ORIGINAL RESEARCH

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Consumption of Fried Foods and Risk of Heart Failure in the Physicians' Health Study

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Background—Consumption of fried foods is highly prevalent in the Western dietary pattern. Though limited studies have reported a positive association between frequency of fried food intake and risk of coronary artery disease, diabetes, or hypertension, other investigators failed to report such an association. It is unclear whether intake of fried foods is associated with a higher risk of heart failure (HF). Hence, we sought to examine the association between the frequency of fried food consumption and the risk of HF.

Methods and Results—This was a prospective cohort study of 15 362 participants from the Physicians' Health Study. Fried food intake frequency was assessed by a food frequency questionnaire (1997–2001), and incident HF was captured by annual questionnaires. We used Cox regression to calculate hazard ratios (HRs) of HF. After an average follow-up of 9.6±2.4 years, a total of 632 new HF cases occurred in this cohort. Compared to subjects who reported fried food consumption of <1 per week, HRs (95% CI) for HF were 1.24 (1.04 to 1.48), 1.28 (1.00 to 1.63), and 2.03 (1.37 to 3.02) for fried food intake of 1 to 3/week, 4 to 6/week, and 7+/week, respectively, after adjustment for age, energy intake, alcohol use, exercise, smoking, and overall diet score (*P* linear trend, 0.0002). Similar results were obtained for intake of fried foods at home or away from home and among subjects with higher dietary score or HF without antecedent myocardial infarction.

Conclusions—Our data are consistent with a positive association of fried food intake frequency with incident HF in male physicians. **(*J Am Heart Assoc*. 2015;4:e001740 doi: 10.1161/JAHA.114.001740)**

Key Words: diet • epidemiology • heart failure • risk factor

Consumption of fried foods, such as French fries, fried chicken, and fried eggs, is common in the United States.[1] The process of frying can increase energy density of fried foods (absorption of fats)[2] and change nutrient composition, including generation of trans fatty acids.[3,4] In addition, the process of frying foods could increase the concentration of oxidized cholesterol[5] through inhibition of paraoxonase enzyme activity.[6] Excess consumption of energy-dense foods can lead to overweight,[7,8] with resulting elevated blood pressure[9] and development of diabetes,[10,11] 3 risk factors for heart failure (HF).[12] Whereas consumption of fried foods has been associated with a higher risk of coronary heart disease (CHD) in the Nurses' Health Study (NHS) and the Health Professional Follow-up Study (HPFS),[13] analysis of data from 40 000 adults in the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition showed no association of fried food consumption with CHD.[14] Despite inconsistent associations between fried food intake and risk factors for HF,[13–16] few studies have evaluated the association of fried food consumption with incident HF.[17,18] It is possible that fried food intake might just be a surrogate of poor dietary habits and may not be causally related to coronary artery disease (CAD) or HF risk. But such a hypothesis has not been well studied. In particular, it is unclear whether fried food consumption is associated with HF risk in subjects with the highest-quality diets, as assessed by alternate healthy eating index (aHEI) score. In the current project, we sought to prospectively test the hypothesis that frequency of fried food consumption is positively associated with the incidence of HF in male physicians after adjustment for major confounders. In secondary analyses, we evaluated whether such association was present (1) among people with the highest diet quality and (2) for HF with and without antecedent myocardial infarction (MI).

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Materials and Methods

Study Population

We used data from the Physicians' Health Study (PHS) I—a randomized trial of 22 071 male physicians designed to study the effects of low-dose aspirin and beta-carotene on cardiovascular disease (CVD) and cancer and PHS II, which was a randomized trial to assess the effects of vitamins on CVD and cancer in 7000 newly recruited physicians and 7641 male physicians from PHS I. A detailed description of PHS studies has been published previously.[19,20] Of the 29 071 PHS subjects, 21 075 subjects completed food frequency questionnaire (FFQ) and we excluded 654 subjects because of missing information on fried foods, 453 subjects for prevalent HF, 4131 for missing covariates relevant to compute aHEI, and 475 for other missing covariates. Thus, a final sample size of 15 362 subjects was used for current analyses. Each participant provided written informed consent and the institutional review board at Brigham and Women's Hospital (Boston, MA) approved the study protocol.

