, 1.63)	1	1.09 (0.92, 1.3)	1.15 (0.96, 1.37)	1.49 (1.22, 1.83)	0.007
	Multivariable-adjusted IRR (95% CI) [a]	1.13 (0.89, 1.44)	1	1.07 (0.9, 1.28)	1.07 (0.89, 1.28)	1.33 (1.07, 1.64)	0.05
Cancer mortality among	No. cases	38	73	180	140	65	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
never smokers	Person-years	13245	28571	72130	52740	19748	
	Multivariable-adjusted incidence/100k person-years [a]	203.3(145.3,284.5)	205.7(161.8,261.5)	205.7(176,240.3)	228.9(191.8,273.3)	284.4(220.8,366.4)	
	Age-adjusted IRR (95% CI) [b]	1.12 (0.76, 1.64)	1	0.99 (0.76, 1.3)	1.1 (0.83, 1.46)	1.43 (1.03, 1.98)	0.06
	Multivariable-adjusted IRR (95% CI) [a]	0.99 (0.67, 1.47)	1	1 (0.76, 1.31)	1.11 (0.84, 1.48)	1.38 (0.98, 1.95)	0.04

Abbreviations: IRR, incident rate ratio.

a Multivariable-adjusted model included age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of diabetes, heart disease and cancer, and weight at young adulthood.

b Age-adjusted model included age at cohort recruitment (continuous).

eTable 3. Association between middle life weight gain and major health outcomes in the Nurses' Health Study and Health Professionals Follow-Up Study with further adjustment of disease status, health screening and medication use [a]

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
Nurses' Health Study							
Type 2 diabetes [b]	Multivariable-adjusted incidence/100k person-years	122.4 (103.2, 146.4)	157.2 (138, 178.8)	270 (253.2, 288)	594 (570, 620.4)	1207.2 (1160.4, 1256.4)	
	Multivariable-adjusted IRR (95% CI)	0.78 (0.63, 0.97)	1	1.72 (1.48, 1.99)	3.78 (3.29, 4.35)	7.69 (6.68, 8.84)	<.001
Cardiovascular disease [c]	Multivariable-adjusted incidence/100k person-years	374.4 (338.4, 414)	327.6 (301.2, 356.4)	384 (364.8, 403.2)	372 (355.2, 391.2)	468 (444, 493.2)	
	Multivariable-adjusted IRR (95% CI)	1.14 (1.01, 1.29)	1	1.17 (1.07, 1.28)	1.14 (1.04, 1.25)	1.43 (1.29, 1.57)	<.001
Obesity-related cancer [d]	Multivariable-adjusted incidence/100k person-years	382.8 (349.2, 417.6)	412.8 (386.4, 440.4)	447.6 (429.6, 466.8)	531.6 (512.4, 552)	627.6 (601.2, 655.2)	
	Multivariable-adjusted IRR (95% CI)	0.93 (0.83, 1.03)	1	1.09 (1.01, 1.17)	1.29 (1.2, 1.39)	1.52 (1.41, 1.65)	<.001
Obesity-related cancer among never smokers [d]	Multivariable-adjusted incidence/100k person-years	355.2 (301.2, 420)	374.4 (336, 417.6)	422.4 (397.2, 450)	512.4 (486, 541.2)	631.2 (594, 669.6)	
	Multivariable-adjusted IRR (95% CI)	0.95 (0.78, 1.15)	1	1.13 (1, 1.28)	1.37 (1.22, 1.54)	1.69 (1.49, 1.91)	<.001

