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Unrestrained eating behavior and risk of mortality: a prospective cohort study

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Author contributions

YZ, KN and ELG were involved in the study concept and design. YZ performed statistical analysis. YZ interpreted data and drafted the manuscript. All authors participated in critical revision of the manuscript for important intellectual content. KN, ELG, FBH, SBR, EBR, WCW, CSF, JAM, MJS, BMW, ESS, ATC, CY and MS contributed to administrative, technical, and material support. KN, ELG, CSF, BMW, ESS, ATC, CY and MS obtained funding. YZ, ELG and KN have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version of this paper and the authorship list. YZ, ELG and KN are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics approval

The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital (Boston, MA), and those of participating registries as required. Informed consent from participants was implied by the completion and return of the questionnaires. Written informed consent was required to retrieve medical records.

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Abstract

Background & Aims—Unrestrained eating behavior has been thought to be a proxy for diet frequency, timing, and caloric intake. We investigated the association of unrestrained eating with mortality risk in the Nurses' Health Study prospectively.

Methods—During follow-up (1994–2016), 21953 deaths were documented among 63999 eligible participants in analyses of eating anything at any time, 22120 deaths were documented among 65839 participants in analyses of no concern with figure change. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models.

Results—Eating anything at any time was associated with an increased mortality from cancer (overall HR, 95%CI: 1.07, 1.00–1.13; driven by gastrointestinal tract cancer: 1.30, 1.10–1.54) and respiratory disease (1.16, 1.05–1.29), and decreased cardiovascular disease-specific mortality (0.92, 0.86–0.99), compared to those without this behavior; however, no association was observed between this behavior and all-cause mortality (1.02, 0.99–1.05). Women who reported having no concern with figure change experienced higher risk of mortality from all-cause (1.08, 1.05–1.11), cancer (1.08, 1.02–1.14), and respiratory disease (1.18, 1.08–1.30), compared to those not reporting this behavior. Their combined effect was associated with a higher all-cause (1.09, 1.04–1.14), cancer-specific (overall: 1.18, 1.09–1.28; gastrointestinal tract cancer: 1.36, 1.08–1.71; lung cancer: 1.09; 1.04–1.14), and respiratory disease-specific (1.30, 1.13–1.50) mortality, and was inversely associated with cardiovascular disease-specific mortality (0.88, 0.80–0.98), compared to those exhibiting the opposite.

Conclusions—Unrestrained eating was associated with increased risk of all-cause, cancer-specific (particularly for gastrointestinal tract cancer and lung cancer), and respiratory disease-specific mortality, and decreased risk of cardiovascular disease-specific mortality.

Keywords

Unrestrained eating behavior; all-cause mortality; cause-specific mortality

Introduction

Major modifiable lifestyle factors (e.g., body weight,[1–5] smoking,[1–5] alcohol intake,[1–5] diet quality,[1, 3–7] physical activity,[1–6] and sedentary behavior,[6] etc.) and their combined effects[1–5] have been associated with all-cause and cause-specific mortality[1, 2, 4, 6, 7] and life expectancy.[3, 5] In addition to diet quality, unrestrained eating behavior, as a potential proxy for diet frequency, timing (typical/inappropriate times with regard to

the circadian system, and related alterations in circadian rhythms or diurnal preference), and caloric intake (with restriction or reckless abandon), has been questioned to play an independent role in these associations.

Although very few studies have explored the association between several related eating habits (eating frequency, snacking) and mortality risk, conflicting findings have been observed.[8, 9] The interpretation of their evidence may have been limited by relatively inadequate sample size and follow-up,[8, 9] incomplete assessment of eating behaviors,[8, 9] incomplete confounding control,[9] and lack of consideration for potential reverse causation.[8, 9] There has been no epidemiological study comprehensively characterizing the effect of unrestrained eating on mortality risk.

With large sample size, long-term follow-up, extensive and validated data on potential confounders,[10–15] and assessments of diverse domains of unrestrained eating exposure, the Nurses' Health Study (NHS) longitudinal cohort[16–19] affords a rich resource to add high-quality epidemiological evidence to this topic. We prospectively investigated unrestrained eating behavior in relation to all-cause and cause-specific mortality within the NHS.

Methods

Study Population

The NHS was established in 1976 and enrolled 121,700 US female registered nurses ages 30 to 55 years, the details of which have been described previously.[16–19] Self-administered biennial questionnaires were sent to participants to update lifestyle and medical information throughout follow-up, with response rates exceeding 90% having been achieved. The baseline was set at 1994 when unrestrained eating behaviors were first assessed. Participants who were alive and free of cancer and cardiovascular disease at baseline, had no missing information on the exposures of interest, and with no implausible energy intakes (<500 or >3500 kcal per day) were eligible for inclusion.

Ascertainment of Exposures

In the 1994 NHS questionnaire, participants answered two questions on whether "I eat anything I want, anytime I want" and "I pay a great deal of attention to changes in my figure" applied to them, with "yes" or "no" as response categories. These questions, using stepwise regression, had previously been identified to be the strongest predictors of the total dietary restraint score in a study that completed a detailed questionnaire measuring three dimensions (dietary restraint, disinhibition, and hunger) of human eating behavior.[20, 21] The second question "I pay a great deal of attention to changes in my figure" is part of the "flexible, but not rigid control' subscale proposed for dietary restraint, which is considered to have greater benefits for counterbalancing dietary disinhibition than other aspects of dietary restraint (attenuate the influence of habitual disinhibition on weight gain and body mass index (BMI)).[22] We examined each question separately and together.

Ascertainment of Deaths

Deaths were confirmed through state vital statistics records, regular searches of the National Death Index, and next-of-kin or postal authority reporting, with an identifying rate of more than 98%.[23, 24] Cohort investigators reviewed death certificates and medical records after permission from next of kin of dead participants, and classified the causes of death according to the International Classification of Diseases, Eighth Revision (ICD-8).

