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# Determinants of sporadic *Campylobacter* infections in Denmark: a nationwide case-control study among children and young adults

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**Background:** Each year more than 4,000 cases of campylobacteriosis are reported in Denmark, making it the most common bacterial gastrointestinal infection. Here we describe a case-control study to identify sources of infection with a focus on environmental factors.

**Methods:** From January to December 2016, we conducted a prospective case-control study among Danish persons aged 1–30 years. Participants were invited by letter to complete an online questionnaire. Crude and adjusted ORs were calculated and final parsimonious multivariate models developed using logistic regression.

**Results:** The study recruited 1366 cases and 4,418 controls, of whom 65% and 66%, respectively, completed the questionnaire. A multivariate model for domestically acquired cases showed, among others, increased risk of infection with bathing in fresh water (OR=5.1), contact to beach sand (OR=1.8), owning a pet dog with diarrhea (OR=4.6), and eating minced beef (OR=2.6) or chicken (OR=2.5). The model for children highlighted similar risk factors but also included bathing in a paddling pool (OR=13.6) and eating fresh strawberries (OR=5.3). A separate analysis for persons reporting foreign travel showed increased infection risk when traveling to Asia, Africa, or Turkey and that eating from street kitchens and having contact to water during traveling were also risk factors.

**Conclusion:** Environmental factors and animal contact account for a sizeable proportion of domestic *Campylobacter* infections in the age group studied. The study also re-confirmed handling/consumption of chicken as an important risk factor while highlighting minced beef as a potential new risk factor. Overall, these results contribute to a better understanding of the transmission dynamics of *Campylobacter* and will be used to improve national guidelines for prevention of infection.

**Keywords:** *Campylobacter*, determinants, case-control, environment, food

## Introduction

*Campylobacter* spp. are a global cause of gastroenteritis in humans, particularly in industrialized countries. In Denmark, incidences have increased since 2012 and campylobacteriosis is now the most frequently reported gastrointestinal infection<sup>1</sup> with 4,243 reported cases in 2017, corresponding to 73.7 cases per 100,000 population. This pattern is repeated throughout Europe, Australia, and the US where incidences remain high and have even increased during the past decade.<sup>2–4</sup> Campylobacteriosis is a zoonotic disease with poultry, wild birds, and domestic pets as the main reservoirs.<sup>5,6</sup> Symptoms in humans manifest as acute watery or bloody diarrhea and treatment is usually only required for severe cases or if infection triggers Guillain–Barré syndrome. Infection occurs in all age groups but incidences are higher in young persons, particularly children younger than 5 years.<sup>1,7</sup> This age pattern of infection is most likely

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influenced by acquired immunity; children are repeatedly exposed to *Campylobacter*, through food and the immediate environment, developing partial immunity which allows them to remain asymptomatic (following most exposures) if infected as adults.<sup>8</sup>

Campylobacteriosis is a mainly sporadic disease. When outbreaks occur, they have often been linked to contaminated water, raw (unpasteurized) milk, animal contact, and environmental exposures such as mud and sand.<sup>9–14</sup> In Denmark, recent evidence from next-generation sequencing suggests that case clustering – and even outbreaks – may be more common than assumed.<sup>15</sup> To identify risk factors for sporadic cases, three Danish<sup>16–18</sup> and numerous foreign case-control studies have been undertaken.<sup>19–26</sup> These consistently identified traveling abroad, poor handling, and/or consumption of raw or undercooked chicken, consumption of raw milk, and animal contact as important determinants of infection, but a large proportion of cases remained unexplained. The current gray areas of *Campylobacter* epidemiology in particular cover the true spectrum of risk factors and the relative importance of poultry in relation to other exposures.<sup>27–29</sup> Further, most case-control studies included persons of all ages which, considering the age-related partial immunity, may introduce bias as they are not all at equal risk of developing disease.<sup>30</sup> In other words, including controls from older age groups are likely to underestimate the importance of some risk factors and potentially miss others.

In this paper, we describe a national case-control study on *Campylobacter* risk factors in Denmark undertaken to identify the most important sources of infection, focusing on possible non-food determinants. To reduce the potential bias caused by partial immunity, we included only persons aged 1–30 years which also covers individuals believed to be at highest risk of disease.

## Methods

### Study design and population

The study was a national prospective case-control frequency-matched study with a population representative control group, conducted over a 12-month period beginning in January 2016. The total population of Denmark at that time was 5,700,000, of which 2,100,000 (37%) persons were aged between 1 and 30 years. Based on historical notification data, we expected approximately 1,300 cases to be reported in this age group during the study period.

### Cases

A case was a person with a confirmed *Campylobacter* infection (all species), diagnosed using either culture, polymerase

chain reaction, or serology, who was aged older than 1 and younger than 31 years and who lived in Denmark at the time of diagnosis. Cases were excluded in two steps: firstly from being invited to participate and secondly from being included in the analysis. The first exclusion step included cases who: 1) did not have a valid Danish address, 2) had their address and/or name protected by law, 3) were aged under 18 years and did not live with either parent, or 4) were not alive at the time of invitation. In the second step, we excluded cases who did not coherently answer the questionnaire. New cases were identified on a weekly basis through the national case notification register based on extraction of data from the Danish Microbiology Database (MiBa)<sup>31</sup> and assessed for inclusion using the criteria presented above. Each notification contains as a minimum information on name, age, gender, date of sample received in the laboratory, and the unique personal Civil Registry System (CPR) number. The CPR allows identification of the person's address and familial status (eg, name and address of parents).

