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Original Research Article

Ultra-processed foods and mortality: analysis from the Prospective Urban and Rural Epidemiology study

Mahshid Dehghan [1,*], Andrew Mente [1], Sumathy Rangarajan [1], Viswanathan Mohan [2], Sumathi Swaminathan [3], Alvaro Avezum [4], Scott A. Lear [5], Annika Rosengren [6], Paul Poirier [7], Fernando Lanas [8], Patricio Lopez-Jaramillo [9], Biju Soman [10], Chuangshi Wang [11], Andrés Orlandini [12], Noushin Mohammadifard [13], Khalid F. AlHabib [14], Jephat Chifamba [15], Afzal Hussein Yusufali [16], Romaina Iqbal [17], Rasha Khatib [18], Karen Yeates [19], Thandi Puoane [20], Yuksel Altuntas [21], Homer Uy Co [22], Sidong Li [11], Weida Liu [11], Katarzyna Zatońska [23], Rita Yusuf [24], Noorhassim Ismail [25], Victoria Miller [1], Salim Yusuf [1], on behalf of the Prospective Urban Rural Epidemiology (PURE) study investigators

[1] *Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada;* [2] *Dr. Mohan's Diabetes Specialities Centre, Chennai, India;* [3] *St John's Research Institute, St John's National Academy of Health Sciences, Sarjapur Road, Koramangala, Bangalore, Karnataka, India;* [4] *International Research Center, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil;* [5] *Faculty of Health Sciences, Simon Fraser University c/o Healthy Heart Program, St. Paul's Hospital, Vancouver, British Columbia, Canada;* [6] *Sahlgrenska Academy, University of Gothenburg and Sahlgrenska University Hospital, VGR Region, Sweden;* [7] *Heart and Lung Institute, Laval University, Quebec City, QC, Canad;* [8] *University of La Frontera, Temuco, Chile;* [9] *Masira Research Institute, Medical School, Universidad de Santander, Bucaramanga, Colombia;* [10] *Health Action by People, Thiruvananthapuram, Kerala, India;* [11] *Medical Research and Biometrics Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China;* [12] *Clinical Studies Latin America, Rosario, Santa Fe, Argentina;* [13] *Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran;* [14] *Department of Cardiac Sciences, King Fahad Cardiac Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia;* [15] *University of Zimbabwe, Faculty of Medicine and Health Sciences, Unit of Physiology, Harare, Zimbabwe;* [16] *Hatta Hospital, Dubai Medical College, Dubai Health Authority, Dubai, United Arab Emirates;* [17] *Department of Community Health Sciences and Medicine, Aga Khan University, Pakistan;* [18] *Institute for Community and Public Health, Birzeit University, Birzeit, Palestine & Advocate Research Institute, Advocate Health Care, IL, USA;* [19] *Department of Medicine, Queen's University, Kingston, Canada;* [20] *School of Public Health, University of the Western Cape, Bellville, South Africa;* [21] *University of Health Sciences Turkey, Faculty of Medicine, Istanbul Sisli Hamidiye Etfal Training and Research Hospital, Clinic of Endocrinology and Metabolism, Sisli, Istanbul, Turkey;* [22] *University of the Philippines College of Medicine, Manila, Philippines;* [23] *Social Medicine Department of Wroclaw Medical University, Poland;* [24] *Independent University, Dhaka, Bangladesh;* [25] *Department of Community Health, Faculty of Medicine, University Kebangsaan, Kuala Lumpur, Malaysia*

A B S T R A C T

Background: Higher intake of ultra-processed foods (UPFs) has been associated with increased risk of CVD and mortality in observational studies from Western countries but data from non-Western countries are limited.

Objectives: We aimed to assess the association between consumption of UPFs and risk of mortality and major CVD in a cohort from multiple world regions.

Design: This analysis includes 138,076 participants without a history of CVD between the ages of 35 and 70 y living on 5 continents, with a median follow-up of 10.2 y. We used country-specific validated food-frequency questionnaires to determine individuals' food intake. We classified foods and beverages based on the NOVA classification into UPFs. The primary outcome was total mortality (CV and non-CV mortality) and secondary outcomes were incident major cardiovascular events. We calculated hazard ratios using multivariable Cox frailty models and evaluated the association of UPFs with total mortality, CV mortality, non-CV mortality, and major CVD events.

Results: In this study, 9227 deaths and 7934 major cardiovascular events were recorded during the follow-up period. We found a diet high in UPFs (≥2 servings/d compared with 0 intake) was associated with higher risk of mortality (HR: 1.28; 95% CI: 1.15, 1.42; *P*-trend < 0.001), CV mortality (HR:

Abbreviations used: EPOCH, the Environmental Profile of a Community's Health; MET, metabolic equivalent of task; PURE, Prospective Urban Rural Epidemiology study; UPF, ultra-processed food.

* Address correspondence to .
E-mail address: mahshid.dehghan@phri.ca (M. Dehghan).

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1.17; 95% CI: 0.98, 1.41; *P*-trend = 0.04), and non-CV mortality (HR: 1.32; 95% CI 1.17, 1.50; *P*-trend < 0.001). We did not find a significant association between UPF intake and risk of major CVD.

Conclusions: A diet with a high intake of UPFs was associated with a higher risk of mortality in a diverse multinational study. Globally, limiting the consumption of UPFs should be encouraged.

Keywords: major cardiovascular disease, minimally processed foods, mortality, NOVA classification, ultra-processed foods

Introduction

The second half of the 20th century witnessed a dramatic transition in the diet of Western populations, characterized by the replacement of fresh or minimally processed foods by ultra-processed foods (UPFs) [1]. These changes brought about unfavorable effects on diet quality, resulting in nutritionally rich fresh foods being replaced with energy-dense foods low in fiber, micronutrients, and high in sugar. Further, in recent decades, there have also been marked increases in the consumption of poor-quality UPFs in low- and middle-income countries [2].

UPFs are prepared mostly from substances derived from foods, with little whole food content. They are affordable, highly palatable, and energy dense. Beyond poor nutrition quality, carcinogenic compounds such as heterocyclic amines, polycyclic aromatic hydrocarbons, and packaging contaminants (e.g., bisphenol S) are present in UPFs [3, 4].

