Long-term diet and risk of SARS -CoV-2 infection and Coronavirus Disease 2019 (COVID-19) severity

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Abbreviations

AHEI, Alternate Healthy Eating Index; AMED, alternative Mediterranean Diet; BMI, body mass index; COVID-19, Coronavirus Disease 2019; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, empirical dietary inflammatory pattern; HPFS, Health Professionals Follow-up Study; IPW, inverse probability weighting; MET, metabolic equivalent of tasks; NHS, Nurses' Health Study; PPE, personal protective equipment; Q, quartile

ABSTRACT

Background

The role of diet on COVID-19 is emerging.

Methods

We included 42,935 participants aged 55 to 99 years in two ongoing cohort studies, Nurses' Health Study II and Health Professionals Follow-up Study, who completed a series of COVID-19 surveys in 2020 and 2021. Using data from food frequency questionnaires prior to COVID-19, we assessed diet quality using the Alternative Healthy Eating Index (AHEI)-2010, the alternative Mediterranean Diet (AMED) score, an Empirical Dietary Index for Hyperinsulinemia (EDIH), and an Empirical Dietary Inflammatory Pattern (EDIP). We calculated multivariable adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for SARS-CoV-2 infection and severity of COVID-19 after controlling for demographic, medical, and lifestyle factors.

Results

Among 19,754 participants tested for SARS-CoV-2, 1,941 participants reported a positive result. Of these, 1,327 reported symptoms needing assistance and another 109 were hospitalized. Healthier diet, represented by higher AHEI-2010 and AMED scores and lower EDIH and EDIP scores, were associated with lower likelihood of SARS-CoV-2 infection (ORs Q (quartile) 4 vs. Q1 (95%CI) were 0.80 (0.69, 0.92) for AHEI-2010; 0.78 (0.67, 0.92) for AMED; 1.36 (1.16, 1.57) for EDIH; and 1.13 (0.99, 1.30) for EDIP; all p for trend $\leqslant 0.01$). In the analysis of COVID-19 severity, participants with healthier diet had lower likelihood of severe infection and were less likely to be hospitalized due to COVID-19. However, associations were no longer significant after controlling for BMI and pre-existing medical conditions.

Conclusion

Diet may be an important modifiable risk factor for SARS-CoV-2 infection, as well as for severity of COVID-19. This association is partially mediated by BMI and pre-existing medical conditions.

Keywords

Dietary quality, SARS-CoV-2 infection, COVID-19 severity, prospective cohort study

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the disease caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has become a major global public health crisis causing nearly five million deaths globally (1). Research has moved rapidly in defining the biological features of the virus, developing vaccines, and finding therapeutic agents to treat SARS-CoV-2 infection (2). In the meantime, several factors have been identified that increase risk of SARS-CoV-2 infection and its severity, including older age and presence of pre-existing medical conditions such as diabetes, high blood pressure, obesity, and cardiovascular disease (3). Despite this, the role of modifiable factors such as diet in susceptibility to SARS-CoV-2 infection and severity are not well understood. Further, whether diet can modify the higher risk of COVID-19 that is associated with the presence of co-morbidities remains unknown.

An important defense against SARS-CoV-2 infection is a well-coordinated immune response from the host (4, 5). Diet may play a crucial role in supporting the immune system's response to SARS-CoV-2 infections, and could consequently modulate the severity of infection (6). For example, higher adherence to a Mediterranean style dietary pattern was associated with a lower risk of respiratory infections (7, 8), and was recently found to be inversely associated with COVID-19 related deaths in an ecological study of 23 countries (9). Also, a healthy diet is associated with a lower risk of several chronic diseases that are strong risk factors for SARS-CoV-2 infection (10, 11).

We therefore investigated the association between usual diet prior to the onset of the pandemic and risk and severity of subsequent SARS-CoV-2 infection using data from two large cohorts, the Nurses' Health Study (NHS) II and Health Professionals Follow-up Study (HPFS). To better capture the complexity and interaction of multiple dietary factors, we evaluated two widely used a priori diet quality indices (12)—the Alternative Healthy Eating Index (AHEI)-2010, emphasizing overall diet quality (13), and alternative Mediterranean Diet (AMED) score, assessing adherence to a Mediterranean Diet style dietary pattern (14); and two empirical hypothesis-oriented indices assessing the insulinemic (Empirical Dietary Index for Hyperinsulinemia, EDIH) and inflammatory (Empirical Dietary Inflammatory Pattern EDIP) potential of diet (15, 16). We are especially interested in the two empirical hypothesis-oriented indices—EDIH and EDIP—because hyperinsulinemia and a proinflammatory status were shown to contribute to disease severity and mortality in COVID-19 (17, 18).

METHODS

Study population

The NHS II is a prospective cohort study of 116, 429 female nurses, aged 25-42 years that began in 1989 (19). The HPFS began in 1986 and includes 51,529 men in health professions who were 40-75 years old at cohort baseline (20). In both cohorts, participants completed questionnaires at baseline and every two years thereafter on demographic, lifestyle factor, and health-related information.

In 2020, we invited participants who had returned the most recent primary cohort questionnaires—2019 in NHS II (n=55, 295) and 2020 in HPFS (n=8,900) —to complete a supplementary COVID-19 online series of surveys regarding their experiences during the COVID-19 pandemic (21) (**Supplementary Figure 1**). The COVID-19 survey collected information on lifestyle factors, current occupational status, demographic factors, personal protective equipment (PPE) use, whether participants were tested for SARS-CoV-2 infection and the corresponding results if applicable, presence of COVID-19 symptoms, hospitalization for

COVID-19, treatment during hospitalization if applicable, interaction with presumed or documented COVID-19 cases, and concern about COVID-19.

