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# Dietary Factors Related to Higher Plasma Fibrinogen Levels of Japanese-Americans in Hawaii Compared With Japanese in Japan

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## Abstract

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Disclosures
None.

**Objective—**We investigated whether dietary factors explain higher plasma fibrinogen levels in Japanese emigrants living a Western lifestyle in Hawaii compared with Japanese in Japan.

**Methods and Results—**Plasma fibrinogen and nutrient intakes were examined by standardized methods in men and women 40 to 59 years of age from a Japanese-American sample in Hawaii (100 men and 106 women) and 4 population samples in Japan (569 men and 567 women). Multiple linear regression models were used to examine the relationship between dietary factors and the plasma fibrinogen difference between Hawaii and Japan. Average plasma fibrinogen was significantly higher in Hawaii compared with Japan ($P<0.001$ in both genders). In multiple linear regression analyses with each dietary variable considered separately, body mass index reduced the plasma fibrinogen difference between Hawaii and Japan by 20.4%; iron intake (mg/1000 kcal) and estimated total sugar intake (%kcal) reduced this difference by 30.0% and 14.4%, respectively. In a model that included body mass index, iron, estimated total sugars, and caffeine (also age and gender), this difference was reduced by 61.3% (from 42.2 to 16.3 mg/dL).

**Conclusions—**Higher intake of iron, sugar, and caffeine, in addition to obesity, account largely for higher fibrinogen levels with Westernized lifestyle.

### Keywords

fibrinogen; nutrition; iron; sugar; caffeine; obesity; population study

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Japanese living in Japan have lower rates of coronary heart disease (CHD) than people in the United States and other Western countries,[1,2] including Japanese-Americans living in Hawaii.[3,4] In recent decades, these trends appear to have continued despite higher smoking rates, higher blood pressure levels, and increasing serum cholesterol levels in Japan with a more Westernized lifestyle.[1,5] Investigation of factors possibly affecting the CHD risk difference among genetically similar Japanese populations living in Japan and Hawaii is of interest in understanding these differences.

Elevated plasma fibrinogen level has been identified as a risk factor for CHD and stroke in both Western and Japanese populations.[6–8] A previous study found plasma fibrinogen levels among 75- to 93-year-old Japanese men living in Japan to be significantly lower than those among Japanese of similar age living in Hawaii.[9] Factors contributing to this difference remain unclear; few data are available on the role of dietary factors.

Here we report standardized comparisons of plasma fibrinogen and dietary factors between Japanese living in Japan and Japanese-Americans living a primarily Western lifestyle in Hawaii, from the INTERLIPID study, an ancillary investigation of the INTERMAP study on diet and blood pressure. We assessed whether dietary factors account for the difference in fibrinogen levels.

## Methods

INTERMAP is an international cooperative study on relationships between multiple dietary factors and blood pressure among 4680 participants 40 to 59 years of age from 17 diverse population samples in China, Japan, the United Kingdom, and the United States. INTERLIPID is an INTERMAP ancillary study focused mainly on relationships of these factors to serum lipids, blood analytes, and other factors in Japanese participants from Japan and Hawaii. Detailed methods of these 2 studies have been described previously,[10–12] and they are summarized below. Participants were men and women 40 to 59 years of age, recruited as random samples by 5 research centers, 4 in Japan, and 1 in Hawaii. Plasma fibrinogen was measured in 569 men and 567 women in Japan and in 100 men and 106 women in Hawaii. The ethical committees of the Shiga University of Medical Science, the Sapporo Medical University, the Kanazawa Medical University, the Wakayama Medical University, and the Pacific Health Research Institute approved the study protocol. Written informed consent was obtained from all participants.

Medical and lifestyle information, 4 in-depth 24-hour dietary recalls, and 2 timed 24-hour urine collections were obtained from each participant. For the INTERLIPID study, nonfasting blood was drawn; serum and plasma were centrifuged within 30 minutes and were stored immediately under refrigeration. Plasma fibrinogen, serum lipids, HbA1c, and other variables were measured in a central laboratory ≈6 to 12 months later. The thrombin coagulation time method was used to measure plasma fibrinogen concentration.

