

Substitutions of animal-based foods consumption and risk of hypertension: a cohort study

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Research

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Abstract

Background This study assessed the association between the consumption of animal-based foods (ABFs) and hypertension, a recognized risk factor for cardiovascular disease. The adverse effects of red and processed meat (RPM) consumption and the beneficial effects of dairy products consumption and other ABFs have been discovered separately; however, the constrained nature of food intake was typically ignored. We aimed to assess the substitution effects between RPM and other ABFs using compositional transformation substitution analysis and further compared this analysis with the traditional substitution analysis method. **Methods** We followed 5394 Chinese adults aged 18-60 years at baseline in the China Health and Nutrition Survey from 2004 to 2011. Food consumption was assessed using a combination of individual-based consecutive 24-h recalls and household-based food weighing approaches. Both traditional substitution analysis and substitution analysis based on compositional transformation were used to assess substitution effects. **Results** One-thousand-two-hundred-and-sixty-seven participants were newly-diagnosed with hypertension in the mean follow-up period of 6.2 ± 0.02 years. The traditional substitution analysis found that substituting eggs for RPM was associated with a lower risk of hypertension (HR = 0.899, 95%CI: 0.818, 0.989). Unlike the traditional model, the compositional transformation substitution analysis (1) found that replacing RPM with any other ABFs was associated with a lower risk of hypertension; (2) implemented substitution of one-to-many between RPM and other all ABFs; (3) found the different substitution effects between RPM and dairy products among participants whose proportions of different ABFs were different; (4) based on the constant substitution amount, substituting dairy products for RPM was associated with a greatest benefit in reducing the risk of hypertension. **Conclusions** The compositional transformation substitution analysis takes the constrained and relative nature of food consumption into account. This is a flexible approach to estimate substitution effects under different substitution patterns, to obtain personalized estimation effects based on different consumptions of ABFs at the individual level, and to provide an individualized dietary recommendation.

Background

Hypertension is a major risk factor for cardiovascular diseases and is the leading risk for premature deaths worldwide, contributing to more than 10 million deaths in 2016¹. From 1975 to 2015, the number of adults with hypertension increased from 594 million to 1.13 billion and is predicted to grow to nearly 1.56 billion by 2025^{2,3}. As the prevalence of hypertension escalates, preventive interventions are urgently needed. Diet is considered to be a critical and amendable factor for hypertension⁴. Accordingly, understanding how dietary components impact on hypertension is most important in constructing preventive strategies from public health perspectives.

Animal-based foods (ABFs), especially meat, are a major component of dietary patterns. Red meat represents 58% of all meat consumed in the USA and its consumption continues to rise⁵. In China, the consumption of ABFs keeps increasing in line with the economic growth, especially regarding meat consumption which has leaped 18 percent, from 64 million to 78 million (metric) tons from 2007 to 2012⁶. As a rich source of protein, minerals and vitamins, ABFs have attracted considerable attention regarding

hypertension prevention⁷. A significant amount of evidence from observational studies has shown that a higher RPM intake is associated with an increased risk of hypertension⁷⁻¹⁰. Meanwhile, the beneficial effects of other ABFs, such as dairy products and eggs, have also been probed^{11,12}. As people do not consume food in isolation, current dietary interventions no longer focus on single ABFs but advocate for the substitution of unhealthy ABFs with diverse healthy foods of animal origin¹³. Therefore, it is essential to explore the substitution effects of healthy and unhealthy ABFs on hypertension.

The traditional substitution analysis (TSA) is based on regression modeling, including the sum consumption of interested foods and all foods, except one, as explanatory variables¹⁴. However, these variables are exactly correlated and cannot independently and correctly predict the substitution effects¹⁵. Besides, TSA can only predict one-to-one substitution effect theoretically without considering the individual dietary differences¹⁶. Thus, whether the predictive results of TSA can correctly and practically guide a reasonable diet behavior at the individual level is questionable. Another substitution method based on compositional data (CoDa) analysis, which was originally used in the time allocation for different behaviors, can be used in nutritional substitution analysis^{17,18}. Daily individual food consumption, just like time allocation, is essentially finite data and one food consumption cannot be shifted without compensatory changes in the others. Thus, data regarding food consumption has a constrained property and exists in the constrained simplex space with the definition of operations differing from those in the real Euclidean space^{19,20}. The CoDa analysis that can work well with constrained data by translating data into real space through the application of isometric log-ratio (*ilr*) coordinate transformation is becoming the new approach to deal with dietary data^{21,22}.

In this study, the compositional transformation substitution analysis (CoTSA), which combines CoDa with the notion of replacement, is first proposed in food substitution. We used CoTSA to implement substitution of RPM and other ABFs and explored the association between different types of replacements and the risk of hypertension. We further compared the findings obtained from the CoTSA with the results from the TSA.

Methods

Study population

The China Health and Nutrition Survey (CHNS) is a large-scale cohort study that was launched in 1989 and has finished eight follow-up panels up until 2011. Furthermore, the CHNS is a prospective, ongoing study that explores the socioeconomic factors, demographic changes, and nutritional behaviors that affect the health status in China. A multi-stage, random-cluster sampling procedure was employed to enroll samples in each of the 9 provinces where the total population accounts for roughly 50% of the Chinese population and represents populations from rural, urban and suburban areas. Details concerning the study project and design have been presented in the cohort profile²³. The study was approved by the institutional review committees of the University of North Carolina at Chapel Hill and the Chinese Institute of Nutrition and Food Safety, China Center for Disease Control and Prevention. All participants provided an informed consent form.

A total of 8240 volunteers aged 18–60 years old were included between 2004 to 2011 on the ground that the participant retention maintained was higher than 80% across all surveys after 2004^{23,24}. Participants with hypertension, diabetes, myocardial infarction, stroke, and cancer, and women who were pregnant at baseline, were not included (n = 2070). Eighty-one participants with missing data on smoke and job status and BMI value at baseline were excluded, as well as 726 vegans, leaving 5394 participants for our final analysis (Fig. 1).

Covariates data collection

Baseline questionnaires provided information about age, gender, residential areas, marital status, educational level, working status, smoking status, and alcohol consumption. Residential areas were divided into urban or rural areas. Marital status was grouped into never, married, divorced, widowed, or separated. Educational attainment was classified into two levels according to a seven-category primary question: middle school degree or below (never, graduation from primary or middle school), high school degree or above (high school, technical or vocational, university or college, master's degree or higher). Working status was classified into jobless, employees, and retirees. Smoking status (never, former, or current) and alcohol consumption (never, current drinking) were also documented in the questionnaire. The weekly time spent on performing physical activities, being sedentary, and lying in bed, were collected. Body mass index (BMI) was calculated by dividing weight in kilograms by height in square meters.