### Controls

In total, 5,102 population controls aged 1–30 years living in Denmark were randomly extracted from the CPR System at the beginning of the study. From this group, a random sample of controls was selected for participation in the study each month. To account for the seasonal variation of campylobacteriosis, the number of controls asked for participation in any given month was correlated to the expected number of cases in that month (resulting in approximately four times more controls than cases each month).

Controls were also excluded in two steps. Firstly for the same reasons as for cases and if they resided in the same household as a previously included control. Secondly, controls who reported symptoms of gastrointestinal illness (diarrhea [bloody or non-bloody] and/or vomiting) during the past month and who did not coherently complete the questionnaire were excluded.

### Recruitment and questionnaire

We recruited all cases and controls using a postal letter-based invitation, containing a rationale for the study, a short description of the questionnaire, and a personalized link (including username and password) to an online questionnaire. At the same webpage, invitees could decline participating in the study. For persons younger than 18 years, the invitation was sent to a parent living at the same address (the mother as a default). Parents completing questionnaires on behalf of children aged 12–17 were encouraged to answer

the questions along with the child. Before recruitment, the vital status of each participant and – for persons under 18 years of age – their parents was assessed through the CPR System. Two postal reminders were sent 7 and 14 days, respectively, after the initial invitation to persons who had not completed the questionnaire and who had not actively declined to participate.

The questionnaire collected information on a range of exposures in the 5 days prior to symptom onset (cases) or the 5 days prior to completion of the questionnaire (controls) and as habits/baseline. Exposures included medical history, demographic information, overseas travel, recreational activities, dining locations, food and drink, kitchen hygiene, and animal contact. Questions on medical history and use of medication were asked based on a 4-week history and questions on travel on a 14-day history. Cases and controls reporting travel abroad provided further information about their journey, including exposures, after which they were excluded from the rest of the questionnaire. Participants could access their questionnaire at any time, save completed parts, and return at a later point. Passwords and usernames were valid for 8 weeks.

## Seasonality

Because campylobacteriosis is highly seasonal in Denmark<sup>1</sup> and exposures relating to the environment in particular are dependent on season, a season variable was included as a confounder. For cases, this variable was the month of self-reported symptom onset or, if they did not provide a symptom onset, the month when their sample was received in the laboratory. For controls, the season variable was defined as the month in which their questionnaire was completed (as they provided answers relating to their activities immediately prior to completing the questionnaire rather than at the time of inclusion in the study).

## Data analysis

We performed univariate analyses on all explanatory variables to generate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Multivariate analyses were performed by backward stepwise logistic regression modeling with elimination of nonsignificant variables based on the model deviance statistics and *P*-values. Two models were constructed: one for all participants in the study (ages 1–30 years) and one for small children (ages 1–5 years). Potential confounders were selected based on knowledge of determinants for *Campylobacter* infection<sup>1</sup> and included age, sex, residential area (urban or rural), and season (as described above). Adjustments were made for these

potential confounders and for two-factor interactions identified from investigative analysis of all explanatory variables.

Population attributable fractions (PAFs) were calculated using adjusted ORs from the final logistic regression models for each explanatory variable associated with an increased risk of infection.

All data were analyzed using STATA version 14 (Stata Corp, College Station, TX, USA).

## Results

### Study population

During 2016 in Denmark, 1,538 cases of *Campylobacter* were reported among persons aged 1–30 years. After exclusions (Figure 1), we invited 1,527 of these (99.3%) to participate. A total of 161 cases (11%) returned the invitation letter to sender and were excluded from the study. Of the remaining 1,366 cases, 887 (65%) responded to the questionnaire, resulting in 556 cases available for the domestic risk factor analysis and 309 cases for the travel risk factor analysis (Figure 1). Of the 5,102 randomly selected controls, 4,808 were eligible for invitation (Figure 1). In total, 390 (8%) of these returned the invitation letter to sender and 4,418 controls therefore had a possibility to fill in the questionnaire. Of these, 2,935 (66%) persons responded, and this resulted in 2,117 controls for the domestic risk factor analysis and 298 for the travel risk factor analysis (Figure 1).

There was no significant difference between cases and controls with respect to the distribution of gender, residential area, and – for persons older than 18 – occupation status (working/studying or unemployed). However, there were proportionally more cases than controls in the age group 1–4 years and more controls than cases in the age groups 5–9 and 10–14 years (Table 1).

### Univariate analysis of risk factors

#### Travel abroad

Traveling abroad was the single most important risk factor for infection for all cases (OR=4.6, 95% CI 3.7–5.7). Participants had traveled to 68 different countries with 29 countries (43%) being represented with a frequency of more than five visits. Cases exhibited a greater variation in the number of countries visited; 62 (91%) of the listed countries were visited by at least one case while for controls this was 37 (54%) countries. Risk of infection was higher for visitors to Asian countries and Turkey, whereas visiting Northern Europe and Scandinavia was associated with a reduced risk of infection (Table 2). For travelers, staying in a Bed & Breakfast (compared to all other types of accommodation, including outdoor camping),