The 4 24-hour dietary recalls were conducted with each participant at 4 visits by specially trained dietary interviewers. Standardized quality control procedures were adopted to assess and maximize quality of dietary data throughout the data collection.[11,13] Nutrient intakes of individual participants are means of the 4 dietary recalls. Dietary data are expressed as nutrient densities as percent total kilocalories (kcal from nutrient/total kcal) × 100 for nutrients supplying energy and as nutrients per 1000 kcal (amount per 24 hours/total kcal) ×1000 for other nutrients.

For descriptive purpose, means and SDs or percentages were calculated for the Hawaii and Japan samples, with *t* tests or $\chi^2$ tests for Hawaii-Japan comparisons. Based on significant differences between Hawaii and Japan for individual nondietary and dietary variables, multiple linear regression models were used to examine relationships between dietary factors and the difference in plasma fibrinogen levels between Hawaii and Japan, with control for age, gender, body mass index (BMI), and current smoking. The basic model (model 1) included age, gender, and an indicator for Hawaii to obtain the age-gender-adjusted coefficient for the fibrinogen difference. Each factor was then added to model 1 separately, and percentage reduction from the model 1 coefficient was calculated to assess influence of the added variable on the fibrinogen difference. These models were computed with and without inclusion of BMI and current smoking (no, yes). Finally, dietary and nondietary variables were included in combinations to assess their joint impact on the fibrinogen difference. From 17 (of 41) dietary and nondietary variables that changed the fibrinogen difference by >5%, 9 variables were selected by the stepwise selection method ($P$<0.15) for multiple linear regression. This stepwise method is a modification of the forward-selection technique and differs in that variables already in the model do not necessarily stay there. These 9 variables were added successively 1 by 1 to model 1 to assess overall percentage reduction in the model 1 coefficient.

# Results

## Descriptive Statistics

Average age and height were similar for participants from Japan and Hawaii for each gender (Table 1). Average BMI was significantly higher in Hawaii than Japan (4.8 U higher in men; 2.5 U higher in women). Mean plasma fibrinogen concentration was significantly higher in Hawaii than Japan (34.1 mg/dL higher in men and 52.0 mg/dL higher in women). Serum total cholesterol, low-density lipoprotein cholesterol, and HbA1c were all significantly higher in Hawaii than Japan. Urinary timed 24-hour sodium and Na/K ratio were significantly higher in Japan than Hawaii. Percentage of current smokers among men was much higher in Japan than Hawaii. Some of these data are published.[12]

Mean intake of most nutrient variables differed significantly between Hawaii and Japan (Table 2). Total energy intake was significantly higher in Hawaii than in Japan in men but not women. Men and women in Hawaii reported significantly higher intakes of animal protein, total fat, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids (PFA), omega-6 fatty acids, trans fatty acids, estimated total sugars, vitamin A, beta carotene, magnesium, iron, and caffeine. Men and women in Hawaii reported significantly lower average intakes of vegetable protein, omega-3 fatty acids, dietary cholesterol, ratio PFA/ saturated fatty acids, total available carbohydrates, starch, alcohol, vitamin E, and selenium.

## Relation of Single Dietary Variables to the Fibrinogen Difference

With adjustment for age and gender in multiple regression analyses, plasma fibrinogen in Hawaii was higher than in Japan by 42.2 mg/dL ($P$<0.001) and by 37.1 mg/dL ($P$<0.001) in models with and without adjustment for BMI and current smoking, respectively (model 1; Table 3). Among 9 non-nutrient variables, 3 (BMI, current smoking, and education) changed the fibrinogen difference by >5% (Table 3). The fibrinogen difference was reduced by 20.4% with BMI in the model (model 2; Table 3) and was increased by 8.7% with current smoking in the model (model 3; Table 3).

Thirty-two dietary variables were included singly in the model; 11 dietary variables changed the fibrinogen difference by >5% in models with or without BMI and current smoking (Table 3). Among dietary variables, iron intake produced the largest reduction in the fibrinogen difference (model 12; Table 3). Several other variables produced reductions in the fibrinogen difference of 5% or more: estimated total sugars, starch, magnesium, vitamin A, beta carotene, caffeine, and urinary Na and Na/K ratio. Omega-3 PFA and dietary cholesterol increased the fibrinogen difference.

