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Title:

REPORTED FRIED FOOD CONSUMPTION AND THE INCIDENCE OF HYPERTENSION IN A SPANISH COHORT: THE SUN PROJECT

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MAM-G helped to design the study and collect data. MB-R and CS-O analyzed the data and drafted the manuscript. AG, IZ, FJB-G edited and critically reviewed the manuscript.

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Key words: Hypertension, fried foods, cohort study.

Abstract

Reported associations between consumption of fried foods and obesity or weight gain make likely that fried food consumption might also be linked with the development of hypertension. However, evidence from long-term prospective studies is scarce. Therefore, the aim of our study was to longitudinally evaluate this association in a prospective cohort. The SUN project is a Mediterranean cohort study of university graduates conducted in Spain, that started in December 1999 and until now it is permanently open. For the present analyses we included 13,679 participants (5,059 men and 8,620 women), free of hypertension at baseline with a mean age of 36.5 y (SD:10.8). Total fried food consumption was estimated at baseline. The outcome was the incidence of a medical diagnosis of self-reported hypertension during follow-up. To assess the relationship between fried food consumption and the subsequent risk of developing incident hypertension during follow-up, Cox regression models were fitted. During a median follow-up of 6.3 years, 1,232 incident cases of hypertension were identified. After adjusting for potential confounders, the adjusted hazard ratio for developing hypertension was 1.18 (95% CI: 1.03-1.36) and 1.21 (95% CI: 1.04-1.41) for the categories of consumption of 2-4/week and >4/week respectively, compared to those who consumed <2 servings/week (p for trend 0.020). In conclusion, our findings suggest that a more frequent consumption of fried foods at baseline was associated with higher risk of hypertension during follow-up in a cohort of university graduates.

Key words: Hypertension, fried foods, cohort study.

Introduction

Hypertension is a strong and modifiable determinant for the development of several chronic diseases (1). Hypertension is the first leading global risk factor for mortality in the world. It is responsible for 13% of deaths (2), and 92 million disability-adjusted life-years (DALYs) (6% of the total). Therefore, complications of hypertension account for 9.4 million deaths worldwide yearly (3) and it is responsible for at least 45% of deaths due to heart disease, and 51% of deaths due to stroke(4).

Available evidence supports the important role of food habits in the etiology of hypertension (5). Cooking methods may modify the role of some foods or nutrients with respect to the risk of hypertension. Among cooking methods, frying is one of the most common methods in Western countries. Fried food consumption is increasing due to its desirable characteristic flavor, brown color, and crispy texture, which make fried foods very popular to consumers (6). The complexity of the frying process consist in many factors that are implicated: Factors that are dependent on the process itself and other factors related to the type of food and fat that are used for frying (7). According to previous studies such as the Seguimiento Universidad de Navarra (SUN) cohort study (8) and the Pizzarra study (9), in Spain most people used olive oil for frying at home. And in contrast the most common oil used for frying away from home especially by the fast-food restaurants is the corn oil (10).

In Spain, frequent fried food consumption has been linked to a higher risk of overweight/obesity (8,11). This association together with some biological mechanisms (trans-fatty acids produced during the frying process may cause an impaired endothelial function which will increase blood pressure) (12), make likely that fried food consumption might also be associated with a higher risk of hypertension. Evidence from epidemiological studies linking fried food consumption and hypertension is scarce and

inconsistent. A cross-sectional study conducted in Spain found that a high prevalence of hypertension was associated with the consumption of fried foods (especially when these foods were fried with vegetable reused oils such as sunflower oil) (13). More evidence exists on the relationship between fried foods consumption and cardiovascular disease. However, results on fried food consumption and cardiovascular disease are inconsistent: one case-control study (14) and one cohort study (15) found a positive association and other cohort study (16) and a case control study (17) reported no association. It is widely known that unhealthy lifestyles are an important factors affecting high blood pressure such as overweight/obesity, physical inactivity, alcohol intake, smoking status among others (18). One clinical trial found that changes in unhealthy lifestyles (for example changing the cooking method frying food for boiling among others) was beneficial in controlling blood pressure and obesity in general population (19).
There are no published results from large prospective studies assessing the role of fried food consumption on the development of hypertension. Our objective was to prospectively evaluate the potential association between fried food consumption and the risk of hypertension in a Mediterranean cohort.

