1 **Fruits and vegetables intake and gastric cancer risk: a pooled analyses within the Stomach**
2 **Cancer Pooling (StoP) Project**
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4 **Running title:** Fruits and vegetables' intake and gastric cancer risk
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83 Keywords: fruits; vegetables; gastric cancer; pooled analyses

84 **Abstract**

85 **Background:** Low intake of fruits and vegetables is a risk factor for gastric cancer, though there
86 is uncertainty regarding the magnitude of the associations. We assessed the relation between
87 fruits and vegetables intake with gastric cancer.

88 **Methods:** Using 25 studies (8498 cases and 21,092 controls) from the "Stomach cancer Pooling
89 (StoP) Project", we pooled study-specific odds ratios (ORs), for highest vs. lowest tertiles of
90 intake through two-stage random effects models. Linear and non-linear dose-response relations
91 were assessed using one and two-order fractional polynomials, selecting the model that
92 minimizes the difference regarding the linear one.

93 **Results:** The risk of gastric cancer risk was significantly lower for fruits (OR: 0.74, 95% confidence
94 interval [95%CI]: 0.64-0.87), fruits other than citrus fruits (OR: 0.81, 95%CI: 0.69-0.94) and
95 vegetables (OR: 0.65, 95%CI: 0.53-0.81), consistent across sociodemographic and lifestyles
96 variables. Dose-response analysis shows increasing protective effect up to intakes of 6
97 portions/day of fruits (OR: 0.44; 95%CI: 0.37-0.53), 3 portions/day of fruits other than citrus (OR:
98 0.67; 95%CI: 0.54-0.84) and 4 portions/day of vegetables (OR: 0.24; 95%CI: 0.19-0.30).

99 **Conclusion:** The significant protective effect of all fruits, fruits other than citrus, and vegetables,
100 reinforces the potential for dietary recommendations to further decrease the burden of gastric
101 cancer.

102

103

104 **Introduction**

105

106 Low intake of fruits and vegetables has long been acknowledged as a risk factor for the
107 occurrence of gastric cancer.[1, 2] However, the findings supporting the classification of this
108 relationship as "probable" by the World Cancer Research Fund (WCRF)[3] have not been
109 corroborated by the most recent studies.[4-7] This led the WCRF to reclassify the evidence as
110 "limited though suggestive" of a protective role of citrus fruits for cardia cancers and an increase
111 in the risk of gastric cancer associated with low intake of fruits. For vegetables, the classification
112 of the evidence regarding a potential protective effect on gastric cancer by the WCRF, varied
113 from "probable" in 2007[3] to "limited and inconclusive" in the most recent report.[8]

114 The inconsistency and heterogeneity of estimates, as well as the small number of studies
115 addressing the different gastric cancer locations and histological types were pointed as
116 limitations of the evidence currently available, contributing to the downgrade of the degree of
117 evidence.[8] The Stomach Cancer Pooling (StoP) Project, a consortium of case-control studies
118 which uses an individual participant data approach for the exploration of the associations
119 between risk factors and gastric cancer,[9] allows to overcome some of the previously referred
120 limitations; the recent report by Bertuccio *et al* showed a significant reduction of the risk of
121 gastric cancer with high intakes of citrus fruits, with similar magnitudes of association between
122 cardia and non-cardia cancers as well as between histological types; the protective effect
123 continued progressively until three servings/week and leveled off thereafter.[10]

124 In the present study we aim to further explore the association between fruits, fruits
125 other than citrus and vegetables intake and gastric cancer, through pooled analyses of individual
126 participant data from studies participating in the StoP Project.

127 **Methods**

128 *Study population*

129 For this study we used the version 2.0 of the StoP Project dataset, which included a total of
130 14,016 cases of gastric cancer (4769 women and 9247 men) and 33,704 controls (13,352 women
131 and 20,352 men) from 30 case-control or nested in cohort studies, as previously described.[9] All
132 data were collected and harmonized according to a pre-specified format at the pooling center.
133 Ethical approval was given to the StoP Project from the University of Milan Review Board
134 (reference 19/15 on 01/04/2015).
135 The present analyses used data from 25 studies, corresponding to 8498 cases and 21,092
136 controls with information on fruits and/or vegetables intake: Brazil (two studies),[11, 12] Canada,[13]
137 China (four studies),[14-17] Greece,[18] Iran (two studies),[19, 20] Italy (four studies),[21-24] Japan,[25] Mexico
138 (three studies),[26-28] Portugal,[29] Russia,[30] Spain (two studies),[31, 32] Sweden (two studies),[33] and
139 United States of America.[34]
140

141 *Variables of interest / exposure*

142 Food frequency questionnaires (FFQ) were used to gather information on the participants'
143 dietary habits for the period of one, two or five years before diagnosis (for cases), onset of
144 disease or hospital admission (for hospital based controls) or recruitment (for population based
145 controls). The FFQs used in the different studies included between 19 and 147 individual food
146 and beverage items; most FFQs included fruits such as apples, pears, oranges, bananas, grapes,
147 peaches, berries (strawberries, cranberries) and watermelon, and vegetables such as
148 cauliflower, broccoli, carrots, lettuce, cabbage, tomato, green pepper, cucumber, onions and
149 garlic were the most common (Supplementary Table 1).
150