Higher intake of UPFs has been shown to be associated with increased risk of CVD, cancer, and mortality in observational studies conducted in Western countries [5–9]. To date, however, there are few studies from low- and middle-income countries [10, 11]. Given the substantial burden of noncommunicable diseases in low- and middle-income countries, the impact of high UPFs on health could be pronounced in these regions.

The Prospective Urban Rural Epidemiology (PURE) study is a unique, large observational cohort in all continents (except Australia) that recorded habitual food intake and classified the consumption of UPFs for each participant based on the NOVA classification. We aimed to assess the association between consumption of UPFs and risk of mortality and major CVD in this cohort from multiple world regions.

Materials and Methods

Study design and participants

The design of the PURE study has been described previously [12]. Briefly, the study is a large-scale multinational prospective cohort study of 185,635 individuals, aged 35–70 years from 25 high-, middle-, and low-income countries, and spanning North and South America, Europe, Africa, the Middle East, and Asia. The first 2 phases of recruitment occurred between January 2003 and March 2013 and participants were followed up at 3, 6, 9, and 12 y. This analysis included 21 countries in which participants had completed ≥1 cycle of follow-up visits. Also, we excluded participants with a history of CVD at baseline (n = 11,619). Details of the sampling, recruitment strategy, and follow-up are provided in Supplementary Table 1 and Supplementary Figure 1. Information on vital status was available in 98% of the participants, and information on CVD in 95% of participants. In the final analysis, we included all cardiovascular outcome events that had happened as of September 2021. Data were collected at the community, household, and individual levels with standardized questionnaires. This study complied with the Declaration of Helsinki and all participants provided written informed consent. The study protocol was approved by the ethics committee at each participating institution (Supplementary Material). The study was co-ordinated by the Population Health Research Institute, Hamilton Health Sciences, and McMaster University, Hamilton, Ontario, Canada.

Assessment of diet by a semiquantitative FFQ

The habitual dietary intake of each participant was recorded using country-specific (or region specific in India) validated FFQs at baseline. If a validated FFQ was not available for a country, we assessed the FFQ validity and reproducibility using the method developed by Willett et al. [13] We enrolled 100–250 participants from both urban and rural areas, and each participant completed the FFQ on 2 occasions and three to four 24-h dietary recalls during a 1-year period. Correlation coefficients and deattenuated correlation coefficients between the means of 24-h dietary recalls and FFQ were calculated for macro- and micronutrients and main food groups. The level of agreement between the 2 methods was evaluated using classification into the same and extreme quartiles and the Bland–Altman method. The reproducibility of the FFQ was assessed by Pearson correlation coefficients and intraclass correlation coefficients. We did not validate the FFQs for UPF intake because in most low- and middle-income countries these foods were not a major source of energy. We previously published the results of the validation studies and a list of publications is included in Supplementary Table 2. In all countries, the FFQ included food items commonly consumed over the previous year with predefined local portion sizes and frequencies of consumption (varied from never to >6 times/d).

We classified UPFs and nonalcoholic beverages based on the NOVA classification [14]. UPFs are "foods containing mainly industrial substances with little or no whole foods." Briefly, this group includes commercially prepared and packaged foods with addition of colors, preservatives (e.g., nitrites), or food enhancers (e.g., sodium mono glutamate). As part of the PURE study, the Environmental Profile of a Community's Health (EPOCH) substudy [15], we collected a sample of packaged foods (e.g., chips, cookies, sweets, chocolate, etc.) from each participating community in PURE [16]. In addition, for each country, local nutritionists and the first author (MD) reviewed the list of food items in the FFQ and identified UPFs. The classification of UPFs was country specific. For example, some types of bread in India and Iran were not classified as UPFs because bread is daily prepared at home (chapati, roti, and dosa) or freshly bought and consumed (Iranian bread), whereas mass-produced breads in Canada and Sweden were classified as UPFs.

Overall, for the present analysis, we only included food items that were most likely to be UPFs; those that we collected a sample of packaged foods or there was no doubt in the level of processing (e.g., soft drink, processed meat, etc.). A list of UPFs by country is included in the supplementary material (Supplemental Material). We did not include alcohol in our definition of UPFs because a substantial proportion of the study population did not consume alcohol. Alcohol intake was not captured in 6 Muslim countries (Bangladesh, Iran, Malaysia, Pakistan, Saudi Arabia, and United Arab Emirates), which is

prohibited. Also, in some low- and middle-income countries (India and China), the reported intake of alcohol among females is low.

Outcomes

The primary outcome was total mortality (CV and non-CV mortality). Non-CV mortality included cancer mortality and other causes of death except death because of injury. Secondary outcomes were incident major cardiovascular events (composite of fatal CVD, and nonfatal myocardial infarction, stroke, and heart failure). Standard case-report forms were used to record data on mortality (classified by cause) and major cardiovascular events during follow-up, which were adjudicated centrally in each country by trained physicians. The definitions of these events have been published previously [12].

Statistical analysis

Standard descriptive statistical methods were used: mean (SD) or median with IQR for continuous data and the absolute and percentages for categorical data. At baseline, trained research assistants measured the weight and height of participants using a standardized protocol. Body weight was measured in light clothes to the nearest 0.1 kg using a digital scale, and height was measured to the nearest 1 cm by a stadiometer. BMI was computed as weight in kilograms divided by the square of the height in meters. We created a wealth index by using information collected on household possessions such as electricity, car, computer, television, and telephone. We created a binary yes/no classification for each item and then used a principal component analysis to extract the component with the largest eigenvalue [17]. We then assigned each household to a score based on factor loadings. Levels of physical activity at work, at home, and during recreational or sport and leisure-time activities were obtained using the International Physical Activity Questionnaire or regional questionnaires with comparable variables. Then for each participant, we converted the reported activities to metabolic equivalent task (MET) min/wk [18].

Age, wealth index, BMI, % energy provided by carbohydrate, protein, total fat, types of fat, fiber (g/d), physical activity (MET/min/wk), and total energy intake (kcal/d) were reported as continuous variables. The location was categorized as urban or rural. Smoking status was categorized as never, former, or current. Categories of education were none or primary school (first 6 y), secondary school (7–11 y), and college, trade school, or university (>11 y). We excluded participants with missing information on age, sex, and implausible value of energy intake (<500 or >5000 kcal/d $n = 14{,}312$).

