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Risk factors for indigenous *Campylobacter jejuni* and *Campylobacter coli* infections in The Netherlands: a case-control study

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SUMMARY

A case-control study comprising 1315 *Campylobacter jejuni* cases, 121 *Campylobacter coli* cases and 3409 frequency-matched controls was conducted in The Netherlands in 2002–2003. Risk factors for both *C. jejuni* and *C. coli* enteritis were consumption of undercooked meat and barbecued meat, ownership of cats and use of proton pump inhibitors. Consumption of chicken was a predominant risk factor for *C. jejuni* enteritis, but many additional risk factors were identified. Unique risk factors for *C. coli* infections were consumption of game and tripe, and swimming. Contact with farm animals and persons with gastroenteritis were predominant risk factors for *C. jejuni* enteritis in young children (0–4 years). Important risk factors for the elderly ($\geqslant$60 years) were eating in a restaurant, use of proton pump inhibitors and having a chronic intestinal illness. Consumption of chicken in spring, steak tartare in autumn and winter and barbecued meat in rural areas showed strong associations with *C. jejuni* infections. This study illustrates that important differences in risk factors exist for different *Campylobacter* spp. and these may differ dependent on age, season or degree of urbanization.

Key words: *Campylobacter*, epidemiology, foodborne infections, gastroenteritis.

INTRODUCTION

Annually, an estimated 4·8 million episodes of gastroenteritis occur in the Dutch population of 16 million [1]. With an estimated 80 000 cases per year, *Campylobacter* is the most common cause of bacterial gastroenteritis in The Netherlands [1, 2]. At least one out of five cases with campylobacteriosis consults a general practitioner [2–4]. About 5650 are laboratory-confirmed each year, but this number may vary up to 10% between years [5].

Apart from acute gastroenteritis, *Campylobacter jejuni* infection occasionally leads to serious sequelae such as Guillain–Barré syndrome and reactive arthritis [6, 7]. In addition, several studies have related *Campylobacter* infections to the development of irritable bowel syndrome and possibly inflammatory

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bowel disease [8–12]. Due to these complications and the high incidence, *Campylobacter* infections cause considerable morbidity and economic costs [2].

Numerous case-control studies in the past 20 years have focused on the identification of risk factors for sporadic *Campylobacter* infections, of which consumption of poultry is most frequently reported [13–20]. Other frequently reported risk factors are consumption of unpasteurized milk [14, 15, 20], eating in a restaurant [14, 17, 19, 21], contact with pets, especially puppies [13, 14, 16, 19, 22, 23], contact with farm animals [13, 14, 17, 19, 20, 23, 24] and foreign travel [13–16, 19, 21].

While these studies have contributed to the understanding of the epidemiology of campylobacteriosis, additional information may be obtained when *Campylobacter* spp. are differentiated. A case-case comparison in the UK revealed important differences in risk factors for *C. jejuni* and *C. coli* [25]. Aggregation of different species, which is done in most case-control studies, may mask important species-specific risks. In addition, risk factors may be age-related, seasonal or regional. To be able to study risk factors in these subgroups, large study sizes are needed.

Sources of *Campylobacter* and dietary habits may vary from country to country, resulting in slight differences in risk factors observed across countries. In The Netherlands, *C. jejuni* is the predominant species in broilers and dairy cattle, whereas *C. coli* is predominant in finishing pigs. In veal calves, mainly *C. coli*, but also *C. jejuni* can frequently be found [26]. Hardly any data on risk factors and transmission routes for human campylobacteriosis are available in The Netherlands.

Therefore a large case-control study, the CaSa study, was conducted to investigate risk factors for indigenous campylobacteriosis in The Netherlands, with a distinction between *C. jejuni* and *C. coli* infections. In addition, specific risk factors for *C. jejuni* according to age, season and degree of urbanization were studied. The study also aimed to quantify the contribution of different risk factors in order to predict the impact of control and intervention measures.

METHODS

A case-control study on risk factors for campylobacteriosis and salmonellosis, the CaSa study, was conducted from April 2002 to April 2003. This article is restricted to the *Campylobacter* part of the study. A detailed description of the methodology and the results of the *Salmonella* part are available elsewhere [27]. In brief, cases were laboratory-confirmed patients with a *Campylobacter* infection, identified by the Regional Public Health Laboratories (RPHL) in The Netherlands, which covers about 50% of the Dutch population for *Campylobacter*. *Campylobacter* isolates were sent to the Central Veterinary Institute for molecular confirmation of the species [28, 29].

Based on historic surveillance information on the numbers of cases with *Campylobacter* and *Salmonella* infections in the RPHL, the expected numbers of cases by age, sex, degree of urbanization and season were obtained. Controls were selected from the population registries of 25 municipalities within the service area of the RPHL by frequency matching according to the expected numbers of cases by age, sex, degree of urbanization and season. Each first working day of the month questionnaires were sent to the controls. Cases and controls received a postal questionnaire with questions regarding food consumption, kitchen hygiene and food processing, contact with animals, occupational exposure, travel, water recreation, use of medication (during the previous 4 weeks) and contact with persons with gastroenteritis symptoms. Questions covered the 7 days prior to symptom onset (cases) or completion of the questionnaire (controls).

The incidence of laboratory-confirmed *C. jejuni* and *C. coli* enteritis was calculated using the total number of cases identified from the RPHL divided by the population covered by these laboratories. Adjustments in the denominator were made for the time each laboratory participated and for underreporting by the laboratories. The latter was based on a comparison between the reported number of *Salmonella* cases in this study and the regular laboratory-based surveillance of *Salmonella*, because in The Netherlands no regular surveillance data with regional information for *Campylobacter* were available at that time.