Fried Food Consumption

Information on the frequency of fried food consumption was obtained by using a FFQ. Participants were asked to report how often they ate fried food at home (excluding "Pam"-type spray) and how often they ate fried food away from home. Possible answers were less than once per week, 1 to 3/week, 4 to 6/week, and daily. Participants were also asked to report their average consumption of French fried potatoes (4 oz) during the past year. Possible answers were never or less than once per month, 1 to 3/month, 1/week, 2 to 4/week, 5 to 6/week, 1/day, 2 to 3/day, 4 to 5/day, and 6+/day. For current analyses, we summed frequencies of fried food consumption at home and away from home. For individuals who reported a greater frequency of French fried potato consumption than their reported fried food consumption both at home and away from home (3%), we used consumption of French fried potatoes to represent fried food consumption. Validity and reproducibility of FFQs have been previously published.[21,22]

Ascertainment of HF

Cardiovascular endpoint (including HF) ascertainment in PHS has been completed using annual follow-up questionnaires mailed to study subjects every 6 months during the first year and yearly thereafter. We have previously validated the diagnosis of self-reported HF diagnosis in this cohort in a subsample with a 91% positive predictive value comparing self-reported HF with HF defined based on review of medical records by 2 independent physicians (κ=0.92).[23]

Other Variables

We obtain information on demographic data, comorbidity, smoking, exercise, and dietary habits (using FFQ) at the time of assessment of fried food. We computed an overall dietary score (aHEI), as described elsewhere.[24]

Statistical Analyses

We classified each subject into one the following categories of fried food consumption: <1 per week; 1 to 3 per week; 4 to 6 per week; and 7+ per week. Baseline characteristics were contrasted across categories of fried food intake along with *P* value for trend using ANOVA for continuous variables and Mantel-Haenszel chi-square for categorical variables. We calculated the Spearman correlation coefficient between frequency of fried food intake and trans fatty acids. We computed person-time of follow-up from the assessment of fried foods until the first occurrence of (1) HF, (2) death, or (3) date of receipt of last follow-up questionnaire. We calculated the incidence rate of HF by dividing the number of cases by the corresponding person-time. We used Cox proportional hazard models to compute hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) using subjects in the lowest category of fried foods as the reference group. We used a priori knowledge to build sequential models. After the crude model, model 1 adjusted for age (5-year group); model 2 adjusted for age, energy intake (quintiles), alcohol intake (never/rarely, monthly, weekly, and daily), exercise (<1 day/week, 1 to 2 days/week, 3 to 4 days/week, and 5+ days/week), smoking (never, former, and current), and quintiles of aHEI. Additional control for trans fat, race, valvular disease, and atrial fibrillation did not alter the results (data not presented). We considered body mass index (BMI), diabetes, hypertension (HTN), and CAD as intermediate variables based on data in the literature showing associations of fried foods with those variables. Assumptions for the proportional hazard models were tested (by including main effects and product terms of covariates and log-transformed person-time) and were met (all *P* values >0.05).

In secondary analyses, we examined the association between frequency of fried food intake and HF with and without antecedent MI. However, we did not have adequate events (n=118) to obtain stable estimates for HF with antecedent MI. Furthermore, we conducted stratified analyses by the quality of the overall diet (upper 3 quintiles of aHEI vs. lower 2 quintiles) and whether fried foods were consumed at home or away from home. We tested statistical interaction using product terms in the Cox model. Because most people reported the use of vegetable oils for frying food (74%), we did not have enough subjects to analyze data for subjects that reported butter (11%), margarine (10%), or lard (0.3%) for

frying foods. Last, we repeated the main analysis after excluding HF events that occurred <24 months of follow-up. All analyses were completed using SAS software (version 9.3; SAS Institute, Cary, NC). Significance level was set at 0.05.

Results

Mean age was 65.8±8.9 years among 15 362 PHS participants analyzed. Median frequency of fried food consumption was <1 per week, and there was a weak positive correlation between fried food frequency and energy-adjusted dietary trans fatty acids (r=0.25; P<0.0001). Table 1 presents baseline characteristics of the study participants. Frequent consumption of fried foods was associated with higher BMI and higher energy intake; higher proportion of current smokers and never drinkers; lower prevalence of regular exercise and CAD; and higher prevalence of HTN and diabetes.

