Dietary fish and meat intake and dementia in Latin America, China, and India: a 10/66 Dementia Research Group population-based study[1–3]

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ABSTRACT

Background: Evidence of an association between fish and meat consumption and risk of dementia is inconsistent and nonexistent in populations in developing countries.

Objective: The objective was to investigate associations between fish and meat consumption with dementia in low- and middle-income countries.

Design: One-phase cross-sectional surveys were conducted in all residents aged ≥65 y in 11 catchment areas in China, India, Cuba, the Dominican Republic, Venezuela, Mexico, and Peru. A total of 14,960 residents were assessed by using the 10/66 standardized protocol, which includes face-to-face interviews for dietary habits and a cross-culturally validated dementia diagnosis.

Results: Dietary intakes and the prevalence of dementia varied between sites. We combined site-specific Poisson regression prevalence ratios (PRs) for the association between fish and meat consumption and dementia in 2 fixed-effect model meta-analyses adjusted for sociodemographic and health characteristics and fish and meat consumption as appropriate. We found a dose-dependent inverse association between fish consumption and dementia (PR: 0.81; 95% CI: 0.72, 0.91) that was consistent across all sites except India and a less-consistent, dose-dependent, direct association between meat consumption and prevalence of dementia (PR: 1.19; 95% CI: 1.07, 1.31).

Conclusions: Our results extend findings on the associations of fish and meat consumption with dementia risk to populations in low- and middle-income countries and are consistent with mechanistic data on the neuroprotective actions of omega-3 (n–3) long-chain polyunsaturated fatty acids commonly found in fish. The inverse association between fish and prevalent dementia is unlikely to result from poorer dietary habits among demented individuals (reverse causality) because meat consumption was higher in those with a diagnosis of dementia. *Am J Clin Nutr* 2009;90:392–400.

INTRODUCTION

Dementia is a chronic and progressive age-related disease characterized by irreversible cognitive decline and functional impairment. Worldwide, >24 million people have dementia, two-thirds of whom live in low- and middle-income countries (LAMICs) (1, 2). Treatment and prevention of dementia in LAMICs remains a largely neglected topic (3, 4).

Oily fish consumption is potentially appropriate for both the primary and secondary prevention of dementia and has biological plausibility (5, 6). Oily fish are a rich source of omega-3 long-chain polyunsaturated fatty acids (n−3 LCPs), which have antiinflammatory, antioxidant, antiatherogenic (5), antiamyloid, and neuroprotective properties (7, 8). Evidence of a benefit of fish consumption on dementia risk is currently limited to developed countries. Most observational studies report an association of high fish intake with better cognition (9, 10) or lower risk of dementia (11–15), although these findings are not consistent across all studies (16, 17). A recent small randomized

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controlled trial in healthy Dutch adults found no benefit of n−3 LCP supplementation over 6 mo (18), further trials are underway (19, 20), and current evidence of a benefit on cognitive health is not convincing (21). Furthermore, fish foods may contain contaminants, such as mercury and dioxins, that might contribute to neurodegenerative disorders. The proposal that the benefits of fish intake outweigh the potential risks (22) cannot currently be extended to LAMICs because of the absence of region-specific data.

Although few studies present data on the association of meat intake with risk of dementia, reports of associations with constituents of meat, such as saturated fat and cholesterol, are more frequent. In a large cohort of French adults followed for 7 y, there was no association of reported meat intake with dementia risk (11). Cross-sectional studies have reported a direct association of cholesterol with risk of cognitive impairment (10, 23), although this is not supported by longitudinal data (24) and gene-nutrient interactions are suggested (25). A direct association of saturated fat intake with cognitive decline (26, 27), vascular dementia (28), and Alzheimer disease (12) has been found in some, but not all (29), cohorts.

The current data were derived from the 10/66 population-based studies on dementia and aging in 10 LAMICs. The objectives of the current report were as follows: *1*) to describe fish and meat intakes and their relation to the health and sociodemographic characteristics of older people across countries, *2*) to test the hypotheses that dietary fish is inversely associated and dietary meat is directly associated with prevalent dementia, and *3*) to test the consistency of the country-specific hypothesized inverse association of fish and dementia with control for the relevant confounders and after having disaggregated the potential concomitant opposing effect of meat consumption.

SUBJECTS AND METHODS

Study design

This was a cross-sectional catchment area one-phase survey of older people (aged ≥65 y) carried out at 11 sites: one urban and one rural in Peru, Mexico, China, and India and in urban sites only in Cuba, the Dominican Republic, and Venezuela. More affluent areas of the countries were avoided. Details on the catchment areas can be found on the 10/66 website (www.alz.co.uk/1066). Recruitment dates ranged from January 2003 to November 2007.

Participants

The chosen areas were mapped, and all residents aged ≥65 y were enumerated by means of door-knocking. Age was ascertained on the basis of self-report, documentation, and a relative's confirmation. No other inclusion or exclusion criteria were applied. Power calculations showed that a sample size of 2000 per country would allow an estimation of a typical dementia prevalence of 4.5% with a precision of ±0.9%.

