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

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ABSTRACT

Background: The role of diet on Coronavirus Disease 2019 (COVID-19) is emerging. We investigated the association between usual diet before the onset of the pandemic and risk and severity of subsequent SARS-CoV-2 infection.

Methods: We included 42,935 participants aged 55–99 y in 2 ongoing cohort studies, the 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 FFQs before 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 ORs and 95% CIs for Severe Acute Respiratory Syndrome Coronavirus 2 (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, 1941 participants reported a positive result. Of these, 1327 reported symptoms needing assistance and another 109 were hospitalized. Healthier diets, represented by higher AHEI-2010 and AMED scores and lower EDIH and EDIP scores, were associated with lower likelihood of SARS-CoV-2 infection (quartile 4 compared with quartile 1: OR: 0.80; 95% CI: 0.69, 0.92 for AHEI-2010; OR: 0.78; 95% CI: 0.67, 0.92 for AMED; OR: 1.36; 95% CI: 1.16, 1.57 for EDIH; and OR: 1.13; 95% CI: 0.99, 1.30 for EDIP; all \( P \)-trend ≤ 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 owing to COVID-19. However, associations were no longer significant after controlling for BMI and pre-existing medical conditions.

Conclusions: 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. Am J Clin Nutr 2022;116:1672–1681.

Keywords: dietary quality, SARS-CoV-2 infection, COVID-19 severity, prospective cohort study, long-term diet, Mediterranean diet, alternate healthy eating index, inflammatory diet, hyperinsulinemia

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 5 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 roles of modifiable factors such as diet in susceptibility to SARS-CoV-2 infection and its severity are not well understood. Further, whether diet can...
modify the higher risk of COVID-19 that is associated with the presence of comorbidities 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 before the onset of the pandemic and risk and severity of subsequent SARS-CoV-2 infection using data from 2 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 2 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 2 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 2 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 in 116,429 female nurses, aged 25–42 y, that began in 1989 (19). The HPFS began in 1986 and includes 51,529 men in health professions who were 40–75 y old at cohort baseline (20). In both cohorts, participants completed questionnaires at baseline and every 2 y 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 the NHS II (n = 55,925) and 2020 in the HPFS (n = 8900)—to complete a supplementary COVID-19 online series of surveys regarding their experiences during the COVID-19 pandemic (19) (Supplemental 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 the 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 2 phases: in phase 1, monthly questionnaires were sent out to all participants until 84 d after the baseline survey was returned. Additional weekly questionnaires were sent to frontline health care providers. In phase 2, all participants received the questionnaire quarterly, whereas additional monthly questionnaires were sent to frontline health care providers. In total, 7 repeated COVID-19 surveys were sent to all participants and an additional 14 surveys were sent to frontline health care providers.

In the HPFS, 8900 men were invited to participate in the COVID-19 study. A total of 4415 men (49.6%) completed the baseline COVID-19 questionnaire sent in September 2020. These participants were then asked to fill out 2 follow-up surveys in January and April 2021.

By the end of the COVID-19 study (April 2021), 38,061 participants had returned the final follow-up questionnaire (34,375 in the NHS II and 3686 in the 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 TH Chan School of Public Health.

Assessment of dietary quality scores

Since 1991 in the NHS II and 1986 in the HPFS, dietary information has been updated every 4 y using validated, self-administered, semiquantitative FFQs (21–24). Each FFQ listed standard portion sizes for >150 foods and asked participants to record intake frequency over the past year, with 9 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 4 dietary quality scores for each participant using FFQ data collected during the 2 most recent available 4-y data cycles completed before the 2020 COVID-19 survey—2011 and 2015 for the NHS II, and 2010 and 2014 for the HPFS.
These scores include the AHEI-2010, AMED, EDIH, and EDIP (Supplemental 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 PUFAs, 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 and 15 g/d for women, 10–25 g/d 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 Supplemental 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, whereas 5 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, whereas 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 Supplemental Table 1) that were most predictive of 3 plasma inflammation markers: IL-6, C-reactive protein, and TNF-α-receptor 2. Of the 18 food groups, 9 food groups were anti-inflammatory, whereas 9 food groups were proinflammatory. Higher scores indicate proinflammatory diets, whereas lower scores indicate anti-inflammatory diets (15).

