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

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

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19

20 **Abstract**

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

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

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

39

40 **Keywords**

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

42

## 43 **1. Introduction**

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

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

69

## 70 **2. Material and methods**

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

73

### 74 **2.1 Systematic review**

75 The literature search was conducted in March 2017 in five bibliographic search engines,  
76 Science Direct, PubMed, Scielo, ISI Web of Science and Scopus. The search strategy was

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

81

82 Each reference record was screened for relevance for inclusion in the meta-analysis study. The  
83 methodological quality of the “candidate” studies was appraised using pre-set quality criteria  
84 comprising (1) appropriate selection of the controls; (2) adjustment to correct for confounders,  
85 (3) comparability between cases and controls; (4) acceptable responses rates for the exposed  
86 and control groups; (5) data analysis appropriate to the study design; (6) provision of Odd ratio  
87 (OR) with confidence interval or p-value; or provision of sufficient data to calculate ORs; (7)  
88 overall quality of the study (Gonzales-Barron et al., 2019). Primary studies that passed the  
89 screening for relevance were marked as having potential for bias if they failed to meet at least  
90 one of the methodological quality assessment criteria.

91 Data from primary studies were then extracted using a standardised spreadsheet. Data extracted  
92 included the relevant study characteristics (Country, year, population, serotype/phage  
93 type/strains, case definition, design, sample size of the groups, type of model, matching and  
94 adjusting criteria), the categorized risk factors, the setting, the handling practices and the  
95 outcome of the study (OR).

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

103

## 104 **2.2 Data synthesis**

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

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

114 The statistical analysis was designed to assess the effect of the geographical region, the study  
115 period and the analysis type (univariate/multivariate) on the final result. The objective of the  
116 region-specific meta-analysis was to inform the decision on the geographical regions that  
117 should be maintained for the subsequent pooling of OR. All meta-analysis models were  
118 essentially weighted random-effects linear regression models. Once a meta-analysis model was  
119 fitted, influential diagnostics statistics were applied in order to remove any influential  
120 observation originating from studies marked as having potential-for-bias. Publication bias was  
121 assessed by funnel plots and a statistical test investigating the effect of the study sample size on  
122 the ORs (Gonzales-Barron et al., 2019). Heterogeneity between studies was assessed by  
123 different indicators, such as the between-study variability ( $\tau^2$ ), the QE test investigating residual  
124 heterogeneity, the variance of residuals and the intra-class correlation  $I^2$  (Gonzales-Barron et  
125 al., 2019). Publication bias and remaining heterogeneity were not further corrected for, but were  
126 taken into account for the interpretation of the results.

127 All analyses were produced in the R software (R Development Core Team, 2008) implemented  
128 with the *metafor* package (Viechtbauer, 2010).

129

### 130 **3. Results**

#### 131 **3.1 Descriptive statistics**

132 From 1902 identified references, 189 passed the relevance screening and 12 passed the quality  
133 assessment stage (Fig. 1). Table 1 summarizes the main features of the case-control studies used  
134 in this meta-analysis. These 12 primary studies investigating sporadic listeriosis were  
135 conducted between 1985 and 2013 and provided 226 ORs. A total of 84% of the meta-analytical  
136 data were produced by case-control studies from Australia (71 ORs), USA (56 ORs), Germany  
137 (35 ORs) and UK (27 ORs).

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

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

147 The majority of primary studies investigated listeriosis caused by undifferentiated serotypes,  
148 except for Varma et al. (2007) whose case patients were infected with either serotype 1/2a or  
149 4b. In all studies, the cases of listeriosis were laboratory-confirmed.

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

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

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

168

### 169 **3.2 Meta-analysis**

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

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

179

### 180 **Meta-analysis for host specific risk factors**

181 The meta-analysis on host-specific factors showed that, immunocompromising conditions,  
182 other medical conditions, chronic diseases and the use of anti-acids exacerbated the risk of  
183 acquiring listeriosis in all of the geographical regions with pooled OR between 2.014 and 5.170.  
184 Suffering from any immunocompromising condition (pooled OR=5.170; 95% CI [1.735 -  
185 15.407]), was the most important predisposing factor for listeriosis among the susceptible  
186 population. Immunocompromising conditions included cancer, chemotherapy, and transplant  
187 (Figure 2). Other medical conditions (pooled OR=3.020; 95% CI [2.326 - 3.923]) included  
188 cardiovascular diseases, pre-existing liver disease, previous hospitalization, gastrointestinal  
189 diseases, and lung diseases.