In NHS II, a total of 55,925 women were invited to participate in the COVID-19 study, and 39,564 (70.7%) women completed the baseline online COVID-19 survey sent in May 2020. Repeated follow-up COVID-19 surveys were sent out until April 2021 through two phases: in phase 1 monthly questionnaires were sent out to all participants until 84 days after the baseline survey was returned. Additional weekly questionnaires were sent to frontline healthcare providers. In phase 2, all participants received the questionnaire quarterly while additional monthly questionnaires were sent to frontline healthcare providers. In total, 7 repeated COVID-19 surveys were sent to all participants and additional 14 surveys were sent to frontline healthcare providers.

In HPFS, 8,900 men were invited to participate in the COVID-19 study. A total of 4,415 men (49.6%) completed the baseline COVID-19 questionnaire sent in September 2020. These participants were then asked to fill out two follow-up surveys in January and April 2021.

By the end of the COVID-19 study (April 2021), 38,061 participants returned the final follow-up questionnaire (34,375 in NHS II and 3,686 HPFS). The follow-up rate for the COVID-19 survey was 86.5%.

The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Assessment of dietary quality scores

Since 1991 in NHS II and 1986 in HPFS, dietary information has been updated every four years using validated, self-administered, semiquantitative food frequency questionnaires

(FFQs) (22-25). Each FFQ listed standard portion sizes for over 150 foods and asked participants to record intake frequency over the past year, with nine possible responses ranging from "never or less than once per month" to "six or more times per day." Average daily nutrient intake was calculated by multiplying the frequency of intake by the nutrient content of each food and summing nutrient values across all foods.

We computed four dietary quality scores for each participant using FFQ data collected during the two most recent available 4-year data cycles completed prior to the 2020 COVID-19 survey—2011 and 2015 for NHS II, and 2010 and 2014 for HPFS. These scores include the AHEI-2010, AMED, EDIH, and EDIP; **Supplementary Table 1).**

The AHEI-2010 was based on 11 foods and nutrients that are predictive of chronic disease risk (13). Each component was scored between 0 and 10 with higher scores being assigned to higher intakes of vegetables, fruit, whole grains, nuts/legumes, long-chain fatty acids, and polyunsaturated fatty acids, moderate alcohol consumption, and lower intake of sugar-sweetened beverages, red/processed meat, trans fatty acids, and sodium. The total AHEI-2010 score ranged from 0 to 110, with higher scores indicating a higher-quality diet.

The AMED score, an indicator of adherence to a Mediterranean-style diet, was calculated as a sum of 9 components (14). For vegetables, fruits, nuts, whole grains, legumes, fish, and the ratio of monounsaturated to saturated fat, a score of 1 was given to intakes above the median. For red and processed meat consumption, a score of 1 was given to intake below the median. For alcohol intake, a score of 1 was given for moderate consumption (between 5-15 g/day for women, 10-25 g/day for men). If participants did not meet the criteria to receive a score of 1 for a given component, they received a score of 0. The component scores were summed to obtain an overall

AMED score ranging from 0 to 9 with higher scores corresponding to higher adherence to a Mediterranean diet.

The EDIH was developed to assess the insulinemic potential of the whole diet. The score was derived as a weighted sum of 18 food groups (see **Supplementary Table 1**) that have been described in detail elsewhere (16). In brief, 13 food groups were positively associated with C-peptide concentrations, a stable marker of insulin resistance and secretion, while five food groups were inversely associated. The weight assigned for each index component was the regression coefficient derived from the stepwise linear regression model to predict circulating C-peptide (16). Higher scores indicate a hyper-insulinemic diet, while lower scores indicate a hypo-insulinemic diet.

The EDIP was developed to assess the overall inflammatory potential of the diet and was constructed in a similar way as the EDIH. The EDIP included 18 food groups (see **Supplementary Table 1)** that were most predictive of three plasma inflammation markers, interleukin 6, C-reactive protein, and tumor necrosis factor-α-receptor 2. Of the 18 food groups, 9 food groups were anti-inflammatory while 9 food groups were proinflammatory. Higher scores indicate pro-inflammatory diets while lower scores indicate anti-inflammatory diets (15).

Assessment of non-dietary factors

Height and weight were reported at baseline, and weight was updated biennially. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Participants self-reported average time spent weekly on seven physical activities using validated questionnaires every 2-4 years (26). Total physical activity in metabolic equivalent of tasks (MET)-hours/week was calculated by multiplying the MET score and hours/week spent in each activity and summing over all activity items (27). These analyses used most recently updated body mass index (BMI) and physical activity data collected in each cohort. Geocoded mailing addresses were linked to 2010 census tracts to obtain information on the following measures of socioeconomic status (SES): census tract median family home value, median family income, and population density.

SARS-CoV-2 infection and severity

Our primary outcome was self-reported SARS-CoV-2 infection, including positive results from an antigen or antibody test. We also classified SARS-CoV-2-positive participants into four categories using a modified WHO clinical progression scale (28): 1) asymptomatic; 2) symptomatic, 3) independent (persistent cough, sore throat, loss of taste, or loss of smell); symptomatic, assistance needed (shortness of breath or difficulty breathing, fever, muscle aches, or digestive symptoms); and 4) hospitalization. The secondary outcome was symptomatic SARS-CoV-2 infection derived using a method similar to Menni and colleagues(29). The final prediction algorithm included age and reported COVID-19 symptoms including fever, sore throat, muscle aches, loss of taste, loss of smell, and other symptoms consistent with COVID-19 infection(30).