151 *Statistical analysis*

152 The study-specific frequency of consumption of each food group (portions per day) was obtained
153 by adding up the frequencies of consumption of the individual items previously described, and
154 then categorized into tertiles on the basis of the distribution in controls.
155 We used a two-stage modeling approach to quantify the association between fruits and
156 vegetables intake and gastric cancer.[35] Firstly, through multivariable unconditional logistic
157 regression models, we estimated the study-specific odds ratios (ORs) and corresponding 95%
158 confidence intervals (95% CI) for the association fruits and vegetables consumption and gastric
159 cancer. Models included terms for age (5-year age groups: <40;40-45; …; 70-75; >75), sex, social
160 class (low, intermediate, or high, as defined in each original study based on education, income
161 or occupation), smoking status (never, former and current smokers of <10 cigarettes per day; 10
162 to 20 cigarettes per day; >20 cigarettes per day), alcohol drinking (never, low: ≤12g/day,
163 intermediate: >12 to ≤47 g/day, high: >47g/day), other fruits or total vegetables intake (study-
164 specific tertiles), total energy intake (study-specific quintiles), study center (for multicenter
165 studies) and race/ethnicity (White, Black/African American, Asian, Hispanic/Latino, other, when
166 appropriate and available (Supplementary Table 2).
167 Then, for the second stage, we computed summary (pooled) effects estimates using random-
168 effects models;[36] heterogeneity between studies was quantified it using the I^2 statistics.[37]
169 We also performed stratified analyses to further explore the effect of high consumption of fruits
170 and vegetables across strata of age (<55, 55-65, >65), sex, cigarette smoking, alcohol drinking,
171 social class, cancer site (cardia, non cardia), histological type (intestinal, diffuse and
172 undifferentiated) and type of controls (hospital-based, population-based). The difference
173 between groups was assessed through the Q test for heterogeneity.[38, 39]
174 We performed sensitivity analyses by defining the same categories of exposure for all studies
175 according to the distribution of fruits, fruits other than citrus, and vegetables consumption in all
176 controls. We further defined the categories of exposure taking into account the maximum
177 amounts of intake recommended by the World Health Organization (WHO), i.e. up to two

178 portions a day for fruits and fruits other than citrus and three portions a day for vegetables,[40]
179 using cut-offs that describe intakes of less than half of the recommended intake, between half
180 and the recommended amount or more than the recommended amount, resulting in three
181 categories. We also analyzed the influence of specific studies to the overall estimates by
182 excluding one study at a time. Further sensitivity analyses included comparing the estimates
183 adjusted and non adjusted for total energy intake, as well as adjusted for the presence of *H.*
184 *pylori* infection, among studies with information on energy intake and infection status,
185 respectively.

186 A one-stage strategy of analysis was used to assess trends for all exposures considered, firstly
187 by considering the variable as continuous in the logistic model and assessing the significance of
188 a linear trend,[35] and secondly through fractional polynomial regression models[41] that take into
189 account the non-linear trend between the exposure and the outcome. First and second order
190 transformations were computed for the continuous term of fruits, fruits other than citrus and
191 vegetables intake, and the model minimizing the deviance difference with respect to the linear
192 model was selected.[41]

193 The statistical analysis was performed with STATA, version 11.2 (Stata Corporation, College
194 Station, TX, USA).

195 **Results**

196 The consumption of fruits and vegetables among the participants in each study considered for
197 the present analyses are described in Table 1. The median fruit intake ranged between 0.1 (China
198 2) and 4.2 (Greece) portions/day for cases, and 0.3 (China 2 and China 4) and 4.7 (Greece)
199 portions/day for controls. When considering fruits other than citrus, the median intake ranged
200 from 0.1 (China 2) and 3.0 (Greece) portions/day for cases, and 0.1 (Iran 2) and 3.1 (Greece)
201 portions/day for controls. Regarding vegetables, the medians of consumption ranged between
202 0.4 (China 1 and Iran 2) and 3.9 (Russia, Mexico 1 and 3) portions/day for cases, and between
203 0.4 (China 1) and 4.2 (Mexico 2) portions/day for controls.

204 A significantly lower risk of gastric cancer was observed with higher intakes of fruits, fruits other
205 than citrus and vegetables (Table 2), with the strongest associations being observed for the
206 comparisons of the highest vs. lowest tertiles (fruits, OR: 0.74, 95% CI: 0.64-0.87; I^2: 64.1%; fruits
207 other than citrus, OR: 0.81, 95% CI: 0.69-0.94; I^2 57.6%; vegetables, OR: 0.65, 95%CI: 0.53-0.81;
208 I^2: 84.1%) (Table 2 and Figure 1).

209 The protective effect of a high intake of all food groups considered was consistent across most
210 strata of sociodemographic and lifestyle variables, with significant differences according to the
211 study region for fruits other than citrus: European studies OR: 0.91 (95%CI: 0.73-1.13; I^2: 66.6%),
212 Asian studies OR: 0.58 (95%CI: 0.43-0.77; I^2: 29.9%) American studies OR: 0.90 (95%CI: 0.75-
213 1.08; I^2: 1.8%) (Table 3). Though the difference was not statistically significant, individuals
214 belonging to the low social class strata presented the highest protection for a higher intake of
215 fruits (OR 0.65, 95%CI 0.53-1.79, I^2 56.6%) and fruits other citrus fruits (OR 0.70, 95%CI 0.57-
216 0.85, I^2 51.1%), compared with the middle (fruits: OR 0.88, 95%CI: 0.72-1.07; I^2 20.2%; fruits
217 other than citrus fruits: OR 0.89, 95%CI 0.65-1.23, I^2 16.6%) and high social classes (fruits: OR
218 0.97, 95%CI 0.76-1.24, I^2 38.8%; fruits other than citrus fruits: OR 1.00, 95%CI 0.70-1.42, I^2
219 26.8%). There were also differences according to the source of the controls, for fruits other than
220 citrus, with a stronger association being observed among studies using population controls (OR:

221 0.72; 95%CI: 0.58-0.89; I^2: 67.5%) when compared with those using hospital-based controls (OR:
222 0.94, 95%CI 0.77-1.15; I^2: 27.2%).
223 Sensitivity analyses did not result in changes in the direction or magnitude of the associations;
224 a significantly lower risk of gastric cancer was still observed when considering OR estimates
225 adjusted for energy intake or accounting for *H. pylori* infection (Table 3). Other strategies to
226 increase homogeneity among studies, namely using the same cut-off for all studies, led to
227 estimates of the same magnitude, with slightly lower heterogeneity, particularly for fruits other
228 than citrus and vegetables intake (Supplementary Table 2).
229 Figure 2 shows the dose-response association between fruits, fruits other than citrus and
230 vegetables intake and gastric cancer risk. The protective effect against the occurrence of gastric
231 cancer increased up to intakes of 6 portions/day of fruits (OR: 0.44; 95%CI: 0.37-0.53), 3
232 portions/day of fruits other than citrus (OR: 0.67; 95%CI: 0.54-0.84) and 4 portions/day of
233 vegetables, and leveled off thereafter.

234 **Discussion**

235 With this individual participant pooled analysis we observed a protective effect of fruits, fruits
236 other than citrus and vegetables on the occurrence of gastric cancer, consistent across
237 sociodemographic variables and further confirmed through analyses of the dose-response
238 association.

239 This study complements a previous work with the same set of studies on the association
240 between citrus fruits and gastric cancer[10] by showing that the protective effect is not restricted
241 to this small subgroup of food items. Citrus fruits contain particular flavanones such as hesperitin
242 and naringenin, that have anti-oxidant activity and, in animal models, inhibit human gastric
243 cancer cell proliferation and migration;[42, 43] however, other classes of flavonoids with similar
244 activity can be found in other fruits, such as apples[44] or berries[45]. Additionally, fruits and
245 vegetables are also rich in fiber, which can act as a scavenger of nitrates, preventing the
246 formation of carcinogenic N-nitroso compounds.[46] Regarding vegetables, our estimates are in
247 accordance with previous evidence, showing similar degree of protection against gastric cancer
248 as the one observed for allium vegetables (OR:0.68 95%CI:0.57–0.81), garlic (OR:0.60; 95%CI:
249 0.47–0.76), onion (OR:0.55; 95%CI: 0.41–0.73)[47] or cruciferous vegetables (OR: 0.78; 95%CI:
250 0.71–0.86).[48] These show high contents in organosulfur compounds, which have protective
251 effects, as well as vitamins, carotenoids and other phytochemicals with anti-inflammatory and
252 antioxidant activity, conveying anti-carcinogenic effects.[49-51]

253 We observed a higher risk reduction among individuals in the low social class group, though
254 differences were not statistically significant, while in the citrus fruits paper the interaction was
255 statistical significant.[10] For both fruits and fruits other than citrus, the association was strongest
256 among Asian studies and those from the Americas yielded a non-significant association, as also
257 observed in the citrus fruits paper.[10] While the items that constitute the ‘fruits other than citrus’
258 group are comparable among Asian studies, there is a higher variation of items across studies
259 from the other regions; moreover, the Canadian study had a particular weight to the American

260 estimate, since it used a FFQ sent by mail rather than one applied face-to-face, possible resulting
261 in a less accurate assessment of fruits intake.
262 Heterogeneity was high for all the food groups considered, which is common in studies
263 evaluating dietary associations,[52] mainly due to the different methods used by each study to
264 collect dietary data, particularly the number and the items present in each food questionnaire.
265 Within the StoP consortium, most studies used validated FFQ; nevertheless, the diversity of
266 items present in each questionnaire and the disagreement regarding what constitutes a portion
267 or a serving of fruit and vegetable likely contributed to the heterogeneity observed.[6] However,
268 the protective effect of fruits and vegetables was consistent among strata of different
269 sociodemographic and lifestyles variables. Moreover, sensitivity analyses, including removing
270 one study at a time or considering the same cut-off for all studies, yielded estimates similar to
271 the ones originally observed and with lower heterogeneity, particularly for fruits other than
272 citrus and vegetables intake. Also, the lack of bias resulting from the fact that the studies were
273 analyzed regardless of having as objective the estimation of the association between fruits and
274 vegetables, as well as the harmonization of adjustment strategies and control of confounding
275 throughout the studies part of the StoP consortium, further contributes to the validity of our
276 estimates.
277 Both cases and controls presented low levels of fruits and vegetables intake, with the median of
278 consumption not reaching the amount recommended of five portions a day (at least two of fruits
279 and three of vegetables)[40] in most studies. Worldwide consumption of fruits and vegetables is
280 low, particularly in low and middle income countries[53] and, when assuming a causal relation
281 between the intake of fruits and vegetables and the occurrence of gastric cancer, an increase of
282 the overall consumption to at least 300g/d and 400 g/d of fruits and vegetables, respectively,
283 was estimated to allow for the prevention of 6.0 to 11.5% of gastric cancer cases in these
284 settings, by 2025.[54]

285 This study adds a pooled analyses to previous evidence, allowing to perform stratified analyses
286 namely by cancer location and histological type, and dose-response analyses. Despite the
287 differences between the food items that constitute these heterogeneous food groups, the
288 protective effect was observed for all those that were analyzed. This contributes to reinforce
289 the recommendations towards a healthier lifestyle in order to pursue the downward trends of
290 gastric cancer.

