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Fruits and vegetables intake and gastric cancer risk: A pooled analysis within the Stomach cancer Pooling Project

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Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; NOS, Newcastle-Ottawa scale; OR, odds ratios; StoP Project, Stomach Cancer Pooling Project; WCRF, World Cancer Research Fund; WHO, World Health Organization.

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Abstract

A low intake of fruits and vegetables is a risk factor for gastric cancer, although there is uncertainty regarding the magnitude of the associations. In our study, the relationship between fruits and vegetables intake and gastric cancer was assessed, complementing a previous work on the association betweenconsumption of citrus fruits and gastric cancer. Data from 25 studies (8456 cases and 21 133 controls) with information on fruits and/or vegetables intake were used. A two-stage approach based on random-effects models was used to pool study-specific adjusted (sex, age and the main known risk factors for gastric cancer) odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). Exposure-response relations, including linear and nonlinear associations, were modeled using one- and two-order fractional polynomials. Gastric cancer risk was lower for a higher intake of fruits (OR: 0.76, 95% CI: 0.64-0.90), noncitrus fruits (OR: 0.86, 95% CI: 0.73-1.02), vegetables (OR: 0.68, 95% CI: 0.56-0.84), and fruits and vegetables (OR: 0.61, 95% CI: 0.49-0.75); results were consistent across sociodemographic and lifestyles categories, as well as study characteristics. Exposure-response analyses showed an increasingly protective effect of portions/day of fruits (OR: 0.64, 95% CI: 0.57-0.73 for six portions), noncitrus fruits (OR: 0.71, 95% CI: 0.61-0.83 for six portions) and vegetables (OR: 0.51, 95% CI: 0.43-0.60 for 10 portions). A protective effect of all fruits, noncitrus fruits and vegetables was confirmed, supporting further dietary recommendations to decrease the burden of gastric cancer.

KEYWORDS
fruits, gastric cancer, nutrition, pooled analyses, vegetables

1 | INTRODUCTION

A low intake of fruits and vegetables has long been acknowledged as a risk factor for gastric cancer.[1,2] However, the findings supporting the classification of this relationship as "probable" by the World Cancer Research Fund (WCRF)[3] have not been corroborated by the most recent studies.[4-7] This observation has led the WCRF to reclassify the evidence as "limited though suggestive" of a protective role of citrus fruits for cardia cancers and an increase in the risk of gastric cancer associated with a low intake of fruits. For vegetables, the classification of the evidence regarding a potential protective effect on gastric cancer has varied over time, and was classified as "limited and inconclusive" in the most recent WCRF report.[8] The inconsistency and heterogeneity of risk estimates, as well as the small number of studies addressing the different gastric cancer anatomical locations and histological types, were pointed as limitations of the evidence currently available.[8]

The Stomach Cancer Pooling (StoP) Project, a consortium of case-control studies, which uses an individual participant data approach for the evaluation of the associations between risk factors and gastric cancer,[9] allows for some of these limitations to be overcome. A recent report, based on StoP data, showed a significant reduction in the risk of gastric cancer with a high intake of citrus fruits, with similar magnitudes of association between cardia and noncardia cancers as well as between histological types; the protective effect increased until three servings/week and leveled off thereafter.[10]

The present study aimed to expand this analysis and further evaluate the association between the intake of fruits, noncitrus and vegetables and gastric cancer, through pooled analyses of individual participant data from studies participating in the StoP Project.

What's new?

Low intake of fruits and vegetables has long been associated with a higher risk of gastric cancer, and citrus fruits may be especially protective. However, results from various studies have been inconsistent. In this large, pooled analysis from a global consortium, the authors found that a higher intake of all types of fruits and vegetables was protective. This effect was seen regardless of gastric cancer location and histological type. These results reinforce current recommendations for an increased intake of both fruits and vegetables to decrease the burden of gastric cancer.

2 | METHODS

2.1 | Study population

For this analysis, version 2.0 of the StoP Project dataset was used, which included a total of 14 016 cases of incident histologically confirmed gastric cancer (4769 women and 9247 men) and 33 704 controls (13 352 women and 20 352 men) from 30 case-control or nested case-control studies, as previously described.[9] Briefly, studies became involved by personal contacts of participating investigators, which were identified through searches in electronic databases, including MEDLINE and Embase, backward citation tracking and contact with experts. Principal investigators of studies were contacted and invited to participate in the consortium with those agreeing to participate providing a signed data transfer agreement and, thereafter, the complete original data set of the study. All data were collected and harmonized according to a prespecified format at the data coordinating center. Ethical approval was obtained by each individual study and the StoP Project was approved by the University of Milan Review Board (reference 19/15 on January 4, 2015).

The present analyses used data from 25 studies (23 case-control and two nested case-control),[11] including 8456 cases and 21 133 controls with information on fruits and/or vegetables intake, they were conducted in Brazil (two studies),[12,13] Canada,[14] China (four studies),[15-18] Greece,[19] Iran (two studies),[20,21] Italy (four studies),[22-25] Japan,[26] Mexico (three studies),[27-29] Portugal,[30] Russia,[31] Spain (two studies),[32,33] Sweden (two studies)[11] and the United States of America.[34]

The quality of studies included was assessed using the Newcastle-Ottawa (NOS) quality assessment scale for case-control studies.[35] The scale evaluates the quality of studies based on three different categories: selection, exposure and comparability. A study can be awarded a maximum of nine stars, which indicates the highest quality.

2.2 | Variables defining the exposure

Food frequency questionnaires (FFQs) were used to gather information on the dietary habits of participants for the period of 1, 2, 3 or 5 years before diagnosis (for cases), onset of disease or hospital admission (for hospital-based controls) or recruitment (for population-based controls). Most studies (n = 20) included face-to-face interviews by trained researchers for the application of FFQs, while five used self-administered FFQs. Fourteen of the included studies reported that the questionnaire used was previously validated by comparison with multiple 24-hour recall interviews and/or diet records (Table S1). The FFQs used in the different studies included between 19 and 147 individual food and beverage items; most FFQs included fruits, such as apples, pears, oranges, bananas, grapes, peaches, berries (eg, strawberries, cranberries) and watermelon, and vegetables, such as cauliflower, broccoli, carrots, lettuce, cabbage, tomato, green pepper, cucumber, onions and garlic were the most common (Table S1). When the consumption of each item was expressed in grams, the weight of the item reported was converted into portions/day considering the standard size of fruits and vegetables retrieved from the tables of reference amounts for foods from various countries.[36-38]

2.3 | Statistical analysis

The frequency of consumption of each food group (portions/day) for each study was obtained by adding up the frequencies of consumption of the individual items described above, and then categorizing them into tertiles, based on the distribution of fruits, noncitrus fruits, vegetables, and fruits and vegetables intake among controls in each study.