Statistical analysis

Of 43,979 (39,564 in NHS II and 4,415 in HPFS) participants who completed the baseline COVID-19 survey, we excluded those who did not complete an FFQ in 2011 or 2015 for NHS II, and 2010 or 2014 for HPFS (prior to completing the baseline COVID-19 survey). We further excluded participants with unreliable dietary data (e.g. extreme energy intake in FFQ [men: <800 or >4,200 kcal/day; women: <600 or >3,500 kcal/day], left 70 or more FFQ items blank), and those with inconsistent self-reported infection status (e.g. reported being hospitalized due to COVID-19 but tested negative for SARS-CoV-2 infection), leaving 42,935 (38,615 in NHS II and 4,320 in HPFS) participants in the final analysis (**Supplementary Figure 2**). To better represent long-term exposures and to reduce within-person variation, we computed the average of each dietary index from the two FFQs (31). In women and men separately, participants were grouped into quartiles by absolute scores for each dietary pattern index, and data were then pooled together.

Multivariable logistic regression models were used to examine the association of each of the four dietary quality scores with the likelihood of SARS-CoV-2 infection. We adjusted for potential confounders in sequential models: Model 1 was adjusted for age (continuous), sex (women or men), and race (white or non-white); model 2 was further adjusted for smoking (never, past, or current), physical activity (continuous), total energy intake (continuous), census tract median family income (continuous), census tract median family home value (continuous), census tract population density (continuous), concern about COVID-19 (yes or no), interaction with people other than patients with presumed or documented COVID-19 (yes or no), and frontline healthcare providers and PPE use (not frontline healthcare providers, frontline healthcare providers without adequate PPE, and frontline healthcare providers with adequate PPE); model 3 was further adjusted for BMI (continuous), history of high cholesterol (yes or no), history of high blood pressure (yes or no), and presence of other pre-existing medical conditions (diabetes, heart attack, or cancer; yes or no). Missing covariates were replaced with medians. Tests for trends were conducted using the median of each index quartile as a continuous variable.

For our primary analysis of SARS-CoV-2 infection status, we first restricted the analysis to those who had reported test results for SARS-CoV-2 infection. We then used inverse probability weighting (IPW) to account for the probability of receiving a test given the potential of differences between people who reported test results for SARS-CoV-2 infection and those who had not. The IPW was a function of the dietary quality score being evaluated, age, sex, race, being a frontline healthcare provider, interaction with people other than patients with presumed or documented COVID-19, census tract median family income, census tract median family home value, census tract population density, and reported COVID-19 symptoms. We also evaluated the associations between dietary quality scores and symptom-based SARS-CoV-2 infection status using the multivariable logistic regression models adjusting for the same set of covariates.

In the analyses of the severity of SARS-CoV-2 infection, we ran logistic regression analysis using a data augmentation method with a single reference group (tested negative and without symptoms) shared by multiple case subtypes (tested positive without any symptoms; tested positive with only independent symptoms; tested positive with assistance-needed symptoms; tested positive and being hospitalized)(32). Statistical significance of heterogeneity across different degrees of severity was evaluated by the likelihood ratio test. In sensitivity analyses, we limited this analysis to only those who tested positive. According to the modified WHO clinical progression scale, participants who tested positive without symptoms received a score of 1 and were considered as the reference group; three case groups received scores from 2 to 4 in order of increasing severity, including tested positive with only independent symptoms; tested positive with assistance-needed symptoms; tested positive and being hospitalized. We also ran ordinal logistic regression in the analysis of progression scale among tested positive participants. Partial proportion odds models were adopted to separate covariate parameters across the logits for model effects exhibiting a lack of proportional.

We conducted subgroup analyses for associations between dietary quality scores and SARS-CoV-2 infection by age, smoking history, being a frontline healthcare provider, being concerned about COVID-19, interaction with people with presumed or documented COVID-19, BMI, pre-existing medical conditions, history of high blood pressure, history of high cholesterol, and presence of diabetes. Tests for interaction were obtained using the Wald test of cross-product interaction terms between each index, modeled as a continuous variable, and the potential effect modifier, modeled as a categorical variable. Given the issue of multiple testing across the various categories, we adjusted the P-interaction for multiple testing by Bonferroni correction.

Analyses were conducted using SAS 9.4 (SAS Institute, Cary, N.C.); p-values <0.05 were considered statistically significant.

RESULTS

Of the 42,935 participants who responded to the COVID-19 survey and had available dietary data, 90% were women, 97% were Caucasian, and 44% had reported at least one test result for SARS-CoV-2 infection or antibodies. At baseline of the COVID-19 study (March 2020), the mean (SD) age was 66.5 (6.1) years. In women, 10% completed no more than three COVID-19 questionnaires, 53% completed six or seven COVID-19 questionnaires, and 22% completed as least ten COVID-19 questionnaires during the follow-up. In men, 76% completed all three questionnaires.