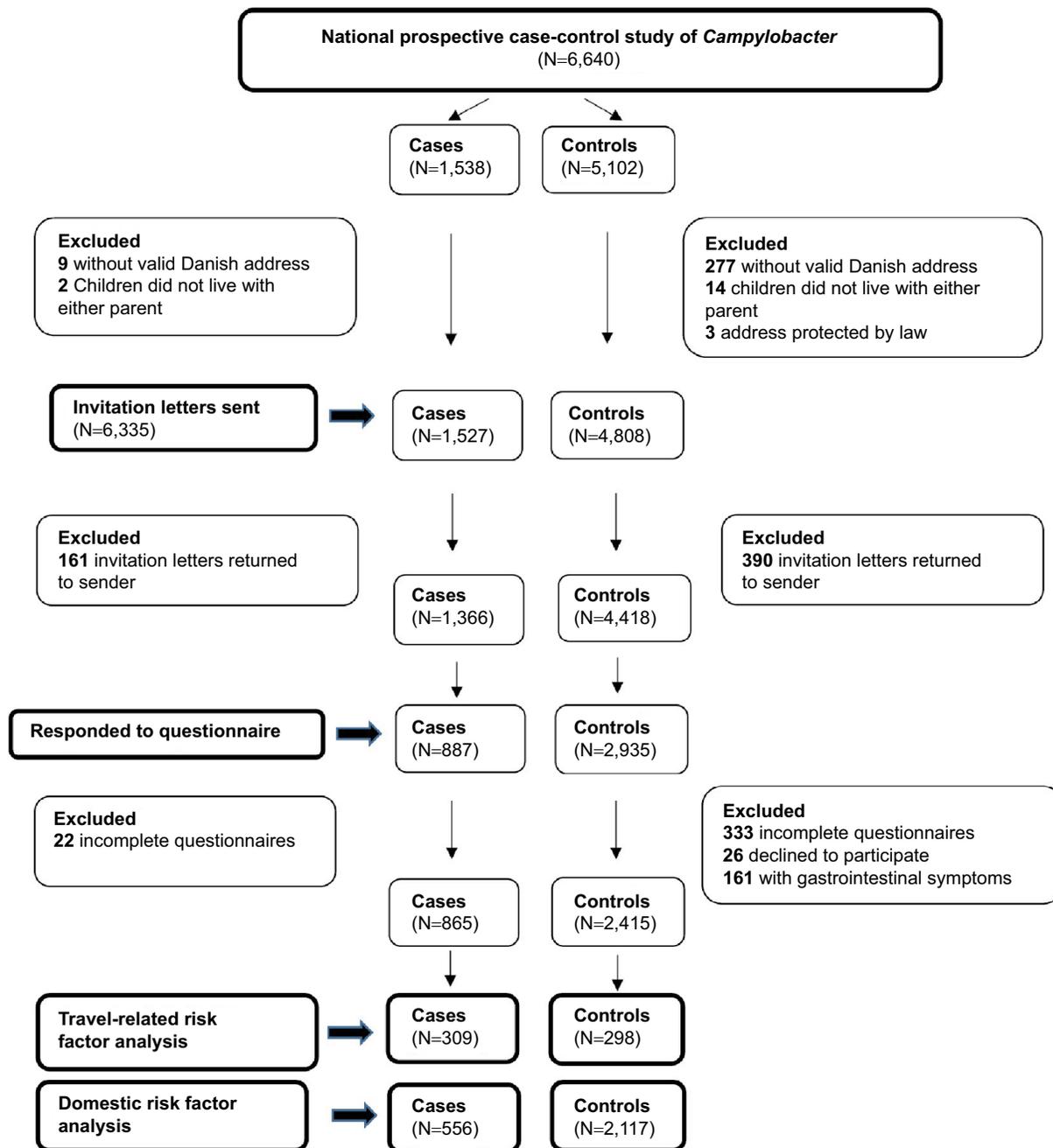


Figure 1 Participant flow chart.

consuming food from street kitchens, having contact to sand, soil, and/or mud, and bathing in sea water carried an increased risk of infection, whereas cooking one’s own food was inversely associated with campylobacteriosis (Table 2).

All subjects reporting travel abroad were excluded from the risk factor analysis for domestic factors presented below.

### Environmental exposures

Contact to water from natural sources was associated with infection. Specifically, cases were more likely to have bathed

in sea- or freshwater or in a paddling pool and have consumed water from a stream or spring in nature (Table 3). There was also a higher risk of infection associated with contact to beach sand and with fishing.

### Animals

There was no association between illness and contact to animals or having a pet in general; however, cases were more likely to have had contact with animal feces (Table 3). Further, there was also an association between illness and

having a pet dog and in particular a dog who had diarrhea in the 5-day exposure period. Lastly, cases were more likely to have had contact with cattle.

**Table 1** Frequency and percentage of study cases and controls by demographic characteristics (excluding persons reporting foreign travel), Denmark 2016

Characteristic	Cases, n (%) n=556	Controls, n (%) N=2,117
Age (years)		
1–4	106 (19)	254 (12)
5–9	53 (10)	339 (16)
10–14	50 (9)	350 (17)
15–19	101 (18)	359 (18)
20–24	118 (21)	395 (19)
25–30	128 (23)	420 (20)
Gender		
Male	284 (52)	1,080 (51)
Female	272 (48)	1,037 (49)
Region of residence		
Capital	189 (34)	741 (35)
Zealand	78 (14)	318 (15)
South	106 (19)	402 (19)
Mid	122 (22)	423 (20)
North	61 (11)	233 (11)
Residential area		
Rural	70 (13)	275 (13)
Urban	409 (74)	1,589 (75)
Unknown	77 (13)	253 (12)
Occupation <sup>a</sup>		
Full-time work/studies	186 (93)	1,051 (92)
Unemployed	15 (7)	92 (8)

Note: <sup>a</sup>Over 18 years only (cases n=267, controls=887).

## Eating habits and kitchen hygiene

Eating in a café/restaurant or fast food restaurant carried an increased risk of infection as did eating food served outdoors and own food consumed during a picnic in the countryside or forest (Table 3). Eating meat cooked on barbecue (at home) was also associated with infection.

Considering hygiene practices at home, handling of fresh chicken in the 5-day exposure period was associated with an increased risk of infection.

