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Risk factors for sporadic listeriosis: a systematic review and meta-analysis

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Abstract

Listeriosis is a major public health concern associated with high hospitalization and mortality rates. The objective of this work was to summarize evidence on the associations between risk factors and sporadic cases by meta-analysing outcomes from currently published case-control studies. Suitable scientific articles were identified through systematic literature search, and subjected to a methodological quality assessment. From each study, odds-ratio (OR) measures as well as study characteristics such as population type, design, type of model and risk factor hierarchy were extracted. Mixed-effects meta-analysis models were adjusted by population type to appropriate data partitions.

Twelve primary studies investigating sporadic listeriosis conducted between 1985 and 2013 passed through a quality assessment stage. These studies provided 226 OR considered for meta-analysis.

According to the meta-analysis, the main risk factor for acquiring listeriosis is suffering from an immunocompromising disease. In relation to the food exposures, this meta-analysis confirmed known risk factors such as consumption of RTE dairy, seafood and processed meat and underlined new food vehicles as fruits and vegetables, recently involved in outbreaks. There were not enough data to appraise travel, animal-contact and person-to-person as transmission pathways for listeriosis. These results will allow refining the case-control studies in the aim of improving risk factors characterisation for listeriosis in the susceptible population.

Keywords

Listeria monocytogenes; research synthesis; case-control studies; observational studies

1. Introduction

Listeriosis is a severe foodborne illness, caused by the bacterium *Listeria monocytogenes*, which is widely distributed in the environment. Listeriosis is a major public health concern as underlined by its hospitalization rate of 98.6% and a case-fatality ratio of 13.8% reported in Europe in 2017 (EFSA and ECDC, 2018). The incidence of listeriosis is low, estimated at around 3 to 6 cases per 1 million population per year (de Noordhout et al., 2014). Two clinical forms of listeriosis exist: non-invasive forms mainly with gastroenteritis, often underestimated in several countries by lack of surveillance, and invasive forms with bacteraemia, neurolisteriosis, maternal-neonatal infections and focal infections in various organ systems (Charlier et al., 2017; Ooi and Lorber, 2005). High- risk populations include the elderly (> 65 years old), immunocompromised people and pregnant women (EFSA BIOHAZ Panel, 2018). Mainly characterized by sporadic cases or small clusters, listeriosis cases have also occurred as outbreaks and large human clusters identified through epidemiological investigations using whole genome sequencing (WGS) methods (Moura et al., 2017; Nielsen et al., 2017; Van Walle et al., 2018). *L. monocytogenes* is mainly recognized to be transmitted by the ingestion of ready-to-eat (RTE) foods that are held for extended periods at refrigeration temperatures and allow growth to high numbers at the time of consumption. Investigation of listeriosis outbreaks has identified various food vehicles such as cheeses, RTE meat products, and fish products (Buchanan et al., 2017). New food vehicles, including foods that do not support the growth of *L. monocytogenes* (e.g. ice-cream) have also been identified through recent outbreak investigations (Buchanan et al., 2017).

Case–control studies of sporadic disease are a valuable tool to identify risk factors for human infections, including routes of transmission, food exposures, behavioural and predisposing factors. A systematic review and a meta-analysis of case-control studies were performed in order to combine the association measures, odds-ratios (OR), between listeriosis and its main risk factors.

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 in five bibliographic search engines, Science Direct, PubMed, Scielo, ISI Web of Science and Scopus. The search strategy was

limited to title/ abstract/ keyword using the following keywords: ("*Listeria monocytogenes" "*OR*" "*listeriosis"*) AND* ("case-control" OR "risk factor" "OR" "cohort") AND (*"*infection" *OR "*disease*").* No restrictions were defined for the year of the article or type of publication. The search was limited to the languages English, French, Portuguese and Spanish.

Each reference record was screened for relevance for inclusion in the meta-analysis study. The methodological quality of the "candidate" studies was appraised using pre-set 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 Odd ratio (OR) with confidence interval or p-value; or provision of sufficient data to calculate ORs; (7) overall quality of the study (Gonzales-Barron et al., 2019). Primary studies that passed the screening for relevance were marked as having 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 (Country, year, population, serotype/phage type/strains, case definition, design, sample size of the groups, type of model, matching and adjusting criteria), the categorized risk factors, the setting, the handling practices and the outcome of the study (OR).

A data categorisation scheme was established to hierarchically group the risk factors into travel, host-specific factors and pathways of exposure (see the methodological paper of this issue (Gonzales-Barron et al., 2019)). Specific partitions were made to investigate the risk related to ready-to-eat foods (i.e., dairy, meat, seafood and produce RTE). The variable "Population" was stratified into specific populations taking into account their respective susceptibility and the clinical form of listeriosis, namely pregnancy related cases ("perinatal") and other forms of invasive listeriosis ("non-perinatal").

2.2 Data synthesis

As described in Gonzales-Barron et al. (2019), the joint meta-analytical data was first described using basic statistics. Next, data was partitioned into subsets of categories of risk factors. Meta-analysis models were then fitted to each of the data partitions or subsets in order to estimate the overall OR due to-travel, host specific factors and transmission pathways related to person-to-person contagion, animal contact, environmental exposures and food vehicles. The meta-

analytical models were fitted separately by population type. For some food classes, the effects of handling (i.e., eating raw, undercooked) and setting (i.e., eating out) on the overall OR were assessed by the calculation of the ratio of the mean OR when food is mishandled (or, alternatively, when food is prepared outside the home) to the base OR.

The statistical analysis was designed to assess the effect of the geographical region, the study period and the analysis type (univariate/multivariate) on the final result. The objective of the region-specific meta-analysis was to inform the decision on the geographical regions that should be maintained for the subsequent pooling of OR. All meta-analysis models were essentially weighted random-effects linear regression models. Once a meta-analysis model was fitted, influential diagnostics statistics were applied in order to remove any influential observation originating from studies marked as having potential-for-bias. Publication bias was assessed by funnel plots and a statistical test investigating the effect of the study sample size on the ORs (Gonzales-Barron et al., 2019). Heterogeneity between studies was assessed by different indicators, such as the between-study variability (τ^2), the QE test investigating residual 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 produced in the R software (R Development Core Team, 2008) implemented with the *metafor* package (Viechtbauer, 2010).

