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ABSTRACT

Campylobacter spp. is an important causative agent of diarrheal illness worldwide. The disease is frequently associated with foodborne transmission, but other routes of exposure are increasingly recognized. A systematic review and meta-analysis of case-control studies were performed to determine the main risk factors associated with sporadic campylobacteriosis. Suitable scientific articles published up to March 2017 were identified through a systematic literature search and subject to methodological quality assessment. From each study, odds ratios (OR) as measures of association were extracted or calculated, as well as study characteristics such as study population, design, type of model used and risk factor categorization. Mixed-effects meta-analytical models were adjusted by population type to appropriate data partitions. From 4453 identified references, the quality assessment stage was passed by 71 case-control studies focusing on sporadic campylobacteriosis. The eligible studies were conducted between 1981 and 2012 and provided 1336 ORs for meta-analysis. The meta-analysis identified international travel (pooled OR=4.626), recent use of gastric antacids (pooled OR=2.911), occupational exposure to animals/carcasses (pooled OR=3.022), and food consumption (in particular raw or undercooked eggs, poultry, beef, and dairy) as the main risks factors for sporadic campylobacteriosis in the mixed population. In the child population, the main risk factors concerned environmental/animal transmission routes (e.g. drinking untreated water (pooled OR=3.261), exposure to recreational water (pooled OR=3.156), exposure to farm/rural environment (pooled OR=3.128), contact with farm animals (pooled OR=2.747), person-to-person transmission (pooled OR=2.736) and consumption of raw milk (pooled OR =2.603). The results of this meta-analysis highlight the importance of overlooked routes and vehicles of transmission (environment, animal contact, and other food vehicles) of Campylobacter that should be explored in dedicated studies.

1. Introduction

Campylobacter spp. are major causative agents of bacterial gastroenteritis in industrialized countries. The 2015 Global Burden of Disease Study estimated that Campylobacter spp. were responsible for 166 million (95% uncertainty interval (UI) 92,227,873– 300,877,905) cases of illness in 2010, 37,604 (95% UI 27,738–55,101) deaths and 3,733, 822 (95% UI 2,857,037–5,273,652) Disability Adjusted Life Years

(DALYs) (Kirk et al., 2015) worldwide. Campylobacter incidence estimates vary greatly world-over, largely depending on the performance of local surveillance systems and reporting procedures. Several studies have reported an increase in human campylobacteriosis incidence over the last two decades (Geissler et al., 2017, EFSA & ECDC, 2018, Trompette et al., 2019).

Campylobacteriosis symptoms include fever and abdominal pain that are often accompanied by watery or bloody diarrhea. The disease is

usually self-limiting and treatment is only required in more severe cases. The burden also includes sequelae following campylobacteriosis, such as Guillain-Barré syndrome, irritable bowel syndrome, and reactive arthritis (Keithlin et al., 2014). Campylobacteriosis is a seasonal disease, with clear seasonal peaks recurrently observed in late summer and autumn (Nylen et al., 2002, EFSA & ECDC, 2018). Among the numerous and increasing number *Campylobacter* species described to date, two thermotolerant species, *C. jejuni* and *C. coli*, account for over 90% of reported human infections in industrialized countries, with *C. lari* and *C. upsaliensis* being minor contributors (EFSA & ECDC, 2018).

Some studies support the idea that by integrating whole-genome-sequencing in the surveillance of *Campylobacter* infections, it is possible to distinguish between clustered and sporadic cases (Cody et al., 2013, Kovanen et al., 2014, Strachan et al., 2009), implying that "diffuse" outbreaks of campylobacteriosis occur more frequently than previously thought. Nevertheless, the biological characteristics of *Campylobacter* explain why human infections mainly occur sporadically and documented outbreaks have often been linked to contaminated water and unpasteurized milk (EFSA & ECDC, 2018, Mungai et al., 2015). The requirements of specific thermal and microaerophilic conditions for growth and a metabolism that is not based on sugar fermentation prevent *Campylobacter* replication during food production, storage and preparation (Guccione et al., 2008, Hinton, 2016). Several source attribution studies have identified poultry as the main source of human *Campylobacter* infection (Domingues et al., 2012a, Hoffmann et al., 2017, Cody et al., 2019), yet other sources of *Campylobacter* have been documented. *Campylobacter* has been isolated from other food-producing animals (Rossler et al., 2019), pets (Bojanić et al., 2017, Mughini Gras et al., 2013)), wild birds and several environmental sources (sand and surface waters) (Strachan et al., 2009, Sheppard et al., 2009). Thus, the potential sources of *Campylobacter* are numerous.

Several case-control studies have been conducted worldwide to elucidate transmission pathways and risk factors of campylobacteriosis. A previous systematic review and meta-analysis conducted by Domingues et al. (2012a) synthetized the evidence on risk factors of sporadic campylobacteriosis through a literature search conducted in February 2008. The objective of the present study was to perform an updated systematic review and meta-analysis of case-control studies on sporadic campylobacteriosis published up to March 2017. A novel protocol for data categorization and meta-analysis of observational studies proposed by Gonzales-Barron et al. (2019) was applied in order to determine the main risk factors for sporadic human *Campylobacter* infection.

2. Material and methods

The protocol of the systematic review and the meta-analysis model are described in depth in the methodological paper of this special issue (Gonzales-Barron et al., 2019).

2.1. Systematic review

The literature search was conducted in March 2017 using a combination of keywords related to (1) "*Campylobacter*" OR "campylobacteriosis", (2) "case-control" OR "risk factor" OR "cohort" (3) "infection" OR "disease", joined by the logical connector "AND". The term "sporadic" was not added because case-control studies conducted during outbreak investigations were also integrated into the reference databases. Relevant studies were identified from five bibliographic search engines, Science Direct, PubMed, Scielo, ISI Web of Science, and Scopus. No restrictions were defined for the year of the study or type of publication.

Each reference record was screened for relevance for inclusion in the meta-analysis. The methodological quality of the "candidate" studies was assessed using pre-defined quality criteria comprising (1) appropriate selection of the controls; (2) adjustment to correct for confounders, (3) comparability between cases and controls, (4) acceptable responses rates for the exposed and control groups, (5) data analysis

appropriate to the study design, (6) provision of odds ratios (ORs) with confidence intervals or p-values, or provision of sufficient data to calculate ORs, and (7) overall quality of the study (Gonzales-Barron et al., 2019). Primary studies that passed the screening for relevance were marked as having a potential for bias if they failed to meet at least one of the methodological quality assessment criteria. Data from primary studies were then extracted using a standardised spreadsheet. Data extracted included the relevant study characteristics (e.g., location, time period, population, *Campylobacter* species, case definition, study design, sample size, type of statistical model used, etc.), categorized risk factors, setting, handling practices, and the measure of association used in the study (i.e. Odds Ratio - OR).

A data categorisation scheme was established to hierarchically group risk factors into: travel, host-specific factors, and pathways of exposure (i.e. person-to-person transmission, animal contact, environmental exposures, and foodborne routes (Gonzales-Barron et al., 2019; Tables 1 and 2). The variable "population" was stratified into mixed (adults or undefined), children, and susceptible (Gonzales-Barron et al., 2019).

2.2. Data synthesis

Following descriptive analysis of the joint meta-analytical results, data were partitioned into subsets of categories of risk factors. Meta-analytical models were fitted to each of the data partitions or subsets to estimate pooled ORs associated with each risk factor (travel and host-specific factors, as well as factors related to transmission from person to person, contact with animals, environmental or food exposures). The meta-analytical models were fitted separately by population type. For some food classes, the effect of mishandling of food (e.g., consuming raw/undercooked meat) and setting (i.e., eating food prepared outside the home) on the pooled ORs were assessed by calculating the ratio of the mean OR of the food class (e.g undercooked meat) to the base OR.

The statistical analysis was designed to assess the effect of the geographical region, the study period and the type of analysis (univariate or multivariate) on the final result. The objective of the region-specific meta-analysis was to inform the decision on whether geographical regions were to be maintained for the subsequent pooling of ORs. A geographical region (Asia, North America, South America, Africa, Europe, Oceania) was removed from a particular meta-analysis partition only if its pooled ORs were different from those associated with the other regions, or if less than 3 ORs represented the region (Gonzales-Barron et al., 2019). All meta-analytical models were essentially weighted random-effects linear regression models. Once a meta-analytical model was fitted, influential diagnostics statistics based on the Cook's distance approach were applied to remove any influential observation originating from studies marked as having a potential for bias. Publication bias was assessed by funnel plots and statistical tests investigating the effect of the study sample size on the ORs (Tables 1, 2 and 3). Heterogeneity between studies was assessed by different indicators, such as the between-study variability (τ^2), the QE test investigating residual between-study heterogeneity, the variance of residuals and the intra-class correlation I^2 (Gonzales-Barron et al., 2019). Publication bias and remaining heterogeneity were not further corrected for, but were taken into account for the interpretation of the results. All analyses were performed in the R statistical environment (R Development Core Team, 2008) using the 'metafor' package (Viechtbauer, 2010).