We expressed the intake of UPFs as a serving of intake per day rather than a proportion of energy to account for the intake of UPFs without energy (artificially sweetened carbonated drinks, chocolate, candy, sauces, salad dressing, etc.). Also, serving intake per day is a reasonable measure of nonnutritional factors such as additives pertain to processing [6]. To examine the association between the consumption of UPFs and outcomes, participants were grouped based on their intake into 0 serving/d, <1 serving/d, 1 to <2 servings/d, and ≥2 servings/d of intake. To calculate hazard proportions (HRs), we used Cox frailty models, with random intercepts to account for clustering by country. Estimates of HRs and 95% CI are presented for categories of intake using the lowest intake as the reference group. To test for trend across categories of UPFs, the median value was assigned to each category of intake of UPFs and evaluated this as a continuous variable in the fully adjusted Cox frailty model. Also, we estimated the linear association between the consumption of UPFs (serving/d) and health outcomes.

The model was adjusted for age, sex, location (urban/rural), education, wealth index, country income level, smoking status, BMI, physical activity, history of diabetes, history of hypertension, and blood pressure medication, and daily energy intake with country considered as a random effect.

We investigated the robustness of the association between UPF intake and outcomes by various risk factors including age, sex, BMI, and by urban/rural location and country income groups. For age, we grouped participants into <60 y, and ≥60 y; and BMI categories were <25, and ≥25 kg/m^2. High-income countries include high- and upper-middle–income countries, middle-income countries include lower-middle–income countries, and low-income countries include low-income countries. Tests of heterogeneity were conducted using the I^2 statistic between categories of UPFs and any of the modifiers including BMI (<25 or ≥25), age (<60 or ≥60 y.), sex (male, female), location (urban, rural), and country income level (high-income, middle-income, and low-income).

We conducted a sensitivity analysis by excluding participants who had CVD events in the first 2 y of follow-up to account for possible reverse causation. For risk factors of primary outcome (BMI, physical activity, or history of hypertension), ≤5% of values were missing and were imputed to the median values. Missing covariates were imputed using data on age, sex, location, education, wealth index, country income level, smoking status, BMI, physical activity, history of diabetes, history of hypertension, blood pressure medication, UPFs, fruits, vegetables, legume, and daily energy intake via multiple imputation (Supplementary Table 3).

Because of cultural similarities in dietary intake, participants were grouped into 7 regions that included North America and Europe, South America, Africa, the Middle East, South Asia, South East Asia, and China.

Finally, we conducted a random-effects meta-analysis to include the results of the PURE study with the results of a recently published meta-analysis [19]. We considered a P value of <0.05 statistically significant. We used the Stata version 15 for all analyses.

Sources of support

The funders and sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; or in the decision to submit the manuscript for publication.

Results

During the median follow-up of 10.2 y (IQR: 8.5, 12.1), we recorded 9227 deaths and 7934 major cardiovascular events. Table 1 shows participant characteristics by categories of intake of UPFs. Higher consumers of UPFs were more likely to live in urban area, have a history of hypertension, diabetes, or cancer, and had higher BMI. Higher UPF consumption was associated with a higher energy, fat, and lower carbohydrate intake ($P < 0.001$ for all variables). The daily intake of UPFs and main types of UPFs by region and country are provided in Supplementary Tables 4 and 5. Also, the number of participants by geographic regions and urban rural location across categories of the UPFs is reported in Supplementary Table 6.

The intake of UPFs was higher in high-income countries (4 servings/d) than in middle-income (0.6 serving/d), and low-income (0.3 serving/d) countries (Supplementary Figure 2).

Association between UPFs and health outcomes

The associations between the servings of intake of UPFs and health outcomes are reported in Table 2. We found that higher consumption of UPFs was associated with a higher risk of total mortality (<1 serving/d HR: 1.08; 95% CI: 1.02, 1.15, 1 to <2 servings/d HR: 1.18; 95% CI: 1.06, 1.31, ≥2 servings/d HR: 1.28; 95% CI: 1.15, 1.42 vs. 0 intake; *P*-trend <0.001), CV-mortality (<1 serving/d HR: 1.11; 95% CI: 1.01, 1.23, 1 to <2 servings/d HR: 1.20; 95% CI: 1.00, 1.44, ≥2 servings/d HR: 1.17; 95% CI: 0.98, 1.41 vs. 0 intake; *P*-trend = 0.04), and non-CV mortality (<1 serving/d HR: 1.08; 95% CI: 1.00, 1.16, 1 to <2 servings/d HR: 1.18; 95% CI: 1.04, 1.35, ≥2 servings/d HR: 1.32; 95% CI: 1.17, 1.50 vs. 0 intake; *P*-trend <0.001). We did not find a significant association between UPF intake and risk of major CVD (<1 serving/d HR: 0.99; 95% CI: 0.93, 1.05, 1 to <2 servings/d HR: 1.01; 95% CI: 0.90, 1.13, ≥2 servings/d HR: 1.01; 95% CI: 0.90, 1.12 vs. 0 intake; *P*-trend = 0.9). In addition, each serving intake of UPF consumption was associated with a higher risk of mortality (5%), non-CV mortality (4%), and CV mortality (5%).

No significant association was observed between UPF intake and MI (<1 serving/d HR: 1.07; 95% CI: 0.98, 1.18, 1 to <2 servings/d HR:1.08; 95% CI: 0.91, 1.27, ≥2 servings/d HR: 1.07; 95% CI: 0.90, 1.27 vs. 0 intake; *P*-trend = 0.34), stroke (<1 serving/d HR: 0.93; 95% CI: 0.86, 1.01, 1 to <2 servings/d HR: 0.91; 95% CI: 0.76, 1.09, ≥2 servings/d HR: 0.88; 95% CI: 0.75, 1.03 vs. 0 intake; *P*-trend = 0.10), and heart failure (<1 serving/d HR: 1.16; 95% CI: 0.96, 1.40, 1 to <2 servings/d HR: 1.15; 95% CI: 0.84, 1.59, ≥2 servings/d HR: 1.22; 95% CI: 0.89, 1.68 vs. 0 intake; *P*-trend = 0.20) (Supplementary Table 7).

