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Association between infections and functional somatic disorders: a cross-sectional population-based cohort study

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ABSTRACT

Objectives It has been suggested that infections can trigger functional somatic disorders (FSD). However, current evidence is limited by inconsistent findings in smaller studies conducted in clinical settings within selected populations and short follow-up times. We aimed to test the hypothesis that former infections are associated with FSD using data from nationwide registries and a large population-based cohort study, the Danish Study of Functional Disorders study.

Design FSD cases were identified in a cross-sectional population-based cohort and linked retrospectively to former hospital contacts with infections identified in the Danish National Patient Registry. The associations between FSD and former infections within 17 years were analysed using logistic regressions to calculate ORs and 95% CIs adjusted for age, sex and subjective social status.

Setting A population-based cohort in Denmark examined between 2011 and 2015.

Participants A total of 9656 men and women aged 18–76 years.

Main outcome measures FSD measured by various delimitations, including bodily distress syndrome (BDS), irritable bowel (IB), chronic fatigue (CF), chronic widespread pain (CWP), and multiple chemical sensitivity (MCS).

Results Overall, infections were associated with increased risk of all delimitations of FSD. The associations were more pronounced for multisystemic FSD. The number of prior infections increased the risk in a dose-response manner (p<0.0001). Bacterial but not viral infections were significantly associated with BDS (OR 1.69 (95% CI 1.46 to 1.96)), IB (OR 1.41 (95% CI 1.06 to 1.88)), CWP (OR 1.47 (95% CI 1.13 to 1.90)) and CF (OR 1.62 (95% CI 1.34 to 1.96)), but not MCS.

Conclusion Former infections leading to hospital contacts were associated with a higher risk of having FSD. These associations were more pronounced for bacterial than viral infections, and more infections increased the risk in a dose-response manner. These results tend to support the idea that severe infections could play a role in FSD.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Functional somatic disorder (FSD) cases were identified in a large cross-sectional population-based cohort (N=9656) and linked retrospectively to former hospital contacts with infections identified in the Danish National Patient Registry.

⇒ Various infection sites and infectious pathogens were assessed as exposures.

⇒ Multiple delimitations of FSD were assessed as outcomes including bodily distress syndrome, irritable bowel, chronic fatigue, chronic widespread pain and multiple chemical sensitivity.

⇒ We do not know the exact time of FSD onset, and we cannot exclude FSD preceding the infection. Thus, the determination of causality in this study, therefore, remains uncertain despite the infections being 17 years prior to baseline.

INTRODUCTION

Little is known about the aetiology of functional somatic disorders (FSD), but it is generally accepted that the aetiology is highly multifactorial,[1] and environmental triggers such as infections have been suggested to initiate the symptoms in FSD. FSD is an umbrella term for a range of conditions characterised by persistent and troublesome physical symptoms fitting characteristic symptom pattern(s) which are accompanied by impairment or disability that cannot be explained better by another physical or mental condition.[1] FSD encompass several delimitations such as irritable bowel syndrome (IBS), fibromyalgia (FM), chronic fatigue syndrome (CFS), multiple chemical sensitivity (MCS) and the unifying diagnostic construct bodily distress syndrome (BDS).[2 3]

Gastroenteritis is already considered a well-established risk factor for IBS,[4–7] where a systematic review and meta-analysis on gastroenteritis and IBS, including 21 421 individuals, found the strongest associations to IBS with parasitic followed by bacterial and, lastly, viral infection,[4] but no single pathogen has been identified. In the absence of gastrointestinal (GI) infections,

Table 1 The associations between any infection in the preceding 17 years and subdivided into time periods and various functional somatic disorder (FSD) delimitations expressed as ORs and 95% CIs adjusted for sex, age and subjective social status