Dietary assessment

In the CHNS, dietary surveys were assessed over three consecutive 24-h recalls at the individual level in combination with weighing inventory at the household level over the same three day period^{25,26}. The consecutive three days were randomly allocated from Monday to Sunday and were equally balanced across the seven days of the week for each sampling unit. At the individual level, all food consumed at home and away from home each day was recorded with food models and pictures by trained interviewers. At the household level, food consumption changes in inventory from the beginning to the end of each day were measured with a weighing scale. By comparing the average daily dietary intake (g/day) calculated from the household survey and 24-hour recall, significant discrepancies were found and solved by revisiting at both levels. One serving of ABFs was defined as one Liang, which is the commonly used unit in China and is equivalent to 50 g or 50 ml. The classification of food groups, such as ABFs, including RPM, poultry, seafood, dairy products, and eggs was based on the dietary consumption data using the Chinese Food Composition Tables²⁷.

Ascertainment of incident hypertension

Arterial blood pressure was measured on the right arm three times using a mercury sphygmomanometer with the cuff maintained at the heart level in the sitting position after at least a 10 minutes rest. An average of three blood pressure measurements was used for hypertension ascertainment. Hypertension ascertainment was based on the follow-up survey in 2011 by meeting at least one of the following criteria:

(1) a systolic blood pressure ≥ 140 mmHg; (2) a diastolic blood pressure ≥ 90 mmHg; (3) a self-reported diagnosis or new diagnosis of hypertension by a physician; (4) a self-reported antihypertensive treatment.

Statistical analysis

The potential confounding covariates were examined by the cross-tabulation of dichotomous ABFs. The mean \pm standard deviation or percentage was presented to describe continuous or categorical variables appropriately. The general linear model and Pearson χ^2 test were performed for examining differences between groups for continuous and categorical variables, respectively. The Pearson correlation coefficient was used to detect the baseline correlations among the different ABFs components. Based on the multivariable Cox proportional hazards model, two substitution analysis methods were conducted to explore the association between substituting RPM for another or all other ABFs, with the risk of hypertension. The proportional hazards assumption was not violated by observing the $-\ln(-\ln)$ survival plots.

Pol, *Dry*, *Egg*, *Sea* and *ABF* represented the consumption of poultry, dairy products, eggs, seafood, and total ABFs, respectively. For the TSA, the effects on outcome $f(x)$ of substituting *RPM* for other factors, like *Pol*, could be estimated by taking *RPM* out of the model that includes *Pol*, *Dry*, *Egg*, *Sea*, and *ABF* as the following formula:

$$f(x) = \beta_1 Pol + \beta_2 Dry + \beta_3 Egg + \beta_4 Sea + \beta_5 ABF + \sum_{e=1}^E \beta_e w_e,$$

β was the estimated regression coefficient. The multivariate model was adjusted for w_e on behalf of the covariates of age, gender, BMI, marriage, urban location, education degree, working status, smoking, alcohol consumption, time spent on physical activity, sedentary and lying on bed, consumption of vegetable, fruit, nuts and legumes, whole grain, sweetened beverages and sodium. The hazard ratio (*HR*) and its 95% confidence intervals (CIs) were reported. The *HR* for β_1 was explained as the risk of hypertension by replacing one serving of *RPM* with the same amount of poultry.

For the CoTSA, the 5 categories of ABFs had a restricted sample space of 5-simplex which was not compatible with operations in real space without transformations. We obtained the compositional values of ABFs for individuals by an operation called closure, which divided out a set of ABFs by its total. These compositional values were actually proportions that adding up to 1. Based on the compositional values, the isometric log-ratio (*ilr*) coordinates constructed by the sequential binary partition (SBP) process were used to accomplish the transformation. The SBP was based on a combination of a priori information of interest and a data-driven approach of the principal balance.

<i>ilr</i> coordinates	<i>RPM</i>	<i>Pol</i>	<i>Dry</i>	<i>Egg</i>	<i>Sea</i>
z_1	1	-1	-1	-1	-1
z_2	0	-1	-1	1	-1
z_3	0	1	-1	0	-1
z_4	0	0	-1	0	1

The *ilr* coordinates pertaining to the above SBP were defined as the following:

$$z_1 = \sqrt{\frac{4}{5}} \ln \left(\frac{RPM}{(Pol \times Dry \times Egg \times Sea)^{1/4}} \right), \quad z_2 = \sqrt{\frac{3}{4}} \ln \left(\frac{Egg}{(Pol \times Dry \times Sea)^{1/3}} \right),$$

$$z_3 = \sqrt{\frac{2}{3}} \ln \left(\frac{Pol}{(Dry \times Sea)^{1/2}} \right), \quad z_4 = \sqrt{\frac{1}{2}} \ln \left(\frac{Sea}{Dry} \right)$$

The coordinates were independent of each other. When substituting RPM for other all ABFs, *RPM* was changed to $[(1+r) RPM]$, and the remaining components were equally reduced through multiplying by $(1-s)$, where $rRPM = s(Pol + Dry + Egg + Sea)$. Accordingly, z_i turned into the following coordinates:

$$z_1^* = \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)RPM}{((1-s)Pol \times (1-s)Dry \times (1-s)Egg \times (1-s)Sea)^{1/4}} \right) = \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) + z_1$$

$$z_2^* = \sqrt{\frac{3}{4}} \ln \left(\frac{(1-s)Egg}{((1-s)Pol \times (1-s)Dry \times (1-s)Sea)^{1/3}} \right) = z_2,$$

$$z_3^* = \sqrt{\frac{2}{3}} \ln \left(\frac{(1-s)Pol}{((1-s)Dry \times (1-s)Sea)^{1/2}} \right) = z_3,$$

$$z_4^* = \sqrt{\frac{1}{2}} \ln \left(\frac{(1-s)Sea}{(1-s)Dry} \right) = z_4$$

Based on the Cox proportional hazards model with *ilr* coordinates, *HR* was given as,

$$HR_{one-for-many} = \frac{h_0 \exp(\beta_1 z_1^* + \beta_2 z_2^* + \beta_3 z_3^* + \beta_4 z_4^* + \beta_5 z_5^* + \beta_6 w_e)}{h_0 \exp(\beta_1 z_1 + \beta_2 z_2 + \beta_3 z_3 + \beta_4 z_4 + \beta_5 z_5 + \beta_6 w_e)} = \exp \left(\beta_1 \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) \right), \text{ and the 95\% CI of } HR_{one-for-many} \text{ was } \exp \left(\beta_1 \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) \pm u_{\alpha/2} S_{\beta_1} \right).$$

The HR was explained as, based on the baseline consumption of RPM and poultry (average or individual consumptions), the risk of hypertension by replacing one serving of RPM with the same amount of poultry.