Subjects and methods

Study population

The SUN project is a Spanish, multipurpose, dynamic, and prospective cohort study that was designed to assess associations between diet and the occurrence of several diseases and chronic conditions including hypertension (20). All participants included in the study are university graduates. They were followed-up every two years by mailed questionnaires. Recruitment of participants started in December 1999, and it is permanently open. Detailed information about the design and methods of the SUN

project has been published elsewhere (20). Up to September 2009, 20,335 participants were recruited. We excluded 2,283 participants with prevalent hypertension; 1,747 participants who reported values for total energy intake at baseline out of predefined limits (less than 800 kcal/d in men and 500 kcal/d in women or more than 4,000 kcal/d in men and 3,500 kcal/d in women) (21); 1,251 participants with chronic diseases at baseline (including cancer, diabetes or cardiovascular disease); 1,178 participants without any follow-up who were considered lost to follow-up (retention rate: 92%); and finally we excluded 197 participants with missing values in variables of interest, leaving a total of 13,679 participants available for the final analysis **(Figure 1)**.

The Institutional Review Board of the University of Navarra approved the study. Voluntary completion of the first self-administrated questionnaire was considered to imply informed consent.

Dietary assessment

A previously validated 136-items semi-quantitative food frequency questionnaire (FFQ) that measure past-year food intake was included in the baseline questionnaire (22). Nutrient scores were calculated as frequency multiplied by nutrient composition of specified portion sizes. For each food items, frequencies of consumption were measured in 9 categories (from never/almost never considering as almost never those who consumed the specific item less than "once per month" to >6 servings/day). Frequency of fried food consumption was evaluated in 2 of these items: the consumption of fried food at home and the consumption of fried food away from home. The total consumption of fried foods per person was estimated using the sum of these two items. In addition, the total amount in grams of fried foods consumed was estimated by adding the proportion of fried foods from the rest of items in the FFQ. The proportion of consumption as a fried food according to typical Spanish culinary uses was multiplied

by the reported frequency in the questionnaire (i.e. if the participant reported he/she ate 1 portion of fried potatoes we multiplied by 1, on the other hand if he/she reported 1 portion of meat we multiplied by 0.5 because we assumed that meat is consumed as a fried food half of the times, taking into account the typical culinary uses in Spain). This approach has been used successfully in a previous study of the SUN cohort (8). And finally an additional question was also assessed at baseline questionnaire; "what kind of fat do you use at home to fry?", in order to know whether participants fried with olive oil or a different kind of oil. The nutrient databank was updated by a trained team of dietitians using available information on food composition tables for Spain (23).

Assessment of non-dietary variables

Other questions (46 items for men and 54 for women) were also included at the baseline questionnaire that assessed the participants' medical history, health related habits, lifestyle, and socio-demographic variables, as well as anthropometric data (weight and height previously validated in a subsample of the cohort) (24). Seventeen activities were inquired at baseline to quantify physical activity, and from them a metabolic equivalent index (MET-h/wk) was computed. Physical activity was also previously validated in a subsample of the cohort (25).

Ascertainment of hypertension

The endpoint of the study was incident hypertension. Participants were asked whether they had received a medical diagnosis of hypertension at baseline and during the follow-up and also we inquired about the date of diagnosis.