Missing values were handled using multiple imputation [30]. Five imputed datasets were created. With these datasets, five different logistic regressions (or other analyses) were performed and the five results were pooled using SAS PROC MIANALYSE in order to obtain a single final result.

Analyses were performed using cross-tabulations, χ^2 tests and univariable logistic regression models (which also included the matching variables and level of education) for significance testing. For further

analyses, only cases and controls who had not travelled abroad were included. Variables which reached a significance level of $P \leqslant 0{\cdot}10$ in the univariable analyses were selected for inclusion in a multivariable logistic regression model. Multivariable models were developed for *C. jejuni* and *C. coli* separately. A manual backwards selection procedure was used in which variables that the likelihood ratio test gave a P value $\leqslant 0{\cdot}05$ were kept in the multivariable model. For *C. jejuni*, multivariable submodels were developed for food consumption, occupational exposure, animal contact, water recreation activities, kitchen hygiene and food processing, and contact with persons with diarrhoea or vomiting. Finally, the submodels were combined in one final model. The population attributable risk (PAR) of each risk factor in the final multivariable logistic regression models was calculated based on multivariable odds ratios (ORs) and the frequency of exposure in cases. In the same way, confidence limits of the PARs were derived from the confidence limits of the multivariable ORs.

To detect specific risk factors for *C. jejuni* according to age, season and degree of urbanization, univariable logistic regression analyses were performed for each age group (0–4, 5–17, 18–29, 30–44, 45–59, $\geqslant$60 years), season (April–June 2002, July–September 2002, October–December 2002, January–March 2003) and degree of urbanization (categorized as 'urban': $>$2500 addresses per km^2; 'urbanized': 500–2500 addresses per km^2; 'rural': $<$500 addresses per km^2). To test formally if risk factors were different between strata, we tested the interaction between age, season and degree of urbanization with the risk factor of interest for significance in a univariable logistic regression model including all *C. jejuni* cases. In these univariable analyses, only for some risk factors were differences observed in season and degree of urbanization. We therefore expanded the final multivariable model for *C. jejuni* with the interaction between these variables. For age, differences in risk factors were observed in young children (0–4 years) and the elderly ($\geqslant$60 years) compared to other age groups. We therefore developed separate multivariable models for *C. jejuni* infection in young children and the elderly.

Finally, a case-case analysis was performed in which *C. coli* patients were designated as a 'case' and *C. jejuni* patients were designated as controls. Ten cases were excluded from this analysis, because the species determination was ambiguous.

RESULTS

The RPHL identified 3178 cases with campylobacteriosis, of which nine cases did not live in The Netherlands. Of the remaining 3169 cases, 2858 (90%) were *C. jejuni* and 257 (8%) were *C. coli* cases. The overall incidences of *C. jejuni* and *C. coli* enteritis were 36 and 3/100 000 person-years, respectively, including travel-related cases (Table 1).

The incidences of *C. jejuni* and *C. coli* were clearly higher for children aged 0–4 years and during the summer. For *C. jejuni*, higher incidences were also found in young adults (18–29 years) and in urbanized places compared to urban and rural regions. For *C. coli*, higher incidences were found in the 45–59 years age group and in urban regions (Table 1).

Questionnaire response and clinical observations of cases

Of the *C. jejuni* and *C. coli* cases 1315 (46%) and 121 (47%), respectively, completed a questionnaire. The questionnaire response was higher in the 45–59 years age group (54% and 60%, respectively) and in urbanized (49% and 53%, respectively) and rural (54% and 53%, respectively) areas (Table 1). Of *C. jejuni* cases, the response was lower for children aged 0–4 years (35%) and for *C. coli* cases the response was lower for children aged 5–17 years (38%). From April to June 2002, a lower response was observed in *C. coli* cases (37%), whereas in January to April 2003, a higher response was observed (60%).

The majority of cases reported diarrhoea (96%), abdominal cramps (85%), stomach ache (75%), fever (59%), mucus in the stool (55%) and nausea (53%), whereas 40% had blood in the stool and 29% reported vomiting. *C. jejuni* cases more frequently reported diarrhoea than *C. coli* cases (97% and 92%, respectively; χ^2 test, $P = 0{\cdot}005$), as well as fever (60% and 50%, respectively; χ^2 test, $P = 0{\cdot}05$) and blood in the stool (41% and 33%, respectively; χ^2 test, $P = 0{\cdot}01$).

At the time the questionnaire was completed, 70% of the *Campylobacter* cases had recovered. The median duration of symptoms for recovered cases was 10 days [25th–75th percentile (P_{25-75}): 7–14 days]. Of the cases that had not yet recovered, the median time between symptom onset and completion of the questionnaire was 21 days for *C. jejuni* infections (P_{25-75}: 13–31 days) and 25·5 days for *C. coli* infections (P_{25-75}: 18–51 days). Of the *C. jejuni* and *C. coli* cases,

Table 1. *Incidence of* Campylobacter jejuni *and* C. coli *campylobacteriosis per 100 000 person-years and questionnaire response by demographic variables, including travel-related cases and controls and cases where species determination was ambiguous, The Netherlands, April 2002 to April 2003*