When substituting RPM for another ABFs, like poultry, *RPM* and *Pol* were respectively changed into $[(1+r) RPM]$ and $[(1-s) Pol]$, where $rRPM = sPol$. The corresponding changes took place in the following coordinate:

$$z_1^* = \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)RPM}{((1-s)Pol \times Dry \times Egg \times Sea)^{1/4}} \right) = \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) + z_1$$

$$z_2^* = \sqrt{\frac{3}{4}} \ln \left(\frac{Egg}{((1-s)Pol \times Dry \times Sea)^{1/3}} \right) = \sqrt{\frac{3}{4}} \ln \left(\frac{1}{(1-s)^{1/3}} \right) + z_2,$$

$$z_3^* = \sqrt{\frac{2}{3}} \ln \left(\frac{(1-s)Pol}{(Dry \times Sea)^{1/2}} \right) = \sqrt{\frac{2}{3}} \ln(1-s) + z_3, \quad z_4^* = \sqrt{\frac{1}{2}} \ln \left(\frac{Sea}{Dry} \right) = z_4$$

Accordingly, the $HR_{one-for-one} = \exp \left(\beta_1 \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) + \beta_2 \sqrt{\frac{3}{4}} \ln \left(\frac{1}{(1-s)^{1/3}} \right) + \beta_3 \sqrt{\frac{2}{3}} \ln(1-s) \right)$ and 95%CI were $\exp \left(\beta_1 \sqrt{\frac{4}{5}} \ln \left(\frac{(1+r)}{(1-s)} \right) + \beta_2 \sqrt{\frac{3}{4}} \ln \left(\frac{1}{(1-s)^{1/3}} \right) + \beta_3 \sqrt{\frac{2}{3}} \ln(1-s) \pm u_{\alpha/2} (S_{\beta_1} + S_{\beta_2} + S_{\beta_3}) \right)$.

Similarly, other substitution patterns could be derived based on this method.

Data cleansing and consolidation were completed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical tests were performed using R software (version 3.6.1). Statistically significant meant a $P < 0.05$ and the 95%CI of *HR* dose not contain 1. All P values were 2-tailed.

Results

Baseline characteristic distribution

Data from 5394 participants were analyzed whom 1267 were newly diagnose hypertensives. The mean follow-up period was 6.2 ± 0.02 years. The baseline characteristics were summarized according to the dichotomous consumption of ABFs (Table 1). The main consumption of ABFs was RPM, with an average of 1.68 servings per day. Participants with higher consumption of all five ABFs were more likely to have a higher educational level, to spend more time sitting and less time doing physical activity, and to consume more fruit. Males, drinkers, and individuals who consumed more sugar-sweetened beverages, also tended to consume more meat and dairy products. Higher consumption of RPM meant more vegetable intake and less whole grains intake. Participants with higher consumption of poultry consumed fewer vegetables, nuts and legumes, as opposed to those who consumed more dairy products. Contrary to individuals with a higher intake of eggs, participants with a higher seafood intake ate less whole grain. Participants, who consumed more RPM, seafood, dairy products, and eggs, consumed more sodium.

TSA

The TSA model was used to predict the associations between changes (serving/day) in specific ABFs components and risk of hypertension (see Table 2). A meaningful substitution effect was found between RPM and eggs. Model A suggested that replacing 1 serving/day of RPM with eggs were associated with a 14.8% lower risk of hypertension ($HR = 0.852$, 95%CI: 0.781–0.934). As expected, the opposite association was seen when eggs was dropped out of the model (Model E). The line where risk of hypertension varies with the amount of substitution is shown in Fig. 2(A). The slopes of lines are different between different ABFs substitute patterns. With the maximum slope of 0.3%, substituting RPM with eggs was associated with the greatest benefit in reducing the risk of hypertension.

However, there was a strong correlation between individual ABFs and total ABFs, especially between RPM and total ABFs consumption ($r = 0.64$), which implies the multi-collinearity (Table 3).

CoTSA

The regression results with *ilr* coordinates are presented by modeling a multivariable Cox proportional hazards regression (Table 4). Coordinates with RPM in the numerator were a significant predictor of hypertension. The first *ilr*-coordinate that contained all the information, regarding RPM relative to the remaining ABFs, was a significant predictor of hypertension ($HR = 1.015$, 95%CI: 1.003–1.027).

The means of the compositional values were 50%, 23%, 17%, 7%, and 3% for RPM, eggs, seafood, poultry, and dairy products, respectively. This implied that the average consumption proportion of different ABFs varied, and the ranges of substitution between different ABFs were dissimilar (Fig. 2(B)). Since the mean consumption proportion of RPM was 50%, the substitution curve between RPM and other ABFs was plotted in a symmetrical range, while the substitution curve between RPM and another ABF was drawn in an asymmetrical range. Based on the proportional means, increasing the intake of RPM by 50%, while decreasing other ABFs, equivalently was associated with the largest expected hypertension risk (*HR*: 1.063, 95%CI: 1.050–1.076); whereas the inverse replacement was negatively associated with a meaningfully expected hypertension risk (*HR*: 0.909, 95%CI: 0.898–0.920). The estimated risk of hypertension by replacing 50% of RPM intake, equivalently, with poultry, seafood, dairy products, and eggs were 0.942 (95%CI: 0.912–0.972), 0.942 (95%CI: 0.900–0.988), 0.919 (95%CI: 0.879–0.962) and 0.944 (95%CI: 0.924–0.964), respectively, yet significant substitution effects were not found when replacing all proportions of poultry (*HR*:1.006, 95%CI: 0.975–1.039), seafood (*HR*:1.010,95%CI:0.965–1.056), dairy products (*HR*:1.045,95%CI: 0.999–1.093), and eggs (*HR*:1.012,95%CI:0.991, 1.034) with RPM. Furthermore, in the case of a fixed amount of substitutes, the maximum risk changes took place, in the substitution between RPM and dairy products.

To investigate the effects of baseline difference in ABFs consumption proportions among individuals on predicting risk of hypertension, we took two participants (Participant A and Participant B) with different consumption proportions of ABFs for example and their substitution effects were further analyzed. The proportions of RPM, poultry, dairy products, eggs, and seafood for Participant A and Participant B were 10%, 13%, 45%, 22%, 10%, and 70%, 9%, 7%, 2%, 12%, respectively. The substitution effects that occurred between RPM and dairy products in participant A and participant B were estimated by CoTSA and TSA, respectively, in Fig. 3. Participant A and participant B needed to make various changes to achieve meaningful substitution effects which implied that when RPM is replaced by dairy products, participant A and participant B need to respectively decrease to 10% and 60% to significantly reduce the risk of hypertension and need to conversely increase to 40% and 6% to significantly increase the risk of hypertension.