## Food and drink

There was no association between illness and consumption of pork, duck, goose, game, or any deli meat as a habit or during the 5-day exposure period. Cases were more likely to consume chicken in general and to have consumed whole chicken, chicken fillet, or chicken thighs in the exposure period. The analyses further identified an increased risk of illness associated with consumption of beef mince and steaks (Table 3).

Consumption of specific vegetables was not associated with illness. However, fresh strawberries, raspberries, and blueberries increased the risk of infection as did consumption of smoothies prepared with frozen berries.

Lastly, cases were more likely than controls to have consumed unpasteurized milk and to live in a household with drinking water supplied from a private water supply.

## Other exposures

Participants were asked about their own and family members' medical history and use of medication. Among these, the use

**Table 2** Determinants for *Campylobacter* infection associated with foreign travel, Denmark 2016

Exposure	Cases (N=302) n (%)	Controls (N=248) n (%)	OR <sup>a</sup>	95% CI
Destination				
Turkey	27 (8.9)	9 (3.6)	3.6	1.4–9.3
Thailand	13 (4.3)	1 (0.4)	9.9	1.2–78.8
Indonesia	22 (7.3)	1 (0.4)	12.2	1.6–92.8
Asia (others)	45 (14.9)	9 (3.6)	3.0	1.4–6.7
Africa	35 (11.6)	3 (1.2)	6.9	2.1–23.1
Northern Europe <sup>b</sup>	18 (6.0)	71 (28.6)	0.2	0.1–0.3
Scandinavia <sup>c</sup>	9 (3.0)	39 (15.7)	0.1	0.06–0.3
Accommodation				
Bed & breakfast	27 (8.9)	11 (4.4)	2.5	1.7–5.3
Meals				
Street kitchens	67 (22.2)	16 (6.5)	2.7	1.4–5.0
Cooked own food	99 (32.8)	124 (50.0)	0.5	0.3–0.7
Environment				
Contact to sand, soil, or mud	239 (79.1)	178 (71.8)	1.8	1.1–2.8
Swimming in sea water	187 (61.9)	116 (46.9)	1.7	1.1–2.8

Notes: <sup>a</sup>ORs are adjusted for the confounding effect of age, sex, and season. <sup>b</sup>Germany, UK, Holland, Austria, and Belgium. <sup>c</sup>Finland, Norway, Sweden, and Iceland.

**Table 3** Univariate determinants for *Campylobacter* infection, Denmark 2016

Exposure	Cases exposed n (%)	Controls exposed n (%)	Adjusted OR <sup>a</sup> (95% CI)	P-value
<b>Demography</b>				
Lives in an urban area*	409 (85)	1,572 (86)	0.8 (0.6, 1.2)	0.32
Visited weekend cottage	28 (6)	116 (6)	0.9 (0.6, 1.4)	0.67
<b>Recreational activities and environmental factors</b>				
Went for a walk	443 (85)	1,791 (88)	0.9 (0.6, 1.2)	0.37
Gardening work	248 (48)	1,118 (55)	1.0 (0.8, 1.4)	0.72
Running on asphalt	298 (58)	1,478 (72)	0.7 (0.6, 0.9)	<0.01
Running on soil	266 (52)	1,301 (64)	0.7 (0.6, 0.9)	<0.05
Riding a bicycle on asphalt	311 (60)	1,366 (67)	0.8 (0.7, 1.0)	0.10
Riding a bicycle on soil	210 (41)	847 (42)	1.0 (0.8, 1.2)	0.99
Outdoor sports	151 (29)	713 (35)	1.2 (1.0, 1.6)	0.10
Stayed outdoors in rain	28 (6)	116 (6)	0.9 (0.6, 1.2)	0.31
Bathed in an indoor swimming pool	48 (9)	333 (16)	0.7 (0.5, 1.1)	0.09
Bathed in sea water	43 (8)	94 (5)	1.6 (1.0, 2.4)	<0.05
Bathed in fresh water	33 (6)	24 (1)	6.0 (3.0, 11.9)	<0.001
Bathed in a paddling pool	54 (10)	79 (4)	3.0 (1.9, 4.6)	<0.001
Contact to beach sand	150 (29)	290 (14)	2.3 (1.8, 3.0)	<0.001
Sailing	19 (4)	59 (3)	1.2 (0.6, 2.1)	0.62
Fishing	22 (4)	43 (2)	2.0 (1.1, 3.7)	<0.05
<b>Eating</b>				
Café or restaurant	256 (50)	758 (37)	1.5 (1.2, 1.8)	<0.01
Fast food restaurant	314 (61)	1,030 (51)	1.4 (1.2, 1.8)	<0.01
Canteen	223 (43)	806 (40)	1.1 (0.9, 1.3)	0.56
Outdoor serving	121 (24)	248 (12)	1.8 (1.4, 2.3)	<0.001
Packed lunch eaten outside	129 (25)	515 (25)	1.0 (0.7, 1.2)	0.75
Eating in own garden	146 (28)	517 (25)	0.9 (0.7, 1.2)	0.43
Picnic in a forest/countryside (own food)	60 (8)	153 (2)	1.8 (1.2, 2.6)	<0.01
<b>Meat</b>				
Vegetarian*	4 (1)	27 (1)	0.4 (0.1, 1.3)	0.13
Eat poultry*	512 (99)	1,986 (97)	3.5 (1.2, 10.1)	<0.05
Eat pork*	479 (93)	1,915 (94)	0.8 (0.5, 1.2)	0.25
Eat beef*	494 (97)	1,971 (98)	1.0 (0.5, 1.9)	0.98
Whole chicken	163 (24)	372 (12)	2.2 (1.8, 2.9)	<0.001
Boneless chicken fillets	386 (75)	1,183 (58)	2.1 (1.6, 2.6)	<0.001
Chicken thighs	169 (33)	501 (25)	1.6 (1.2, 2.0)	<0.001
Minced chicken	88 (17)	254 (13)	1.3 (1.0, 1.8)	0.06
Turkey	28 (5)	151 (7)	0.6 (0.4, 1.0)	<0.05
Duck or goose	25 (5)	134 (7)	0.7 (0.4, 1.0)	0.07
Chicken bought fresh, prepared home	445 (86)	1,734/ (85)	1.2 (0.9, 1.6)	0.28
Chicken bought frozen, prepared home	200 (39)	761 (38)	1.0 (0.8, 1.3)	0.79
Chicken liver	8 (2)	48 (2)	0.6 (0.3, 1.4)	0.27
Pork chops	253 (53)	908 (48)	1.2 (0.9, 1.5)	0.07
Minced pork	269 (56)	1,004 (53)	1.1 (0.9, 1.4)	0.27
Pork sausages	262 (55)	1,078 (57)	1.0 (0.8, 1.2)	0.76
Beef (steak)	249 (51)	803 (41)	1.3 (1.1, 1.7)	<0.01
Minced beef	449 (91)	1,618 (82)	2.5 (1.8, 3.6)	<0.001
<b>Vegetables and fruit</b>				
Lettuce	352 (69)	1,299 (64)	1.1 (0.9, 1.4)	0.40
Raw carrots	339 (67)	1,462 (72)	0.9 (0.7, 1.1)	0.31
Raw fresh peas	144 (28)	445 (22)	1.2 (1.0, 1.6)	0.09
Unpeeled apples	357 (70)	1,519 (72)	1.0 (0.7, 1.2)	0.70
Grapes	284 (56)	1,048 (51)	1.2 (1.0, 1.5)	0.10
Strawberries (fresh)	184 (36)	505 (25)	1.6 (1.3, 2.1)	<0.001
Raspberries (fresh)	106 (21)	281 (14)	1.5 (1.1, 1.9)	<0.01
Blueberries (fresh)	129 (25)	370 (18)	1.4 (1.1, 1.8)	<0.01
Smoothie prepared with frozen berries	95 (19)	306 (15)	1.3 (1.0, 1.8)	<0.05