	0–17 years before baseline		0–2 years before baseline		2–9 years before baseline		9–17 years before baseline	
	% FSD (N any infection)*	OR (95% CI)	% FSD (N any infection)*	OR (95% CI)	% FSD (N any infection)*	OR (95% CI)	% FSD (N any infection)*	OR (95% CI)
Bodily distress syndrome	21.9 (2228)	**1.68 (1.48 to 1.90)**	26.7 (454)	**2.02 (1.61 to 2.52)**	21.9 (1007)	**1.51 (1.28 to 1.78)**	23.2 (1129)	**1.67 (1.43 to 1.94)**
Oligo-organ bodily distress syndrome	20.3 (2185)	**1.63 (1.43 to 1.85)**	23.5 (435)	**1.83 (1.45 to 2.32)**	20.3 (988)	**1.47 (1.24 to 1.75)**	21.5 (1106)	**1.63 (1.39 to 1.91)**
Multi-organ bodily distress syndrome	2.4 (1784)	**2.74 (1.81 to 4.16)**	5.4 (352)	**5.89 (3.43 to 10.11)**	2.4 (806)	**2.14 (1.28 to 3.58)**	2.6 (891)	**2.39 (1.47 to 3.88)**
Irritable bowel	5.1 (2199)	**1.58 (1.25 to 2.00)**	5.1 (449)	1.51 (0.97 to 2.34)	4.4 (995)	1.23 (0.89 to 1.71)	5.1 (1113)	**1.41 (1.05 to 1.90)**
Chronic widespread pain	6.2 (2210)	**1.55 (1.25 to 1.93)**	8.2 (453)	**1.98 (1.37 to 2.85)**	6.0 (999)	**1.35 (1.01 to 1.81)**	6.0 (1120)	**1.36 (1.03 to 1.79)**
Chronic fatigue	12.7 (2214)	**1.69 (1.44 to 1.98)**	16.0 (451)	**2.10 (1.59 to 2.76)**	12.7 (998)	**1.51 (1.23 to 1.86)**	13.1 (1120)	**1.54 (1.26 to 1.88)**
Multiple chemical sensitivity	2.8 (2208)	**1.60 (1.17 to 2.19)**	2.7 (448)	1.29 (0.70 to 2.39)	2.7 (995)	1.46 (0.96 to 2.21)	2.9 (1121)	**1.62 (1.10 to 2.38)**
Pure irritable bowel	3.2 (1766)	**1.55 (1.13 to 2.14)**	2.6 (341)	1.20 (0.61 to 2.36)	3.0 (801)	1.37 (0.88 to 2.12)	2.9 (889)	1.28 (0.84 to 1.95)
Pure chronic widespread pain	3.4 (1777)	**1.51 (1.12 to 2.02)**	4.9 (349)	**1.81 (1.08 to 3.03)**	3.7 (807)	1.33 (0.89 to 1.99)	3.5 (894)	1.31 (0.89 to 1.94)
Pure chronic fatigue	9.2 (1884)	**1.60 (1.32 to 1.95)**	11.5 (375)	**1.95 (1.39 to 2.75)**	9.3 (857)	**1.49 (1.15 to 1.92)**	9.3 (951)	**1.43 (1.12 to 1.83)**
Pure multiple chemical sensitivity	1.8 (1741)	1.39 (0.91 to 2.12)	†	†	1.7 (790)	1.23 (0.69 to 2.21)	1.9 (880)	1.52 (0.90 to 2.57)

Logistic regression analyses of the association between any infection versus no infection and FSDs. Analyses were performed for the 17 preceding years, 0–2 years, 2–9 years and 9–17 years and were adjusted for sex, age and subjective social status. Numbers marked with bold are significant with a p-value <0.05

*N varies as analyses were done on complete cases; thus, only participants with data on the specific FSD delimitation *and* specific infection were included in analyses.

†Time period not subdivided due to few cases.

N, number of participants;

Table 2 The associations between the number of infections in the preceding 17 years and bodily distress syndrome (BDS) and various infection sites in the preceding 17 years and BDS expressed as ORs and 95% CIs adjusted for sex, age and subjective social status

Number of infections	% BDS (N any infections*)	OR (95% CI)
1	20.7 (1248)	**1.58 (1.36 to 1.84)**
2	18.2 (510)	**1.36 (1.07 to 1.72)**
3	26.8 (224)	**2.23 (1.65 to 3.04)**
4	29.0 (93)	**2.42 (1.53 to 3.82)**
≥ 5	32.0 (153)	**2.93 (2.06 to 4.16)**
Test for trend		**1.26 (1.20 to 1.32)** p<0.0001
Infection site†	% BDS (N infection site*)	OR (95% CI)
Sepsis	32.3 (62)	**2.65 (1.52 to 4.63)**
Hepatitis	25.0 (20)	1.68 (0.60 to 4.73)
Reproductive system	22.3 (130)	1.40 (0.91 to 2.15)
Pregnancy related	22.7 (75)	1.31 (0.74 to 2.31)
Central nervous system	26.3 (38)	1.97 (0.94 to 4.15)
Ear	24.7 (85)	**1.70 (1.02 to 2.82)**
Skin	21.8 (607)	**1.59 (1.29 to 1.95)**
Urinary tract system	25.9 (247)	**1.58 (1.17 to 2.13)**

Logistic regression analyses of the association between the number of any infections versus no record of any infection in the preceding 17 years and BDS adjusted for sex, age and subjective social status, and logistic regression analyses of the association between various infections sites versus no record of specific infection site and BDS in the preceding 17 years adjusted for sex, age and subjective social status. Numbers marked with bold are significant with a p-value <0.05

*N varies as analyses were done on complete cases; thus, only participants with data on the specific functional somatic disorder delimitation *and* specific infection measures were included for analyses.

