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

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4 **Anne Thébault^b, Vasco Cadavez^d, Ursula Gonzales-Barron^d, Moez Sanaa^b**

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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 (τ^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

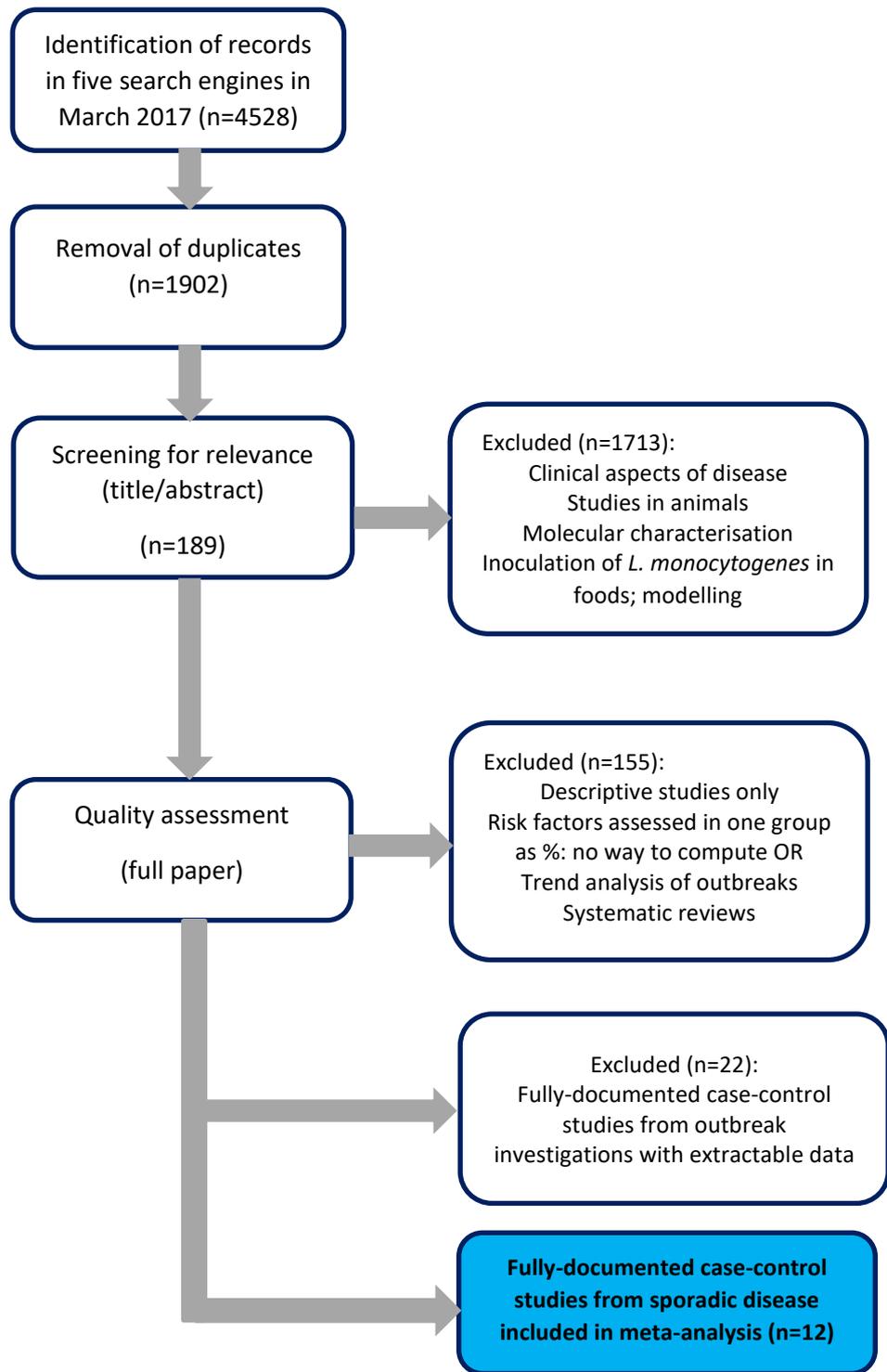
352 Table 2. Results of the meta-analysis on main risk factors