Pooled ORs were considered significant when the lower bound of the 95% confidence interval (CI) was equal or greater than 1.0, except for breastfeeding where the upper bound of the confidence interval had to be below 1 for it to be deemed as significant (protective). The meta-analysed risk factors are presented in summary tables only when significant; results for risk factors not meeting the definition of significant are listed in Appendix 3.
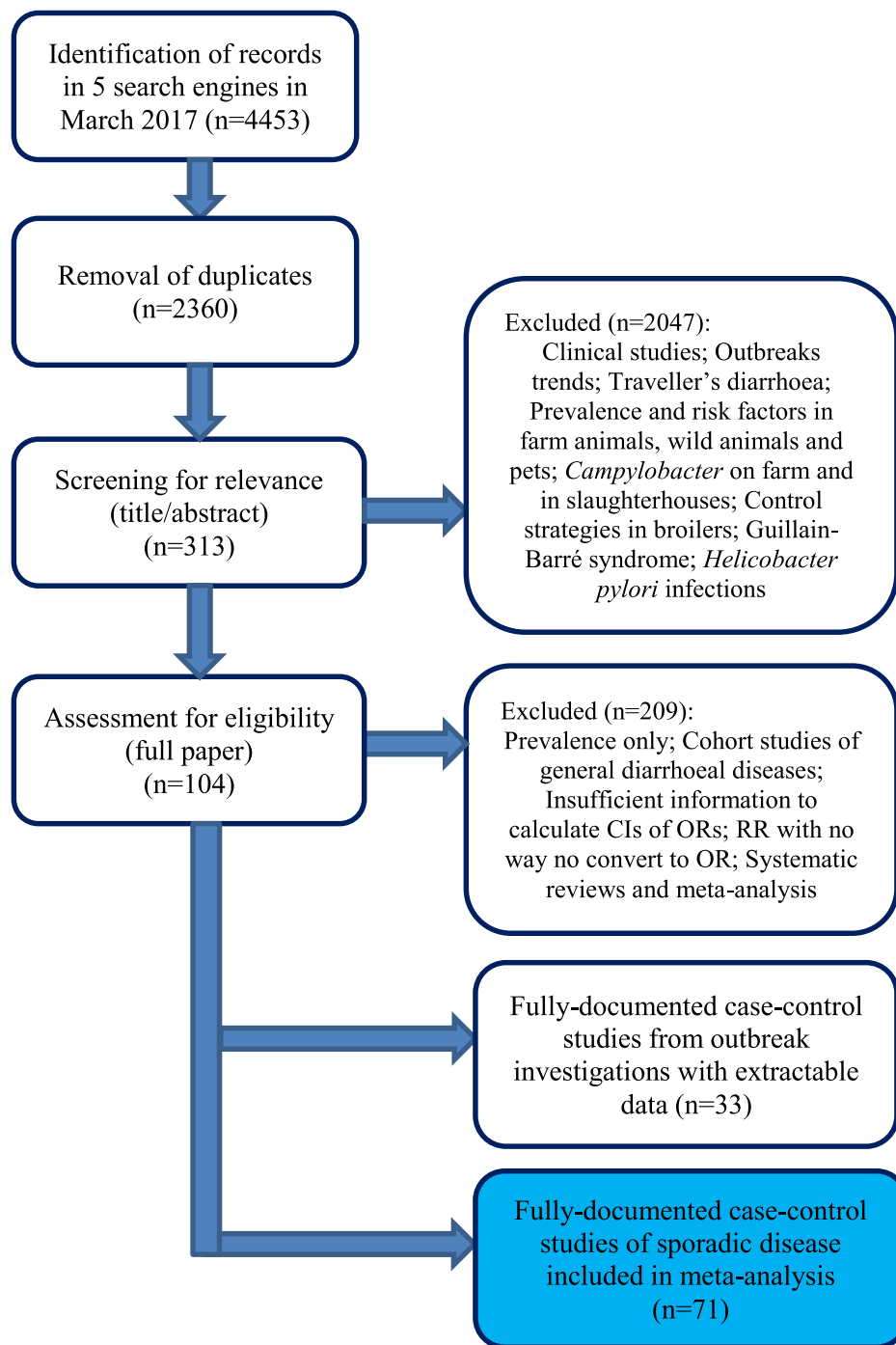
Fig. 1. Prisma flow chart of literature search for case-control studies of human campylobacteriosis.

3. Results

3.1. Descriptive statistics

Out of 4453 bibliographic references identified, 104 passed the preliminary screening for relevance, comprising case-control studies from both sporadic illnesses (71) and outbreaks (33) (Fig. 1). The quality assessment stage was passed by 71 primary studies investigating only sporadic campylobacteriosis, which were conducted between 1981 and 2012 (Fig. 1). Of the 71 studies included here, 19 investigated exposures in children and infants, 55 in the adult/mixed population, and two focused on susceptible groups of the population i.e. the elderly (Doorduyn et al., 2010) and patients with ulcerative colitis (Arora et al.,

2016). For the susceptible population, data were so fragmented (only 22 ORs) that no meta-analysis model could be adjusted exclusively for this population. In 70 studies, campylobacteriosis cases were laboratory-confirmed, while only in one study (Eberhart-Phillips et al., 1997) some cases were defined based on clinical signs. While most studies focused on illness caused by any *Campylobacter* species (1032 ORs), relatively fewer ORs were reported for cases caused specifically by *C. jejuni* (25 ORs) or *C. coli* (39 ORs).

The 71 primary studies provided 1336 ORs categorised by risk factor for the meta-analysis, with 72% of the data originating from case-control studies conducted in the UK (14), USA (12), Australia (6), Norway (4), and Denmark (4). Regarding risk factor categories, studies focused mostly on multiple pathways of exposure: food (771 ORs), contact with

Table 1
Results of the meta-analysis on the main risk factors.

Population	Geographical Area	Risk factor	Pooled OR [IC95%]	N/ n*	p-value of risk factor	Publication biasp-value	Points removed**	Heterogeneity analysis***
Travel Mixed	Asia removed (1 OR)	Abroad	4.626 [3.522 - 6.075]	14/ 20	<.0001	0.034	1	τ^2=0.133 QE(df = 22) = 61.884; p-val < .0001 S^2=0.491 I^2=21.323
		Inside	1.747 [1.075 - 2.840]	4/4	0.024			
Host specific Mixed		Chronic diseases	2.606[2.193 - 3.097]	6/12	<.0001	0.798	0	τ^2=0.962 QE(df = 61) = 400.55; p-val < .0001 S^2=0.694 I^2=58,091
		Antacids	2.911 [2.040 - 4.154]	11/ 19	<.0001			
Children and susceptible		Chronic diseases	2.343 [1.753 - 3.131]	7/18	<.0001	0.905	0	τ^2=0.918 QE(df = 54) = 386.82; p-val < .0001 S^2=1.004 I^2=47.739
		Breastfeeding	0.360 [0.242 - 0.535]	3/3	<.0001			
Animals Mixed (at)	Asia removed (1 OR)	Occupational exposure	3.022 [2.264 - 4.036]	13/ 51	<.0001	0.925	3	τ^2=0.407 QE(df = 221) = 474.41; p-val < .0001 S^2= 0.511 I^2=44.317
		Pets	1.543 [1.327 - 1.794]	35/ 105	<.0001			
		Farm animals	2.235 [1.891 - 2.641]	18/ 61	<.0001			
		Wild animals	1.628 [1.107 - 2.392]	6/9	0.013			
Children	Asia (2 OR) Africa (3 OR higher) South America(3 OR lower) removed	Pets	2.200[1.645 - 2.944	8/30	<.0001	0.184	0	τ^2=0.187 QE(df = 49) = 99.738; p-val < .0001 S^2= 0.633 I^2=22.779
		Farm animals	2.747[1.703 - 4.432]	6/21	<.0001			
Environment Mixed	All	Untreated drinking water	1.766[1.394 - 2.237]	26/ 65	<.0001	0.317	0	τ^2=0.598 QE(df = 115) = 372.89; p-val < .0001 S^2=0.447 I^2=57,211
		Recreational water	1.551 [1.189 - 2.023]	13/ 23	0.001			
		Farm/rural environment	1.790[1.333 - 2.405]	15/ 26	0.0001			
		Playground	2.721[1.928 - 3.840]	3/3	<.0001			
		Daycare	1.419[1.048 - 1.920]	2/3	0.023			
Children (y)	South America excluded (1 OR)	Untreated drinking water	3.261[2.290 - 4.645]	6/8	<.0001	0.132	1	τ^2=0.007 QE(df = 24) = 24.652; p-val = 0.4248 S^2=0.281 I^2 =2.662
		Playground	1.489[1.144 - 1.936]	6/8	0.0030			
		Farm/rural environment	3.128 [2.108- 4.640]	4/7	<.0001			
		Recreational water	3.156[2.067 - 4.819]	3/6	<.0001			
Person to person Children	All		2.736 [1.905 - 3.930]	6/8	<.0001	0.013	0	τ^2=0.110 QE(df = 15) = 22.722; p-val = 0.0902 S^2=0.331 I^2=24.960
Mixed				6/9	0.004			