Ascertainment of Covariates

Throughout follow-up, participants biennially reported body weight (which we used to calculate participants' BMI with height), smoking behavior (to calculate pack-years of smoking and time since quit smoking), menopausal status, history of aspirin, multivitamin, and postmenopausal hormone use, history of hypertension, hypercholesterolemia and diabetes, antidepressant medication use (selective serotonin reuptake inhibitors and other antidepressants) and physician-diagnosed depression. Dietary data, physical activity (metabolic equivalent of tasks (MET) scores were assigned to every specific type of physical activity, and total physical activity in MET-hours/week was calculated), and family history of cancer and cardiovascular disease were updated quadrennially. Depressive symptoms were assessed quadrennially using the 5-item Mental Health Index (MHI-5) from the Short-Form 36 Health Status Survey.[25] The Alternative Healthy Eating Index (AHEI) was calculated based on food frequency questionnaire data to measure overall dietary quality.[26] The empirical dietary index for hyperinsulinemia (EDIH) was calculated as a measurement of the potential to stimulate insulin secretion (higher scores indicating hyperinsulinemic diets).[27, 28] Diagnosis of depression was defined based on self-reported physician-diagnosed depression, the MHI-5 [25] (score≤52),[29, 30] and antidepressant medication use. Except for the above-mentioned time-varying variables, height, race, BMI at age 18, history of rotating night shiftwork, socioeconomic status (husband's educational level), and waist circumference were captured once at the initial or subsequent questionnaires before the analytic cohort baseline. Meal frequency and breakfast consumption were assessed in 2002. The validity and reproducibility of information on anthropometrics, lifestyle, diet, and disease outcomes have been reported.[10, 12–14, 26, 31]

Statistical Analysis

Person-years of follow-up accrued from the return date of the 1994 questionnaire until the date of death recorded, loss to follow-up, or follow-up completion (defined as June 30, 2016), whichever occurred earliest.

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) associated with unrestrained eating and all-cause and cause-specific (cancer, cardiovascular disease, and respiratory disease) mortality risk. The proportionality assumption was verified using interactions between the exposures of interest and the (log-)time scale. We controlled for age (continuous, months) and follow-up cycle (each 2-year interval) in age-adjusted models. In multivariable analyses, we additionally adjusted a priori for a wide spectrum of covariates, including race (White, Black, other), cumulative average BMI (<20.0, 20.0–24.9, 25.0–29.9, and ≥30.0 kg/m^2, implementing a 4-year lag-time to account for potential reverse causation), BMI at age 18 (<20.0, 20.0–

24.9, 25.0–29.9, and ≥30.0 kg/m^2), smoking status (never, past smoker ≥10 years since quit smoking, past smoker <10 years since quit smoking, current smoker <25 cigs/day, current smoker ≥25 cigs/day), pack-years of smoking (0, >0 to 5, >5 to 15, and >15 pack-years), alcohol intake (0, 0.1–4.9, 5–14.9, and ≥15 g/day), physical activity (MET-hours/week, continuous), total calories intake (kcal/day, quintiles), EDIH (quintiles), regular use of aspirin (yes, no), multivitamin use (yes, no), menopausal status (premenopausal, postmenopausal), postmenopausal hormone use (no use, past use, current use), history of hypertension (yes, no), history of hypercholesterolemia (yes, no, implementing a 4-year lag-time), history of diabetes (yes, no, implementing a 4-year lag-time), family history of cancer (yes, no), and family history of cardiovascular disease (yes, no).

In sensitivity analyses, 4-, 8-, and 12-year latency analyses were performed to minimize the potential influence of reverse causation on our results, and to examine whether these exposure assessments may reflect a long-term eating behavior status. We further tested various combinations of covariates in multivariable models, e.g., by removing cumulative average BMI or EDIH, replacing EDIH with AHEI (quintiles), or additionally adjusting for history of depression (yes, no), history of rotating night shiftwork (0, 1–14, and ≥15 years), socioeconomic status (husbands' educational level: less than high school, some high school, high school graduate, college, graduate school), waist circumference (continuous, cm), meal frequency (1–2, 3–4, 5 or more times/day), and breakfast consumption (0–2, 3–5, 6–7 times/week), to comprehensively investigate how the specific adjustment for these factors affect the results (listed in table footnotes). To address the possibility of residual confounding, we estimated the predicted probability of reporting unrestrained eating using logistic regression models that included all the covariates (grouped into 3 categories: lifestyle, diet, and disease history), and additionally adjusted for the propensity score. Given the results observed for mortality from respiratory disease and lung cancer, to be prudent, our main analyses for all endpoints were then repeated specifically among participants smoked ≤ 3 lifetime pack-years to further validate the robustness of these findings.

Analyses were conducted using SAS software (version 9.4 for UNIX; SAS Institute Inc., Cary, NC), with 2-sided *P* values <.05 indicating statistical significance for all tests.

Results

Population Characteristics

During up to 22 years of follow-up, we documented 21953 deaths among 63999 eligible participants in analyses of eating anything at any time, 22120 deaths among 65839 eligible participants in analyses of having no concern with their figure change, and 13313 deaths among 40461 eligible participants when examining their combined effect. The sample size differs across these analyses due to the different missingness of exposures. Individuals who "ate anything at any time but cared about their figure change", and those who "did not eat anything at any time but did not care about their figure change" were excluded specifically in analyses of the combined effect of these two unrestrained eating behaviors to have a clear contrast. Variations were observed across exposures for BMI, waist circumference, smoking status, pack-years of smoking, physical activity, overall diet quality, dietary insulinemic potential, total energy intake, meal frequency, breakfast skipping

behavior, menopausal status, use of multivitamin and postmenopausal hormone, history of hypertension, hypercholesterolemia, diabetes, depression, and rotating night shift work, family history of cancer and cardiovascular disease, and husbands' educational level. (Table 1)

Unrestrained Eating Behavior and Mortality Risk (Primary Analyses)

In multivariable-adjusted analyses, women with the behavior of eating anything at any time had an increased mortality from cancer (driven by gastrointestinal tract cancer) and respiratory disease, and decreased mortality from cardiovascular disease, compared to those without this behavior. Women who reported having no concern with figure change experienced higher risk of mortality from all-cause, cancer, and respiratory disease, compared to those not reporting this behavior. The combined effect of both eating anything at any time and having no concern with figure change was associated with a higher all-cause, cancer-specific (driven by cancers of gastrointestinal tract and lung), and respiratory disease-specific mortality, and was inversely associated with cardiovascular disease-specific mortality, compared to those exhibiting the opposite. Compared with age-adjusted analyses, the associations were attenuated after additionally adjusting for multiple covariates. Of note, controlling for EDIH attenuated the effect estimates for most of the aggregated and specific disease endpoints. Variations in the effect of adjustment for BMI were observed across exposures for lung cancer, breast cancer, hematopoietic cancer, and respiratory disease mortality. (Tables 2 and 3)

Unrestrained Eating Behavior and Mortality Risk (Sensitivity Analyses)

The robustness of these results was confirmed in sensitivity analyses. We performed latency analyses by excluding the first 4, 8, and 12 years of follow-up; however, this did not materially attenuate the observed associations for most of the endpoints, except for a suggestion of decreasing risk of respiratory disease mortality with longer lag-time. Replacing the EDIH with AHEI in confounding control, additionally controlling for history of depression, history of rotating night shiftwork, socioeconomic status, waist circumference, meal frequency, and breakfast consumption, and additionally adjusting for propensity score did not materially change our results for all the endpoints, with the only exception observed for lung cancer where slight to moderate attenuations of the effect estimates were observed after adjusting for propensity score. In sensitivity analyses restricted to participants reported ≤ 3 lifetime pack-years of smoking, the effect estimates remained pronounced. (Tables 4 and 5, and Supplementary Tables 1–8)

Discussion

In this large prospective investigation, unrestrained eating behaviors were associated with increased risk of all-cause mortality. When exploring contributors to these relationships, the risk elevation was predominately driven by mortalities from cancer (particularly for cancers of gastrointestinal tract and lung) and respiratory disease, rather than cardiovascular disease. On the contrary, unrestrained eating behaviors were associated with decreased risk of cardiovascular disease-specific mortality.