## Relation of Combinations of Dietary Variables to the Fibrinogen Difference

The stepwise selection method of multiple linear regression was done using site, age, gender, and 14 other variables (Table 3); each of these considered singly changed the fibrinogen difference by >5%. Nine variables, site, age, gender, BMI, iron, estimated total sugars, caffeine, current smoking, and urinary Na/K ratio, were selected at the 0.15 significance level. In this model, the site-fibrinogen coefficient (the fibrinogen difference) was 17.9 mg/dL (ie, reduced by 57.6% from the model 1 coefficient, with only age and gender [model 6; Table 4]). Two of these variables, current smoking and urinary Na/K ratio, increased the site-fibrinogen coefficient. With step-by-step addition of 7 other variables into the multiple linear regression model, the site-fibrinogen coefficient was gradually reduced from 42.2 mg/dL (model 1; Table 4) to 16.3 mg/dL (model 5; Table 4). Model 5 showed that inclusion of BMI, iron, estimated total sugar, and caffeine reduced the fibrinogen difference by 61.3%; this smaller difference was still significant ($P$=0.034). Results were similar when analyses were done for men and women separately.

## Discussion

In this standardized epidemiological study, ancillary to the INTERMAP study, we found significantly higher plasma fibrinogen levels in both Japanese-American men and women living in Hawaii compared with those of native Japanese. Multiple linear regression models showed that 61.3% of the fibrinogen difference was explained by higher BMI and higher intake of iron, sugar, and caffeine in Hawaii. Neither laboratory errors nor genetic differences appear to be responsible for the fibrinogen difference because quality control procedure assured high comparability of fibrinogen measurements, and the 2 study populations had a common genetic background.

A strength of this study is that data on nutrient intakes were from INTERMAP, a highly standardized international cooperative study on macronutrients and micronutrients and blood pressure. These data were from state-of-the-art nutritional surveys involving 4 in-depth 24-hour dietary recalls per person using comprehensive high-quality comparable databases on the nutrient composition of all reported foods from the 4 countries.[10–15]

Lower plasma fibrinogen levels have been reported in native Japanese compared with white Americans[16,17] and with Japanese-Americans.[9] The gender-specific magnitudes of the fibrinogen difference in this study were similar to these found previously. These studies tried to identify factors explaining the fibrinogen difference and reported that higher BMI contributed strongly to the difference. However, a large part of the difference could not be explained; further studies on dietary factors were suggested. In the present study, we again demonstrated that obesity was responsible for a sizable part (≈20%) of the fibrinogen difference and further recorded independent additional influences of dietary iron, sugars, and caffeine.

Free iron catalyzes free radical production, which generates a range of potent oxidants that can induce oxidation of lipids.[18,19] This pathway has been suggested as a possible explanation of the higher incidence of CHD in men than in premenopausal women because ferritin concentrations are 3× higher in men than in premenopausal women.[20,21] A Finnish cohort study reported that higher stored iron level and higher dietary iron intake were significant risk factors for CHD.[22] In our study, higher dietary iron intake of Hawaiian Japanese-Americans substantially explained the fibrinogen difference, independently of other nutrient intakes, BMI, and other possible confounders. To the best of our knowledge, there is no previous report on a relationship between iron intake and plasma fibrinogen;[23] a recent cross-sectional study in the United States found a positive relationship between ferritin, an indicator of body iron stores, and C-reactive protein, a marker of inflammation.[24] The authors hypothesized that iron-catalyzed oxidation of low-density lipoprotein is an important step in the development of inflammation and that such a mechanism may exist for another marker of inflammation: fibrinogen. Thus, the higher incidence of CHD in Western countries may be partly attributable to higher iron intake, causing higher fibrinogen level.

Our study suggested a substantial contribution of higher total sugar intake to higher fibrinogen levels in Hawaii. To the best of our knowledge, there is no previous report on a relationship between sugar intake and plasma fibrinogen.[23] A recent study reported an association between high dietary glycemic load and elevated C-reactive protein.[25] Inflammation may result from recurrent postprandial hyperglycemia, hyperinsulinemia, and insulin resistance that may occur with long-term high dietary glycemic load.[26] Therefore, foods with higher glycemic index, including sugars, may be related to elevated fibrinogen.