Subgroup analyses

The direction of associations between UPF intake and mortality (comparing ≥2 servings/d vs. 0 intake) was similar among females (HR: 1.36; 95% CI: 1.17, 1.60) and males (HR: 1.23; 95% CI: 1.07, 1.41, *P*-interaction = 0.34), younger adults (HR: 1.24; 95% CI: 1.07, 1.45) and older adults (HR: 1.32; 95% CI: 1.14, 1.53, *P*-interaction = 0.56) and individuals with BMI < 25 (HR: 1.35; 95% CI: 1.17, 1.57) and BMI ≥25 (HR: 1.14; 95% CI: 0.97, 1.34, *P*-interaction = 0.13) (Table 3). However, the magnitude of association between UPF intake and CV mortality was stronger among those with BMI <25 (HR: 1.43; 95% CI: 1.11, 1.84) than BMI ≥25 (HR: 0.91; 95% CI: 0.69, 1.19, *P*-interaction = 0.02). Similar results were observed for major CVD [BMI<25 (HR: 1.13; 95% CI: 0.96, 1.34) than BMI ≥25 (HR: 0.88; 95% CI: 0.75, 1.02, *P*-interaction = 0.03)].

TABLE 1
Characteristics of participants without history of CVD at baseline by level of consumption of UPFs (*n* = 138,076)

	Overall (*n* = 138,076)	Zero (*n* = 34,462)	<1 serving/d (*n* = 59,787)	1 to <2 servings/d (*n* = 14,273)	≥2 servings/d (*n* = 29,554)	*P* value[1]
Country income level, *n* (%)[2]						
High-income	49,262 (35.7)	1173 (3.4)	16,345 (27.3)	8727 (61.1)	23,017 (77.9)	<0.001
Middle-income	57,190 (41.4)	22,299 (67.7)	25,049 (41.9)	4220 (29.6)	5622 (19.0)	<0.001
Low-income	31,624 (22.9)	10,990 (31.9)	18,393 (30.8)	1326 (9.3)	915 (3.1)	<0.001
Age (y), mean (SD)	50.1 (10)	50.3 (1.0)	49.7 (9.9)	50.1 (9.7)	50.9 (9.6)	<0.001
Female, %	58.5	58.0	59.0	58.4	58.0	0.004
Urban, %	53.0	38.9	56.2	57.7	60.0	<0.001
Current smoker, %	20.8	23.8	20.7	19.1	18.6	<0.001
Sedentary, %	18.0	18.7	20.2	18.2	12.6	<0.001
Hypertensive, %	39.0	38.2	37.9	40.9	41.2	<0.001
History of diabetes, %	7.2	6.2	7.9	7.8	6.5	<0.001
History of cancer, %	1.3	0.5	0.7	1.6	3.1	<0.001
BMI (kg/m^2), mean (SD)	25.7 (5.3)	23.9 (4.5)	25.5 (5.2)	27.0 (5.3)	27.3 (5.5)	<0.001
Unprocessed/minimally processed foods (serving/d), median (IQR)						
Dairy	0.8 (0.1, 1.8)	0.1 (0.0, 1.0)	0.6 (0.1, 1.3)	1.3 (0.5, 2.4)	2.2 (1.0, 4.0)	<0.001
Fruits	0.9 (0.4, 1.9)	0.4 (0.2, 0.9)	0.9 (0.4, 1.8)	1.6 (0.8, 2.9)	1.6 (0.8, 2.7)	<0.001
Vegetables	1.8 (1.3, 3.1)	1.7 (1.1, 1.9)	1.7 (1.2, 2.6)	2.4 (1.6, 4.1)	3.2 (1.8, 5.9)	<0.001
Unprocessed red meat	0.4 (0.1, 1.0)	0.2 (0.0, 0.6)	0.3 (0.1, 0.8)	0.6 (0.3, 1.1)	0.9 (0.5, 1.5)	<0.001
Poultry	0.1 (0.0, 0.4)	0.0 (0.0, 0.9)	0.1 (0.0, 0.3)	0.3 (0.1, 0.5)	0.3 (0.1, 0.6)	<0.001
Fish	0.1 (0.0, 0.3)	0.0 (0.0, 0.2)	0.1 (0.0, 0.3)	0.1 (0.0, 0.5)	0.2 (0.1, 0.5)	<0.001
Starchy foods	6.0 (4.1, 8.4)	6.4 (4.7, 9.2)	5.9 (4.1, 8.1)	4.8 (3.5, 6.7)	6.0 (4.1, 8.7)	<0.001
Total and types of UPFs (serving/d), median (IQR)						
Total UPFs	0.3 (0.0, 1.6)	0.0 (0.0, 0.0)	0.2 (0.1, 0.5)	1.4 (1.2, 1.7)	4.6 (2.9, 8.0)	<0.001
Sweets	1.2 (0.3, 2.9)	0.1 (0.0, 0.5)	0.8 (0.3, 2.0)	2.1 (1.3, 3.6)	3.2 (1.9, 5.3)	<0.001
Soft drinks	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.1 (0.0, 0.2)	0.1 (0.0, 0.6)	<0.001
Packaged bread	0.2 (0.0, 1.0)	0.0 (0.0, 0.0)	0.1 (0.0, 0.7)	0.6 (0.1, 1.4)	1.1 (0.4, 2.5)	<0.001
Processed meat	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.1 (0.0, 0.4)	0.2 (0.0, 0.6)	<0.001
Daily energy and nutrient intake						
Energy intake (kcal/d)	2030 (1567, 2625)	1782 (1393, 2300)	1966 (1535, 2524)	2149 (1697, 2719)	2464 (1927, 3100)	<0.001
% energy from carbohydrate	61 (53, 69)	70 (61, 77)	61 (54, 69)	56 (50, 62)	54 (48, 60)	<0.001
% energy from fat	24 (17, 31)	15 (10, 23)	24 (17, 30)	28 (23, 32)	29 (25, 33)	<0.001
% energy from protein	15 (13, 17)	14 (12, 16)	15 (12, 17)	16 (14, 18)	16 (14, 18)	<0.001
% energy from SFA	7 (5, 10)	4.8 (3.0, 7.5)	7.0 (4.6, 10.0)	8.6 (6.1, 11.2)	9.7 (7.3, 12.1)	<0.001
% energy from MUFA	7 (5, 10)	5.4 (3.7, 7.5)	7.0 (5.0, 9.3)	8.7 (6.3, 11.0)	10.2 (7.9, 12.2)	<0.001
% energy from PUFA poly unsaturated fatty acids	4 (3, 6)	3.2 (2.1, 5.1)	4.8 (3.3, 7.0)	4.6 (3.5, 6.3)	4.7 (3.8, 5.8)	<0.001
Fiber (g/d)	19 (11, 29)	16 (10, 29)	17 (11, 27)	21 (13, 31)	23 (15, 33)	<0.001
Sodium (mg/d)	3048 (1900, 4440)	3014 (1327, 4941)	2909 (1750, 4302)	3116 (2174, 4181)	3266 (2408, 4378)	<0.001