Compared with participants with lower dietary quality (higher EDIH and EDIP scores and lower AHEI-2010 and AMED scores), participants with higher dietary quality had a lower

BMI and more likely to be physically active, as well as have a higher SES. At the same time, these participants were less likely to smoke or have pre-existing medical conditions **(Table 1)**. Compared to participants who did not report test results, participants who reported test results were more likely to be frontline healthcare providers, have interacted with others with presumed or documented COVID-19, and have a higher SES **(Supplementary Table 2)**. We observed the strongest correlation between the a priori diet quality indices: AHEI-2010 and AMED (r_s=0.74) The two empirical hypothesis-oriented indices—EDIH and EDIP—showed weaker correlations with each other (r_s =0.58) and two a priori diet quality indices ($|r_s| \leq 0.45$**; Supplementary Table 3)**.

A total of 1941 participants (4.5%) reported a positive test for SARS-CoV-2 infection or antibodies. Higher dietary quality, represented by higher AHEI-2010 and AMED as well as lower EDIH and EDIP scores, was associated with a lower risk of SARS-CoV-2 infection in the fully adjusted model (model 3). The multivariable adjusted OR (95% CI) comparing the top versus bottom quartile were 0.80 (0.69, 0.92), P for trend=0.001 for AHEI-2010; 0.78 (0.67, 0.92), P for trend=0.003 for AMED; 1.36 (1.16, 1.58), P for trend=0.0001 for EDIH; and 1.13 (0.99, 1.30), P for trend=0.01 for EDIP. When we accounted for potential selection bias using IPW, results remained unchanged (**Table 2**). Furthermore, higher dietary quality was also associated with lower risk of symptomatic SARS-CoV-2 infection, and the strongest association was observed for EDIH (OR quartile 4 vs.1 (95% CI) were 1.18 (1.06, 1.31); **Supplementary Table 4)**.

Higher adherence to the AHEI and AMED and lower adherence to the EDIP and EDIH were associated with lower likelihood of severe infection. In multivariable model 2, participants with one standard deviation higher scores of the AHEI-2010 and AMED were 20%-22% less likely to be hospitalized due to SARS-CoV-2 infection. On the other hand, participants with one standard deviation higher scores of EDIH and EDIP had a 23-37% higher likelihood of hospitalization. Further adjustment for BMI and pre-existing medical conditions largely attenuated these associations which were no longer significant (**Figure 1)**. In sensitivity analyses with tested positive participants only, we also observed an inverse association between higher dietary quality and severity of COVID-19 before adjusting for the BMI and pre-existing medical conditions (**Supplementary Figure 3**).

The associations between dietary quality scores and likelihood of a positive test were not significantly modified by lifestyle factors, knowledge of exposure to SARS-CoV-2 virus, or any pre-existing medical conditions **(Table 3)**.

Discussion

In a sub-study of two large cohorts of 42,935 health professionals who responded to a COVID-19 survey and had available data on usual long-term diet prior to the survey, we found that long-term adherence to healthy dietary patterns, represented by higher AHEI-2010 and AMED as well as lower EDIH and EDIP, were associated with a lower risk of both SARS-CoV-2 infection and disease severity. BMI and pre-existing medical conditions could be mediators for COVID-19 severity but not for SARS-CoV-2 infection itself.

Emerging evidence supports a role of diet in the development of COVID-19. Using data from a smartphone-based COVID-19 symptom study, we observed that a recent diet characterized by healthy plant-based foods was associated with lower risk and severity of COVID-19 (10). Similar to our findings, a recent population-based case-control study of healthcare workers found adherence to a plant-based diet, which was assessed retrospectively through self-identified dietary patterns, was associated with lower odds of moderate-to-severe COVID-19 (33). Another retrospective cross-sectional study of COVID patients who visited the respiratory emergency department in Iran also found that a healthier dietary pattern assessed by a 16-item FFQ was associated with less severe COVID-19 symptoms (34). An earlier ecological study of 23 countries in the Organization for Economic Co-operation and Development supported a role for the Mediterranean diet in the prevention of COVID-19 (9). After adjusting for country-level indicators of income, education, housing, environment, life satisfaction, and physical inactivity, the authors found a negative association between Mediterranean diet adherence and COVID-19 related deaths (9).

Adherence to AHEI-2010 and AMED indicates higher fruits and vegetable consumption that may lead an enhanced immune cell profile (35). Moreover, a diet rich in these foods have been inversely associated with the severity of several respiratory diseases (36). In addition, adherence to AHEI-2010 and AMED increased the consumption of polyphenols which could mitigate the exaggerated inflammatory and pro-thrombotic milieu associated with severe COVID-19 illness due to their anti-inflammatory, antioxidant, and anti-thrombotic properties (37). An overall healthy diet, therefore, could plausibly play a role in preventing SARS-CoV-2 infection and reducing the severity, if infected(38).

We also examined the EDIH and EDIP in relation to COVID-19, as diets with high insulinemic and inflammatory potential could increase the risk of SARS-CoV-2 infection and worsen the severity(39, 40). Studies with mice models demonstrated that insulin can influence lung mechanical parameters, including tissue resistance and elastance, and hyperinsulinemia can induce bronchoconstriction. Hence, hyperinsulinemia could be a driver of lung dysfunction arising from virus infections (41). A high insulinemic diet directly contributes to sustained hyperglycemia and hyperinsulinemia and the SARS-CoV-2 virus can replicate more rapidly in settings of elevated glucose levels in *ex vivo* studies (18). Response to the SARS-CoV-2 infection can also cause excessive production of pro-inflammatory molecules, with an abnormal inflammatory response, termed the cytokine storm (42). Thus, a cytokine storm might be exacerbated by diets with high insulinemic or inflammatory potential. Recently, a meta-analysis of 56 studies including 8,719 COVID patients found that patients with severe COVID-19 had higher levels of inflammatory markers compared to those with mild disease (43).