In addition, to achieve equally beneficial substitution effects, participant A and participant B needed to replace RPM with different consumption proportions of dairy products. For example, when the risk of hypertension decreased by 5% (*HR* decreased to 0.95), participant A had to replace all RPM (10%) with dairy products, while the amount of substitution was 64% for participant B. However, the risks estimated by TSA were consistent regardless of the differences in baseline ABFs consumption.

We further estimated the substitution effects between RPM and poultry, seafood, eggs, and all other ABFs in participant A and participant B respectively (Fig. 4). Whether based on the average or individual (Participant A and participant B) consumption of ABFs, substituting dairy products for RPM was associated with a greatest benefit in reducing the risk of hypertension. This implies that, to achieve the same *HR*, the lowest amount of substitution was required between RPM and dairy products. For instance, the risk of hypertension for participant B could be reduced by 5% (*HR* = 0.95) most effectively by replacing approximately 62% of RPM with dairy products, compared to the replacement of about 65% RPM by all

other ABFs, and 68% by eggs, poultry, and seafood (Fig. 4), while for the average consumption of ABFs the amounts of replacement were 43%, 47%, and 48% respectively (Fig. 2(B)).

Discussion

Main findings

In this prospective cohort of Chinese adults, for TSA models, a decrease in RPM consumption and a simultaneous increase in the consumption of eggs were associated with a lower risk of hypertension. For CoTSA models, substituting RPM for other ABFs with the equivalent consumption, including one-to-one and one-to-many substitution, were associated with a higher risk of hypertension.

Systematic reviews and meta-analyses of prospective cohort studies have pointed out an adverse association of RPM consumption and a beneficial association of the consumption of seafood, eggs and dairy products, with hypertension^{28,29}. For instance, a recent meta-analysis that summarized 10 prospective cohorts, suggested that the highest level of red meat consumption was associated with a 22% higher risk of hypertension, while the highest level of egg consumption was associated with a 21% lower risk of hypertension, both compared to its lowest consumption level²⁸. Furthermore, a systematic review supported favorable associations between dairy product consumption and risk of hypertension³⁰. Increasing the consumption of dairy products by 200 g per day was associated with a 3% reduction in hypertension risk³¹. Similarly, a beneficial association was shown between fish and the risk of hypertension³².

However, none of these studies took the constrained nature of food consumption into account. Since the shifts of RPM consumption accompany compensatory changes in ABFs intakes, it is important to consider the impact of both changes on hypertension simultaneously. In our study, substitution analysis was used to estimate the substitution effects in real-world dietary interventions, which advocate for a decrease of adverse foods, like RPM, and are accompanied by compensatory increases in one or more beneficial foods, such as dairy products, seafood, eggs, and poultry. Our findings, based on TSA and CoTSA modeling, are consistent with previous evidence that an equivalent substitution for a decreased consumption of RPM and increased consumption of other benefit ABFs was meaningful for preventing hypertension. Since the assessment of the substitution effects is based on an equal amount of replacement, and the number of food intakes varied individually, we further extended the results to the individual level by using CoTSA, and compared its results with TSA.

Comparison of TSA and CoTSA

Although parts of the findings are the same from both the TSA and CoTSA methods, there are fundamental differences between them. The peculiarity of CoTSA is its inherently compositional nature that considers the intrinsic correlation of food intake and analyzes the relative importance of different food consumptions as a proportion.

Conceptually, ABFs consumption has an inherent dependency, which implies that the total consumption of ABFs is constrained to a certain level for each individual¹⁵. TSA takes the constrained nature of ABFs consumption into account by assuming a finite sum and including the total consumption of ABFs. However, the inclusion of dependent food components in regression model as dependent variables will directly lead to multicollinearity, negatively bias the covariance structure of data and likely bring about spurious results¹⁵. The standard statistical model fails to analyze data with a compositional property because it exists in a constrained space called the simplex, governed by Aitchison geometry³³. However, this problem can be solved by applying the *ilr* coordinate transformation^{15,33}. On one hand, the *ilr* coordinates do not produce multicollinearity because they are mutually independent. On the other hand, *ilr* coordinates emphasize the fact that any dietary pattern is essentially a tradeoff between consuming more of some foods and less of others, which nicely fits the substitution concept in the dietary recommendations¹⁹.

The TSA, that deals with modelling all ABFs except one of them, is limited to assessing only estimates for the replacement of one ABFs (e.g., dairy products) for another (e.g., RPM). Whereas, CoTSA breaks through this limitation and flexibly deals with the different substitution combinations within ABFs, such as the one-to-one replacement between RPM and another ABFs, or the one-to-many substitution between RPM and the total amount of ABFs considered in our current study, or the substitution between any ABFs which researchers are interested in.

Since the substitution effect is estimated based on equivalent consumption replacement, the ABFs should be replaced with a reasonable amount of consumption¹⁶. In this cohort, the average consumption of RPM was three times more than that of eggs (1.68 vs. 0.59 servings/day). This difference may partly conduce to the statistically significant association based on TSA. This association is hard to interpret and can easily be questioned regarding the real meaning and has confined the practical application for guiding dietary recommendations. This limitation of TSA arises on the grounds that it does not consider the relativity of ABFs consumption and constitutes a theoretical substitution model without taking the real consumption into account³⁴. Unlike TSA, CoTSA concerns the importance of the relative consumption of each ABFs, namely the proportion. The average proportions of each ABFs consumption are different; therefore, the variable ranges of the replacement amount are diverse among different substitution groups. For example, RPM could only replace 3% of dairy products, while the converse replacement can be 50%; this is due to the different mean proportions of RPM and dairy products to the total ABFs (50% and 3%). Similarly, the proportion of any kind of ABFs varies at the individual level, and CoTSA can assess substitution effects in accordance with individual proportions of ABFs consumption. For different proportions of ABFs, a different amount of substitution is required to get the same substitution effect. Therefore, we can provide a personalized dietary recommendation based on the substitution effect estimated by the CoTSA.

Possible explanations and implications

The adverse impact of RPM consumption on hypertension may be attributed to a combination of multiple components. Saturated fat and cholesterol, which are the major components of red meat, could adversely affect the incidence of hypertension^{35,36}. Heme iron, another important component of red meat, could promote insulin resistance and atherosclerosis³⁷. L-carnitine, phosphatidylcholine and their metabolism by

gut microbiota (trimethylamine-*N*-oxide) in red meat have been found to accelerate the atherosclerotic processes³⁸. The high concentration of salt contained in processed meat is an important risk factor for the prevalence of hypertension³⁹. In our current study, substituting dairy and its products for all RPM would bring the greatest benefit of decreasing risk of hypertension. Based on current evidences, the high content of potassium and calcium in dairy products has been associated with lower blood pressure^{40,41}. Moreover, substituting eggs, poultry and seafood for RPM were associated with a reduced risk of hypertension, respectively. However, the evidence on these foods is limited and need to be further confirmed²⁸.