[1] To test for differences across categories of intake of UPFs, we used ANOVA test of means and chi-square test for categorical variables.
[2] Column percent. UPF, ultra-processed food.

TABLE 2
Association between ultra-processed foods (serving/d) and health outcomes[1]

Outcomes	HR (95% CI)				*P*-trend[2]	Per serving
	Zero (n = 34,462)	<1 serving/d (n = 59,787)	1 to <2 servings/d (n = 14,273)	≥2 servings/d (n = 29,554)		
Total mortality						
Events (n)	2844	4084	779	1520		
Fully adjusted	1	1.08 (1.02, 1.15)	1.18 (1.06, 1.31)	1.28 (1.15, 1.42)	<0.001	1.05 (1.03, 1.07)
CV mortality						
Events (n)	1001	1457	236	379		
Fully adjusted	1	1.11 (1.01, 1.23)	1.20 (1.00, 1.44)	1.17 (0.98, 1.41)	0.04	1.04 (1.01, 1.08)
Non-CV mortality						
Events (n)	1866	2685	557	1165		
Fully adjusted	1	1.08 (1.00, 1.16)	1.18 (1.04, 1.35)	1.32 (1.17, 1.50)	<0.001	1.05 (1.02, 1.07)
Major CVD						
Events (n)	2818	3361	577	1178		
Fully adjusted	1	0.99 (0.93, 1.05)	1.01 (0.90, 1.13)	1.01 (0.90, 1.12)	0.9	1.01 (0.99, 1.03)

[1] Models were adjusted for age, sex, urban/rural location, education, wealth index, country income level, smoking, body mass index, physical activity, history of diabetes, history of cancer, history of hypertension, blood pressure medication, daily energy intake, and country as random effect.
[2] *P*-trend was calculated by assigning median values to each group and treated as continuous values. CV, cardiovascular.

In a stratified analysis by urban/rural location, the strength of the association between UPF intake (≥2 servings/d vs. 0 intake) and mortality were similar in urban (HR: 1.20; 95% CI: 1.01, 1.42) and rural areas (HR: 1.21; 95% CI: 1.05, 1.40, *P*-interaction = 0.94). Stratified analysis by income country level showed stronger associations between UPF intake (≥2 servings/d vs. 0 intake) and mortality in middle- and low-income countries (HR: 1.48; 95% CI: 1.22, 1.78, and HR: 1.10; 95% CI: 0.84, 1.43, respectively) than high-income countries (HR: 0.94; 95% CI: 0.71, 1.24, *P*-interaction = 0.02) (Table 4).

In sensitivity analyses, when individuals with events occurring with 24 mo of follow-up were excluded, the results were similar (Supplementary Table 8).

Also, after imputating missing covariate values (<5% missing), the results were unchanged (Supplementary Table 9).

By including the results of PURE study with the meta-analysis conducted by Taneri et al. [19], we found a higher risk of mortality for high intake of UPFs than low intake of UPFs (HR: 1.24; 95% CI: 1.17, 1.32; *P* for heterogeneity = 0.27) (Figure 1).

Discussion

In this large, multinational cohort study from 21 countries, we found that a higher intake of UPFs was associated with a higher risk of mortality, CV mortality, and non-CV mortality. Associations between UPF intake and mortality were stronger among participants in low- and middle-income countries than high-income countries.

Since the NOVA classification was introduced in 2009, only 5 cohort studies from the United States and Europe have investigated the association between the consumption of UPFs and total mortality [5, 7, 20–22]. A recent meta-analysis of these individual studies found that higher intake of UPFs was associated with a higher risk of all-cause mortality (RR: 1.29, 95% CI: 1.17, 1.42) with low between study heterogeneity [19]. To our knowledge, the PURE study is the only multinational large cohort study to use the NOVA classification to investigate the relationship between UPF intake with mortality and CVD events. We found a 28% higher risk of mortality among the highest intake group (≥2 servings/d) than the reference group (0 intake). The magnitude of association in our study is in line with a large cohort study that found the highest intake of UPFs (>14.6% of total food compared with <6.6%) was associated with 26% higher risk of mortality [20]. Also, a large cohort study from France, showed a 14% higher risk of mortality for each 10% increase in UPF consumption [22].

In our study, we did not find a significant association between the intake of UPFs and major CVD. The NutriNet-Santé study examining 105,109 individuals and 1409 major CV events, reported that the consumers of UPFs had a 13% higher risk of coronary artery diesease [8]. Similarly, the prospective Framingham Offspring cohort reported a 5% increase in the risk of CVD for each additional daily serving of UPFs [6]. Differences in findings could be because of differences in the amount and types of UPFs consumed in regions of the world, the duration of consumption of UPFs, and the background dietary patterns of the study population. Most participants in the PURE study were from low- and middle-income countries, where UPFs were more recently introduced to the food supply and consumption of UPFs was low compared with high-income countries. Also, a longer duration of consumption may be required for the harmful impacts of UPFs to become evident. Further, individuals with a low intake of UPFs reported lower consumption of unprocessed red meat and poultry, and higher intake of whole grains. Overall and in all countries, we found that sweets including pastries, cake, chocolate, and pudding were the most consumed UPFs, and in North America/Europe and South America, packaged bread was a major source of UPFs.

