

Dietary nutrients associated with preservation of lung function in Hispanic and non-Hispanic white smokers from New Mexico

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Background: COPD is the third leading cause of death in the United States. Cigarette smoking accelerates the age-related forced expiratory volume in 1 s (FEV₁) decline, an important determinant for the genesis of COPD. Hispanic smokers have lower COPD prevalence and FEV₁ decline than non-Hispanic whites (NHWs).

Patients and methods: A nutritional epidemiological study was conducted in the Lovelace Smokers cohort (LSC; n=1,829) and the Veterans Smokers cohort (n=508) to identify dietary nutrients (n=139) associated with average FEV₁ and its decline and to assess whether nutrient intakes could explain ethnic disparity in FEV₁ decline between Hispanics and NHW smokers.

Results: Nutrients discovered and replicated to be significantly associated with better average FEV₁ included magnesium, folate, niacin, vitamins A and D, eicosenoic fatty acid (20:1n9), eicosapentaenoic acid (20:5n3), docosapentaenoic acid (DPA; 22:5n3), docosahexaenoic acid (22:6n3), and fiber. In addition, greater intakes of eicosenoic fatty acid and DPA were associated with slower FEV₁ decline in the LSC. Among omega 3 polyunsaturated fatty acids, DPA is the most potent nutrient associated with better average FEV₁ and slower FEV₁ decline. Adverse effect of continuous current smoking on FEV₁ decline was completely negated in LSC members with high DPA intake (>20 mg/day). Slower FEV₁ decline in Hispanics compared to NHWs may be due to the greater protection of eicosenoic fatty acid and DPA for FEV₁ decline rather than greater intake of protective nutrients in this ethnic group.

Conclusion: The protective nutrients for the preservation of FEV₁ in ever smokers could lay foundation for designing individualized nutritional intervention targeting “optimal physiological levels” in human to improve lung function in ever smokers. Ethnic disparity in FEV₁ decline may be explained by difference in magnitude of protection of dietary intakes of eicosenoic fatty acid and DPA between Hispanics and NHWs.

Keywords: nutrientomics, spirometry, ethnic disparity

Background

COPD, characterized by a progressive and partially irreversible airflow limitation, is the third leading cause of death in the United States. Cigarette smoking, exposure to second-hand smoke, bacterial and viral infections, and indoor and outdoor air pollutants, are common risk factors, which may affect the maximally attained forced expiratory volume in 1 s (FEV₁) in early adulthood or accelerate the age-related FEV₁ decline at older age, two important determinants in the genesis of COPD.¹⁻³ Several dietary factors and patterns may be protective for obstructive lung diseases. Using cross-sectional or case-control designs, candidate dietary nutrients and food items including vitamins A, C, and E, β -carotene, omega 3 polyunsaturated fatty acids (n-3 PUFAs), magnesium,

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dietary fiber, and hard fruit such as apple were associated with better FEV₁ or lower prevalence of COPD.^{4–6} A few studies collected longitudinal spirometry data and identified greater intake of vitamin C and fresh fruit and serum carotenoids at baseline or increased consumption or level over time as being associated with slower FEV₁ decline, although the results were inconsistent.^{7–12} In addition, a prudent diet rich in fruit, vegetables, whole-meal cereals, and fish was inversely associated with prevalent COPD.^{9,13–15}

New Mexico (NM) has the highest percentage (47%) of Hispanics of any state with the majority of Hispanics born in the United States.¹⁶ The ancestry of NM Hispanics is mainly composed of 63% European and 35% Native American ancestry.^{1,17} NM Hispanic smokers have lower prevalence of COPD compared to non-Hispanic whites (NHWs) that may be attributed to lower exposure to cigarette smoke, slower FEV₁ decline, having Native American ancestry and protective sequence variants that are polymorphic only in Hispanics.^{1,18,19} The effect of dietary intakes on this ethnic disparity has never been explored before.

In this study, we used the validated Harvard food frequency questionnaire (FFQ) to assess dietary intake of 139 nutrients at study entry in current and former smokers from the Lovelace Smokers cohort (LSC; n=1,829) and the Veteran Smokers cohort (VSC; n=508). Protective dietary nutrients associated with better FEV₁ were discovered in the LSC and replicated in the VSC. We further assessed whether the nutrients associated with better FEV₁ had any effect on age-related FEV₁ decline in the LSC due to the availability of longitudinal spirometry data. Finally, the ethnic disparity of dietary intake of protective nutrients and their potential contribution to the ethnic disparity of FEV₁ decline were explored in 327 Hispanics and 1,502 NHWs in the LSC.

Methods

LSC and VSC

Enrollment in the LSC started in 2001 with the goal to conduct longitudinal studies on biomarkers of respiratory diseases, including COPD and lung cancer in biospecimens from smokers.²⁰ Enrollment was restricted to current and former smokers aged 40–74 years with a minimum of 10 pack-years of smoking. Cohort members returned approximately every 18 months, and a spirometry test was conducted at every visit by certified and registered respiratory therapists strictly adhering to the 1994 American Thoracic Society guidelines.²¹ The VSC began recruitment of smokers in 2000 with enrollment criteria similar to the LSC except that most VSC participants were males (96.7%) and had

smoked at least 100 cigarettes during their life time. All participants signed a consent form written in English, and the institutional review boards of the Lovelace Respiratory Research Institute (Western institutional review board) and New Mexico Veteran Health Care System approved all investigations using human tissues and clinical data.