A notable strength of our study was that we had access to validated and repeated measures of long-term diet. Additionally, information on SARS-CoV-2 infection and symptoms, as well as comprehensive information on covariates, were captured in a timely manner. At the same time, all our study participants were health professionals which allowed us to capture high quality health information (44). However, the results of the present study need to be interpreted in the context of several limitations. First, we only invited participants who completed the most recent survey to the COVID-19 study, which could lead to selection bias. However, we have high active follow-up rates in bour main cohorts (~90%). Second, we had no information on fatal COVID-19 cases and the outcomes were based on self-report data. However, our study population were dedicated health professionals followed by decades already. Third, there were only a small number of hospitalized COVID-19 cases which limited our power to observe associations. Last, while we carefully adjusted for several confounders, the possibility of residual confounding due to socioeconomic, lifestyle, and health conditions cannot be ruled out given the observational nature of our study. Specifically, we cannot rule out the possibility that participants who chose a healthier diet might also have been more careful in lowering their exposure to SARS-CoV-2 virus.

In conclusion, we found that a higher quality diet was associated with a lower risk of SARS-CoV-2 infection and its severity. At the same time, a diet with a higher inflammatory and insulinemic potential was associated with a higher risk of SARS-CoV2 infection and severity. While we carefully adjusted for several confounders, the possibility of residual confounding cannot be ruled out. Still, our results suggest that dietary quality may be important for lowering the burden and severity of COVID-19. While our data were mainly collected prior to the time when COVID-19 vaccines became available, further research is warranted to investigate whether the observed associations change or are modified with time, treatments, and vaccination status during the pandemic.

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Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval. Further information including the procedures to obtain and access data is described at https://www.nurseshealthstudy.org/researchers (contact email: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hpfs/for-collaborators/

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Table 1. Characteristics of 42,935 participants in the COVID-19 survey by quartiles of dietary quality scores[1] in the Nurses' Health Study II and Health Professionals Follow-up Study

	Overall	AHEI-2010		AMED		EDIH		EDIP	
		Q1	Q4	Q1	Q4	Q1	Q4	Q1	Q4
Median of the quartile, women/men		52.1/55.1	80.6/81.1	2.0/2.0	6.5/6.5	0.0/0.0	0.5/0.7	-1.3/-0.5	0.8/0.2
Age, years	66.5 (6.1)	66.2 (6.2)	66.8 (5.8)	66.2 (6.1)	66.8 (6.0)	66.8 (6.0)	66.2 (6.1)	66.2 (6.1)	66.8 (5.9)
Received Covid-19 test(s), %	46.0	44.5	46.5	45.0	46.9	47.9	45.2	47.4	45.5
Body mass index, kg/m^2	27.4(6.0)	29.2 (6.7)	25.4 (4.8)	29.0 (6.6)	25.8 (5.2)	25.2 (4.7)	29.9 (6.8)	25.8 (5.0)	29.3 (6.7)
Energy intake, kcal/day	1789 (531)	1788 (540)	1831 (497)	1497 (450)	2091 (500)	1680 (511)	2040 (536)	1831 (526)	1842 (551)
Total activity, MET-hrs/week	30.6 (32.1)	22.0 (26.6)	40.6 (36.2)	21.0 (25.4)	41.1 (37.1)	37.0 (35.3)	25.3 (29.4)	36.0 (34.6)	26.0 (30.1)
Smoking status									
- Past smoker, %	32.3	29.5	34.4	30.0	33.5	37.6	28.5	37.3	27.4
- Current smoker, %	2.0	3.2	1.0	3.2	1.1	2.1	2.1	1.7	2.3
History of cancer, %	4.2	4.5	3.9	4.4	3.8	4.0	4.4	4.0	4.7
History of heart attack, %	0.5	0.7	0.4	0.7	0.4	0.4	0.6	0.3	0.7
History of high blood pressure, %	25.2	31.2	18.8	29.5	20.9	19.1	32.2	21.1	30.7
History of hypercholesterolemia, %	27.8	31.5	24.5	30.3	25.1	23.6	31.5	24.7	31.2
History of diabetes, %	5.4	7.0	3.2	7.4	3.5	2.2	9.7	2.5	9.0
Frontline healthcare providers, %	28.1	28.3	27.5	29.0	27.3	27.8	28.6	28.3	28.0
Community interaction with people with presumed or documented COVID-19, %	8.6	7.8	9.4	7.8	9.2	8.8	8.6	8.9	8.2
Expressed concern about COVID-19, %	72.8	71.3	74.4	70.7	74.5	74.6	71.0	74.1	71.3
Median family home value (2010 Census)	291,766 (211,999)	233,968 (170,253)	355,774 (238,005)	245,813 (178,032)	333,498 (230,757)	341,607 (233,548)	242,375 (178,745)	320,537 (222,689)	264,253 (197,244)
Median family income (2010 Census)	84,366 (32,931)	77,161 (28,484)	91,456 (35,776)	78,847 (29,378)	89,110 (35,009)	90,338 (35,634)	77,918 (29,617)	88,837 (34,411)	79,792 (30,944)
Population density number of people per sq km (2010 Census)	1196 (3380)	966 (2,654)	1,471 (4,019)	1,029 (2,885)	1,359 (3,753)	1,410 (4,072)	1,000 (2,810)	1,304 (3,796)	1,116 (3,118)

AHEI-2010, Alternative Healthy Eating Index-2010; AMED, alternative Mediterranean Diet; COVID-19, Coronavirus Disease 2019; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, Empirical Dietary Inflammatory Pattern; MET, metabolic equivalent of tasks

Values are means (SD) or percentages standardized to the distribution of age, with the exception of age itself.