	C. jejuni cases			*C. coli* cases			Controls	
	No. (%)	Inc.	No. (%) enrolled	No. (%)	Inc.	No. (%) enrolled	No. (%)	No. (%) enrolled
Total	2858*	36	1315	257*	3	121	10 250	3409*
Age (years)								
0–4	336 (12)	68	118 (9)	22 (9)	4	11 (9)	1460 (14)	495 (15)
5–17	428 (15)	35	190 (14)	32 (12)	3	12 (10)	2056 (20)	528 (15)
18–29	601 (21)	50	273 (21)	41 (16)	3	19 (16)	2288 (22)	641 (19)
30–44	586 (21)	30	273 (21)	54 (21)	3	24 (20)	1529 (15)	761 (22)
45–59	498 (17)	31	270 (21)	62 (24)	4	37 (31)	1548 (15)	553 (16)
⩾60	382 (13)	26	190 (14)	42 (16)	3	18 (15)	1369 (13)	406 (12)
Sex								
Male	1479 (52)	38	657 (50)	121 (47)	3	61 (50)	5044 (49)	1517 (44)
Female	1321 (46)	33	658 (50)	129 (50)	3	60 (50)	5206 (51)	1878 (55)
Degree of urbanization								
Urban	573 (20)	30	224 (17)	73 (28)	4	31 (26)	2747 (27)	838 (25)
Urbanized	1601 (56)	37	792 (60)	134 (52)	3	71 (59)	6320 (62)	2092 (61)
Rural	557 (19)	33	299 (23)	36 (14)	2	19 (16)	1183 (12)	466 (14)
Season								
Apr.–June 2002	626 (22)	32	290 (22)	52 (20)	3	19 (16)	2184 (21)	760 (22)
July–Sept. 2002	1130 (40)	57	532 (40)	113 (44)	6	56 (46)	3936 (38)	1323 (39)
Oct.–Dec. 2002	628 (22)	32	299 (23)	58 (23)	3	28 (23)	2394 (23)	768 (23)
Jan.–Apr. 2003	453 (16)	23	194 (15)	30 (12)	2	18 (15)	1736 (17)	557 (16)

Inc., Incidence per 100 000 person-years.
* Totals do not always add up because of missing values.

124 (9%) and 16 (13%), respectively, were admitted to hospital (χ^2 test, $P=0{\cdot}14$).

Travel history and demography of cases and controls

In total 10 250 controls were approached and 3409 (33%) completed the questionnaire. Twenty-five controls did not provide demographic data. Of the remaining 3384 controls, 244 (7%) had travelled. Travelling abroad within 7 days prior to symptom onset was reported by 287 *C. jejuni* (22%) and 39 *C. coli* cases (32%). For nine *C. jejuni* cases, three *C. coli* cases and 21 controls, the travel history was unknown. In a univariable analysis, foreign travel was strongly associated with campylobacteriosis (*C. jejuni*: OR 3·8, 95% CI 3·2–4·7; PAR 16%, 95% CI 16–17; *C. coli*: OR 7·4, 95% CI 4·8–11·3; PAR 29%, 95% CI 26–30).

Compared to controls who had not travelled, patients with indigenous *C. jejuni* infections were more often male (50% *vs.* 44% of controls) and from rural areas (24% *vs.* 14%). They were less often from urban areas (17% *vs.* 24%). Indigenous *C. coli* patients were more often in the 45–59 years age group (30% *vs.* 16%) and returned the questionnaire more often in the summer (52% *vs.* 37%). All risk analyses were adjusted for differences in demography between cases and controls.

Risk factors for *C. jejuni* infection

Several food and non-food factors were associated with indigenous *C. jejuni* infections (Table 2). With a PAR of 28%, consumption of chicken was the most important risk factor, followed by consumption of meat prepared at a barbecue, grill or microwave oven (12%), eating in a restaurant (10%) and consumption of undercooked meat (9%). Less important risk factors were consumption of steak tartare (3%) and undercooked seafood (4%).

Of the non-food factors, strong associations were found for use of proton pump inhibitors, occupational exposure to raw meat and having one of the following chronic intestinal illnesses: inflammatory

Table 2. *Univariable and multivariable logistic regression analyses and population attributable risk of risk factors associated with indigenous* Campylobacter jejuni *campylobacteriosis. A case-control study in The Netherlands, April 2002 to April 2003*