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Table 1 (*continued*)

Population	Geographical Area	Risk factor	Pooled OR [IC95%]	N/ n*	p-value of risk factor	Publication biasp-value	Points removed**	Heterogeneity analysis***
			1.633 [1.171 - 2.277]					
Food Mixed	Asia excluded (1 OR)	Meat	1.597[1.323 - 1.928]	43/ 425	<.0001	0.021	5	τ^2= 0.148 QE(df = 610) = 2559.3; p-val < .0001 S^2= 0.599 I^2=19.812
		Dairy	1.798[1.425 - 2.268]	23/ 46	<.0001			
		Produce	1.355 [1.076 - 1.706]	12/ 49	0.010			
		Composite	1.604 [1.290 - 1.993]	20/ 53	<.0001			
		Beverages	1.405[1.099 - 1.796]	11/ 18	0.007			
		Seafood	1.4157 [1.083 - 1.850]	7/18	0.011			
		Eggs	1.604 [1.147 - 2.244]	3/5	0.006			
Children	Asia excluded (9 OR from same publication lower than other ORs)	Dairy	2.750 [1.84 - 4.109]	8/15	<.0001	0.131	0	τ^2=0.983 QE(df = 73) = 144.139; p-val < .0001 S^2= 0.417 I^2=70.198
		Meat	1.787[1.435 - 2.224]	10/ 36	<.0001			
		Eggs	1.854 [1.002- 3.431]	5/9	0.049			
		Produce	2.471 [1.504 - 4.062]	5/7	0.001			
		Composite	1.597 [1.140 - 2.238]	6/11	0.007			

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2). (at): analysis type is significant in this model and the estimates are taking this effect into account

animals (289 ORs), the environment (152 ORs), and person-to-person transmission (17 ORs). Host- (69 ORs) and travel-specific (28 ORs) factors were also investigated. After methodological quality assessment, 18 case-control studies were marked as being below standards; they provided 86 potentially biased ORs whose influence on the meta-analysed OR estimates was appraised by means of the Cook's distance. Forty case-control studies (56%) employed a matched study design. Combining the matched and unmatched studies, 673 ORs were not adjusted by any confounder (i.e., crude ORs), while 653 ORs were adjusted using either Mantel-Haenzel or multivariable logistic regression analysis.

3.2. Meta-analysis

The meta-analysed significant risk factors are presented in summary tables (Tables 1 and 2). Non-significant results on the main risk factors are compiled in Appendix 3.

3.2.1. Meta-analysis for travel
Foreign travel was an important risk factor for campylobacteriosis. For residents in the USA, UK, Switzerland, Ireland, France, Germany, Australia, or New Zealand, travelling abroad increased the odds of acquiring campylobacteriosis (pooled OR=4.626; 95% CI: 3.522–6.075) (Table 1). Domestic travel was also a risk factor, but with a less sizeable effect (pooled OR=1.747; 95% CI: 1.075-2.840) as derived from residents in Spain, USA, Greece, and the UK. Information on travel destination was not available in the included studies (Fig. 2).

3.2.2. Meta-analysis for host-specific risk factors
Underlying medical conditions acted as predisposing factors for

campylobacteriosis (Table 1). Chronic conditions such as chronic gastrointestinal illness, stomach ulcer, coeliac disease, liver disease, asthma, or diabetes were associated with campylobacteriosis in the mixed population (pooled OR=2.601; 95% CI: 2.193-3.097) and in the children and susceptible populations (pooled OR=2.343; 95% CI: 1.753-3.131). In the mixed population, the strongest association with campylobacteriosis was found with recent use of gastric antacids (pooled OR=2.911; 95% CI: 2.040-4.154). Considering the 545 campylobacteriosis cases among children aged 0-2 years and 1217 healthy children from the USA, Spain, and Algeria, it was estimated that breastfeeding exerts a significant protective effect (pooled OR=0.36; 95% CI: 0.242-0.535).

3.2.3. Meta-analysis for animal contact
Contact with animals was a significant risk factor for acquiring campylobacteriosis. In the mixed population, the strongest associations were found with occupational exposure to animals or food thereof (pooled OR=3.022; 95% CI: 2.264-4.036), such as working in a slaughterhouse, farm, pet shop or zoo, as well as working in food handling/preparation or animal husbandry (Table 1; Fig. 3). Significant risk factors included contact with farm animals (pooled OR=2.235; 95% CI: 1.891-2.641), wild animals (pooled OR=1.628; 95% CI: 1.107-2.392) and pets (pooled OR=1.543; 95% CI: 1.327-1.794). Children were found to be more susceptible to acquiring campylobacteriosis through contact with animals than the general population (Fig. 4). The odds of infection for children who had contact with farm animals (pooled OR=2.747; 95% CI: 1.703-4.432) and pets at home (pooled OR=2.200; 95% CI: 1.645-2.944) were higher than those of the mixed population, in the respective categories (Table 1).

Table 2
Results of the meta-analysis on disaggregated risk factors.

Risk Factor	Population	Geographical area	Risk factorPrecise	Pooled OR [IC95%]	N/ n*	p-value of risk factor	Publication biasp-value	Points removed**	Heterogeneity analysis***
Meat	Mixed	Asia removed (1 OR)	Poultry	1.682 [1.471 - 1.923]	40/ 227	<.0001	0.218	1	τ^2=0.762 QE(df = 420) = 1431.4; p-val < .0001 S^2 = 0.670 I^2=53.216
			Beef	1.293 [1.115 - 1.499]	16/ 43	0.001			
			Pork	1.397 [1.072 - 1.820]	12/ 22	0.013			
			Process meat	1.255 [1.082 - 1.454]	20/ 58	0.002			
			Other red meats	1.396 [1.131 - 1.722]	10/ 14	0.002			
			Others	1.933 [1.695 - 2.204]	26/ 62	<.0001			
Meat	Children	Asia removed (8 OR same publication lower than other region)	Poultry	1.776 [1.266 - 2.492]	8/11	0.001	0.700	0	τ^2=0.320 QE(df = 26) = 34.497; p-val = 0.123 S^2=0.304 I^2=51.247
			Others	1.976[1.503 - 2.598]	4/8	<.0001			
			Pork and other red meats	1.623[1.156 - 2.279]	3/4	0.005			
Eggs	Mixed	All	Egg products	4.062 [2.566 - 6.432]	2/4	<.0001	0.291	0	τ^2=0,050 QE(df = 12) = 20.956; p-val = 0.051 S^2=0.292 I^2=14,578
Dairy	Mixed	All	Milk (raw milk)	1.828 [1.313 - 2.545]	18/ 32	0.001	0.500	0	τ^2=1,432 QE(df = 42) = 122.33; p-val < .0001 S^2=0.610 I^2=70.116
			Fats	2.825 [1.051 - 7.593]	3/3	0.039			
Dairy	Children	All	Powder	2.451[1.301 - 4.615]	2/3	0.005	0.149	0	τ^2=0.000 QE(df = 12) = 12.190; p-val = 0.430 S^2=0.434 I^2=0.000
			Undefined	1.581[1.083 - 2.308]	3/4	0.018			
			Milk	2.603 [1.736 - 3.901]	5/8	<.0001			
Seafood	Mixed	Oceania removed (1 OR)	Undefined	1.538 [1.159 - 2.042]	2/4	0.003	0.732	0	τ^2=0.023 QE(df = 15) = 24.003; p-val = 0.065 S^2=0.171 I^2=12.063
Produce	Mixed	All	Spices	2.520 [1.273- 4.987]	2/3	0.008	0.918	1	τ^2=1,527 QE(df = 44) = 283.52; p-val < .0001 S^2= 0.372 I^2=80,420
Produce	Children	All	Spices	3.417 [1.508 - 7.741]	2/3	0.003	0.227	0	τ^2=0.378 QE(df = 5) = 13.352; p-val = 0.0203 S^2=0.329 I^2=53.413
Beverages	Mixed	All	Bottled water	1.395 [1.240 - 1.568]	12/ 17	<.0001	0.115	0	τ^2=0.046 QE(df = 18) = 69.085; p-val < .0001 S^2=0.131 I^2=25.987
Compo-site	Mixed		Dishes	1.342 [1.239 - 1.452]	15/ 33	<.0001	0.305	2	τ^2=0.114 QE(df = 49) = 92.689; p-val = 0.0002 S^2=0.311 I^2=26.781
			Fast Food	1.729 [1.344 - 2.224]	9/14	<.0001			
Compo-site	Children	Asia (1 OR) and Oceania (2 OR removed)		1.594 [1.054 - 2.414]	4/9	0.0273	<.0001	0	τ^2=0.1475 Q(df = 8) = 39.763; p-val < .0001

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Table 2 (*continued*)

Risk Factor	Population	Geographical area	Risk factorPrecise	Pooled OR [IC95%]	N/n*	p-value of risk factor	Publication biasp-value	Points removed**	Heterogeneity analysis***
BBQ	All	North America removed (2 OR))	Uni	1.752 [1.437 - 2.135]	16/31	<.0001	0.135	0	S^2=0.259 I^2=36,227 τ^2= 0.129 QE(df = 47) = 115.48; p-val < .0001
			Multi	1.937 [1.651 - 2.273]	11/18	<.0001			S^2=2.068 I^2=5.871

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2).