Study protocol and operational procedures

The 10/66 Dementia Research Group standardized protocol was administered in full to all study participants (30). Development and validation of the 10/66 dementia diagnosis was previously successfully conducted in 25 LAMICs, including the 7 reported here (31). The participant interviews and assessments lasted from 2 to 3 h and were generally carried out at the participant's household. All materials, questionnaires, and assessments were translated into the local languages by bilingual local clinicians. In two 1-wk intensive training courses, held in London (United Kingdom) and Barcelona (Spain), the 10/66 London team trained the local principal investigators (PIs) on the 10/66 protocols and procedures. A detailed manual and a video training course were prepared on the physical and neurological examinations covering all aspects of the 10/66 protocol, the assessments, and the study procedures. Local interviewers were medical doctors in Cuba and China and lay interviewers (generally health workers) in all other centers. All received the same standard training on the 10/66 protocol and assessments. Moreover, the local PIs carried out periodic quality-control assessments and random checks throughout the data collection process. Data were recorded on paper data entry sheets and entered locally onto computers by using EpiData (32) files on which conditional skips and range checks were predefined. Data were then exported to SPSS (33) and STATA (34), cleaned, and combined into a single data set. The institutional review boards of the Institute of Psychiatry, KCL in London. and the institutional ethics committees in each of the countries that took part in this study approved the study protocol and its procedures.

Measures

The 10/66 protocol comprises questionnaires on participants' sociodemographic characteristics, health status, health behaviors, and risk factor exposures; physical and neurological examinations; and an extensive informant interview. In situations in which the participant was too cognitively impaired to answer questions, information was gathered from an informant. Details on measures and assessments are extensively described elsewhere (30). For the purposes of this study we considered the following variables:

1) Sociodemographic characteristics: sex, age, educational level, household living circumstances, and number of assets (motor vehicles, television, refrigerator and/or freezer, water utilities, electricity utilities, telephone, plumbed toilet, and plumbed bathroom).

2) Diagnosis of dementia: according to the 10/66 diagnostic algorithm (31).

3) Dietary habits: standardized questions on average weekly fish and meat intakes were measured in face-to-face interviews. Response options for "how often do you eat fish/meat in a week?" were "never," "some days," "most days," and "every day." The average daily portions of vegetables and fruit consumed were also recorded as was the alcohol units drunk per week.

4) Depressive episodes (mild, moderate, or severe): ascertained by using the Geriatric Mental State Examination (35) according to the *International Classification of Diseases, 10th edition* (ICD-10) (36).

5) Diastolic and systolic blood pressures: measured on 2 occasions, and the mean was calculated. Hypertension was defined according to the European Society of Hypertension (ESH) definition (average systolic blood pressure ≥140 mm Hg and/or average diastolic blood pressure ≥95 mm Hg) (37).

6) Self-reported chronic disease diagnoses: standardized questions ("have you ever been told by a doctor that you had a stroke/heart attack/angina or have diabetes?") were asked for stroke, ischemic heart disease, and diabetes.
7) Smoking habits: ever smoked, current smoker, and lifetime smoking.

Data analysis

Participants' characteristics by country

We present descriptive statistics to illustrate the sociodemographic and health characteristics of participants and their weekly fish and meat intakes by country. On inspection of the data, we combined participants who reported fish or meat intakes on "most days" and "every day" given the small numbers in these groups.

We calculated correlations (Kendall's τ) between fish and meat consumption by country. We then used unadjusted ordered logistic regressions to measure the associations between fish and meat consumption (entered in the model as ordered categorical variables) and participants' health and sociodemographic characteristics after having dichotomized age (<75 y vs ≥ 75 y), educational level (no or very limited education vs at least completed primary school), smoking habits (never smoked vs ex- and current smokers), living arrangements (alone or with spouse only vs with ≥ 2 people), and number of assets (less vs >3 assets).

Association between prevalent dementia and diet

Dementia status was determined by applying the 10/66 diagnostic algorithm (31). To ascertain the risk of dementia associated with fish consumption we first calculated unadjusted robust prevalence ratios (PRs) with 95% CIs using Poisson regression, with control for household clustering and dietary intakes as continuous variables. Units of increase for all PRs are per fish and meat consumption level, year of age, education level (5 grades from none to tertiary), number of assets (0 to 7), number of servings of fruit and vegetables per week, and alcohol consumption (units/wk). The assumption was made that the levels of fish consumption had a natural ordering (low to high), with unknown distances between adjacent levels. We then performed the same analysis entering fish consumption in the model as an ordinal categorical variable. We carried out a likelihood ratio test to compare the 2 models by country. Because in none of the countries except China ($\chi^2 = 4.03$, $P = 0.04$) (Table 4) were the 2 models significantly different, PRs (with 95% CI) from the former model—interpreted as a test for trend—were considered and a linear effect of fish consumption on prevalent dementia was implied.

We repeated the statistical procedure for meat consumption and again found no significant departures from linearity (Table 5). Therefore all PRs for the association between dementia and dietary meat intake were again calculated after meat intake was entered as a continuous variable in the Poisson regression models.

In 3 further models, we used Poisson regressions to generate adjusted PRs for the associations between prevalent dementia and weekly intakes of fish foods and meat. In model 1 we controlled for age, sex, and educational level. On the basis of the evidence in the literature, family history of dementia, self-reported chronic disease diagnoses (namely stroke, diabetes and coronary heart disease), ICD-10 depression, and smoking habits were included in model 2 along with living arrangements (living alone or with spouse only as opposed to living in multigenerational families) and number of assets (less vs >3 assets) as proxies of food availability and affordability. All variables were considered potential confounders, likely associated with both dietary habits and dementia status. Finally, to assess the independent effect of fish with control for other nutritional factors, we estimated model 3 in which the average daily number of fruit and vegetable portions and the weekly intake of meat (or fish as appropriate) and alcohol were added to the covariates of model 2. We carried out likelihood tests to test for departures from linearity and to test for the hypothesis of a linear association between dietary intake and dementia prevalence.