Comparison with Other Studies

To our knowledge, no previous study has been able to investigate unrestrained eating behavior in relation to all-cause or cause-specific mortality, though very few surrogate eating habits (eating frequency, snacking) have been explored by two investigations, with conflicting findings reported.[8, 9] In the National Health and Nutrition Examination Survey (NHANES) III, an inverse association was found between eating frequency and all-cause (suggestive) and cardiovascular disease mortality.[8] In another smaller study, snacking between meals was not associated with total mortality.[9] The associations of unrestrained eating and a wide range of related surrogate eating habits (e.g., overeating, frequent eating, mistimed/irregular meals, and snacking, etc.) with risk of other major health outcomes have been explored before; with mixed findings reported. Risk of cancer and cardiovascular disease are most frequently investigated in relation to eating behavior. A prior analysis from the NHS reported the behavior of eating anything at any time to be associated with higher gastrointestinal tract cancer risk.[32] A meta-analysis, pooling data from 3 cohort studies and 12 case-control studies, reported a positive association between eating frequency and colorectal cancer risk among case-control studies, but not among cohort studies.[33] Interestingly, controversial findings have been observed when disentangling the effect from snacking frequency with frequency of regular meals.[34–37] The relationships between surrogate eating habits and risk of overall digestive system cancer,[38, 39] several specific gastrointestinal tract cancers,[40, 41] and breast cancer[42–46] have also been explored, though the existing evidence remains relatively sparse. With very few exceptions,[41, 44] most of the studies supported positive associations.[38–43, 45, 46] Several surrogate eating habits have also been linked with cardiometabolic health.[47, 48] In 2017, the American Heart Association (AHA), after critical review of prior evidence, indicated the potential implications of modifying the timing and frequency of eating (including both meals and snacks) for cardiovascular disease prevention in their scientific statement as a crucial step.[48] There has been no evidence regarding the association of unrestrained eating (or surrogate eating habits) with risk or mortality of lung cancer and respiratory disease.

Of note, the prior epidemiological evidence examining surrogate eating habits may have been limited by their study design (relatively small sample size, predominantly case-control studies, imprecise/incomplete assessment of eating behaviors, inadequate confounding control, and lack of consideration for potential reverse causation in data analyses and result interpretation), offering possible explanations of the significant heterogeneity detected in these studies and the discrepancy observed in their findings. Interventional studies have also been limited in their scope, and are too diverse to draw definitive conclusions or make recommendations.[48] Our present study, overcoming most of the above-mentioned limitations, contradicts the prior reports on all-cause mortality, but largely corroborates the previous evidence linking surrogate eating habits with risk of other major health outcomes. Nevertheless, it is not possible to compare our results with most of these studies directly, due to the variations in their exposures (unrestrained eating vs. surrogate eating habits), outcomes (mortality vs. incidence), and study methods. In addition, given the NHS participants have previously been suggested to have healthier lifestyles than the general population,[2] the possibility that there could be differences in the magnitudes of the associations when assessing the general US population cannot be ruled out. Interestingly,

although the second question “I pay a great deal of attention to changes in my figure” is part of the “flexible, but not rigid control’ subscale proposed for dietary restraint, which is considered to have greater benefits for counterbalancing dietary disinhibition than other aspects of dietary restraint,[22] we observed similar effects in analyses across all three exposures.

A higher mortality risk from all-cause, cancers of gastrointestinal tract and lung, and respiratory disease observed among unrestrained eaters is biologically plausible. Disturbed food intake rhythms among unrestrained eaters may cause circadian disruption,[42, 49–51] and affect multiple glucose homeostasis regulation (e.g., insulin sensitivity), energy metabolism, and immune function,[49, 52–54] which have been associated with higher all-cause and cause-specific mortality.[55–60] Moreover, it may operate in conjunction with other altered lifestyle behaviors that are more prevalent among unrestrained eaters (e.g., late-night eating, large meals, fatty or fried foods, alcohol and tobacco use, obesity, etc.), further increase the chance of mucus-lined barrier injury, chronic inflammation, and malignant transformation in the gastrointestinal tract. The mechanisms specifically driving the observed association of unrestrained eating with mortality from respiratory disease and lung cancer remain to be elucidated, with insulin resistance having been suggested by prior investigations,[61–70] including evidence from Mendelian randomization studies.[69, 70] It is noteworthy that in our multivariable analyses, controlling for EDIH (an empirical index developed to specifically assess the insulinemic potential of usual diets, comprising 18 food groups previously identified to be most predictive of fasting plasma C-peptide in stepwise regression),[71] attenuated the effect estimates for most of the aggregated and specific disease endpoints, including mortality from all-cause, gastrointestinal tract cancer, lung cancer, and respiratory disease. On the other hand, replacing EDIH with AHEI-2010 (which has been strongly associated with major chronic disease risk, including diabetes)[72] did not materially change the effect estimates for all the above-mentioned endpoints. Our results support the potential role of prolonged hyperinsulinemia in the putative mechanisms linking unrestrained eating with mortality risk.

The observation of a statistically significant lower risk of cardiovascular disease-specific mortality associated with unrestrained eaters in analyses of the combined effect of both eating anything at any time and having no concern with figure change is unexpected. The AHA statement generally suggests the benefit of daily breakfast consumption in promoting cardiometabolic health, [48] whereas evidence regarding the effect of eating frequency remains inconclusive.[48] In the only large prospective cohort study that quantified the relationship between eating frequency and risk of coronary heart disease, no association was observed after rigorous confounding control.[73] Interestingly, in the NHANES III, eating frequency was inversely associated with cardiovascular disease-specific mortality.[8] In our sensitivity analyses, however, additionally controlling for eating frequency and breakfast skipping did not change the effect estimates for mortality from cardiovascular disease. (Supplementary Tables 3–5) Of note, in all the combined effect analyses, we specifically excluded participants who “ate anything at any time but cared about their figure change” and those who “did not eat anything at any time but did not care about their figure change” to have a clear contrast, and we used those exhibiting dietary restraint as the reference group. Until this finding can be confirmed in other large epidemiologic or interventional

studies and the underlying causes of the association could be identified, it requires cautious interpretation.