Risk factor (% imputed missing values*)	*C. jejuni* cases ($n=1019$)	Controls ($n=3119$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)
Food consumption					
Chicken (2)	784 (77)	2197 (70)	1·5 (1·2–1·8)		28 (14–38)
April–December	657 (76)	1851 (71)	1·3 (1·1–1·6)	1·4 (1·2–1·8)	
January–March	127 (83)	346 (66)	2·7 (1·6–4·3)	3·0 (1·8–5·1)	
Pork (3)	787 (77)	2452 (79)	0·8 (0·7–1·0)		
Meat in paste (croquette, sausage roll, pastry) (5)	343 (34)	1282 (41)	0·7 (0·6–0·8)		
Sausage (5)	472 (46)	1735 (56)	0·7 (0·6–0·8)	0·8 (0·7–1·0)	
Steak tartare (7)	183 (18)	558 (18)	1·0 (0·8–1·2)		3 (1–5)
April–September	87 (14)	324 (17)	0·8 (0·6–1·0)	0·8 (0·6–1·1)	
October–March	95 (25)	234 (19)	1·4 (1·1–1·9)	1·5 (1·1–2·2)	
Meat salad (6)	181 (18)	640 (21)	0·7 (0·6–0·9)		
Tofu or other meat substitutes (7)	33 (3)	206 (7)	0·6 (0·4–0·8)		
Undercooked meat (12)	185 (18)	317 (10)	2·0 (1·6–2·5)	2·0 (1·5–2·6)	9 (6–11)
Cold meat (9)	256 (25)	939 (30)	0·8 (0·7–0·9)		
Meat prepared at a barbecue, grill or microwave oven (8)	298 (29)	628 (20)	1·7 (1·5–2·0)		12 (5–17)
Urban	37 (22)	169 (22)	1·0 (0·7–1·5)	1·0 (0·6–1·6)	
Urbanized	191 (32)	398 (21)	1·8 (1·4–2·2)	1·7 (1·3–2·2)	
Rural	70 (29)	61 (14)	2·7 (1·8–4·1)	2·9 (1·8–4·6)	
Fish (4)	359 (35)	1462 (47)	0·6 (0·5–0·7)	0·6 (0·5–0·7)	
Shellfish/crustacean (18)	135 (13)	530 (17)	0·7 (0·6–1·0)		
Undercooked seafood (7)	84 (8)	201 (6)	1·3 (1·0–1·7)	1·8 (1·2–2·7)	4 (2–5)
Products containing raw egg (3)	57 (6)	236 (8)	0·7 (0·5–1·0)		
Hard-boiled egg (4)	531 (52)	1877 (60)	0·7 (0·6–0·8)		
Pasteurized milk (2)	662 (65)	2361 (75)	0·6 (0·5–0·7)	0·8 (0·7–1·0)	
Cheese made of pasteurized milk (3)	824 (81)	2692 (86)	0·6 (0·5–0·8)		
Dairy other than cheese or milk (3)	757 (74)	2698 (86)	0·5 (0·4–0·6)	0·6 (0·5–0·7)	
Salad (3)	208 (20)	803 (26)	0·7 (0·6–0·8)	0·7 (0·6–0·9)	
Stir-fried vegetables (4)	287 (28)	1158 (37)	0·7 (0·6–0·8)	0·8 (0·6–0·9)	
Fruit with skin (3)	389 (38)	1678 (54)	0·5 (0·4–0·6)	0·6 (0·5–0·8)	
Berries (6)	61 (6)	252 (8)	0·7 (0·5–1·0)		
Home-made dressing or sauce (3)	144 (14)	588 (19)	0·8 (0·6–0·9)		
Chocolate (3)	591 (58)	2292 (73)	0·5 (0·4–0·6)	0·6 (0·5–0·7)	
Nuts (4)	364 (36)	1504 (48)	0·5 (0·5–0·6)	0·7 (0·6–0·8)	
Eating in a restaurant (1)	464 (45)	1257 (40)	1·3 (1·1–1·5)	1·3 (1·1–1·5)	10 (4–16)
Vegetarian diet (1)	15 (1)	117 (4)	0·5 (0·3–0·8)		
Animal contact					
Ownership of dogs (2)					4 (0–10)
One dog ⩾1-year-old	182 (18)	524 (17)	0·7 (0·5–0·8)	1·0 (0·8–1·2)	
One dog <1-year-old	35 (3)	59 (2)	1·1 (0·7–1·8)	1·8 (1·0–3·0)	
Several dogs, all ⩾1 year old	50 (5)	84 (3)	1·2 (0·8–1·6)	1·7 (1·1–2·6)	
Several dogs, at least one dog <1-year-old	17 (2)	17 (1)	1·8 (1·0–3·2)	2·8 (1·3–6·1)	
Ownership of cats (1)	271 (27)	682 (22)	1·4 (1·2–1·6)	1·3 (1·1–1·6)	7 (2–10)
Visiting animals outside the household (3)					
Visiting a dog	198 (19)	801 (26)	0·7 (0·6–0·8)	0·7 (0·6–0·9)	
Visiting a cat	129 (13)	571 (18)	0·7 (0·6–0·9)	0·7 (0·6–0·9)	

Table 2 (*cont.*)

Risk factor (% imputed missing values*)	*C. jejuni* cases ($n=1019$)	Controls ($n=3119$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)
Recent use of medication					
Antibiotics (0)	23 (2)	105 (3)	0·7 (0·4–1·1)		
Proton pump inhibitors (0)	103 (10)	69 (2)	4·8 (3·4–6·6)	4·3 (2·9–6·2)	8 (7–9)
H2 antagonists (0)	16 (2)	23 (1)	2·2 (1·2–4·3)		
Kitchen hygiene					
Preparing meat other than chicken, pork or beef in the household (2)	121 (12)	440 (14)	0·8 (0·6–1·0)		
Changing dish cloth less often than once a week (1)	116 (11)	418 (15)	0·8 (0·6–1·0)	0·7 (0·6–1·0)	
Not cleaning a knife when using it for raw meat and other foods (4)	57 (6)	97 (3)	1·7 (1·2–2·5)	1·5 (1·0–2·3)	2 (0–3)
Other					
Having IBD, IBS or coeliac disease	48 (5)	49 (2)	3·4 (2·1–5·4)	2·6 (1·5–4·4)	3 (2–4)
Occupational exposure to raw meat (6)					2 (0–3)
Cook	20 (2)	23 (1)	2·6 (1·4–4·8)	2·0 (1·0–4·2)	
Butcher	12 (1)	14 (0)	2·7 (1·2–5·9)	2·5 (1·1–5·8)	
Other	9 (1)	25 (1)	1·1 (0·5–2·6)	1·0 (0·4–2·4)	
Contact with persons with gastroenteritis symptoms outside the household	122 (12)	327 (10)	1·3 (1·0–1·6)	1·5 (1·1–1·9)	4 (1–6)

CI, Confidence interval; OR, odds ratio; PAR, population attributable risk; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

* Fraction of imputed missing values in cases and controls together.

† Adjusted for age, sex, degree of urbanization and level of education.

‡ Based on the multivariable odds ratio.

bowel disease (IBD), irritable bowel syndrome (IBS) or coeliac disease. However, because only limited numbers of cases were exposed to these risk factors, the corresponding PARs were relatively low. Ownership of dogs, especially several young dogs, and ownership of cats were identified as risk factors with relatively low PARs.

For some risk factors significant differences were observed between seasons and degrees of urbanization: consumption of chicken in the spring was more strongly associated with *C. jejuni* infections than in the rest of the year; consumption of steak tartare was only a risk factor in autumn and winter and meat prepared at a barbecue, grill or microwave oven was a stronger risk factor in rural areas compared to urban areas.