A two-stage modeling approach was used to quantify the association between fruits and vegetables intake and gastric cancer.[39] First, through multivariable unconditional logistic regression models, the study-specific odds ratios (ORs) and corresponding 95% confidence intervals (95% CI) were estimated for the association between fruits and vegetables consumption and gastric cancer, compared to the lowest intake tertile as the reference group. Considering that the proportion of missing data was low, a complete case approach was adopted. Models included terms for sex, age (five-year age groups: <40;40-45; …; 70-75; >75), socioeconomic status (low, intermediate or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11-20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: 13-47 g of ethanol/day, high: >47 g of ethanol/day), salt intake (study-specific tertiles), red and processed meat intake (study-specific tertiles), other fruits or total vegetables intake (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies) and ethnicity (White, Black/African American, Asian, Hispanic/Latino, other), when appropriate and available (Table S3).

Then, for the second stage, summary (pooled) effects estimates were computed using random-effects models;[40] heterogeneity between studies was quantified using the I^2 statistic.[41]

Stratified analyses were also performed to further explore the effect of high consumption of fruits and vegetables across categories of sex, age, geographical region of the studies, socioeconomic status, smoking status, alcohol drinking, type of controls (hospital-based, population-based), cancer anatomical subsite (cardia, noncardia) and histological type (intestinal, diffuse and undifferentiated, as defined by the Lauren classification). For the strata of cancer subsite and histological type, multinomial logistic regression models were used to estimate the ORs for each type of cancer separately (ie, cardia and noncardia or intestinal, diffuse and undifferentiated).The difference between groups was assessed through the Q test for heterogeneity.[42,43]

Several sensitivity analyses were performed: first, by defining the same categories of exposure for all studies according to the distribution of all fruits, noncitrus and vegetables consumption in all controls. Second, the categories of exposure were defined using as reference the minimum amounts of consumption recommended by the World Health Organization (WHO) to prevent noncommunicable diseases and their risk factors, that is, at least two portions/day for fruits, three portions/day for vegetables, and five portions/day for fruits and vegetables.[44] The cut-offs that describe consumption of less than half of the recommended amount, between half and the recommended amount or more than the recommended amount were used, resulting in three categories. Third, excluding the consumption of fruit juice from fruit and noncitrus fruit intake, and excluding the consumption of legumes, such as beans, lentils, chickpeas and peas, from vegetable intake. Fourth, removing studies that used a self-administered FFQ (n = 5) and nonvalidated FFQs (n = 11), as well as studies that scored five or less stars in the NOS (n = 5). Fifth, analyses were restricted to studies evaluating participants more than 1 year before the gastric cancer diagnosis, and to case-control studies. Further sensitivity analyses were carried out to compare the estimates adjusted and unadjusted for total energy intake, as well as adjusted for the presence of *Helicobacter pylori* infection, among studies with information on energy intake and infection status, respectively. Finally, the influence of specific studies to the overall estimates was also analyzed by excluding one study at a time.

A one-stage strategy of analysis was used to assess the shape of the dose-response relationship for all exposures considered, first by considering the variable as continuous in the logistic model and assessing the significance of a linear trend,[39] and second through fractional polynomial regression models[45] that take into account the nonlinear trend between the exposure and the outcome. First- and second-order transformations were computed for the continuous term of fruits, noncitrus and vegetables intake, and the model minimizing the deviance difference with respect to the linear model was selected.[45]

The statistical analysis was performed with STATA, version 15.1 (Stata Corporation, College Station, Texas).

3 | RESULTS

The consumption of fruits and vegetables among the participants in each study is described in Table 1. In most studies, controls had a higher median consumption of both fruits and vegetables, when compared to cases. For fruits, the median consumption ranged between 0.0 (China 4) and 4.2 (Greece) portions/day for cases, and 0.3 (China 2 and China 4) and 4.7 (Greece) portions/day for controls. For noncitrus, the median consumption ranged from 0.1 (Iran 1) and 3.0 (Greece) portions/day for cases, and 0.1 (Iran 1) and 3.1 (Greece) portions/day for controls. Regarding vegetables, the median consumption ranged between 0.4 (China 1) and 3.9 (Russia, Mexico 1 and Mexico 3) portions/day for cases, and 0.4 (China 1) and 4.4 (Japan 3) portions/day for controls. For fruits and vegetables together, the median consumption ranged from 1.2 (Iran 1) to 7.8 (Greece) portions/day among cases, and 1.5 (Iran 1) to 9.0 (Greece) portions/day among controls. The main sociodemographic characteristics of the cases and controls are described in Table S2.

A significantly lower risk of gastric cancer was observed for a higher consumption of fruits, vegetables, and fruits and vegetables (Table 2), with the strongest associations being observed for the comparisons of the highest vs the lowest tertiles (fruits, OR: 0.76, 95% CI: 0.64-0.90, I^2: 59.7%; vegetables, OR: 0.68, 95% CI: 0.56-0.84, I^2: 74.5%; fruits and vegetables, OR: 0.61, 95% CI: 0.49-0.75, I^2: 75.5%). Although not statistically significant, a higher consumption of

TABLE 1 Median and percentiles 25 and 75 (portions/day) of fruits, noncitrus fruits, vegetables, and fruits and vegetables consumption by area and study