Of interest, the magnitude of associations between UPFs and both CV mortality and major CVD were stronger among normal-weight participants (BMI <25) compared with overweight and obese individuals (BMI ≥25). Similar results have been previously reported (23). This might be partly explained by the under-reporting of food intake by overweight and obese participants.

In this global study, we identified stronger associations between UPF intake and mortality in low- and middle-income countries than high-income countries (*P*-interaction = 0.02). Because 80% of the CVD burden occurs in low- and middle-income countries, emphasizing the harm of UPF intake may play an important role in the prevention of mortality in those areas.

A meta-analysis of our data with a recently published meta-analysis by Taneri et al. [19] doubled the number of participants and events and emphasized the strong positive association between the consumption of UPFs and mortality.

Several hypotheses may explain the adverse association between UPF intake and health outcomes. Higher consumption of UPFs

TABLE 3
Association between ultra-processed intake (serving/d) and health outcomes by some risk factors[1]

Outcomes	Zero	HR (95% CI)			*P*-interaction
		<1 serving/d	1 to <2 servings/d	≥2 servings/d	
Total mortality					
Sex					
Female (n = 80,719)	1	1.17 (1.07, 1.28)	1.23 (1.05, 1.44)	1.36 (1.17, 1.60)	
Male (n = 57,357)	1	1.03 (0.95, 1.11)	1.15 (0.99, 1.32)	1.23 (1.07, 1.41)	0.34
Age, y					
<60 (n = 109,558)	1	1.10 (1.01, 1.20)	1.13 (0.97, 1.32)	1.24 (1.07, 1.45)	
≥60 (n = 28,470)	1	1.08 (1.00, 1.18)	1.24 (1.07, 1.44)	1.32 (1.14, 1.53)	0.56
BMI					
<25 (n = 63,839)	1	1.12 (1.04, 1.20)	1.26 (1.08, 1.46)	1.35 (1.17, 1.57)	
≥25 (n = 66,566)	1	1.02 (0.92, 1.14)	1.07 (0.91, 1.25)	1.14 (0.97, 1.34)	0.13
CV mortality					
Sex					
Female (n = 80,719)	1	1.25 (1.07, 1.45)	1.31 (0.98, 1.74)	1.30 (0.97, 1.74)	
Male (n = 57,357)	1	1.03 (0.91, 1.18)	1.13 (0.89, 1.43)	1.11 (0.87, 1.41)	0.42
Age, y					
<60 (n = 109,558)	1	1.07 (0.92, 1.24)	1.18 (0.90, 1.55)	1.19 (0.90, 1.57)	
≥60 (n = 28,470)	1	1.16 (1.01, 1.32)	1.24 (0.97, 1.59)	1.19 (0.93, 1.52)	0.99
BMI					
<25 (n= 63,839)	1	1.18 (1.04, 1.33)	1.46 (1.13, 1.89)	1.43 (1.11, 1.84)	
≥25 (n = 66,566)	1	0.98 (0.83, 1.16)	0.95 (0.72, 1.24)	0.91 (0.69, 1.19)	0.02
Non-CV mortality					
Sex					
Female (n = 80,719)	1	1.15 (1.03, 1.29)	1.20 (0.99, 1.45)	1.40 (1.16, 1.68)	
Male (n = 57,357)	1	1.03 (0.93, 1.14)	1.19 (0.99, 1.42)	1.30 (1.09, 1.54)	0.57
Age, y					
<60 (n = 109,558)	1	1.13 (1.02, 1.25)	1.13 (0.94, 1.35)	1.27 (1.06, 1.52)	
≥60 (n = 28,470)	1	1.04 (0.94, 1.16)	1.27 (1.06, 1.52)	1.40 (1.17, 1.67)	0.45
BMI					
<25 (n = 63,839)	1	1.10 (1.01, 1.20)	1.17 (0.97, 1.41)	1.32 (1.11, 1.59)	
≥25 (n = 66,566)	1	1.05 (0.92, 1.21)	1.16 (0.96, 1.41)	1.26 (1.04, 1.53)	0.72
Major CVD					
Sex					
Female (n = 80,719)	1	0.98 (0.90, 1.06)	1.00 (0.85, 1.19)	0.95 (0.80, 1.12)	
Male (n = 57,357)	1	0.99 (0.91, 1.08)	0.99 (0.85, 1.16)	1.03 (0.89, 1.20)	0.48
Age, y					
<60 (n = 109,558)	1	0.97 (0.90, 1.05)	0.96 (0.82, 1.11)	0.95 (0.82, 1.10)	
≥60 (n = 28,470)	1	1.02 (0.93, 1.12)	1.10 (0.93, 1.31)	1.10 (0.93, 1.30)	0.20
BMI					
<25 (n = 63,839)	1	1.04 (0.96, 1.12)	1.08 (0.90, 1.29)	1.13 (0.96, 1.34)	
≥25 (n = 66,566)	1	0.91 (0.83, 1.00)	0.91 (0.78, 1.06)	0.88 (0.75, 1.02)	0.03

[1] Models are adjusted for age (as continuous variable for age analyses), sex (not for sex analyses), urban/rural location, education, wealth index, country income level, smoking, body mass index (as continuous variable for BMI analyses), physical activity, history of diabetes, history of cancer, history of hypertension, blood pressure medication, daily energy intake, and country as random effect. CV, cardiovascular.

increases exposure to trans fats, artificial ingredients, colors, and other environmental contaminants. In addition, compounds such as acrylamide, which is formed during the thermal processing of high-carbohydrate foods, may be neurotoxic and carcinogenic [3]. Exposure to plasticizers such as bisphenol S, used in packaging may also explain the harmful effects of UPFs [24]. The measure of urinary concentration of phthalates among 2212 participants of NHANES showed each 10% higher in energy from UPFs was associated with 8% increase in urinary mono-carboxyisoctyl phthalates [25].