190

### 191 **Meta-analysis for food consumption**

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

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

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

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



209 [0.984 - 4.004]) and processed fish (pooled OR=2.790; 95% CI [0.981 - 7.932]) (cf.  
210 Supplementary Material 2).

211 Within dairy, the consumption of cheese (in majority soft cheese; pooled OR=1.832; 95% CI  
212 [1.270 - 2.643]) and fats (raw milk, raw cream and raw butter; pooled OR=2.139; 95% CI [1.314  
213 - 3.481]) were significantly associated with listeriosis in the general susceptible population  
214 (Table 4; Figure 4).

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

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

225

## 226 **Meta-analysis on the effects of handling and preparation of foods**

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

230 On meta-analysis, it was found that susceptible people who claimed having eaten raw processed  
231 meats or undercooked poultry had their odds of infection significantly increased by a factor of  
232 2.168. Eating out came up as a significant factor increasing the risk of listeriosis infection. On  
233 average, susceptible people who had consumed fruits prepared in a food establishment had  
234 theirs their odds of infection significantly increased by a factor of 2.358.

235 For some partitions (whole food, meat, produce, composite), both the formal tests and the funnel  
236 plots indicated that publication bias is likely (Figure 5). A significant publication bias p-value  
237 implies that the OR value measured by the researchers depends upon the sample size. In this  
238 case, it is likely that small-sized studies have remained unpublished because of their failure to  
239 detect significant OR (Gonzales-Barron et al., 2019). Moreover, the intra-class correlation  $I^2$   
240 indicates low to moderate heterogeneity (<75%) for most of the data partitions (Tables 2, 3,  
241 4,5).

242

#### 243 **4. Discussion**

244 The meta-analysis showed that underlying health conditions or diseases and the consumption  
245 of RTE foods (seafood, dairy and meat) were the most important risk factors for sporadic  
246 listeriosis. Host-specific related risk factors presented higher pooled OR ranging from 2.014 to  
247 5.170 for the susceptible population. These host susceptibility risk factors were also confirmed  
248 by analysis of epidemiological data (Pouillot et al., 2015) and the recent prospective cohort  
249 study (Charlier et al., 2017). The relative host susceptibility derived for 11 population  
250 subgroups, showed that the highest susceptible population (hematological cancer) is a thousand  
251 more susceptible than general healthy population (Pouillot et al., 2015).

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

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

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

280 On the other hand, crustaceans and molluscs are not identified in this meta-analysis as  
281 significant factors. In France, crustaceans such as shrimps involved in food safety incidents  
282 (withdraw/recall) are contaminated by hypovirulent clones of *L. monocytogenes* such as CC121  
283 and CC9 (Maury et al., 2019; Maury et al., 2016) that could explain the low number of sporadic  
284 cases associated to these foods (EFSA and ECDC, 2018; Fritsch et al., 2018; Painset et al.,  
285 2019).

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

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

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

307

308

309

## 310 **5. Conclusions**

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

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

325 **Appendices: Supplementary material**

326 Appendix 1: References of the 12 primary studies

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

328

329 **Data statement**

330 **Acknowledgments**

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337 scientific employment programme.