For the present analyses, participants were considered to have prevalent hypertension at baseline if they reported a medical diagnosis of hypertension, a systolic blood pressure (SBP) ≥140 mmHg, a diastolic blood pressure (DBP) ≥90 mmHg, or any use of antihypertensive medication (26). New cases of hypertension were defined as those

participants who did not have hypertension at baseline and reported a new medical diagnosis of hypertension during the follow-up. The validity of self-reported hypertension diagnosis was assessed in a subsample of the cohort. That validation study showed an adequate validity of the self-reported diagnosis of hypertension: among those participants who reported a diagnosis of hypertension 82.3% (95% CI: 72.8–92.8) were confirmed through conventional measurement of blood pressure, and among those who did not report a diagnosis of hypertension, 85.4% (95% CI: 72.4–89.1) were confirmed as non-hypertensive (27). Moreover, in a recent study we have validated each component of metabolic syndrome (including high blood pressure) finding an intraclass correlation coefficients for systolic blood pressure of 0.47 (0.36-0.57) and for diastolic blood pressure 0.46 (0.34-0.56), using as gold standard direct assessments by an experienced physician (28).

Statistical Analyses

We classified participants into three categories according to the distribution of their frequency of fried food consumption: 0-2/week, >2-4/week, and >4/week. Participants were also classified into tertiles of total consumption of fried foods (g/d) (food items and serving size of fried food considered from the food frequency questionnaire (FFQ) are shown on a supplemental table). We considered the group with the lowest frequency of consumption (<2/week) or the lowest tertile as the reference category. As an additional analysis, we classified participants into 4 categories: 0-2/week, >2-4/week, >4-<7/week and ≥7/week, also considering the category of lowet frequency of consumption as the reference category.

Nutrient intake was adjusted for total energy intake with the residuals methods, and separated regression models were conducted to obtain sex-specific residuals.

Person-time of follow-up was calculated for each participant, from the date of completion the baseline questionnaire till the date of completion of the last follow-up questionnaire, the date of diagnosis of hypertension, or death, whichever occurred first. To assess the relationship between fried food consumption at baseline and the subsequent risk of developing incident hypertension during follow-up, Cox regression models were fitted. Tests of linear trend across increasing categories of consumption were conducted by assigning medians for the frequency of consumption of fried foods within each category and treating this variable as a continuous variable.

Additionally, we examined the relationship between home and non-home fried food consumption separately and the risk of hypertension.

Interaction between age categories (<40 and ≥40 years), sex and the frequency of consumption of fried foods were calculated through likelihood ratio tests between the fully adjusted model and the same model but introducing the interaction product-term. We also tested the interaction between the type of fat participants use for frying (olive oil or others) and the frequency of consumption of fried foods.

For all the analyses we fitted a crude univariate model, an age- and sex-adjusted model, and two multivariable models after additional adjustment for the following potential confounders; Model 1: family history of hypertension (yes/no), self-reported history of hypercholesterolemia (yes/no), physical activity (METs-h/week) smoking status (non-smoker, current smoker and former smoker), total energy intake (kcal/day), alcohol intake (g/day), and energy adjusted sodium (mg/day), potassium (mg/day), caffeine (mg/day), fiber (g/day), olive oil (g/day), fruits (g/day), vegetables (g/day), and low-fat and high-fat dairy, sugar-sweetened beverage (ml/day), fast food (g/day),sweets (g/day) consumption, and time spent watching tv (hr/day); and model 2: additionally adjusted for baseline BMI. For the selection of the potential confounders in the multivariate

model, and as its currently recommended (29), we took into account the previously published scientific literature including our own results based on the cohort about risk factors for hypertension, avoiding exclusively the statistic approach as the p value, the stepwise procedures or the changes in the point estimates after adjusting for potential confounders.

To account for multicollinearity across independent variables a statistical model was constructed and the Variance Inflation Factor (VIF) was calculated.