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
Mortality [c]	Multivariable-adjusted incidence/100k person-years	1102.8 (1056, 1150.8)	1034.4 (998.4, 1072.8)	1046.4 (1021.2, 1072.8)	1090.8 (1064.4, 1116)	1278 (1246.8, 1310.4)	
	Multivariable-adjusted IRR (95% CI)	1.07 (1.01, 1.12)	1	1.01 (0.97, 1.05)	1.05 (1.01, 1.09)	1.24 (1.19, 1.29)	<.001
Mortality among never smokers [c]	Multivariable-adjusted incidence/100k person-years	746.4 (679.2, 819.6)	766.8 (716.4, 819.6)	801.6 (766.8, 837.6)	865.2 (832.8, 900)	1059.6 (1017.6, 1102.8)	
	Multivariable-adjusted IRR (95% CI)	0.97 (0.87, 1.08)	1	1.05 (0.97, 1.12)	1.13 (1.05, 1.21)	1.38 (1.29, 1.49)	<.001
Health Professionals Follow-Up Study							
Type 2 diabetes [b]	Multivariable-adjusted incidence/100k person-years	132(99.6, 175.2)	146.4(118.8, 182.4)	254.4(229.2, 282)	507.6(465.6, 554.4)	1057.2(954, 1171.2)	
	Multivariable-adjusted IRR (95% CI)	0.9 (0.64, 1.27)	1	1.73 (1.37, 2.19)	3.46 (2.75, 4.35)	7.2 (5.69, 9.12)	<.001
Cardiovascular disease [c]	Multivariable-adjusted incidence/100k person-years	308.4(250.8, 378)	345.6(300, 398.4)	384(351.6, 420)	457.2(418.8, 499.2)	494.4(434.4, 562.8)	
	Multivariable-adjusted IRR (95% CI)	0.89 (0.71, 1.13)	1	1.11 (0.95, 1.31)	1.32 (1.12, 1.56)	1.43 (1.18, 1.74)	<.001
Obesity-related cancer [d]	Multivariable-adjusted incidence/100k person-years	190.8(146.4, 247.2)	164.4(134.4, 201.6)	206.4(183.6, 232.8)	184.8(162, 211.2)	231.6(192, 278.4)	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	Multivariable-adjusted IRR (95% CI)	1.15 (0.84, 1.59)	1	1.25 (1, 1.57)	1.12 (0.88, 1.42)	1.4 (1.07, 1.84)	0.14
Obesity-related cancer among never smokers [d]	Multivariable-adjusted incidence/100k person-years	144(96, 216)	162(123.6, 213.6)	181.2(151.2, 216)	160.8(129.6, 198)	235.2(176.4, 313.2)	
	Multivariable-adjusted IRR (95% CI)	0.89 (0.55, 1.43)	1	1.11 (0.81, 1.53)	0.99 (0.7, 1.4)	1.45 (0.97, 2.16)	0.10
Mortality [c]	Multivariable-adjusted incidence/100k person-years	763.2(681.6, 853.2)	772.8(709.2, 841.2)	742.8(702, 786)	786(740.4, 835.2)	1014(936, 1099.2)	
	Multivariable-adjusted IRR (95% CI)	0.99 (0.87, 1.13)	1	0.96 (0.87, 1.06)	1.02 (0.92, 1.12)	1.31 (1.17, 1.47)	<.001
Mortality among never smokers [c]	Multivariable-adjusted incidence/100k person-years	550.8(456, 666)	596.4(522, 681.6)	596.4(544.8, 651.6)	656.4(594, 724.8)	886.8(776.4, 1014)	
	Multivariable-adjusted IRR (95% CI)	0.92 (0.74, 1.15)	1	1 (0.86, 1.16)	1.1 (0.94, 1.29)	1.49 (1.24, 1.79)	<.001

Abbreviations: IRR, incident rate ratio.

[a] All multivariable-adjusted model included age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases and weight at young adulthood.

[b] Multivariable-adjusted model for type 2 diabetes further included prevalent hypertension, antihypertensive medication use, hypercholesterolemia, and lipid medication use at baseline.
[c] Multivariable-adjusted models for cardiovascular disease and mortality further included prevalent diabetes, hypertension, antihypertensive medication use, hypercholesterolemia, and lipid medication use at baseline.
[d] Multivariable-adjusted models for cancer further included history of lower gastrointestinal endoscopy, history of physical exam, mammography (women only), and prostate-specific antigen test (men only) at baseline.

eTable 4. Association between middle life weight gain and major health outcomes in the Nurses' Health Study and Health Professionals Follow-Up Study with further adjustment of use of antidepressants and oral steroids [a]