Baseline dietary assessment

The English version of the validated Harvard semiquantitative FFQ was completed at study entry.²² The FFQ collects the consumption frequency and serving size for ~150 food items over the previous 12 months and has excellent coverage for food items of the US Southwestern style.²³ Daily estimates of the nutrient intakes are derived by summing over all foods, the products of the reported frequency of each food by the amount of nutrient in a specified (or assumed) serving of that food, based primarily on US Department of Agriculture publications.²² The applicability of this FFQ in New Mexicans is further introduced in Supplementary material. This study focused on 139 nutrients with <40% missing rate in 1,829 LSC and 508 VSC members. A convenient set of 28 LSC cohort members filled the FFQ for a second time at follow-up visits ~9.4 years after the study entry and these were used to assess the stability of the dietary pattern over time.

Statistical analysis

In discovery analysis, we assessed the association between dietary nutrients and repeated FEV₁ measurements collected at multiple visits in the LSC (n=1,829) using linear mixed effects (LME) model with a subject-specific random intercept. A total of 8,468 postbronchodilator FEV₁ measures were obtained from 1,829 LSC members over a median follow-up period of 5.3 years (interquartile range [IQR]: 1.5–10 years). The average interval between visits was 1.45 years with an IQR of 1.32–1.61 years. Covariates included baseline variables (eg, age, sex, ethnicity, smoking history [smoking status and pack-years], body mass index, educational level, and height), total calorie intake, and time since enrollment (TSE) at each PFT test. This analysis tested whether higher intake of protective or harmful nutrients was associated with on average better or worse FEV₁ across multiple visits. Nutrients associated with repeated spirometry measurements with false discovery rate (FDR) <0.05 in the LSC were further assessed in the replication cohort (VSC, n=508). Because only spirometry data at study entry were available from the VSC, multivariate linear regression was used to assess the association between nutrients and FEV₁. Nutrients associated with FEV₁ with FDR <0.05 in the VSC were deemed

as being replicated. Second, the effect of nutrients on FEV₁ decline was assessed in LSC members (n=1,499) with at least one follow-up visit and by including an interaction term between nutrient and TSE at each spirometry test in the LME model. In addition to the variables listed earlier, baseline FEV₁ was further included as an independent variable for adjustment. Third, the ethnic disparity in nutrient intakes was assessed using multivariate linear regressions with natural log transformed nutrients as the outcome which had improved normality of the residual and satisfied the homoscedasticity assumption.²² Covariates for adjustment included age, sex, smoking history (smoking status and pack-years), and total calorie intake. Finally, ethnic difference in magnitude of association between nutrients and FEV₁ decline was assessed in the LSC by including a three-way interaction term among dietary intake, ethnicity, and TSE in the LME model. All statistical analyses were conducted in SAS 9.4.

Results

Characteristics of the study subjects

A total of 327 Hispanics and 1,502 NHWs from LSC and 164 Hispanics and 344 NHWs from VSC who had complete data for dietary intake and spirometry data were studied (Table 1). VSC members were older and predominantly male and had more former smokers and Hispanics compared to the LSC members. In addition, VSC enrolled light smokers (<10 pack-years) who make up 16.7% of the cohort. The completeness of the FFQ and spirometry data at baseline was comparable between the two cohorts.

Stability of dietary intake pattern

A moderate to high correlation was identified for dietary nutrient intake between baseline and follow-up visits that were 9.4 years apart with a median spearman correlation coefficient >0.60. The median percentage of changes in nutrient levels in the second FFQ relative to the baseline one is 12.2% with an IQR of 6.7%–22.4%. These findings support a relatively stable dietary pattern over a decade for the studied population.

Nutrients affecting FEV₁

Thirty-three nutrient measurements were discovered to be associated with FEV₁ with FDR <0.05 (not shown) and were further tested in the VSC. Fifteen nutrient measurements that assessed the dietary intakes of one mineral (magnesium), four vitamins (folate, niacin, A, and D), four long-chain unsaturated fatty acids (eicosenoic fatty acid [20:1n9], eicosapentaenoic acid [EPA, 20:5n3], docosapentaenoic acid

Table 1 Characteristics of LSC and VSC members

Variable	LSC	VSC
n	1,829	508
Age (years, mean ± SD)	57.2±9.4	62.1±8.5
Sex (male, %)	22.4	96.7
Hispanics (%)	17.9	32.3
Current smokers (%)	55.7	37.0
Packyears (pys, median [Q1–Q3])	35.0 (26.0–49.0)	32.5 (15.0–58.0)
<10 (%)	0	16.7
10–29 (%)	33.4	28.8
29–43 (%)	33.4	17.0
≥43 (%)	33.2	37.4
Number of unanswered food items	0 (0–2)	0 (0–1)
Total calorie intake (kcal)	1,724.7 (1,343.7–2,177.4)	1,903.4 (1,405.3–2,493.5)
Number of spirometry (median [Q1–Q3])	4 (2–7)	1 ^a
Spirometry at baseline		
FEV ₁ (L/s, mean ± SD)	2.5±0.7	2.6±0.6
FVC (L, mean ± SD)	3.4±0.9	3.5±0.7
FEV ₁ /FVC (%; mean ± SD)	72.8±10.7	72.5±11.6