During an average follow-up of 9.6±2.4 years, 632 new cases of HF (4.1%) occurred in this cohort. Crude incidence rate of HF were 3.77, 4.64, 4.89, and 7.39 cases of HF per 1000 person-years for frequency of fried food intake of <1, 1 to 3, 4 to 6, and 7+/week, respectively (Table 2). Corresponding crude HRs (95% CI) were 1.0 (ref), 1.23 (1.03 to 1.46), 1.30 (1.02 to 1.65), and 1.96 (1.34 to 2.87), P for trend <0.0001. In the multivariable Cox regression model, adjustment for age, energy intake, alcohol use, exercise, smoking, and aHEI did not alter the results (HR [95% CI]=1.0 [ref], 1.24 [1.04 to 1.48], 1.28 [1.00 to 1.63], and 2.03 [1.37 to 3.02] across consecutive categories of fried foods; P for trend, 0.0002; Table 2). Exclusion of HF subjects with follow-up time below 2 years did not alter the conclusions (multivariable

Table 1. Characteristics of the 15 362 Participants in the Physicians Health Study by Fried Food Intake

	Fried Food Consumption				
	<1/Week (n=7853)	1 to 3/Week (n=5220)	4 to 6/Week (n=1869)	7+/Week (n=420)	P for Trend
Age, y	66.0±8.6	65.5±9.2	65.9±9.1	65.5±9.1	0.46
Body mass index, kg/m^2	25.4±3.2	26.0±3.4	26.4±3.5	26.7±4.0	<0.0001
Energy intake, Kcal	1604±484	1736±513	1884±566	2044±605	<0.0001
Trans fat, g/day	1.47±0.78	1.89±0.88	2.19±0.97	2.50±1.18	<0.0001
Race, % white	93.3	92.7	90.8	83.5	<0.0001
Smoking, %					
Never	56.1	54.0	51.7	50.7	<0.0001
Past	41.4	42.3	43.4	43.8	0.07
Current	2.50	3.70	4.92	5.48	<0.0001
Exercise, %					
<1 day a week	33.7	40.0	43.9	48.6	<0.0001
1 to 2 days a week	17.0	17.0	16.8	14.1	0.32
3 to 4 days a week	32.5	29.4	25.3	27.4	<0.0001
5 to 7 days a week	16.9	13.5	14.0	10.2	<0.0001
Alcohol intake, %					
Never	15.5	16.8	18.5	24.3	<0.0001
Monthly	7.28	7.59	8.67	11.67	0.002
Weekly	38.9	38.6	36.7	32.4	0.009
Daily	38.25	36.93	36.17	31.67	0.003
aHEI	49.7±11.7	46.2±10.7	45.2±10.9	43.9±10.5	<0.0001
Hypertension, %	43.3	46.4	47.1	47.6	<0.0001
Diabetes, %	5.6	7.7	8.1	11.4	<0.0001
Atrial fibrillation, %	7.9	8.5	8.6	7.4	0.41
CHD, %	12.8	10.6	10.7	10.5	0.0004
VHD, %	1.53	1.28	1.12	1.43	0.18

aHEI indicates alternate healthy eating index; CHD, coronary heart disease; VHD, valvular heart disease.

Table 2. Incidence Rates and Hazard Ratio of Heart Failure by Fried Food Intake in Male Physicians

Fried Food Intake	Cases/n	Incidence Rate*	Hazard Ratios (95% CI)		
			Crude	Model 1†	Model 2‡
<1/week	284/7853	3.77	1	1	1
1 to 3/week	231/5220	4.64	1.23 (1.03 to 1.46)	1.25 (1.05 to 1.48)	1.24 (1.04 to 1.48)
4 to 6/week	88/1869	4.89	1.30 (1.02 to 1.65)	1.29 (1.02 to 1.64)	1.28 (1.00 to 1.63)
7+/week	29/420	7.39	1.96 (1.34 to 2.87)	2.03 (1.39 to 2.98)	2.03 (1.37 to 3.02)
P for linear trend			<0.0001	<0.0001	0.0002

CI indicates confidence interval.
*Per 1000 person-years.
†Adjusted for age.
‡Adjusted for age, smoking, exercise, energy intake, alcohol, and diet score.

adjusted HR [95% CI]: 1.0 [ref], 1.24 [1.02 to 1.51], 1.27 [0.97 to 1.66], and 2.21 [1.46 to 3.32] from the lowest to the highest frequency of fried food intake; *P* for trend, 0.0002). As expected, additional adjustment for potential mediators, including BMI, diabetes, HTN, and CAD, attenuated slightly the results (HR [95% CI]: 1.0 [ref], 1.21 [1.01 to 1.44], 1.20 [0.94 to 1.54], and 1.76 [1.19 to 2.61] across consecutive categories of fried foods; *P* trend, 0.003).