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
Nurses' Health Study							
Type 2 diabetes	No. cases	18	32	129	407	1000	
	Person-years	15249.3	29721.5	79272.1	95544.0	77455.1	
	Multivariable-adjusted incidence/100k person-years [b]	67.2 (37.2, 121.2)	97.2 (64.8, 145.2)	130.8 (105.6, 162)	392.4 (351.6, 436.8)	1057.2 (980.4, 1138.8)	
	Age-adjusted IRR (95% CI) [c]	1.09 (0.61, 1.95)	1	1.53 (1.04, 2.25)	4.05 (2.82, 5.81)	12.42 (8.71, 17.73)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	0.69 (0.34, 1.41)	1	1.35 (0.86, 2.12)	4.05 (2.68, 6.13)	10.93 (7.28, 16.42)	<.001
Cardiovascular disease	No. cases	55	74	234	259	237	
	Person-years	15460.2	30199.8	80696.7	101185.7	93570.4	
	Multivariable-adjusted incidence/100k person-years [b]	126 (80.4, 199.2)	67.2 (42, 108)	157.2 (129.6, 189.6)	151.2 (128.4, 178.8)	159.6 (135.6, 187.2)	
	Age-adjusted IRR (95% CI) [c]	1.40 (1.00, 1.97)	1	1.35 (1.05, 1.74)	1.43 (1.11, 1.83)	1.73 (1.34, 2.24)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	1.88 (1.00, 3.55)	1	2.33 (1.41, 3.85)	2.25 (1.37, 3.70)	2.37 (1.44, 3.90)	0.04
Obesity-	No. cases	66	132	352	474	544	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
related cancer [d]	Person-years	15535.6	29902.3	80211.0	100925.8	94399.1	
	Multivariable-adjusted incidence/100k person-years [b]	432 (324, 577.2)	418.8 (340.8, 514.8)	415.2 (367.2, 469.2)	451.2 (409.2, 498)	553.2 (505.2, 606)	
	Age-adjusted IRR (95% CI) [c]	0.96 (0.71, 1.29)	1	1.00 (0.82, 1.22)	1.08 (0.89, 1.31)	1.34 (1.10, 1.62)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	1.03 (0.73, 1.46)	1	0.99 (0.78, 1.26)	1.08 (0.86, 1.35)	1.32 (1.05, 1.65)	<.001
Mortality	No. cases	257	361	795	840	732	
	Person-years	15761.3	30725.3	82100.8	102818.2	94948.5	
	Multivariable-adjusted incidence/100k person-years [b]	589.2 (477.6, 727.2)	454.8 (379.2, 544.8)	412.8 (367.2, 464.4)	428.4 (388.8, 472.8)	477.6 (435.6, 524.4)	
	Age-adjusted IRR (95% CI) [c]	1.34 (1.18, 1.52)	1	0.95 (0.86, 1.05)	0.97 (0.88, 1.07)	1.15 (1.03, 1.27)	0.36
	Multivariable-adjusted IRR (95% CI) [b]	1.30 (1.01, 1.66)	1	0.91 (0.74, 1.11)	0.94 (0.77, 1.14)	1.05 (0.87, 1.28)	0.72
Health Professionals Follow-Up Study							
Type 2 diabetes	No. cases	37	61	257	448	394	
	Person-years	18345.0	36975.0	95745.0	79294.0	29552.0	
	Multivariable-adjusted incidence/100k person-years [b]	118.9(84.6,167.2)	141.1(109.5,181.6)	247.2(218.4,279.9)	508(461.1,559.6)	1129(1008, 1265)	

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
	Age-adjusted IRR (95% CI) [c]	1.22 (0.81, 1.84)	1	1.64 (1.24, 2.16)	3.46 (2.65, 4.52)	8.22 (6.28, 10.77)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	0.84 (0.55, 1.28)	1	1.75 (1.33, 2.32)	3.6 (2.75, 4.71)	8 (6.07, 10.55)	<.001
Cardiovascular disease	No. cases	70	134	385	386	186	
	Person-years	18849.8	37653.2	97365.4	82909.1	34210.3	
	Multivariable-adjusted incidence/100k person-years [b]	263(204.5,338.1)	303.9(254.8,362.5)	350.6(315.4,389.8)	413.9(372.2,460.2)	487.8(419.7,567)	
	Age-adjusted IRR (95% CI) [c]	1.04 (0.78, 1.38)	1	1.13 (0.93, 1.38)	1.36 (1.12, 1.65)	1.64 (1.31, 2.04)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	0.87 (0.65, 1.16)	1	1.15 (0.94, 1.41)	1.36 (1.11, 1.67)	1.61 (1.27, 2.03)	<.001
Obesity-related cancer [d]	No. cases	38	58	203	165	87	
	Person-years	19665.4	39644.8	101458.8	87388.8	36419.9	
	Multivariable-adjusted incidence/100k person-years [b]	160.2(114.4,224.2)	130.9(100.5,170.6)	181.3(156.5,210)	171.3(146.2,200.7)	214.8(172.2,267.9)	
	Age-adjusted IRR (95% CI) [c]	1.32 (0.88, 1.98)	1	1.39 (1.04, 1.86)	1.33 (0.98, 1.79)	1.71 (1.23, 2.39)	0.02
	Multivariable-adjusted IRR (95% CI) [b]	1.22 (0.81,	1	1.38 (1.03, 1.86)	1.31 (0.96, 1.78)	1.64 (1.16, 2.32)	0.03

		weight loss > 2.5kg	-2.5kg ≤ weight change < 2.5kg	2.5kg ≤ weight gain < 10kg	10kg ≤ weight gain < 20kg	weight gain ≥ 20kg	P for trend
		1.85)					
Mortality	No. cases	179	323	760	689	398	
	Person-years	19217.7	38386.6	99812.0	85338.8	35170.7	
	Multivariable-adjusted incidence/100k person-years [b]	591.7 (509.2, 687.6)	670.8 (601.2, 748.5)	634.4 (590, 682.2)	659.1 (610.4, 711.7)	925 (838.2, 1021)	
	Age-adjusted IRR (95% CI) [c]	1.10 (0.93, 1.31)	1	0.93 (0.82, 1.05)	1.01 (0.89, 1.14)	1.47 (1.28, 1.69)	<.001
	Multivariable-adjusted IRR (95% CI) [b]	0.88 (0.74, 1.05)	1	0.95 (0.84, 1.07)	0.98 (0.86, 1.12)	1.38 (1.19, 1.59)	<.001