Note: ^aOnly spirometry data at study entry in the VSC was available for this study.
Abbreviations: LSC, Lovelace Smokers cohort; VSC, Veteran Smokers cohort; SD, standard deviation; Q, quartile; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

[DPA; 22:5n3], docosahexaenoic acid [DHA; 22:6n3]), and the Association of Official Agricultural Chemists (AOAC) fiber were significantly associated with greater FEV₁, while *trans*-oleic fatty acid measurement was associated with worse FEV₁ in the VSC (FDR <0.05; Table 2). A combinational effect of the protective nutrients (magnesium, folate, niacin, vitamins A and D, long chain N3 fatty acids [EPA + DPA + DHA], and AOAC fiber) was assessed by creating a score that sums the standardized intakes of these nutrients. The differences of FEV₁ between cohort members with high (upper quartile) versus low (lower quartile) scores were 183.4±42.2 mL/s (*P*<0.0001) in the LSC and 307.4±93.4 mL/s (*P*=0.0011) in the VSC.

Nutrients affecting FEV₁ decline

The effect of dietary nutrients on FEV₁ decline was assessed by including an interaction term between each individual nutrient and TSE in the LME model in 1,499 LSC members with ≥2 spirometry tests. This analysis was conducted for

Table 2 Nutrients associated with FEV₁ (mL/s) in the LSC and VSC^a

Nutrient (U/day) ^b	LSC (n=1,829)		VSC (n=508)	
	Estimate (SE)	FDR	Estimate (SE)	FDR
Minerals				
Magnesium (174.7 mg)	82.2 (20.0)	0.0027	202.6 (55.8)	0.011
Magnesium (144.7 mg) ^c	107.1 (24.2)	0.0014	156.8 (58.1)	0.031
Vitamins				
Total folate intake (478.6 µg)	61.4 (17.7)	0.010	136.1 (42.5)	0.021
Folic acid (411.0 µg)	43.5 (16.4)	0.039	112.2 (38.7)	0.026
Folate equivalents (860.5 µg)	52.6 (16.8)	0.022	128.1 (40.6)	0.021
Niacin (24.8 mg)	24.0 (7.8)	0.022	93.1 (33.2)	0.027
Vitamin A (9,160.2 IU)	37.6 (13.5)	0.030	66.7 (29.3)	0.050
Vitamin D (468.9 IU)	40.4 (15.2)	0.039	119.6 (41.8)	0.026
Fatty acids				
Eicosenoic fatty acid (135 mg)	34.4 (13.5)	0.049	70.6 (29.7)	0.045
EPA (100 mg)	17.9 (6.1)	0.025	34.0 (14.5)	0.045
DPA (20 mg)	29.9 (10.2)	0.025	68.0 (22.3)	0.021
DHA (150 mg)	27.6 (10.3)	0.039	61.4 (23.7)	0.033
EPA + DPA + DHA (310 mg)	28.0 (9.7)	0.025	57.0 (22.3)	0.033
EPA + DHA (290 mg)	27.6 (9.6)	0.025	55.8 (22.2)	0.034
trans-oleic (1.2 g)	-75.9 (29.8)	0.049	-112.3 (42.0)	0.031
AOAC fiber (10.5 g)	80.9 (20.3)	0.0032	97.8 (41.8)	0.045

Notes: EPA, eicosapentaenoic fatty acid 20:5n3; DPA, docosapentaenoic fatty acid 22:5n3; DHA, docosahexaenoic fatty acid 22:6n3; eicosenoic fatty acid 20:1n9. ^aIQR is used for calculating the estimate and SE. Association analysis in the LSC was conducted based on longitudinal spirometry data using LME model with adjustment for important covariates. ^bAssessment of total folate intake and folate equivalents includes all sources (ie, natural food, supplements, and fortified foods). Folic acid is from supplements and fortified foods. A total of 38% study subjects have missing data for trans-oleic fatty acid. ^cEstimate of intake without counting supplement.

Abbreviations: FEV₁, forced expiratory volume in 1 s; LSC, Lovelace Smokers cohort; VSC, Veteran Smokers cohort; SE, standard error; FDR, false discovery rate; AOAC, the Association of Official Agricultural Chemists; IQR, interquartile range; LME, linear mixed effects.

nutrients significantly associated with FEV₁ (Table 2) to minimize the number of comparisons and it found eicosenoic fatty acid and DPA significantly associated with slower FEV₁ decline ($P < 0.05$, Table 3).

Antagonism of nutrients against cigarette smoking induced FEV₁ decline

Cohort members were classified into continuous current smokers (n=507), continuous abstainers (n=620), quitters (current smokers at baseline who quit during follow-up visits and maintained the abstinence status afterward, n=215), and relapsers (n=157). Compared to continuous current smokers (-27.1±1.1 mL/s per year), continuous abstainers (-18.9 mL/s per year, $P < 0.0001$), quitters (-22 mL/s per year, $P = 0.0069$), and relapsers (-19.2 mL/s per year, $P = 0.0003$)

Table 3 The association between long chain unsaturated fatty acid and FEV₁ decline (mL/s) in the LSC (n=1,499)^a