(Continued)

Table 3 (Continued)

Exposure	Cases exposed n (%)	Controls exposed n (%)	Adjusted OR <sup>a</sup> (95% CI)	P-value
<b>Food handling and preparation</b>				
Handled raw chicken	161 (59)	336 (35)	2.1 (1.6, 2.9)	<0.001
Handles raw chicken*	274 (55)	951 (48)	0.8 (0.6, 1.1)	0.20
Washes hands before and after handling chicken*	245 (90)	847 (89)	1.4 (0.9, 2.3)	0.13
Does not wash hands when handling chicken*	2 (1)	4 (0.5)	1.4 (0.2, 8.9)	0.71
Cleans handling surface with a cloth*	13 (5)	82 (9)	0.5 (0.2, 0.9)	<0.05
Cleans handling surface with water and soap*	235 (86)	793 (83)	1.3 (0.8, 2.0)	0.24
Does not clean handling surface*	6 (2)	25 (3)	0.8 (0.3, 2.1)	0.62
Prepares chicken pink or rare*	15 (3)	34 (2)	1.3 (0.7, 2.6)	0.40
Meat prepared on a barbecue	182 (36)	512 (25)	1.4 (1.1, 1.8)	<0.01
Meat prepared in a microwave	173 (34)	611 (30)	1.1 (0.8, 1.3)	0.59
<b>Drink</b>				
Unpasteurized milk	27 (5)	52 (3)	1.9 (1.1, 3.1)	<0.05
Tap water	485 (95)	1,979 (93)	0.4 (0.2, 0.7)	<0.01
Water from a spring or stream	15 (3)	22 (1)	2.7 (1.2, 5.8)	<0.05
Household drinking water from private well	27 (6)	39 (2)	2.9 (1.6, 5.2)	<0.001
<b>Animals</b>				
Contact to animals	360 (73)	1,548 (78)	0.7 (0.6, 0.9)	0.2
Dogs	290 (59)	1,186 (60)	1.0 (0.8, 1.2)	0.67
Cats	180 (36)	797 (40)	0.8 (0.7, 1.1)	0.14
Birds/poultry	7 (1)	73 (4)	1.0 (0.7, 1.5)	0.94
Pigs	16 (3)	36 (2)	1.7 (0.9, 3.4)	0.1
Cattle	53 (11)	82 (4)	2.4 (1.6, 3.6)	<0.001
Contact to animal feces	111 (31)	96 (6)	6.8 (4.7, 9.7)	<0.001
Owens a pet*	233 (42)	1,019 (48)	1.1 (0.8, 1.3)	0.64
Dog*	175 (31)	594 (28)	1.5 (1.1, 2.1)	<0.05
Handles feces*	70 (13)	279 (13)	1.0 (0.6, 1.7)	0.89
Dog had diarrhea	29 (5)	29 (1)	5.9 (2.8, 12.1)	<0.001
Cat*	89 (16)	480 (23)	0.6 (0.4, 0.8)	<0.01
Handles feces/empties litter tray*	10 (2)	80 (4)	0.5 (0.2, 1.2)	0.12
Cat had diarrhea	3 (1)	13 (1)	1.3 (0.3, 5.5)	0.76
Birds/chickens*	23 (4)	88 (4)	1.0 (0.6, 1.8)	0.91
Handles feces/cleans chicken coop*	4 (1)	29 (1)	0.3 (0.1, 1.0)	0.06
Contact to eggs*	19 (3)	73 (3)	2.2 (0.5, 9.6)	0.30
<b>Other exposures</b>				
Suffers from chronic disease*	52 (10)	185 (9)	0.9 (0.7, 1.3)	0.66
Use of antibiotics++	17 (3)	34 (1)	2.0 (1.0, 4.0)	<0.05
Use of proton pump inhibitors++	29 (6)	20 (1)	3.9 (2.0, 7.5)	<0.001
Travel abroad with overnight stay+	309 (35)	298 (10)	4.6 (3.7, 5.7)	<0.001
Household member with diarrhea	40 (8)	110 (6)	1.6 (1.0, 2.4)	<0.05
<b>Exposures relevant only for persons &gt;18*</b>				
Currently working	128 (48)	319 (36)	1.8 (1.3, 2.4)	<0.001
Contact to hospital admitted patients	11 (4)	62 (7)	0.5 (0.2, 1.5)	0.2
Contact to patients in non-hospital settings	29 (11)	44 (5)	2.2 (1.0, 4.9)	<0.05
Contact to water or sewage	8 (3)	27 (3)	1.3 (0.4, 4.9)	0.7
<b>Exposures relevant only for persons &lt;18*</b>				
Forest nursery/kindergarten	81 (28)	271 (22)	1.2 (0.6, 0.9)	0.2
Animals in the nursery/kindergarten	121 (42)	394 (32)	1.3 (1.0, 1.8)	<0.05
Uses a dummy	110 (38)	394 (32)	1.0 (0.1, 1.7)	0.9
Uses a snuggle toy	46 (16)	234 (19)	1.0 (0.5, 1.7)	0.9
Animals at school/college	32 (11)	86 (7)	1.6 (0.7, 3.3)	0.1
After school job	72 (25)	221 (18)	1.2 (0.7, 2.0)	0.5
Babysitting	17 (6)	49 (4)	2.5 (0.4, 16.1)	0.3
Contact to animals	46 (16)	98 (8)	2.7 (1.1, 3.0)	<0.01
Contact to food	38 (13)	160 (13)	0.9 (0.3, 3.3)	0.9