†Specific International Classification of Diseases 10th revision (ICD-10) codes may be found in online supplemental table S1.

N, number of participants.

the risk factors of IBS are less well-established.[7] Opposite, literature remains inconclusive on the association between infections and CFS despite intensive research. Various viral agents as triggers of CFS have been investigated with conflicting findings, for example, human herpesvirus, B19 virus and enterovirus,[8] and similarly, various latent bacterial infections such as Coxiella burnetii, borrelia burgdorferi and brucella.[9] The relationship between infections and FM has likewise been debated for decades,[10] where bacterial infections such as borrelia burgdorferi and mycoplasma and viral

infections, for example, HIV and hepatitis C, have been associated with FM,[11 12] but no evidence of a causal link has been established.[13] To our knowledge, no specific infections have been assessed regarding MCS, but MCS has been associated with self-reported inflammatory airway diseases.[14]

With the exceptions of larger cohort studies on IBS, most of the prior studies of infections and the associations with FSDs are limited by small sample sizes and highly heterogenic study designs ranging from case reports and case–control studies to fewer prospective cohort studies conducted in highly specialised clinical settings. Furthermore, most studies only had a short follow-up time, limiting the knowledge of the long-term effects of infections in the development of FSD. The indicators of infection and delimitations of FSD vary greatly, making it difficult to analyse and compare the current studies in a systematic and consistent manner. Most prior studies only assessed one delimitation of FSD at a time without taking the overlap into account, and similarly, few specific infection sites or pathogen types at a time, thereby lacking the broader focus on infections and FSD in general.

The present study aimed to systematically assess whether former infections identified in nationwide registers were associated with FSD identified in a population-based cohort. Furthermore, we aimed to analyse if the possible association between former infections and FSD was based on viral, bacterial or other pathogens and on specific infection sites. We hypothesised that former infections were associated with a higher risk of FSD.

METHODS
Study population
The present population-based cohort study was part of the Danish Study of Functional Disorders (DanFunD).[15] The participants were born in Denmark, between 18 and 76 years of age and living in the western part of greater Copenhagen. The participants were randomly invited from the nationwide Danish Civil Registration System. A total of 9656 (33.7%) out of 28 433 invited persons were included in the baseline DanFunD cohort investigation in 2011–2015 and answered extensive questionnaires previously described.[15]

Patient and public involvement
Patients or the public were not involved in this study's design, conduct, reporting or dissemination plans.

Exposure: infections
All inpatient and outpatient hospital contacts with a primary or secondary diagnosis of any infection occurring 0–17 years (subdivided into 0–2 years, 2–9 years and 9–17 years) before the individual date of inclusion in DanFunD were identified in the Danish National Patient Registry,[16 17] which contains complete information on all Danish citizens regarding both inpatients and outpatients treatment since 1995. The longest period in this registry available for each individual in the population was 17 years, which was applied for all participants to ensure equal period of observation.

Infections were subcategorised into pathogen type (bacteria, virus and others (parasites, fungi and unspecified)), infection site (respiratory, GI, skin, urological, sepsis, genital, pregnancy-related, central nervous system and otitis) and the number of hospital contacts with an infection (1, 2, 3, 4, ≥5) within the preceding 17 years. See online supplemental table S1 for specific International Classification of Diseases 10th revision (ICD-10) codes applied.

Outcome: FSD
Multiple delimitations of FSD based on self-reported symptom questionnaires at DanFunD baseline were included as outcomes.[18]

The BDS concept[3] is based on four symptom clusters: cardiopulmonary, GI, musculoskeletal and general symptoms. The 25-item BDS checklist was used[19] to identify BDS cases. Oligo-organ BDS was assigned to participants with at least four symptoms within one or two of the symptom clusters. Multi-organ BDS was assigned to participants with at least four symptoms from at least three symptom clusters.

Irritable bowel (IB) was defined using the definition by Kay and Jørgensen.[20] Chronic widespread pain (CWP) was defined using the American College of Rheumatology Criteria[21] and the definition by White *et al*,[22] and chronic fatigue (CF) was defined using the definition by Chalder *et al*.[23] MCS was defined as an abridged adaptation of the 1999 consensus definition[24] with modifications by Lacour *et al*.[25 26] Due to disagreements on terminology and criteria, we will use broader symptom criteria: the term irritable bowel (IB) is used to describe IBS, chronic fatigue (CF) is used for describing CFS,and chronic widespread pain (CWP) is used for describing FM when referring to our findings. See online supplemental table S2 for diagnostic criteria.