Nutrient (U/day)	Time Estimate (SE) ^b	Nutrients		Time × nutrients	
		Estimate (SE)	P-value	Estimate (SE)	P-value
Eicosenoic fatty acid (135 mg)	-24.0 (1.1)	3.2 (5.3)	0.55	1.6 (0.6)	0.0064
EPA (100 mg)	-22.0 (0.7)	2.4 (2.5)	0.33	0.3 (0.3)	0.28
DPA (20 mg)	-23.1 (0.9)	3.5 (4.1)	0.40	1.2 (0.5)	0.022
DHA (150 mg)	-22.6 (0.9)	2.7 (4.2)	0.52	0.9 (0.5)	0.073
EPA + DPA + DHA (310 mg)	-22.3 (0.8)	3.2 (3.9)	0.41	0.7 (0.5)	0.14
EPA + DHA (290 mg)	-22.3 (0.8)	3.2 (3.9)	0.40	0.7 (0.5)	0.15

Notes: EPA, eicosapentaenoic fatty acid 20:5n3; DPA, docosapentaenoic fatty acid 22:5n3; DHA, docosahexaenoic fatty acid 22:6n3; eicosenoic fatty acid 20:1n9. ^aIQR is used for calculating the estimate and SE. Association analysis in the LSC was conducted based on longitudinal spirometry data using linear mixed effects model with adjustment for important covariates. ^b $P < 0.0001$.

Abbreviations: FEV₁, forced expiratory volume in 1 s; LSC, Lovelace Smokers cohort; SE, standard error; IQR, interquartile range.

had a significantly reduced FEV₁ decline. Eicosenoic fatty acid and DPA were converted into binary variables based on the median levels seen in the LSC to facilitate the assessment of three-way interactions among nutrients, smoking behavior change, and TSE using the LME model (Table 4). Continuous abstainers, quitters, and relapsers were combined into one group as noncontinuous current smokers because their FEV₁ decline rates were similar and the effect of nutrients on FEV₁ decline showed no difference among these three subgroups (all $P > 0.65$). Significant three-way interaction was identified among DPA intake status (>20 versus ≤20 mg/day), continuous current smoking, and TSE (6.4±3.0, $P = 0.031$,

Table 4 Antagonism of nutrients against cigarette smoking induced FEV₁ decline (mL/s) in the LSC (n=1,499)^a

Nutrient (U/day)	Time Estimate (SE) ^b	Continuous smoking		Time × continuous smoking	
		Estimate (SE)	P-value	Estimate (SE)	P-value
All	-19.6 (0.7)	8.5 (12.5)	0.50	-7.5 (1.3)	<0.0001
DPA^c					
>20 mg	-19.7 (1.0)	-5.2 (23.5)	0.82	-2.8 (2.5)	0.26
≤20 mg	-19.5 (0.9)	16.0 (14.9)	0.28	-9.2 (1.6)	<0.0001
Eicosenoic fatty acid^d					
>135 mg	-18.7 (1.0)	24.6 (19.3)	0.20	-7.5 (2.1)	0.0004
≤135 mg	-20.3 (0.9)	-0.3 (16.3)	0.99	-7.4 (1.7)	<0.0001

Notes: DPA, docosapentaenoic fatty acid 22:5n3. ^aAssociation analysis in the LSC was conducted based on longitudinal spirometry data using linear mixed effects model with adjustment for important covariates. ^b $P < 0.0001$. ^c P -value for three-way interaction among DPA, continuous smoking, and TSE =0.031. ^d P -value for three-way interaction among eicosenoic fatty acid, continuous smoking, and TSE =0.99.

Abbreviations: FEV₁, forced expiratory volume in 1 s; LSC, Lovelace Smokers cohort; SE, standard error; TSE, time since enrollment.

Table 5 Ethnic disparity in dietary intakes of eicosenoic fatty acid and DPA in the LSC and VSC^a

Cohort	Nutrient (U/day)	NHWs	Hispanics	P-value
LSC		n=1,502	n=327	
	Eicosenoic fatty acid (mg)	173.3 (120.1–250.1)	169.3 (120.1–260.1)	0.41
VSC	DPA (mg)	14.3 (10.1–30.1)	8.0 (10.1–30.1)	1.6×10 ⁻⁵
		n=344	n=164	
	Eicosenoic fatty acid (mg)	212.9 (140.1–320.1)	200.7 (130.1–305.0)	0.0016
	DPA (mg)	12.1 (10.1–30.1)	8.7 (10.1–20.1)	0.0092

Notes: DPA, docosapentaenoic fatty acid 22:5n3. ^aAge, sex, smoking history (smoking status and pack-years), BMI, educational level, and total calorie intake were adjusted in multivariate linear regression with natural log transformed nutrients as the outcome. Data are shown as geometric means with lower and upper quartiles. Total calorie intake was 1,890.2±716.1 versus 1,796.4±619.1 for Hispanics and NHWs (Wilcoxon test, $P=0.067$) in the LSC and 2,184.3±1,247.6 versus 2,001.3±793.4 for Hispanics and NHWs (Wilcoxon test, $P=0.65$) in the VSC.

Abbreviations: LSC, Lovelace Smokers cohort; VSC, Veteran Smokers cohort; NHWs, non-Hispanic whites; BMI, body mass index.

Table 4). Stratified analysis by DPA intake status identified that the adverse effect of continuous current smoking on FEV₁ decline was completely negated in LSC members with higher DPA intake status ($P=0.26$, Table 4). The association between continuous smoking and FEV₁ decline was independent of intake status of eicosenoic fatty acid.