3. Results

3.1 Descriptive statistics

From 1902 identified references, 189 passed the relevance screening and 12 passed the quality assessment stage (Fig. 1). Table 1 summarizes the main features of the case-control studies used in this meta-analysis. These 12 primary studies investigating sporadic listeriosis were conducted between 1985 and 2013 and provided 226 ORs. A total of 84% of the meta-analytical data were produced by case-control studies from Australia (71 ORs), USA (56 ORs), Germany (35 ORs) and UK (27 ORs).

All studies targeted susceptible populations. Seven case-control studies investigated exposures in the non-perinatal population – comprising immunocompromised and elderly (139 ORs), six case-control studies focused on the broad susceptible population with no distinction between perinatal and non-perinatal cases (labelled as “perinatal/non-perinatal” – 63 ORs) and one study (Dalton et al., 2011) conducted a case-control investigation on the perinatal population (24 ORs

extracted). Because the amount of data for the perinatal population was limited, separate meta-analysis models could not be adjusted for this population class. However, separate meta-analyses could be fitted for the non-perinatal population (139 ORs) and to the broad susceptible population (combined non-perinatal, perinatal and perinatal/non-perinatal data of 226 ORs).

The majority of primary studies investigated listeriosis caused by undifferentiated serotypes, except for Varma et al. (2007) whose case patients were infected with either serotype 1/2a or 4b. In all studies, the cases of listeriosis were laboratory-confirmed.

With regards to the risk factor classes, sporadic illness investigations focused on host specific factors (68 OR) and multiple pathways of exposure: food (149 ORs), environment (8 ORs) and contact with animals (1 OR). Travel and person-to-person contagion were not investigated as potential risk factors for listeriosis among the case-control studies included in this meta-analysis.

After methodological quality assessment, three case-control studies were marked as being below standards. In Gillespie et al. (2010), controls were not necessarily healthy people, whilst in Schlech et al. (2005), controls were patients with campylobacteriosis or salmonellosis. Finally, the OR measures from Jensen et al. (1994) were assigned the potential-for-bias status because the study, in general terms, was not clearly described, and some of the OR extracted were approximated. Those three case-control studies furnished 16 potentially biased OR whose influence on the pooled OR estimates was appraised by means of the Cook's distance. Whenever they were determined to be influential, they were removed from the meta-analysis models (Tables 2, 3, 4, 5).

Four case-control studies employed a matched experimental design and produced a total of 103 matched ORs. Bringing together the matched and unmatched designs, 127 extracted OR were not adjusted by any confounder (crude OR), while 100 OR were adjusted using either Mantel-Haenzel method or logistic regressions.

3.2 Meta-analysis

For every data partition, the meta-analysed risk factors are presented in summary tables only when significant (Tables 2, 3, 4). Pooled ORs were considered as significant when the lower bound of the 95% CI was equal or greater than 1. Non-significant results on main risk factors are presented in Supplementary Material 2. More detailed descriptive results, in particular funnel plots, forest plots, and OR of non-significant results, are in a complete report available upon request.

The pathways of exposure that on meta-analysis had non-significant association with listeriosis were farm environment and food subcategories such as vegetables, red meats, crustaceans, molluscs, processed seafood and composite dishes (Supplementary Material 2).

Meta-analysis for host specific risk factors

The meta-analysis on host-specific factors showed that, immunocompromising conditions, other medical conditions, chronic diseases and the use of anti-acids exacerbated the risk of acquiring listeriosis in all of the geographical regions with pooled OR between 2.014 and 5.170. Suffering from any immunocompromising condition (pooled OR=5.170; 95% CI [1.735 - 15.407]), was the most important predisposing factor for listeriosis among the susceptible population. Immunocompromising conditions included cancer, chemotherapy, and transplant (Figure 2). Other medical conditions (pooled OR=3.020; 95% CI [2.326 - 3.923]) included cardiovascular diseases, pre-existing liver disease, previous hospitalization, gastrointestinal diseases, and lung diseases.

Meta-analysis for food consumption

Most of the routes of transmission of listeriosis recovered in the systematic review were related to consumption of foods such as meat, dairy, seafood, composite dishes and produce. Very limited data were available for food subcategories such as eggs, grains and beverages (juice), so the significance of these sources as potential vehicles of transmission of listeriosis could not be appraised.

The food categories followed a similar ranking as sources of listeriosis in the general susceptible population and the non-perinatal subset. According to their association with listeriosis in the susceptible population, the global food categories ranked in decreasing order were: seafood (pooled OR=2.148; 95% CI [1.190 - 3.877)), dairy (pooled OR=1.867; 95% CI [1.292 - 2.699]), composite foods (pooled OR=1.621; 95% CI [1.014 - 2.590]), produce (pooled OR=1.415 95% CI [1.003 - 1.995]) and meat (pooled OR =1.371 [1.027 - 1.830]) (Table 2).

The meta-analyses by RTE class revealed that the consumption of RTE seafood (pooled OR ranged from 6.273 to 10.746) and dairy products (pooled OR ranged from 1.636 to 1.830) are the main risk factors for listeriosis in the general susceptible population and the non-perinatal population subset (Table 3).

The meta-analysis on the seafood data partition did not reveal significant associations for crustaceans (pooled OR =1.033; 95% CI [0.677 - 1.574]), molluscs (pooled OR=1.985; 95% CI

[0.984 - 4.004]) and processed fish (pooled OR=2.790; 95% CI [0.981 - 7.932]) (cf. Supplementary Material 2).

Within dairy, the consumption of cheese (in majority soft cheese; pooled OR=1.832; 95% CI [1.270 - 2.643]) and fats (raw milk, raw cream and raw butter; pooled OR=2.139; 95% CI [1.314 - 3.481]) were significantly associated with listeriosis in the general susceptible population (Table 4; Figure 4).