**Notes:** <sup>a</sup>ORs are adjusted for the confounding effect of gender, age, residential area (urban or rural), and season. Exposures refer to a 5-day exposure period prior to onset of symptoms (cases) or completion of questionnaire (controls) apart from (\*) habits or baseline, (+) 14-day exposure period, and (++) 1-month exposure period.

of antibiotics and proton pump inhibitors (PPIs) in the last month/month prior to developing symptoms and a household member suffering from diarrhea in the 5-day exposure period were associated with illness.

### Specific exposures for adults and children

To account for age-specific exposures, adults (over 18 years of age) and children were asked different questions relating to occupation or schooling. Analyses showed that adults who worked – and in particular work involving patient contact in non-hospital settings (eg, home care) – were at higher risk of infection. Children who had an after school job with contact to animals (eg, dog walking) also had a higher risk of campylobacteriosis.

### Protective factors

A number of factors were independently associated with a reduced risk of infection, including running (on both soil and asphalt) and having a pet cat (Table 3). With respect to food and drink, consumption of turkey and tap water (at home) also carried a lower risk of infection.

## Multivariate analysis of risk factors

### All study participants, ages 1–30 years

A range of both food- and non-food-related exposures were associated with illness after adjusting for the effect of other variables (Table 4). The explorative analyses identified an interaction between minced beef and barbecued meat which was included in this model. Consumption of chicken fillets, whole chicken, beef mince, and meat prepared on a barbecue were all associated with an increased risk of illness.

Of environmental factors, bathing in fresh water, contact to beach sand, and having household drinking water from a private well carried increased risk of disease in the final model. In addition, the model showed that contact to animal feces, owning a pet dog with diarrhea, and the use of PPIs were associated with illness.

These independent determinants predicted almost half of the variation in illness ( $R^2=0.48$ ).

The calculated PAFs showed that avoiding consumption of chicken and minced beef, and contact to animals and pet dogs with diarrhea would result in the highest reduction in the number of infections (Table 4). The remaining variables accounted for a smaller proportion of the number of campylobacteriosis cases.

### Small children, ages 1–5 years

The separate model constructed for small children indicated that both food and non-food exposures were important and independently associated with campylobacteriosis (Table 4). Contact to animal feces and bathing in a paddling pool were the two sole environmental factors included. Having a pet dog was also associated with illness. With respect to food, the model included consumption of minced beef, whole chicken, and fresh strawberries.

These independent determinants predicted slightly more than half of the variation in illness ( $R^2=0.51$ ).

For children, not consuming chicken and minced beef and not having contact with animal feces and dogs would also result in a notable reduction in the number of infections (Table 4). Further, consumption of strawberries alone accounted for a relative 16% of cases.

**Table 4** Multivariable risk factors for *Campylobacter* infection, Denmark 2016

All persons (N=556 cases, 2,117 controls)			Children 1–5 years (N=125 cases, 321 controls)		
Exposure	OR <sup>a</sup> (95% CI)	PAF (%)	Exposure	OR <sup>b</sup> (95% CI)	PAF (%)
Use of proton pump inhibitors	10.1 (1.9–54.0)	3	Contact to animal feces	62.4 (8.2–472.6)	8
Bathing in fresh water	5.1 (1.4–17.9)	4	Bathing in paddling pool	13.6 (1.9–97.0)	8
Pet dog had diarrhea	4.6 (2.0–10.7)	8	Consumption of whole chicken	12.3 (2.8–53.0)	14
Contact to animal feces	4.3 (2.1–8.6)	12	Consumption of minced beef	11.2 (1.2–104.1)	33
Household water from private well	2.7 (1.0–7.6)	2	Consumption of fresh strawberries	5.3 (1.3–20.5)	16
Consumption of minced beef	2.6 (1.1–6.3)	29	Having a pet dog	3.8 (1.1–13.1)	21
Consumption of chicken fillets	2.5 (1.4–4.5)	23			
Consumption of whole chicken	2.1 (1.2–3.7)	6			
Contact to beach sand	1.8 (1.0–3.4)	7			
Consumption of barbecued meat	1.6 (1.1–3.4)	7			

**Notes:** <sup>a</sup>ORs are adjusted for the confounding effect of gender, age, residential area (urban or rural), and season. <sup>b</sup>ORs are adjusted for the confounding effect of gender, residential area (urban or rural), and season.