Abbreviations: IRR, incident rate ratio.
a Analyses were conducted among the participants who had information of use of antidepressants and oral steroids collected only.
b Multivariable-adjusted model included use of antidepressants and oral steroids, as well as the other covariates, i.e., age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (women only: premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (women only: nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (women: 0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d; men: 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases, weight at young adulthood.
c Age-adjusted model included age at cohort recruitment (continuous).
d Obesity-related cancer included cancers of the esophagus (adenocarcinoma only), colon and rectum, pancreas, breast [after menopause], endometrium, ovaries, kidney, liver and gallbladder.

eTable 5. Association between quintiles of early/middle adulthood weight change and major health outcomes in the Nurses' Health Study

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
Type 2 diabetes	No. cases	465	732	1254	1962	3394	
	Person-years	365315	368615	343596	310756	245678	
	Multivariable-adjusted incidence/100k person-years [a]	100.2(91.4, 109.9)	186(173,200)	349.1(330.2,369.2)	596.3(569.9,624)	1226(1180,1273)	
	Multivariable-adjusted ARD/100k person-years [a]	0	85.8 (65.4, 108.7)	248.9 (213.5, 288.3)	496 (437.9, 560.3)	1125 (1008.4, 1253.9)	
	Age-adjusted IRR (95% CI) [b]	1	1.57(1.39,1.76)	2.89(2.6,3.22)	5.03(4.54,5.56)	11.11(10.07,12.25)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.86(1.65,2.09)	3.48(3.13,3.88)	5.95(5.37,6.59)	12.23(11.06,13.51)	<.001
Hypertension	No. cases	6658	7152	7100	6729	5354	
	Person-years	230885	212859	183276	147009	92754	
	Multivariable-adjusted incidence/100k person-years [a]	2687(2623, 2752)	3352(3278,3427)	3930(3844,4018)	4703(4595,4813)	5874(5714,6038)	
	Multivariable-adjusted ARD/100k person-years [a]	0	664.5 (558.9, 773.9)	1243.5 (1116.7, 1374.4)	2016.1 (1858.9, 2178.9)	3186.5 (2970.7, 3410.6)	
	Age-adjusted IRR (95% CI) [b]	1	1.16(1.13,1.2)	1.34(1.3,1.38)	1.58(1.53,1.64)	2(1.93,2.07)	<.001

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
	Multivariable-adjusted IRR (95% CI) [a]	1	1.25(1.21,1.29)	1.46(1.42,1.51)	1.75(1.69,1.81)	2.19(2.11,2.27)	<.001
Cardiovascular disease	No. cases	1555	1611	1446	1450	1585	
	Person-years	367403	372538	357127	336641	300572	
	Multivariable-adjusted incidence/100k person-years [a]	257.9(243.5,273.2)	311.5(295.5, 328.4)	313(296.4,330.6)	353.7(335.2,373.1)	474.6(451,499.4)	
	Multivariable-adjusted ARD/100k person-years [a]	0	53.6 (32.3, 76.3)	55.1 (32.9, 79)	95.7 (70.3, 123.1)	216.6 (182.5, 253.4)	
	Age-adjusted IRR (95% CI) [b]	1	1.05(0.98,1.13)	1.04(0.97,1.11)	1.16(1.08,1.25)	1.59(1.48,1.71)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.21(1.13,1.3)	1.21(1.13,1.31)	1.37(1.27,1.48)	1.84(1.71,1.98)	<.001
Obesity-related cancer [c]	No. cases	1554	1747	1837	1847	1919	
	Person-years	364095	369107	354941	336976	304219	
	Multivariable-adjusted incidence/100k person-years [a]	403.8(382.8,426)	453.3(432,475.6)	503.8(481,527.7)	542(517.6,567.6)	638.8(610.3,668.6)	
	Multivariable-adjusted ARD/100k person-years [a]	0	49.4 (18.8, 82.3)	100 (65.9, 136.6)	138.1 (101, 178.1)	234.9 (190.8, 282.4)	
	Age-adjusted IRR (95% CI) [b]	1	1.11(1.04,1.19)	1.22(1.14,1.31)	1.3(1.21,1.39)	1.51(1.41,1.61)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.12(1.05,1.2)	1.25(1.16,1.34)	1.34(1.25,1.44)	1.58(1.47,1.7)	<.001