Table 3
Effect of food handling and setting on pooled OR.

Risk Factor	Risk factor precise	Pooled OR [IC95%]	N/n*	p-value of risk factor	OR ratios and CI95%	Points removed**	Publication bias p-value	Heterogeneity analysis***
Poultry (at)	Undercooked	3.709 [2.776 - 4.955]	19/28	<.0001	2.235 [1.887 - 2.647]	0	0.841	τ^2=0.090 QE(df = 236) = 547.23; p-val < .0001 S^2=0.272 I^2=25,025
	Eating out	2.298 [1.830 - 2.885]	21/63	<.0001	1.385 [1.244 - 1.541]			
	Poultry (base)	1.659 [1.471 - 1.872]	46/213 (h) 37/152 (s)	<.0001	-			
Beef (at)	Raw / undercooked	2.463 [1.291 - 4.698]	4/7	0.0007	1.775 [1.273 - 2.473]	1	0.029	τ^2= 0.049 QE (df = 45) = 74.808; p-val = 0.003 S^2=1.369 I^2=3.461
	Eating out	2.343 [1.211 - 4.534]	5/12	0.0030	1.688 [1.194 - 2.386]			
	Base	1.387[1.014 - 1.899]	17/42 (h) 17/37 (s)	0.0407	-			
Eggs(at)	Raw	4.987 [1.143 - 21.75]	3/4	0.0664	1.917 [0.957 - 3.842]	0	0.477	τ^2=0.070 QE(df = 11) = 28.396; p-val = 0.003 S^2=0.302 I^2=18.879
	Base	2.601 [1.194 - 5.664]	7/10	0.0161	-			
Seafood	Raw /undercooked	1.581 [1.203 - 2.078]	4/9	<.0001	1.568 [1.298 - 1.896]	0	0.187	τ^2=0.000 QE(df = 18) = 19.350; p-val = 0.370 S^2=0.107 I^2=0.000
	Base	1.007 [0.927 - 1.096]	6/11	0.854	-			
Milk and Cheese	Raw	2.474 [1.202 - 5.089]	20/36	<.0001	2.482 [1.690 - 3.644]	1	0.668	τ^2=0.1692 QE(df = 43) = 72.181; p-val = 0.004 S^2=0.473 I^2=26,342
	Base	0.996 [0.711 - 1.396]	7/9	0.984	-			

*N/n Number of studies/number of OR;** points removed by sensitivity analysis, all results are given after removing data concerned; ***Between-study variability (τ^2), test for residual heterogeneity (QE), variance of residuals (s^2), intra-class correlation (I^2). (at): analysis type is significant in this model and the estimates are taking this effect into account

3.2.4. Meta-analysis for environmental factors

In both the mixed and children population, **several environmental exposures** were significantly associated with campylobacteriosis: exposure to playground, contaminated drinking water, farm environment, or recreational water (Table 1). Children presented generally higher odds of acquiring campylobacteriosis than the mixed population, from contaminated drinking water (pooled OR=3.261; 95% CI 2.290-4.645) (Fig. 5), farm environment (pooled OR=3.128; 95% CI 2.108-4.640) and recreational water (pooled OR=3.156; 95% CI: 2.067-4.819).

3.2.5. Meta-analysis for person-to-person transmission factors

Person-to-person transmission (i.e. contact with an ill person) was a significant risk factor for campylobacteriosis in children (pooled OR=2.736; 95% CI: 1.905-3.930) and the mixed population (pooled OR=1.633; 95% CI: 1.171-2.277) (Table 1).

3.2.6. Meta-analysis for food consumption

Regarding **food consumption,** food items in all categories were significant risk factors for campylobacteriosis. These were: dairy products (comprising unpasteurized milk and cheese made with unpasteurised milk and soft cheese), eggs (mostly raw eggs and mayonnaise), composite products, meat and meat products, seafood, produce and beverages (mostly bottled water) (Table 1). In children, like for other exposure categories, the pooled ORs were generally higher than those in the general population.

Within the food vehicles, the strongest associations in the mixed population were observed for egg products (pooled OR=4.062, 95% CI: 2.566-6.432), dairy fats (i.e. butter and unpasteurized cream, pooled OR=2.825, 95% CI 1.051-7.593), spices (pooled OR=2.520, 95% CI: 1.273-4.987), barbecued meats (pooled OR=1.937, 95% CI: 1.651-2.273), other meats (pooled OR=1.933; 95% CI: 1.695-2.20), raw milk (pooled OR=1.828, 95% CI: 1.313-2.545), fast-food (pooled OR=1.729, 95% CI: 1.344-2.224), poultry (pooled OR=1.682, 95% CI: 1.471-1.923), and raw seafood (pooled OR=1.538, 95% CI: 1.159-2.042) (Table 2).

In children, the strongest associations were observed for spices (pooled OR=3.417, 95% CI: 1.508-7.741), raw milk (pooled OR=2.603, 95% CI: 1.736-3.901), milk powder (pooled OR=2.451, 95% CI: 1.301-4.615), other meats (pooled OR=1.976, 95% CI: 1.503-2.598), poultry (pooled OR=1.776, 95% CI: 1.266-2.492), pork and other red meats (pooled OR=1.623, 95% CI: 1.156-2.279), composite foods (e.g. fast food meals, sandwiches) (pooled OR=1.594, 95% CI: 1.054-2.414) and undefined dairy products (pooled OR=1.581, 95% CI: 1.083-2.308) (Table 2).

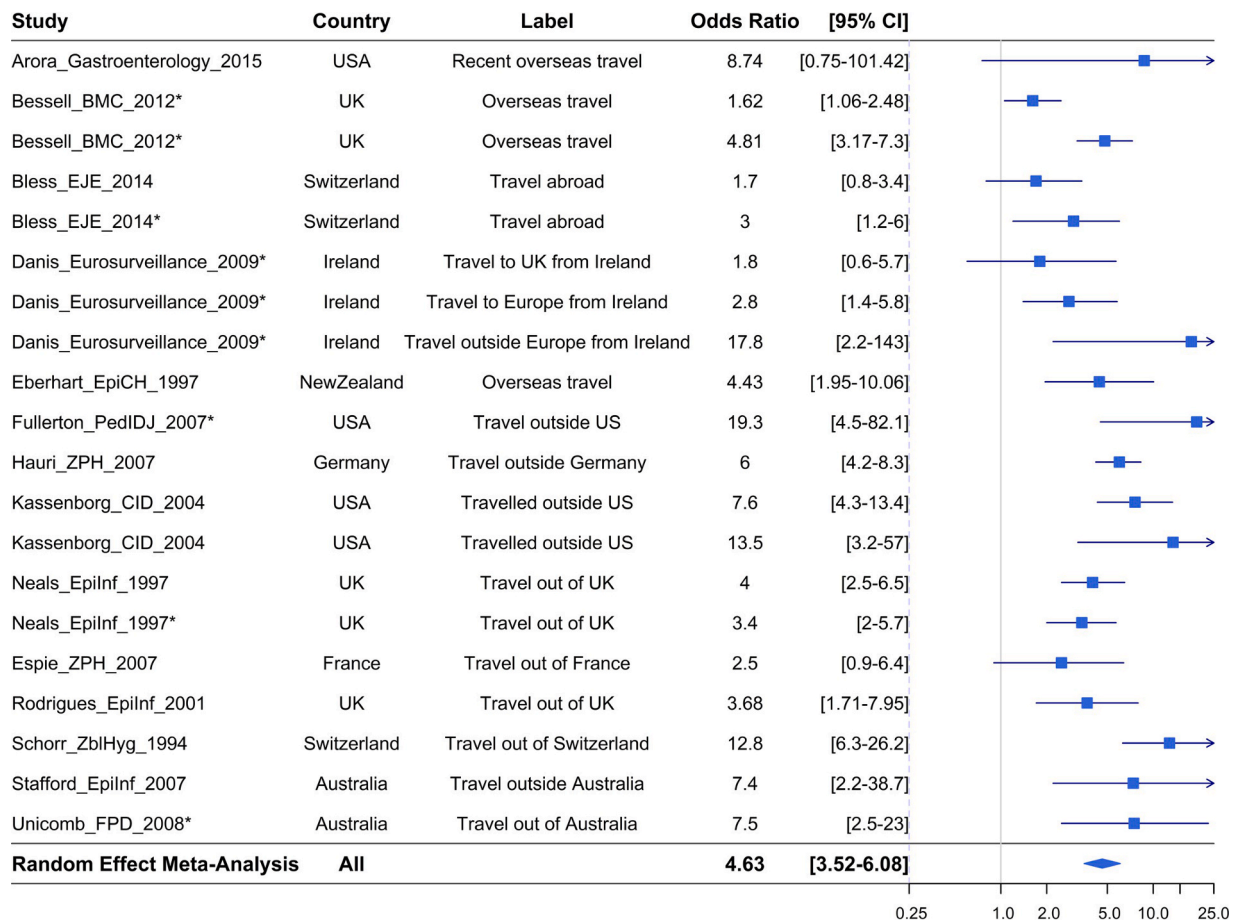Among all the food subcategories, meat was the one whose multiple