As IB, CF, CWP and MCS show a significant overlap,[18] 'pure'' delimitations, including individuals without comorbid FSD (ie, IB, CWP, CF and MCS), were assessed in individual analyses (ie, pure IB, pure CF, pure CWP and pure MCS).

Subjective social status
Subjective social status was based on the individual's evaluation of social status.[22] In the DanFunD baseline questionnaire, participants were asked to rate their social status on a scale from 1 to 10, 10 being the highest and 1 being the lowest. Subjective social status was included as a categorical variable with four levels: low,[1–4] average,[5] high[6 7] and highest.[8–10]

Data analysis
Participant characteristics were presented using percentages or mean and SD and were stratified by any infection versus no infection. Differences in age and sex were analysed using a t-test and χ^2 test.

The associations between preceding infections and FSD at baseline were analysed using logistic regression analysis and expressed as ORs with 95% CIs. All analyses were adjusted for sex, age and subjective social status at the DanFunD baseline examination. The exposures were any infection versus no infection and infection with a specific pathogen/site vs no record of infection with the specific pathogen/site.

All individual analyses were conducted on complete samples; thus, participants had complete data on both individual exposure and outcome. The same individual could be included in more than one analysis, as individuals could qualify for multiple delimitations of FSD and may be exposed to several different infections in various periods.

The associations between any infection and FSD were analysed separately for each delimitation of FSD and in subdivided periods. However, we did not have enough cases to assess the association between any infection 0–2 years before baseline and pure MCS.

The associations between specific pathogen types (bacteria, virus and other pathogens) and GI and respiratory infections were analysed separately for each period of BDS, IB, CWP and CF. We did not have enough cases to assess the association between viral infection 0–2 years before baseline and IB. The periods were not subdivided for the associations with MCS due to few cases, nor was BDS assessed as oligo/multi-organ BDS due to few cases.

Analyses of pure IB, pure CWP, pure CF and pure MCS were conducted for a period of 0–17 years. We did not have enough cases to assess the association between viral and GI infections and pure MCS. Additionally, analyses of the remaining infection sites (sepsis, reproductive system, hepatitis, pregnancy-related, central nervous system, ear, skin and urinary tract system) were only conducted for BDS for the entire period of 0–17 years, as this outcome had the most cases.

The dose-response associations between the number of infections and BDS were assessed. BDS was chosen as the outcome because of the high number of cases. The association was assessed by including the number of infections as a categorical variable in the model and as a continuous variable (test for trend). Only linear associations were assessed.

RESULTS
Participant characteristics
A total of 9656 were included in the study, among which the prevalence of FSD was 16.1% for BDS, 3.6% for IB, 4.6% for CWP, 8.6% for CF and 2.0% for MCS. Participants who had hospital contact with any infection in the preceding 17 years numbered 2253 (23.4%). Participants with any infection in the preceding 17 years were younger (mean 51.0 years) than participants without any infection (mean 53.0 years, p<0.0001), whereas there was no difference regarding sex (p=0.699) and subjective social status (online supplemental table S3).

Overall associations between infections and FSD

Overall, any infection in the preceding 17 years was significantly associated with all delimitations of FSD except pure MCS (table 1). The associations were more pronounced for multi-organ BDS (OR: 2.74; 95% CI 1.81 to 4.16). The number of infections in the preceding 17 years was associated with BDS in a dose-response association both when the number of infections was included as a continuous and categorical variable (linear association and test for trend (p<0.0001)) (table 2).

INFECTION SITES

GI infections in the preceding 17 years were significantly associated with all delimitations except pure CWP (table 3, table 4). Respiratory infections in the preceding 17 years were significantly associated with all delimitations, except MCS, pure IB, pure CWP and pure MCS (table 3, table 4). Sepsis, ear infections, skin infections and urological infection in the preceding 17 years were significantly associated with BDS, whereas hepatitis, genital infections, pregnancy-related infections and infections in the central nervous system were not (table 2).

Pathogen type

We found bacterial infections in the preceding 17 years to be significantly associated with all FSD delimitations except MCS, pure IB and pure MCS (table 4, table 5), whereas viral pathogens were not significantly associated with any FSD delimitation at any time (table 4, table 5). Infections with other pathogens in the preceding 17 years were significantly associated with all delimitations except pure IB and pure CWP (table 4, table 5).