291 **Additional information**

292 Ethics approval and consent to participate: Ethical approval was given to the StoP Project from
293 the University of Milan Review Board (reference 19/15 on 01/04/2015).

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316 the data, as part of the StoP Project. CLV and NL supervised the analysis and interpretation of

317 data, and reviewed the manuscript. NL defined the study hypotheses and designed the
318 investigation. All authors contributed to the discussion of the results. All authors read and
319 approved the final version of the manuscript.

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477

478 **Figure legends**

479

480 Figure 1 – Forest plots describing the association between the intake of fruits, fruits other than citrus,

481 and vegetables (highest versus lowest tertile, portions/day) and gastric cancer using the estimates

482 from the Stomach Cancer Pooling (Stop) Project database.

483

484 NA – Non applicable; OR – Odds Ratio, 95% CI – 95% Confidence Interval

485

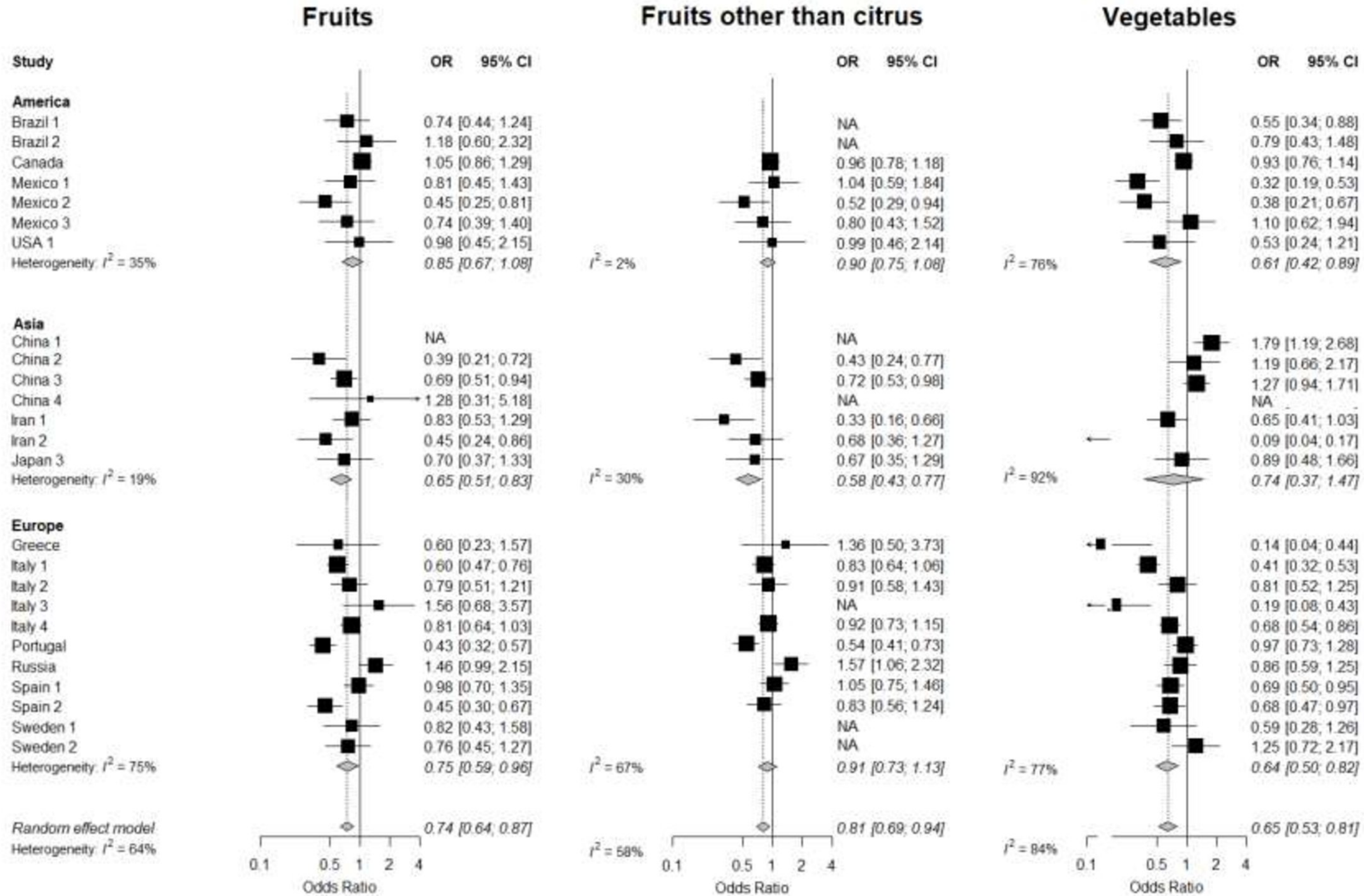
486 Figure 2 – Dose-response relationship between fruits (A), fruits other than citrus (B) and vegetables

487 (C) and gastric cancer, fitted by a fractional polynomial.