Within meats, the higher association with disease in the susceptible population was found for poultry (essentially undercooked poultry; pooled OR=2.157; 95% CI [1.177 - 3.951]), although it should be kept in mind that only 5 ORs were available for this pathway of exposure. Moreover, a significant association with listeriosis was found for the consumption of processed meats (pooled OR=1.624; 95% CI [1.230 - 2.143]) that included processed pork, processed poultry, cooked sausages, raw fermented spreadable sausages, dry-cured ham, deli meats, hotdogs, pate, cold meats and uncooked hotdogs.

Within produce, a significant association was found for the consumption of fruits (melons, cantaloupe, strawberries, RTE fruit salads; pooled OR=1.538; 95% CI [1.1431 - 2.070]) by the susceptible population.

Meta-analysis on the effects of handling and preparation of foods

For some food classes, for which relevant information was available, the effects of handling (raw and undercooked) and setting (eating out) were appraised (Table 5). The data partitions suitable for this analysis were: (i) processed meats and poultry, and (ii) fruits.

On meta-analysis, it was found that susceptible people who claimed having eaten raw processed meats or undercooked poultry had their odds of infection significantly increased by a factor of 2.168. Eating out came up as a significant factor increasing the risk of listeriosis infection. On average, susceptible people who had consumed fruits prepared in a food establishment had theirs their odds of infection significantly increased by a factor of 2.358.

For some partitions (whole food, meat, produce, composite), both the formal tests and the funnel plots indicated that publication bias is likely (Figure 5). A significant publication bias p-value implies that the OR value measured by the researchers depends upon the sample size. In this case, it is likely that small-sized studies have remained unpublished because of their failure to detect significant OR (Gonzales-Barron et al., 2019). Moreover, the intra-class correlation I^2 indicates low to moderate heterogeneity (<75%) for most of the data partitions (Tables 2, 3, 4,5).

4. Discussion

The meta-analysis showed that underlying health conditions or diseases and the consumption of RTE foods (seafood, dairy and meat) were the most important risk factors for sporadic listeriosis. Host-specific related risk factors presented higher pooled OR ranging from 2.014 to 5.170 for the susceptible population. These host susceptibility risk factors were also confirmed by analysis of epidemiological data (Pouillot et al., 2015) and the recent prospective cohort study (Charlier et al., 2017). The relative host susceptibility derived for 11 population subgroups, showed that the highest susceptible population (hematological cancer) is a thousand more susceptible than general healthy population (Pouillot et al., 2015).

The pooled OR assigned to main food categories ranged from 1.371 to 2.477. For specific foods such cheeses or processed meat, the odds ratios increase. The highest pooled OR is observed for RTE fish products in the susceptible populations other than pregnant women with a value of 10.746. This probably illustrates the fact that many foods can be contaminated by *L. monocytogenes* and that the practices associated with these foods (manufacturing, storage, consumption) strongly affect the risk associated to them. In these conditions, it is very difficult to identify specific food at risk as the food categories are disparate in terms of ability to support the growth of *L. monocytogenes*. Moreover, the diversity of food questionnaire at national and regional levels concerning the list of foods at risk, the methodology used to perform them and the understanding of patients have always been recognised as a source of bias.

However, this meta-analysis identified the RTE such as seafood, dairy and processed meats as the main risks factors of listeriosis. These food categories have been already identified by more than 100 outbreaks worldwide as foods at risk for listeriosis (Buchanan et al., 2017). The estimated ORs from this meta-analysis are not a direct assessment of attribution of the different food to the sporadic cases. Meanwhile, existing source attribution models published on *L. monocytogenes* revealed the importance of the same food categories. The EFSA BIOHAZ panel based on a bottom-up approach with data on prevalence, levels of contamination, growth and consumption data together with dose-response assessment yielded estimates that RTE meat products accounted for 67% of human cases, RTE fish products for 32% and soft and semi-soft cheeses for 1% (EFSA BIOHAZ Panel, 2018). Another approach using WGS showed that different source attribution models applied on a set of European human sporadic strains for different levels of molecular analysis (from MLST to wgMLST) tended to place bovine, and thus cheese, as the main source of human listeriosis (32% to 64%) (Nielsen et al., 2017). This difference of the importance of cheese could be explained by one assumption done in quantitative risk assessments. Usually, the variability of strain virulence is considered to be the

same whatever the food type. However, between-strain virulence variability is huge for *L. monocytogenes* (Maury et al., 2019). A small change in proportion of most virulent strains in a food category could thus considerably change the estimated contribution of that food.

On the other hand, crustaceans and molluscs are not identified in this meta-analysis as significant factors. In France, crustaceans such as shrimps involved in food safety incidents (withdraw/recall) are contaminated by hypovirulent clones of *L. monocytogenes* such as CC121 and CC9 (Maury et al., 2019; Maury et al., 2016) that could explain the low number of sporadic cases associated to these foods (EFSA and ECDC, 2018; Fritsch et al., 2018; Painset et al., 2019).

Two studies in USA and Australia identified the fruits consumption (cantaloupes) as a risk factor (Dalton et al., 2011; Varma et al., 2007). Cantaloupes present neutral pH value and thus support the growth of *L. monocytogenes* (Bassett and McClure, 2008; Hoelzer et al., 2012). More generally, the importance of produce is supported with recent advances in detection of unknown source of listeriosis outbreaks allowed by genomic methods (Buchanan et al., 2017; Chen et al., 2016; EFSA and ECDC, 2018; Nyarko et al., 2016). This point emphasizes the need to develop a risk assessment on produce and especially fruits for *L. monocytogenes.*

The results of this meta-analysis based on studies conducted before 2013 did not take into account new discovered food vehicles identified thanks to the combination of listeriosis surveillance data and genomic data (Desai et al., 2019). Furthermore, the high discrimination power of genomic methods has recently conducted to the evolution of the definition of sporadic and outbreak cases of listeriosis, distinguishing them more finely (Moura et al., 2017; Van Walle et al., 2018). Food questionnaires shall be permanently updated in each country based on the evolution of food habits and the discovering of new contaminated products based on food surveillance (EFSA and ECDC, 2018; Self, 2016). Results from the upcoming case control studies might be different because of the change of both the knowledge of the potential food vehicle, the definition of sporadic cases and the new consumption patterns.