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
Obesity-related cancer [c] **in never smokers**	No. cases	680	768	787	825	874	
	Person-years	168554	165612	157556	151559	136057	
	Multivariable-adjusted incidence/100k person-years [a]	375.7(346.8,407)	438.8(408,471.8)	488.1(455,523.7)	538.3(502.4,576.7)	651.3(609,696.5)	
	Multivariable-adjusted ARD/100k person-years [a]	0	63.1 (19.5, 111.5)	112.4 (63.7, 166.6)	162.6 (108.9, 222.2)	275.6 (210.3, 348.3)	
	Age-adjusted IRR (95% CI) [b]	1	1.15(1.04,1.28)	1.25(1.13,1.39)	1.37(1.24,1.51)	1.63(1.48,1.81)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.17(1.05,1.3)	1.3(1.17,1.44)	1.43(1.29,1.59)	1.73(1.56,1.93)	<.001
Cholelithiasis	No. cases	1154	1516	1761	2005	2115	
	Person-years	337864	337569	312078	287246	228721	
	Multivariable-adjusted incidence/100k person-years [a]	288.6(271.3,307)	425.4(403.4, 448.5)	554.5(528.1,582.1)	689.6(656.5,724.3)	904.2(861.3,949.2)	
	Multivariable-adjusted ARD/100k person-years [a]	0	136.7 (104.2, 172)	265.9 (224.3, 310.8)	401 (348.4, 457.9)	615.6 (546.7, 690.1)	
	Age-adjusted IRR (95% CI) [b]	1	1.32(1.22,1.43)	1.67(1.55,1.8)	2.08(1.93,2.25)	2.8(2.59,3.01)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.47(1.36,1.6)	1.92(1.78,2.08)	2.39(2.21,2.59)	3.13(2.89,3.39)	<.001
Severe	No. cases	557	577	573	500	449	

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
Osteoarthritis	Person-years	360386	366751	350963	332158	301083	
	Multivariable-adjusted incidence/100k person-years [a]	91.2(82.8,100.8)	109.2(99.6,118.8)	121.2(110.4,132)	118.8(108,130.8)	128.4(116.4,141.6)	
	Multivariable-adjusted ARD/100k person-years [a]	0	17.3 (4.8, 31.3)	29 (15, 44.9)	26.9 (12.6, 43.3)	36.4 (20.3, 54.9)	
	Age-adjusted IRR (95% CI) [b]	1	1.05(0.94,1.18)	1.15(1.03,1.3)	1.12(0.99,1.27)	1.25(1.1,1.42)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.19(1.05,1.34)	1.32(1.16,1.49)	1.3(1.14,1.47)	1.4(1.22,1.6)	<.001
Cataract extraction	No. cases	7808	7958	7454	7093	6411	
	Person-years	316909	323679	314323	298868	273020	
	Multivariable-adjusted incidence/100k person-years [a]	2214(2171,2258)	2271(2229,2314)	2245(2202,2288)	2298(2253,2344)	2363(2314,2414)	
	Multivariable-adjusted ARD/100k person-years [a]	0	56.5 (-0.8, 115.4)	30.4 (-28.6, 90.9)	83.6 (21.2, 147.6)	148.7 (80.8, 218.6)	
	Age-adjusted IRR (95% CI) [b]	1	1.01(0.99,1.04)	0.99(0.97,1.02)	1.02(0.99,1.04)	1.05(1.02,1.08)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.03(1,1.05)	1.01(0.99,1.04)	1.04(1.01,1.07)	1.07(1.04,1.1)	<.001
Mortality	No. cases	6894	5916	5501	5099	5099	
	Person-years	378024	384373	367688	347435	311851	

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
	Multivariable-adjusted incidence/100k person-years [a]	1070(1045,1096)	1059(1034,1084)	1108(1082,1134)	1161(1134,1189)	1439(1405,1473)	
	Multivariable-adjusted ARD/100k person-years [a]	0	-11.8 (-40.8, 18.1)	37.4 (5.8, 70.1)	90.8 (56.5, 126.3)	368.2 (324.6, 413)	
	Age-adjusted IRR (95% CI) [b]	1	0.87(0.85,0.9)	0.9(0.87,0.92)	0.93(0.9,0.96)	1.17(1.14,1.2)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	0.99(0.96,1.02)	1.04(1.01,1.07)	1.08(1.05,1.12)	1.34(1.3,1.39)	<.001
Mortality among Never smokers	No. cases	2175	2113	2013	2015	2151	
	Person-years	174738	172307	163745	156545	139653	
	Multivariable-adjusted incidence/100k person-years [a]	754.1(723,786.4)	794.5(762.6, 827.8)	861.9(827.5,897.7)	918.4(882.4,956)	1197(1152,1244)	
	Multivariable-adjusted ARD/100k person-years [a]	0	40.5 (2.2, 80.7)	107.9 (65.2, 152.7)	164.4 (118.9, 212.3)	442.9 (384.2, 504.6)	
	Age-adjusted IRR (95% CI) [b]	1	1.01(0.96,1.06)	1.09(1.03,1.14)	1.18(1.12,1.24)	1.6(1.53,1.68)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.05(1,1.11)	1.14(1.09,1.2)	1.22(1.16,1.28)	1.59(1.51,1.67)	<.001
Composite Healthy Aging [d]	Sample size	10207	10140	10085	10320	10188	
	No. healthy agers	2664	2495	2319	2107	1334	
	Age-adjusted OR (95% CI) [b]	1	0.85(0.8,0.91)	0.69(0.65,0.74)	0.53(0.49,0.57)	0.25(0.23,0.27)	<.001