Limitations

Our study has drawn on a large prospective cohort study and proposed a flexible and efficient approach of CoTSA to assess the substitution effects of ABFs consumption. However, this study has several limitations. Although we have comprehensively controlled demographic, lifestyle, and dietary factors, we cannot ensure the causality of the observed association since the residual confounding factors, especially unmeasured confounders cannot be completely excluded. There are inherent disadvantages of CoTSA in that non-zero elements are required because of the log-transforms. We deal with essential zeros with random values between a tenth and a half of the smallest positive value, using the modified EM algorithm before transformation¹⁵. The participants we studied come from China, which may limit the generalizability of the results to populations from other countries.

Conclusions

In the results of CoTSA, replacing RPM with healthier ABFs was associated with a lower risk of hypertension, moreover, in the case of constant substitution, substituting dairy products for RPM was associated with a greatest benefit in reducing the risk of hypertension. While the TSA has only found that substituting eggs for RPM was associated with a lower risk of hypertension, our analysis provided an alternative substitution approach of CoTSA. Compared with TSA, CoTSA avoids the multicollinearity problem caused by correlation between foods consumption, estimates substitution effects under different substitution patterns that are not limited to the one-to-one replacement pattern, and provides a flexible strategy for personalized substitution based on the relative amount of each ABFs consumption at the individual level.

Abbreviations

RPM: Red and Processed Meat; ABFs: Animal-Based Foods; TSA: Traditional Substitution Analysis; CoTSA: Compositional Transformation Substitution Analysis; CoDa: Compositional Data; *ilr*: isometric log-ratio; CHNS: China Health and Nutrition Survey; BMI: Body Mass Index; SBP: Sequential Binary Partition

Declarations

Ethics approval and consent to participate

All participants provided their written informed consent prior to participation. The China Health and Nutrition Survey (CHNS) study was conducted according to the Helsinki declaration and approved by the institutional review committees of the University of North Carolina at Chapel Hill and the Chinese Institute of Nutrition and Food Safety, China Center for Disease Control and Prevention.

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the China Health and Nutrition Survey (CHNS) repository, [<https://www.cpc.unc.edu/projects/china/data/datasets>].

Competing interests

The authors have no conflicts of interest.

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Authors' contribution

Authors' contributions to manuscript: J. Liang and T. Wang designed the research; J. Liang and J.Zhao contributed to acquisition of the data; J. Liang, J.Zhao, J. Wang and X. Gao models the CoTSA; J. Liang and J.Zhao analyzed data; J. Liang wrote the paper; T. Wang and J.Zhao revised the paper; T. Wang had primary responsibility for the final content. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristics of participants according to dichotomous consumption of ABFs which was split by mean of each component (N=5394),

CHNS, China, 2004-2011.

Characters	RPM		Poultry		Seafood	
	(1.68±1.54) serving/day		(0.31±0.82) serving/day		(0.72±1.20) serving/day	
	≤Mean	> Mean	≤Mean	> Mean	≤Mean	> Mean
Age (years)	41.25±10.5	40.41±10.5	41.10±10.4	40.25±10.6	40.84±10.5	41.09±10.6
<i>P</i> trend	0.0040		0.0143		0.4198	
Male (%)	40.83	51.19	44.12	47.96	43.83	47.26
<i>P</i> trend	<0.001		0.0195		0.0176	
Urban location (%)	27.35	39.47	30.00	40.03	31.48	33.63
<i>P</i> trend	<0.0001		<0.0001		0.1111	
Married(%)	89.18	85.63	88.08	86.63	87.28	88.75
<i>P</i> trend	0.0001		0.0023		0.1927	
High school degree and above(%)	26.58	37.28	28.39	39.69	28.58	35.50
<i>P</i> trend	<0.0001		<0.0001		<0.0001	
Employees (%)	70.46	69.13	70.69	67.21	70.70	68.34
<i>P</i> trend	0.4572		0.0658		0.0004	
Never smoke (%)	71.88	65.36	69.83	67.29	69.63	68.57
<i>P</i> trend	<0.0001		0.1300		0.0281	
Never drinking (%)	69.35	62.72	68.03	61.93	68.47	63.09
<i>P</i> trend	<0.0001		<0.0001		0.0044	
BMI (kg/m ²)	22.80±3.1	22.73±3.0	22.77±3.05	22.91±3.0	22.83±3.1	22.73±3.0
<i>P</i> trend	0.4963		0.1736		0.2700	
PA	2.55±3.2	2.17±3.0	2.49±3.2	2.04±3.1	2.51±3.3	2.17±3.0
<i>P</i> trend	<0.0001		<0.0001		0.0002	
Sedentary	4.26±3.4	4.87±3.6	4.36±3.4	5.03±3.7	4.38±3.4	4.78±3.5
<i>P</i> trend	<0.0001		<0.0001		<0.0001	
Lying in bed	8.08±1.1	8.08±1.1	8.09±1.1	8.06±1.1	8.07±1.1	8.11±1.1
<i>P</i> trend	0.9889		0.4914		0.1747	
Vegetable intake(serving/day)	6.43±3.5	7.09±3.5	6.76±3.6	6.46±2.9	6.63±3.6	6.81±3.2
<i>P</i> trend	<0.0001		0.0052		0.0773	
Fruit intake(serving/day)	0.63±1.6	0.76±1.7	0.63±1.6	0.89±1.8	0.61±1.6	0.84±1.8
<i>P</i> trend	0.0077		<0.0001		<0.0001	
Nuts and legumes intake(serving/day)	1.02±1.3	1.07±1.3	1.07±1.4	0.96±1.2	1.06±1.4	1.02±1.3
<i>P</i> trend	0.1575		0.0098		0.4356	
Whole grain intake(serving/day)	0.35±1.1	0.17±0.6	0.29±0.8	0.25±1.2	0.33±1.0	0.18±0.8

<i>P</i> trend	<0.0001		0.4046		<0.0001	
Sugar-sweetened beverage intake(serving/day)	0.01±0.2	0.03±0.3	0.01±0.2	0.05±0.4	0.01±0.2	0.03±0.4
<i>P</i> trend	0.0263		0.0005		0.0182	
Sodium intake(g/day)	219.9±253.1	248.5±267.2	230.3±271	234.9±208.3	215.0±245.4	264.8±282
<i>P</i> trend	<0.0001		0.5350		<0.0001	