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

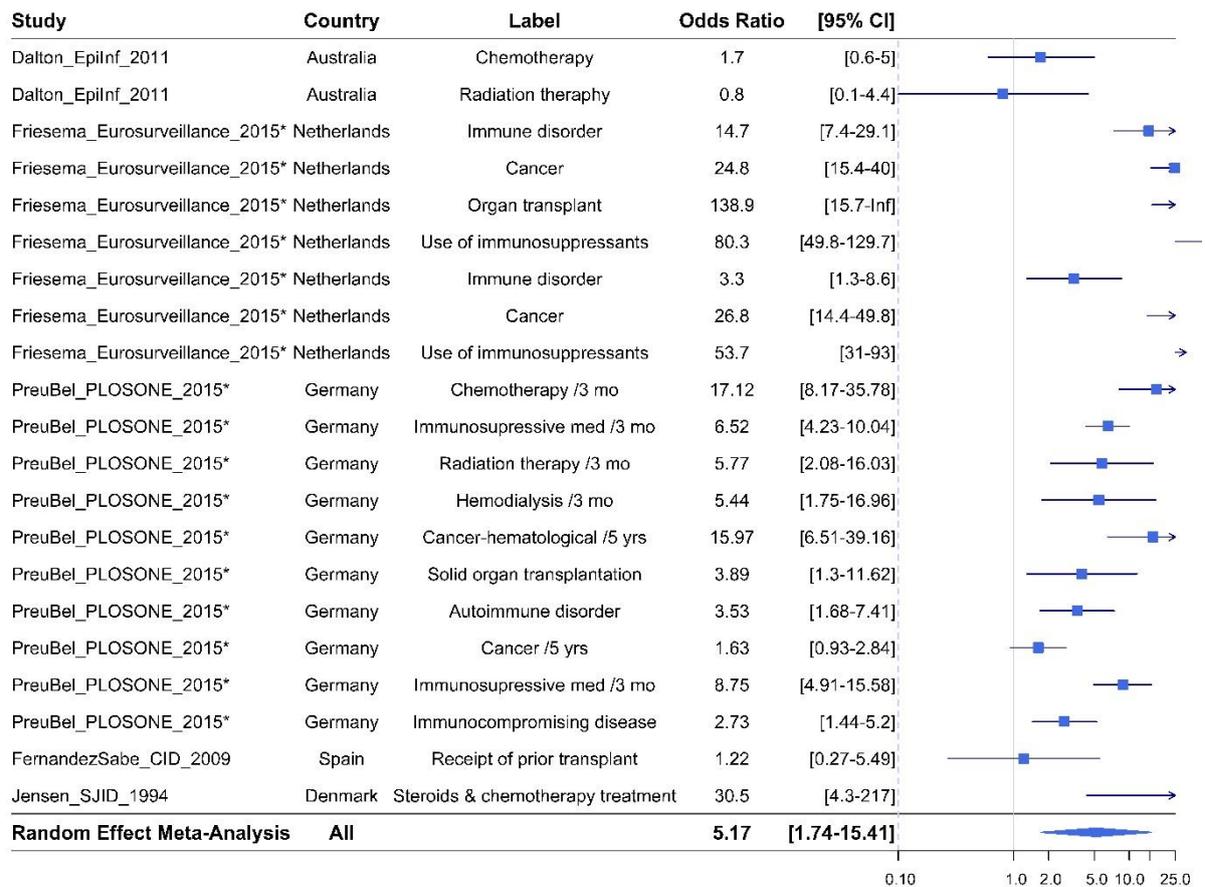
355 Table 5. Effect of food handling on the pooled OR