Finally, to summarize the associations between dietary fish, dietary meat, and prevalent dementia, we assumed that the true association was the same in all countries and combined the country-adjusted PRs from model 3 (*see* above) in 2 fixed-effect model meta-analytic forest plots. We did not use random-effect models because we wished to summarize the countries within this study rather than generalize to a hypothetical population of centers. A formal test for between-studies heterogeneity (Cochran's Q) was performed, and I^2 Higgins values (38) were calculated (larger values meaning higher heterogeneity). Descriptive and analytic statistics were carried out by using release 1_7 of the 10/66 data set with STATA 9.2 software (StatCorp 2007, Stata Statistical Software: release 10; StataCorp, College Station, TX).

Role of the funding source

Study design, data collection and analysis, and interpretation of the findings were independent of all sponsors. All authors agreed on the contents of the article, and the ultimate decision and responsibility of submission lies with the corresponding author.

RESULTS

This article includes data on 14,960 participants from urban sites in Cuba, the Dominican Republic, Venezuela, and urban and rural sites in Peru, Mexico, China, and India. Response rates among eligible enumerated older people (≥ 65 y) ranged from 80% to 94% (**Table 1**) (2). Missing values for each variable are reported by country in Table 1.

Participants' sociodemographic and health characteristics by country

The sociodemographic and health characteristics of participants are presented by country (Table 1). The age distribution across countries was fairly consistent, with Venezuelan, Chinese, and Indian participants being slightly younger than in other countries. There were more women than men in the sample in every site. Participants in Cuba and Peru were better educated than were those in other countries. Extended family living arrangements were the norm, particularly in Venezuela and Peru. Socioeconomic disadvantage, as indexed by having ≤ 3 household assets, was most prevalent in the Indian sample and in the Dominican Republic and Mexico. The prevalence of hypertension and cardiovascular disease was highest in the more developed Latin American centers, particularly Cuba. However, the prevalence of hypertension in Peru was strikingly low.

TABLE 1
Sociodemographic and health characteristics of participants by country[1]

Variable	Cuba	Dominican Republic	Peru	Venezuela	Mexico	China	India
	Country						
Sample size (*n*)	2934	1999	1927	1939	1997	2162	1998
Response rate (%)	94	95	84	80	85	85	85
Age [*n* (%)]							
65–69 y	760 (25.9)	533 (26.5)	554 (28.7)	823 (41.2)	544 (27.12)	699 (32.3)	746 (37.3)
70–74 y	789 (26.9)	520 (25.9)	493 (25.5)	469 (23.51)	581 (29.02)	658 (30.43)	668 (33.4)
75–79 y	639 (21.8)	397 (19.7)	399 (20.6)	346 (17.34)	426 (21.28)	456 (21.09)	321 (16.1)
≥80 y	749 (25.5)	561 (28.0)	486 (25.2)	309 (15.49)	451 (22.53)	349 (16.14)	265 (13.2)
Missing values	7	0	2	23	1	0	4
Females (%)	64.9	65.9	61.2	64.2	63.3	56.3	56.1
Missing values (*n*)	10	3	7	60	0	0	15
Educational level [*n* (%)]							
No education	75 (2.5)	392 (19.5)	121 (6.3)	158 (7.8)	554 (27.7)	811 (37.5)	1088 (54.3)
Some education	655 (22.3)	1022 (50.8)	231 (11.9)	453 (22.5)	864 (43.1)	267 (12.4)	429 (21.4)
Completed primary school	979 (33.3)	370 (18.4)	727 (37.6)	977 (48.4)	351 (17.5)	562 (26.0)	328 (16.4)
Completed secondary school	728 (24.7)	135 (6.7)	517 (26.7)	271 (13.4)	124 (6.2)	380 (17.6)	113 (5.6)
Completed tertiary school	499 (16.9)	73 (3.6)	321 (16.6)	96 (4.8)	110 (5.5)	142 (6.6)	44 (2.2)
Missing values	8	19	16	63	0	0	2
Live alone or with spouse only [*n* (%)]	706 (24.1)	389 (19.3)	274 (14.2)	218 (10.8)	525 (26.2)	712 (33.0)	412 (20.6)
Missing values	0	0	0	0	0	0	0
Three or fewer assets [*n* (%)]	87 (3.1)	310 (15.4)	95 (4.9)	58 (2.9)	432 (21.6)	114 (5.3)	1052 (52.5)
Missing values	0	0	0	0	0	0	0
10/66 Dementia [*n* (%)]	316 (10.8)	235 (11.7)	165 (8.5)	140 (7.1)	171 (8.5)	137 (6.3)	181 (9)
Missing values	13	0	2	0	0	0	0
Meets ESH hypertension criteria [*n* (%)]	1639 (55.7)	915 (45.5)	224 (11.6)	682 (44.8)	717 (35.8)	958 (44.3)	730 (36.4)
Missing values	0	0	0	0	0	0	0
Self-reported stroke [*n* (%)]	230 (7.8)	175 (8.7)	132 (6.9)	138 (7.1)	141 (7.1)	127 (5.9)	31 (1.5)
Missing values	9	6	10	68	0	0	1
Self-reported diabetes [*n* (%)]	543 (18.5)	281 (14.0)	173 (9.0)	314 (16.1)	435 (21.7)	204 (9.4)	187 (9.3)
Missing values	16	4	11	62	1	1	1
Self-reported CHD [*n* (%)]	415 (14.1)	60 (3.0)	115 (6.0)	121 (6.2)	54 (2.7)	127 (5.9)	77 (3.8)
Missing values	6	2	2	56	0	0	1
ICD-10 depressive episode [*n* (%)]	144 (4.9)	278 (13.8)	103 (5.3)	108 (5.3)	92 (4.6)	10 (0.5)	165 (8.2)
Missing values	0	0	0	0	0	0	0
Alcohol (units/wk)[2]	2.1 ± 13.7	9.7 ± 37.2	0.3 ± 4.9	2 ± 5.2	1 ± 5.5	2.2 ± 10	0.2 ± 1.6
Missing values	52	15	51	821	17	0	129
Current or ex-smoker [*n* (%)]	1319 (24.2)	955 (17.5)	324 (5.9)	823 (15.1)	624 (11.4)	620 (11.4)	797 (14.6)
Missing values	8	2	8	88	0	0	8