Characters	Dairy products		Eggs	
	(0.28±1.05) serving/day		(0.59±0.76) serving/day	
	≤Mean	> Mean	≤Mean	> Mean
Age (years)	40.86±10.4	41.48±10.8	40.92±10.5	40.91±10.5
<i>P</i> trend	0.2061		0.9807	
Male (%)	45.40	40.71	44.49	45.64
<i>P</i> trend	0.0437		0.4037	
Urban location (%)	29.44	58.70	28.38	37.75
<i>P</i> trend	<0.0001		<0.0001	
Married(%)	88.03	85.18	88.29	86.99
<i>P</i> trend	0.0188		0.1797	
High school degree and above(%)	27.74	60.87	27.76	35.37
<i>P</i> trend	<0.0001		<0.0001	
Employees (%)	70.27	66.60	70.53	69.06
<i>P</i> trend	<0.0001		<0.0001	
Never smoke (%)	69.03	71.74	69.72	68.64
<i>P</i> trend	0.0588		0.6808	
Never drinking (%)	66.68	65.22	67.47	65.59
<i>P</i> trend	0.0621		0.2055	
BMI (kg/m ²)	22.80±3.0	22.75±3.1	22.61±3.0	23.08±3.1
<i>P</i> trend	0.7278		<0.001	
Time spending (hours/day)				
PA	2.51±3.3	1.24±2.5	2.56±3.2	2.16±3.0
<i>P</i> trend	<0.0001		<0.0001	
Sedentary	4.32±3.4	6.26±3.7	4.30±3.4	4.81±3.5
<i>P</i> trend	<0.0001		<0.0001	
Lying in bed	8.10±1.1	8.00±1.1	8.08±1.1	8.08±1.0
<i>P</i> trend	0.0878		0.9440	
Vegetable intake(serving/day)	6.78±3.5	5.87±3.0	6.73±3.5	6.64±3.6
<i>P</i> trend	<0.0001		0.3757	
Fruit intake(serving/day)	0.55±1.4	1.99±2.7	0.53±1.4	0.91±1.9
<i>P</i> trend	<0.0001		<0.0001	
Nuts and legumes intake (serving/day)	1.03±1.3	1.18±1.3	1.03±1.3	1.07±1.4
<i>P</i> trend	0.0147		0.1855	

Whole grain intake(serving/day)	0.28±0.9	0.27±0.8	0.24±0.7	0.34±1.2
<i>P</i> trend	0.7006		0.0005	
Sugar-sweetened beverage intake (serving/day)	0.02±0.2	0.08±0.5	0.02±0.3	0.02±0.3
<i>P</i> trend	0.0027		0.8984	
Sodium intake (g/day)	227.6±257.2	267.4±274.5	215.4±262	254.7±252
<i>P</i> trend	0.0019		<0.0001	

Values are mean± SD for continuous variables and % for categorical variables. The general linear model was used for continuous variables and the Chi-square test was performed for categorical variables.

Table 2. Risk of hypertension according to multivariable-adjusted traditional substitution analyses in ABFs, CHNS, China, 2004-2011.

Substitution model*	RPM		Poultry		Seafood		Dairy products		Eggs		Total ABFS	
	<i>HR</i>	95% <i>CI</i>	<i>HR</i>	95% <i>CI</i>	<i>HR</i>	95% <i>CI</i>	<i>HR</i>	95% <i>CI</i>	<i>HR</i>	95% <i>CI</i>	<i>HR</i>	95% <i>CI</i>
Model A	Dropped		0.925	0.848,1.009	0.948	0.892,1.007	0.931	0.862,1.005	0.852	0.781,0.934	1.015	0.980,1.052
Model B	1.081	0.991,1.179	Dropped		1.024	0.932,1.126	1.007	0.909,1.114	0.921	0.822,1.032	0.939	0.868,1.016
Model C	1.055	0.993,1.121	0.976	0.888,1.073	Dropped		0.982	0.904,1.067	0.899	0.818,0.989	0.962	0.917,1.008
Model D	1.073	0.994,1.159	0.993	0.897,1.099	1.017	0.936,1.105	Dropped		0.915	0.820,1.022	0.945	0.885,1.010
Model E	1.172	1.073,1.280	1.084	0.968,1.215	1.111	1.010,1.222	1.092	0.978,1.219	Dropped		0.865	0.795,0.942

*Substitution of one serving/day of one component replaces one serving/day of another food item.

The substitution models were adjusted for age, gender, BMI, marriage, urban location, education degree, working status, smoking, alcohol consumption, time spent on physical activity, sedentary and lying on bed, consumption of vegetable, fruit, nuts and legumes, whole grain, sweetened beverages and sodium.

Table 3. Pearson correlation coefficients (*r*) for consumption of ABFs in Liang/day, CHNS, China, 2004-2011.

	Total ABFSs	RPM	Poultry	Seafood	Dairy products	Eggs
Total ABFSs	Reference	0.631	0.387	0.541	0.492	0.295
<i>P</i>		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
RPM	-	Reference	0.053	0.085	0.057	-0.063
<i>P</i>	-		<0.0001	<0.0001	<0.0001	<0.0001
Poultry	-	-	Reference	0.072	0.028	0.014
<i>P</i>	-	-		<0.0001	0.0359	0.2829
Seafood	-	-	-	Reference	0.061	-0.05
<i>P</i>	-	-	-		<0.0001	0.6638
Dairy products	-	-	-	-	Reference	0.115
<i>P</i>	-	-	-	-		<0.0001

Values are linear correlation coefficients among the different ABFs consumptions at baseline, $p < 0.05$ indicates statistical significance.

Table 4. Results of adjusted Cox regression analysis modeling the relationship between the *ilr* coordinates and hypertension, CHNS, China, 2004-2011.

<i>ilr</i> coordinates	SE (<i>b</i>)	<i>p</i>	HR	HR95%CI
<i>ilr</i> ₁ (Red and Processed Meat: Eggs & Poultry & Seafood & Dairy)	0.0140	0.0060	0.0227	1.0141 1.0020,1.0264
<i>ilr</i> ₂ (Eggs: Poultry & Seafood & Dairy)	0.0036	0.0047	0.4333	1.0037 0.9945,1.0129
<i>ilr</i> ₃ (Poultry: Seafood & Dairy)	0.0039	0.0054	0.4700	1.0039 0.9934,1.0145
<i>ilr</i> ₄ (Seafood: Dairy)	0.0060	0.0068	0.3762	1.0061 0.9927,1.0196

ilr: isometric log ratio, β : estimated regression coefficient, SE(*b*): standard error of *b*. All models were adjusted for age, gender, BMI, marriage, urban location, education degree, working status, smoking, alcohol consumption, time spent on physical activity, sedentary and lying on bed, consumption of vegetable, fruit, nuts and legumes, whole grain, sweetened beverages and sodium.