488

489

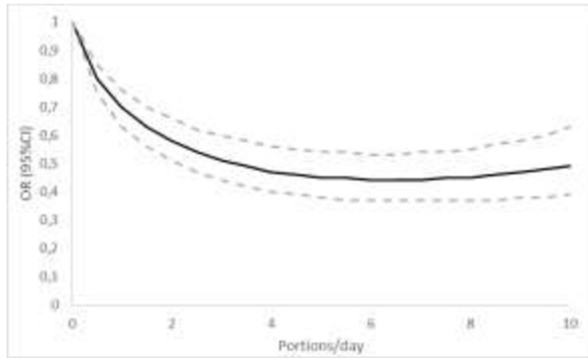
Figure 1 – Forest plots describing the association between the intake of fruits, fruits other than citrus, and vegetables (highest versus lowest tertile, portions/day) and gastric cancer using the estimates from the Stomach Cancer Pooling (Stop) Project database.



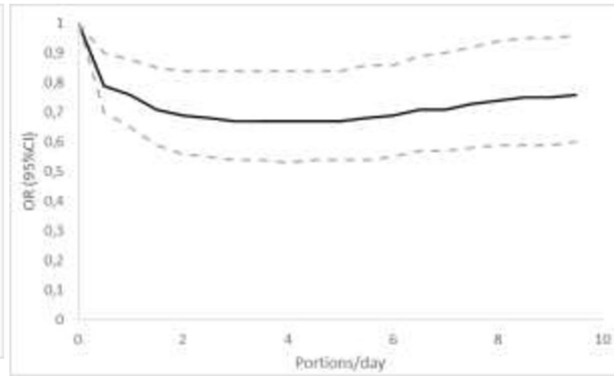
NA –Non applicable; OR – Odds Ratio, 95% CI – 95% Confidence Interval

Figure 2 – Dose-response relationship between fruits (A), fruits other than citrus (B) and vegetables (C) and gastric cancer, fitted by a fractional polynomial.

A) Fruits



B) Fruits other than citrus



C) Vegetables

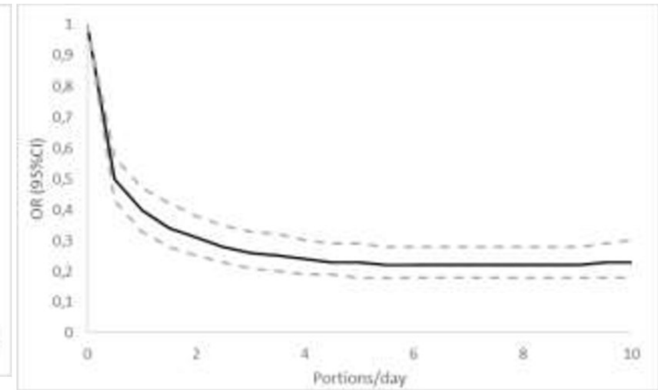


Table 1 – Median and interquartile range (portions/day) of fruits, fruits other than citrus and vegetables consumption by study.