338

339 **Figures**

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

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

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

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

348 Figure 5. Funnel-plots from meta-analyses

349 **Tables**

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

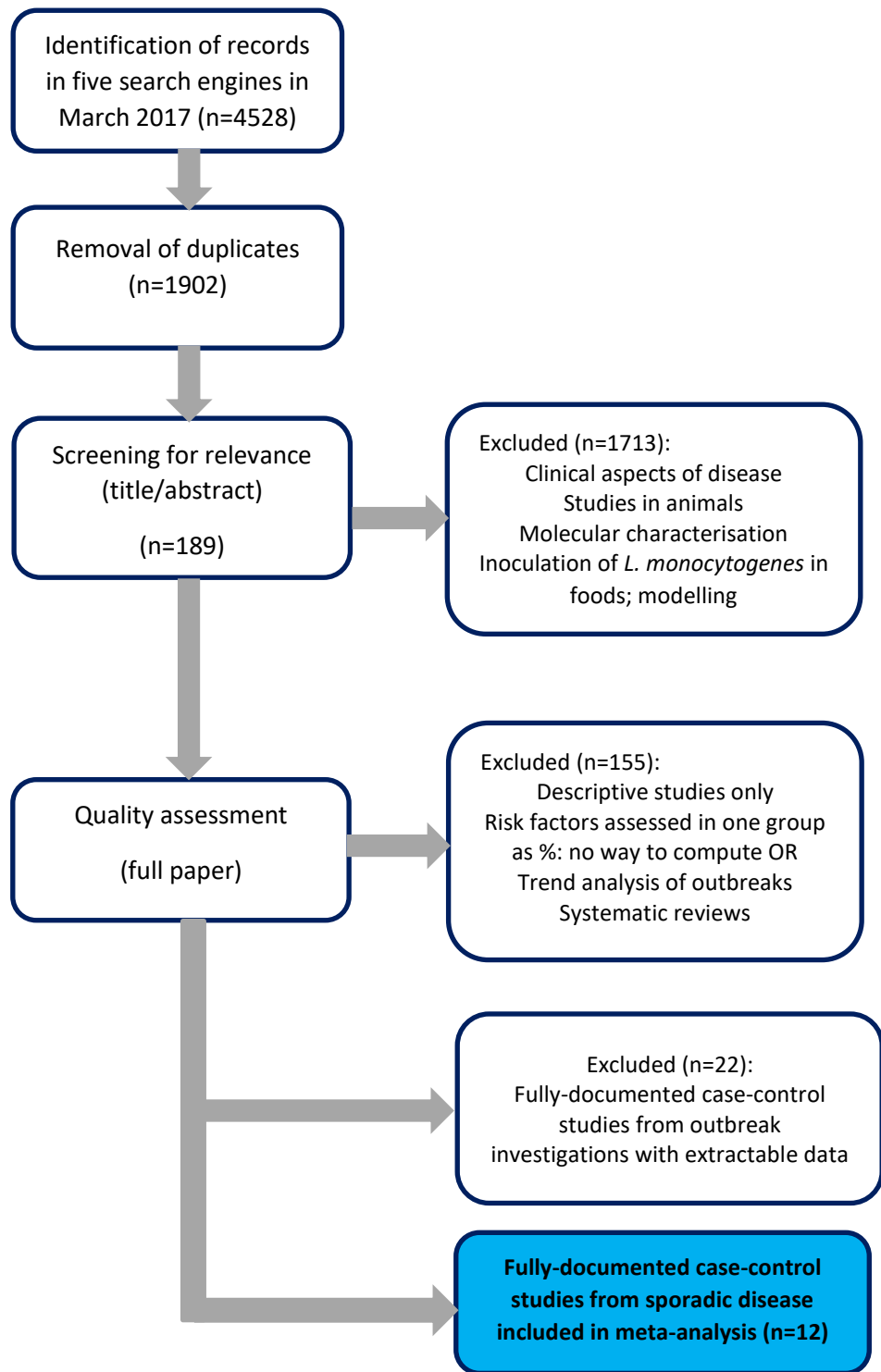
352 Table 2. Results of the meta-analysis on main risk factors