[1] ESH, European Society of Hypertension; CHD, coronary heart disease (including angina and myocardial infarction); ICD-10, *International Classification of Disease, 10th edition.*

[2] Values are means ± SDs.

Smoking was very uncommon among older people in Peru and considerably more common in Cuba, India, and China. The prevalence of dementia in the samples has been reported in detail elsewhere (2). In brief, there were 1340 prevalent dementia cases in the whole sample, and the prevalence varied from 6.3% to 11.7% by country, being higher in the Latin American countries than in China and India (Table 1).

Fish and meat consumption

Fish and meat consumptions varied considerably across countries (**Table 2** and **Table 3**). Fish consumption was highest in Venezuela and China and lowest in India and the Dominican Republic. Meat consumption was lowest in Venezuela and highest in the Dominican Republic, China, Peru, and Cuba.

Fish and meat consumption was modestly positively correlated in Cuba (Kendall's $\tau = 0.14$), the Dominican Republic (0.10), Peru (0.19), and Mexico (0.14); strongly correlated in China (0.56) and India (0.77); and not correlated in Venezuela (−0.05). In all countries but Venezuela ($P = 0.21$), the correlations were statistically significant ($P < 0.001$). There was a general trend toward lower consumption of both fish and meat among older participants; however, this trend was only statistically significant in Cuba and China for fish and in Venezuela for meat. The ordered logistic regression models showed that in all countries except China, alcohol consumption was consistently higher among those with higher fish and meat intakes. Those with higher educational levels and more assets reported higher fish and meat intake across all countries. Crude associations between fish and meat intakes and history of stroke, self-reported

TABLE 2
Weekly fish consumption and unadjusted odds ratios (and 95% CIs) for the ordered logistic regression model for fish consumption and health and sociodemographic characteristics by country[1]

	Country						
Variable	Cuba	Dominican Republic	Peru	Venezuela	Mexico	China	India
Sample size (*n*)	2934	1999	1927	1939	1997	2162	1998
Weekly fish intake [*n* (%)]							
Never	287 (9.8)	684 (34.2)	161 (8.4)	88 (4.7)	567 (28.4)	67 (3.1)	422 (21.1)
Some days	2348 (80.0)	1158 (57.9)	1413 (73.3)	850 (45.0)	1328 (66.5)	1467 (67.9)	1424 (71.3)
Most/every day	299 (10.2)	157 (7.9)	353 (18.3)	953 (50.4)	102 (5.1)	628 (29.1)	152 (7.6)
Missing values	10	12	6	79	6	0	6
Age[2]	0.71 (0.59, 0.86)	0.85 (0.71, 1.01)	1.00 (0.81, 1.23)	1.01 (0.84, 1.22)	0.86 (0.71, 1.03)	0.73 (0.60, 0.90)	0.84 (0.68, 1.04)
Sex (F vs M)	1.24 (1.05, 1.46)	1.44 (1.21, 1.71)	1.21 (1.00, 1.47)	1.00 (0.84, 1.18)	0.85 (0.71, 1.02)	1.19 (1.04, 1.37)	1.11 (0.92, 1.34)
Education[2]	1.62 (1.31, 2.00)	1.51 (1.24, 1.83)	0.60 (0.47, 0.78)	1.39 (1.15, 1.69)	2.42 (1.95, 2.99)	1.02 (0.85, 1.23)	0.73 (0.57, 0.93)
Self-reported stroke	0.87 (0.60, 1.27)	1.00 (0.74, 1.36)	1.02 (0.69, 1.50)	1.06 (0.75, 1.49)	0.80 (0.56, 1.13)	0.47 (0.30, 0.73)	0.87 (0.37, 2.03)
Self-reported CHD	1.13 (0.87, 1.47)	1.01 (0.59, 1.72)	1.14 (0.75, 1.73)	1.09 (0.74, 1.60)	1.62 (0.83, 3.16)	0.46 (0.31, 0.68)	1.07 (0.66, 1.75)
Self-reported diabetes	1.07 (0.85, 1.35)	1.56 (1.23, 1.96)	1.18 (0.87, 1.62)	1.20 (0.95, 1.53)	1.14 (0.91, 1.42)	0.67 (0.48, 0.95)	1.33 (0.92, 1.93)
ICD-10 depression	0.67 (0.47, 0.97)	0.96 (0.76, 1.23)	0.64 (0.40, 1.03)	0.60 (0.41, 0.88)	0.72 (0.46, 1.14)	0.82 (0.15, 4.55)	1.22 (0.88, 1.69)
Alcohol consumption[2]	1.32 (1.04, 1.68)	1.49 (1.19, 1.87)	1.91 (1.21, 3.03)	1.37 (1.08, 1.75)	1.41 (1.12, 1.78)	0.63 (0.47, 0.83)	1.6 (1.24, 2.06)
Smoking status[2]	1.12 (0.93, 1.34)	0.80 (0.67, 0.95)	1.08 (0.82, 1.4)	0.96 (0.80, 1.14)	1.24 (1.01, 1.51)	0.95 (0.78, 1.16)	1.28 (1.05, 1.55)
Living arrangements[2]	1.12 (0.89, 1.41)	0.87 (0.70, 1.09)	0.74 (0.54, 1.01)	0.76 (0.56, 1.04)	1.09 (0.87, 1.36)	0.90 (0.72, 1.13)	1.20 (0.95, 1.53)
Assets[2]	1.19 (0.68, 2.09)	1.76 (1.39, 2.24)	0.48 (0.32, 0.74)	1.07 (0.65, 1.78)	3.96 (3.14, 4.99)	1.13 (0.69, 1.85)	0.99 (0.81, 1.21)