Effect of dietary intakes of eicosenoic fatty acid and DPA on the ethnic disparity of FEV₁ decline

Our previous study identified that Hispanics smokers had significantly lower COPD prevalence than NHWs in the LSC and this ethnic disparity may be due to the slower FEV₁ decline in Hispanics.¹ We hypothesized that ethnic disparity in FEV₁ decline may be partially explained by the dietary intakes of eicosenoic fatty acid and DPA. We first assessed whether Hispanic smokers consume more protective nutrients. Surprisingly, although the total calorie intake was quite comparable between Hispanics and NHWs, Hispanics consume 44 and 28% less DPA than NHWs in LSC and VSC, respectively ($P<0.01$, Table 5). The difference of consumption of eicosenoic fatty acid between Hispanics and NHWs is very minimal in both cohorts (Table 5). Second, we

assessed whether protective nutrients have a stronger favorable association with FEV₁ decline in Hispanics compared to NHWs. A significant three-way interaction among DPA intake status, ethnicity, and TSE was identified (9.3 ± 3.6 , $P=0.0095$, Table 6), while the three-way interaction among eicosenoic fatty acid intake status, ethnicity, and TSE was of borderline significance (5.7 ± 3.3 , $P=0.082$, Table 6). Most importantly, the associations between greater intake status of DPA and eicosenoic fatty acid and reduced FEV₁ decline were 8.8- and 5.7-fold greater in Hispanics compared to NHWs for DPA and eicosenoic fatty acid, respectively (Table 6). Thus, the ethnic disparity in FEV₁ decline may be due to the greater protective effects on FEV₁ decline seen in Hispanics versus NHWs.

Discussion

Our comprehensive nutritional study through assessing dietary intake of 139 nutrients in 2,367 smokers from NM identified magnesium, folate, niacin, vitamins A and D, and long chain unsaturated fatty acids (eicosenoic fatty acid and n-3 PUFAs), and dietary fiber as associated with on average better FEV₁ in chronic smokers. In addition, the effect of these protective nutrients on lung function showed an obstructive

Table 6 Magnitude of association between dietary nutrients and FEV₁ decline (mL/s) in Hispanics and NHWs in the LSC (n=1,499)^a

Nutrient ^b	Ethnicity	Time	Nutrient		Time × nutrient	
		Estimate (SE) ^c	Estimate (SE)	P-value	Estimate (SE)	P-value
DPA ^d	Hispanics	-22.3 (1.8)	4.2 (26.4)	0.87	10.5 (3.4)	0.0020
	NHWs	-22.5 (0.8)	17.2 (10.8)	0.11	1.2 (1.3)	0.35
Eicosenoic fatty acid ^e	Hispanics	-22.0 (1.9)	-29.1 (26.5)	0.27	6.8 (3.1)	0.028
	NHWs	-22.5 (0.8)	17.6 (11.6)	0.13	1.2 (1.3)	0.34

Notes: DPA, docosapentaenoic fatty acid 22:5n3. ^aAssociation analysis in the LSC was conducted based on longitudinal spirometry data using linear mixed effects model with adjustment for important covariates. ^bEicosenoic fatty acid and DPA were converted into binary variables based on the median levels seen in the LSC (Table 4). ^c $P<0.0001$. ^dP-value for three-way interaction among DPA, ethnicity, and TSE =0.0095. ^eP-value for three-way interaction among eicosenoic fatty acid, ethnicity, and TSE =0.082.

Abbreviations: FEV₁, forced expiratory volume in 1 s; NHWs, non-Hispanic whites; LSC, Lovelace Smokers cohort; SE, standard error; TSE, time since enrollment.

pattern as their associations with FEV_1/FVC were significant as well (Table S1).²⁴ The differences of FEV_1 between cohort members consuming high (upper quartile) versus low (lower quartile) levels of individual protective nutrients ranged from 17.9 to 107.1 mL/s with a combinational effect of 183.4 mL/s in the LSC. The protective effects became even greater in an older population comprising of predominantly males (VSC). The factors contributing to the observed greater effects in the VSC compared to the LSC are largely unknown and may include sample size, sex difference, age, smoking status, etc. These differences are of substantial public health impact because normal FEV_1 loss per year in the LSC is ~22 mL/s per year and the FEV_1 difference between current and former smokers is 82 mL/s. Our study is also the first to identify two long chain unsaturated fatty acids (ie, eicosenoic fatty acid and DPA) associated with on average better FEV_1 through reducing age-related FEV_1 decline in moderate and heavy smokers. In addition, the effect of these two nutrients on lung function decline showed an obstructive pattern as their associations with FEV_1/FVC were significant as well (Table S2). Our findings together with others^{7-9,11,12} suggest that protective dietary nutrients may improve lung function through two hypothetical patterns: symptom-improving pattern for magnesium, folate, niacin, vitamins A and D, EPA, DHA, and dietary fiber (Figure 1A) and slowing the age-related lung function decline pattern for eicosenoic fatty acid and DPA (Figure 1B).

Among n-3 PUFAs, daily intake of n-3 DPA is <20% of EPA and DHA in the LSC. Similar dietary intake pattern was also observed in 13,000 Dutch adults.²⁵ However, the protective effect of DPA for average FEV_1 is the most potent, as per 100 mg increase in daily intake FEV_1 increases by 149.5 mL/s for DPA, 17.9 mL/s for EPA, and 18.4 mL/s for DHA. Furthermore, DPA is the only one that has a statistically significant association with a slower FEV_1 decline ($P=0.022$).