	Cases					**Controls**				
	N	**%**	**Median (P25-P75)** portions/day			**N**	**%**	**Median (P25-P75)** portions/day		
			Fruits	**Fruits other than citrus***	**Vegetables**			**Fruits**	**Fruits other than citrus***	**Vegetables**
Total	*8498*		*1.7 (0.9-2.9)*	*1.4 (0.7-2.4)*	*1.7 (0.7-3.1)*	*21092*		*1.9 (1.0-3.0)*	*1.4 (0.8-2.4)*	*2.1 (1.3-3.4)*
Study center										
Europe	*4345*	*51.3*	*1.9 (1.1-3.0)*	*1.5 (0.9-2.4)*	*1.6 (0.6-2.9)*	*10,701*	*52.4*	*2.1 (1.3-3.3)*	*1.7 (1.0-2.6)*	*2.1 (1.0-3.4)*
Greece (Lagiou et al., 2004)	**110**	1.3	4.2 (2.6-6.4)	3.0 (1.9-4.9)	3.1 (2.2-4.4)	**100**	0.5	4.7 (3.7-5.9)	3.1 (2.1-4.1)	3.9 (2.9-5.2)
Italy 1 (La Vecchia et al., 1995)	**769**	9.1	2.4 (1.6-3.6)	2.0 (1.3-3.4)	2.2 (1.6-3.0)	**2081**	9.9	3.0 (2.0-4.0)	2.1 (1.4-3.1)	2.7 (2.1-3.7)
Italy 2 (Lucenteforte et al, 2008)	**230**	2.7	3.9 (1.9-5.4)	2.8 (1.4-4.0)	0.9 (0.6-1.4)	**547**	2.6	3.6 (2.1-5.4)	2.7 (1.6-4.1)	0.9 (0.6-1.4)
Italy 3 (De Feo et al., 2012)	**157**	1.9	1.6 (1.0-1.6)	NA	1.0 (1.0-1.6)	**429**	2.0	1.0 (1.0-1.6)	NA	1.0 (1.0-1.6)
Italy 4 (Buiatti et al., 1989)	**1016**	12.0	1.6 (1.0-2.1)	1.2 (0.8-1.7)	0.5 (0.3-0.7)	**1159**	5.5	1.7 (1.2-2.2)	1.3 (0.9-1.7)	0.5 (0.4-0.7)
Portugal (Lunet et al., 2007)	**633**	7.5	1.5 (0.9-2.2)	1.3 (0.8-1.9)	1.8 (1.1-2.7)	**1600**	7.6	2.0 (1.4-2.8)	1.6 (1.1-2.4)	2.1 (1.3-3.1)
Russia (Zaridze et al., 2000)	**444**	5.2	2.7 (1.5-4.5)	2.2 (1.1-4.0)	3.9 (2.0-6.4)	**606**	2.9	2.7 (1.4-4.4)	2.1 (1.0-3.7)	4.1 (2.4-6.1)
Spain 1 (Castaño-Vinyals, 2015)	**339**	4.0	2.5 (1.6-3.5)	1.7 (1.0-2.5)	2.6 (1.5-3.8)	**2728**	14.4	2.5 (1.5-3.5)	1.6 (0.9-2.4)	2.6 (1.7-3.8)
Spain 2 (Santibanez et al., 2012)	**398**	4.7	1.8 (1.2-2.5)	1.2 (0.8-1.6)	2.0 (1.3-3.2)	**455**	2.2	2.0 (1.4-2.8)	1.2 (0.8-1.6)	2.2 (1.5-3.5)
Sweden 1 (Harris et al, 2013)	**88**	1.0	1.5 (0.5-2.0)	NA	2.0 (1.5-3.8)	**352**	1.7	1.5 (1.0-2.5)	NA	2.5 (1.5-4.0)
Sweden 2 (Harris et al, 2013)	**161**	1.9	1.0 (0.5-1.5)	NA	2.0 (1.0-3.0)	**644**	3.1	1.0 (0.5-2.0)	NA	2.0 (1.0-3.0)
Asia	*1905*	*22.3*	*1.1 (0.3-2.6)*	*1.0 (0.4-2.4)*	*1.6 (0.5-3.1)*	*2964*	*14.0*	*1.0 (0.3-2.7)*	*1.0 (0.3-2.7)*	*1.5 (0.5-3.0)*
China 1 (Deandrea et al, 2010)	**266**	3.1	NA	NA	0.4 (0.3-0.5)	**533**	2.5	NA	NA	0.4 (0.2-0.5)
China 2 (Mu et al., 2005)	**206**	2.4	0.1 (0.0-0.4)	0.1 (0.0-0.4)	2.0 (1.2-3.2)	**405**	1.9	0.3 (0.1-0.7)	0.3 (0.1-0.6)	2.2 (1.3-3.7)
China 3 (Setiawan et al, 2005)	**702**	8.3	2.0 (0.8-4.7)	1.9 (0.8-4.5)	2.8 (1.9-3.9)	**696**	3.3	2.4 (1.1-5.5)	2.2 (1.0-5.1)	2.8 (1.9-3.9)
China 4 (Setiawan et al., 2001)	**115**	1.3	0.0 (0.0-0.3)	NA	NA	**390**	1.8	0.3 (0.0-0.3)	NA	NA
Iran 1 (Pourfarzi et al., 2009)	**216**	2.5	0.3 (0.1-0.9)	0.1 (0.1-0.5)	0.7 (0.5-1.1)	**393**	1.9	0.4 (0.3-1.1)	0.1 (0.1-0.5)	1.0 (0.4-1.4)
Iran 2 (Pakseresht et al, 2011)	**247**	2.9	1.3 (0.9-2.2)	0.9 (0.5-1.5)	0.4 (0.2-0.6)	**244**	1.2	2.0 (1.2-3.4)	1.3 (0.7-2.2)	1.0 (0.6-1.6)
Japan 3 (Inoue et al., 1997)	**153**	1.8	2.5 (1.6-3.9)	2.3 (1.5-3.6)	3.7 (2.3-5.8)	**303**	1.4	3.0 (1.9-4.1)	2.7 (1.7-3.7)	4.4 (2.6-6.3)

Americas	*2246*	*26.4*	*1.6 (0.8-2.6)*	*1.3 (0.6-2.2)*	*2.1 (1.2-3.4)*	*7115*	*33.6*	*1.5 (0.8-2.5)*	*1.1 (0.6-2.0)*	*2.1 (1.3-3.4)*
Brazil 1 (Nishimoto et al, 2002)	**226**	2.7	1.2 (0.5-2.0)	NA	1.2 (0.4-1.7)	**226**	1.1	1.5 (1.0-2.2)	NA	1.4 (0.7-2.0)
Brazil 2 (Hamada et al, 2002)	**91**	1.1	1.5 (1.0-2.2)	NA	1.5 (1.2-2.2)	**186**	0.9	1.4 (1.0-2.2)	NA	2.0 (1.2-2.2)
Canada (Mao et al., 2002)	**1170**	13.8	1.3 (0.6-2.1)	1.0 (0.4-1.7)	1.8 (1.1-2.6)	**5023**	23.8	1.4 (0.6-2.1)	1.1 (0.5-1.7)	1.8 (1.1-2.6)
Mexico 1 (Hernandez-Ramirez et al, 2009)	**248**	2.9	1.9 (1.2-3.0)	1.6 (1.0-2.5)	3.9 (3.1-4.5)	**478**	2.3	1.4 (0.7-2.5)	1.1 (0.6-2.1)	3.9 (3.1-4.5)
Mexico 2 (Lopez-Carrillo et al., 1994)	**220**	2.6	2.7 (1.6-4.1)	2.3 (1.3-3.8)	3.7 (2.5-4.8)	**752**	3.6	2.9 (1.6-4.5)	2.3 (1.3-4.1)	4.2 (3.3-5.6)
Mexico 3 (Lopez-Carrillo et al., 2003)	**159**	1.9	3.5 (1.9-5.9)	2.2 (1.3-3.8)	3.9 (2.9-4.9)	**318**	1.5	3.4 (1.9-6.2)	2.3 (1.3-4.1)	3.9 (3.2-4.9)
USA 1 (Zhang et al., 1999)	**132**	1.5	1.5 (0.7-2.7)	1.4 (0.6-2.4)	1.7 (1.1-2.7)	**132**	0.6	1.6 (0.6-2.9)	1.4 (0.6-2.5)	1.9 (1.1-3.1)