Sensitivity analyses were conducted and all the models were repeated after 1) excluding early cases of incident hypertension (cases reported within the first two years of follow-up), 2) excluding late cases of hypertension (reported after ≥8 years of follow-up), 3) excluding participants who reported incident chronic diseases during follow-up period, 4) excluding those participants who were under the 5^{th} percentile and over the 95^{th} percentile of total energy intake, 5) excluding those participants who did not answer 9 or more items in the FFQ, and 6) including participants who reported SBP ≥140 and/or DBP ≥90 at baseline. Finally, an additional analysis were conducted, adjusting for calendar year of participant's inclusion in the cohort.

All *p* values presented are two-tailed; $p<0.05$ was considered statistically significant. Analyses were performed using STATA/SE version 12.0 (StataCorp, College Station, TX, USA).

Results

Our analyses included 5,059 men and 8,620 women. The main baseline characteristics of participants according to their frequency of fried food consumption are presented in **Table 1.** The mean age of participants was 36.5 y (SD: 10.8) and the mean BMI was 23.2 kg/m^2 (SD: 3.3). Participants in the highest category of baseline fried food consumption (>4/week) compared with the lowest category (≤2/week) had a higher BMI, were less physically active, were more likely to have a history of hypercholesterolemia, but less likely to have a family history of hypertension, they had

higher total energy and fat intake, lower protein and carbohydrate intake, higher intakes of sodium, magnesium, and caffeine, but a lower intake of fiber, fruits, vegetables and low-fat dairy products and higher means of baseline SBP and DBP.

During the follow-up period (median of 6.3-y) we observed 1,232 incident cases of hypertension. A higher frequency of fried food consumption was positively associated with a higher risk of developing hypertension. Participants consuming fried foods >2-4/week and >4/week exhibited a significantly greater risk of developing hypertension compared with those who consumed 0-2/week [HR= 1.18 (95% CI: 1.03-1.36) and 1.21 (95% CI: 1.04-1.41) respectively; *p* for trend= 0.020], after adjusting for potential confounders **(Table 2)**. When we analyzed total fried food consumption (g/d) in tertiles we observed a HR= 1.04 (95% CI: 0.90-1.20) for 2nd tertile and HR=1.18 (95% CI: 1.00-1.38) for the 3rd tertile versus the first tertile of consumption for the fully-adjusted model **(data not shown).** The Pearson correlation coefficient between frequency of fried food consumption and total fried food consumption in grams was r=0.912 p<0.001. And when we analyzed the 4 categories of consumption we also observed a greater risk in the highest category of consumption (≥7/week) in comparison with the lowest [HR= 1.20 (95% CI: 1.00-1.45) p for trend=0.017] **(data not shown).**

As we thought that intake for this type of food might change over time and/or over the study period (i.e. early vs late entry into the dynamic cohort), we conducted an additional analysis adjusting for calendar year of participant's inclusion in the cohort. We observed that the HR were attenuated, but remained statistically significant 1.15 (95% CI: 1.00-1.31) and 1.16 (95% CI: 1.01-1.34) for consuming fried foods >2-4/week and >4/week versus <2/week respectively.

When we analyzed separately frequency of consumption of fried food at home and fried food away from home, we observed very similar results in both groups. For those who consume fried food at home >2 times/week we observed a HR= 1.16 (95% CI: 1.03-

1.32); and for those who consume fried food away from home a HR= 1.15 (0.97-1.38) **(Table 3).**

The interaction between fried food consumption and age, sex, and type of oil used for frying were not statistically significant (p for interaction=0.711, 0.567 and 0.870 respectively).

We conducted multiple sensitivity analyses to account for the potential uncertainties of our assumptions regarding the induction period and also for possible sources of bias including measurement errors. In all these sensitivity analyses the results were not meaningfully changed (**Table 4**).

Testing for multicollinearity revealed satisfactory values of the VIF.

Discussion

In this Mediterranean cohort a higher baseline consumption of fried foods was significantly associated with a higher risk of incident hypertension.