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

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

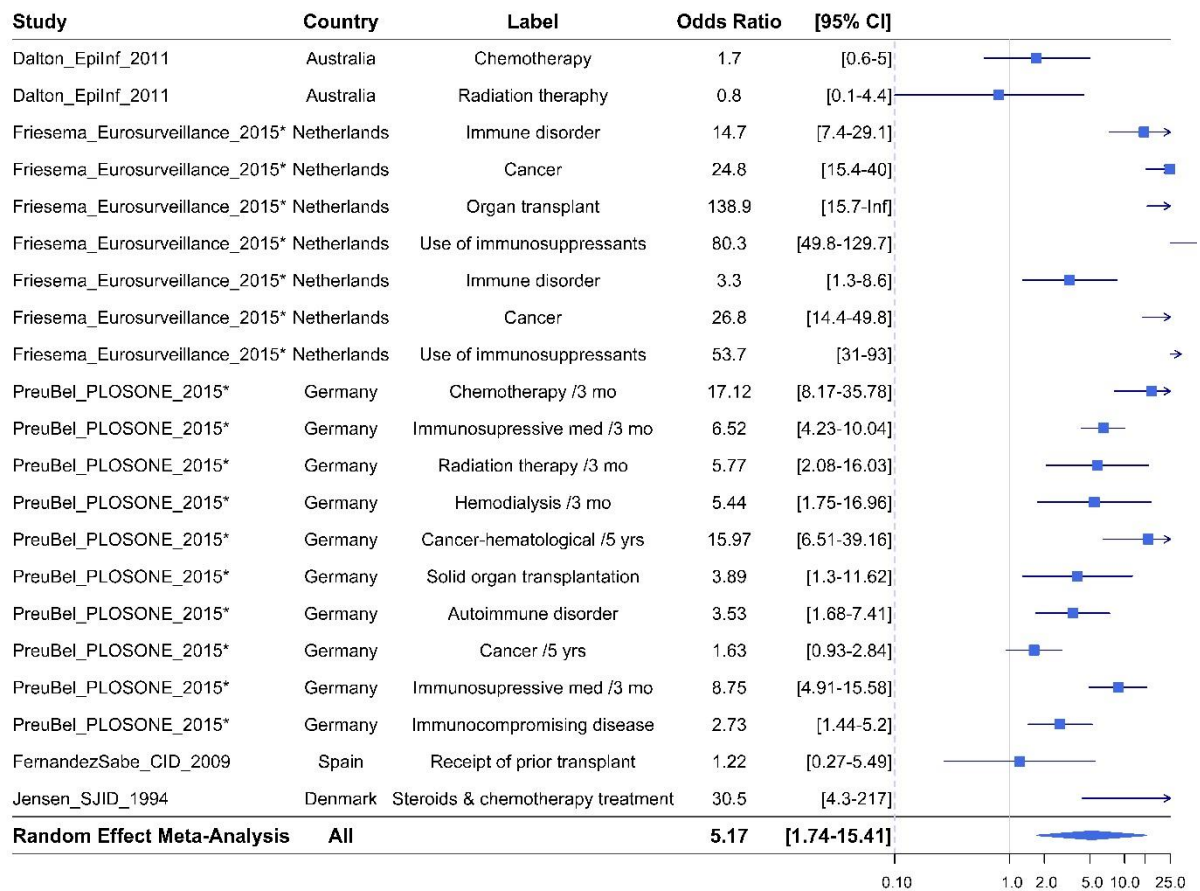
355 Table 5. Effect of food handling on the pooled OR