The different case-control studies of this meta-analysis published before March 2017 are stored in a database. It will be updated with relevant studies published after this date (e.g. Kvistholm Jensen et al. (2017)) and future case-control studies. Future analysis will help to identify the potential evolution of risk factors.

5. Conclusions

This meta-analysis confirmed known risk factors of listeriosis: consumption of RTE food such as milk products or fish products and consumption of processed meat. The risk is probably linked to their intrinsic characteristics allowing the growth of *L. monocytogenes* and their mode of consumption. These risk factors concerned sporadic cases but have also been reported for outbreaks worldwide. A risk assessment related to *L. monocytogenes* in fruits and vegetables should be investigated based on the increasing consumption of this type of products.

Future case control studies should be conducted by refining the categories of RTE food and including vegetables and fruits that have been the source of human cases. It would be necessary to consider a typology of foods that is more representative of the level of risk and takes into account the processing method (raw, cooked, fermented, etc.), the intrinsic characteristics (pH, water activity, preservatives, background microflora), the storage (short or long shelf-life) and the mode of consumption (immediate consumption, reheating, cooking). It would be interesting to carry out these studies on elderly people that constituted the main part of the susceptible population.

Appendices: Supplementary material

Appendix 1: References of the 12 primary studies

Appendix 2: Non-significant results on the main risk factors

Data statement

Acknowledgments

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Figures

Figure 1: PRISMA flow chart for the selection of case-control studies of human listeriosis included in this meta-analysis

Figure 2: Forest-plot of the association of listeriosis with immunocompromising conditions in the general susceptible population

Figure 3: Forest-plot of the association of listeriosis with the consumption of seafood in the general susceptible population

Figure 4: Forest-plot of the association of listeriosis with consumption of cheeses in the general susceptible population

Figure 5. Funnel-plots from meta-analyses

Tables

Table 1. Characteristics of case-control studies investigating sources of sporadic human listeriosis included in the meta-analysis