Strengths and Limitations of Study

Our study has several major strengths. First, the prospective cohort study design, large sample size, high follow-up rate, large number of deaths documented during long follow-up, in conjunction with a standard review of death and medical records by investigators, offers a high-quality dataset to investigate this topic. Second, repeatedly assessed and extensively validated information on anthropometrics, lifestyle, diet, and medical and family histories allowed for rigorous confounding adjustment.[10–12, 14, 15, 23, 24, 31] In fact, methods developed from the NHS for reducing bias attributable to measurement error and misclassification have been intensively applied to other epidemiological studies, and have been increasingly applied to implementation science, comparative effectiveness research, and the evaluation of public health interventions.[31] Third, the nature of our study participants (all health professionals) further ensured data quality, enhanced internal validity, and reduced socioeconomic confounding. Lastly, we were able to perform comprehensive sensitivity analyses to test the robustness of our findings.

Limitations of this study also deserve comment. First, we were not able to cumulatively update exposure assessment during follow-up. However, given the effect estimates were generally not attenuated in latency analyses, potential concerns about reverse causation and whether these assessments may reflect a long-term eating behavior status have been alleviated. Of note, although a validation study of measurements of unrestrained eating has not been performed, we have similar confidence in the reliability of our exposure assessments given a wide range of diet and lifestyle measurements have previously been demonstrated to be highly valid in the NHS cohort. Further, the fact that exposures were measured once at baseline could have attenuated the effect estimates towards the null. Nevertheless, future investigations with more refined assessments of exposure are warranted. Second, despite the extensive control for all available confounding factors, residual and unmeasured confounding cannot be ruled out. Especially, our exposure of interest may be both a behavior and an attitude (Table 1: unrestrained eaters generally have less health conscious behaviors), and the possibility of bias in dietary reporting by restrained versus unrestrained eaters[74] may have added further complexity. However, we performed the propensity score analyses, and results remained largely robust. Lastly, restricting the study sample to predominantly white female healthcare professionals aged 48–73 years in 1994 when information on unrestrained eating behaviors were first assessed may limit the generalizability of our findings.

Conclusion

This large prospective investigation supports the associations between unrestrained eating and increased risk of all-cause, cancer-specific (particularly for gastrointestinal tract cancer and lung cancer), and respiratory disease-specific mortality. These findings highlight the importance of unrestrained eating behavior modification, independent of major lifestyle, diet, anthropometric, and demographic predictors of mortality, in preventing death. The

inverse association observed between unrestrained eating and cardiovascular disease-specific mortality should be interpreted with caution, and warrants further exploration and validation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest

BMW declares research funding from Celgene and Eli Lilly and Company and consulting for BioLineRx, Celgene, G1 Therapeutics, and GRAIL, outside the submitted work. ATC declares research funding from Bayer and consulting for Bayer, Pfizer Inc. and Boehringer Ingelheim, outside the submitted work. JAM declares institutional research funding from Boston Biomedical and consulting for Ignyta, Taiho Pharmaceutical, and Cota, outside the submitted work. CSF declares consulting for Agios, Bain Capital, Bayer, Celgene, Dicerna Pharmaceuticals, Eli Lilly and Company, Entrinsic Health Solutions, Five Prime Therapeutics, Genentech, Gilead Sciences, KEW, Merck & Co., Merrimack Pharmaceuticals, Pfizer, Sanofi, Taiho Pharmaceutical, and Unum Therapeutics, outside the submitted work. He also serves as a Director for CytomX Therapeutics and owns unexercised stock options for CytomX Therapeutics and Entrinsic Health Solutions, outside the submitted work. KN declares institutional research funding from Revolution Medicines, Celgene, Genentech, Gilead Sciences, Pharmavite, Tarrex Biopharma, and Trovagene, and consulting/advisory board fees from Array Biopharma, Bayer, Eli Lilly, Genentech, Seattle Genetics, and Tarrex Biopharma, outside the submitted work. Other authors declare no potential conflicts of interest.

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Table 1.

Characteristics [a] of the study population in the NHS (1994) across self-reported unrestrained eating [b,c]

Characteristic	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No n=49333	Yes n=14666	No n=42423	Yes n=23416	No [i] n=32890	yes n=7571
Age, years, mean (SD)	60.3 (7.1)	59.9 (7.2)	60.2 (7.1)	60.1 (7.2)	60.3 (7.1)	59.7 (7.3)
Race						
White	97.7	97.0	97.4	98.0	97.4	97.2
Black	1.4	1.4	1.6	0.9	1.6	1.1
Other	0.9	1.6	1.0	1.1	1.0	1.6
BMI, kg/m^2, mean (SD) [d,e]	26.3 (4.9)	27.1 (6.1)	25.3 (4.3)	28 (5.9)	25.3 (4.2)	27.9 (6.3)
BMI at age 18, kg/m^2, mean (SD) [d]	21.3 (2.9)	21.2 (3)	21.1 (2.8)	21.6 (3.1)	21.2 (2.8)	21.4 (3.1)
Waist circumference, cm, mean (SD)	86.8 (11.7)	88.4 (13.1)	85.2 (11.2)	89.9 (12.7)	85.3 (11.1)	89.9 (13.4)
Smoking status						
Never smoked	45.4	40.8	44.6	44.3	45.1	40.7
Past smoker	43.6	36.9	44.1	40.1	44.5	36.7
Current smoker<25 cigs/day	9.2	17.5	9.6	12.4	8.8	17.4
Current smoker≥25 cigs/day	1.8	4.7	1.7	3.3	1.5	5.2
Pack-years of smoking, mean (SD) [f]	22.6 (19.8)	29.5 (23.1)	22.2 (19.5)	26.4 (22.0)	21.7 (19.2)	30.1 (23.5)
Alcohol intake, g/day, mean (SD)	5.0 (8.9)	5.2 (10.2)	5.2 (8.8)	4.8 (9.5)	5.2 (8.8)	5.2 (10.5)
Physical activity, MET-hours/week, mean (SD) [g]	21.2 (24.6)	17.7 (23.5)	23 (26.2)	17 (21.6)	23.1 (25.9)	16.4 (22.2)
AHEI, mean (SD)	49.4 (9.7)	45.1 (9.7)	49.9 (9.7)	46.7 (9.7)	50.2 (9.6)	44.3 (9.5)
EDIH, ≥ median	50.3	64.9	47.0	62.2	46.1	68.3
Total calories intake, kcal/day, mean (SD)	1711.0 (501.6)	1824.8 (557)	1699.1 (504.6)	1783.9 (526.4)	1691.5 (498.5)	1849.1 (559.5)
Regular use of aspirin, >2 tablets/week	28.1	27.2	27.8	28.1	27.8	27.4
Multivitamin use	48.3	41.9	49.5	43.5	49.9	40.6
Postmenopausal	89.2	88.3	89.4	88.2	89.5	88.0
Current postmenopausal hormone use	40.5	34.5	42.7	34.9	42.8	32.8
History of hypertension	23.7	21.5	21.2	26.0	21.9	23.3