[1] CHD, coronary heart disease (including angina and myocardial infarction); ICD-10, *International Classification of Diseases, 10th edition.*

[2] Dichotomized variables: age (>75 vs ≤75 y), sex (F vs M), education (no or some education vs completed at least primary school), alcohol consumption (0 vs ≥1 unit/wk), smoking status (never vs ex- or current smoker), living alone or with spouse only, and assets (≥3 vs <3).

diabetes (type 1 or 2), smoking habit, and depression were inconsistent across countries (Table 2 and Table 3).

Association between prevalent dementia and dietary fish

There was a consistent finding in all countries, except India, of an inverse association between reported fish consumption and dementia prevalence. In the crude model, the PRs for each increase in fish consumption category ranged from 0.40 (95% CI: 0.26, 0.60) in China to 1.13 (95% CI: 0.84, 1.50) in India (Table 4). In model 1 the inverse association of dietary fish with dementia was attenuated somewhat after age, sex, and educational level were adjusted for. PRs did not substantially change in model 2 after family history of dementia, self-reported chronic disease

TABLE 3
Weekly meat consumption and unadjusted odds ratios (and 95% CIs) for the ordered logistic regression model for consumption and health and sociodemographic characteristics by country[1]

	Country						
Variable	Cuba	Dominican Republic	Peru	Venezuela	Mexico	China	India
Sample size (*n*)	2934	1999	1927	1939	1997	2162	1998
Weekly meat intake [*n* (%)]	102 (3.5)	114 (5.7)	155 (8.1)	358 (18.9)	177 (8.9)	60 (2.8)	378 (18.9)
Never	102 (3.5)	114 (5.7)	155 (8.1)	358 (18.9)	177 (8.9)	60 (2.8)	378 (18.9)
Some days	1752 (59.7)	790 (39.5)	1021 (53)	1251 (66.1)	1439 (72.1)	926 (42.8)	1479 (74)
Most/every day	1080 (36.8)	1096 (54.8)	750 (38.9)	285 (15.1)	381 (19.1)	1176 (54.4)	142 (7.1)
Missing values	10	11	7	76	6	0	5
Age[2]	1.00 (0.86, 1.16)	0.99 (0.83, 1.18)	1.06 (0.89, 1.27)	0.80 (0.65, 0.98)	0.94 (0.77, 1.15)	0.94 (0.78–1.14)	0.86 (0.69–1.07)
Sex (F vs M)	0.86 (0.75, 0.99)	1.21 (1.01, 1.44)	0.81 (0.68, 0.97)	1.36 (1.14, 1.63)	1.03 (0.85, 1.24)	1.37 (1.20–1.57)	1.04 (0.85–1.26)
Education[2]	1.35 (1.13, 1.61)	1.18 (0.97, 1.43)	1.34 (1.08, 1.66)	1.30 (1.05, 1.59)	1.30 (1.04, 1.63)	1.58 (1.32–1.88)	0.51 (0.39–0.66)
Self-reported stroke	1.25 (0.94, 1.64)	1.07 (0.79, 1.47)	1.08 (0.72, 1.62)	0.69 (0.48, 1.00)	1.04 (0.72, 1.49)	1.11 (0.76–1.62)	0.68 (0.27–1.67)
Self-reported CHD	0.87 (0.70, 1.08)	0.84 (0.52, 1.36)	1.46 (1.04, 2.06)	0.88 (0.57, 1.36)	1.14 (0.58, 2.21)	0.98 (0.67–1.42)	0.98 (0.56–1.72)
Self-reported diabetes	1.47 (1.22, 1.79)	1.18 (0.92, 1.52)	1.09 (0.79, 1.49)	1.01 (0.79, 1.29)	1.11 (0.88, 1.41)	1.40 (1.04–1.89)	1.53 (1.02–2.29)
ICD-10 depression	0.85 (0.61, 1.18)	0.75 (0.58, 0.97)	1.33 (0.86, 2.06)	1.11 (0.69, 1.78)	0.98 (0.59, 1.65)	1.44 (0.23–9.14)	0.98 (0.70–1.37)
Alcohol consumption[2]	1.32 (1.04, 1.68)	1.49 (1.19, 1.87)	1.91 (1.21, 3.03)	1.37 (1.08, 1.75)	1.41 (1.12, 1.78)	0.63 (0.47–0.83)	1.6 (1.24–2.06)
Smoking status[2]	0.87 (0.76, 1.01)	0.83 (0.69, 0.99)	1.41 (1.10, 1.81)	1.26 (1.04, 1.52)	1.39 (1.13, 1.72)	1.33 (1.10–1.61)	1.43 (1.17–1.75)
Living arrangements[2]	1.11 (0.91, 1.35)	0.96 (0.76, 1.20)	1.05 (0.80, 1.37)	0.87 (0.63, 1.22)	1.40 (1.12, 1.74)	0.77 (0.62–0.95)	1.15 (0.89–1.49)
Assets[2]	2.01 (1.20, 3.37)	1.76 (1.40, 2.21)	1.44 (1.03, 2.01)	0.34 (0.19, 0.62)	2.14 (1.73, 2.65)	1.93 (1.26–2.95)	0.72 (0.58–0.89)