	Cases						Controls					
			Median (P25-P75) portions/day						Median (P25-P75) portions/day			
	n	%	Fruits	Noncitrus fruits	Vegetables	Fruits and vegetables	n	%	Fruits	Noncitrus fruits	Vegetables	Fruits and vegetables
Total	8456		1.7 (0.9-2.9)	1.4 (0.7-2.4)	1.7 (0.8-3.1)	3.6 (2.2-5.8)	21 133		1.8 (1.0-3.0)	1.4 (0.8-2.4)	2.1 (1.1-3.4)	4.1 (2.6-6.3)
Study												
Europe	4345	51.4	1.9 (1.1-3.0)	1.5 (0.9-2.4)	1.6 (0.6-2.9)	3.6 (2.2-5.7)	11 013	52.1	2.1 (1.3-3.3)	1.7 (1.0-2.6)	2.1 (1.0-3.4)	4.5 (2.8-6.5)
Greece (Lagiou et al., 2004)[19]	110	1.3	4.2 (2.6-6.4)	3.0 (1.9-4.9)	3.1 (2.2-4.4)	7.8 (5.5.-10.6)	100	0.5	4.7 (3.7-5.9)	3.1 (2.1-4.1)	3.9 (2.9-5.2)	9.0 (6.7-10.6)
Italy 1 (La Vecchia et al., 1995)[22]	769	9.1	2.4 (1.6-3.6)	2.0 (1.3-3.0)	2.2 (1.6-3.1)	4.8 (3.5-6.4)	2081	9.8	3.0 (2.0-4.0)	2.1 (1.4-3.1)	2.7 (2.1-3.7)	5.6 (4.2-7.3)
Italy 2 (Lucenteforte et al., 2008)[23]	230	2.7	3.9 (1.9-5.4)	2.8 (1.4-4.0)	0.9 (0.6-1.4)	4.8 (2.8-6.6)	547	2.6	3.6 (2.1-5.4)	2.7 (1.6-4.1)	0.9 (0.6-1.4)	4.7 (2.9-6.8)
Italy 3 (De Feo et al., 2012)[24]	157	1.9	1.6 (1.0-1.6)	NA	1.0 (1.0-1.6)	2.6 (2.0-3.3)	429	2.0	1.0 (1.0-1.6)	NA	1.0 (1.0-1.6)	2.0 (1.6-3.0)
Italy 4 (Buiatti et al., 1989)[25]	1016	12.0	1.6 (1.0-2.1)	1.2 (0.8-1.7)	0.5 (0.3-0.7)	2.1 (1.5-2.7)	1159	5.5	1.7 (1.2-2.2)	1.3 (0.9-1.7)	0.5 (0.4-0.7)	2.2 (1.7-2.9)
Portugal (Lunet et al., 2007)[30]	633	7.5	1.5 (0.9-2.2)	1.3 (0.8-1.9)	1.8 (1.1-2.7)	3.4 (2.2-4.8)	1600	7.6	2.0 (1.4-2.8)	1.6 (1.1-2.4)	2.1 (1.3-3.1)	4.3 (3.0-5.8)
Russia (Zaridze et al., 2000)[31]	444	5.2	2.7 (1.5-4.5)	2.2 (1.1-4.0)	3.9 (2.0-6.4)	7.3 (3.9-10.7)	606	2.9	2.6 (1.4-4.4)	2.1 (1.0-3.7)	4.1 (2.4-6.1)	7.0 (4.1-10.4)
Spain 1 (Castaño-Vinyals, 2015)[32]	339	4.0	2.5 (1.6-3.5)	1.7 (1.0-2.5)	2.6 (1.5-3.8)	5.2 (3.6-7.2)	3040	14.4	2.5 (1.5-3.5)	1.6 (0.9-2.4)	2.6 (1.7-3.8)	5.3 (3.6-7.1)
Spain 2 (Santibanez et al., 2012)[33]	398	4.7	1.8 (1.2-2.5)	1.1 (0.8-1.6)	2.0 (1.2-3.2)	4.0 (2.9-5.4)	455	2.1	2.0 (1.4-2.7)	1.1 (0.8-1.6)	2.2 (1.5-3.5)	4.5 (3.2-6.0)
Sweden 1 (Harris et al., 2013)[11]	88	1.0	1.5 (0.5-2.0)	NA	2.0 (1.5-3.8)	4.0 (2.5-5.5)	352	1.7	1.5 (1.0-2.5)	NA	2.5 (1.5-4.0)	4.0 (3.0-6.0)
Sweden 2 (Harris et al., 2013)[11]	161	1.9	1.0 (0.5-1.5)	NA	2.0 (1.0-3.0)	3.0 (2.0-4.5)	644	3.0	1.0 (0.5-2.0)	NA	2.0 (1.0-3.0)	3.0 (2.0-4.5)
Asia	1863	22.0	1.2 (0.3-2.8)	1.1 (0.4-2.5)	1.6 (0.6-3.2)	3.6 (2.2-5.7)	3005	14.2	1.0 (0.3-2.6)	1.0 (0.3-2.6)	1.5 (0.5-3.0)	3.7 (1.9-6.8)
China 1 (Deandrea et al., 2010)[17]	266	3.1	NA	NA	0.4 (0.3-0.5)	NA	533	2.5	NA	NA	0.4 (0.2-0.5)	NA
China 2 (Mu et al., 2005)[15]	201	2.4	0.2 (0.0-0.6)	0.2 (0.0-0.6)	2.1 (1.1-3.6)	2.5 (1.4-4.0)	410	1.9	0.3 (0.0-0.6)	0.3 (0.0-0.6)	2.1 (1.3-3.4)	2.6 (1.9-4.4)
China 3 (Setiawan et al., 2005)[16]	702	8.3	2.0 (0.8-4.7)	1.9 (0.8-4.5)	2.8 (1.9-3.9)	5.1 (3.2-8.9)	696	3.3	2.4 (1.1-5.5)	2.2 (1.0-5.1)	2.8 (1.9-3.9)	5.4 (3.5-9.8)
China 4 (Setiawan et al., 2000)[18]	115	1.4	0.0 (0.0-0.3)	NA	NA	NA	390	1.8	0.3 (0.0-0.3)	NA	NA	NA
Iran 1 (Pourfarzi et al., 2009)[20]	216	2.5	0.3 (0.1-0.9)	0.1 (0.1-0.5)	0.7 (0.5-1.1)	1.2 (0.7-2.0)	392	1.9	0.4 (0.3-1.0)	0.1 (0.1-0.5)	1.0 (0.4-1.4)	1.5 (0.8-2.4)
Iran 2 (Pakseresht et al., 2011)[21]	210	2.5	1.8 (1.0-2.8)	1.1 (0.6-1.7)	0.5 (0.3-1.1)	2.6 (1.6-3.6)	281	1.3	1.6 (1.0-2.9)	1.0 (0.6-1.8)	0.7 (0.4-1.4)	2.5 (1.5-4.3)
Japan 3 (Machida-Montani et al., 2004)[26]	153	1.8	2.5 (1.6-3.9)	2.3 (1.5-3.6)	3.7 (2.3-5.8)	6.5 (4.2-9.6)	303	1.4	3.0 (1.9-4.1)	2.7 (1.7-3.7)	4.4 (2.6-6.3)	7.7 (5.0-10.2)
Americas	2248	26.6	1.6 (0.8-2.6)	1.3 (0.6-2.2)	2.1 (1.2-3.4)	3.8 (2.4-5.8)	7115	33.7	1.5 (0.8-2.5)	1.1 (0.6-2.0)	2.1 (1.3-3.4)	3.8 (2.4-5.6)
Brazil 1 (Nishimoto et al., 2002)[13]	226	2.7	1.2 (0.5-2.0)	NA	1.2 (0.4-1.7)	2.5 (1.4-3.6)	226	1.1	1.5 (1.0-2.2)	NA	1.4 (0.7-2.0)	3.1 (2.1-4.0)
Brazil 2 (Hamada et al., 2002)[12]	93	1.1	1.5 (1.0-2.2)	NA	1.5 (1.2-2.2)	3.5 (2.2-4.5)	186	0.9	1.4 (1.0-2.2)	NA	2.0 (1.2-2.2)	3.5 (2.6-4.4)
Canada (Mao et al., 2002)[14]	1170	13.8	1.3 (0.6-2.1)	1.0 (0.4-1.7)	1.8 (1.1-2.6)	3.3 (2.1-4.7)	5023	23.8	1.4 (0.6-2.1)	1.1 (0.5-1.7)	1.8 (1.1-2.6)	3.3 (2.1-4.6)
Mexico 1 (Hernandez-Ramirez et al., 2009)[27]	248	2.9	1.9 (1.2-3.0)	1.6 (1.0-2.5)	3.9 (3.1-4.5)	5.8 (4.6-7.5)	478	2.3	1.4 (0.7-2.5)	1.1 (0.6-2.1)	3.9 (3.1-4.5)	5.4 (4.2-7.0)
Mexico 2 (Lopez-Carrillo et al., 1994)[28]	220	2.6	2.7 (1.6-4.1)	2.3 (1.3-3.4)	3.7 (2.5-4.8)	6.4 (4.5-9.0)	752	3.6	2.9 (1.6-4.5)	2.3 (1.3-3.6)	4.2 (3.3-5.6)	7.3 (5.1-9.7)
Mexico 3 (Lopez-Carrillo et al., 2003)[29]	159	1.9	3.5 (1.9-5.9)	2.2 (1.3-3.8)	3.9 (3.0-5.0)	7.5 (5.3-10.5)	318	1.5	3.4 (1.9-6.2)	2.3 (1.3-4.1)	3.9 (3.2-4.9)	7.7 (5.5-10.8)
USA 1 (Zhang et al., 1999)[34]	132	1.6	1.5 (0.7-2.7)	1.4 (0.6-2.4)	1.7 (1.1-2.7)	3.6 (2.0-5.4)	132	0.6	1.6 (0.6-2.9)	1.4 (0.6-2.5)	1.9 (1.1-3.1)	3.7 (2.0-5.5)