[1]Quartiles were determined in women and men separately.

Table 2. Associations (odds ratio and 95% confidence interval) between dietary quality scores and risk of SARS-CoV-2 infection in the Nurses' Health Study II and Health Professionals Follow-up Study

	AHEI-2010					
	Q1	Q2	Q3	Q4	P-trend[1]	Continuous[2]
Cases/Non-cases[3]	576/4213	492/4358	454/4476	419/4766		1,941/17,813
Model 1[4]	1 (ref)	0.83 (0.73, 0.95)	0.75 (0.66, 0.86)	0.65 (0.57, 0.75)	<.0001	0.83 (0.80, 0.88)
Model 2[5]	1 (ref)	0.87 (0.76, 0.99)	0.82 (0.71, 0.93)	0.75 (0.65, 0.86)	<.0001	0.88 (0.84, 0.93)
Model 3[6]	1 (ref)	0.90 (0.79, 1.02)	0.86 (0.75, 0.98)	0.80 (0.69, 0.92)	0.0014	0.90 (0.86, 0.95)
Model 3 +IPW[7]	1 (ref)	0.90 (0.79, 1.04)	0.87 (0.76, 1.01)	0.81 (0.69, 0.94)	0.0051	0.91 (0.86, 0.96)
	AMED					
	Q1	Q2	Q3	Q4	P-trend[1]	Continuous[2]
Cases/Non-cases[3]	495/3678	540/4756	489/4689	417/4690		1941/17813
Model 1[4]	1 (ref)	0.85 (0.74, 0.97)	0.78 (0.69, 0.90)	0.67 (0.58, 0.77)	<.0001	0.85 (0.82, 0.90)
Model 2[5]	1 (ref)	0.90 (0.78, 1.02)	0.86 (0.74, 0.99)	0.76 (0.65, 0.89)	0.0008	0.89 (0.84, 0.94)
Model 3[6]	1 (ref)	0.90 (0.79, 1.03)	0.87 (0.76, 1.01)	0.78 (0.67, 0.92)	0.0032	0.90 (0.85, 0.95)
Model 3 +IPW[7]	1 (ref)	0.92 (0.81, 1.06)	0.90 (0.78, 1.05)	0.79 (0.67, 0.94)	0.0091	0.90 (0.85, 0.96)
	EDIH					
	Q1	Q2	Q3	Q4	P-trend[1]	Continuous[2]
Cases/Non-cases	382/4739	466/4439	524/4335	569/4300		1941/17813
Model 1[4]	1 (ref)	1.30 (1.13, 1.50)	1.48 (1.29, 1.70)	1.61 (1.41, 1.85)	<.0001	1.18 (1.12, 1.23)
Model 2[4]	1 (ref)	1.23 (1.07, 1.42)	1.38 (1.20, 1.60)	1.45 (1.25, 1.68)	<.0001	1.14 (1.08, 1.20)
Model 3 [5]	1 (ref)	1.21 (1.04, 1.40)	1.35 (1.16, 1.56)	1.36 (1.16, 1.58)	0.0001	1.12 (1.06, 1.18)
Model 3 +IPW	1 (ref)	1.24 (1.07, 1.44)	1.38 (1.19, 1.60)	1.40 (1.20, 1.64)	<.0001	1.12 (1.06, 1.18)
	EDIP					
	Q1	Q2	Q3	Q4	P-trend[1]	Continuous[2]
Cases/Non-cases[3]	451/4648	449/4553	501/4287	540/4325		1941/17813
Model 1[4]	1 (ref)	1.02 (0.89, 1.17)	1.22 (1.06, 1.39)	1.31 (1.14, 1.49)	<.0001	1.10 (1.06, 1.16)
Model 2[5]	1 (ref)	0.99 (0.86, 1.13)	1.13 (0.99, 1.30)	1.17 (1.02, 1.34)	0.0023	1.06 (1.01, 1.11)
Model 3[6]	1 (ref)	0.98 (0.85. 1.12)	1.11 (0.97, 1.28)	1.13 (0.99, 1.30)	0.0109	1.04 (0.99, 1.10)
Model 3 +IPW[7]	1 (ref)	0.99 (0.86, 1.15)	1.09 (0.95, 1.26)	1.13 (0.98, 1.31)	0.0104	1.04 (0.99, 1.09)

AHEI, Alternate Healthy Eating Index; AMED, alternative Mediterranean Diet; BMI, body mass index; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, empirical dietary inflammatory pattern; IPW, inverse probability weighting; PPE, personal protective equipment; Q, quartile

[1]P for linear trend across quartiles was calculated using the median of each quartile as a continuous variable.

[2]Continuous analyses for a 1 standard deviation increment

[3]Non-cases number for model 1-3

[4]Model 1 was adjusted for age (continuous), sex (women or men), and race (white or non-white)

[5]Model 2 was further adjusted for smoking (never, past, or current), physical activity (continous), total energy intake (continuous), census tract median family income (continuous), census tract median family home value (continuous), census tract population density (continuous), concern about COVID-19 (yes or no), interaction with people other than patients with presumed or documented COVID-19 (yes or no), and frontline healthcare providers and PPE use (not frontline healthcare providers, frontline healthcare providers without adequate PPE, and frontline healthcare providers with adequate PPE).