* The values may be larger than those described for all fruits, because the number of studies with data available for fruits and fruits other than citrus is different.

Table 2. Pooled odds ratio of gastric cancer according to study-specific tertiles of fruits, fruits other than citrus and vegetables consumption (portions/day).

	Cases			Controls				
	N	%	portions/day Median (P25-P75)	N	%	portions/day Median (P25-P75)	OR (CI 95%)[1]	I^2 (%)
Fruits[2]								
1st third	3304	38.8	0.8 (0.4-1.2)	7140	33.9	0.8 (0.4-1.2)	1	
2nd third	2538	29.9	1.9 (1.5-2.6)	6677	31.7	1.9 (1.4-2.7)	0.82 (0.74-0.91)	38.6
3rd third	2315	27.2	3.6 (2.5-5.3)	6644	31.5	3.6 (2.5-4.7)	0.74 (0.64-0.87)	64.1
Missing	*341*	*4.6*		*631*	*3.0*			
P value for trend							<0.001	
Fruits other than citrus[3]								
1st third	2769	36.5	0.6 (0.3-1.0)	6046	32.0	0.6 (0.3-1.0)	1	
2nd third	2361	31.1	1.5 (1.1-2.1)	6234	33.1	1.4 (1.1-2.0)	0.83 (0.72-0.95)	59.7
3rd third	2182	28.8	3.1 (2.0-4.4)	5940	31.6	2.9 (2.1-3.9)	0.81 (0.69-0.94)	57.6
Missing	*272*	*3.6*		*621*	*3.3*			
P value for trend							0.099	
Vegetables[4]								
1st third	3331	39.2	0.9 (0.4-1.5)	6843	32.4	1.0 (0.5-1.5)	1	
2nd third	2600	30.6	2.1 (1.2-2.8)	6892	32.7	2.1 (1.6-2.7)	0.78 (0.66-0.92)	77.4
3rd third	2444	28.8	3.6 (2.3-5.1)	6946	32.9	3.8 (2.8-5.0)	0.65 (0.53-0.81)	84.1
Missing	*123*	*1.5*		*411*	*2.0*			
P value for trend							<0.001	

[1] Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for age (5-year age groups: <40;40-45; ...; 70-75; >75), sex, social class (low, intermediate, or high, as defined in each original study based on education, income or occupation), smoking status (never, former and current smokers of less than 10 cigarettes per day; 10 to 20 cigarettes per day; over 20 cigarettes per day), alcohol drinking (never, low: ≤12g/day, intermediate: >12 to ≤47 g/day, high: >47g/day), other fruits/vegetables intake (study-specific tertiles) total energy intake (study-specific quintiles), study center (for multicenter studies) and race/ethnicity.

[2] No information for studies China 1.[16].

[3] No information for studies Brazil 1,[12] Brazil 2,[11] China 1,[16] China 4,[55] Italy 3,[23] Sweden 1[33] and Sweden 2.[33]

[4] No information for studies China 4.[55]

Table 3- Pooled odds ratio of gastric cancer for the highest versus the lowest study-specific tertile of fruits, fruits other than citrus and vegetables consumption (portions/day) according to strata of selected variables