Abbreviations: NA, not available; P25-P75, percentile 25-percentile 75.

noncitrus fruits also had a lower risk of gastric (OR: 0.86, 95% CI: 0.73-1.02, I^2: 55.0%) (Table 2 and Figure 1).

The protective effect of a high consumption of all these food groups was consistent across most strata of sociodemographic and lifestyle variables (Table 3). Although the difference was not statistically significant, individuals belonging to the low socioeconomic status strata presented the highest protection for a higher consumption of fruits (OR: 0.66, 95% CI: 0.52-0.84, I^2: 56.9%) and noncitrus fruits (OR: 0.72, 95% CI: 0.56-0.93, I^2: 54.6%), compared to subjects in intermediate (fruits: OR: 0.96, 95% CI: 0.75-1.23, I^2: 26.9%; noncitrus fruits: OR: 1.06, 95% CI: 0.81-1.38, I^2: 36.0%) and high socioeconomic status (fruits: OR: 0.95, 95% CI: 0.60-1.51, I^2: 32.1%; noncitrus fruits: OR: 1.14, 95% CI: 0.78-1.66, I^2: 19.9%). There were also slight differences according to the site of gastric cancer, for vegetables, with a stronger association being observed among noncardia gastric cancer (OR: 0.61, 95% CI: 0.50-0.73, I^2: 60.3%) when compared to those with cardia gastric cancer (OR: 0.86, 95% CI: 0.64-1.14, I^2: 18.9%).

Sensitivity analyses did not result in changes in the direction or magnitude of the associations; a significantly lower risk of gastric cancer was still observed when considering OR estimates adjusted for total energy intake or accounting for *H. pylori* infection (Table 3). Other strategies to reduce heterogeneity among studies, namely, using the same cut-off for all studies, defined either by the overall

TABLE 2 Pooled odds ratios of gastric cancer according to study-specific tertiles of fruits, noncitrus fruits, vegetables, and fruits and vegetables consumption (portions/day)