Assessment of nondietary factors

Height and weight were reported at baseline, and weight was updated biennially. BMI (in kg/m²) was calculated as weight in kilograms divided by height in meters squared. Participants self-reported average time spent weekly on 7 physical activities using validated questionnaires every 2–4 y (25). Total physical activity in metabolic equivalent of tasks (MET)-hours per week was calculated by multiplying the MET score for, and hours per week spent in, each activity and summing over all activity items (26). These analyses used the most recently updated 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 4 categories using a modified WHO clinical progression scale (27): 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 that of Menni et al. (28). 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 (29).

Statistical analysis

Of 43,979 (39,564 in the NHS II and 4415 in the HPFS) participants who completed the baseline COVID-19 survey, we excluded those who did not complete an FFQ in 2011 or 2015 for the NHS II, and 2010 or 2014 for the HPFS (before completing the baseline COVID-19 survey). We further excluded participants with unreliable dietary data [e.g., extreme energy intake in FFQ (men: <800 or >4200 kcal/d; women: <600 or >3500 kcal/d), left ≥70 FFQ items blank] and those with inconsistent self-reported infection status (e.g., reported being hospitalized owing to COVID-19 but tested negative for SARS-CoV-2 infection), leaving 42,935 (38,615 in the NHS II and 4320 in the HPFS) participants in the final analysis (Supplemental Figure 2). To better represent long-term exposures and to reduce within-person variation, we computed the mean of each dietary index from the 2 FFQs (30). 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 4 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 nonwhite); 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 health care providers and PPE use (not frontline health care providers, frontline health care providers without adequate PPE, and frontline health care 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 health care 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 was hospitalized) (31). 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; 3 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, and tested positive and was hospitalized. We also ran ordinal logistic regression in analysis of the 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 proportionality.

We conducted subgroup analyses for associations between dietary quality scores and SARS-CoV-2 infection by age, smoking history, being a frontline health care 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 categoric 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 version 9.4 (SAS Institute); 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 ≥1 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 y. In women, 10% completed no more than 3 COVID-19 questionnaires, 53% completed 6 or 7 COVID-19 questionnaires, and 22% completed ≥10 COVID-19 questionnaires during the follow-up. In men, 76% completed all 3 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 were 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 with participants who did not report test results, participants who reported test results were more likely to be frontline health care providers, have interacted with others with presumed or documented COVID-19, and have a higher SES (Supplemental Table 2). We observed the strongest correlation between the a priori diet quality indices: AHEI-2010 and AMED (r = 0.74). The 2 empirical hypothesis-oriented indices—EDIH and EDIP—showed weaker correlations with each other (r = 0.58) and the 2 a priori diet quality indices (|r| ≤ 0.45) (Supplemental 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 ORs comparing the top with the bottom quartile were 0.80 (95% CI: 0.69, 0.92; P-trend = 0.001) for AHEI-2010; 0.78 (95% CI: 0.67, 0.92; P-trend = 0.003) for AMED; 1.36 (95% CI: 1.16, 1.58; P-trend = 0.0001) for EDIH; and 1.13 (95% CI: 0.99, 1.30; P-trend = 0.041) 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 (quartile 4 compared with quartile 1: OR: 1.18; 95% CI: 1.06, 1.31) (Supplemental 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 1-SD higher scores of the AHEI-2010 and AMED were 20%–22% less likely to be hospitalized owing to SARS-CoV-2 infection. On the other hand, participants with 1-SD higher scores of the 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 (Supplemental 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).
| Characteristics                                                                 | AHEI-2010 | AMED | EDIH | EDIP          |
|---------------------------------------------------------------------------------|-----------|------|------|---------------|
| **Quartile median (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, y**                                                                      | 66.5 ± 6.1 | 66.2 ± 6.2 | 66.8 ± 5.8 | 66.2 ± 6.1 | 66.8 ± 6.0 | 66.2 ± 6.1 | 66.2 ± 6.1 | 66.8 ± 5.9 |
| **BMI, kg/m²**                                                                  | 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 |
| **Total activity, MET-h/wk**                                                     | 30.6 ± 32.1 | 220 ± 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 |
| **Energy intake, kcal/d**                                                        | 1789 ± 531 | 1788 ± 540 | 1831 ± 497 | 1497 ± 450 | 2091 ± 500 | 1680 ± 511 | 2040 ± 536 | 1831 ± 526 | 1842 ± 551 |
| **Smoking status, %**                                                            | 32.3%      | 29.5%  | 34.4% | 30.0% | 33.5% | 37.6% | 28.5% | 37.3% | 27.4% |
| **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 health care 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 |
| **Median family income, $ (2010 census)**                                       | 84,366 ± 32931 | 71,126 ± 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: people per sq km, n (2010 census)**                       | 1196 ± 3380 | 966 ± 2654 | 1471 ± 4019 | 1029 ± 2885 | 1359 ± 3753 | 1410 ± 4072 | 1000 ± 2810 | 1304 ± 3796 | 1116 ± 3118 |