Among the three n-3 PUFAs, a more potent effect associated with DPA intake has also been seen in the Edinburgh Artery Study in which DPA was the only n-3 PUFA that reduced the likelihood of developing atherosclerosis.²⁶ In addition, in a multiethnic cohort of 2,837 American adults, dietary intake of DPA was the most potent n-3 PUFA associated with reduced risk for incident cardiovascular disease and coronary heart disease, and plasma phospholipid DPA had the strongest inverse correlation with systemic inflammation markers (ie, IL-6 and CRP).²⁷ The mechanism underlying the protective effect of DPA on lung function may be related to its anti-inflammatory, antiproteolytic, and antioxidative ability. EPA supplementation in macrophages exerts anti-inflammatory effects indirectly through its elongation to DPA that inhibited the proinflammatory mediators derived from cyclooxygenase metabolism.²⁸ In a rat model of pulmonary hypertension, oral administration of DPA for 3 weeks decreased NF- κ B and p38 MAPK activation, leading to a reduction in MMP-2, MMP-9, and VEGF expression levels in lung tissue homogenates.²⁹ The degradation of the extracellular matrix by specialized proteolytic enzymes such as matrix metalloproteinases has been shown to play a key pathogenic role in the development of important COPD phenotype emphysema.³⁰ In aged rats, DPA-supplemented diet restored the neuronal function through blocking oxidative changes as quantified by measuring 8-OHdG in the hippocampus and its subsequent activation of sphingomyelinase and caspase 3 activity.³¹ 8-OHdG is an indicator of reactive oxygen species-induced oxidative DNA damage, and compared to healthy smokers, smokers with COPD had significantly elevated levels of 8-OHdG in peripheral blood DNA, a biomarker highly correlated with 8-OHdG in the lung and reduced FEV_1 .³² The antioxidant role of DPA was further supported by the finding that a significant interaction between DPA intake

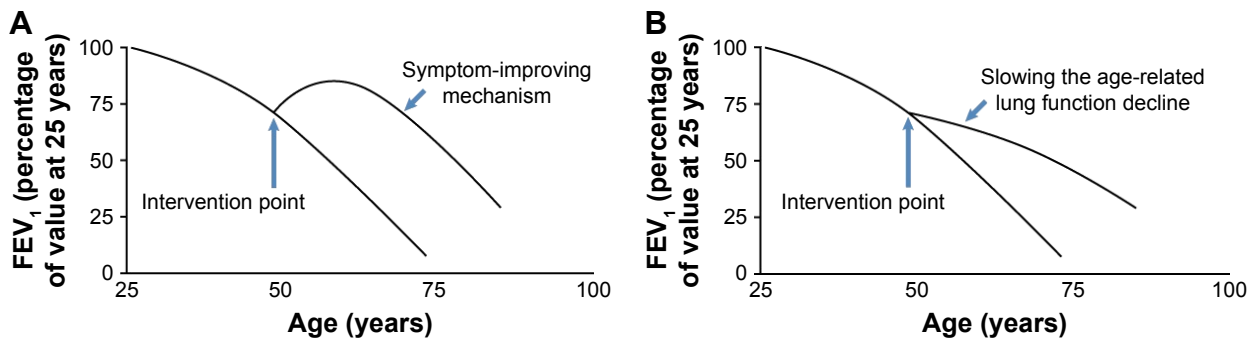


Figure 1 Two hypothetical models for the effect of dietary intervention on lung function.

Notes: (A) The nutrient supplementation at optimal physiological level may improve lung function that in turn offsets the age-related decline over time. In this pattern, the onset of the intervention improves the lung function without affecting the decline slope. (B) The intervention could directly slow down the age-related lung function decline as reflected by a less steep slope.

Abbreviation: FEV_1 , forced expiratory volume in 1 s.

and continuous smoking on FEV₁ decline was identified and the greater intake of DPA <20 mg/day completely negated the effect of continuous smoking on FEV₁ decline.

Eicosenoic fatty acid is a monounsaturated fatty acid with fatty fish as the main food source. Its average intake in human diet is 207.0 mg/day. Using the lipopolysaccharide (LPS)-induced RAW 264.7 macrophages model of inflammation, preincubation of macrophages with eicosenoic fatty acid significantly reduced LPS-induced inducible nitric oxide synthase (iNOS) levels.³³ iNOS plays an important role in determining nitrosative stress in the lung, as it produces large amounts of nitric oxide (NO) in response to many endogenous (such as chemokines and cytokines) and exogenous stimuli (such as bacterial toxins, virus infection, allergens, environmental pollutants [ozone, oxidative stress, and silica], hypoxia, and tumors).³⁴ NO reacts with superoxides to form the highly reactive peroxynitrites that have been shown to further produce airway inflammation and cause airway remodeling.^{35–37} However, cigarette smoking has been shown to reduce the proinflammatory factors induced iNOS expression in lung epithelial cells and exhaled NO levels among smokers.^{38,39} Interestingly, we did not find any interaction between eicosenoic fatty acid and continuous smoking on FEV₁ decline in our study. Taken together, our results suggest that greater intake of eicosenoic fatty acid may reduce the FEV₁ decline through alleviating iNOS-mediated nitrosative stress in a cigarette smoke-independent manner.