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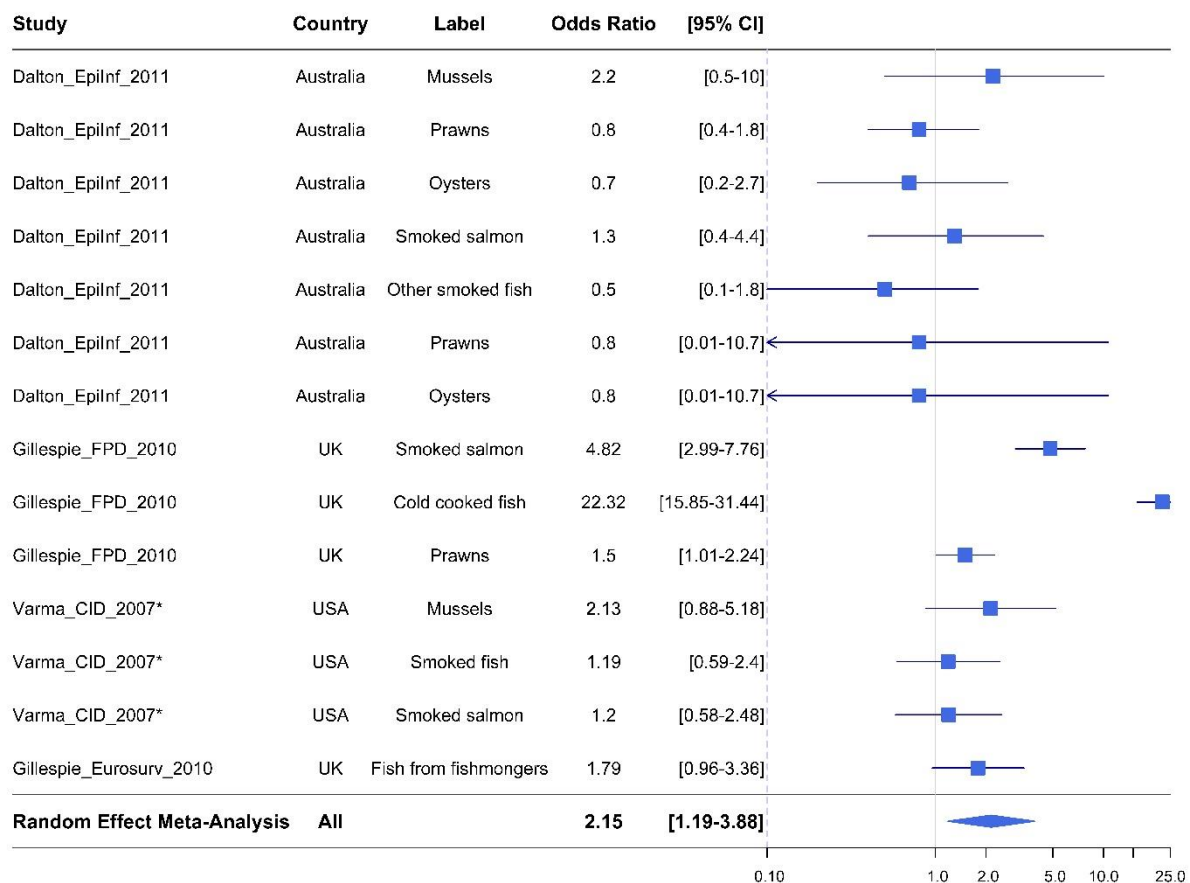
378 **Figure 1.** PRISMA flow chart for the selection of case-control studies of human listeriosis  
379 included in this meta-analysis