1Values are means ± SDs or percentages standardized to the distribution of age, with the exception of age itself. Quartiles were determined in women and men separately. AHEI, Alternative Healthy Eating Index; 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; Q, quartile.
Discussion

In a study in 2 large cohorts of 42,935 health professionals who responded to a COVID-19 survey and had available data on usual long-term diet before the survey, we found that long-term adherence to healthy dietary patterns, represented by higher AHEI-2010 and AMED, indicates higher 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 (32). Another retrospective cross-sectional study in 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 (33).

An earlier ecological study of 23 countries in the Organisation 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 the AHEI-2010 and AMED indicates higher fruit and vegetable consumption that may lead to an enhanced immune cell profile (34). Moreover, a diet rich in these foods has been inversely associated with the severity of several respiratory
diseases (35). In addition, adherence to the AHEI-2010 and AMED increased the consumption of polyphenols which could mitigate the exaggerated inflammatory and prothrombotic milieu associated with severe COVID-19 illness owing to their anti-inflammatory, antioxidant, and antithrombotic properties (36). An overall healthy diet, therefore, could plausibly play a role in preventing SARS-CoV-2 infection and reducing the severity, if infected (37).

We also examined the EDIH and EDIP in relation to COVID-19, because diets with high insulinemic and inflammatory potential could increase the risk of SARS-CoV-2 infection and worsen the severity (38, 39). 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 (40). 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 concentrations in ex vivo studies (18). Response to the SARS-CoV-2 infection can also cause excessive production of proinflammatory molecules, with an abnormal inflammatory response, termed the cytokine storm (41). Thus, a cytokine storm might be exacerbated by diets with high insulinemic or inflammatory potential. Recently, a meta-analysis of 56 studies including 8719 COVID patients found that patients with severe COVID-19 had higher concentrations of inflammatory markers than those with mild disease (42).

A notable strength of our study was that we had access to validated and repeated measures of long-term diet. In addition, 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 (43). 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 (∼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 for decades already. Third, there were only a small number of hospitalized COVID-19 cases, which limited our power to observe associations. Last, although 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
TABLE 3  Associations (ORs and 95% CIs) between dietary quality scores and risk of a positive COVID-19 test by demographic, lifestyle, medical, and personal characteristics in the Nurses’ Health Study II and Health Professionals Follow-up Study