[1] CHD, coronary heart disease (including angina and myocardial infarction); ICD-10, *International Classification of Diseases, 10th edition.*

[2] Dichotomized variables: age (>75 vs ≤75 y), sex (F vs M), education (no or some education vs completed at least primary school), alcohol consumption (0 vs ≥1 unit/wk), smoking status (never vs ex- or current smoker), living alone or with spouse only, and assets (≥3 vs <3).

diagnoses, ICD-10 depression, smoking habits, living arrangements, and number of assets were adjusted for. Further adjustment for the effect of dietary meat, alcohol consumption, and daily portions of fruit and vegetables (model 3) did not substantially alter the estimates. Likelihood ratio tests showed no significant departures from linearity in any country (**Table 4**), although the inverse linear trend was only statistically significant in China (Table 4). To summarize the effect of fish consumption on prevalent dementia across the whole sample, the country-specific robust PRs (and 95% CI) from model 3 were combined into a meta-analysis that estimated a combined PR from the fixed-effect model of 0.81 (95% CI: 0.72, 0.91) among those who ate fish more often (**Figure 1**). The heterogeneity of effect between countries was not significant (P = 0.16), and the degree of inconsistency in results was very low (Higgins I^2 = 36%; 95% CI: 0, 73). In no country was there a significant association between fish consumption and degree of dementia severity (according to the Clinical Dementia Rating scale).

Association between prevalent dementia and dietary meat

The crude association between meat intake and prevalent dementia was inconsistent across countries. In Cuba (1.28; 95% CI: 1.04, 1.58) and Peru (1.52; 95% CI: 1.16, 1.99), PRs showed a statistically significant direct association between meat consumption and dementia risk, which remained statistically significant after potential confounders were adjusted for (**Table 5**). In China the crude PR suggested a statistically significant inverse association between meat consumption and risk of dementia (0.67; 95% CI: 0.50, 0.90), which became statistically nonsignificant after adjustment (Table 5). The likelihood ratio tests showed no departure from linearity, whereas the hypothesis that meat consumption would be associated with a higher risk of dementia was only supported in Cuba and Peru. When we combined the country-specific robust PRs (with 95% CI) of model 3 into a fixed-effect model meta-analysis, we estimated a combined PR of 1.19 (95% CI: 1.07, 1.31) for the association between meat consumption and prevalent dementia (**Figure 2**). There was no statistically significant heterogeneity of estimates between countries (P = 0.15), and the degree of inconsistency in results was very low (Higgins I^2 = 37%; 95% CI: 0, 73). In Cuba there was a significant association between severity of dementia and meat consumption, with higher meat consumption among those with more severe dementia according to the Clinical Dementia Rating scale (χ^2 = 6.1, df = 1, P = 0.014).

DISCUSSION

We showed for the first time that a statistically significant trend toward a lower prevalence of dementia among those with higher dietary fish intake in large population-based samples of older people living in 5 countries in Latin America, China, and India. The country-specific association of fish intake with dementia was only statistically significant in China, but meta-analysis combining data from all countries showed a statistically significant association (PR: 0.81; 95% CI: 0.72, 0.91) that remained even after adjustment for a large array of potentially relevant socio-demographic and health-related factors. The negative association was not present in India (PR: 1.47; 95% CI: 0.92, 2.35). Reported fish and meat consumption was positively correlated in most countries, and there was also evidence of a modest increased risk of dementia among those with higher meat consumption (PR: 1.19; 95% CI: 1.07, 1.31). We did not have information on type of fish and meat consumed, portion size, and method of cooking, which may all be relevant factors.

To our knowledge, this is the largest population-based study on this topic to date from either developing or developed country samples. Our findings are consistent with some (12, 15, 39) but not all (16, 17) studies on fish intake in Western countries and support previous associations of saturated fat (12, 26–28), although not meat (11), with cognitive health. We are not able to say whether the inconsistency in findings was due to the type of fish and meat reportedly consumed in our study. Our findings should be interpreted with caution given the cross-sectional study design and the limitations in our dietary assessments. Moreover, although our study's internal validity and intercountry

TABLE 4
Prevalence ratios from robust Poisson regression models for the association of fish consumption with 10/66 dementia, with likelihood ratio tests for linearity and for test of hypothesis, by country[1]