[6]Model 3 was further adjusted for BMI (continuous), history of high cholesterol (yes or no), history of high blood pressure (yes or no), and presence of other pre-existing medical conditions (diabetes, heart attack, cancer; yes or no).

[7]IPW: Probability of receiving a COVID-19 test was modeled using the dietary quality score being evaluated, age, sex, race, being frontline healthcare worker, interaction with people other than patients with presumed or documented COVID-19, census tract median family income, census tract median family home value, census tract population density, and occurrences of COVID-19 related symptoms. We then weighted the study population by the inverse of the probability of receiving a COVID-19 test and then adjusted for covariates in the model 3

Table 3. Associations (odds ratio and 95% confidence interval) between dietary quality scores and risk of a positive COVID-19 test by demographic, lifestyle, medical, and personal characteristics [1] in the Nurses' Health Study II and Health Professionals Follow-up Study

Characteristics

Age (years)	< 65	≥65	P_{inter}[2]
Cases/Non-cases	884/6,995	1,057/10,818	
AHEI-2010	0.91 (0.84, 0.98)	0.90 (0.84, 0.96)	0.23
AMED	0.90 (0.83, 0.98)	0.90 (0.84, 0.98)	0.38
EDIH	1.12 (1.04, 1.22)	1.13 (1.05, 1.21)	0.56
EDIP	1.04 (0.97, 1.12)	1.05 (0.98, 1.12)	0.37

Smoking	Never	Ever	P_{inter}[2]
Cases/Non-cases	1,231/10,777	710/7,036	
AHEI-2010	0.92 (0.86, 0.98)	0.87 (0.80, 0.95)	0.14
AMED	0.91 (0.85, 0.98)	0.89 (0.81, 0.97)	0.24
EDIH	1.13 (1.06, 1.21)	1.11 (1.02, 1.21)	0.36
EDIP	1.05 (0.99, 1.12)	1.03 (0.95, 1.11)	0.72

Frontline healthcare worker	No	Yes	P_{inter}[2]
Cases/Non-cases	1,213/12,475	728/5,338	
AHEI-2010	0.91 (0.85, 0.97)	0.88 (0.81, 0.96)	0.71
AMED	0.91 (0.84, 0.97)	0.90 (0.82, 0.98)	0.63
EDIH	1.13 (1.06, 1.21)	1.12 (1.03, 1.22)	0.34
EDIP	1.04 (0.98, 1.11)	1.06 (0.98, 1.14)	0.84

Concern about COVID-19	No	Yes	P_{inter}[2]
Cases/Non-cases	630/4,467	1,311/13,346	
AHEI-2010	0.89 (0.82, 0.98)	0.91 (0.85, 0.97)	0.57
AMED	0.88 (0.80, 0.97)	0.92 (0.86, 0.98)	0.61
EDIH	1.09 (1.00, 1.20)	1.15 (1.08, 1.22)	0.48
EDIP	1.05 (0.96, 1.14)	1.05 (0.99, 1.11)	0.85

Community interaction with people with presumed or documented COVID-19	No	Yes	P_{inter}[2]
Cases/Non-cases	1,586/15,956	355/1,857	
AHEI-2010	0.90 (0.85, 0.95)	0.89 (0.79, 1.01)	0.15
AMED	0.91 (0.85, 0.96)	0.86 (0.75, 0.98)	0.89
EDIH	1.13 (1.07, 1.20)	1.09 (0.96, 1.24)	0.08
EDIP	1.05 (1.00, 1.11)	1.03 (0.92, 1.15)	0.19

BMI (kg/m^2)	< 25	25-<30	≥30	P_{inter}[2]
Cases/Non-cases	673/7,292	682/5,997	586/4,524	
AHEI-2010	0.89 (0.82, 0.97)	0.87 (0.60, 1.28)	0.90 (0.81, 0.99)	0.86
AMED	0.91 (0.83, 1.00)	0.90 (0.82, 0.99)	0.88 (0.79, 0.98)	0.97
EDIH	1.14 (1.04, 1.25)	1.12 (1.02, 1.22)	1.12 (1.02, 1.23)	0.87
EDIP	1.05 (0.97, 1.14)	1.04 (0.95, 1.13)	1.06 (0.96, 1.15)	0.92

Pre-existing medical conditions	No	Yes	P_{inter}[2]
Cases/Non-cases	1,063/23,131	878/17,863	

AHEI-2010	0.90 (0.84, 0.96)	0.92 (0.86, 0.99)	0.38
AMED	0.89 (0.83, 0.96)	0.92 (0.85, 1.00)	0.36
EDIH	1.10 (1.03, 1.18)	1.14 (1.06, 1.23)	0.64
EDIP	1.07 (1.00, 1.14)	1.01 (0.94, 1.08)	0.19
	History of high blood pressure		
	No	Yes	P_{inter}[2]
Cases/Non-cases	1428/13409	513/4,404	
AHEI-2010	0.90 (0.85, 0.96)	0.89 (0.80, 0.99)	0.53
AMED	0.90 (0.84, 0.96)	0.91 (0.80, 1.02)	0.41
EDIH	1.11 (1.05, 1.19)	1.16 (1.05, 1.28)	0.58
EDIP	1.07 (1.01, 1.14)	0.98 (0.90, 1.08)	0.12
	History of high cholesterol		
	No	Yes	P_{inter}[2]
Cases/Non-cases	1,390/12,771	551/5,042	
AHEI-2010	0.90 (0.84, 0.95)	0.90 (0.82, 1.00)	0.79
AMED	0.89 (0.83, 0.95)	0.92 (0.83, 1.02)	0.54
EDIH	1.11 (1.04, 1.18)	1.18 (1.06, 1.30)	0.44
EDIP	1.05 (0.99, 1.11)	1.04 (0.95, 1.14)	0.83
	Type II diabetes		
	No	Yes	P_{inter}[2]
Cases/Non-cases	1,829/16,863	112/950	
AHEI-2010	0.89 (0.85, 0.94)	1.01 (0.79, 1.28)	0.82
AMED	0.90 (0.85, 0.95)	9,96 (0.75, 1.23)	0.60
EDIH	1.13 (1.07, 1.20)	1.05 (0.85, 1.31)	0.43
EDIP	1.05 (1.00, 1.10)	1.01 (0.82, 1.25)	0.93