| Characteristics                        | Cases/noncases, n | AHEI-2010 | AMED | EDIH | EDIP |
|----------------------------------------|-------------------|-----------|------|------|------|
| **Age, y**                             |                   |           |      |      |      |
| <65                                    | 884/6995          | 0.91 (0.84, 0.98) | 0.90 (0.83, 0.98) | 1.12 (1.04, 1.22) | 1.04 (0.97, 1.12) |
| ≥65                                    | 1057/10818        | 0.90 (0.84, 0.96) | 0.90 (0.84, 0.98) | 1.13 (1.05, 1.21) | 1.05 (0.98, 1.12) |
| **P**                                  | 0.23              | 0.38      | 0.56 | 0.37 |      |
| **Smoking**                            |                   |           |      |      |      |
| Never                                  | 1231/10777        | 0.92 (0.86, 0.98) | 0.91 (0.85, 0.98) | 1.13 (1.06, 1.21) | 1.05 (0.99, 1.12) |
| Ever                                   | 710/7036          | 0.87 (0.80, 0.95) | 0.89 (0.81, 0.97) | 1.11 (1.02, 1.21) | 1.03 (0.95, 1.11) |
| **P**                                  | 0.14              | 0.24      | 0.36 | 0.72 |      |
| **Frontline health care worker**        |                   |           |      |      |      |
| No                                     | 1213/12475        | 0.91 (0.85, 0.97) | 0.91 (0.84, 0.97) | 1.13 (1.06, 1.21) | 1.04 (0.98, 1.11) |
| Yes                                    | 728/5338          | 0.88 (0.81, 0.96) | 0.90 (0.82, 0.98) | 1.12 (1.03, 1.22) | 1.06 (0.98, 1.14) |
| **P**                                  | 0.71              | 0.63      | 0.34 | 0.84 |      |
| **Concern about COVID-19**              |                   |           |      |      |      |
| No                                     | 630/4467          | 0.89 (0.82, 0.98) | 0.88 (0.80, 0.97) | 1.09 (1.00, 1.20) | 1.05 (0.96, 1.14) |
| Yes                                    | 1311/13346        | 0.91 (0.85, 0.97) | 0.92 (0.86, 0.98) | 1.15 (1.08, 1.22) | 1.05 (0.99, 1.11) |
| **P**                                  | 0.57              | 0.61      | 0.48 | 0.85 |      |
| **Community interaction with people with presumed or documented COVID-19** |                   |           |      |      |      |
| No                                     | 1586/15956        | 0.90 (0.85, 0.95) | 0.91 (0.85, 0.96) | 1.13 (1.07, 1.20) | 1.05 (1.00, 1.11) |
| Yes                                    | 355/1857          | 0.89 (0.79, 1.01) | 0.86 (0.75, 0.98) | 1.09 (0.96, 1.24) | 1.03 (0.92, 1.15) |
| **P**                                  | 0.15              | 0.89      | 0.08 | 0.19 |      |
| **BMI, kg/m²**                         |                   |           |      |      |      |
| <25                                    | 673/7292          | 0.89 (0.82, 0.97) | 0.91 (0.83, 1.00) | 1.14 (1.04, 1.25) | 1.05 (0.97, 1.14) |
| 25 to <30                              | 682/5997          | 0.87 (0.60, 1.28) | 0.90 (0.82, 0.99) | 1.12 (1.02, 1.22) | 1.04 (0.95, 1.13) |
| ≥30                                    | 586/4524          | 0.90 (0.81, 0.99) | 0.88 (0.79, 0.98) | 1.12 (1.02, 1.23) | 1.06 (0.96, 1.15) |
| **P**                                  | 0.86              | 0.97      | 0.87 | 0.92 |      |
| **Pre-existing medical conditions**     |                   |           |      |      |      |
| No                                     | 1063/23131        | 0.90 (0.84, 0.96) | 0.89 (0.83, 0.96) | 1.10 (1.03, 1.18) | 1.07 (1.00, 1.14) |
| Yes                                    | 878/17863         | 0.92 (0.86, 0.99) | 0.92 (0.85, 1.00) | 1.14 (1.06, 1.23) | 1.01 (0.94, 1.08) |
| **P**                                  | 0.38              | 0.36      | 0.64 | 0.19 |      |
| **History of high blood pressure**      |                   |           |      |      |      |
| No                                     | 1428/13409        | 0.90 (0.85, 0.96) | 0.90 (0.84, 0.96) | 1.11 (1.05, 1.19) | 1.07 (1.01, 1.14) |
| Yes                                    | 513/4404          | 0.89 (0.80, 0.99) | 0.91 (0.80, 1.02) | 1.16 (1.05, 1.28) | 0.98 (0.90, 1.08) |
| **P**                                  | 0.53              | 0.41      | 0.58 | 0.12 |      |
| **History of high cholesterol**         |                   |           |      |      |      |
| No                                     | 1390/12771        | 0.90 (0.84, 0.95) | 0.89 (0.83, 0.95) | 1.11 (1.04, 1.18) | 1.05 (0.99, 1.11) |
| Yes                                    | 551/5042          | 0.90 (0.82, 1.00) | 0.92 (0.83, 1.02) | 1.18 (1.06, 1.30) | 1.04 (0.95, 1.14) |
| **P**                                  | 0.79              | 0.54      | 0.44 | 0.83 |      |
| **Type 2 diabetes**                    |                   |           |      |      |      |
| No                                     | 1829/16863        | 0.89 (0.85, 0.94) | 0.90 (0.85, 0.95) | 1.13 (1.07, 1.20) | 1.05 (1.00, 1.10) |
| Yes                                    | 112/950           | 1.01 (0.79, 1.28) | 0.96 (0.75, 1.23) | 1.05 (0.85, 1.31) | 1.01 (0.82, 1.25) |
| **P**                                  | 0.82              | 0.60      | 0.43 | 0.93 |      |

1Continuous analyses for a 1-SD increment. The multivariable model was adjusted for age (continuous), sex (women or men), race (white or nonwhite), 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 health care providers and PPE use (not frontline health care providers, frontline health care providers without adequate PPE, and frontline health care 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). AHEI, Alternate Healthy Eating Index; AMED, alternative Mediterranean Diet; COVID-19, Coronavirus Disease 2019; EDIH, Empirical Dietary Index for Hyperinsulinemia; EDIP, Empirical Dietary Inflammatory Pattern; PPE, personal protective equipment.