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

Table 3. Results of the meta-analysis on ready-to-eat foods

Table 4. Results of the meta-analysis on disaggregated risk factors

Table 5. Effect of food handling on the pooled OR

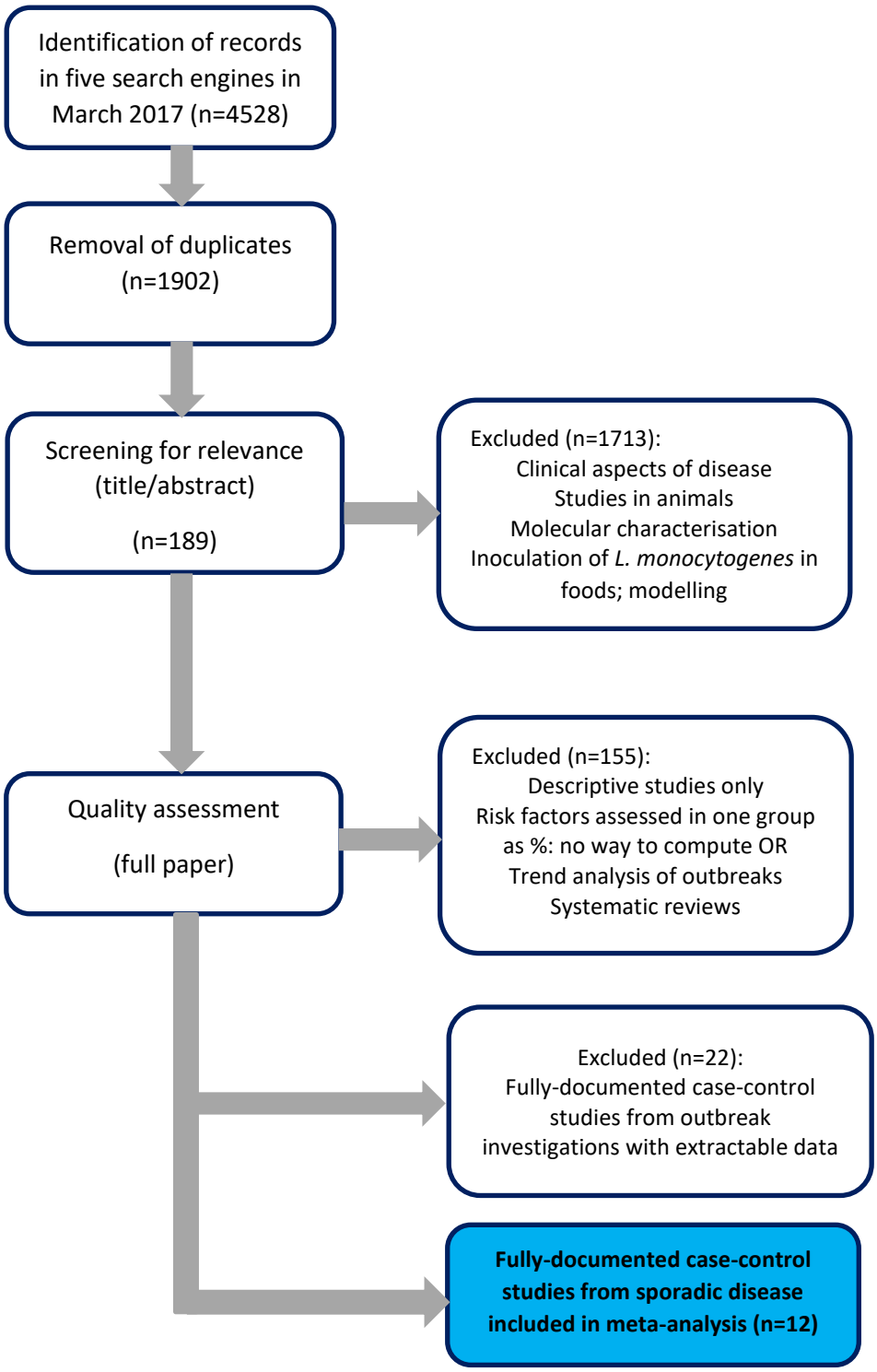


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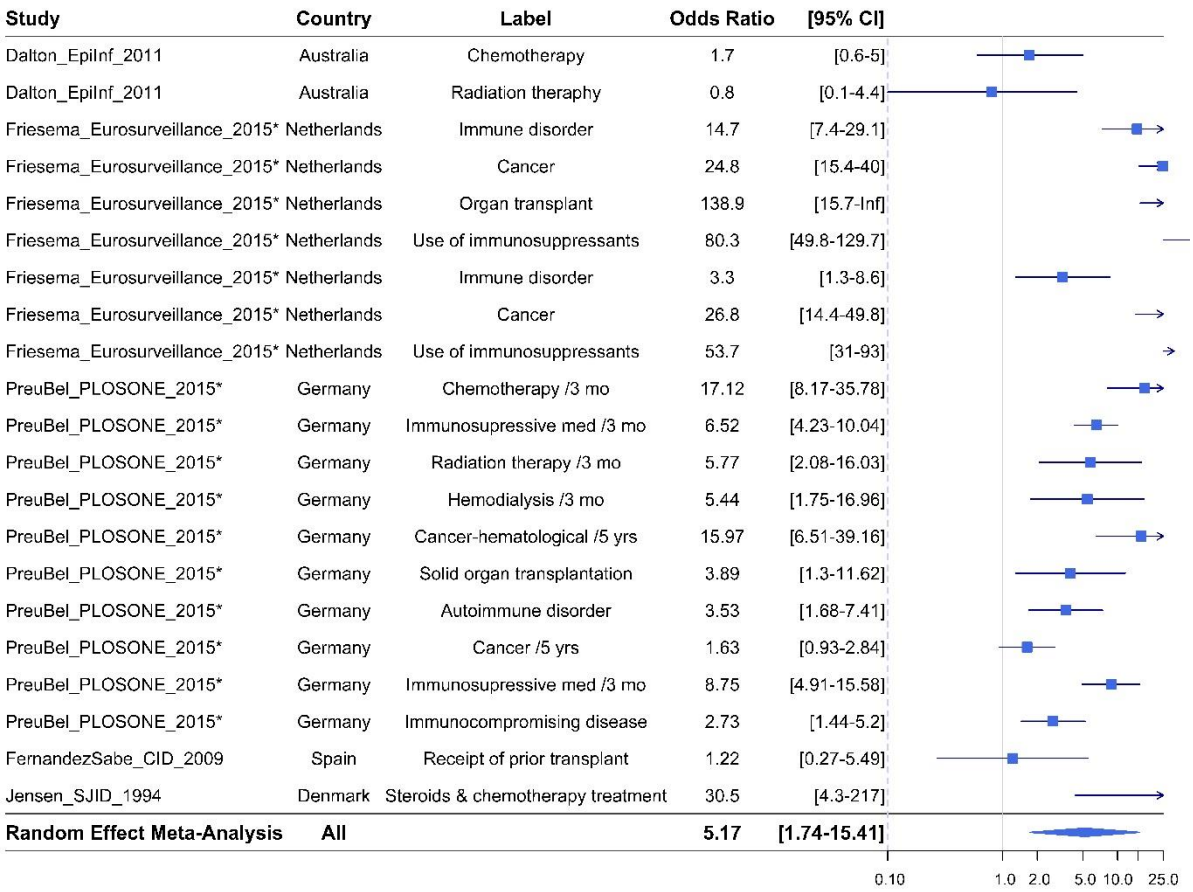


Figure 2. Forest-plot of the association of listeriosis with immunocompromising conditions in the general susceptible population (n=21) *adjusted OR