**Abbreviation:** PAF, population attributable fraction.

## Discussion

In this national case-control study of campylobacteriosis determinants, we found that exposures related to the environment, animal contact, and food were associated with an increased risk of illness. The study is the largest ever undertaken in Denmark. Because it focuses on the younger age groups, the results are less influenced by bias from persons with partial immunity. The investigation generated response rates at high levels (65% for cases and 66% for controls) for a non-telephone-based survey, highlighting the usefulness of online questionnaires but also the validity of the results.<sup>32</sup> Lastly, we asked persons who reported traveling to provide specific information regarding exposures during their trip, rather than immediately excluding them from the study.

One of the primary aims of this study was to identify environmental risk factors for campylobacteriosis. The results show that contact to water in the environment was particularly important. There is a well-established link between *Campylobacter* infection and recreational water contact,<sup>22,25,33</sup> especially in outbreak situations.<sup>12,34</sup> Both fresh and sea water harbor *Campylobacter* spp.<sup>35,36</sup> and our study suggests that 4% of sporadic Danish campylobacteriosis cases may be caused by recreational water contact – even double that for children using a paddling pool. Ingestion of water from a private (rather than public) household well also increased the risk of infection. Drinking water was implicated in several *Campylobacter* outbreaks<sup>37,38</sup> and associated with disease in case-control studies from other countries.<sup>21,23,39</sup> However, as the public water supply in Denmark, unlike most other European countries, is drawn almost exclusively from ground water rather than surface water,<sup>40</sup> it is not unexpected that our study associates disease with drinking water from a private well. The final environmental determinant identified in this study was beach sand. Although not previously identified in any case-control study, it is not surprising as *Campylobacter* spp. are present in beach sand<sup>41</sup> and indeed several *Campylobacter* outbreaks have been linked to incidental ingestion of mud.<sup>13,14</sup>

Another known risk factor for *Campylobacter* infection is interaction with animals. We found that contact to animal feces was a particular determinant for infection, accounting for as much as 12% of cases. Further, we confirm that contact to dogs, especially if the dog has diarrhea, also increases the risk of infection. For small children, having a pet dog was the second most important determinant identified in the study. On the contrary, having a pet cat was associated with a reduced risk of infection, possibly indicating the distinction “cat people” vs “dog people” (although this was not confirmed

by interactions between the variables). These results confirm previous findings that contact to dogs and their feces carries an increased risk of campylobacteriosis for humans.<sup>20,23</sup> In general, the importance of proper hygiene measures during and after contact to dogs and their feces, especially for children, needs to be emphasized in public health settings.

For food-related exposures, consumption of chicken (whole chicken and chicken fillets) was associated with domestic *Campylobacter* infection. Our study showed that almost one third of *Campylobacter* cases in Denmark each year may be attributed to chicken. Although chicken liver, in the form of liver paté, has been identified as the source of several outbreaks as well as a risk factor for sporadic disease in other countries,<sup>42</sup> it was not a determinant for infection in our study. Rather than eliminating chicken livers as a potential risk factor, we attribute this result to the low risk of exposure among our study population – which most likely reflects the age group studied (the frequency of chicken liver consumption increases with age).<sup>42</sup> As an unexpected outcome, the results show that consumption of minced beef may be associated with campylobacteriosis. *Campylobacter* spp. have been isolated from cattle in both Denmark and other European countries,<sup>43–47</sup> but the prevalence in beef is reported as minor.<sup>48–51</sup> Minced beef/hamburger meat was identified as a risk factor in other case-control studies<sup>52,53</sup> and even as a source of outbreaks,<sup>54–56</sup> but it is not considered an important transmission route for *Campylobacter* in Denmark. The risk associated with minced beef may be a recent occurrence due to the introduction of Modified Atmosphere Packaging (MAP). Minced meat in a MAP has lower concentrations of O<sub>2</sub>, improving the shelf life and reducing discoloration, but during preparation the meat rapidly turns brown, increasing the risk of consumption before properly cooked. The separate model for small children indicated fresh strawberries as a source of infection. This is also an unexpected result given previous findings that fresh berries reduce the risk of infection.<sup>52,57</sup> The risk from strawberries may be linked to hygiene practices (not washing the berries) as Danish children frequently eat strawberries either from the field when picking them or directly from the box if bought in retail. Our results point to minced beef and fresh strawberries as two new possible sources of infection to be investigated, and both of these are presently being examined by the Danish Food and Veterinary Administration as part of the national action plan against *Campylobacter*.

The questionnaire also examined medical history and use of medication, and our results confirm previous findings that the use of PPIs increases the risk of *Campylobacter*

infection.<sup>58,59</sup> Use of over-the-counter PPIs has increased during recent years, and this may be one of the driving factors behind the observed increase in *Campylobacter* in many countries.<sup>28,60</sup> Interestingly, our study found an age-independent risk for the use of PPIs with very young children also reporting use of this medication. PPIs are not contraindicated for the use in children, and are prescribed for treatment of complicated reflux.<sup>61</sup> For this age group in particular, our results highlight a potential public health concern correlated with the use of PPIs.