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

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-CoV-2 infection and severity. Although 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. Because our data were mainly collected before 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 availability

Data described in the article, 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://nurseshealthstudy.org/researchers (contact e-mail: nhsaccess@channing.harvard.edu) and https://sites.sph.harvard.edu/hbps/for-collaborators/.

References

1 Wu D, Wu T, Liu Q, Yang Z. The SARS-CoV-2 outbreak: what we know. Int J Infect Dis 2020;94:44–8.
2 Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci 2020;6(3):315–31.
3 Wolff D, Nee S, Hickey NS, Marschollek M. Risk factors for COVID-19 severity and fatality: a structured literature review. Infection 2021;49(1):15–28.
4 Hosseini A, Hashemi V, Shomali N, Asghari F, Akbari M, et al. Innate and adaptive immune responses against coronavirus. Biomed Pharmacother 2020;132:110859.
5 Catanzano M, Fugiano F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther 2020;5(1):84.
6 Suardi C, Cazzaniga E, Graci S, Dongo D, Palestini P. Link between viral infections, immune system, inflammation and diet. Int J Environ Res Public Health 2021;18(5):2455.
7 Maiorino MI, Bellastella G, Longo M, Caruso P, Esposito K. Mediterranean diet and COVID-19: hypothesizing potential benefits in people with diabetes. Front Endocrinol 2020;11:574315.
8 Moscatelli F, Sessa F, Valenzano A, Polito R, Monda V, Ciliberti G, et al. COVID-19: role of nutrition and supplementation. Nutrients 2021;13(5):976.
9 Greene MW, Roberts AP, Frugé AD. Negative association between Mediterranean diet adherence and COVID-19 cases and related deaths in Spain and 23 OECD countries: an ecological study. Front Nutr 2021;8:591964.
10 Merino J, Joshi AD, Nguyen LH, Leeming ER, Mazidi M, Drew DA, et al. Diet quality and risk and severity of COVID-19: a prospective cohort study. Gut 2021;70(11):2096–104.
11 Schwingshackl L, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. J Acad Nutr Diet 2015;115(5):780–800.e5.
12 Tabung FK, Brown LS, Fung TT. Dietary patterns and colorectal cancer risk: a review of 17 years of evidence (2000–2016). Curr Colorectal Cancer Rep 2017;13(6):440–54.
13 Chiue SE, Fung TT, Rimn EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142(6):1009–15.
14 Fung TT, Hu FB, McCullough ML, Newby PK, Willett WC, Holmes MD. Diet quality is associated with the risk of estrogen receptor–negative breast cancer in postmenopausal women. J Nutr 2010;136(2):466–72.
15 Tabung FK, Smith-Warner SA, Chavarro JE, Wu K, Fuchs SF, Hu FB, et al. Development and validation of an empirical dietary inflammatory index. J Nutr 2016;146(8):1560–70.
16 Tabung FK, Wang W, Fung TT, Hu FB, Smith-Warner SA, Chavarro JE, et al. Development and validation of empirical indices to assess the insulin-like potential of diet and lifestyle. Br J Nutr 2016;116(10):1787–98.
17 Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. Am J Pathol 2021;191(1):4–17.
18 Codo AC, Davanzo GG, Monteiro LB, de Souza GF, Muraro SP, Virgilio-da-Silva JV, et al. Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1α/glycolysis-dependent axis. Cell Metab 2020;32(3):437–46.e5.
19 Bao Y, Bertola ML, Lenart EB, Stamper MJ, Willett WC, Speizer FE, et al. Origin, methods, and evolution of the three Nurses’ Health Studies. Am J Public Health 2016;106(9):1573–81.
20 Rimm EB, Giovannucci EL, Willett WC, Colditz GA, Ascherio A, Rosner B, et al. Prospective study of alcohol consumption and risk of coronary disease in men. Lancet 1991;338(8765):464–8.
21 Yue Y, Petimar J, Willett WC, Smith-Warner SA, Yuan C, Rosato S, et al. Dietary flavonoids and flavonoid-rich foods: validity and reproducibility of FFQ-derived intake estimates. Public Health Nutr 2020;23(18):3295–303.