	Prevalence ratio (95% CI)				Chi-square test with df = 1 (P value)	
	Crude model	Model 1[2]	Model 2[3]	Model 3[4]	Linearity test	Test for the hypothesis
Cuba	0.67 (0.52, 0.88)	0.86 (0.68, 1.08)	0.83 (0.66, 1.04)	0.81 (0.65, 1.02)	2.41 (0.12)	2.86 (0.09)
Dominican Republic	0.74 (0.60, 0.91)	0.77 (0.62, 0.94)	0.78 (0.64, 0.95)	0.80 (0.65, 1.00)	0.59 (0.44)	3.90 (0.05)
Peru	0.83 (0.61, 1.14)	0.87 (0.64, 1.20)	0.84 (0.61, 1.14)	0.76 (0.56, 1.05)	1.32 (0.25)	2.17 (0.14)
Venezuela	1.11 (0.83, 1.49)	0.92 (0.69, 1.23)	0.92 (0.68, 1.26)	0.87 (0.56, 1.34)	0.02 (0.88)	0.33 (0.57)
Mexico	0.64 (0.49, 0.85)	0.83 (0.64, 1.08)	0.85 (0.65, 1.11)	0.81 (0.62, 1.08)	0.78 (0.38)	2.52 (0.11)
China	0.40 (0.26, 0.60)	0.45 (0.31, 0.67)	0.50 (0.36, 0.71)	0.58 (0.39, 0.85)	4.03 (0.04)	6.94 (0.01)
India	1.13 (0.84, 1.50)	1.18 (0.88, 1.58)	1.18 (0.88, 1.59)	1.47 (0.92, 2.35)	1.09 (0.30)	2.40 (0.12)

[1] Prevalence ratios were adjusted for household clustering. Unit of increase in prevalence ratios are per fish, per meat consumption (none per week, some days, most days, or all days), per year, per level of education (5 levels from none to completed tertiary school), per number of assets (0 to 7), fruit and vegetable intake (servings/wk), and alcohol consumption (units/wk).

[2] Adjusted for age, sex, educational level, and number of household assets.

[3] As for model 1 plus family history of dementia; number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoking habit; living arrangements (live alone or only with spouse); and number of assets.

[4] As for model 2 plus meat intake, alcohol consumption, and number of daily portions of fruit and vegetables.

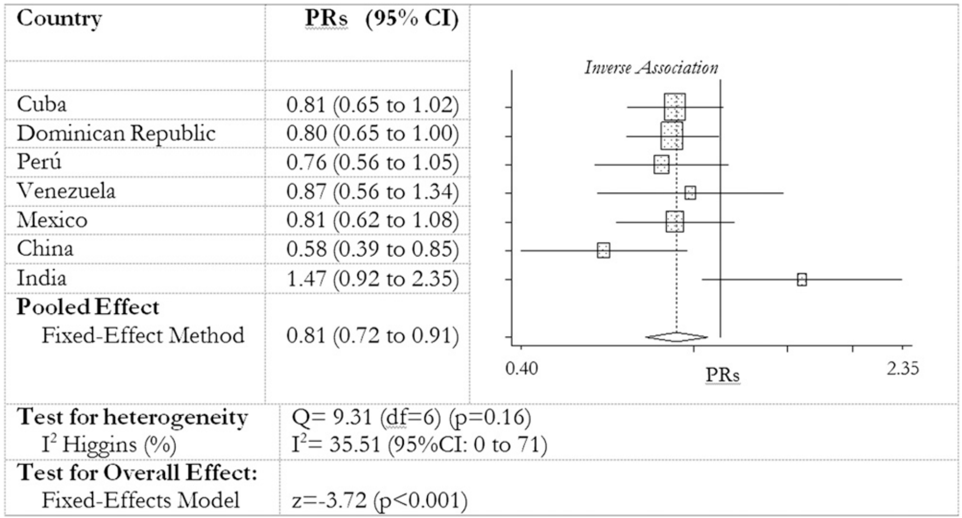

FIGURE 1. Meta-analysis (fixed-effect model) of country prevalence ratios (PRs) (and 95% CIs) for the association between fish consumption and 10/66 dementia. PRs are from robust Poisson regression models adjusted for household clustering as for model 3 in Table 4, ie, adjusted for age, sex, educational level, and family history of dementia and controlled for number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoking habit; living arrangements (live alone or only with spouse); number of assets; meat intake; and number of daily portions of fruit and vegetables.

comparisons are strong, we recognize that our findings should only be generalized to populations with similar dietary and health characteristics.

Identical study protocols were used across the 7 LAMICs. The validity of the dementia outcome has been shown in cross-cultural pilot studies in 25 countries worldwide (31). Our face-to-face questions to assess dietary habits were simple and well tolerated both by healthy participants and by those with dementia, whose answers were confirmed by an informant. The major limitations of this report arise from the cross-sectional design. We cannot entirely exclude the possibility that reverse causality, information bias, differential mortality, or residual confounding may have accounted for the observed findings (40). Whereas those with dementia might be expected to have a lower food intake, this seems unlikely to have accounted for the potential protective effect of fish intake given that those with dementia generally reported a higher intake of meat. There was no evidence among those with dementia that progression of the disease was associated with reduced fish intake. Those with a more sufficient diet of meat may have survived longer with dementia, accounting for the positive cross-sectional association. This would be consistent with the finding in Cuba that those with more advanced dementia had higher meat intakes. This association may also have arisen from information bias because those with dementia may have been selectively likely to over- or underreport their dietary exposure to meat or fish. Random errors in reporting of dietary exposures will also have occurred and may have led to an underestimate of the true associations. Attrition was avoided in our one-phase design (41), and high response rates were obtained in all countries. We cannot exclude the possibility of selection bias,

TABLE 5

Prevalence ratios from robust Poisson regression models for the association of meat consumption with 10/66 dementia, with likelihood ratio tests for linearity and for test of hypothesis, by country[1]