In stratified analysis, we observed similar results when subjects reported their frequencies of consumption of fried foods at home (multivariable adjusted HR: 1.0 [ref], 1.04 [0.87 to 1.25], and 1.49 [1.05 to 2.11] for intake of fried foods at home of <1, 1 to 3, and 4+/week, respectively; *P* trend, 0.095). We collapsed the upper adjacent categories of exposure to obtain stable estimates. Corresponding HR (95% CI) for fried foods consumed away from home were 1.0 (ref), 1.44 (1.21 to 1.71), and 1.34 (0.80 to 2.27), *P* for trend 0.0001, *P* for interaction between place of fried food consumption and its frequency 0.56. When stratified by aHEI, the positive association between frequency of fried food intake and HF was only observed among people in the top 3 quintiles of aHEI (Table 3). When restricted to HF without antecedent MI (n=514), the positive relation of fried food intake frequency with HF was slightly stronger (multivariable adjusted HR: 1.0 [ref], 1.28 [1.05 to 1.57], 1.45 [1.11 to 1.89], and 2.33 [1.54 to 3.54] for fried food intake of <1, 1 to 3, 4 to 6, and 7+/week, respectively; *P* trend, <0.0001), *P* for interaction between HF with/without previous MI and frequency of fried food intake 0.56. Similar results were observed when restricted to subjects reporting the use of vegetable oil for frying foods (data not shown).

Table 3. Hazard Ratio (95% CI) of Heart Failure by Fried Food Intake Stratified by aHEI

Fried Food Intake	Hazard Ratios (95% CI)	
	Q1 to Q2*	Q3 to Q5*
<1/week	1	1
1 to 3/week	1.16 (0.87 to 1.55)	1.29 (1.02 to 1.62)
4+/week	1.30 (0.91 to 1.85)	1.48 (1.10 to 1.99)
P for linear trend	0.08	0.0006
P interaction†	0.76	

aHEI indicates alternate healthy eating index; CI, confidence interval.
*Adjusted for age, smoking, exercise, energy intake, alcohol, and aHEI score.
†*P* interaction between groups of aHEI and frequency of fried food intake 0.76.

Discussion

In this prospective cohort, we demonstrated that frequent consumption of fried foods was positively associated with the incidence of HF after adjustment for traditional confounding factors. Such an association persisted for subjects reporting consumption of fried foods at home or away from home and subjects who developed HF without antecedent MI. However, a statistically significant positive association was only observed among people in the top 3 quintiles of aHEI. To the best of our knowledge, this is the first study to examine whether frequency of fried food consumption is associated with a higher risk of HF. Nonetheless, limited studies have previously evaluated the relation of fried foods with risk factors of HF. Although findings have not been consistent across studies, reported positive relation of fried foods with HF risk factors lend support for a causal relation of our findings.

In a case-control design (485 survivors of first MI and 508 matched controls), fried food intake was not associated with the risk of MI in a multivariable model (OR [95% CI]: 1.0, 0.86 [0.50 to 1.48], 1.01 [0.59 to 1.75], 1.15 [0.66 to 2.03], and 1.06 [0.59 to 1.91] across consecutive quintiles of fried foods).[25] Furthermore, in a large prospective cohort of 40 757 adults in Spain, fried food consumption was not associated with incident CHD (adjusted relative risk [RR] [95% CI]: 1.01 [0.91 to 1.12] per 100-g increase of fried foods).[14] In

contrast, other investigators have reported positive association of fried foods with MI. In the INTERHEART study (a large case-control study involving 52 countries), being in the highest quartile of fried foods was associated with 13% higher odds of MI (95% CI: 2% to 25%), when compared to people in the lowest quartile after adjustment for demographics, lifestyle factors, and anthropometric measures.[26] Findings from 2 prospective cohorts (NHS and HPFS) also reported positive associations between fried food intake and incident CHD: multivariable adjusted pooled estimate of 1.0 (ref), 1.06 (0.98 to 1.15), 1.23 (1.14 to 1.33), and 1.21 (1.06 to 1.39), for fried food intake of <1, 1 to 3, 4 to 6, and 7+/week, respectively, *P* trend <0.001.[13]