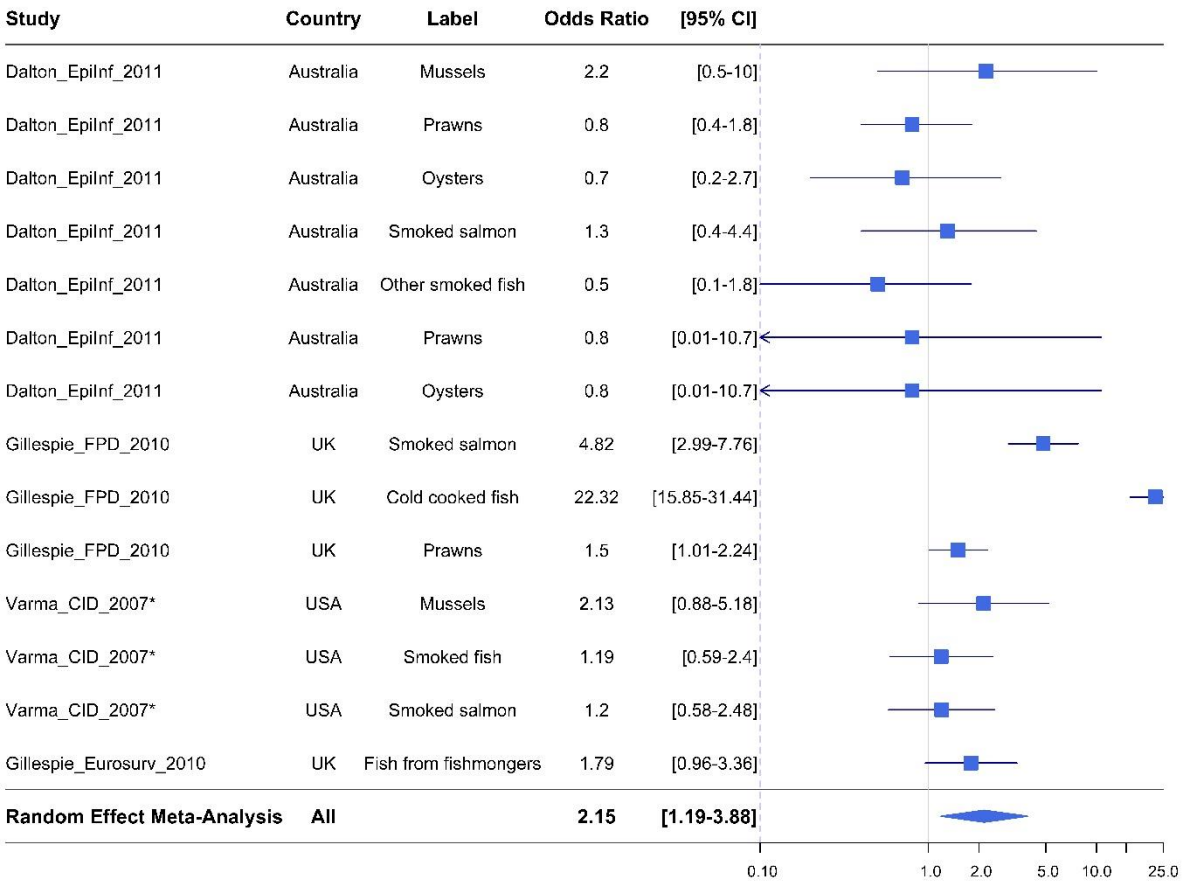
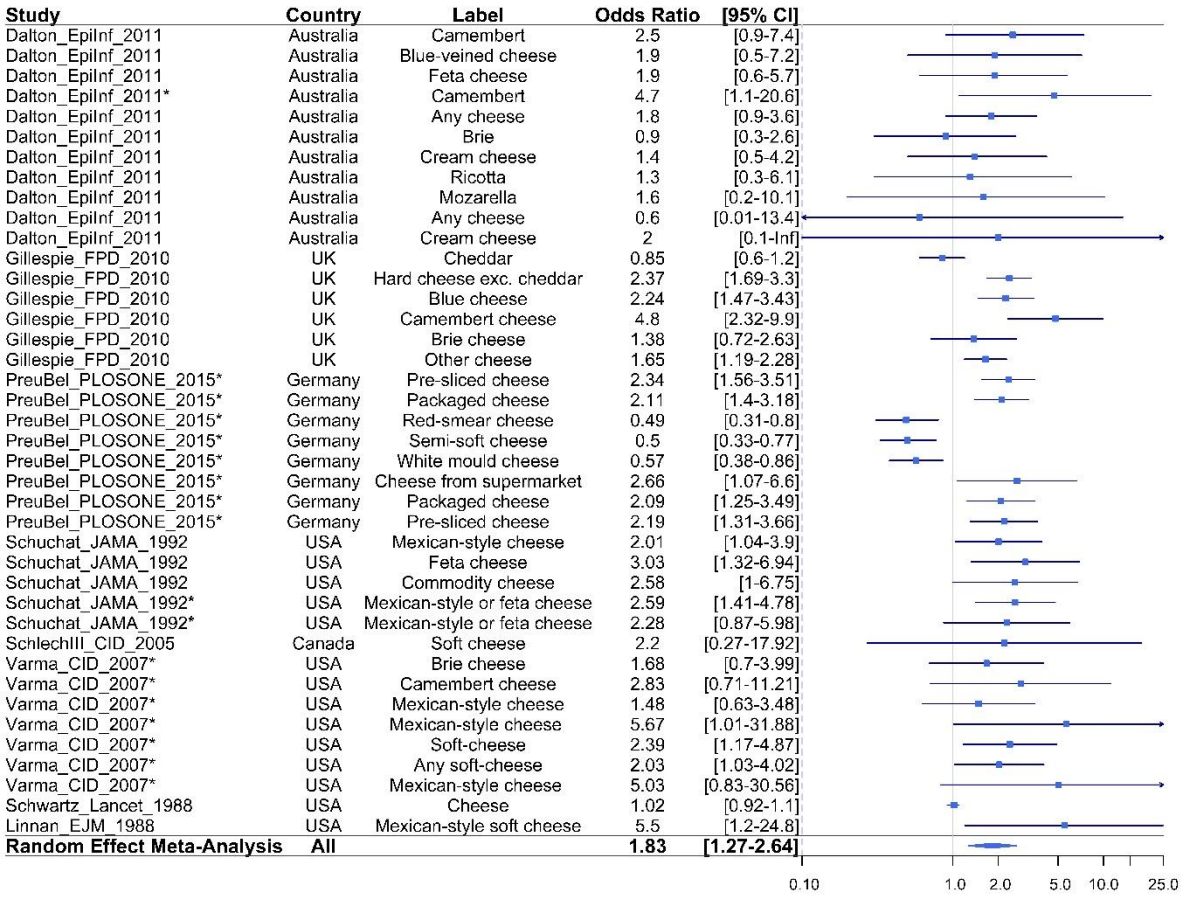


Figure 3. Forest-plot of the association of listeriosis with the consumption of seafood in the general susceptible population (n=14) *adjusted OR



390

391 **Figure 4.** Forest-plot of the association of listeriosis with the consumption of cheese in the
392 general susceptible population (n=40) *adjusted OR