	Fruits		Fruits other than citrus		Vegetables	
	OR (95% CI) [1]	**I^2 (%)**	**OR (95% CI)** [1]	**I^2 (%)**	**OR (95% CI)**[1]	**I^2 (%)**
Overall	0.74 (0.64-0.87)	64.1	0.81 (0.69-0.94)	57.6	0.65 (0.53-0.81)	84.1
Sex						
Men	0.76 (0.62-0.93)	66.0	0.80 (0.67-0.98)	56.7	0.66 (0.52-0.84)	78.4
Women	0.72 (0.60-0.86)	26.2	0.78 (0.62-0.99)	51.0	0.67 (0.52-0.86)	64.0
p for interaction	0.672		0.846		0.961	
Age (years)						
≤55	0.80 (0.66-0.98)	22.6	0.91 (0.75-1.12)	16.2	0.66 (0.50-0.88)	62.0
>55 to ≤65	0.65 (0.51-0.82)	42.4	0.69 (0.52-0.93)	56.3	0.70 (0.52-0.96)	68.3
>65	0.74 (0.60-0.90)	48.8	0.83 (0.67-1.02)	43.7	0.68 (0.54-0.86)	62.2
p for interaction	0.396		0.319		0.965	
Area						
Europe	0.75 (0.59-0.96)	75.1	0.91 (0.73-1.13)	66.6	0.64 (0.50-0.83)	77.3
Asia	0.65 (0.51-0.83)	18.9	0.58 (0.43-0.77)	29.9	0.74 (0.37-1.47)	92.2
Americas	0.85 (0.67-1.08)	35.3	0.90 (0.75-1.08)	1.8	0.61 (0.42-0.89)	75.7
p for interaction	0.307		0.023		0.899	
Social Class						
Low	0.65 (0.53-0.79)	56.6	0.70 (0.57-0.85)	51.1	0.73 (0.57-0.92)	72.2
Intermediate	0.88 (0.72-1.07)	20.2	0.97 (0.76-1.24)	38.8	0.71 (0.52-0.97)	68.5
High	0.89 (0.65-1.23)	16.6	1.00 (0.70-1.42)	26.8	0.55 (0.36-0.84)	48.3
p for interaction	0.069		0.065		0.512	
Controls						
Hospital base[2]	0.80 (0.62-1.04)	62.1	0.94 (0.77-1.15)	27.2	0.65 (0.47-0.91)	81.9
Population based[3]	0.70 (0.58-0.86)	68.1	0.72 (0.58-0.89)	67.5	0.65 (0.48-0.88)	86.5
p for interaction	0.426		0.068		0.982	
Cigarette smoking						
Never	0.69 (0.57-0.84)	49.2	0.75 (0.60-0.94)	54.4	0.66 (0.52-0.85)	72.1
Former	0.85 (0.67-1.09)	36.4	0.95 (0.75-1.21)	28.4	0.73 (0.59-0.92)	32.6
Current	0.71 (0.55-0.92)	35.0	0.73 (0.58-0.92)	20.4	0.73 (0.52-1.01)	62.9
p for interaction	0.389		0.229		0.815	
Alcohol intake						

Non drinker	0.71 (0.58-0.87)	42.4	0.70 (0.56-0.88)	46.5	0.60 (0.44-0.80)	75.2
Drinker						
<1drink/day	0.69 (0.53-0.91)	14.1	0.88 (0.62-1.27)	40.1	0.64 (0.46-0.90)	44.7
2-4 drinks/day	0.83 (0.58-1.19)	67.9	0.87 (0.68-1.11)	35.4	0.77 (0.53-1.11)	68.3
>4 drinks/day	0.71 (0.53-0.95)	0.0	0.95 (0.68-1.34)	16.6	0.70 (0.53-0.93)	0.0
p for interaction	0.872		0.419		0.728	
Site[4]						
Cardia	0.82 (0.64-1.04)	16.3	0.75 (0.54-1.06)	41.4	0.76 (0.56-1.03)	38.8
Non cardia	0.76 (0.63-0.92)	69.0	0.87 (0.74-1.03)	55.4	0.58 (0.48-0.72)	74.1
p for interaction	0.646		0.439		0.153	
Histotype[5]						
Intestinal	0.80 (0.59-1.08)	67.5	0.81 (0.61-1.07)	57.3	0.68 (0.53-0.87)	57.5
Diffuse	0.71 (0.56-0.90)	32.1	0.85 (0.70-1.04)	0.0	0.62 (0.49-0.78)	36.8
Undifferentiated	1.00 (0.69-1.45)	51.6	1.11 (0.77-1.60)	47.0	0.70 (0.53-0.91)	21.7
p for interaction	0.291		0.358		0.779	
Studies with information on energy intake[6]						
Adjusting for energy intake	0.64 (0.54-0.76)	52.9	0.80 (0.70-0.91)	25.3	0.56 (0.41-0.77)	87.6
Not adjusting for energy	0.80 (0.64-1.01)	79.3	0.93 (0.75-1.17)	78.9	0.68 (0.54-0.87)	81.6
Studies with information on *H. pylori* (HP) infection status[7]						
Adjusting for HP infection	0.77 (0.58-1.02)	63.2	0.67 (0.46-0.98)	74.0	0.71 (0.56-0.90)	55.1
Not adjusting for HP infection	0.75 (0.57-0.99)	69.9	0.74 (0.53-1.02)	75.2	0.64 (0.45-0.89)	83.1

[1] Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and applicable, for sex, age, race/ethnicity, social class, tobacco smoking, alcohol intake, study-specific tertiles of fruits/vegetables, quintiles of total energy intake and study center for multicentric studies.

[2] Includes studies Brazil 1,[12] Brazil 2,[11] China 1,[16] Greece,[18] Italy 1,[21] Italy 2,[22] Italy 3,[23] Japan 3,[25] Mexico 3,[28] Russia,[30] Spain 2[32] and USA 1.[34]

[3] Includes studies Canada,[13] China 2,[14] China 3,[15] Iran 1,[19] Iran 2,[20] Italy 4,[24] Mexico 1,[26] Mexico 2,[27] Portugal,[29] Spain 1,[31] Sweden 1[33] and Sweden 2[33].

[4] Excluding studies China 2,[14] China 3,[15] China 4[17] and Mexico 3[28].

[5] Excluding studies China 1,[16] China 2,[14] China 3,[15] China 4,[17] Greece,[18] Italy 1,[21] Japan 3,[25] Mexico 2,[27] Sweden 1[33] and Sweden 2[33].

[6] No information for studies Canada,[13] Russia,[30] Iran 1,[19] Brazil 1[12] and Brazil 2[11].

[7] *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 (8 studies)[11, 12, 19, 25, 26, 28-30, 55] or Western Blot (one study)[20] to determine immunoglobulin G (IgG) antibody titers in serum, and in one study through multiplex serology.[31] 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