Findings on the relationship of caffeine consumption with plasma fibrinogen have been inconsistent.[23] Findings on coffee or tea consumption tend to be confounded because coffee and tea contain other nutrients such as flavonoids. Further studies on caffeine and fibrinogen are needed. Some previous studies showed an inverse association between omega-3 PFA and plasma fibrinogen, although these findings have been inconsistent.[23] In our study, higher omega-3 PFA intake in Japanese in Japan did not independently explain lower fibrinogen levels in Japan. This may be because of a relatively small difference in omega-3 PFA intake across the samples from Japan and Hawaii, with fish intake relatively high at both sites.

Limitations of these findings are as follows. First, the study design was cross-sectional. Thus, some high-risk individuals may have changed their diet. For example, obese people, whose fibrinogen levels are higher, may have reduced their sugar intake. This would have led to underestimation of the relationship between sugar intake and fibrinogen. Second, other markers of inflammation (eg, C-reactive protein, coagulation, and fibrinolysis) were not measured. Third, nutrient intakes were evaluated from 4 24-hour dietary recalls done in close proximity, hence the data may not fully represent long-term nutrient intake of some individuals.

As to possible practical implications of these findings, the INTERMAP study demonstrated that iron intake was similarly high in its 7 other US samples.[15] A US national survey found that 31% of iron intake was from meat sources.[27] A recent INTERMAP report also showed that dietary supplement users ingest iron at levels 5- to 6-fold above estimated average requirement.[28] High iron intake from meats and supplements may be problematic. High sugar intake from sweets and drinks in the United States has been repeatedly designated a remedial behavior adverse to health (eg, in relation to obesity). Importance of reducing this excess sugar intake may be a valuable public health implications of our study. Similarly, high caffeine intake from coffee, tea, soft drinks, etc, is amenable to reduction.

In conclusion, it was shown in this highly standardized epidemiological study performed as a part of the INTERMAP study that plasma fibrinogen levels in Japanese-Americans living in Hawaii are higher than in native Japanese and that >60% of this difference is attributable to higher intakes of iron, sugar, and caffeine in Hawaii, and to obesity. These dietary factors may, through their influence on fibrinogen, partly explain the large difference in CHD risk between Eastern and Western countries, independent of genetic factors.

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**TABLE 1.**

Descriptive Statistics, Japanese in Japan and Japanese-Americans in Hawaii, by Gender