UPFs may stimulate the growth of gut microbiomes that promote inflammation, which in turn increases the risk of CVD and mortality [26]. UPFs are energy-dense foods, high in sugar, trans fat, and low in protein and fiber and they may promote over-consumption. Meta--analyses of prospective cohort studies have shown high risk of overweight/obesity among those who consume high level of UPFs [10]. Further, replacing nutritionally rich fresh foods with nutritionally poor UPFs may have adverse effects on an individual's health.

Strength and limitations

Our study has several strengths. First, PURE is the largest study with data on intake of UPFs from non-Western countries and includes a diverse population with varying dietary patterns. Also, it is the largest multinational study to use the NOVA classification to investigate the association between UPF intake and health outcomes. Second, country-specific validated FFQs were used for the collection of the dietary data by well-trained staff. The methods of cooking were collected by 24-h dietary recalls as part of the FFQ validation studies, and the EPOCH substudy collected information on food packaging, which helped inform the classification of UPFs. Third, we presented the consumption of UPFs as a serving of intake per day to account for artificially sweetened UPFs and nonnutritional factors related to processing. Fourth, our study had a high follow-up rate (96% at 10 y). In addition, using the NOVA classification, we previously showed that higher intake of UPFs was associated with a higher risk of incident inflammatory bowel disease (HR: 1.82; 95% CI: 1.22, 2.72 for ≥5 servings/

TABLE 4
Association between ultra-processed foods (serving/d) and health outcomes by urban rural locations and income country level

Outcomes	Zero	HR (95% CI)			*P*-interaction
		<1 serving/d	1 to <2 servings/d	≥2 servings/d	
Total mortality					
Location					
Urban (n = 72,946)	1	1.07 (0.96, 1.19)	1.11 (0.93, 1.31)	1.20 (1.01, 1.42)	
Rural (n = 65,130)	1	1.09 (1.01, 1.17)	1.16 (1.00, 1.34)	1.21 (1.05, 1.40)	0.94
Income country					
High income (n = 49,262)	1	0.87 (0.67, 1.14)	0.93 (0.70, 1.23)	0.94 (0.71, 1.24)	
Middle income (n = 57,190)	1	1.12 (1.02, 1.23)	1.22 (0.99, 1.50)	1.48 (1.22, 1.78)	
Low income (n = 31,624)	1	1.05 (0.97, 1.15)	1.17 (0.93, 1.47)	1.10 (0.84, 1.43)	0.02
CV mortality					
Location					
Urban (n = 72,946)	1	0.98 (0.82, 1.16)	0.97 (0.73, 1.30)	0.89 (0.66, 1.20)	
Rural (n = 65,130)	1	1.19 (1.05, 1.34)	1.32 (1.04, 1.68)	1.29 (1.01, 1.64)	0.06
Income country					
High income (n = 49,262)	1	1.05 (0.63, 1.76)	0.93 (0.54, 1.60)	0.82 (0.47, 1.42)	
Middle income (n = 57,190)	1	1.13 (0.97, 1.32)	1.45 (1.06, 2.00)	1.83 (1.37, 2.44)	
Low income (31,624)	1	1.03 (0.90, 1.18)	1.19 (0.83, 1.70)	0.92 (0.58, 1.45)	0.01
Non-CV mortality					
Location					
Urban (n = 72,946)	1	1.12 (0.98, 1.28)	1.19 (0.97, 1.46)	1.35 (1.11, 1.65)	
Rural (n = 65,130)	1	1.05 (0.96, 1.15)	1.10 (0.92, 1.31)	1.18 (1.00, 1.40)	0.82
Income country					
High income (n = 49,262)	1	0.79 (0.59, 1.08)	0.91 (0.66, 1.25)	0.94 (0.68, 1.30)	
Middle income (n = 57,190)	1	1.12 (1.00, 1.25)	1.13 (0.86, 1.47)	1.30 (1.02, 1.66)	
Low income (31,624)	1	1.08 (0.98, 1.21)	1.16 (0.86, 1.57)	1.26 (0.91, 1.75)	0.26
Major CVD					
Location					
Urban (n = 72,946)	1	0.95 (0.86, 1.04)	0.93 (0.79, 1.09)	0.86 (0.73, 1.01)	
Rural (n = 65,130)	1	0.99 (0.92, 1.08)	1.03 (0.88, 1.21)	1.09 (0.93, 1.27)	0.29
Income country					
High income (n = 49,262)	1	1.13 (0.81, 1.58)	1.17 (0.83, 1.66)	1.08 (0.76, 1.53)	
Middle income (n = 57,190)	1	0.94 (0.88, 1.02)	0.92 (0.76, 1.12)	1.10 (0.93, 1.29)	
Low income (31,624)	1	1.06 (0.94, 1.18)	0.94 (0.70, 1.26)	0.75 (0.52, 1.08)	0.17

Models are adjusted for age, sex, urban/rural location (not for location analyses), education, wealth index, country income level (not for income country analyses), smoking, body mass index, physical activity, history of diabetes, history of cancer, history of hypertension, blood pressure medication, daily energy intake, and country as random effect.

d and HR: 1.67; 95% CI: 1.18, 2.37 for 1–4 servings/d compared with <1 serving/d, $P = 0.006$ for trend) [27].

Nonetheless, our study also has some potential limitations. First, the diet was self-reported, and variations in reporting might lead to random errors and divert the associations. We did not measure the diet after the baseline assessment and the consumption of UPFs may have changed in some individuals over time, particularly in low- and middle-income countries. However, large observational studies have shown similar associations between dietary fat and coronary artery diesease using repeated dietary measurements at baseline only, most recent diet, or estimates of cumulative average diet [28]. Nutritionists in each country were involved in the NOVA classification and the method of cooking for mixed dishes was considered. However, some degree of misclassification of UPFs cannot be ruled out, which might have diluted the true association between UPF intake and health outcomes. Further, we did not capture changes in the grade of processing that may happen over time. In addition, the intake of some UPFs, such as sausages, was not specifically recorded in China because UPFs were not frequently consumed or were not available. By including only "the most likely UPFs" we may have underestimated intake and consequently weakened the observed association. As with any observational study, despite extensive adjustments for covariates, residual confounding cannot be excluded. However, we adjusted for established and potential risk factors of mortality and CVD. Finally, the relatively modest number of events in some regions precluded separate analysis in these geographic regions. With further follow-up future analyses will have adequate statistical power to examine the association between UPF intake and health outcome within each region.