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 3.1kg, reference)	**Quintile 2 (weight gain of 3.1 to 8.3kg)**	**Quintile 3 (weight gain of 8.4 to 13.6kg)**	**Quintile 4 (weight gain of 13.7 to 21.3kg)**	**Quintile 5 (weight gain of >21.3kg)**	**P for trend**
	Multivariable-adjusted OR (95% CI) [a]	1	0.77(0.72,0.82)	0.63(0.59,0.68)	0.5(0.46,0.54)	0.26(0.24,0.28)	<.001

Abbreviations: ARD, absolute rate difference; IRR, incident rate ratio; OR, odds ratio.

[a] Multivariable-adjusted model included age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20), regular aspirin use (yes or no), status of menopause and hormone therapy (premenopausal, postmenopausal and never user, postmenopausal and current use, or postmenopausal and past user), parity (nulliparous, 1, 2, 3, or 4 and more children), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption (0, 0.1−0.4, 0.5−1.9, 2−7, or ≥8 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases and weight at 18 years old.

[b] Age-adjusted model included age at cohort recruitment (continuous).

[c] Obesity-related cancer included cancers of the esophagus (adenocarcinoma only), colon and rectum, pancreas, breast [after menopause], endometrium, ovaries, kidney, liver and gallbladder.

[d] Composite healthy aging was defined as meeting all of the following criteria: (1) no self-reported history of cancer, diabetes, coronary heart disease, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis; (2) no cognitive decline; and (3) no physical limitations.

eTable 6. Association between quintiles of early to middle adulthood weight gain and health outcomes in the Health Professionals Follow-Up Study

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 2.2kg, reference)	**Quintile 2 (weight gain of 2.2 to 6.8kg)**	**Quintile 3 (weight gain of 6.9 to 10.8kg)**	**Quintile 4 (weight gain of 10.9 to 16.6kg)**	**Quintile 5 (weight gain of >16.6kg)**	**P for trend**
Type 2 diabetes	No. cases	139	179	243	390	661	
	Person-years	74270	72673	71545	69416	60492	
	Multivariable-adjusted incidence/100k person-years [a]	138.5(116.5,164.7)	221.9(191.9,256.7)	314.2(276.5,357.1)	503.8(454.4,558.6)	976.6(896.5,1064)	
	Multivariable-adjusted ARD/100k person-years [a]	0	83.4 (38.7,139.3)	175.7 (115.7,249.9)	365.2 (274.3,476.2)	837.9 (668.3,1043.2)	
	Age-adjusted IRR (95% CI) [b]	1	1.32(1.06,1.64)	1.83(1.48,2.25)	3.03(2.50,3.68)	5.93(4.94,7.12)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.60(1.28,2.01)	2.27(1.84,2.80)	3.64(2.98,4.44)	7.05(5.83,8.53)	<.001
Hypertension	No. cases	1202	1281	1348	1443	1318	
	Person-years	49644	46389	42747	37871	28294	
	Multivariable-adjusted incidence/100k person-years [a]	2226(2099,2362)	2695(2551,2847)	3116(2952,3289)	3786(3592,3990)	4770(4502,5054)	
	Multivariable-adjusted ARD/100k person-years [a]	0	468.2 (263.9,689.2)	889.4 (650.8,1147.8)	1559.1 (1269.3,1872.9)	2543.3 (2154.5,2966.7)	
	Age-adjusted IRR (95% CI) [b]	1	1.14(1.06,1.23)	1.30(1.21,1.41)	1.58(1.46,1.70)	1.93(1.79,2.09)	<.001
	Multivariable-adjusted IRR (95%	1	1.21(1.12,1.	1.40(1.29,1.5	1.70(1.57,1.84)	2.14(1.97,2.33)	<.0