	Cases			Controls				
	n	%	Portions/day median (P25-P75)	n	%	Portions/day median (P25-P75)	OR (95% CI)[a]	I^2 (%)
Fruits[b]								
1st tertile	3164	37.6	0.8 (0.4-1.2)	7041	33.3	0.8 (0.4-1.2)	1	
2nd tertile	2604	31.0	1.9 (1.5-2.5)	6841	32.3	1.9 (1.4-2.6)	0.81 (0.71-0.93)	49.2
3rd tertile	2350	27.9	3.6 (2.5-5.3)	6617	31.2	3.6 (2.5-4.7)	0.76 (0.64-0.90)	59.7
Missing	292	3.5		673	3.2			
P value for trend							<.001	
Noncitrus fruits[c]								
1st tertile	2686	35.6	0.6 (0.3-1.0)	6121	32.4	0.6 (0.3-1.0)	1	
2nd tertile	2353	31.2	1.4 (1.1-2.1)	6181	32.7	1.4 (1.1-2.0)	0.83 (0.70-0.98)	61.8
3rd tertile	2234	29.6	3.0 (2.0-4.4)	5956	31.5	2.8 (2.1-3.9)	0.86 (0.73-1.02)	55.0
Missing	275	3.6		625	3.3			
P value for trend							<.001	
Vegetables[d]								
1st tertile	3311	38.8	1.0 (0.4-1.6)	7028	33.0	1.0 (0.5-1.5)	1	
2nd tertile	2552	29.9	2.1 (1.1-2.8)	6826	32.1	2.2 (1.6-2.8)	0.81 (0.69-0.95)	65.8
3rd tertile	2471	28.9	3.6 (2.3-5.1)	6867	32.3	3.8 (2.8-5.0)	0.68 (0.56-0.84)	74.5
Missing	208	2.4		547	2.6			
P value for trend							<.001	
Fruits and vegetables[e]								
1st tertile	3200	38.7	2.0 (1.4-3.1)	6888	33.2	2.2 (1.5-3.2)	1	
2nd tertile	2493	30.1	4.1 (2.8-5.6)	6532	31.5	4.3 (3.1-5.6)	0.76 (0.65-0.88)	59.2
3rd tertile	2303	27.8	7.0 (4.7-9.9)	6667	32.1	7.1 (5.3-9.1)	0.61 (0.49-0.75)	75.5
Missing	280	3.4		648	3.1			
P value for trend							<.001	

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; P25-P75, percentile 25-percentile 75.

[a]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age (five-year age groups: <40; 40-45; …; 70-75; >75), socioeconomic status (low, intermediate or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11-20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: 13-47 g/day, high: >47 g/day), salt intake (study-specific tertiles), red and processed meat intake (study-specific tertiles), other fruits or total vegetables intake (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies) and ethnicity (White, Black/African American, Asian, Hispanic/Latino, other).

[b]No information for study China 1.[17]

[c]No information for studies Brazil 1,[13] Brazil 2,[12] China 1,[17] China 4,[18] Italy 3,[24] Sweden 1[11] and Sweden 2.[11]

[d]No information for study China 4.[18]

[e]No information for studies China 1[17] and China 4.[18]

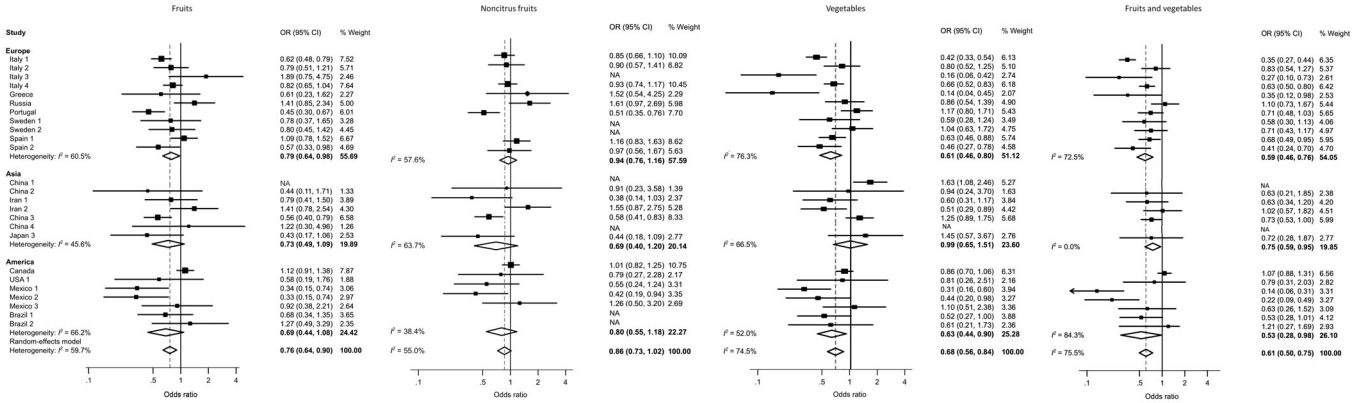

FIGURE 1 Forest plots describing the association between the intake of fruits, noncitrus fruits, vegetables and fruits and vegetables (highest vs lowest tertile, portions/day) and gastric cancer using the estimates from the Stomach Cancer Pooling (Stop) Project database. 95% CI, 95% confidence interval; NA, not available; OR, odds ratio

TABLE 3 Pooled odds ratio of gastric cancer for the highest vs the lowest study-specific tertile of fruits, noncitrus fruits, vegetables and fruits and vegetables consumption (portions/day) according to strata of selected variables