Characteristic	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No n=49333	Yes n=14666	No n=42423	Yes n=23416	No [i] n=32890	yes n=7571
History of hypercholesterolemia [e]	29.8	23.4	28.7	28.1	29.5	23.8
History of diabetes [e]	2.8	1.6	1.9	3.4	2.0	1.9
Family history of cancer	25.3	24.9	25.2	24.8	25.4	24.7
Family history of cardiovascular disease	7.7	7.5	7.5	7.7	7.6	7.7
History of depression	6.0	7.4	6.0	6.6	5.9	7.4
History of rotating night shiftwork	51.7	52.6	51.4	52.6	51.6	53.8
Husbands' educational level						
Less than high school	1.4	2.1	1.3	1.8	1.3	2.3
Some high school	3.0	3.7	2.9	3.6	2.8	4.2
High school graduate	31.0	32.8	30.4	32.4	30.6	33.9
College	24.0	21.6	23.9	23.1	24.2	21.4
Graduate school	20.4	17.1	20.5	18.8	20.6	16.3
Meal frequency [h]						
1–2 times/day	3.7	5.8	4.2	4.0	4.0	5.5
3–4 times/day	65.8	62.0	65.5	64.4	65.9	62.2
5 or more times/day	30.5	32.2	30.3	31.7	30.1	32.3
Breakfast consumption [h]						
0–2 times/week	7.4	12.9	8.0	9.0	7.6	13.0
3–5 times/week	9.4	13.1	9.7	10.9	9.3	13.5
6–7 times/week	83.2	74.0	82.3	80.2	83.1	73.6

Abbreviations: NHS, Nurses' Health Study; SD, standard deviation; BMI, body mass index; kg, kilogram; m, meter; cigs, cigarettes; g, gram; MET, metabolic equivalent task; AHEI, alternate healthy eating index; EDIH, empirical dietary index for hyperinsulinemia; NSAIDs, nonsteroidal anti-inflammatory drugs; kcal, kilocalorie, ug, microgram; mg, milligram; IU, international unit.

[a] Data are expressed as percentages unless otherwise indicated.

[b] Percentages are of non-missing values.

[c] Percentages may not sum to 100% after rounding.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Implementing a 4-year lag-time.

[f] Cumulative among smokers.

[g] Weekly energy expenditure in MET-hours/week from recreational and leisure time physical activity.

[h] Assessed in 2002.

[i] Defined as those exhibiting dietary restraint, i.e. those who reported both “not having the behavior of eating anything at any time” and “paying a great deal of attention to changes in their figure”.

Table 2.

Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause and cause-specific mortality according to self-reported unrestrained eating

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
All-cause mortality						
Cases	16440	5513	13395	8725	10394	2919
Age-adjusted [a]	1 [Reference]	1.26 (1.23–1.30)	1	1.29 (1.26–1.33)	1	1.46 (1.40–1.52)
Multivariable (without BMI) [b]	1	1.04 (1.01–1.07)	1	1.08 (1.05–1.11)	1	1.11 (1.06–1.16)
Multivariable (without EDIH) [b]	1	1.05 (1.02–1.08)	1	1.09 (1.06–1.12)	1	1.12 (1.07–1.17)
Multivariable [b]	1	1.02 (0.99–1.06)	1	1.08 (1.05–1.11)	1	1.09 (1.04–1.14)
Cancer mortality						
Cases	4336	1581	3601	2353	2792	873
Age-adjusted [a]	1	1.33 (1.25–1.41)	1	1.25 (1.18–1.31)	1	1.53 (1.42–1.65)
Multivariable (without BMI) [b]	1	1.08 (1.01–1.14)	1	1.09 (1.03–1.15)	1	1.19 (1.10–1.29)
Multivariable (without EDIH) [b]	1	1.09 (1.02–1.16)	1	1.10 (1.04–1.16)	1	1.21 (1.11–1.31)
Multivariable [b]	1	1.07 (1.01–1.14)	1	1.08 (1.03–1.14)	1	1.19 (1.10–1.29)
Cardiovascular disease mortality						
Cases	3493	1034	2756	1798	2158	518
Age-adjusted [a]	1	1.12 (1.04–1.20)	1	1.30 (1.23–1.38)	1	1.26 (1.14–1.39)
Multivariable (without BMI) [b]	1	0.94 (0.88–1.01)	1	1.05 (0.99–1.12)	1	0.94 (0.85–1.04)
Multivariable (without EDIH) [b]	1	0.94 (0.88–1.01)	1	1.03 (0.96–1.09)	1	0.90 (0.82–1.00)
Multivariable [b]	1	0.93 (0.86–1.00)	1	1.02 (0.95–1.08)	1	0.89 (0.80–0.98)
Respiratory disease mortality						
Cases	1322	632	1093	823	832	342
Age-adjusted [a]	1	1.79 (1.62–1.97)	1	1.48 (1.35–1.62)	1	2.13 (1.87–2.42)
Multivariable (without BMI) [b]	1	1.24 (1.12–1.37)	1	1.14 (1.04–1.25)	1	1.33 (1.16–1.52)

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
Multivariable (without EDIH) [b]	1	1.23 (1.11–1.36)	1	1.22 (1.11–1.35)	1	1.40 (1.22–1.61)
Multivariable [b]	1	1.17 (1.06–1.29)	1	1.18 (1.07–1.30)	1	1.31 (1.14–1.51)

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; EDIH, the empirical dietary index for hyperinsulinemia.

[a]Models were controlled for age and follow-up cycle.

[b]Models were controlled for age, follow-up cycle, race, cumulative average BMI (with 4-year lag time), BMI at age 18, smoking status, time since quit smoking, pack-years of smoking, alcohol intake, physical activity, total calories intake, EDIH, regular use of aspirin, multivitamin use, menopausal status, postmenopausal hormone use, history of hypertension, history of hypercholesterolemia (with 4-year lag time), history of diabetes (with 4-year lag time), family history of cancer, and family history of cardiovascular disease.

[c]Defined as those exhibiting dietary restraint, i.e. those who reported both “not having the behavior of eating anything at any time” and “paying a great deal of attention to changes in their figure”.

Table 3.