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Study	Country	Label	Odds Ratio	[95% CI]
Arora_Gastroenterology_2015	USA	Recent overseas travel	8.74	[0.75-101.42]
Bessell_BMC_2012*	UK	Overseas travel	1.62	[1.06-2.48]
Bessell_BMC_2012*	UK	Overseas travel	4.81	[3.17-7.3]
Bless_EJE_2014	Switzerland	Travel abroad	1.7	[0.8-3.4]
Bless_EJE_2014*	Switzerland	Travel abroad	3	[1.2-6]
Danis_Eurosurveillance_2009*	Ireland	Travel to UK from Ireland	1.8	[0.6-5.7]
Danis_Eurosurveillance_2009*	Ireland	Travel to Europe from Ireland	2.8	[1.4-5.8]
Danis_Eurosurveillance_2009*	Ireland	Travel outside Europe from Ireland	17.8	[2.2-143]
Eberhart_EpiCH_1997	NewZealand	Overseas travel	4.43	[1.95-10.06]
Fullerton_PedIDJ_2007*	USA	Travel outside US	19.3	[4.5-82.1]
Hauri_ZPH_2007	Germany	Travel outside Germany	6	[4.2-8.3]
Kassenborg_CID_2004	USA	Travelled outside US	7.6	[4.3-13.4]
Kassenborg_CID_2004	USA	Travelled outside US	13.5	[3.2-57]
Neals_EpiInf_1997	UK	Travel out of UK	4	[2.5-6.5]
Neals_EpiInf_1997*	UK	Travel out of UK	3.4	[2-5.7]
Espie_ZPH_2007	France	Travel out of France	2.5	[0.9-6.4]
Rodrigues_EpiInf_2001	UK	Travel out of UK	3.68	[1.71-7.95]
Schorr_ZblHyg_1994	Switzerland	Travel out of Switzerland	12.8	[6.3-26.2]
Stafford_EpiInf_2007	Australia	Travel outside Australia	7.4	[2.2-38.7]
Unicomb_FPD_2008*	Australia	Travel out of Australia	7.5	[2.5-23]
Random Effect Meta-Analysis	**All**		**4.63**	**[3.52-6.08]**

0.25   1.0 2.0   5.0 10.0   25.0

Fig. 2. Forest plot of the association of campylobacteriosis with travel abroad exposure in the mixed population (n=20) (* Adjusted OR).

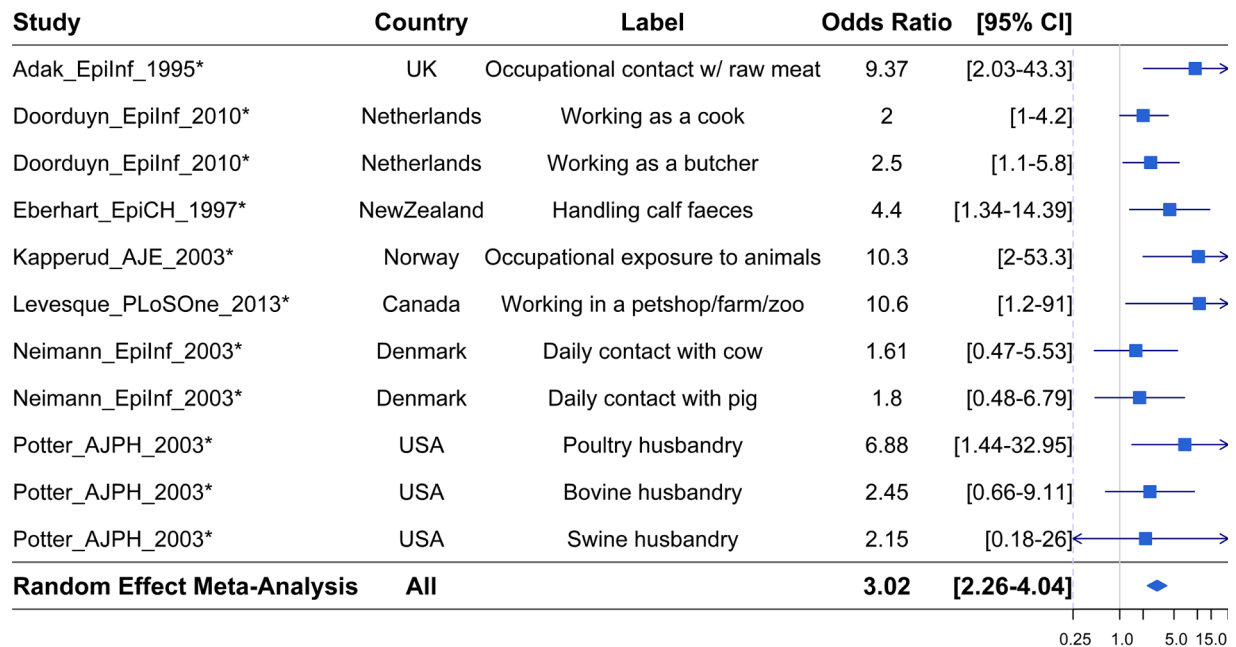| Study	Country	Label	Odds Ratio	[95% CI]
Adak_EpiInf_1995*	UK	Occupational contact w/ raw meat	9.37	[2.03-43.3]
Doorduyn_EpiInf_2010*	Netherlands	Working as a cook	2	[1-4.2]
Doorduyn_EpiInf_2010*	Netherlands	Working as a butcher	2.5	[1.1-5.8]
Eberhart_EpiCH_1997*	NewZealand	Handling calf faeces	4.4	[1.34-14.39]
Kapperud_AJE_2003*	Norway	Occupational exposure to animals	10.3	[2-53.3]
Levesque_PLoSOne_2013*	Canada	Working in a petshop/farm/zoo	10.6	[1.2-91]
Neimann_EpiInf_2003*	Denmark	Daily contact with cow	1.61	[0.47-5.53]
Neimann_EpiInf_2003*	Denmark	Daily contact with pig	1.8	[0.48-6.79]
Potter_AJPH_2003*	USA	Poultry husbandry	6.88	[1.44-32.95]
Potter_AJPH_2003*	USA	Bovine husbandry	2.45	[0.66-9.11]
Potter_AJPH_2003*	USA	Swine husbandry	2.15	[0.18-26]
Random Effect Meta-Analysis	**All**		**3.02**	**[2.26-4.04]**