Many exposures were negatively associated with *C. jejuni* campylobacteriosis, such as consumption of sausage, fish, pasteurized milk, fruit, salad, stir-fried vegetables, chocolate and nuts and visiting dogs or cats outside the household (Table 2).

Risk factors for *C. jejuni* infection in young children and the elderly

In Table 3 the results of the separate risk analyses for young children (0–4 years) and the elderly ($\geqslant 60$ years) are displayed. Consumption of undercooked meat and meat prepared at a barbecue, grill or microwave oven remained risk factors in these age-specific models. Visiting farm animals, contact with persons with gastroenteritis symptoms and ownership of farm animals were predominant risk factors for *C. jejuni* enteritis in young children: an estimated 19%, 12% and 9% of the cases in this age group were attributable to these factors, respectively. Consumption of products containing raw egg was a unique risk factor for young children and was not associated with illness in any other age group. Predominant risk factors for *C. jejuni* enteritis in the elderly were eating in a restaurant (PAR 19%), use of proton pump inhibitors (PAR 14%) and having a chronic

Table 3. *Univariable and multivariable logistic regression analyses of risk factors associated with indigenous* Campylobacter jejuni *campylobacteriosis in the very young (0–4 years) and the elderly (⩾60 years). A case-control study in The Netherlands, April 2002 to April 2003*

Risk factor (% imputed missing values*)	*C. jejuni* cases aged 0–4 years					*C. jejuni* cases aged ⩾60 years				
	Cases ($n=105$)	Controls ($n=467$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)	Cases ($n=147$)	Controls ($n=382$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)
Food consumption										
Meat in paste (croquette, sausage roll, pastry) (5)	24 (23)	157 (34)	0·5 (0·3–0·9)	0·5 (0·3–0·9)		38 (26)	118 (31)			
Sausage (5)	48 (46)	267 (75)	0·6 (0·4–1·0)			65 (44)	198 (52)	0·7 (0·5–1·0)		
Undercooked meat (12)	9 (8)	14 (3)	3·1 (1·2–8·1)	3·2 (1·0–10·1)	6 (0–7)	24 (16)	44 (11)	1·6 (0·9–2·8)	2·2 (1·1–4·3)	9 (2–12)
Cold meat (9)	18 (17)	97 (21)				31 (21)	117 (31)	0·6 (0·3–0·9)	0·4 (0·2–0·8)	
Meat prepared at a barbecue, grill or microwave oven (8)	23 (22)	60 (13)	1·9 (1·1–3·3)	2·1 (1·2–3·8)	11 (3–16)	29 (20)	37 (10)	2·3 (1·3–4·1)	2·2 (1·1–4·5)	11 (2–15)
Fish (4)	34 (33)	187 (40)				77 (53)	257 (67)	0·5 (0·4–0·8)	0·6 (0·3–0·9)	
Hard-boiled egg (4)	50 (47)	239 (51)				82 (56)	267 (70)	0·5 (0·3–0·9)		
Products containing raw egg (3)	11 (11)	15 (3)	3·8 (1·6–8·7)	4·5 (1·8–11·5)	8 (5–10)	8 (6)	15 (4)			
Unpasteurized milk (2)	4 (4)	8 (2)	2·6 (0·7–9·0)			13 (9)	20 (5)	2·0 (0·9–4·2)		
Cheese made of pasteurized milk (3)	64 (61)	336 (72)	0·6 (0·4–0·9)	0·5 (0·3–0·9)		133 (90)	364 (95)	0·4 (0·2–1·0)		
Dairy products other than milk and cheese (3)	91 (86)	416 (89)				101 (69)	313 (82)	0·5 (0·3–0·7)	0·5 (0·3–0·9)	
Ready-to-eat sandwich (4)	13 (12)	36 (8)				17 (11)	22 (6)	2·1 (1·0–4·4)	2·7 (1·1–6·6)	7 (1–10)
Raw vegetables (3)	41 (39)	182 (39)				83 (57)	272 (71)	0·5 (0·3–0·8)		
Stir-fried vegetables (4)	23 (22)	123 (26)				30 (20)	127 (33)	0·5 (0·3–0·8)	0·5 (0·3–0·8)	
Fruit (3)	31 (30)	168 (36)				42 (29)	167 (44)	0·5 (0·3–0·7)	0·5 (0·3–0·8)	
Home-made dressing or sauce (3)	9 (8)	46 (10)				13 (9)	61 (16)	0·5 (0·2–0·9)	0·4 (0·2–1·0)	
Chocolate (3)	19 (18)	123 (26)	0·7 (0·4–1·0)			79 (53)	280 (73)	0·4 (0·3–0·6)	0·4 (0·3–0·7)	
Nuts (4)	17 (16)	85 (18)				65 (44)	229 (60)	0·5 (0·3–0·8)		
Eating in a restaurant (1)	464 (45)	1257 (40)	0·6 (0·3–1·1)	0·5 (0·3–1·0)		44 (30)	65 (17)	2·1 (1·3–3·3)	2·8 (1·6–4·9)	19 (11–24)
Animal contact										
Ownership of dogs (1)	30 (28)	87 (19)	1·6 (1·0–2·7)							
Ownership of cats (1)	34 (32)	108 (23)	1·7 (1·1–2·8)							
Ownership of farm animals (2)	15 (14)	23 (5)	2·6 (1·2–5·4)	2·8 (1·2–6·4)	9 (3–12)	13 (9)	14 (4)	2·3 (1·0–5·3)	2·6 (1·0–6·6)	5 (0–8)
Visiting farm animals outside the household (3)	34 (32)	88 (19)	2·1 (1·3–3·6)	2·4 (1·4–4·4)	19 (9–25)	27 (18)	109 (28)	0·6 (0·3–0·9)		
Contact with animal faeces (6)	17 (16)	54 (11)				9 (6)	41 (11)	0·5 (0·2–1·1)		