393

394

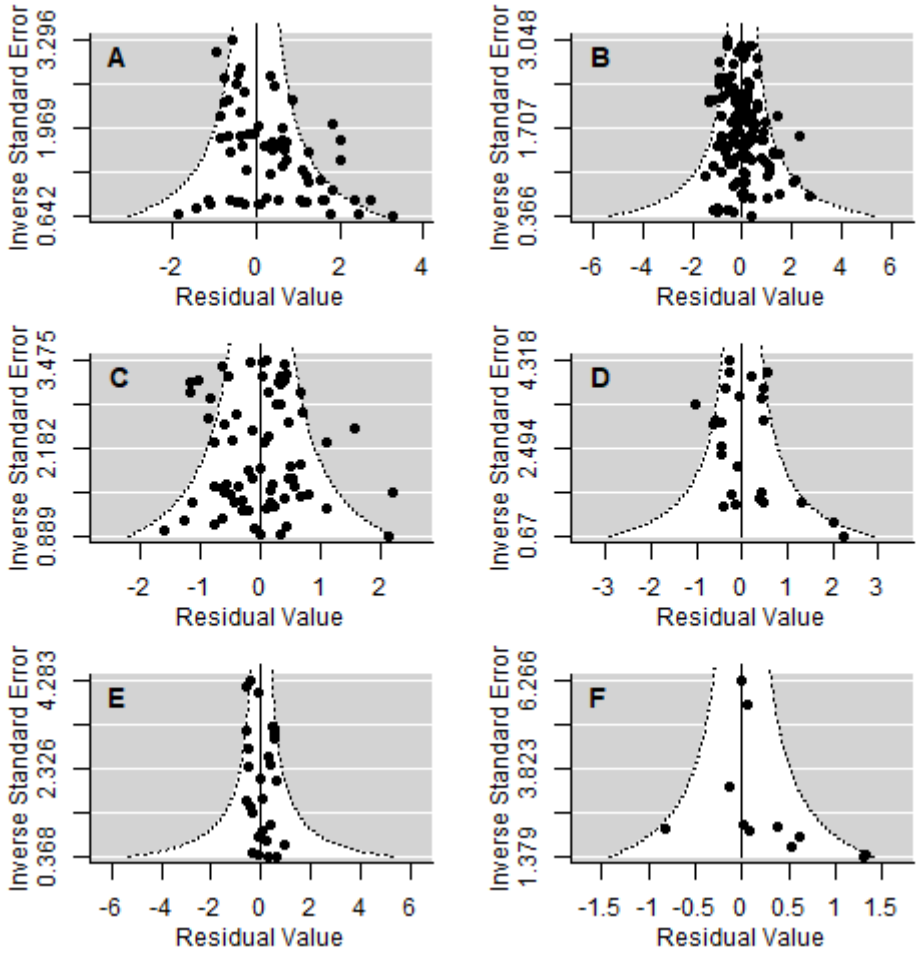


Figure 5: Funnel-plots from meta-analyses investigating

A. Host-specific factors
B. Food risk factors in the general susceptible population
C. Food risk factors in the non-perinatal population
D. Meat in the general susceptible population
E. Produce in the general susceptible population
F. Composite in the general susceptible population

406 **Table 1. Characteristics of case-control studies investigating sources of sporadic human**

407 **listeriosis included in the meta-analysis**

Study ID*	Country	Study period	Population	Design	Analysis & model**	Cases/controls	Quality
Dalton et al. 2011	Australia	2001-2004	Non-perinatal (immuno-compromised)	Matched	Uni-CL Multi-CL	117 cases 85 controls	Good
			Perinatal	Matched	Uni-UL Multi-UL	19 cases 12 controls	
Fernández et al. 2009	Spain	1995-2007	Non-perinatal (transplant-recipients)	Matched	Uni-Chi Multi-CL	30 cases 60 controls	Good
Friesema et al. 2015	Netherlands	2008-2013	Non-perinatal (immuno-compromised)	Unmatched	Uni-UL Multi-UL	279 cases 1733 controls	Good
Gillespie et al. 2010a	UK	2001-2007	Peri/non-peri	Unmatched	Uni-Chi	171 cases 60646 controls	Poor
			Non-perinatal (elderly)	Unmatched	Uni-Chi	104 cases 15177 controls	
Gillespie et al. 2010b	UK	2005-2008	Non-perinatal (Elderly)	Unmatched	Uni-Chi	159 cases 18115 controls	Good
Jensen et al. 1994	Denmark	1989-1990	Perinatal/non-perinatal (pregnant and immuno-compromised)	Unmatched	Uni-Chi	66 cases 33 controls	Poor
Linnan et al. 1988	USA	1985-1987	Perinatal/non-perinatal	Unmatched	Uni-Chi	? cases ? controls	Good
Preussel et al. 2015	Germany	2012-2013	Non-perinatal (Immuno-compromised)	Unmatched	Uni-UL Multi-UL	109 cases 1982 controls	Good
Schlech et al. 2005	Canada	2002-2004	Non-perinatal (Underlying GI diseases)	Unmatched	Uni-Chi	12 cases 24 cases	Poor
Schuchat et al. 1992	USA	1988-1990	Perinatal/non-perinatal (pregnant and immuno-compromised)	Matched	Uni-MH Multi-CL	165 cases 376 controls	Good
Schwartz et al. 1988	USA	1986-1987	Perinatal/non-perinatal (pregnant and immuno-compromised)	Matched	Uni-MH Multi-CL	80 cases 239 controls	Good
Varma et al. 2007	USA	2000-2003	Perinatal/non-perinatal (pregnant and immuno-compromised)	Unmatched (frequency-matched)	Uni-UL Multi-UL	169 cases 376 controls	Good

408 *References are listed in Appendix 1;** Univariate analysis can be univariate (Uni) and multivariate
409 (Model) while model can be chi-square (Chi), Mantel-Haenzel (MH), unconditional logistic (UL) and
410 conditional logistic (CL)
411

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

Population	Risk factor	Pooled OR [95% CI]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Host-specific							
All susceptible	Other medical conditions	3.020 [2.326 - 3.923]	8/24	<.0001	<.0001	0	τ^2=2.015 QE(df = 61) = 437.088, p-val < .0001 S^2=1.180 I^2=63.06
	Antiacids	2.014 [1.260 - 3.218]	5/9	0.003			
	Immunocompromising conditions	5.170 [1.735 - 15.407]	5/21	0.003			
	Chronic diseases	2.927[1.913 - 4.480]	3/11	<.0001			
Food							
All susceptible	Produce	1.415 [1.003 - 1.995]	7/27	0.048	0.001	1	τ^2= 0.688 QE(df = 136) = 615.478, p-val < .0001 S^2=0.549 I^2=55.61
	Meat	1.371 [1.027 - 1.830]	8/44	0.032			
	Dairy	1.867 [1.292 - 2.699]	9/45	0.001			
	Seafood	2.148 [1.190 - 3.877]	4/14	0.011			
	Composite	1.621 [1.014 - 2.590]	4/11	0.044			
Non-perinatal	Dairy	1.605 [1.187 - 2.170]	4/27	0.002	0.807	1	τ^2=1.087 QE(df = 69) = 439.237, p-val <.0001 S^2=0.516 I^2=67.80
	Seafood	2.477 [1.098 - 5.59]	3/9	0.029			