	Prevalence ratio (95% CI)				Chi-square test with df = 1 (*P* value)	
	Crude model	Model 1[2]	Model 2[3]	Model 3[4]	Linearity test	Test for the hypothesis
Cuba	1.28 (1.04, 1.58)	1.28 (1.05, 1.55)	1.22 (1.00, 1.48)	1.31 (1.07, 1.60)	1.40 (0.24)	6.05 (0.01)
Dominican Republic	1.11 (0.91, 1.37)	1.14 (0.93, 1.4)	1.12 (0.93, 1.36)	1.19 (0.98, 1.45)	0.04 (0.85)	2.39 (0.12)
Peru	1.52 (1.16, 1.99)	1.45 (1.13, 1.88)	1.40 (1.10, 1.78)	1.41 (1.09, 1.81)	0.70 (0.40)	6.04 (0.01)
Venezuela	1.36 (0.99, 1.87)	0.83 (0.61, 1.13)	0.84 (0.62, 1.14)	0.91 (0.59–1.40)	0.03 (0.86)	0.04 (0.84)
Mexico	1.07 (0.81, 1.41)	1.17 (0.90, 1.52)	1.19 (0.91, 1.54)	1.24 (0.94, 1.64)	0.61 (0.44)	1.78 (0.18)
China	0.67 (0.50, 0.90)	0.72 (0.53, 0.97)	0.67 (0.52, 0.88)	0.95 (0.69, 1.31)	1.04 (0.31)	0.11 (0.74)
India	1.04 (0.78, 1.39)	1.02 (0.75, 1.38)	1.01 (0.75, 1.36)	0.77 (0.48, 1.21)	0.03 (0.87)	1.10 (0.29)

[1] Prevalence ratios were adjusted for household clustering. Unit of increase in prevalence ratios are per fish, per meat consumption (none per week, some days, most days, or all days), per year, per level of education (5 levels from none to completed tertiary school), per number of assets (0 to 7), fruit and vegetable intake (servings/wk), and alcohol consumption (units/wk).

[2] Adjusted for age, sex, educational level, and number of household assets.

[3] As for model 1 plus family history of dementia; number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoking habit; living arrangements (live alone or only with spouse); and number of assets.

[4] As for model 2 plus meat intake, alcohol consumption, and number of daily portions of fruit and vegetables.

Country	PRs (95% CI)
Cuba	1.31 (1.07 to 1.60)
Dominican Republic	1.19 (0.98 to 1.45)
Perú	1.41 (1.09 to 1.81)
Venezuela	0.91 (0.59 to 1.40)
Mexico	1.24 (0.94 to 1.64)
China	0.95 (0.69 to 1.31)
India	0.77 (0.48 to 1.21)
Pooled Effect	
Fixed-Effect Method	1.19 (1.07 to 1.31)
Test for heterogeneity[1]	Q= 9.46 (6 df) (p=0.15)
I^2 Higgins (%)	I^2= 36.55 (95% C.I. 0 to 57.4)
Test for Overall Effect:	
Fixed-Effects Model	z=3.37 (p=0.001)

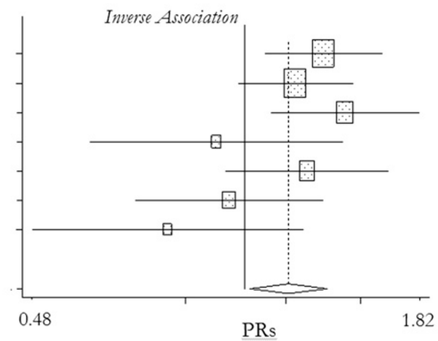

FIGURE 2. Meta-analysis (fixed-effect model) of country prevalence ratios (PRs) (and 95% CIs) for the association between meat consumption and 10/66 dementia. PRs are from robust Poisson regression models adjusted for household clustering as for model 3 in Table 5, ie, adjusted for age, sex, educational level, and family history of dementia and controlled for the number of *International Classification of Diseases, 10th edition*, depressive symptoms; self-reported stroke; self-reported diabetes; self-reported coronary heart disease (including angina and myocardial infarction); smoke habit; living arrangements (live alone or only with spouse); number of assets; fish intake; and number of daily portions of fruit and vegetables.

which might explain our findings if those without dementia reporting higher fish intakes were more likely to participate in the study. However, in our experience, healthy persons were less available than impaired persons for interviews; moreover, older persons in LAMICs may have scant awareness of the health-related properties of fish.

Our results extend previous findings on the beneficial effects of fish consumption on dementia in LAMICS and provide preliminary evidence of the etiological significance of diet in dementia. More substantive evidence will come from the incidence phase of our project, in which we will be able to compare the incidence of dementia according to dietary exposure at baseline (30), and from randomized controlled trials of the effectiveness of n−3 LCP supplementation for the prevention of cognitive decline (19, 20).

The authors' responsibilities were as follows—MJP: leader of the 10/66 Dementia Research Group; CF and EA: research coordinators; JLdR (Cuba), DA (Dominican Republic), MG (Peru), AS (Venezuela), ALS (Mexico), KSJ (Vellore, India), JW (Chennai, India), and YH (China): principal investigators responsible for the fieldwork in their countries; EA: wrote the first draft of the manuscript and conducted the analyses; and ADD, MJP, and RU: extensively revised the manuscript at all stages. All other authors reviewed the report and provided further contributions and suggestions. There were no conflicts of interest to declare.

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