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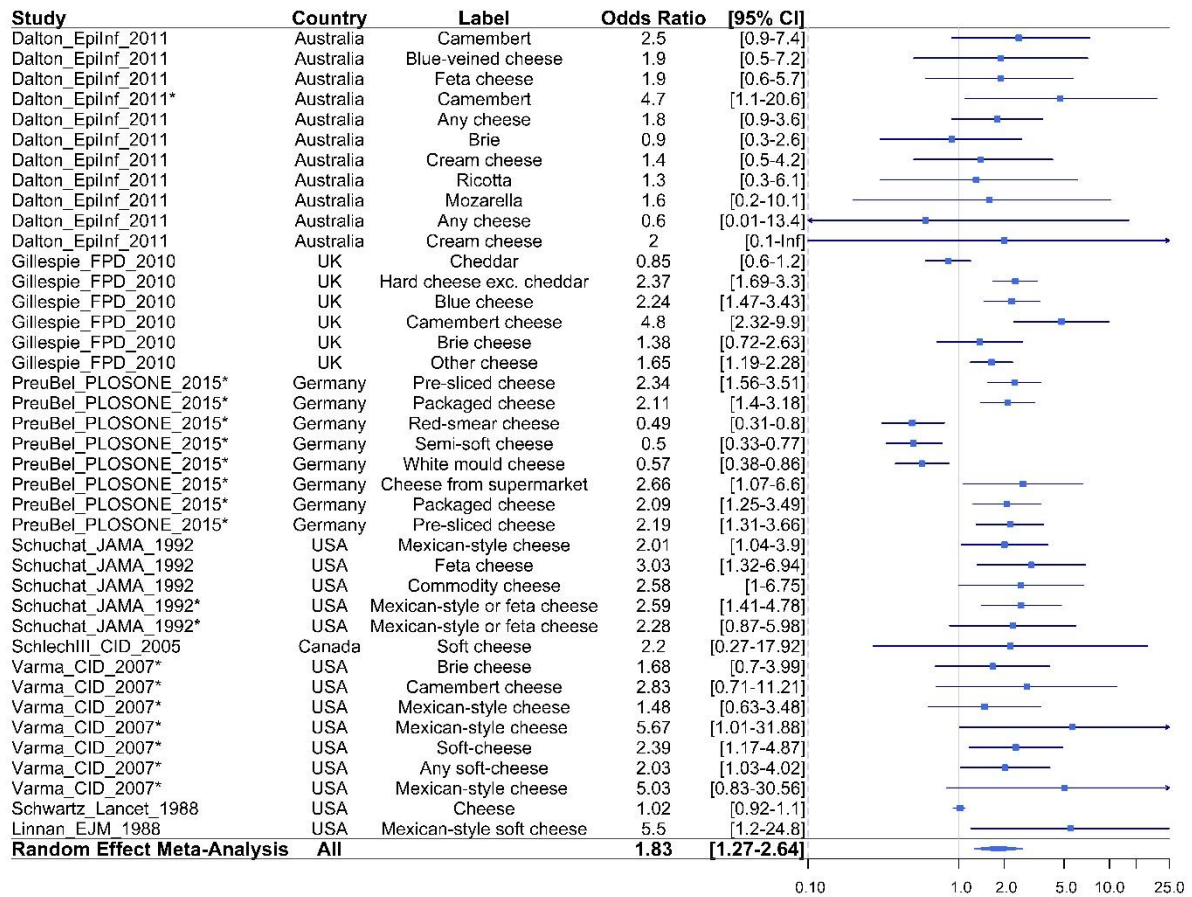
383 **Figure 2.** Forest-plot of the association of listeriosis with immunocompromising conditions in  
 384 the general susceptible population (n=21) \*adjusted OR  
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387 **Figure 3.** Forest-plot of the association of listeriosis with the consumption of seafood in the  
 388 general susceptible population (n=14) \*adjusted OR  
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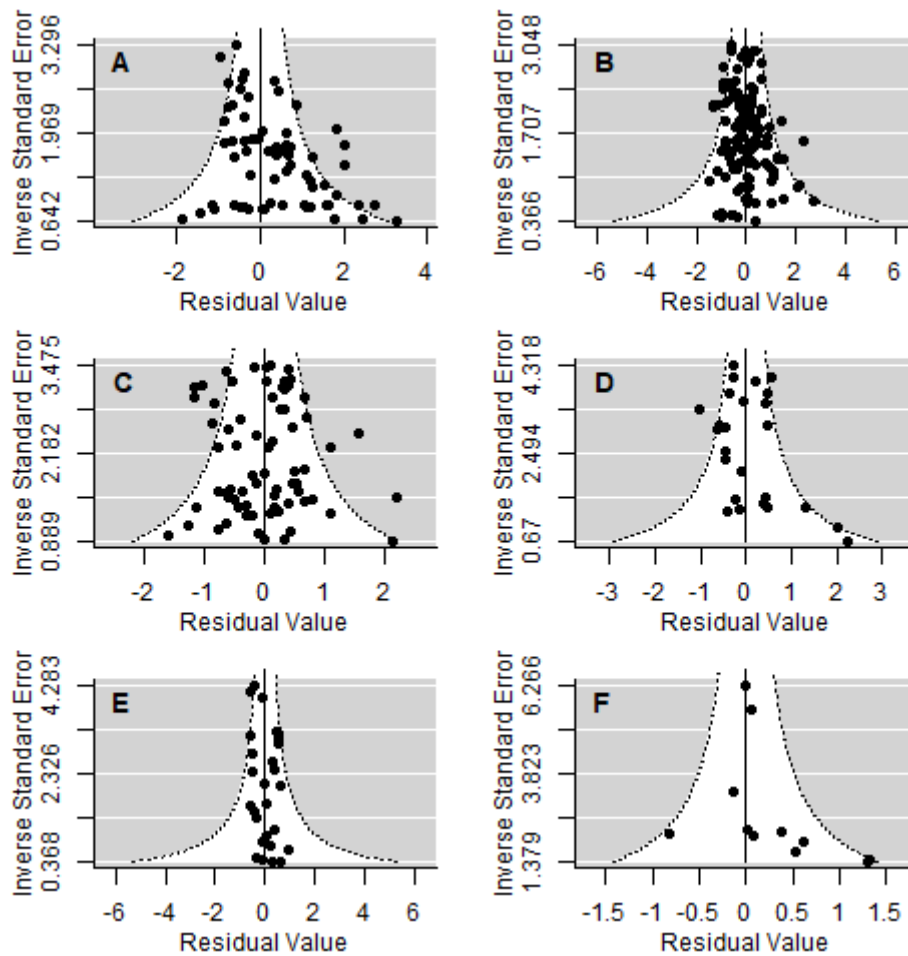