Table 3 (*cont.*)

Risk factor (% imputed missing values*)	*C. jejuni* cases aged 0–4 years					*C. jejuni* cases aged ⩾60 years				
	Cases ($n=105$)	Controls ($n=467$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)	Cases ($n=147$)	Controls ($n=382$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)
Other										
Use of proton pump inhibitors (0)	0 (0)	0 (0)				32 (22)	28 (7)	3·6 (2·0–6·2)	2·9 (1·5–5·7)	14 (7–18)
Having a chronic intestinal illness (1)	7 (7)	17 (4)				33 (23)	45 (12)	2·4 (1·4–4·0)	2·7 (1·5–5·0)	14 (7–18)
Contact with persons with gastroenteritis symptoms outside the household (20)	21 (20)	38 (8)	2·8 (1·3–5·8)	2·5 (1·1–5·6)	12 (3–16)					

CI, Confidence interval; OR, odds ratio; PAR, population attributable risk.
* Fraction of imputed missing values in *C. jejuni* cases and controls of all ages together.
† Adjusted for sex, degree of urbanization and level of education.
‡ Based on the multivariable odds ratio.

intestinal illness (PAR 14%). Consumption of ready-to-eat sandwiches was a unique risk factor for the elderly.

Risk factors for *C. coli* infection

Consumption of undercooked meat, meat prepared at a barbecue, grill or microwave oven, ownership of cats and use of proton pump inhibitors were not only identified as risk factors for indigenous *C. jejuni* campylobacteriosis, but also for indigenous *C. coli* campylobacteriosis (Table 4). For *C. coli* infections, consumption of game, tripe and foods bought from a stall, e.g. a mobile caterer or market stall, and swimming were also identified as risk factors. The PAR was highest for consumption of undercooked meat (25%), followed by consumption of meat prepared at a barbecue, grill or microwave (19%), use of proton pump inhibitors (18%), ownership of cats (15%) and swimming (14%).

Case-case comparison

The case-case analysis highlighted the differences in risks between *C. coli* and *C. jejuni* infections (Table 5). Compared to *C. jejuni* infections, consumption of poultry other than chicken, tripe and undercooked meat were strongly associated with *C. coli* infections, as well as eating foods bought from a stall, contact with animals outside the household and swimming.

DISCUSSION

This is the first case-control study of risk factors for sporadic *C. jejuni* and *C. coli* campylobacteriosis in The Netherlands. Extrapolation of the incidences of these species found in this study, according to the Dutch population at 1 January 2003, yields an estimate of 5829 and 527 laboratory-confirmed cases, respectively, and a total of around 81 300 and 7350 community cases, respectively, per year [1, 2].

We included a large number of cases and controls in this study, enabling us to study risk factors for different *Campylobacter* spp. and age-, season- and urbanization-specific risk factors for *C. jejuni* enteritis. The PAR provided information about the impact of each risk factor on the incidence, whereas the OR provided information about the individual risk of infection after exposure. In general, in order to reduce *Campylobacter* incidence, the highest impact may be expected from public health interventions targeted at those risk factors displaying the highest PARs.

Table 4. *Univariable and multivariable logistic regression analyses and population attributable risk of risk factors associated with indigenous* Campylobacter coli *campylobacteriosis. A case-control study in The Netherlands, April 2002 to April 2003*

Risk factor (% imputed missing values*)	*C. coli* cases ($n=79$)	Controls ($n=3119$)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)	PAR‡ (95% CI)
Food consumption					
Fowl other than chicken (22)	15 (19)	322 (10)	2·0 (1·1–3·6)		
Pork (3)	54 (68)	2452 (79)	0·5 (0·3–0·8)	0·5 (0·3–1·0)	
Game (8)	7 (8)	97 (3)	2·7 (1·1–6·4)	3·1 (1·2–8·2)	5 (1–7)
Tripe (7)	4 (5)	43 (1)	3·9 (1·3–11·5)	4·9 (1·5–1·6)	4 (2–5)
Sausage (4)	30 (37)	1735 (56)	0·5 (0·3–0·8)	0·5 (0·3–0·9)	
Undercooked meat (7)	25 (31)	317 (10)	4·2 (2·4–7·5)	4·6 (2·3–9·3)	25 (18–28)
Meat prepared at a barbecue, grill or microwave oven (7)	27 (34)	628 (20)	2·3 (1·2–4·4)	2·3 (1·1–4·9)	19 (2–27)
Fish (3)	25 (31)	1462 (47)	0·4 (0·3–0·7)	0·4 (0·2–0·6)	
Dairy products other than milk and cheese (2)	57 (73)	2698 (86)	0·4 (0·3–0·8)	0·5 (0·3–1·0)	
Raw vegetables (2)	46 (58)	2111 (68)	0·6 (0·4–0·9)		
Chocolate (2)	44 (56)	2292 (73)	0·5 (0·3–0·8)	0·5 (0·3–0·9)	
Nuts (3)	23 (29)	1504 (48)	0·3 (0·2–0·6)	0·5 (0·3–0·8)	
Foods bought at a stall (1)	14 (18)	349 (11)	1·7 (0·9–3·1)	2·2 (1·1–4·3)	10 (2–14)
Other					
Swimming (3)	21 (27)	634 (20)	2·0 (1·1–3·4)	2·0 (1·1–3·7)	14 (2–20)
Ownership of cats (1)	24 (30)	682 (22)	1·7 (1·0–2·8)	2·0 (1·1–3·4)	15 (4–22)
Having asthma (2)	12 (15)	274 (9)	2·0 (1·1–2·8)		
Having a chronic intestinal illness (1)	18 (23)	214 (7)	3·8 (2·2–6·7)		
Use of proton pump inhibitors (0)	16 (20)	69 (2)	9·2 (4·8–17·5)	9·5 (4·4–20·3)	18 (16–19)

CI, Confidence interval; OR, odds ratio; PAR, population attributable risk.
* Fraction of imputed missing values in *C. coli* cases and controls together.
† Adjusted for age, sex, degree of urbanization and level of education.
‡ Based on the multivariable odds ratio.