0.25   1.0   5.0 15.0

Fig. 3. Forest plot of the association of campylobacteriosis with occupational exposure to animals in the mixed population (n=51) (Only the 11 ORs obtained through multivariate analysis are presented).
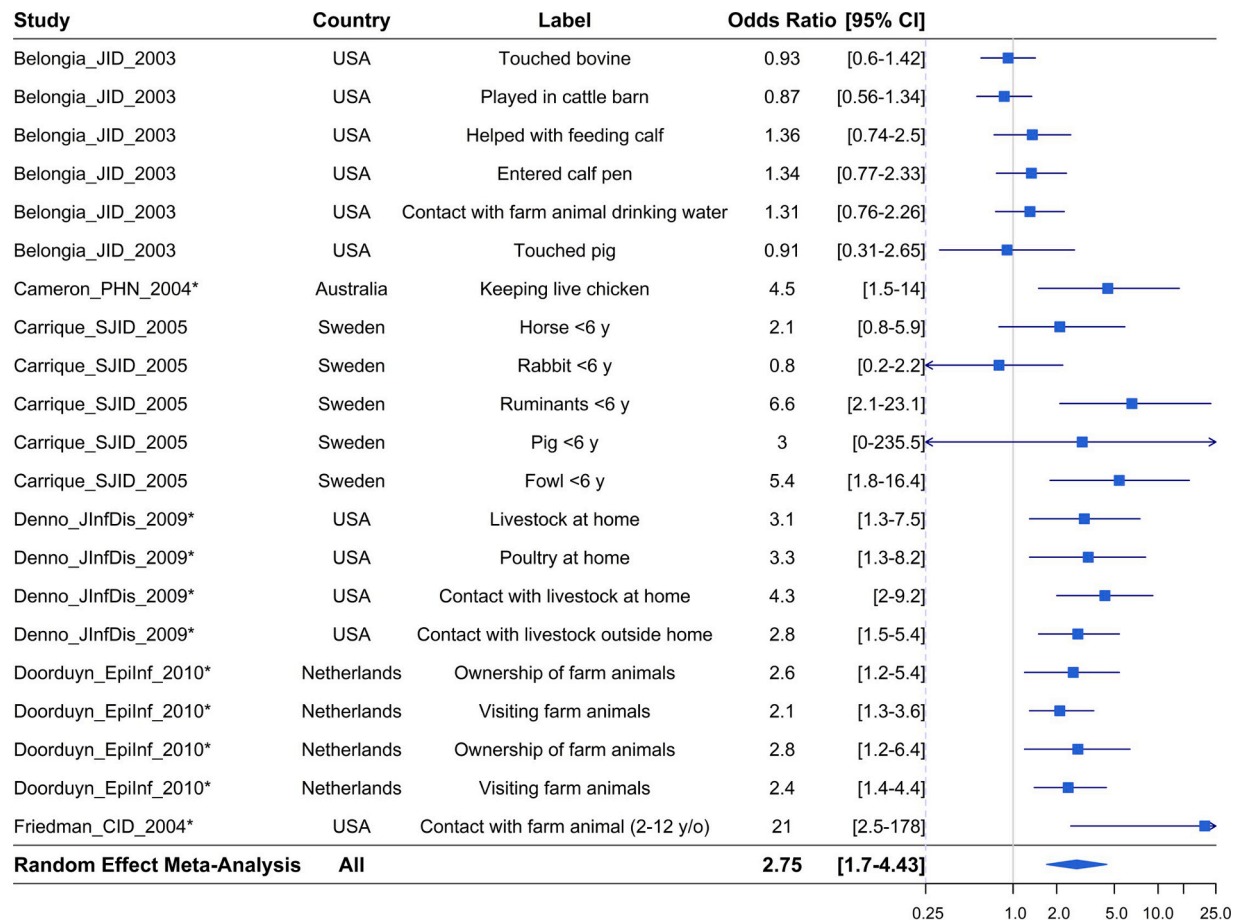
Study	Country	Label	Odds Ratio	[95% CI]
Belongia_JID_2003	USA	Touched bovine	0.93	[0.6-1.42]
Belongia_JID_2003	USA	Played in cattle barn	0.87	[0.56-1.34]
Belongia_JID_2003	USA	Helped with feeding calf	1.36	[0.74-2.5]
Belongia_JID_2003	USA	Entered calf pen	1.34	[0.77-2.33]
Belongia_JID_2003	USA	Contact with farm animal drinking water	1.31	[0.76-2.26]
Belongia_JID_2003	USA	Touched pig	0.91	[0.31-2.65]
Cameron_PHN_2004*	Australia	Keeping live chicken	4.5	[1.5-14]
Carrique_SJID_2005	Sweden	Horse <6 y	2.1	[0.8-5.9]
Carrique_SJID_2005	Sweden	Rabbit <6 y	0.8	[0.2-2.2]
Carrique_SJID_2005	Sweden	Ruminants <6 y	6.6	[2.1-23.1]
Carrique_SJID_2005	Sweden	Pig <6 y	3	[0-235.5]
Carrique_SJID_2005	Sweden	Fowl <6 y	5.4	[1.8-16.4]
Denno_JInfDis_2009*	USA	Livestock at home	3.1	[1.3-7.5]
Denno_JInfDis_2009*	USA	Poultry at home	3.3	[1.3-8.2]
Denno_JInfDis_2009*	USA	Contact with livestock at home	4.3	[2-9.2]
Denno_JInfDis_2009*	USA	Contact with livestock outside home	2.8	[1.5-5.4]
Doorduyn_EpiInf_2010*	Netherlands	Ownership of farm animals	2.6	[1.2-5.4]
Doorduyn_EpiInf_2010*	Netherlands	Visiting farm animals	2.1	[1.3-3.6]
Doorduyn_EpiInf_2010*	Netherlands	Ownership of farm animals	2.8	[1.2-6.4]
Doorduyn_EpiInf_2010*	Netherlands	Visiting farm animals	2.4	[1.4-4.4]
Friedman_CID_2004*	USA	Contact with farm animal (2-12 y/o)	21	[2.5-178]
Random Effect Meta-Analysis	**All**		**2.75**	**[1.7-4.43]**

0.25   1.0 2.0   5.0 10.0   25.0

Fig. 4. Forest plot of the association of campylobacteriosis with contact with farm animals in children (n=21) (*Adjusted OR).

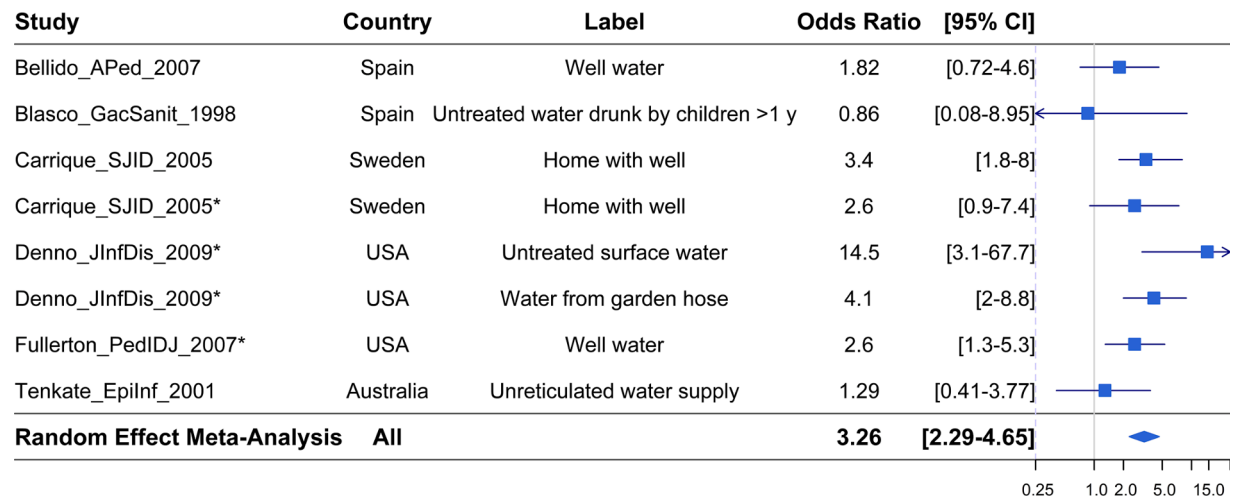| Study	Country	Label	Odds Ratio	[95% CI]
Bellido_APed_2007	Spain	Well water	1.82	[0.72-4.6]
Blasco_GacSanit_1998	Spain	Untreated water drunk by children >1 y	0.86	[0.08-8.95]
Carrique_SJID_2005	Sweden	Home with well	3.4	[1.8-8]
Carrique_SJID_2005*	Sweden	Home with well	2.6	[0.9-7.4]
Denno_JInfDis_2009*	USA	Untreated surface water	14.5	[3.1-67.7]
Denno_JInfDis_2009*	USA	Water from garden hose	4.1	[2-8.8]
Fullerton_PedIDJ_2007*	USA	Well water	2.6	[1.3-5.3]
Tenkate_EpiInf_2001	Australia	Unreticulated water supply	1.29	[0.41-3.77]
Random Effect Meta-Analysis	**All**		**3.26**	**[2.29-4.65]**

0.25   1.0 2.0   5.0   15.0

Fig. 5. Forest plot of the association of campylobacteriosis with untreated drinking water in children (n=8) (*Adjusted OR).

exposures were the most investigated in case-control studies (producing 471 ORs). Within meats, the highest pooled ORs were obtained for the categories "other meats" and "poultry". The category "other meats" was created to accommodate meats of non-specified origin encompassing meat fondue, barbecued meat, grilled meat, minced meat, offal and tripe.

3.3. Risk factors associated with poor handling and preparation of foods

Specific meta-analytical models were fitted to estimate the effects of food handling or eating behaviour (e.g. eating raw and undercooked foods) and setting (i.e. eating food prepared outside home) on the pooled ORs (base OR) in selected food classes (Table 3). In general, eating raw or undercooked foods was associated with increased campylobacteriosis risk. It was found that people eating undercooked chicken and beef had odds of infection significantly increased by a factor of 2.235 and 1.775

respectively. Eating unpasteurised milk and raw milk cheese and raw eggs also increased the odds of acquiring campylobacteriosis by 2.482 and 1.917 times, respectively. Eating out was also an important risk factor for acquiring campylobacteriosis. People who ate poultry and beef prepared outside home had odds of infection significantly increased by a factor of 1.385 and 1.688, respectively.