Hazard ratios (HR) and 95% confidence intervals (CI) of cancer-specific mortality according to self-reported unrestrained eating

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
Gastrointestinal tract cancer mortality						
Cases	507	216	439	280	339	116
Age-adjusted [a]	1 [Reference]	1.54 (1.32–1.81)	1	1.21 (1.04–1.41)	1	1.64 (1.33–2.03)
Multivariable (without BMI) [b]	1	1.31 (1.11–1.54)	1	1.05 (0.90–1.23)	1	1.35 (1.08–1.69)
Multivariable (without EDIH) [b]	1	1.34 (1.14–1.58)	1	1.08 (0.93–1.27)	1	1.39 (1.11–1.74)
Multivariable [b]	1	1.31 (1.11–1.55)	1	1.06 (0.91–1.25)	1	1.36 (1.08–1.71)
Colorectal cancer mortality						
Cases	356	138	301	194	240	79
Age-adjusted [a]	1	1.41 (1.16–1.72)	1	1.23 (1.02–1.47)	1	1.59 (1.23–2.06)
Multivariable (without BMI) [b]	1	1.22 (1.00–1.50)	1	1.10 (0.91–1.33)	1	1.40 (1.07–1.84)
Multivariable (without EDIH) [b]	1	1.25 (1.02–1.53)	1	1.14 (0.94–1.38)	1	1.39 (1.06–1.82)
Multivariable [b]	1	1.23 (1.00–1.51)	1	1.13 (0.93–1.36)	1	1.41 (1.07–1.86)
Digestive organ cancer mortality						
Cases	528	151	402	271	327	82
Age-adjusted [a]	1	1.04 (0.87–1.25)	1	1.28 (1.10–1.50)	1	1.23 (0.96–1.57)
Multivariable (without BMI) [b]	1	0.92 (0.76–1.11)	1	1.12 (0.95–1.31)	1	0.99 (0.77–1.29)
Multivariable (without EDIH) [b]	1	0.93 (0.77–1.12)	1	1.09 (0.93–1.28)	1	0.97 (0.75–1.26)
Multivariable [b]	1	0.92 (0.76–1.11)	1	1.08 (0.92–1.27)	1	0.96 (0.74–1.24)
Pancreatic cancer mortality						
Cases	371	107	287	188	231	55
Age-adjusted [a]	1	1.06 (0.86–1.32)	1	1.26 (1.05–1.52)	1	1.18 (0.88–1.59)
Multivariable (without BMI) [b]	1	0.92 (0.74–1.16)	1	1.10 (0.91–1.34)	1	0.96 (0.70–1.31)

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
Multivariable (without EDIH) [b]	1	0.93 (0.75–1.16)	1	1.08 (0.89–1.32)	1	0.95 (0.69–1.29)
Multivariable [b]	1	0.92 (0.74–1.15)	1	1.08 (0.88–1.31)	1	0.93 (0.68–1.28)
Lung cancer mortality						
Cases	1006	466	844	613	643	259
Age-adjusted [a]	1	1.70 (1.52–1.89)	1	1.38 (1.25–1.54)	1	1.99 (1.72–2.30)
Multivariable (without BMI) [b]	1	1.13 (1.00–1.27)	1	1.13 (1.02–1.26)	1	1.28 (1.09–1.49)
Multivariable (without EDIH) [b]	1	1.13 (1.01–1.28)	1	1.21 (1.09–1.35)	1	1.35 (1.15–1.58)
Multivariable [b]	1	1.12 (1.00–1.26)	1	1.20 (1.08–1.34)	1	1.33 (1.14–1.56)
Breast cancer mortality						
Cases	525	173	424	286	324	91
Age-adjusted [a]	1	1.18 (0.99–1.40)	1	1.28 (1.10–1.48)	1	1.33 (1.06–1.69)
Multivariable (without BMI) [b]	1	1.02 (0.85–1.21)	1	1.12 (0.96–1.31)	1	1.10 (0.86–1.40)
Multivariable (without EDIH) [b]	1	1.02 (0.86–1.22)	1	1.11 (0.95–1.30)	1	1.09 (0.85–1.40)
Multivariable [b]	1	1.02 (0.85–1.22)	1	1.10 (0.94–1.29)	1	1.10 (0.86–1.42)
Ovarian cancer mortality						
Cases	305	114	272	156	206	60
Age-adjusted [a]	1	1.33 (1.07–1.65)	1	1.09 (0.90–1.33)	1	1.40 (1.05–1.87)
Multivariable (without BMI) [b]	1	1.16 (0.93–1.45)	1	0.99 (0.81–1.22)	1	1.26 (0.93–1.72)
Multivariable (without EDIH) [b]	1	1.19 (0.95–1.49)	1	1.01 (0.82–1.24)	1	1.29 (0.94–1.75)
Multivariable [b]	1	1.13 (0.90–1.42)	1	0.99 (0.80–1.21)	1	1.25 (0.91–1.70)
Hematopoietic cancer mortality						
Cases	555	173	460	276	366	100
Age-adjusted [a]	1	1.13 (0.95–1.34)	1	1.15 (0.99–1.34)	1	1.34 (1.07–1.68)
Multivariable (without BMI) [b]	1	1.03 (0.86–1.23)	1	1.05 (0.90–1.22)	1	1.16 (0.91–1.46)

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
Multivariable (without EDIH) [b]	1	1.04 (0.87–1.24)	1	1.04 (0.89–1.22)	1	1.16 (0.92–1.48)
Multivariable [b]	1	1.04 (0.87–1.24)	1	1.03 (0.88–1.21)	1	1.17 (0.92–1.48)

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; EDIH, the empirical dietary index for hyperinsulinemia.

[a]Models were controlled for age and follow-up cycle.

[b]Models were controlled for the same sets of covariates as denoted in Table 2.

[c]Defined as those exhibiting dietary restraint, i.e. those who reported both “not having the behavior of eating anything at any time” and “paying a great deal of attention to changes in their figure”.

Table 4.

Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause and cause-specific mortality according to self-reported unrestrained eating (sensitivity analyses: assuming 4-, 8- and 12-year latency)