In this study, we provided the first evidence that instead of greater intakes of these two protective nutrients, it was the much larger protective effect of eicosenoic fatty acid and DPA on FEV₁ decline seen in Hispanics that may partially explain why Hispanics had slower FEV₁ decline. The underlying mechanism for dietary intake of DPA-mediated ethnic disparity in FEV₁ decline may be related to the ethnic disparity in the metabolism of DPA. Only weak associations were identified between fish consumption and plasma phospholipid DPA, suggesting that endogenous metabolism influences circulating DPA concentrations, for example, by chain elongation and desaturation of EPA.^{27,40,41} In addition, although average dietary intake of DPA in Hispanics was ~75% of that seen in NHWs, plasma phospholipid DPA level was very similar between the two ethnic groups.²⁷ Sequence variants of enzymes involved in this metabolic conversion are associated with DPA levels with several clearly showing ethnic differences in minor allele frequency between HapMap populations of European and Hispanic ancestry.⁴² For example, C allele of rs3734398 in elongase gene *ELOVL2* was associated with higher levels of

EPA and DPA and lower levels of DHA, suggesting that C allele decreases the conversion of EPA and DPA to DHA. Frequency of the C allele of rs3734398 was 0.44 and 0.71 in HapMap populations of European and Hispanic ancestry, respectively. Thus, greater C allele frequency in Hispanics may potentially contribute to greater circulating DPA concentrations, which in turn exaggerate the health effects of DPA. Thus, the larger protective effect of dietary intake of DPA on FEV₁ decline seen in Hispanics compared to NHWs may be due to greater metabolism favoring DPA accumulation and its subsequent lung effects in Hispanics.

This study has several strengths. First, this is one of the first studies taking an unbiased approach to identify nutrients associated with longitudinal spirometry measurements in moderate and heavy smokers. Second, a rigorous analytical plan that incorporated a discovery and replication approach and FDR correction was taken to minimize the chance of false-positive findings. Finally, NM populations provided a unique opportunity to reliably assess the ethnic disparity in lung function. NM Hispanics are distinct from Hispanic or Latino populations living in other states because they mainly include descendants of Spanish colonists who have settled the area of NM and Southern Colorado since the 1600s. Thus, our findings of ethnic disparity are not likely to be affected by immigration-related factors such as acculturation status, healthy migrant effect, and salmon bias. However, this may be an indicator that the study results may not be generalized to the overall Hispanic populations across the United States.

This study has two limitations. First, our studies and others have shown that the dietary pattern in adults is reasonably stable over several years.²² However, because the FFQ was not implemented in follow-up visits, we are not able to identify nutrients whose changes over time will affect lung function decline. The implementation of the FFQ in follow-up visits in the future would make this test possible. Second, the average lung function in the LSC members is relatively healthy with only 25% of subjects with COPD disease defined by Global Initiative for Chronic Obstructive Lung Disease criteria, most of whom have mild-to-moderate COPD. Thus, whether our findings could be generalized to COPD patients is uncertain.

Conclusion

Through an unbiased nutrientomics study, we identified magnesium, folate, niacin, vitamins A and D, long chain unsaturated fatty acids (eicosenoic fatty acid and n-3 PUFA), and dietary fiber associated with on average better FEV₁ in chronic smokers. In addition, dietary intakes of eicosenoic fatty acid and DPA were associated with reduced FEV₁ decline. These findings

could lay foundation for the design of an individualized nutritional intervention targeting “optimal physiological levels” in human to improve lung function in ever smokers. Furthermore, slower FEV₁ decline in Hispanics versus NHWs may be partially due to greater protective effect of eicosenoic fatty acid and DPA on age-related FEV₁ decline.

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Disclosure

The authors report no financial and nonfinancial competing interests in this work.

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Supplementary materials

Methods

Baseline dietary assessment

Cohort members completed the adult English version of validated Harvard Food Frequency Questionnaire (FFQ), a self-administered instrument that includes ~150 food items distributed within the eight major dietary categories, at the study entry.¹ The FFQ collects the consumption frequency and serving size of each specified food item during the past 12 months and has good coverage for food items of the US Southwestern style. The FFQ also has open-ended questions that collect use of food items consumed at least once per week but not listed in the eight major dietary categories. The validity of the application of the FFQ in New Mexico Hispanics was further supported by the results from a previous study that compared the energy and nutrient source between elderly Hispanics and non-Hispanic whites (NHWs) in New Mexico and identified no exclusive pattern for consumption of Southwestern regional foods in Hispanics compared to NHWs.² In addition, the estimated consumption of vitamins A and C in the current study was highly comparable to the data from a study that itemized all chili-containing traditional

Southwestern foods commonly consumed in New Mexico, suggesting the sufficiency of Harvard FFQ in capturing the chili-derived nutrients.² Furthermore, serum vitamins B12 and C and folate levels were reported to be significantly lower in Hispanics versus NHWs in a previous study of an elderly New Mexican population.³ These three vitamins also showed the ethnic difference in the dietary assessment (not shown). Estimates of daily nutrient intakes are derived by summing over all foods the products of the reported frequency of each food by the amount of nutrient in a specified (or assumed) serving of that food, based primarily on US Department of Agriculture publications.¹ Individual nutrient intakes were estimated with and without taking supplement use into consideration, and two values were provided. Because the number of nutrients in the output varied over time (from 104 to 254 nutrients from 2005 to 2014), a total of 139 nutrients with <40% missing rate was included in this study. Cohort members with extremely low or high total caloric intake were excluded.⁴ None of our participants were removed due to having >70 missing items on the FFQ. A total of 1,829 Lovelace Smokers cohort and 508 Veteran Smokers cohort members completed the FFQ that passed the quality check.