A previous cross-sectional study from Spain including 1226 participants (13) evaluated the association between fried food consumption and the prevalence of hypertension previously and found that the risk of hypertension was directly associated with the consumption of fried foods especially when vegetable oils such as sunflower oil were reused (13). Some studies have evaluated the association between fried food consumption and the risk of cardiovascular disease with inconsistent results (14-17). The Spanish EPIC cohort, conducted on 40,757 adults aged 29 to 69 y, free of coronary heart disease at baseline, found that the consumption of fried foods was not associated with coronary heart disease with a HR of 1.08 (95% CI: 0.82 -1.43) for the fourth quartile of consumption in comparison with the first quartile (16). Additionally, a case-control study in Costa Rica likewise found no association between fried food consumption and the risk of myocardial infarction (17). Conversely, the large

INTERHEART case-control study observed a positive association between the consumption of fried foods and the risk of acute myocardial infarction (14). The Cardiovascular Heart Study found that fried fish consumption exhibited a non-significant trend towards to a higher risk (15).

The frying process involves many factors, some dependent on the process itself, and others on the food and type of fat used (7). For example, during the frying process, trans-fatty acids in foods increase. The amount of trans-fatty acids generated depends on several aspects such as the frying technique (if its deep frying or pan frying), the type of oil and food, and the degree of degradation of the oil (6). Wang *et al*. (30) in one large American cohort which included 28,100 women aged ≥ 39 years and free of cardiovascular disease and cancer at baseline, found that a higher intake of *trans* fatty-acids were associated with increased risk of hypertension. Therefore, this mechanism may account for the association found in our study. Another plausible mechanism involved in the association between fried food consumption and hypertension might be explained by the weight gained during the follow-up due to fried food consumption. A previous study in our cohort showed a significant positive association between high frequency of fried food consumption and the risk of overweight/obesity (8). The association between hypertension and obesity is widely known (31). In this context, we conducted a secondary analysis, additionally adjusting for incident obesity (yes/no). We found an attenuation of the risk estimate and the association between fried food consumption (>4/week versus ≤2/week) and hypertension became non-significant [HR= 1.15 (95% CI: 0.97-1.36)]. The results were very similar when we adjusted for yearly body weight change [HR=1.14 (95% CI: 0.96-1.46)].Therefore, incident obesity and yearly body weight change might be mediators in the causal chain and it is likely to act

as one of the potential mechanisms that might explain the association between fried food consumption and the incidence of hypertension.

A potential limitation of our study is the self-reported outcome. However, a self-reported diagnosis of hypertension was previously validated in our cohort finding a fairly adequate validity for the self-reported diagnosis of hypertension (26-27).

Another limitation could be that participants may tend to under-report their fried food consumption because they perceived it as unhealthy (social desirability bias), however this misclassification is expected to be non-differential and therefore could more likely bias our results to the null value (32).

Our study also has important strengths, including its prospective design, which avoids the possibility of reverse causation bias. Other strengths are the use of a validated FFQ (22), the large sample size, and the long follow-up period.

Including only university graduates might be thought to be a potential limitation of our study, because it is not a representative sample. This issue may have affected the generalizability of our findings; therefore, we have to be cautious in extrapolating these results to the general population. Nevertheless, it could also have actually enhanced the internal validity of our study because the high level of education and homogeneity of the cohort reduced the potential confounding related to socioeconomic status. However, the generalizability of our findings, as some other important cohort, must be based on biological mechanisms and not in the representativeness of our sample in the statistical sense of the term. In addition, the high educational level of our participants provides us a better quality in the information and increases the internal validity of the study.

In conclusion, in this Mediterranean cohort study, a more frequent consumption of fried foods at baseline was associated with a higher risk of developing hypertension during the follow-up period.

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Conflict of interest

The authors declare no conflicts of interest.

Authorship:

MAM-G helped to design the study and collect data. MB-R and CS-O analyzed the data and drafted the manuscript. AG, IZ, FJB-G edited and critically reviewed the manuscript.

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