NHS	Eating anything at any time			No concern with figure change			Eating anything at any time + no concern with figure change		
	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)
	Yes vs. No			Yes vs. No			Yes vs. No [c]		
All-cause mortality									
Cases	20735	18512	15184	20914	18706	15368	12596	11299	9325
Age-adjusted [a]	1.25 (1.21–1.29)	1.22 (1.18–1.27)	1.20 (1.15–1.24)	1.28 (1.25–1.32)	1.27 (1.24–1.31)	1.26 (1.22–1.30)	1.44 (1.38–1.50)	1.41 (1.34–1.47)	1.37 (1.30–1.44)
Multivariable (without BMI) [b]	1.03 (1.00–1.07)	1.02 (0.98–1.06)	1.01 (0.98–1.05)	1.08 (1.04–1.11)	1.08 (1.04–1.11)	1.07 (1.04–1.11)	1.09 (1.04–1.14)	1.09 (1.04–1.14)	1.08 (1.02–1.14)
Multivariable (without EDIH) [b]	1.04 (1.01–1.07)	1.02 (0.99–1.06)	1.02 (0.98–1.06)	1.09 (1.06–1.12)	1.08 (1.05–1.12)	1.08 (1.04–1.12)	1.11 (1.06–1.16)	1.10 (1.04–1.15)	1.09 (1.03–1.15)
Multivariable [b]	1.02 (0.98–1.05)	1.00 (0.97–1.04)	1.00 (0.96–1.04)	1.07 (1.04–1.10)	1.07 (1.04–1.10)	1.07 (1.03–1.11)	1.08 (1.03–1.13)	1.07 (1.02–1.12)	1.06 (1.01–1.12)
Cancer mortality									
Cases	5346	4356	3057	5393	4397	3087	3318	2723	1936
Age-adjusted [a]	1.31 (1.23–1.39)	1.30 (1.21–1.39)	1.31 (1.20–1.42)	1.23 (1.17–1.30)	1.23 (1.16–1.31)	1.18 (1.10–1.27)	1.50 (1.39–1.63)	1.52 (1.39–1.67)	1.48 (1.33–1.65)
Multivariable (without BMI) [b]	1.07 (1.00–1.14)	1.07 (0.99–1.14)	1.09 (1.00–1.18)	1.08 (1.02–1.14)	1.10 (1.03–1.17)	1.06 (0.98–1.14)	1.18 (1.08–1.28)	1.22 (1.11–1.34)	1.21 (1.08–1.35)
Multivariable (without EDIH) [b]	1.08 (1.01–1.15)	1.07 (1.00–1.15)	1.10 (1.01–1.20)	N.09 (1.03–1.15)	1.10 (1.03–1.17)	1.06 (0.98–1.14)	1.19 (1.09–1.29)	1.22 (1.11–1.34)	1.22 (1.08–1.36)
Multivariable [b]	1.06 (1.00–1.13)	1.07 (0.99–1.14)	1.09 (1.00–1.19)	1.08 (1.02–1.14)	1.09 (1.02–1.16)	1.05 (0.97–1.14)	1.17 (1.08–1.28)	1.22 (1.10–1.34)	1.21 (1.08–1.36)
Cardiovascular disease mortality									
Cases	4253	3748	3065	4278	3778	3081	2526	2242	1848
Age-adjusted [a]	1.11 (1.04–1.20)	1.09 (1.01–1.18)	1.09 (1.00–1.19)	1.30 (1.22–1.38)	1.28 (1.20–1.37)	1.27 (1.18–1.37)	1.26 (1.14–1.39)	1.23 (1.10–1.37)	1.23 (1.09–1.38)

NHS	Eating anything at any time			No concern with figure change			Eating anything at any time + no concern with figure change		
	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)
		Yes vs. No			Yes vs. No			Yes vs. No [c]	
Multivariable (without BMI) [b]	0.95 (0.88–1.02)	0.93 (0.86–1.01)	0.95 (0.87–1.04)	1.06 (1.00–1.13)	1.06 (0.99–1.14)	1.07 (0.99–1.15)	0.95 (0.86–1.05)	0.95 (0.85–1.06)	0.97 (0.85–1.09)
Multivariable (without EDIH) [b]	0.95 (0.88–1.02)	0.93 (0.86–1.01)	0.95 (0.87–1.04)	1.03 (0.97–1.10)	1.03 (0.96–1.10)	1.04 (0.96–1.12)	0.91 (0.82–1.02)	0.91 (0.81–1.01)	0.94 (0.83–1.06)
Multivariable [b]	0.93 (0.86–1.00)	0.92 (0.85–0.99)	0.94 (0.86–1.03)	1.02 (0.96–1.09)	1.02 (0.95–1.09)	1.03 (0.95–1.11)	0.89 (0.80–0.99)	0.89 (0.79–1.00)	0.92 (0.81–1.04)
Respiratory disease mortality									
Cases	1832	1621	1310	1802	1607	1310	1107	987	800
Age-adjusted [a]	1.74 (1.57–1.92)	1.64 (1.47–1.82)	1.52 (1.34–1.71)	1.45 (1.32–1.60)	1.39 (1.26–1.54)	1.35 (1.20–1.50)	2.05 (1.80–2.35)	1.91 (1.66–2.21)	1.75 (1.49–2.06)
Multivariable (without BMI) [b]	1.21 (1.09–1.34)	1.16 (1.04–1.30)	1.11 (0.97–1.26)	1.13 (1.03–1.25)	1.10 (0.99–1.22)	1.08 (0.96–1.21)	1.30 (1.13–1.49)	1.23 (1.05–1.43)	1.16 (0.98–1.38)
Multivariable (without EDIH) [b]	1.20 (1.08–1.33)	1.15 (1.03–1.29)	1.10 (0.97–1.25)	1.20 (1.09–1.33)	1.16 (1.04–1.29)	1.13 (1.01–1.27)	1.36 (1.17–1.57)	1.27 (1.08–1.48)	1.20 (1.01–1.43)
Multivariable [b]	1.14 (1.03–1.27)	1.10 (0.98–1.23)	1.06 (0.93–1.20)	1.17 (1.06–1.29)	1.13 (1.01–1.25)	1.11 (0.98–1.24)	1.28 (1.11–1.48)	1.20 (1.03–1.41)	1.15 (0.97–1.38)
Gastrointestinal tract cancer mortality									
Cases	656	535	355	657	526	353	411	334	227
Age-adjusted [a]	1.49 (1.26–1.76)	1.55 (1.29–1.87)	1.56 (1.24–1.97)	1.20 (1.03–1.41)	1.23 (1.03–1.47)	1.27 (1.02–1.57)	1.59 (1.27–1.99)	1.67 (1.30–2.14)	1.77 (1.32–2.39)
Multivariable (without BMI) [b]	1.27 (1.07–1.52)	1.34 (1.11–1.63)	1.41 (1.11–1.78)	1.05 (0.89–1.23)	1.07 (0.89–1.28)	1.11 (0.89–1.39)	1.31 (1.03–1.66)	1.37 (1.05–1.78)	1.50 (1.09–2.05)
Multivariable (without EDIH) [b]	1.30 (1.09–1.55)	1.39 (1.14–1.68)	1.44 (1.14–1.83)	1.08 (0.91–1.27)	1.10 (0.91–1.32)	1.16 (0.92–1.45)	1.32 (1.04–1.68)	1.41 (1.09–1.84)	1.54 (1.12–2.11)
Multivariable [b]	1.27 (1.07–1.52)	1.35 (1.12–1.64)	1.43 (1.13–1.81)	1.06 (0.89–1.25)	1.08 (0.90–1.30)	1.14 (0.91–1.43)	1.30 (1.02–1.66)	1.38 (1.06–1.81)	1.53 (1.11–2.11)
Colorectal cancer mortality									
Cases	447	367	243	452	360	241	285	233	157