3.4. Publication bias

For most of the meta-analytical models reported in Tables 1, 2 and 3, the statistical tests indicated the absence of potential significant publication bias ($p > 0.05$). Exceptions were observed in data partitions related to travel (Table 2), person-to-person transmission (Table 2) and food in the mixed population (Table 2), and composite foods in children (Table 3). The funnel plots for these data partitions (Fig. 8) suggest that small studies associated with non-significant results (i.e., ORs not showing significant associations between food consumption and disease) may have remained unpublished. Intra-class correlation (I^2) appeared low ($< 25\%$) to moderate (50% or around 50%), while residual between-study heterogeneity was observed in all data partitions (Tables 1, 2, 3).

4. Discussion

The meta-analysis of risk factors for sporadic campylobacteriosis identified foreign travel, host-specific factors and exposures related to environment, animal contact, and food as the main risk factors for campylobacteriosis. These results are comparable to the meta-analysis conducted by Domingues et al. (2012b) who found that travelling abroad, eating undercooked chicken, environmental sources, and direct contact with farm animals were significant risk factors for campylobacteriosis. Some differences can be noted, however, concerning the relative importance of some food vehicles. The observed stronger effects of some non-food exposures, as compared to the food-related exposures, suggest the risk of acquiring *Campylobacter* infection is multi-factorial and that foodborne sources alone are sometimes questionable.

Travelling appeared to be an important risk factor for acquiring campylobacteriosis, which is consistent with potential increased exposure to exotic *Campylobacter* strains for travel abroad and at-risk behaviors, such as eating more often at restaurants for both abroad and inland travel (Mughini-Gras et al., 2014). Host-specific factors (use of antacids and chronic diseases) are associated with increased risk of campylobacteriosis which is consistent with the fact that the induced increase of gastric pH may facilitate *Campylobacter* crossing the gastric barrier particularly with high exposure inoculum (Bavishi & Dupont, 2011). Contact with an ill person was a significant risk factor for campylobacteriosis, both for children and the mixed population, and could be related to exposure to a high load of *Campylobacter* and poor hygiene conditions.

The role of environmental and animal contact routes in the transmission of campylobacteriosis, in particular for children, is highlighted in the present meta-analysis similar to previous source attribution studies (Domingues et al., 2012a, Mughini Gras et al., 2012, Levesque et al., 2013, Pintar et al., 2017). *Campylobacter* spp are frequently detected in surface water (Denis et al., 2011, Guy et al., 2018) as a result of fecal contamination from wastewater effluents, farm animals and wild birds (Pitkänen, 2013, Mughini-Gras et al., 2016). Furthermore, several outbreaks were linked to recreational and drinking water (Dale et al., 2010, Pitkänen, 2013, Moreira & Bondelind, 2017). Among animal contact routes, direct or indirect contact with farm animals and pets are significant risk factors for children and the mixed population. Furthermore, occupational exposure (*i.e.* contact with animals and food products thereof) appeared to be an important risk factor in the mixed population (Fig. 3). The importance of the animal contact route is confirmed in other recent studies (Pintar et al., 2015, Pintar et al., 2017, Kuhn et al., 2018, Conrad et al., 2018). Based on a comparative exposure

assessment approach, animal contact exposures (household pets, living in a farm, visiting a farm) were ranked in the top five transmission routes of *Campylobacter* in Ontario, Canada (Pintar et al., 2017). Children presented stronger associations with campylobacteriosis for the exposures drinking water, living on a farm, contact with farm animals, and contact with recreational water. This is in line with previous reports sustaining that children from rural areas are at higher risk of acquiring campylobacteriosis than those from urban areas (Fitzenberger et al., 2010, Spencer et al., 2012, Levesque et al., 2013). Children living in non-urban areas have more opportunities for direct or indirect contact with animals or their excrement, for consuming water from a private well, or for accessing to rivers or lakes. In addition, the higher susceptibility to campylobacteriosis in children may be related to a lack of hand hygiene and naïve immune status (Conrad et al., 2017).

Source attribution studies conducted in several countries identified poultry and cattle as the main sources of *Campylobacter* (Cody et al., 2019). Interestingly, some food subcategories had slightly stronger associations with campylobacteriosis than the types of meat usually recognized as being high-risk foods, such as poultry meat (e.g. eggs, dairy, produce). In our analysis, nearly all meat categories were identified as risk factors. Moreover, some food items were not identified in the previous meta-analysis (*i.e.* eggs, meat other than poultry, seafood and produce). In addition to the food itself, the role of food preparation practices (e.g. undercooking, cross-contamination, out-of-home catering) is highlighted in the present meta-analysis. The consumption of raw and undercooked foods (eggs, poultry, beef, and dairy) significantly increased the risk of campylobacteriosis. The role of undercooked poultry was demonstrated by previous studies (Domingues et al., 2012a, Rosner et al., 2017, Kuhn et al., 2018) and several campylobacteriosis outbreaks have been attributed to raw milk (EFSA BIOHAZ Panel, 2015, Costard et al., 2017). Indeed, the transfer of *Campylobacter* bacteria from one food product to another due to improper food preparation/handling practices may hinder the identification of the real source of exposure. The identification of eggs as a risk factor, both in the general population and in children, was not an expected outcome, since in poultry production, the egg itself is not ascribed as a possible vehicle of *Campylobacter* (Battersby et al., 2016); and the egg surface has been mentioned merely as a possible source of early contamination of the chick (Cox et al., 2012). Nonetheless, few studies have reported the presence of Campylobacter spp. in eggshells and eggs: for instance, Adesiyun et al. (2005) estimated an incidence of 1.1% of thermotolerant *Campylobacter* in egg contents in Trinidad; whereas, in Germany, 4.1% eggshell samples were found to be contaminated with thermotolerant *Campylobacter* (Messelhäusser et al., 2011). Although the pooled ORs for eggs obtained in this meta-analysis were the result of few ORs (five for the mixed population and nine for children) from a relatively small number (three to five) of studies (Fig. 6); still, it can be presumed if *Campylobacter* is present on the eggshell, it can be transmitted to the egg content during the cracking of the eggshell. This would create the risk of contaminating the egg yolk with the pathogen, and therefore the risk of infection if egg contents are consumed raw, undercooked, or in a raw preparation such as mayonnaise. As the surface contamination of eggs is generally low, the conditions necessary for *Campylobacter* growth in the egg are yet to be established (Neira et al., 2017) as well as the development of risk assessment studies relating the role of eggs and egg products as sources of human campylobacteriosis.

One limitation for the interpretation of the results of the meta-analysis is the broad or imprecise definition of exposures in the included studies. Moreover, the diversity of consumption and food handling practices (hygiene and cooking), as well as production systems and regulations between countries should be considered for the direct application of these results for a particular country. An example of the difficulty of interpreting the risk factors revealed by the meta-analysis is exemplified by the risk factor "drinking bottled water", which may reflect more the unhygienic contexts in which people consume bottled water (e.g. non-potable tap water, low hygiene standards, etc.) than
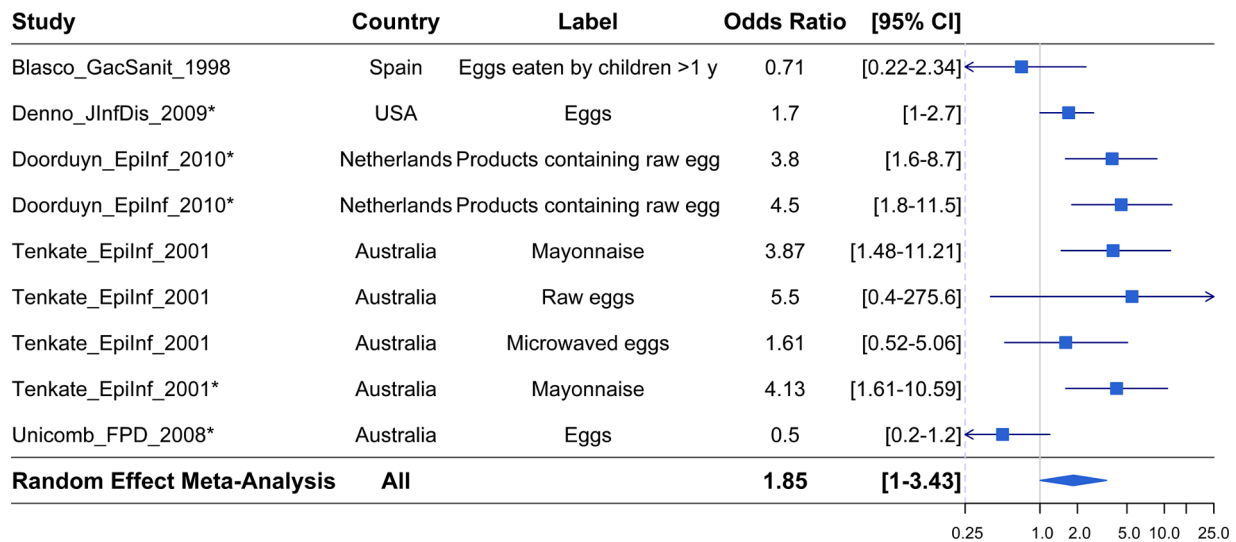
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Study	Country	Label	Odds Ratio	[95% CI]
Blasco_GacSanit_1998	Spain	Eggs eaten by children >1 y	0.71	[0.22-2.34]
Denno_JInfDis_2009*	USA	Eggs	1.7	[1-2.7]
Doorduyn_EpiInf_2010*	Netherlands	Products containing raw egg	3.8	[1.6-8.7]
Doorduyn_EpiInf_2010*	Netherlands	Products containing raw egg	4.5	[1.8-11.5]
Tenkate_EpiInf_2001	Australia	Mayonnaise	3.87	[1.48-11.21]
Tenkate_EpiInf_2001	Australia	Raw eggs	5.5	[0.4-275.6]
Tenkate_EpiInf_2001	Australia	Microwaved eggs	1.61	[0.52-5.06]
Tenkate_EpiInf_2001*	Australia	Mayonnaise	4.13	[1.61-10.59]
Unicomb_FPD_2008*	Australia	Eggs	0.5	[0.2-1.2]
Random Effect Meta-Analysis	**All**		**1.85**	**[1-3.43]**

Fig. 6. Forest plot of the association of campylobacteriosis with eggs in children (n=9) (*Adjusted OR).