As a new addition to case-control studies of sporadic campylobacteriosis, we included an expanded analysis of travel-related cases. Our results confirm that infection abroad primarily occurs in Indonesia, Thailand, Africa, and Turkey. Cases in general could be classified as “adventurous” travelers, visiting more countries, and in particular countries outside Europe. Here, eating in street kitchens and staying in a Bed & Breakfast carried the highest risk of infection, but also contact to water, sand soil, or mud were determinants of infection. On the other hand, persons who traveled to Scandinavia or Northern Europe and who cooked their own food had lower risk of infection. These countries are not “protective” in themselves as campylobacteriosis rates are also high in Northern Europe, but the low infection risk is most likely an indicator for better hygiene and consumption of safer foods when traveling closer to home. Several studies report that travelers in more exotic locations, frequently Asia, often do not follow the rules of eating and drinking safely.<sup>62–64</sup>

Campylobacteriosis is a disease of many unanswered questions, in particular with respect to determination of risk factors and their relative importance. For instance, persistently high incidences of *Campylobacter* in many countries despite intense poultry control efforts has been an argument for chicken not being the primary source of human infections.<sup>65,66</sup> Overall, our results confirm that chicken meat is an important risk factor for campylobacteriosis. However, they also cast new light on the ongoing question of whether infections arise from more complex transmission routes<sup>66</sup> – such as those from other food sources and the environment. The results presented here suggest that campylobacteriosis is not attributable to one primary food source but rather a combination of non-food and food factors. The relative importance of these factors is likely to vary between persons, locations, and even throughout the year.

The study size, age-specific inclusion criteria, and high response rates are all important strengths when interpreting our findings. Additionally, the independent determinants identified in the analyses all confirm previous knowledge about *Campylobacter* – albeit in more detail. Nevertheless,

it is necessary to consider the potential biases commonly affecting case-control studies. Firstly, participation rates among cases and controls were high, resulting in an even distribution of exposures between the two groups. Secondly, using an online questionnaire eliminated interviewer bias. The third issue to consider is imperfect recall. Cases probably received their invitation 14–20 days after symptom onset and may have forgotten exposures in the period before symptom onset. However, all questions relating to the 5-day exposure period were also asked as “habit” questions (ie, “how often do you...”). Including these questions helps generate an overall image of each participant. For instance, a case who reports generally eating chicken up to five times per week is also likely to have eaten it in the 5 days before symptom onset. We therefore argue that the impact of recollection bias is negligible. In this study, we chose to exclude controls who reported suffering from symptoms of a gastrointestinal illness in the month prior to completing the questionnaire. Although often a standard practice in case-control studies, it has been suggested that such exclusions create bias as the control group has been amended to not exactly represent the population which gave rise to the cases.<sup>67</sup> This may have resulted in the identification of artificial associations – particularly if the unknown gastrointestinal illness was associated with some of the determinants identified in this study. However, considering that only 5% of controls were excluded for this reason, this bias is unlikely to have had an impact on the results. Another source of bias was only including persons aged 1–30 years and effectively omitting around 60% of all notified campylobacteriosis cases from the study. This improves the estimates for the identified determinants but may also have caused bias by missing specific determinants in the older population. The potential effect of bias is also visible in the wide confidence intervals calculated for some risk factors in the multivariate models, particularly for small children. This indicates a higher degree of uncertainty associated with the results and most likely reflects the smaller sample size for some exposures. Another limitation of the study is not distinguishing between different *Campylobacter* spp. which may have overlooked species-specific risk factors. However, as 95% of all reported infections in Denmark are *Campylobacter jejuni*,<sup>68</sup> variation between species is unlikely to have impacted the results. Indeed, omitting known *Campylobacter coli* infections from the analyses did not alter the outcomes (results not shown). Seasonality had the potential for causing bias in the results presented. Both *Campylobacter* infection rates<sup>1</sup> and recreational/environmental exposures are highly seasonal. We aimed to minimize this bias by frequency-matching, ensur-

ing that the number of controls included in any given month proportionally reflected the number of reported cases and that the relevant exposures were given appropriate weight in relation to the season. Finally, interpreting the results for risks of traveling need to be interpreted with the caution that all exposures whilst traveling were assumed to be equal, irrespective of destination – something which is most likely not the case.

## Conclusion

Overall, the results from this study underpin that *Campylobacter* infection remains primarily a foodborne infection albeit with an important environmental component. The role of environmental factors in relation to *Campylobacter* infection is poorly understood and the Population Attributable Fractions calculated in this study indicate that environmental factors – primarily recreational water contact and contact to sand – could account for a large proportion of campylobacteriosis cases in this young population.

With respect to food, our findings confirm published evidence that chicken remains an important risk factor for campylobacteriosis. However, they also suggest minced beef as a potentially new source of infection. In order to confirm or reject this result, minced beef needs to be closely investigated for *Campylobacter* contamination at several levels of the food chain.

Combined, our results contribute significantly to a better understanding of the marked peak in cases during summer and of the “unexplained” cases of *Campylobacter* infection which are not related to chicken. Our results will be used to guide not only further research and control efforts but also to improve national guidelines for prevention of infection.

## Ethical considerations

The Danish Data Protection Agency approved the study (journal 2012-54-0029). According to Danish regulations, ethical committee approval is not required for this study, as it did not involve analysis of biological material from human subjects.

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## Disclosure

The authors report no conflicts of interest in this work.

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