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| **Variable** | **Japan** | **Hawaii** | ***P**** | **Japan** | **Hawaii** | ***P**** |
| No. of participants | 569 | 100 | | 567 | 106 | |
| Age, y | 49.5±5.3 | 50.6±5.2 | 0.078 | 49.2±5.3 | 49.8±4.9 | 0.332 |
| Height, m | 1.68±0.06 | 1.67±0.06 | 0.308 | 1.55±0.06 | 1.54±0.05 | 0.088 |
| Weight, kg | 66.9±8.8 | 80.0±14.7 | <0.001 | 55.5±8.0 | 60.8±12.6 | <0.001 |
| Body mass index, $kg/m^2$ | 23.7±2.7 | 28.5±4.6 | <0.001 | 23.2±3.1 | 25.7±5.4 | <0.001 |
| Systolic blood pressure, mm Hg | 120.4±12.9 | 119.0±11.8 | 0.329 | 114.1±14.0 | 115.2±13.7 | 0.451 |
| Diastolic blood pressure, mm Hg | 76.8±10.0 | 74.7±8.6 | 0.054 | 70.5±9.6 | 70.1±8.8 | 0.663 |
| Fibrinogen, mg/dL | 253.7±69.0 | 287.8±57.8 | <0.001 | 258.6±65.3 | 310.6±60.6 | <0.001 |
| Serum total cholesterol, mg/dL | 199.3±28.8 | 209.8±29.0 | <0.001 | 202.2±30.7 | 211.5±32.2 | 0.005 |
| HDL cholesterol, mg/dL | 53.7±13.7 | 50.2±10.2 | 0.014 | 60.0±14.2 | 59.7±13.2 | 0.827 |
| LDL cholesterol, mg/dL | 120.4±28.6 | 134.1±28.2 | <0.001 | 123.9±29.9 | 137.0±33.5 | <0.001 |
| HbA1c, % | 4.8±0.6 | 5.0±0.8 | <0.001 | 4.6±0.4 | 4.7±0.7 | 0.003 |
| Urinary sodium, mmol/24 hours | 210.4±56.6 | 174.4±52.3 | <0.001 | 186.1±53.2 | 133.5±44.6 | <0.001 |
| Urinary potassium, mmol/24 hours | 49±13 | 55±16 | <0.001 | 48±14 | 42±13 | <0.001 |
| Urinary Na/K ratio | 4.5±1.3 | 3.4±1.2 | <0.001 | 4.1±1.2 | 3.4±1.1 | <0.001 |
| Education, years | 12.3±2.1 | 15.4±2.5 | <0.001 | 11.6±2.0 | 15.6±2.3 | <0.001 |
| History of CVD, % | 1.2 | 3.0 | 0.179 | 0.4 | 0.9 | 0.402 |
| Drug treatment for hypertension, % | 6.0 | 28.0 | <0.001 | 6.5 | 24.5 | <0.001 |
| Taking vitamin/mineral supplements, % | 23.6 | 58.0 | <0.001 | 23.6 | 76.4 | <0.001 |
| On any special diet, % | 5.5 | 12.0 | 0.014 | 7.9 | 20.8 | <0.001 |
| Hours of heavy or moderate physical activity, hours/24 hours | 2.5±3.6 | 2.2±2.7 | 0.348 | 2.6±3.5 | 1.1±1.6 | <0.001 |
| Current smoker, % | 51.7 | 10.0 | <0.001 | 8.6 | 4.7 | 0.172 |
| No. of cigarettes per day, smokers | 22.6±9.3 | 14.2±10.6 | 0.006 | 11.5±7.0 | 13.0±7.6 | 0.646 |

Values are means±SD or percentage (prevalence).

* *P* values for Japan vs Hawaii by *t* test or $\chi^2$ test.