Study	Country	Label	Odds Ratio	[95% CI]
Blasco_GacSanit_1998	Spain	Formula <1 y	13.2	[1.48-107]
Blasco_GacSanit_1998*	Spain	Formula <1 y	10	[1.11-93.6]
Cameron_PHN_2004*	Australia	Butter	1.91	[1.11-3.3]
Carrique_SJID_2005	Sweden	Unpasteurised milk	5.1	[1.8-19.9]
Carrique_SJID_2005*	Sweden	Unpasteurised milk	3.7	[0.9-16.1]
Denno_JInfDis_2009*	USA	Unpasteurised milk	4.3	[1-18.1]
Doorduyn_EpiInf_2010*	Netherlands	Unpasteurised milk	2.6	[0.7-9]
Doorduyn_EpiInf_2010*	Netherlands	Unpasteurised milk	2	[0.9-4.2]
Fullerton_PedIDJ_2007*	USA	Concentrated formula	1.8	[0.9-3.3]
Fullerton_PedIDJ_2007*	USA	Unpasteurised dairy products	1.5	[0.3-5.8]
Mellou_EpiInf_2010	Greece	Milk	2.86	[0.9-9.15]
Tenkate_EpiInf_2001	Australia	Soft cheese	2.31	[0.7-8.19]
Tenkate_EpiInf_2001	Australia	Ice-cream	1.11	[0.59-2.07]
Tenkate_EpiInf_2001	Australia	Milk	1.07	[0.37-3.09]
Tenkate_EpiInf_2001	Australia	Milk - bottled fed only	3.29	[0.71-19.81]
Random Effect Meta-Analysis	**All**		**2.75**	**[1.84-4.11]**

Fig. 7. Forest plot of the association of campylobacteriosis with dairy in children (n=15) (*Adjusted OR).

contamination of the bottled water itself (Mughini-Gras et al., 2014). Studies that more accurately define bottled water (e.g. spring water or mineral water treated and distributed in a crimped cap bottle) showed a protective effect (Ravel et al., 2016). Another example is the definition of dairy products, which may vary from one country to another, resulting in a heterogeneous category (Fig. 7). In France, for example, cheeses fall into this category whether they are made from raw or pasteurized milk. The consumption of "cheese" and "dairy products" would deserve to be studied by including classification of raw versus pasteurized milk.

5. Conclusion

The results of this meta-analysis help going beyond the usual suspicion of poultry meat as the source of *Campylobacter* exposure and stress the importance of refining the assessment of other food vehicles and practices, routes such as environmental and animal contact, and distinguishing between food-producing animals and other animals (pets and wildlife). The contribution of environmental or animal contact to the risk of sporadic campylobacteriosis should be the focus of dedicated studies. It may be appropriate to include factors related to professional activities, in particular those differentiating between contact with farm
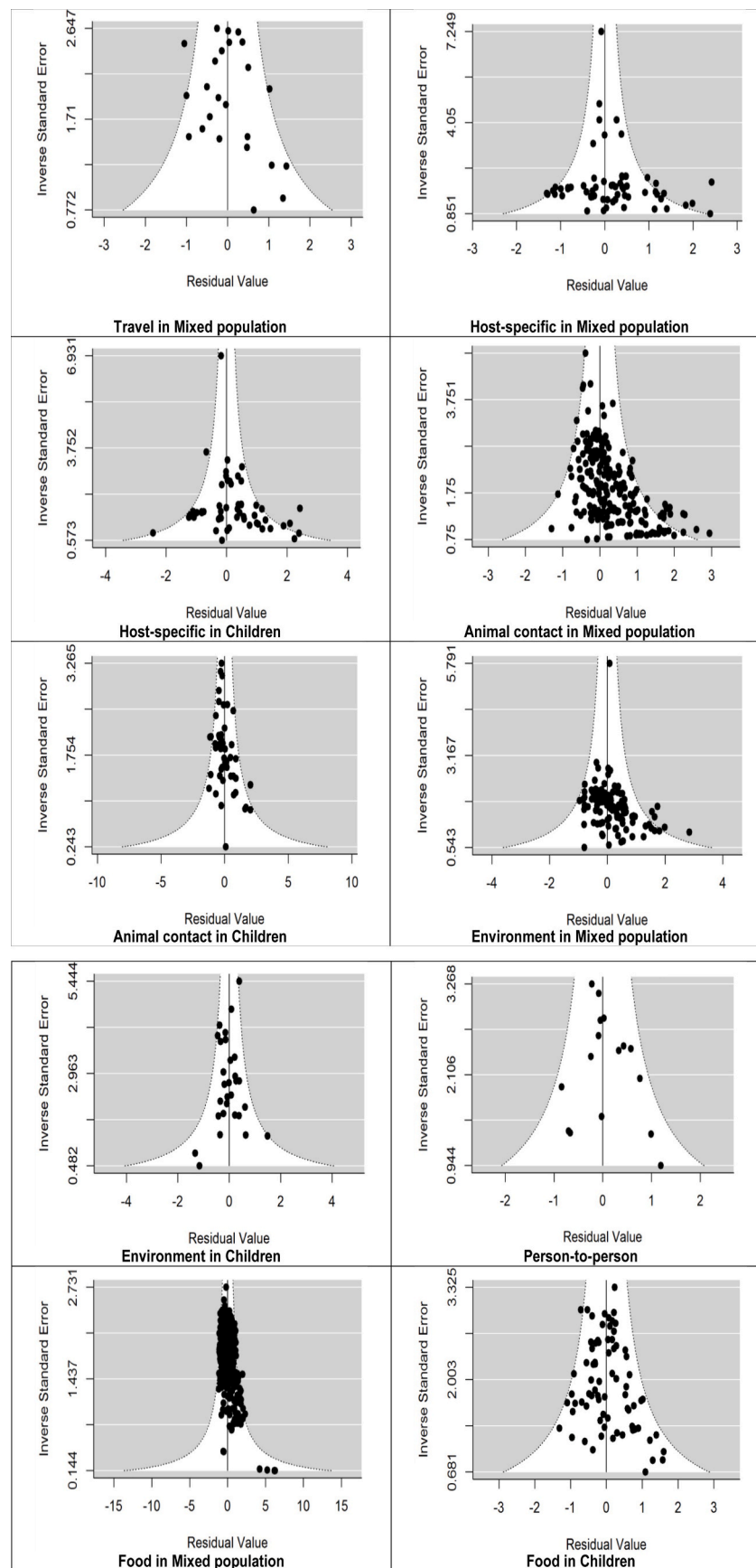
Fig. 8. Funnel plots of separate meta-analyses investigating categorized risk factors (travel, host-specific, environment, animal contact, person-to-person and food).

animals and their products (e.g. carcasses) and those relating to contact with pets or even wild animals. It would also be relevant to consider the role of surface freshwater (used for consumption or through leisure activities), since in some countries where these practices are common, infections acquired via water are also common. Moreover, this meta-analysis, by evidencing such environmental sources as important ones of campylobacteriosis in young children, underscores the need for better understanding the reservoirs and transmission pathways of *Campylobacter* in this population. Finally, risk factors could be investigated by *Campylobacter* species and by strains attributed to different reservoirs in a "source-assigned case-control" study design (Mullner et al., 2010, Mughini Gras et al., 2012, Mossong et al., 2016, Rosner et al., 2017). This approach could allow identification of source-specific risk factors and underlying transmission pathways.

CRediT authorship contribution statement

Philippe Fravalo: Writing - original draft. **Pauline Kooh:** Methodology, Project administration, Writing - original draft. **Lapo Mughini-Gras:** Writing - review & editing. **Julie David:** Writing - review & editing. **Anne Thébault:** Methodology, Formal analysis, Visualization. **Vasco Cadavez:** Methodology, Investigation, Formal analysis. **Ursula Gonzales-Barron:** Methodology, Investigation, Formal analysis, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mran.2020.100118.

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