Figures

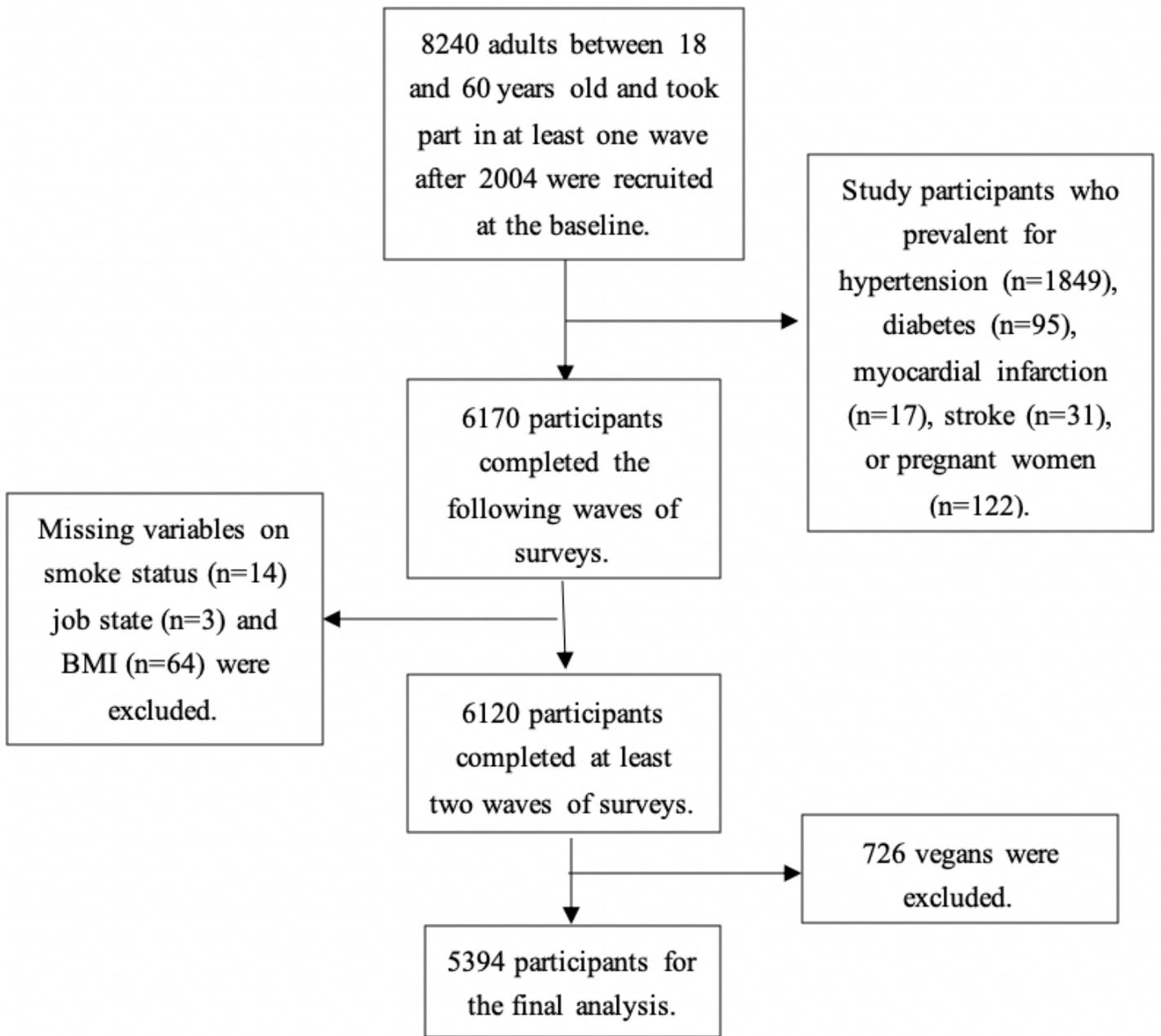


Figure 1

Flow chart.

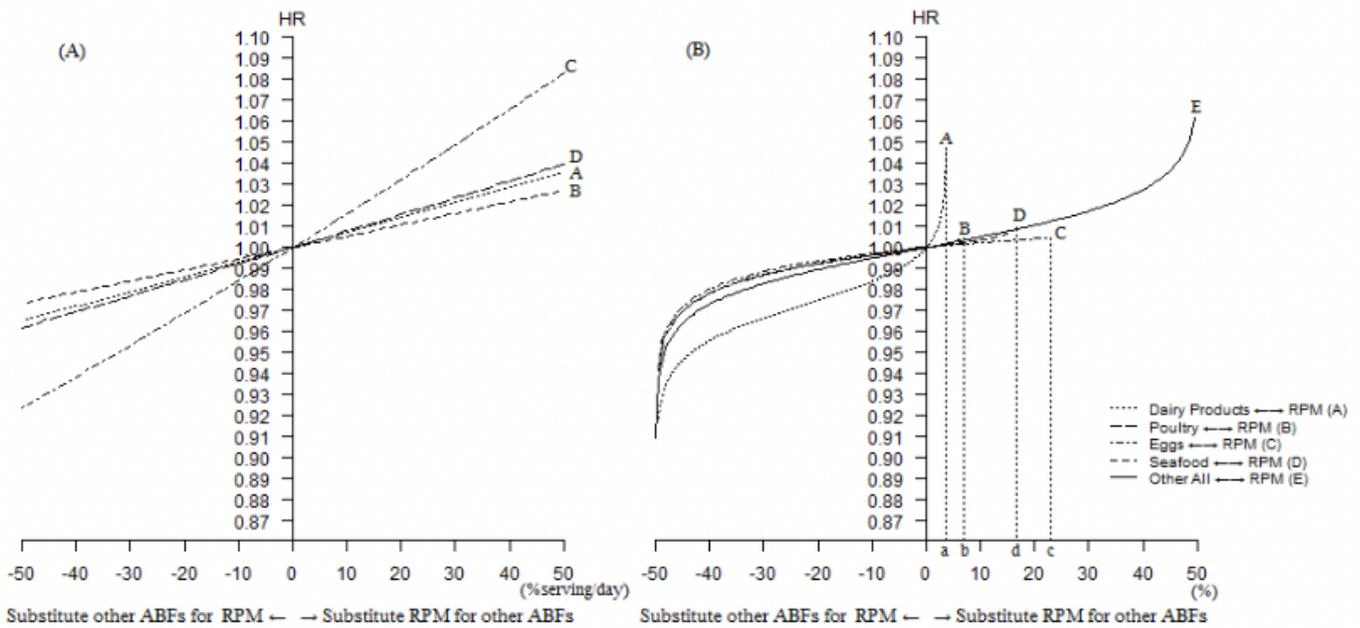


Figure 2

The HR varies with the change in consumption substitution under different substitution patterns with the method of TSA (left) and CoTSA (right). Figure A and B indicate HR variation with the changes in ABFs consumption substituted under the method of TSA and CoTSA. The x-axis is the amount of substitution (%serving/day for A and % for B), the left side of zero indicates a decrease in RPM that accompanied by compensatory increases in dairy products (A), poultry (B), eggs (C), and seafood (D), respectively. While the right side of zero indicates a replacement of dairy products, (A), poultry (B), eggs (C), and seafood (D) by RPM, respectively. The intersections of a, b, d, and c on x-axis in figure B indicate the maximum substitution amount that replacing dairy products, poultry, seafood, and eggs with RPM. The curve E in figure B is the replacement between RPM and other all ABFs.