Table S1 Nutrients associated with FEV₁/FVC ratio (%) in the LSC and VSC^a

Nutrient (U/day) ^b	LSC (n=1,829)		VSC (n=508)	
	Estimate (SE)	FDR	Estimate (SE)	FDR
Minerals				
Magnesium (174.7 mg)	0.732 (0.396)	0.074	2.421 (1.024)	0.023
Magnesium (144.7 mg) ^c	1.256 (0.481)	0.025	2.161 (1.063)	0.045
Vitamins				
Total folate intake (478.6 µg)	1.019 (0.349)	0.025	2.231 (0.775)	0.009
Folic acid (411.0 µg)	0.671 (0.325)	0.048	1.858 (0.706)	0.013
Folate equivalents (860.5 µg)	0.857 (0.333)	0.025	2.144 (0.741)	0.009
Niacin (24.8 mg)	0.374 (0.154)	0.025	1.861 (0.605)	0.009
Vitamin A (9,160.2 IU)	0.754 (0.266)	0.025	1.245 (0.534)	0.023
Vitamin D (468.9 IU)	0.454 (0.300)	0.139	1.337 (0.765)	0.081
Fatty acids				
Eicosenoic fatty acid (135 mg)	0.638 (0.267)	0.025	1.541 (0.540)	0.009
EPA (100 mg)	0.290 (0.121)	0.025	0.740 (0.263)	0.009
DPA (20 mg)	0.513 (0.202)	0.025	1.393 (0.405)	0.009
DHA (150 mg)	0.456 (0.205)	0.034	1.319 (0.432)	0.009
EPA + DPA + DHA (310 mg)	0.460 (0.192)	0.025	1.229 (0.405)	0.009
EPA + DHA (290 mg)	0.452 (0.190)	0.025	1.207 (0.404)	0.009
<i>trans</i> -oleic (1.2 g)	-0.716 (0.559)	0.20	-1.847 (0.767)	0.022
AOAC fiber (10.5 g)	1.075 (0.403)	0.025	2.018 (0.761)	0.013

Notes: EPA, eicosapentaenoic fatty acid 20:5n3; DPA, docosapentaenoic fatty acid 22:5n3; DHA, docosahexaenoic fatty acid 22:6n3; eicosenoic fatty acid 20:1n9. ^aIQR is used for calculating the estimate and 95% CI. Association analysis in the LSC was conducted based on longitudinal spirometry data using linear mixed effects model with adjustment for important covariates. Association analysis in the VSC was conducted based on baseline spirometry data using linear regression with adjustment for important covariates.

^bAssessment of total folate intake and folate equivalents includes all sources (ie, natural food, supplements, and fortified foods). Folic acid is from supplements and fortified foods. A total of 38% study subjects have missing data for *trans*-oleic fatty acid. ^cEstimate of intake without counting supplement.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LSC, Lovelace Smokers cohort; VSC, Veteran Smokers cohort; SE, standard error; FDR, false discovery rate; AOAC, the Association of Official Agricultural Chemists; IQR, interquartile range.

Table S2 The association between long chain unsaturated fatty acid and FEV₁/FVC decline (%) in the LSC (n=1,499)^a

Nutrient (U/day)	Time	Nutrients		Time × nutrients	
	Estimate (SE) ^b	Estimate (SE)	P-value	Estimate (SE)	P-value
Eicosenoic fatty acid (135 mg)	-0.47 (0.02)	-0.048 (0.11)	0.67	0.032 (0.012)	0.0081
EPA (100 mg)	-0.44 (0.01)	0.010 (0.052)	0.85	0.019 (0.006)	0.0030
DPA (20 mg)	-0.46 (0.02)	-0.003 (0.087)	0.98	0.032 (0.011)	0.0028
DHA (150 mg)	-0.46 (0.02)	-0.037 (0.088)	0.67	0.031 (0.011)	0.0031
EPA + DPA + DHA (310 mg)	-0.45 (0.02)	-0.007 (0.083)	0.94	0.030 (0.010)	0.0028
EPA + DHA (290 mg)	-0.45 (0.02)	-0.006 (0.082)	0.94	0.030 (0.010)	0.0028

Notes: EPA, eicosapentaenoic fatty acid 20:5n3; DPA, docosapentaenoic fatty acid 22:5n3; DHA, docosahexaenoic fatty acid 22:6n3; eicosenoic fatty acid 20:1n9. ^aIQR is used for calculating the estimate and SE. Association analysis in the LSC was conducted based on longitudinal spirometry data using linear mixed effects model with adjustment for important covariates. ^bP<0.0001.

Abbreviations: FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LSC, Lovelace Smokers cohort; SE, standard error; IQR, interquartile range.

A convenient set of 28 cohort members completed an FFQ for a second time at follow-up visits ~9.4 years after the study entry. Spearman correlation analysis was conducted for 102 nutrients with no missing data for these 28 cohort members to assess the stability of the dietary pattern over time.

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