NHS	Eating anything at any time			No concern with figure change			Eating anything at any time + no concern with figure change		
	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)	4-year latency (1998–2016)	8-year latency (2002–2016)	12-year latency (2006–2016)
		Yes vs. No			Yes vs. No			Yes vs. No [c]	
Age-adjusted [a]	1.32 (1.07–1.63)	1.41 (1.12–1.77)	1.35 (1.02–1.80)	1.22 (1.01–1.48)	1.25 (1.01–1.54)	1.28 (0.99–1.66)	1.49 (1.13–1.97)	1.56 (1.15–2.11)	1.60 (1.10–2.31)
Multivariable (without BMI) [b]	1.14 (0.92–1.42)	1.23 (0.97–1.56)	1.21 (0.91–1.63)	1.08 (0.89–1.32)	1.10 (0.89–1.38)	1.14 (0.87–1.49)	1.30 (0.97–1.74)	1.36 (0.99–1.87)	1.40 (0.95–2.07)
Multivariable (without EDIH) [b]	1.16 (0.93–1.44)	1.26 (1.00–1.60)	1.25 (0.94–1.68)	1.11 (0.91–1.36)	1.16 (0.92–1.44)	1.20 (0.92–1.58)	1.26 (0.94–1.69)	1.39 (1.00–1.91)	1.43 (0.96–2.12)
Multivariable [b]	1.14 (0.92–1.42)	1.24 (0.98–1.58)	1.24 (0.92–1.66)	1.10 (0.90–1.35)	1.14 (0.91–1.43)	1.19 (0.91–1.57)	1.28 (0.95–1.72)	1.40 (1.01–1.94)	1.45 (0.97–2.15)
Lung cancer mortality									
Cases	1298	1063	736	1285	1047	737	805	667	470
Age-adjusted [a]	1.67 (1.49–1.88)	1.71 (1.51–1.95)	1.72 (1.47–2.01)	1.34 (1.20–1.50)	1.41 (1.25–1.60)	1.32 (1.14–1.53)	1.92 (1.65–2.25)	2.08 (1.75–2.46)	2.02 (1.65–2.47)
Multivariable (without BMI) [b]	1.12 (0.99–1.27)	1.14 (0.99–1.30)	1.16 (0.99–1.37)	1.11 (0.99–1.25)	1.19 (1.05–1.35)	1.13 (0.97–1.32)	1.25 (1.06–1.48)	1.36 (1.13–1.63)	1.36 (1.09–1.70)
Multivariable (without EDIH) [b]	1.12 (0.99–1.27)	1.14 (0.99–1.31)	1.18 (1.00–1.40)	1.18 (1.05–1.33)	1.26 (1.10–1.43)	1.20 (1.02–1.40)	1.31 (1.11–1.55)	1.41 (1.18–1.70)	1.44 (1.16–1.80)
Multivariable [b]	1.11 (0.98–1.26)	1.14 (0.99–1.30)	1.17 (0.99–1.38)	1.18 (1.04–1.32)	1.25 (1.10–1.43)	1.19 (1.02–1.39)	1.30 (1.10–1.55)	1.41 (1.17–1.70)	1.42 (1.14–1.78)

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; EDIH, the empirical dietary index for hyperinsulinemia.

[a] Models were controlled for age and follow-up cycle.

[b] Models were controlled for the same sets of covariates as denoted in Table 2.

[c] Defined as those exhibiting dietary restraint, i.e. those who reported both “not having the behavior of eating anything at any time” and “paying a great deal of attention to changes in their figure”.

Table 5.

Hazard ratios (HR) and 95% confidence intervals (CI) of all-cause and cause-specific mortality according to self-reported unrestrained eating (sensitivity analyses: further adjusted for propensity score)

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
All-cause mortality						
Cases	16440	5513	13395	8725	10394	2919
Multivariable 1 [a]	1 [Reference]	1.02 (0.99–1.06)	1	1.08 (1.05–1.11)	1	1.09 (1.04–1.14)
Multivariable 2 [b]	1	1.02 (0.99–1.05)	1	1.08 (1.05–1.11)	1	1.09 (1.04–1.14)
Cancer mortality						
Cases	4336	1581	3601	2353	2792	873
Multivariable 1 [a]	1	1.07 (1.01–1.14)	1	1.08 (1.03–1.15)	1	1.19 (1.10–1.29)
Multivariable 2 [b]	1	1.07 (1.00–1.13)	1	1.08 (1.02–1.14)	1	1.18 (1.09–1.28)
Cardiovascular disease mortality						
Cases	3493	1034	2756	1798	2158	518
Multivariable 1 [a]	1	0.93 (0.86–1.00)	1	1.02 (0.96–1.08)	1	0.89 (0.80–0.98)
Multivariable 2 [b]	1	0.92 (0.86–0.99)	1	1.02 (0.96–1.08)	1	0.88 (0.80–0.98)
Respiratory disease mortality						
Cases	1322	632	1093	823	832	342
Multivariable 1 [a]	1	1.17 (1.06–1.30)	1	1.19 (1.08–1.31)	1	1.32 (1.15–1.52)
Multivariable 2 [b]	1	1.16 (1.05–1.29)	1	1.18 (1.08–1.30)	1	1.30 (1.13–1.50)
Gastrointestinal tract cancer mortality						
Cases	507	216	439	280	339	116
Multivariable 1 [a]	1	1.31 (1.11–1.55)	1	1.06 (0.91–1.25)	1	1.36 (1.08–1.70)
Multivariable 2 [b]	1	1.30 (1.10–1.54)	1	1.06 (0.91–1.24)	1	1.36 (1.08–1.71)
Colorectal cancer mortality						
Cases	356	138	301	194	240	79

NHS	Eating anything at any time		No concern with figure change		Eating anything at any time + no concern with figure change	
	No	Yes	No	Yes	No [c]	Yes
Multivariable 1 [a]	1	1.23 (1.00–1.51)	1	1.12 (0.93–1.36)	1	1.40 (1.07–1.85)
Multivariable 2 [b]	1	1.23 (1.00–1.51)	1	1.12 (0.93–1.36)	1	1.41 (1.07–1.86)
Lung cancer mortality						
Cases	1006	466	844	613	643	259
Multivariable 1 [a]	1	1.12 (1.00–1.26)	1	1.20 (1.08–1.34)	1	1.34 (1.14–1.57)
Multivariable 2 [b]	1	1.02 (0.99–1.05)	1	1.08 (1.05–1.11)	1	1.09 (1.04–1.14)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Models were controlled for the same sets of covariates as denoted in Table 2.

[b]Models were controlled for the same sets of covariates as denoted in Table 2, and were further adjusted for propensity score.

[c]Defined as those exhibiting dietary restraint, i.e. those who reported both “not having the behavior of eating anything at any time” and “paying a great deal of attention to changes in their figure”.