22 Yuan C, Spiegelman D, Rimm EB, Rosner BA, Stamper MJ, Barnett JB, et al. Validity of a dietary questionnaire assessed by comparison with multiple weighed dietary records or 24-hour recalls. Am J Epidemiol 2017;185(7):570–84.
23 Yue Y, Yuan C, Wang DD, Wang M, Song M, Shan Z, et al. Reproducibility and validity of diet quality scores derived from food-frequency questionnaires. Am J Clin Nutr 2022;115(3):843–53.
24 Al-Shaar L, Yuan C, Rosner B, Dean SB, Ivy KL, Clowery CM, et al. Reproducibility and validity of a semi-quantitative food frequency questionnaire in men assessed by multiple methods. Am J Epidemiol 2021;190(6):1122–32.
25 Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stamper MJ, Corsano KA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23(5):991–9.
26 Ainsworth BE, Haskell WL, Leon AS, Jacobs JD, Montoye HJ, Sallis JF, et al. Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25(1):71–80.
27 WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192–7.
28 Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med 2020;26(7):1037–40.
29 Rich-Ewards JW, Ding M, Rocheleau CM, Boiano JM, Kang JH, Becune I, et al. American frontline healthcare personnel’s access to and use of personal protective equipment early in the COVID-19 pandemic. J Occup Environ Med 2021;63(11):913–20.
30 Tabung FK, Wang W, Fung TT, Smith-Warner SA, Keum N, Wu K, et al. Association of dietary insulinlike potential and colorectal cancer risk in men and women. Am J Clin Nutr 2018;108(2):363–70.
31 Wang M, Spiegelman D, Kuchiba A, Lochhead P, Kim S, Chan AT, et al. Statistical methods for studying disease subtype heterogeneity. Stat Med 2016;35(5):782–800.
32 Kim H, Rehbolz CM, Hegde S, LaFuria C, Raghavan M, Lloyd JF, et al. Plant-based diets, pescatarian diets and COVID-19 severity: a population-based case–control study in six countries. BMJ Nutr Prev Heal 2021;4(1):257–66.
33 Tavakol Z, Ghannadi S, Tabesh MR, Al-Habchi F, Noormohammadpour P, Akbarpour S, et al. Relationship between physical activity, healthy lifestyle and COVID-19 disease severity: a cross-sectional study. Z Gesundh Wiss 2021 Feb 4 (Epub ahead of print; doi: 10.1007/s10389-020-01468-9).
34 Hosseini B, Berthon BS, Saedisomeilia A, Starkey MR, Collison A, Wark PAB, et al. Effects of fruit and vegetable consumption on some cardiovascular disease risk factors in people with diabetes. Gesundh Wiss 2021 Feb 4 (Epub ahead of print; doi: 10.1007/s10389-020-01468-9).
35 Li W, Liu Q, Chen Y, Yang B, Huang X, Li Y, et al. Effects of indoor environment and lifestyle on respiratory health of children in Chongqing, China. J Thorac Dis 2020;12(10):6327–41.
36 Angelidi AM, Kokkinos A, Katechaki E, Ros E, Mantzoros CS. Mediterranean diet as a nutritional approach for COVID-19. Metabolism 2021;114:154407.
37 Calder PC. Nutrition, immunity and COVID-19. BMJ Nutr Prev Health 2020;3(1):74–92.
38 Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: the inflammation link and the role of nutrition in potential mitigation. Nutrients 2020;12(5):1466.
39 Lim S, Bae JH, Kwon H-S, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol 2021;17(1):11–30.
40 Santos A, Magro DO, Evangelista-Poderoso R, Saad MJA. Diabetes, obesity, and insulin resistance in COVID-19: molecular interrelationship and therapeutic implications. Diabetol Metab Syndr 2021;13(1):23.
41 Leung C. Clinical features of deaths in the novel coronavirus epidemic in China. Rev Med Virol 2020;30(3):e2103.
42 Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. Medicine (Baltimore) 2020;99(47):e23315.
43 Belanger MJ, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. Covid-19 and disparities in nutrition and obesity. N Engl J Med 2020;383(11):e69.