CVD indicates cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

## TABLE 2.

Nutrient Intake, Japanese in Japan and Japanese-Americans in Hawaii by Gender

| Variable | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Japan | Hawaii | *P** | Japan | Hawaii | *P** |
| Energy, kcal/day | 2280±428 | 2427±613 | 0.003 | 1797±324 | 1765±391 | 0.369 |
| Total protein, %kcal | 15.8±2.3 | 17.2±2.9 | <0.001 | 16.1±2.3 | 16.6±3.0 | 0.091 |
| Animal protein, %kcal | 8.9±2.5 | 11.1±3.2 | <0.001 | 8.8±2.4 | 10.4±3.5 | <0.001 |
| Vegetable protein, %kcal | 6.9±1.1 | 5.9±1.5 | <0.001 | 7.3±1.1 | 6.1±1.8 | <0.001 |
| Total fat, %kcal | 23.7±4.8 | 31.9±6.3 | <0.001 | 26.1±4.9 | 31.9±7.7 | <0.001 |
| SFA, %kcal | 6.1±1.6 | 9.1±2.2 | <0.001 | 7.1±1.8 | 9.4±2.7 | <0.001 |
| MFA, %kcal | 8.6±2.1 | 11.9±2.8 | <0.001 | 9.4±2.2 | 11.7±3.6 | <0.001 |
| PFA, %kcal | 6.2±1.5 | 7.5±1.8 | <0.001 | 6.6±1.4 | 7.5±2.3 | <0.001 |
| PFA/SFA ratio | 1.1±0.3 | 0.9±0.2 | <0.001 | 1.0±0.3 | 0.9±0.3 | <0.001 |
| Omega-3 PFA, %kcal | 1.3±0.4 | 0.9±0.3 | <0.001 | 1.4±0.4 | 0.9±0.3 | <0.001 |
| Omega-6 PFA, %kcal | 4.8±1.3 | 6.8±1.7 | <0.001 | 5.2±1.3 | 6.7±2.1 | <0.001 |
| Total trans fatty acid, %kcal | 0.3±0.2 | 1.5±0.6 | <0.001 | 0.5±0.3 | 1.6±0.7 | <0.001 |
| Cholesterol, mg/1000 kcal | 195.7±7.4 | 128.9±49.4 | <0.001 | 198.7±66.7 | 134.0±57.8 | <0.001 |
| Keys dietary lipid score | 28.7±6.0 | 31.2± 7.6 | <0.001 | 31.0±6.5 | 32.2±9.5 | 0.111 |
| Total available carbohydrate, %kcal | 52.2±7.7 | 48.1±7.6 | <0.001 | 56.2±6.4 | 50.9±8.7 | <0.001 |
| Starch, %kcal | 35.4±8.0 | 26.6±5.5 | <0.001 | 35.6±6.5 | 27.6±6.6 | <0.001 |
| Total dietary fiber, g/1000 kcal | 6.9±1.9 | 8.3±2.3 | <0.001 | 8.9±2.3 | 9.1±3.5 | 0.474 |
| Estimated total sugars, %kcal | 13.2±3.8 | 20.1±7.2 | <0.001 | 15.9±4.1 | 21.8±6.5 | <0.001 |
| Alcohol, g/day | 28.0±25.7 | 10.0±15.8 | <0.001 | 4.0±8.3 | 1.4±4.0 | 0.002 |
| Vitamin A, IU/1000 kcal | 2760±1851 | 4079±2772 | <0.001 | 3526±2034 | 5074±4161 | <0.001 |
| Retinol, mcg/1000 kcal | 182.9±361.6 | 133.0±104.0 | 0.171 | 177.2±236.6 | 178.0±244.9 | 0.974 |
| Beta-carotene, mcg/1000 kcal | 1290±877 | 2178±1636 | <0.001 | 1762±1162 | 2684±2499 | <0.001 |
| Vitamin C, mg/1000 kcal | 56.3±36.1 | 58.6±37.0 | 0.564 | 75.3±40.8 | 63.7±37.1 | 0.007 |
| Total vitamin E, mg ATE/1000 kcal | 4.6±1.0 | 4.3±1.2 | 0.012 | 5.3±1.6 | 4.6±1.8 | <0.001 |
| Calcium, mg/1000 kcal | 270.1±91.5 | 277.1±118.9 | 0.502 | 341.2±113.0 | 301.8±111.4 | 0.001 |
| Magnesium, mg/1000 kcal | 128.0±23.4 | 166.7±45.3 | <0.001 | 140.9±25.3 | 161.7±42.6 | <0.001 |
| Iron, mg/1000 kcal | 5.1±1.1 | 8.5±2.0 | <0.001 | 5.6±1.1 | 8.7±2.1 | <0.001 |

| Variable | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Japan | Hawaii | *P** | Japan | Hawaii | *P** |
| Phosphorus, mg/1000 kcal | 545±89 | 585±118 | <0.001 | 580±97 | 576±95 | 0.680 |
| Selenium, mcg/1000 kcal | 84.7±32.9 | 73.6±15.0 | 0.001 | 84.7±32.2 | 71.1±15.4 | <0.001 |
| Caffeine, mg/1000 kcal | 69.7±50.9 | 108.0±89.8 | <0.001 | 67.6±43.8 | 100.9±94.8 | <0.001 |

Values are means±SD.

SFA indicates saturated fatty acids; MFA, monounsaturated fatty acids; total available carbohydrate, exclusive of dietary fiber; estimated total sugars, total available carbohydrate minus starch; ATE, alpha-tocopherol equivalents.

* *P* values for Japan vs Hawaii by *t* test.