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 2.2kg, reference)	**Quintile 2 (weight gain of 2.2 to 6.8kg)**	**Quintile 3 (weight gain of 6.9 to 10.8kg)**	**Quintile 4 (weight gain of 10.9 to 16.6kg)**	**Quintile 5 (weight gain of >16.6kg)**	**P for trend**
	CI) [a]		31)	2)			01
Cardiovascular disease	No. cases	310	311	343	386	402	
	Person-years	75640	73524	72654	71944	67831	
	Multivariable-adjusted incidence/100k person-years [a]	323(285.4,365.5)	356.6(317.7, 400.2)	414.5(371.3, 462.9)	470.2(423.8,521.7)	527.8(476,585.2)	
	Multivariable-adjusted ARD/100k person-years [a]	0	33.6 (-19.4, 96)	91.6 (29.8, 164.1)	147.2 (78.1, 228.2)	204.8 (126.5, 296.7)	
	Age-adjusted IRR (95% CI) [b]	1	1.03(0.88,1.20)	1.19(1.02,1.39)	1.37(1.18,1.58)	1.55(1.33,1.79)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.10(0.94,1.30)	1.28(1.09,1.51)	1.46(1.24,1.71)	1.63(1.39,1.92)	<.001
Obesity-related cancer [c]	No. cases	160	184	178	166	175	
	Person-years	79322	76872	75865	76043	72567	
	Multivariable-adjusted incidence/100k person-years [a]	171.1(145,201.9)	205.6(176.4, 239.5)	206.9(177.4, 241.4)	190.9(163.1,223.4)	210.4(179.8,246.1)	
	Multivariable-adjusted ARD/100k person-years [a]	0	34.4 (-5.4, 83.8)	35.8 (-5.4, 87.4)	19.7 (-18.7, 67.9)	39.3 (-3.6, 93)	
	Age-adjusted IRR (95% CI) [b]	1	1.18(0.96,1.46)	1.20(0.97,1.48)	1.12(0.90,1.40)	1.27(1.03,1.57)	0.07
	Multivariable-adjusted IRR (95% CI) [a]	1	1.20(0.97,1.49)	1.21(0.97,1.51)	1.12(0.89,1.40)	1.23(0.98,1.54)	0.2
Obesity-	No. cases	74	84	77	64	80	

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 2.2kg, reference)	**Quintile 2 (weight gain of 2.2 to 6.8kg)**	**Quintile 3 (weight gain of 6.9 to 10.8kg)**	**Quintile 4 (weight gain of 10.9 to 16.6kg)**	**Quintile 5 (weight gain of >16.6kg)**	**P for trend**
related cancer [c] among never smokers	Person-years	38088	38001	37623	35942	35772	
	Multivariable-adjusted incidence/100k person-years [a]	159(124.7,202.8)	188.1(149.8,236.2)	178.5(140.7,226.4)	159.7(124.1,205.6)	206.5(163.8,260.3)	
	Multivariable-adjusted ARD/100k person-years [a]	0	29.1 (-22.2,99.6)	19.5 (-31,89.9)	0.7 (-46.3,67.4)	47.5 (-11.9,130.8)	
	Age-adjusted IRR (95% CI) [b]	1	1.13(0.83,1.54)	1.08(0.79,1.48)	0.95(0.68,1.33)	1.23(0.90,1.69)	0.21
	Multivariable-adjusted IRR (95% CI) [a]	1	1.18(0.86,1.63)	1.12(0.81,1.57)	1.00(0.71,1.42)	1.30(0.92,1.82)	0.14
Cholelithiasis	No. cases	175	172	189	225	233	
	Person-years	73281	71352	70871	69092	63894	
	Multivariable-adjusted incidence/100k person-years [a]	180.8(153.5,212.9)	198.5(170.1,231.7)	229.1(198,265.1)	277.9(241.7,319.6)	314(273.2,360.8)	
	Multivariable-adjusted ARD/100k person-years [a]	0	17.7 (-21,65.8)	48.3 (4.4,102.6)	97.1 (44.8,161.6)	133.2 (73.2,207.3)	
	Age-adjusted IRR (95% CI) [b]	1	1.01(0.82,1.24)	1.15(0.94,1.42)	1.42(1.16,1.73)	1.64(1.34,1.99)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.10(0.88,1.36)	1.27(1.02,1.57)	1.54(1.25,1.89)	1.74(1.40,2.15)	<.001
Severe osteoarthritis	No. cases	98	84	99	78	75	
	Person-years	77798	76081	75152	75386	72306	
	Multivariable-adjusted incidence/100k person-years [a]	70.8(56.4,91.2)	81.6(64.8,103.2)	109.2(88.8,133.2)	90(70.8,112.8)	98.4(78,124.8)	