	Fruits		Noncitrus fruits		Vegetables		Fruits and vegetables	
	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)
Overall	0.76 (0.64-0.90)	59.7	0.86 (0.73-1.02)	55.0	0.68 (0.56-0.84)	74.5	0.61 (0.49-0.75)	75.5
Sex								
Men	0.74 (0.57-0.95)	67.9	0.76 (0.59-0.97)	63.3	0.72 (0.57-0.91)	67.7	0.62 (0.48-0.80)	72.7
Women	0.75 (0.60-0.94)	31.4	0.94 (0.68-1.30)	60.9	0.66 (0.51-0.86)	46.6	0.59 (0.45-0.78)	55.3
P for interaction	.938		.308		.627		.796	
Age (years)								
≤55	0.83 (0.66-1.05)	18.4	0.92 (0.76-1.12)	0.0	0.72 (0.55-0.95)	46.0	0.67 (0.52-0.86)	32.1
>55 to ≤65	0.65 (0.48-0.88)	44.6	0.83 (0.59-1.15)	51.0	0.82 (0.57-1.19)	67.6	0.60 (0.41-0.88)	70.5
>65	0.79 (0.63-0.99)	39.9	0.89 (0.71-1.11)	34.9	0.67 (0.54-0.84)	40.2	0.65 (0.53-0.80)	37.5
P for interaction	.438		.871		.650		.894	
Area								
Europe	0.79 (0.64-0.98)	60.5	0.94 (0.76-1.16)	57.6	0.61 (0.46-0.80)	76.3	0.59 (0.46-0.76)	72.5
Asia	0.73 (0.49-1.09)	45.6	0.69 (0.40-1.19)	63.7	0.99 (0.65-1.51)	66.5	0.75 (0.59-0.95)	0.0
Americas	0.69 (0.44-1.08)	65.2	0.80 (0.55-1.18)	38.4	0.62 (0.44-0.89)	52.0	0.53 (0.28-0.98)	84.3
P for interaction	.843		.502		.142		.310	
Socioeconomic status[b]								
Low	0.66 (0.52-0.84)	56.9	0.72 (0.56-0.93)	54.6	0.66 (0.50-0.88)	70.0	0.59 (0.46-0.75)	64.1
Intermediate	0.96 (0.75-1.23)	26.9	1.06 (0.81-1.38)	36.0	0.79 (0.62-1.00)	31.4	0.75 (0.56-0.99)	54.7
High	0.95 (0.60-1.51)	32.1	1.14 (0.78-1.66)	19.9	0.63 (0.36-1.11)	50.2	0.75 (0.49-1.17)	41.7
P for interaction	.079		.052		.561		.387	
Cigarette smoking[c]								
Never	0.75 (0.61-0.91)	34.7	0.90 (0.70-1.15)	48.4	0.69 (0.54-0.88)	56.7	0.60 (0.47-0.78)	62.5
Former	0.86 (0.62-1.19)	48.6	0.96 (0.69-1.36)	49.6	0.72 (0.54-0.98)	37.9	0.60 (0.44-0.81)	48.6
Current	0.63 (0.46-0.86)	36.1	0.60 (0.42-0.86)	45.5	0.78 (0.56-1.08)	49.5	0.55 (0.38-0.78)	53.1
P for interaction	.397		.119		.842		.917	
Alcohol intake[d]								
Non drinker	0.61 (0.43-0.86)	54.0	0.64 (0.43-0.95)	56.0	0.60 (0.44-0.84)	54.4	0.48 (0.34-0.69)	60.9
Drinker								

TABLE 3 (Continued)

	Fruits		Noncitrus fruits		Vegetables		Fruits and vegetables	
	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)	OR (95% CI)[a]	I^2 (%)
≤12 g of ethanol/day	0.84 (0.60-1.17)	48.3	0.99 (0.72-1.35)	34.7	0.71 (0.48-1.01)	55.5	0.62 (0.43-0.88)	59.0
>12-47 g of ethanol/day	0.82 (0.57-1.18)	59.7	0.86 (0.67-1.09)	21.8	0.75 (0.51-1.08)	63.8	0.66 (0.47-0.93)	59.1
>47 g of ethanol/day	0.78 (0.50-1.22)	23.7	1.02 (0.56-1.84)	49.9	0.57 (0.42-0.79)	0.0	0.55 (0.37-0.82)	18.9
P for interaction	.559		.359		.647		.605	
Controls								
Hospital-based[e]	0.67 (0.56-0.79)	0.0	0.88 (0.73-1.06)	0.0	0.60 (0.39-0.95)	82.9	0.50 (0.37-0.68)	51.6
Population-based[f]	0.74 (0.58-0.94)	69.3	0.78 (0.61-1.00)	68.1	0.74 (0.59-0.91)	63.9	0.63 (0.50-0.81)	74.1
P for interaction	.511		.445		.406		.243	
Site[g]								
Cardia	0.81 (0.62-1.07)	11.1	0.82 (0.55-1.21)	39.8	0.86 (0.64-1.14)	18.9	0.75 (0.57-1.00)	22.9
Noncardia	0.74 (0.60-0.91)	64.9	0.88 (0.72-1.08)	59.3	0.61 (0.50-0.73)	60.3	0.58 (0.45-0.74)	78.4
P for interaction	.606		.755		.051		.179	
Histotype[h]								
Intestinal	0.83 (0.61-1.13)	54.3	0.87 (0.61-1.24)	60.0	0.72 (0.52-1.00)	62.5	0.73 (0.55-0.98)	52.3
Diffuse	0.74 (0.55-1.00)	34.3	0.89 (0.66-1.20)	30.4	0.62 (0.48-0.80)	19.8	0.58 (0.42-0.81)	50.2
Undifferentiated	1.04 (0.71-1.41)	47.5	1.08 (0.84-1.40)	28.9	0.77 (0.57-1.02)	40.6	0.93 (0.64-1.36)	65.3
P for interaction	.337		.508		.526		.179	
Studies with information on energy intake[i]								
Adjusting for energy intake	0.66 (0.54-0.82)	60.6	0.82 (0.68-1.00)	56.2	0.64 (0.49-0.84)	78.2	0.54 (0.42-0.69)	74.7
Not adjusting for energy intake	0.81 (0.66-1.00)	65.1	0.99 (0.79-1.25)	72.1	0.75 (0.62-0.90)	60.1	0.68 (0.60-0.78)	29.6
Studies with information on *H. pylori* (HP) infection status[j]								
Adjusting for HP infection	0.70 (0.49-1.00)	58.0	0.76 (0.49-1.19)	64.7	0.69 (0.51-0.93)	45.4	0.59 (0.41-0.84)	62.6
Not adjusting for HP infection	0.70 (0.50-1.00)	58.4	0.76 (0.48-1.19)	66.5	0.68 (0.51-0.91)	43.9	0.59 (0.42-0.83)	61.2

Abbreviations: 95% CI, 95% confidence interval; HP, *Helicobacter pylori*; OR, odds ratio.

[a]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age (five-year age groups: <40;40-45; …; 70-75; >75), socioeconomic status (low, intermediate or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of ≤10 cigarettes/day; 11-20 cigarettes/day; >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: 13-47 g/day, high: >47 g/day), salt intake (study-specific tertiles), red and processed meat intake (study-specific tertiles), other fruits or total vegetables intake (study-specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter studies) and ethnicity (White, Black/African American, Asian, Hispanic/Latino, other).