Based on the PAR, the dominant risk factor for *C. jejuni* enteritis was consumption of chicken. The higher risk from consumption of chicken in spring was unexpected. We hypothesized that the risk of chicken consumption would be higher in the summer, because the prevalence of *Campylobacter* in broilers peaks in the summer months, corresponding with a peak in *Campylobacter*-contaminated poultry products in this period [31]. It is conceivable that in spring chickens encounter uncommon *Campylobacter* strains from the environment for which humans do not yet have protective immunity.

Consumption of steak tartare, a raw beef product, was associated with illness in autumn and winter only. In recent years, we experienced several outbreaks of Shiga toxin-producing *Escherichia coli* (STEC) and *Salmonella* due to consumption of steak tartare in The Netherlands, all occurring in autumn and winter [32–34]. The risk of contamination of steak tartare may not only be confined to *Salmonella* and STEC and may also include *Campylobacter*. However, because *Campylobacter* is not able to multiply in foods and has a longer and more variable incubation period, contamination would less often lead to outbreaks. In addition, it has been shown that pork, beef and veal products are rarely *Campylobacter* contaminated and where contamination exists, it is at a low dose [35].

Consumption of undercooked seafood was associated with an increased risk of *C. jejuni* infection, as was also found in the Foodnet case-control study [14]. Although *Campylobacter* has been isolated from shellfish and crustaceans [36], the predominant species identified was *C. lari* [37]. The risk of undercooked seafood consumption may also mirror the effect of cross-contamination of undercooked food products in general.

Healthy cats and dogs are carriers of different *Campylobacter* spp. and high prevalences of

Table 5. *Case-case comparison of* Campylobacter coli *and* C. jejuni *campylobacteriosis: Univariable and multivariable logistic regression analyses of risk factors for* C. coli *campylobacteriosis. A case-control study in The Netherlands, April 2002 to April 2003*

Risk factor (% imputed missing values*)	*C. jejuni* cases ($n=1009$‡)	*C. coli* cases ($n=69$‡)	Univariable OR† (95% CI)	Multivariable OR† (95% CI)
Food consumption				
Poultry other than chicken (29)	93 (9)	13 (19)	2·3 (1·2–4·6)	2·4 (1·2–4·8)
Game (8)	27 (3)	6 (9)	3·7 (1·4–9·5)	
Tripe (8)	20 (2)	4 (6)	3·1 (1·0–9·8)	3·5 (1·0–12·0)
Sausage (7)	467 (46)	25 (36)	0·7 (0·4–1·2)	0·5 (0·3–0·9)
Undercooked meat (29)	181 (18)	21 (31)	2·1 (1·1–4·0)	1·9 (1·0–3·6)
Eating foods bought at a stall (2)	109 (11)	14 (20)	2·1 (1·1–3·9)	2·0 (1·0–3·9)
Contact with animals				
Contact with animals outside the household (5)	267 (27)	24 (35)	1·9 (1·1–3·3)	1·9 (1·1–3·3)
Water activities				
Swimming (5)	192 (19)	18 (26)	2·2 (1·2–4·1)	2·0 (1·1–3·9)
Medication in previous 4 weeks				
Proton pump inhibitors (0)	102 (10)	15 (22)	1·9 (1·0–3·6)	
Kitchen hygiene				
Length of work top (3)				
<1 m	14 (1)	4 (6)	3·5 (1·0–11·5)	
1–2 m	360 (36)	31 (45)	1·0	
>2 m	635 (63)	34 (50)	0·6 (0·4–1·1)	

CI, Confidence interval; OR, odds ratio.
* Fraction of imputed missing values in *C. coli* and *C. jejuni* cases together.
† Adjusted for age, sex, degree of urbanization and level of education.
‡ Cases where species determination was ambiguous are excluded from the analyses.

Campylobacter are found in young animals and animals with diarrhoea [38–40]. This corresponds well with our observation that having dogs and especially several young dogs poses a risk for *C. jejuni* enteritis and ownership of cats is a risk for both *C. jejuni* and *C. coli* enteritis.

Use of proton pump inhibitors has previously been associated with *Campylobacter* infections [16] and was identified as a risk factor for *Salmonella* infections in The Netherlands [27]. The neutralization of gastric acid by anti-secretory drugs may facilitate *Campylobacter* (and other bacteria) to survive this hostile environment. The current study showed that the use of these drugs is frequent in the elderly, resulting in a relatively high PAR in this age group.

Chronic intestinal illnesses such as IBD, IBS and coeliac disease appeared to increase the risk for *C. jejuni* infections, which suggests that patients with these chronic diseases are more susceptible to infection. This seems paradoxical to observations of other studies that indicated that gastrointestinal infections may be a cause of chronic intestinal illnesses [8–12]. However, it is conceivable that patients with IBD or IBS have a disturbed intestinal function which may facilitate enteric pathogens to cause infection. Especially in elderly cases, chronic intestinal illnesses, also including other illnesses than those mentioned above, were prevalent and a relatively high proportion of elderly cases were attributable to this risk factor.

Occupational exposure to raw meat was strongly associated with *C. jejuni* infections. Due to the low frequency of exposure in cases, the corresponding PAR remained low. A large public health impact from regulations to reduce transmission of *Campylobacter* for persons working with raw meat is therefore unexpected, but the regulations may have impact at the individual level and may reduce illness and absence from work.