**TABLE 3.**

Relation of Variables Considered Singly to Hawaii–Japan Difference in Plasma Fibrinogen

| Model | Variables in Multiple Linear Regression Model | Model Without BMI and Current Smoking | Model With BMI and Current Smoking |
|---|---|---|---|
| 1 | Site (Hawaii/Japan), age, gender | 42.2* (<0.001)† | 37.1 (<0.001) |
| | | | −12.0%‡ |
| 2 | Model 1+BMI, kg/m$^2$ | 33.6 (<0.001) | – |
| | | −20.4%‡ | |
| 3 | Model 1 +current smoking (no, yes) | 45.8 (<0.001) | – |
| | | +8.7%‡ | |
| 4 | Model 1 +education, years | 41.0 (<0.001) | 34.8 (<0.001) |
| | | −2.7%‡ | −6.3%§ |
| 5 | Model 1 +urinary sodium, mmol/24 hours | 42.3 (<0.001) | 34.1 (<0.001) |
| | | +0.2%‡ | −8.1%§ |
| 6 | Model 1 +urinary Na/K ratio | 40.4 (<0.001) | 33.7 (<0.001) |
| | | −4.1%‡ | −9.2%§ |
| 7 | Model 1 +omega-3 PFA, %kcal | 44.4 (<0.001) | 38.6 (<0.001) |
| | | +5.3%‡ | +4.0%§ |
| 8 | Model 1+cholesterol, mg/1000 kcal | 45.1 (<0.001) | 39.5 (<0.001) |
| | | +7.0%‡ | +6.5%§ |
| 9 | Model 1 +starch, %kcal | 39.7 (<0.001) | 35.4 (<0.001) |
| | | −5.9%‡ | −4.6%§ |
| 10 | Model 1 +estimated total sugars, %kcal | 38.1 (<0.001) | 31.8 (<0.001) |
| | | −9.7%‡ | −14.4%§ |
| 11 | Model 1+magnesium, mg/1000 kcal | 40.9 (<0.001) | 34.4 (<0.001) |
| | | −3.0%‡ | −7.2%§ |
| 12 | Model 1+iron, mg/1000 kcal | 32.8 (<0.001) | 26.0 (<0.001) |
| | | −22.2%‡ | −30.0%§ |
| 13 | Model 1+vitamin A, IU/1000 kcal | 40.6 (<0.001) | 35.1 (<0.001) |
| | | −3.7%‡ | −5.4%§ |

| Model | Variables in Multiple Linear Regression Model | Model Without BMI and Current Smoking | Model With BMI and Current Smoking |
|---|---|---|---|
| 14 | Model 1+beta-carotene, mcg/1000 kcal | 40.3 (<0.001) | 34.5 (<0.001) |
| | | −4.4%[‡] | −7.1%[§] |
| 15 | Model 1+caffeine, mg/1000 kcal | 39.7 (<0.001) | 34.8 (<0.001) |
| | | −5.9%[‡] | −6.3%[§] |

[*] Coefficient for difference in fibrinogen (mg/dL) between Hawaii and Japan

[†] *P* value for site-fibrinogen coefficient

[‡] percent change in site-fibrinogen coefficient compared with model 1 without BMI and smoking

[§] percent change in site-fibrinogen coefficient compared with model 1 with BMI and smoking.

Detailed data not shown for variables influencing fibrinogen coefficient <5.0%.

## TABLE 4.

Relation of Combinations of Variables to Hawaii–Japan Difference in Plasma Fibrinogen

| Model | Variables in Multiple Linear Regression Model | Fibrinogen |
|---|---|---|
| 1 | Site (Hawaii/Japan), age, gender | 42.2[*] (<0.001)[†] |
| 2 | Model 1+BMI, $kg/m^2$ | 33.6 (<0.001) |
| | | −20.4%[‡] |
| 3 | Model 2+iron, mg/1000 kcal | 24.9 (<0.001) |
| | | −41.0%[‡] |
| 4 | Model 3+estimated total sugars, %kcal | 18.0 (0.019) |
| | | −57.3%[‡] |
| 5 | Model 4+caffeine, mg/1000 kcal | 16.3 (0.034) |
| | | −61.3%[‡] |
| 6[§] | Model 5+current smoking, urinary Na/K ratio | 17.9 (0.020) |
| | | −57.6%[‡] |

[*] Coefficient for difference in fibrinogen (mg/dL) between Hawaii and Japan

[†] *P* value for site-fibrinogen coefficient

[‡] percent reduction in site-fibrinogen coefficient compared with model 1

[§] nine variables in model 6 (site, age, gender, BMI, iron, estimated total sugars, caffeine, current smoking, and urinary Na/K ratio) were selected in the multiple linear regression model by stepwise selection method ($P<0.15$) from 17 variables shown in Table 3.