In this large, multinational cohort study, we report that individuals with a higher intake of UPFs have a higher risk of mortality than those who consumed a diet with low UPFs. Based on the existing evidence, public health agencies should encourage people to limit their consumption of UPFs.

The authors' responsibilities were as follows – SY: conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct, and reviewed and commented on draft; MD: coordinated the entire nutrition component of the PURE study, conducted all data analyses, and prepared the first draft of the manuscript; SR: coordinated the worldwide study and reviewed and commented on drafts; MD, AM, SR, SY: had full access to the data and were responsible for

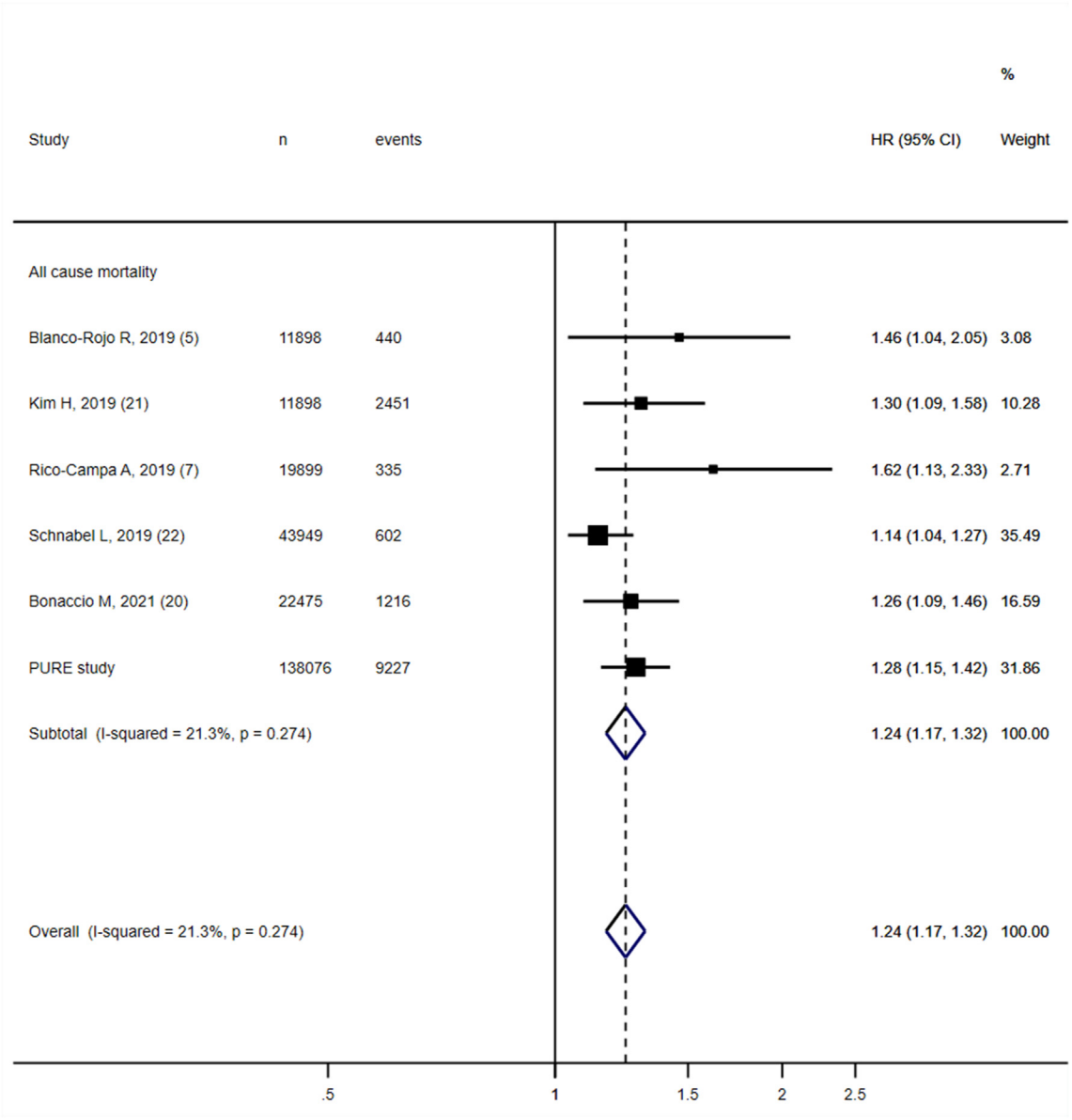

FIGURE 1. Association of ultra-processed foods (UPFs) and the risk of mortality. Comparison groups: Kim et al. (2019) > 5.2 times/d vs. <2.6 times/d ; Rico-Campa et al. (2019) >4 servings/d vs. <2 servings/d; Schnabel et al. (2019) 10% increase in proportion of UPFs to total foods; Blanco-Rojo et al. (2019) 641g/d vs. 156 g/d; Bonaccion et al. (2021) >14.6% vs. <6.6% of UPFs to total foods; and PURE study ≥2 servings/d vs. zero intake. PURE, Prospective Urban Rural Epidemiology study.

the decision to submit for publication; all other authors: co-ordinated the study in their respective countries and provided comments on drafts of the manuscript; and all authors: read and approved the manuscript.

Conflicts of Interest

The authors report no conflicts of interest.

Data Availability

The Prospective Urban Rural Epidemiology (PURE) study data described in the manuscript, code book, and analytic code will not be made available because this is an ongoing study, and during the conduct, only the investigators who have participated/contributed to the study can have access to the data. Select summary data may be shared with policy makers for specific purposes. The study executive will consider specific requests for data analyses by noncontributing individuals 3 y after the study has been completed (i.e., complete recruitment and a minimum of 10 y follow-up in all), and the participating investigators have had an opportunity to explore questions that they were interested in. Costs related to data curating and related efforts will need to be met by anybody not contributing to the conduct of the study and requesting analyses.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2022.10.014.

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