[b]As defined in each original study based on education, income or occupation.

[c]Excluding study China 4.[18]

[d]Excluding studies China 3,[16] China 4[18] and Iran 2.[21]

[e]Includes studies Brazil 1,[13] China 1,[17] Greece,[19] Italy 1,[22] Italy 2,[23] Italy 3,[24] Japan 3,[26] Mexico 3,[29] Spain 2[33] and USA 1.[34] Excluding studies Brazil 2[12] and Russia[31] as they include both hospital- and population-based controls.

[f]Includes studies Canada,[14] China 2,[15] China 3,[16] China 4,[18] Iran 1,[20] Iran 2,[21] Italy 4,[25] Mexico 1,[27] Mexico 2,[28] Portugal,[30] Spain 1,[32] Sweden 1[11] and Sweden 2.[11] Excluding studies Brazil 2[12] and Russia[31] as they include both hospital- and population-based controls.

[g]Excluding studies China 1,[17] China 2,[15] China 3,[16] China 4[18] and Mexico 3.[29]

[h]Excluding studies China 1,[17] China 2,[15] China 3,[16] China 4,[18] Greece,[19] Italy 1,[22] Japan 3,[26] Mexico 2,[28] Sweden 1[11] and Sweden 2.[11]

[i]No information for studies Brazil 1,[13] Brazil 2,[12] Canada,[14] China 1,[17] China 2,[15] China 4,[18] Iran 1,[20] Italy 3,[24] Russia,[31] Sweden 1,[11] Sweden 2[11] and USA1.[34]

[j]No information for studies Canada,[14] China 1,[17] China 3,[16] China 4,[18] Greece,[19] Italy 1,[22] Italy 2,[23] Italy 3,[24] Italy 4,[25] Mexico 2,[28] Spain 2,[33] Sweden 1,[11] Sweden 2[11] and USA1.[34] *H. pylori* infection was defined using the same criteria of the original studies, according to the following serological tests: enzyme-linked immunosorbent assay (ELISA) tests (nine studies)[12,13,15,20,26,27,29-31] or Western Blot (one study)[21] to determine immunoglobulin G (IgG) antibody titers in serum, and in one study through multiplex serology.[32] When anti-*H. pylori* serum IgG titers were assessed using an ELISA-based method, participants with borderline results were classified as testing positive for *H. pylori* infection.

distribution in controls or taking the amounts recommended by the WHO into account, led to estimates of the same magnitude, with slightly lower heterogeneity, particularly for noncitrus and vegetables intake (Table S4).

Additional stratified analyses according to study characteristics also yielded similar and consistent results throughout (Table S5). The results excluding fruit juices and legumes from the fruit and vegetable intakes, respectively, also did not materially differ from those of the

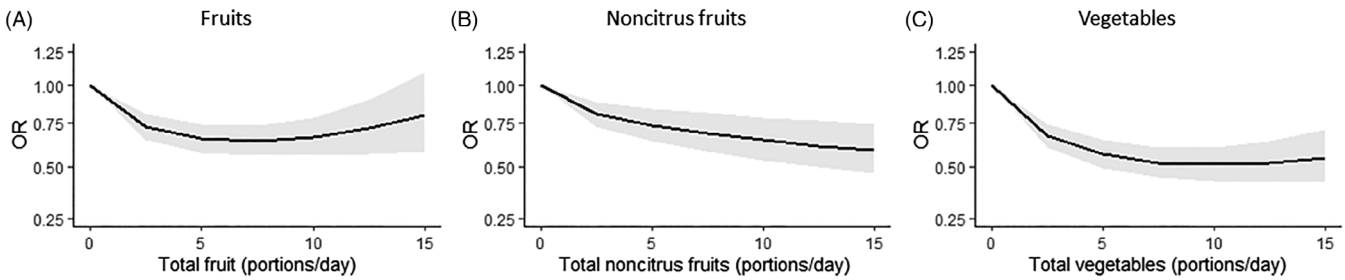

FIGURE 2 Dose-response relationship between A, fruits; B, noncitrus fruits; and C, vegetables and gastric cancer, fitted by a fractional polynomial. 95% CI, 95% confidence interval; OR, odds ratio

main analyses. Similarly, the magnitude of estimates remained essentially unchanged when considering the validity of the FFQ, method of administration, as well as the period of assessment. Finally, applying the NOS to the included studies and removing those with five stars or less, also did not substantively change the associations observed in the overall analyses.

Figure 2 shows the dose-response relationships between the intake of fruits, noncitrus fruits and vegetables and gastric cancer risk. There was an increasingly protective effect of portions/day of fruits (OR: 0.64, 95% CI: 0.57-0.73 for six portions), noncitrus fruits (OR: 0.71, 95% CI: 0.61-0.83 for six portions) and vegetables (OR: 0.51, 95% CI: 0.43-0.60 for 10 portions).

4 | DISCUSSION

With this uniquely large individual participant pooled analysis, we observed and quantified, better than previously available, a protective effect of fruits and vegetables on the occurrence of gastric cancer, consistent across sociodemographic categories and study characteristics, and further confirmed through analyses of the dose-response association.

Our study complements a previous work with the same set of studies on the association between citrus fruits and gastric cancer[10] by showing that the protective effect is not only restricted to this small subgroup of food items. Citrus fruits contain, besides vitamin C and other carotenoid antioxidants, particular flavanones, such as hesperitin and naringenin, that have anti-oxidant activity and, in animal models, inhibit human gastric cancer cell proliferation and migration.[46,47] However, other classes of flavonoids with similar activity can be found in other fruits, such as apples[48] or berries.[49] Additionally, fruits and vegetables are also rich in fiber, which can act as a scavenger of nitrates, preventing the formation of carcinogenic N-nitroso compounds,[50] and possibly other cancer preventive agents. Regarding vegetables, our estimates are in line with previous evidence, showing a similar degree of protection against gastric cancer as the one observed for a high consumption of allium vegetables (OR: 0.68, 95% CI: 0.57-0.81), garlic (OR: 0.60, 95% CI: 0.47-0.76), onion (OR: 0.55, 95% CI: 0.41-0.73)[51] or cruciferous vegetables (OR: 0.78, 95% CI: 0.71-0.86).[52] These vegetables have high contents of organosulfur compounds, which may have protective effects, as well as vitamins, carotenoids and other phytochemicals with potential anti-inflammatory and antioxidant activity, conveying anticarcinogenic effects.[53-55]