Fried food consumption may also influence the risk of HF through other intermediate factors. For example, diabetes is a major risk factor for HF and several studies have reported positive relations of fried foods with diabetes. Bao et al.[27] reported a graded and positive association between frequency of fried food consumption and incidence of gestational diabetes (adjusted RR=2.18 [95% CI: 1.53 to 3.09] comparing fried food intake of 7+ to <1 times per week). Prospective data from the Black Women's Health Study found a 27% higher risk of diabetes with 2+/week intake of fried chicken, compared to never (adjusted RR=1.27 [95% CI: 1.02 to 1.57]).[28] Similar associations were observed in the NHS cohort, with a 70% higher risk of diabetes comparing fried food intake of 7+/week to <1/week (adjusted RR=1.70 [95% CI: 1.50 to 1.94]).[13] Last, data from the HPFS showed positive and graded relation between fried foods and incident diabetes (adjusted RR=1.69 [95% CI: 1.47 to 1.95]),[13] and in the Spanish cohort, consumption of fried foods was positively associated with incidence of HTN (*P* trend, 0.009)[16] as well as overweight/obesity (*P* trend, 0.02).[15,29]

Unlike baked or broiled fish that is associated with a lower risk of CHD[30] and HF,[31] fried fish has also been associated with non-fatal MI (adjusted RR=2.30 [95% CI: 1.18 to 4.46 comparing 3+ servings/week of fried fish with <1/month]).[32] Fried fish has also been associated with reduced ejection fraction, lower cardiac output, and higher systemic vascular resistance in older adults.[33] These data suggest that frequent intake of fried foods can heighten the risk of HF through several mechanisms and lend support for a causal association observed in our study. As expected, additional adjustment for BMI, diabetes, and prevalent CHD attenuated the effect size without loss of statistical significance (*P* trend, 0.003).

Could the observed positive association of frequent fried food intake with HF be a consequence of residual confounding by poor diet associated with fried food intake? We addressed this question by stratifying our analysis by the overall quality of diet. If such a hypothesis were true, then we would not observe an association of fried food intake frequency with HF in subjects with overall good quality of diet. The fact that we observed a positive and graded relation between frequency of fried food intake and incident HF in the upper 3 quintiles of aHEI lends support for an independent association of fried foods with HF. A lack of a significant association among people with lower aHEI score could be owing to a lack of statistical power to detect small effect size in a subgroup with elevated background risk of HF.

At present, it is unclear what specific biological mechanisms contribute to a heightened risk of HF when fried foods are consumed frequently. Frying increases the fat content of certain foods, including potatoes.[3] For example, in a study where pork loin meat was fried with sunflower oil at different temperatures, total fat content increased from 5.6% in fresh loin to 7.3%, 7.8%, and 12.1% at 160, 170, and 180°C, respectively.[5] In the same study, frying also increased the concentration of cholesterol oxidation products (ie, 7-ketocholesterol and 7beta-hydroxycholesterol) from <1 parts per million (ppm; μg/g of sample) in fresh loin to 10.89 ppm in fried loin.[5] Pan-frying salmon with olive oil or soya oil increased the fat content by 2-fold (with no difference between oils) and increased total cholesterol oxidized products by 4-fold (0.74, 2.98, and 3.35 μg/g fat in raw, fried with olive oil, and fried with soya oil, respectively).[2] The concentration of trans fatty acids in foods can also increase with frying.[34] Last, frying inhibits the activity of paraoxonase, an enzyme that inhibits low-density lipoprotein (LDL)-cholesterol oxidation.[6] Oxidized LDL plays an important role in the pathogenesis of atherosclerosis,[35] and there is a positive relation of trans fats with coronary disease[36] and major risk factor for HF.

Our study has some limitations. We were not able to assess the influence of type of oils used for frying foods on HF risk given that 74% of subjects used vegetable oils and very few used butter, margarine, or lard. However, the Spanish cohort did not find a difference between the use of olive oil or sunflower oil for frying foods on CHD risk.[14] We lacked information on absolute amounts of fried food consumed and on frying procedure (deep and pan frying), temperature and duration of frying, and how often oils were reused. We did not have adequate events to repeat analyses restricted to HF preceded by MI nor information on ejection fraction to further classify HF phenotype. The generalizability of our results is limited by the fact that all of our subjects were male physicians and mostly Caucasian. Despite excellent validation results of self-reported HF in a subsample, we cannot exclude potential misclassification of HF in this cohort, especially mild cases of HF. On the other hand, the large sample size, the long-term follow up, the prospective design, and the robustness of our findings in sensitivity analyses are major strengths of the present study.

In conclusion, our data showed a positive and graded association between fried food consumption and incidence of

HF. Confirmation of these findings is warranted along with exploration of underlying biological mechanisms.

Authors' Contribution

Djoussé: Designed study, collected data, conducted data analyses, obtained funding, and drafted manuscript. Petrone: Conducted statistical analyses and critically reviewed the manuscript. Gaziano: Collected data, provided significant advice for data analysis, critically reviewed the manuscript, and obtained funding.

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Disclosures

None.

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