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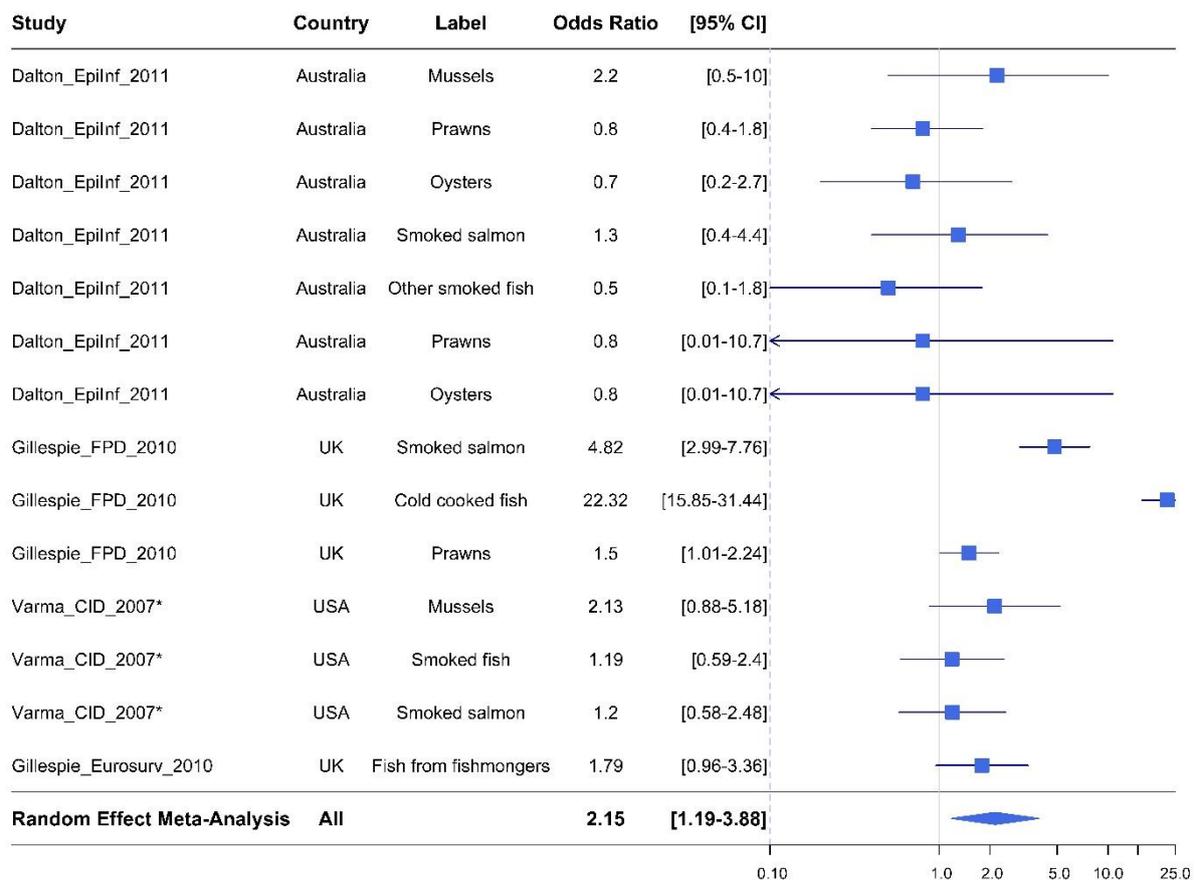
378 **Figure 1.** PRISMA flow chart for the selection of case-control studies of human listeriosis
379 included in this meta-analysis

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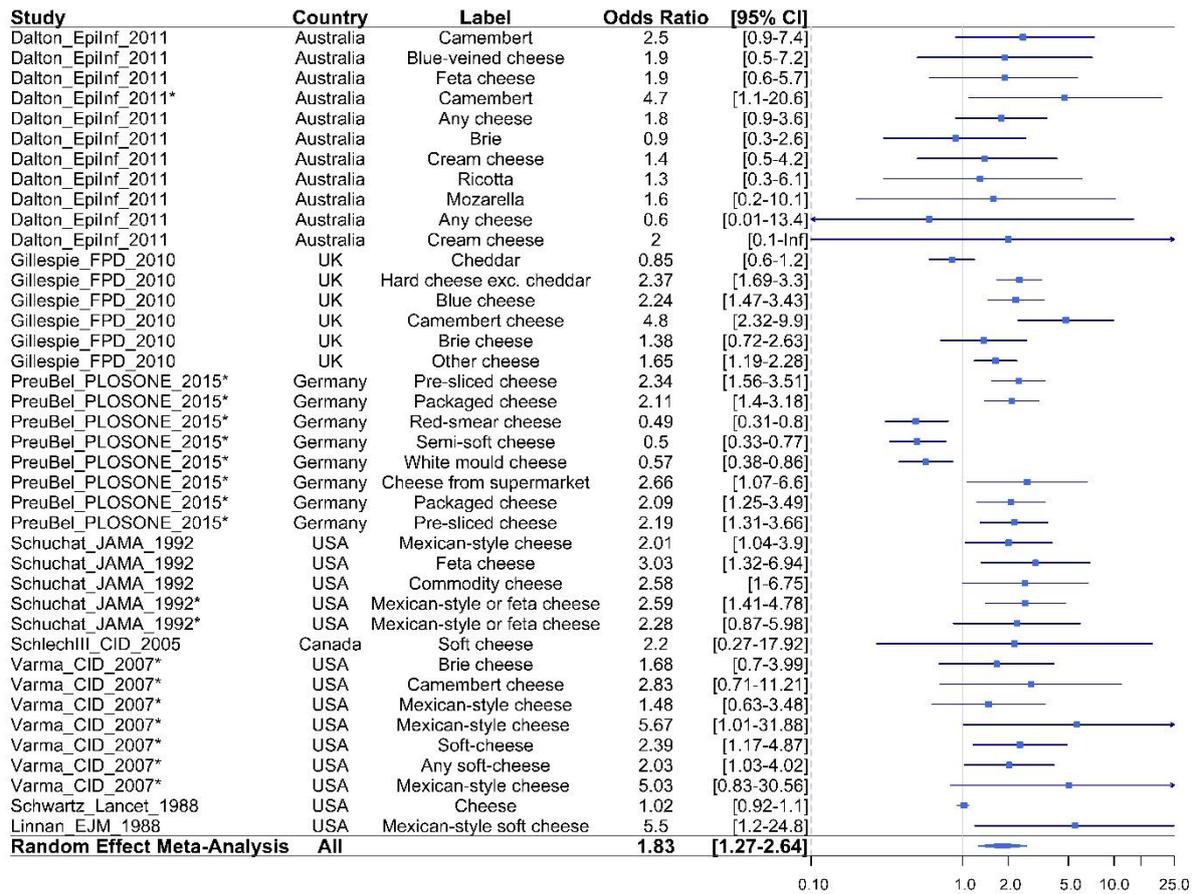
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383 **Figure 2.** Forest-plot of the association of listeriosis with immunocompromising conditions in
 384 the general susceptible population (n=21) *adjusted OR
 385