Person-to-person transmission of *Campylobacter* is considered uncommon. However, a Danish study showed that household outbreaks of *Campylobacter*

are more common than expected [41]. This raises the question whether all of these outbreaks are related to a common source exposure or whether person-to-person transmission to some extent may play a role. The risk of contact with persons with gastroenteritis symptoms outside the household found in the current study was particularly pronounced in young children, which may be in favour of the hypothesis that person-to-person transmission is more common than believed.

In studies focusing on risk factors for children with *Campylobacter* infections, contact with farm animals has been associated with illness [14, 23]. In our study, based on the PAR estimates, we concluded that contact with farm animals is the dominant source of infection in children.

Cross-contamination and poor kitchen hygiene within the household is considered to play a major role in the transmission of *Campylobacter*. However, this is difficult to measure in a case-control study, since questionnaires may not be adequate to measure these risks and study participants may not be willing to disclose unhygienic behaviour. In the current study, many questions about kitchen hygiene were asked. Of these, only using a knife for raw meat and other foods without cleaning was found as a risk factor for *C. jejuni* infections. This indicates that poor kitchen hygiene does play a role in the transmission and it is likely that the true association is underestimated in this study.

The unique association between consumption of ready-to-eat sandwiches and *C. jejuni* infections in the elderly may also mirror cross-contamination, since the preparation of ready-to-eat sandwiches involves considerable handling of food.

Consumption of products containing raw egg was a risk factor for young children only. In a previous study, consumption of mayonnaise, possibly made of raw egg, was associated with *Campylobacter* infections in infants [23]. Since contamination of eggs with *Campylobacter* is very unlikely [42], this finding might be the result of cross-contamination.

Drinking unpasteurized milk has been identified as a risk factor for sporadic *Campylobacter* infections [14, 15, 19, 20] and outbreaks [43, 44]. Although Dutch outbreaks of *C. jejuni* due to unpasteurized milk are also described [45, 46], it was not identified as a risk factor in the current study.

Some distinct risk factors were found for *C. coli* infections, compared to *C. jejuni* infections. The risk of consumption of the internal organs of animals, e.g. tripe, for *C. coli* enteritis has been confirmed in a previous study [25]. Swimming was an important risk factor for *C. coli* infections. In a Dutch investigation, *Campylobacter* spp. was found in 58–92% of the samples of recreational water, with *C. jejuni*, *C. coli* and *C. lari* found in equal amounts [47]. In our study, a higher proportion of *C. coli* cases swam in open water or the sea compared to controls, who more often swam in swimming pools (data not shown).

Consumption of pork was associated with a reduced risk for *C. coli* campylobacteriosis, although *C. coli* is highly prevalent in finishing pigs [26]. On the other hand it has been shown that *Campylobacter* contamination of red meat is rare and contamination involves low doses [35].

A variety of foods were negatively associated with *C. jejuni* and *C. coli* infections. Such 'protective' effects have been observed in many previous case-control studies [13, 15, 18]. Frequently mentioned explanations are differences in food preferences or immune status between cases and controls, statistical coincidences or bias. For fruits and vegetables it has been proposed that consumption may have a truly protective effect, as these foods contain high levels of antioxidants and carotenoids which inhibit bacterial growth and enhance general immunity to infection. In addition, these foods may alter the intestinal microflora in a way that would prevent infection [13, 15, 18]. However, for most of the negative associations in the current study, we were unable to find a biologically plausible mechanism that could explain the effect.

It has been postulated that repeated exposure to different *Campylobacter* strains may lead to sufficient immunity to provide at least partial protection against clinical illness [48, 49]. In case-control studies, this protective immunity would lead to misclassification, since part of the control group may consist of persons in whom exposure to *Campylobacter* does not lead to clinical illness because of protective immunity. This would result in biased OR and PAR estimates towards the null and thus in underreporting and underestimation of risk factors. This may also explain the fact that in most case-control studies the majority of the cases remain unexplained. In addition, mathematical models have shown that in epidemiological studies negative associations may be found for risk factors where exposure is consistent over years and at low dose, given the assumption that lifelong immunity occurs [50]. Therefore, case-control studies may better identify risk factors where exposure is only occasional

and in high doses or involves uncommon *Campylobacter* strains like *C. coli* [48, 50].

Other concerns in case-control studies are recall and selection bias. In our study, the recall period for cases was longer than for controls: cases answered questions about the 7 days prior to symptom onset, which was a median 20 days before completion of the questionnaire, whereas controls answered questions about the 7 days before completion of the questionnaire. We used multiple imputation to handle missing values. Before using this statistical method, in several questions cases more frequently answered 'I don't know' than controls. However, after using multiple imputation, results of the risk analyses were similar. This suggests that missing values were randomly distributed over the response categories and independent from exposure status. From the approached controls, we obtained a 33% response for the postal questionnaire. Interested controls may have a healthier lifestyle including a preference for eating fruits, vegetables, nuts, fish and less takeaway foods or eating out. This bias may provide an alternative explanation why we found a reduced risk for these food products and an increased risk for foods bought at a stall, ready-to-eat sandwiches and eating in a restaurant.

An advantage of conducting a case-case analysis is that selection bias and recall bias is less likely to occur than in a case-control design, because *C. jejuni* and *C. coli* cases are selected in exactly the same way and have a similar recall period. Results from the case-case analysis corresponded with the risk factors found for *C. coli* in comparison with controls, supporting our belief that recall bias and selection bias had limited impact on our results.

In conclusion, this large case-control study on campylobacteriosis identified several and distinct risk factors for indigenous *C. jejuni* and *C. coli* infections. This study also confirms that risk factors differ dependent on age, season and degree of urbanization. PAR estimates provided insight in the relative importance of different risk factors on public health.

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DECLARATION OF INTEREST

None.

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