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 2.2kg, reference)	**Quintile 2 (weight gain of 2.2 to 6.8kg)**	**Quintile 3 (weight gain of 6.9 to 10.8kg)**	**Quintile 4 (weight gain of 10.9 to 16.6kg)**	**Quintile 5 (weight gain of >16.6kg)**	**P for trend**
	Multivariable-adjusted ARD/100k person-years [a]	0	10.3 (-10.7, 38.7)	37.1 (9.6, 74)	18.4 (-5.6, 51.1)	27.4 (0.8, 63.8)	
	Age-adjusted IRR (95% CI) [b]	1	0.88(0.65,1.17)	1.07(0.81,1.41)	0.84(0.63,1.14)	0.86(0.63,1.16)	0.31
	Multivariable-adjusted IRR (95% CI) [a]	1	1.15(0.85,1.55)	1.52(1.14,2.04)	1.26(0.92,1.72)	1.39(1.01,1.90)	0.04
Cataract extraction	No. cases	983	951	963	998	981	
	Person-years	74726	72305	71695	71104	67843	
	Multivariable-adjusted incidence/100k person-years [a]	1122(1052,1196)	1147(1079,1219)	1207(1135,1283)	1262(1189,1339)	1306(1228,1390)	
	Multivariable-adjusted ARD/100k person-years [a]	0	25 (-67.3, 125.3)	84.8 (-13.5, 191.9)	139.9 (36.5, 252.6)	184.7 (74.2, 305.4)	
	Age-adjusted IRR (95% CI) [b]	1	1.00(0.92,1.09)	1.05(0.97,1.14)	1.11(1.03,1.21)	1.17(1.08,1.27)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.02(0.94,1.11)	1.08(0.99,1.17)	1.12(1.03,1.23)	1.16(1.07,1.27)	<.001
Mortality	No. cases	837	708	719	768	881	
	Person-years	77459	75647	75136	74593	70284	
	Multivariable-adjusted incidence/100k person-years [a]	775.7(721.8,833.5)	717.6(666.8, 772.2)	767.7(715.5, 823.7)	811.6(756.8,870.4)	988.8(925.4,1056)	
	Multivariable-adjusted ARD/100k person-years [a]	0	-58.1 (-122.4, 12.6)	-8 (-77.5, 68.4)	35.9 (-37.4, 116.6)	213.1 (124.7, 310.2)	

		Quintiles of weight change					
		Quintile 1 (weight loss or weight gain of < 2.2kg, reference)	**Quintile 2 (weight gain of 2.2 to 6.8kg)**	**Quintile 3 (weight gain of 6.9 to 10.8kg)**	**Quintile 4 (weight gain of 10.9 to 16.6kg)**	**Quintile 5 (weight gain of >16.6kg)**	**P for trend**
	Age-adjusted IRR (95% CI) [b]	1	0.86(0.79,0.94)	0.92(0.84,1.01)	1.01(0.92,1.10)	1.27(1.16,1.38)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	0.93(0.84,1.02)	0.99(0.9,1.09)	1.05(0.95,1.15)	1.27(1.16,1.40)	<.001
Mortality among never smokers	No. cases	308	301	281	294	346	
	Person-years	37500	37661	37406	35459	35040	
	Multivariable-adjusted incidence/100k person-years [a]	575.5(510.6,648.5)	600.7(534.8,674.7)	598.1(533.4,670.7)	677.1(604.1,759)	822.1(740.1,913.1)	
	Multivariable-adjusted ARD/100k person-years [a]	0	25.2 (-59.2,123.5)	22.6 (-63.7,123.5)	101.7 (3.8,216.1)	246.6 (131.5,380.5)	
	Age-adjusted IRR (95% CI) [b]	1	0.96(0.83,1.11)	0.95(0.82,1.1)	1.07(0.92,1.25)	1.34(1.16,1.55)	<.001
	Multivariable-adjusted IRR (95% CI) [a]	1	1.04(0.90,1.21)	1.04(0.89,1.21)	1.18(1.01,1.38)	1.43(1.23,1.66)	<.001
Composite healthy aging [d]	Sample size	3519	3580	3534	3481	3620	
	No. healthy agers	1346	1320	1294	1108	973	
	Age-adjusted OR (95% CI) [b]	1	0.93(0.84,1.03)	0.87(0.78,0.96)	0.67(0.6,0.74)	0.49(0.44,0.55)	<.001
	Multivariable-adjusted OR (95% CI) [a]	1	0.88(0.79,0.97)	0.83(0.74,0.92)	0.65(0.58,0.73)	0.50(0.44,0.56)	<.001

Abbreviations: ARD, absolute rate difference; IRR, incident rate ratio; OR, odds ratio.

[a] Multivariable-adjusted model included age at cohort recruitment (continuous), height (continuous), race (non-white or white), pack-years of smoking (never smokers; past smoker with pack-years<5, 5-20, >20; and current smoker with pack-years <5, 5-20, >20),

regular aspirin use (yes or no), physical activity (in quintiles of metabolic equivalent task–hours/week), alcohol consumption 0−4, 5−9, 10−14, 15−29, or ≥30 g/d), dietary qualify (Alternative Healthy Eating Index, in quintiles), family history of respective diseases and weight at 21 years old.

[b] Age-adjusted model included age at cohort recruitment (continuous).

[c] Obesity-related cancer included cancers of the esophagus (adenocarcinoma only), colon and rectum, pancreas, prostate (advanced only), kidney, liver and gallbladder.

[d] Composite healthy aging was defined as meeting all of the following criteria: (1) no self-reported history of cancer, diabetes, coronary heart disease, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, congestive heart failure, stroke, kidney failure, chronic obstructive pulmonary disease, Parkinson's disease, multiple sclerosis, or amyotrophic lateral sclerosis; (2) no cognitive decline; and (3) no physical limitations.