386

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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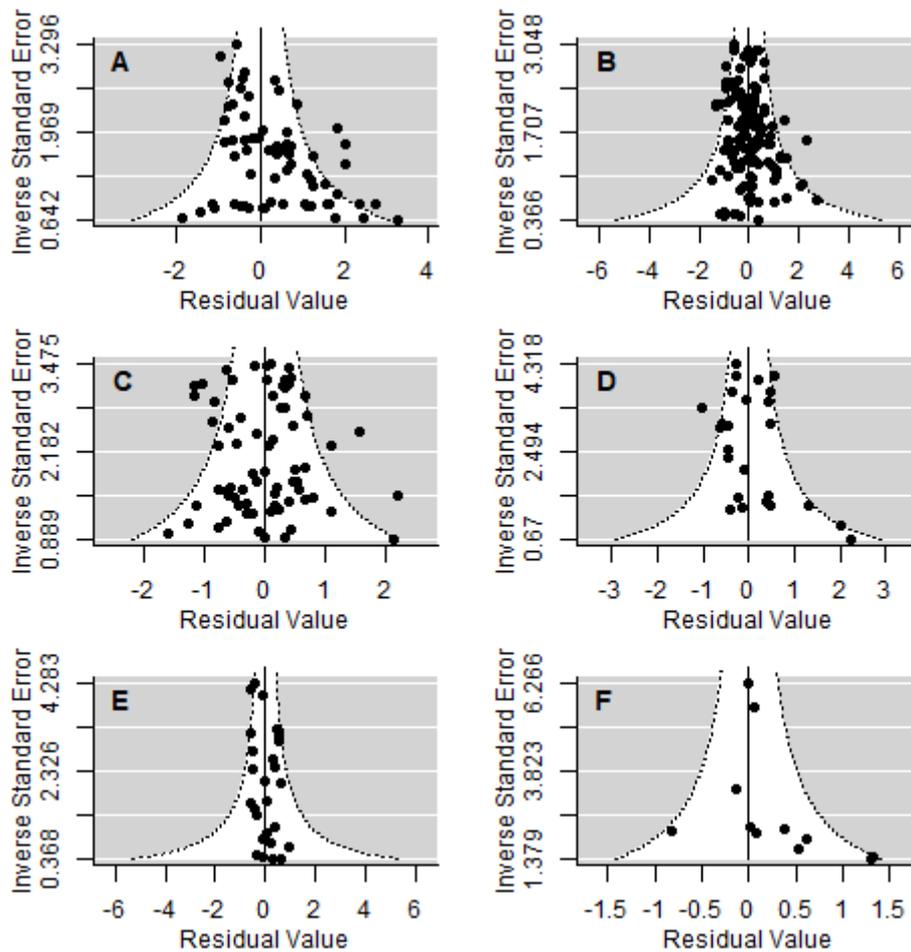


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391 **Figure 4.** Forest-plot of the association of listeriosis with the consumption of cheese in the
 392 general susceptible population (n=40) *adjusted OR

393

394



395

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

403

404

405

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)

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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***
Host-specific							
All susceptible	Other medical conditions	3.020 [2.326 - 3.923]	8/24	<.0001	<.0001	0	$\tau^2=2.015$ 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	$\tau^2= 0.688$ 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	$\tau^2=1.087$ 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			

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 (τ^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	$\tau^2=3.177$ 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	$\tau^2=2,964$ 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			

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 (τ^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	$\tau^2=0.174$ 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	$\tau^2= 0.092$ 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	$\tau^2=0.305$ 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	$\tau^2=0.000$ 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	$\tau^2=0.054$ 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	$\tau^2=0.244$ QE(df = 9) = 24.60, p-val = 0.003 S ² =0.397 I ² =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 (τ^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	$\tau^2=0.052$ 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	$\tau^2=0.000$ 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	-			

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 (τ^2), test for residual heterogeneity (QE), variance of
461 residuals (s^2), intra-class correlation (I²).

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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*
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

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633 • **Ready-to-eat foods**

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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

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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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