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391 **Figure 4.** Forest-plot of the association of listeriosis with the consumption of cheese in the  
 392 general susceptible population (n=40) \*adjusted OR

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396 **Figure 5:** Funnel-plots from meta-analyses investigating

- 397 A. Host-specific factors
- 398 B. Food risk factors in the general susceptible population
- 399 C. Food risk factors in the non-perinatal population
- 400 D. Meat in the general susceptible population
- 401 E. Produce in the general susceptible population
- 402 F. Composite in the general susceptible population

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

412 **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***  |
|------------------------|-------------------------------|------------------------|------|------------------------|--------------------------|-------------------|--|
| <b>Host-specific</b>   |                               |                        |      |                        |                          |                   |  |
| <b>All susceptible</b> | Other medical conditions      | 3.020 [2.326 - 3.923 ] | 8/24 | <.0001                 | <.0001                   | 0                 | $\tau^2=2.015$<br>QE(df = 61) = 437.088, p-val < .0001<br>S <sup>2</sup> =1.180<br>I <sup>2</sup> =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                 |                          |                   |  |
| <b>Food</b>            |                               |                        |      |                        |                          |                   |  |
| <b>All susceptible</b> | Produce                       | 1.415 [ 1.003 - 1.995] | 7/27 | 0.048                  | 0.001                    | 1                 | $\tau^2= 0.688$<br>QE(df = 136) = 615.478, p-val < .0001<br>S <sup>2</sup> =0.549<br>I <sup>2</sup> =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                  |                          |                   |  |
| <b>Non-perinatal</b>   | Dairy                         | 1.605 [1.187 - 2.170 ] | 4/27 | 0.002                  | 0.807                    | 1                 | $\tau^2=1.087$<br>QE(df = 69) = 439.237, p-val <.0001<br>S <sup>2</sup> =0.516<br>I <sup>2</sup> =67.80    |
|                        | Seafood                       | 2.477 [1.098 - 5.59 ]  | 3/9  | 0.029                  |                          |                   |  |

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

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

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| 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                 | $\tau^2=3.177$<br>QE(df = 77) = 410.8, p-val <.0001<br>S <sup>2</sup> =0.510<br>I <sup>2</sup> =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                 | $\tau^2=2,964$<br>QE(df = 48) = 291.1, p-val <.0001<br>S <sup>2</sup> =0.608<br>I <sup>2</sup> =83.00 |
|                 | Seafood          | 10.746 [1.541 - 74.91] | 2/4  | 0.017                  |                          |                   |   |

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

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

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| 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                 | $\tau^2=0.174$<br>QE(df = 22) = 89.90, p-val < .0001<br>S <sup>2</sup> =0.625<br>I <sup>2</sup> =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                 | $\tau^2= 0.092$<br>QE(df = 11) = 63.06, p-val <.0001<br>S <sup>2</sup> =0.277<br>I <sup>2</sup> =24.92  |
| Dairy       | All susceptible | Cheese              | 1.832 [1.270 - 2.643]  | 8/40 | 0.001                  | 0.813                    | 0                 | $\tau^2=0.305$<br>QE(df = 43) = 196.182, p-val <.0001<br>S <sup>2</sup> =0.417<br>I <sup>2</sup> =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                 | $\tau^2=0.000$<br>QE(df = 25) = 141.29, p-val <.0001<br>S <sup>2</sup> =0.396<br>I <sup>2</sup> =0.00   |
| Produce     | All susceptible | Fruits              | 1.538 [1.1431 - 2.070] | 2/11 | 0.005                  | 0.002                    | 0                 | $\tau^2=0.054$<br>QE(df = 25) = 53.736, p-val = 0.001<br>S <sup>2</sup> =0.209<br>I <sup>2</sup> =20.67 |
| Composite   | All susceptible | RTE                 | 1.486 [1.1263 - 1.960] | 2/3  | 0.005                  | <.0001                   | 0                 | $\tau^2=0.244$<br>QE(df = 9) = 24.60, p-val = 0.003<br>S <sup>2</sup> =0.397<br>I <sup>2</sup> =38.07   |

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

| 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                    | $\tau^2=0.052$<br>QE(df = 30) = 63.10, p-val = 0.001<br>S <sup>2</sup> =0.487<br>I <sup>2</sup> =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                    | $\tau^2=0.000$<br>QE(df = 9) = 5.945, p-val = 0.745<br>S <sup>2</sup> =0.226<br>I <sup>2</sup> =0.000  |
|                                 | Base                | 1.063 [ 0.820 - 1.378 ] | 2/8   | 0.645                  | -  |                   |                          |  |

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

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

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

629 • **Main risk factors**

| Population         | Risk factor      | Pooled OR [IC95%]       | N/n* |
|--------------------|------------------|-------------------------|------|
| <b>Environment</b> |                  |                         |      |
| All susceptible    | Farm environment | 3.253 [ 0.930- 11.378]  | 2/8  |
| <b>Food</b>        |                  |                         |      |
| 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

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631  
632

633 • **Ready-to-eat foods**

634

| 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

635  
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641 • **Disaggregated risk factors**

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| 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

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