AHEI, Alternate Healthy Eating Index; AMED, alternative Mediterranean Diet; BMI, body mass index; COVID-19, Coronavirus Disease 2019; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, empirical dietary inflammatory pattern; PPE, personal protective equipment

[2]Continuous analyses for a standard deviation increment; Multivariable model was adjusted for age (continuous), sex (women or men), race (white or non-white), smoking (never, past, or current), physical activity (continuous), total energy intake (continuous), census tract median family income (continuous), census tract median family home value (continuous), census tract population density (continuous), concern about COVID-19 (yes or no), interaction with people other than patients with presumed or documented COVID-19 (yes or no), frontline healthcare providers and PPE use (not frontline healthcare providers, frontline healthcare providers without adequate PPE, and frontline healthcare providers with adequate PPE), BMI (continuous), history of high cholesterol (yes or no), history of high blood pressure (yes or no), and presence of other pre-existing medical conditions (diabetes, heart attack, cancer; yes or no).

[2]P for linear trend across quartiles was calculated using the median of each quartile as a continuous variable.

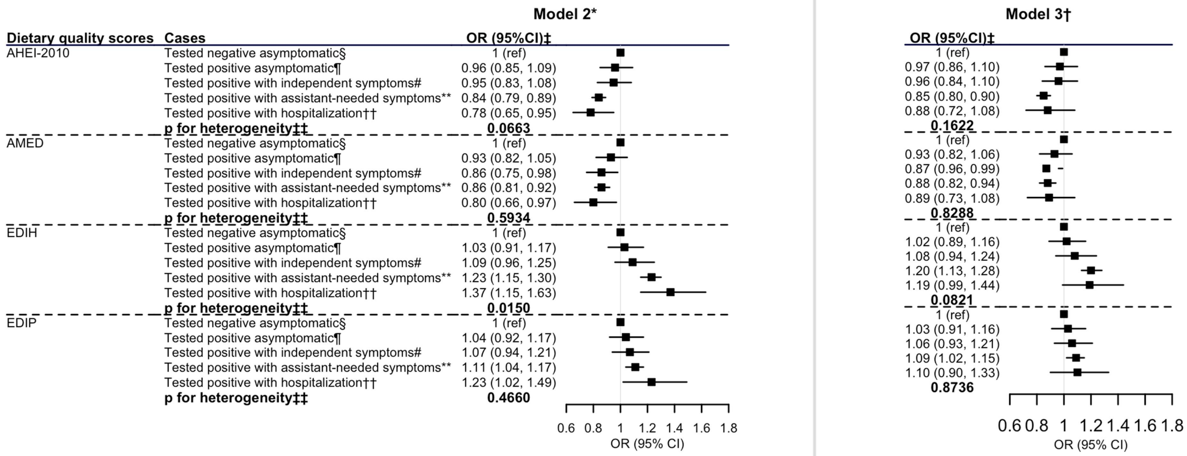

Figure 1. Associations (odds ratio and 95% confidence interval) between one standard increment of dietary quality scores and COVID-19 severity in the Nurses' Health Study II and Health Professionals Follow-up Study
AHEI, Alternate Healthy Eating Index; AMED, alternative Mediterranean Diet; BMI, body mass index; CI, confidence interval; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, empirical dietary inflammatory pattern; OR, odds ratio; PPE, personal protective equipment.

*Model 2 was adjusted for age (continuous), sex (women or men), race (white or non-white), smoking (never, past, or current), physical activity(continuous), total energy intake (continuous), census tract median family income (continuous), census tract median family home value (continuous), census tract population density (continuous), concern about COVID-19 (yes or no) , interaction with people other than patients with presumed or documented COVID-19 (yes or no), frontline healthcare providers and PPE use (not frontline healthcare providers, frontline healthcare providers without adequate PPE, and frontline healthcare providers with adequate PPE).

†Model 3 was further adjusted for BMI (continuous), history of high cholesterol (yes or no), history of high blood pressure (yes or no), and presence of other pre-existing medical conditions (diabetes, heart attack, cancer; yes or no).

‡Continuous analyses for a standard deviation increment.

§Tested negative and without symptoms (n=10231).

¶Tested positive without any symptoms (n=270).

#Tested positive with only independent symptoms (persistent cough, sore throat, loss of taste, or loss of smell) (n=235)

**Tested positive with assistance-needed symptoms (shortness of breath or difficulty breathing, fever, muscle aches, or digestive symptoms) (n= 1327)

††Test positive and being hospitalized (n=109)

‡‡P for heterogeneity across different degree of severity was evaluated by the likelihood ratio test