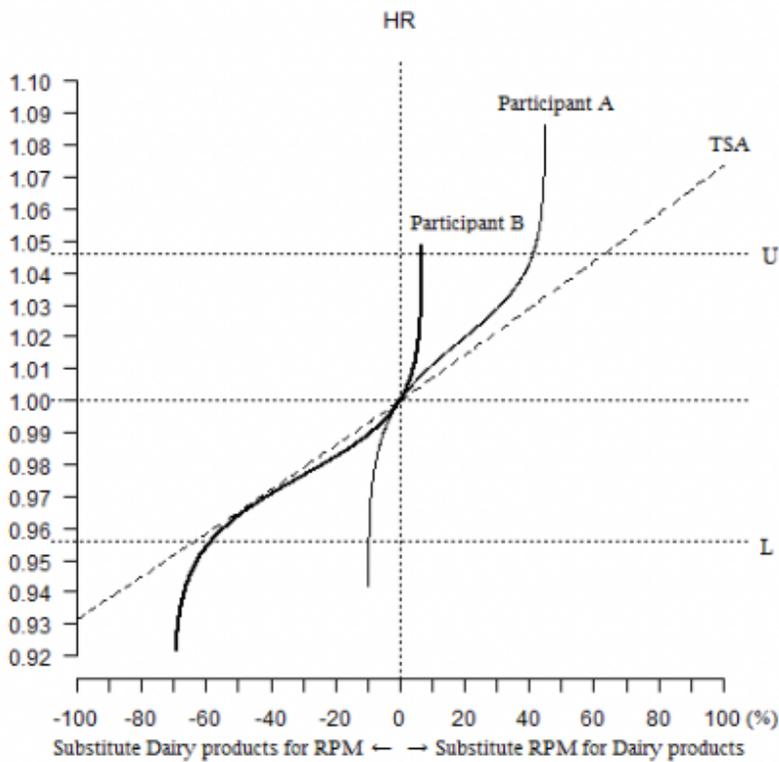


Figure 3

The HR varies with the change in consumption of substitutes between RPM and dairy products with the method of TSA (the dotted line) and CoTSA (the solid line). The thin solid line represents participant A whose consumption proportions of RPM and dairy products were 10% and 45%; The thick solid line represents participant A whose consumption proportions of RPM and dairy products were 70% and 7%. The 95% CI of HR calculated by CoTSA within the horizontal dashed line range (L and U) contains 1.

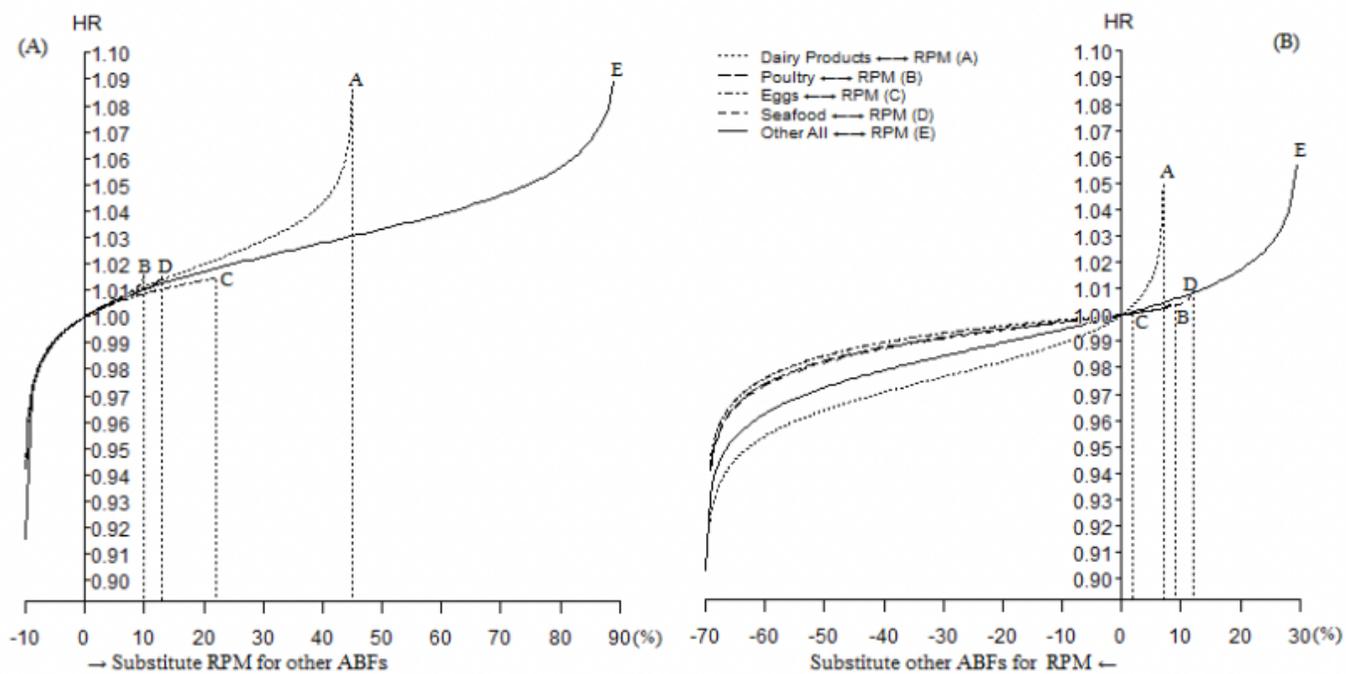


Figure 4

The HR varies with the changes in consumption of substitutes under different substitution patterns for participant A (left) and participant B (right) estimated by CoTSA. The curve of A-E represent substitution between RPM and dairy products, poultry, eggs, seafood and other all ABFs. The intersection points of dashed lines and x-axis represent the maximum range of substitution amount for different substitution patterns.

Supplementary Files

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