Most previous meta-analyses of cohort studies have shown a protective effect of a high consumption of fruit,[4,6,7] leading the WCRF to conclude that "there is some evidence that suggests consuming little or no fruit increases the risk of stomach cancer".[8] However, evidence regarding vegetable intake has been less consistent and the most recent WCRF report was unable to come to any conclusion.[8] In particular, a pooled analysis of prospective studies in China, Japan and Korea showed a weak, nondose-response of an inverse association of vegetable intake with noncardia gastric cancer risk;[7] while, a reanalysis of the European Prospective Investigation into Cancer and Nutrition study did not find an association between total or specific vegetables intake and gastric cancer risk.[4] Nevertheless, the results of the current study add to previous evidence pooled estimates, including the characterization of the exposure-relationships for all fruits and vegetables, which show that a higher consumption of fruits and vegetables was associated with a lower risk of gastric cancer.

Generally, cohort studies have not confirmed the strong associations often seen in case-control studies; likewise, our stratified analysis including only case-control studies had a stronger estimate than that using nested case-control studies. This was also observed in our dose-response analyses, for which strong estimates were obtained for the consumption of ten portions/day of vegetables. These results may be partially explained by the bias due to dietary recall or dietary changes accompanying disease associated with case-control studies. However, a previous systematic review and meta-analysis of cohort studies on the effect of fruit and vegetable consumption on gastric cancer showed that the association is stronger among studies with longer follow-up times,[56] which may suggest different effects of exposures depending on when they occur.

We observed a higher risk reduction among individuals in the low socioeconomic group for the consumption of fruits and noncitrus fruits, though, differences were not statistically significant, while in the StoP Project's citrus fruits study, the interaction was statistically significant.[10] This suggests that not only citrus fruits but all fruits and vegetables might counterbalance the negative effects of the lifestyle risk factors associated with low socioeconomic status.[57] Regional

differences were also observed, reflecting not only the different diets but also the detail of the FFQs applied regarding the number and types of food items included. For noncitrus fruits, the association was strongest among Asian studies, as also observed in the citrus fruits study.[10] While the items that constitute the "noncitrus" group are comparable among Asian studies, there is a wider variation of items across studies from the other regions. Moreover, the Canadian study had a particular weight to the Americas risk estimate, since it used an FFQ sent by mail rather than one applied face-to-face, possibly resulting in a less accurate assessment of fruits intake.

Heterogeneity was high for all the food groups considered, which is common in studies evaluating dietary associations,[58] mainly due to the different methods used by each study to collect dietary data, particularly the period of dietary assessment, the number and the items present in each food questionnaire. Within the StoP consortium, most studies used FFQ designed not only to be representative of the countries' diet but also to take into account the seasonality of the items included. However, the diversity of items present in each questionnaire and the disagreement regarding what constitutes a portion or a serving of fruit and vegetable likely contributed to the heterogeneity observed.[6] Nevertheless, 14 studies in the StoP project used previously validated FFQs, while 20 studies collected data using face-to-face interviewers, which have been shown to have lower random within-person variation than other dietary assessment and have an acceptable validity when compared to reference measures.[59,60] In fact, our sensitivity analyses showed no significant differences, providing further support to the robustness of our findings.

Studies were considered for analysis regardless of having addressed the association between fruits and vegetables intake and gastric cancer in a previous report, which prevented publication bias. The harmonization of adjustment strategies and control of confounding throughout the studies of the StoP consortium, further contributes to the validity of our estimates. Additionally, the protective effect of fruits and vegetables detected in the main analysis was consistently observed among strata of different sociodemographic and lifestyles variables, as well as study characteristics. Sensitivity analyses, either removing one study at a time or considering the same cut-off for all studies, yielded estimates similar to those observed in the main analysis, albeit with less heterogeneity, particularly for noncitrus and vegetables intake.

Both cases and controls reported low levels of fruits and vegetables intake, with the median of consumption not reaching the amount recommended of five portions a day (at least two of fruits and three of vegetables)[44] in most studies. The worldwide consumption of fruits and vegetables is low, particularly in low and middle-income countries[61] and, when assuming a causal relationship between fruits and vegetables intake and the occurrence of gastric cancer, an increase in the overall consumption to at least 300 g of fruits/day and 400 g vegetables/day, was estimated to prevent 6.0% to 11.5% of gastric cancer cases in these settings, by 2025.[62]

The main limitation of the current study is the case-control design of the included studies, which may have potentially yielded inaccurate measures of fruit and vegetable consumption. As past dietary habits were reported by participants, recall bias may have occurred, particularly among patients, as changes in lifestyle may occur as cancer develops and becomes symptomatic.[63] Nevertheless, all studies recruited incident, histologically confirmed gastric cancer cases, and most obtained dietary information regarding at least the year before diagnosis or the period before changes in dietary habits. We conducted a sensitivity analysis excluding studies in which FFQs were within 1 year of gastric cancer diagnosis, and the estimates obtained were essentially the same. Additionally, case-control studies may be prone to selection bias. It is possible that hospital-based controls include individuals with conditions that could potentially be related to fruit and vegetable intake, while population-based controls are considered to be more representative of the population under study, however, the latter may be healthier, and have higher fruit and vegetable intake. Nevertheless, the results of our stratified analysis by type of controls showed negligible differences.

Our study adds a pooled analysis to previous evidence, allowing to perform stratified analyses namely by cancer anatomical location and histological type, and exposure-response analyses. Despite the differences between the food items that constitute these heterogeneous food groups, a protective effect was observed for all those that were analyzed. This contributes to reinforce the recommendations for healthier lifestyles, including an increased intake of fruits and vegetables.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA ACCESSIBILITY

The data that support the findings of our study are available from the StoP Project but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. Data are, however, available from the authors upon reasonable request and permission of the Steering Committee of the StoP Project.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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