*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. Results of the meta-analysis on ready-to-eat foods

Population	Type of RTE food	Pooled OR [95% CI]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
All susceptible	Dairy	1.830 [1.252 - 2.676]	8/44	0.002	0.553	0	τ^2=3.177 QE(df = 77) = 410.8, p-val <.0001 S^2=0.510 I^2=86.16
	Seafood	6.273 [1.457 - 27.01]	3/6	0.014			
Non perinatal	Dairy	1.636 [1.189 - 2.250]	4/27	0.003	0.610	0	τ^2=2,964 QE(df = 48) = 291.1, p-val <.0001 S^2=0.608 I^2=83.00
	Seafood	10.746 [1.541 - 74.91]	2/4	0.017			

*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 4. Results of the meta-analysis on disaggregated risk factors

Risk Factor	Population	Risk factor precise	Pooled OR [95% CI]	N/n*	p-value of risk factor	Publication bias p-value	Points removed **	Heterogeneity analysis***
Meat	All susceptible	Poultry	2.157 [1.177 - 3.951]	3/5	0.013	0.002	0	τ^2=0.174 QE(df = 22) = 89.90, p-val < .0001 S^2=0.625 I^2=21.75
		Processed meat	1.624 [1.230 - 2.143]	6/13	0.001			
Meat	Non perinatal	Processed meat	1.549 [1.307 - 1.836]	3/7	<.0001	0.226	0	τ^2= 0.092 QE(df = 11) = 63.06, p-val <.0001 S^2=0.277 I^2=24.92
Dairy	All susceptible	Cheese	1.832 [1.270 - 2.643]	8/40	0.001	0.813	0	τ^2=0.305 QE(df = 43) = 196.182, p-val <.0001 S^2=0.417 I^2=42.21
		Fats	2.139 [1.314 - 3.481]	3/5	0.002			
Dairy	Non perinatal	Cheese	1.586 [1.188 - 2.119]	4/24	0.002	0.160	0	τ^2=0.000 QE(df = 25) = 141.29, p-val <.0001 S^2=0.396 I^2=0.00
Produce	All susceptible	Fruits	1.538 [1.1431 - 2.070]	2/11	0.005	0.002	0	τ^2=0.054 QE(df = 25) = 53.736, p-val = 0.001 S^2=0.209 I^2=20.67
Composite	All susceptible	RTE	1.486 [1.1263 - 1.960]	2/3	0.005	<.0001	0	τ^2=0.244 QE(df = 9) = 24.60, p-val = 0.003 S^2=0.397 I^2=38.07

*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 5. Effect of food handling on the pooled OR

Risk Factor	Risk factor precise	Pooled OR [95% CI]	N/n *	p-value of risk factor	Increase in OR due to poor handling [95% CI]	Points removed **	Publication bias p-value	Heterogeneity analysis***
Processed meat and poultry (at)	Undercooked	5.013 [1.776 - 14.142]	3/7	0.001	2.168 [1.297 - 3.623]	0	0.069	τ^2=0.052 QE(df = 30) = 63.10, p-val = 0.001 S^2=0.487 I^2=9.681
	Base	2.312 [1.370 - 3.904]	7/26	0.003	-			
Fruits	Eating out	2.506 [1.216 - 5.167]	1/3	0.001	2.358 [1.483 - 3.750]	0	0.077	τ^2=0.000 QE(df = 9) = 5.945, p-val = 0.745 S^2=0.226 I^2=0.000
	Base	1.063 [0.820 - 1.378]	2/8	0.645	-			

*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).

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Appendix 1:References of Twelve case-control studies for L. monocytogenes

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Appendix 2. Results of the meta-analysis - non-significant results

- **Main risk factors**

Population	Risk factor	Pooled OR [IC95%]	N/n*
Environment			
All susceptible	Farm environment	3.253 [0.930- 11.378]	2/8
Food			
Non perinatal	Produce	1.096 [0.700- 1.717]	5/11
	Meat	1.320 [0.946 - 1.841]	4/23
	Composite	1.283 [0.568 - 2.899]	2/4

*N/n Number of studies/number of OR

- **Ready-to-eat foods**

Risk Factor	Population	Risk factor precise	Pooled OR [IC95%]	N/n*
RTE	All susceptible	Produce	1.606 [0.903 - 2.856]	3/6
		Meat	1.185 [0.879 - 1.595]	7/25
RTE	Non perinatal	Produce	1.367 [0.813 - 2.298]	3/4
		Meat	1.203 [0.784 - 1.847]	4/17

*N/n Number of studies/number of OR

- **Disaggregated risk factors**

Risk Factor	Population	Risk factor precise	Pooled OR [IC95%]	N/n*
Meat	All susceptible	Others	1.017 [0.756 - 1.370]	5/7
Meat	Non perinatal	Others	0.870[0.582 - 1.302]	4/6
Produce	All susceptible	Vegetables	1.102 [0.820 - 1.480]	7/16
Produce	Non perinatal	Vegetables	0.918 [0.605 - 1.394]	5/8
Seafood	All susceptible	Molluscs	1.985 [0.984 - 4.004]	2/4
		Crustaceans	1.033 [0.677 - 1.574]	2/3
		Processed	2.789[0.981 - 7.932]	4/8
Composite	All susceptible	Dishes	1.550 [0.845 - 2.846]	3/8

*N/n Number of studies/number of OR