Temporal associations

Any infection was significantly associated with BDS (oligo-organ and multi-organ type), CWP, CF and pure CF in all subdivided periods (table 1), while the associations between infections in the preceding 0–2 years and 2–9 years and IB and MCS were not significant. Concerning the pure types, no significant associations between any infections and pure IB and pure MCS were seen in any subdivided periods and with pure CWP in the time 2–9 years and 9–17 years.

The associations between GI infections and BDS, IB, CWP and CF were significant in all subdivided periods except for IB in the time 0–2 years and 9–17 years, and CWP in the time 0–2 years (table 3).

Respiratory infections 0–2 years before baseline were significantly associated with BDS, IB, CWP and CF, but not 9–17 years before baseline. Further, the associations with BDS and CF in the time 2–9 years were also significant, but the associations with IB and CWP were not (table 3).

Bacterial infections were significantly associated with BDS, CWP and CF in all subdivided periods except 2–9 years with CWP and 9–17 years with CF (table 5). Bacterial infections were not significantly associated with IB in any subdivided time.

The associations between other pathogens and all delimitations of FSD were significant in all subdivided periods except for infections in the preceding 2–9 years and 9–17 years with IB (table 5).

DISCUSSION

Statement of principal findings

Overall, we found that any infection in the preceding 17 years was significantly associated with all delimitations of FSD except pure MCS. Moreover, the association with prior infections was strongest for multisystemic FSD (multi-organ BDS), and there was a dose-response association between the number of infections and FSD. Bacterial and other pathogens and respiratory and GI infection sites were associated with most FSD delimitations.

Strengths and limitations

To our knowledge, this is the first larger population-based study investigating the long-term associations between various infection sites and pathogens with various delimitations of FSD, and the largest period assessed regarding infections and FSD. Furthermore, this is the first study to investigate a possible dose-response association between the number of infections and FSD.

The cohort being population-based limits the selection bias and strengthens the external validity. However, the lack of clinically diagnosed FSD is an important limitation, as the FSD delimitations in this study were based on self-reported symptoms and did not consider comorbidities or differential diagnoses.[27] However, the FSD delimitations were based on internationally recognised criteria and thereby comparable to other studies. Infections and pathogens were clinically diagnosed during hospital admittance, including only severe cases. Unless only severe infections are associated with FSD, this might lead to a general underestimation of the associations, as infections treated in primary care are not included. This might also explain our study's lack of association between viral infections and FSD. A low number of observations could also explain the lack of associations with other pure profiles. Future studies are needed to assess milder infections' associations with FSD.

The validity of national registers is generally high,[16] and infections were defined using ICD-10 codes, making the exposures valid and reliable. Nonetheless, some misclassification in the type of infection may be expected, especially in the category 'other', where we were unable to subgroup into parasites, fungi and unspecific infections due to small numbers of observations. Therefore, our findings of associations with other pathogens might be additional support that infections, in general, are associated with FSD. The lack of subgrouping of other pathogens is a significant limitation; for example, specific associations between the parasite Giardia and IBS (prevalence=292/733) and CF (prevalence=226/733) up to 6 years after the infection have been found.[28]

Table 3 The associations between gastrointestinal or respiratory infection in the preceding 17 years and subdivided into time periods and various functional somatic disorder (FSD) delimitations expressed as ORs and 95% CIs adjusted for sex, age and subjective social status

	0–17 years before baseline		0–2 years before baseline		2–9 years before baseline		9–17 years before baseline	
	% FSD (N infection site*)	OR (95% CI)	% FSD (N infection site*)	OR (95% CI)	% FSD (N infection site*)	OR (95% CI)	% FSD (N infection site*)	OR (95% CI)
Gastrointestinal infection								
Bodily distress syndrome	27.5 (393)	**2.01 (1.58 to 2.55)**	30.9 (55)	**2.31 (1.28 to 4.17)**	24.0 (146)	**1.68 (1.12 to 2.51)**	31.7 (208)	**2.40 (1.76 to 3.27)**
Irritable bowel	7.0 (387)	**1.84 (1.22 to 2.79)**	9.4 (53)	2.45 (0.96 to 6.26)	8.2 (146)	**2.31 (1.25 to 4.25)**	5.4 (204)	1.28 (0.69 to 2.40)
Chronic widespread pain	7.9 (392)	**1.87 (1.25 to 2.78)**	9.1 (55)	2.11 (0.81 to 5.51)	8.2 (146)	**2.10 (1.13 to 3.90)**	8.2 (207)	**1.84 (1.08 to 3.15)**
Chronic fatigue	18.6 (387)	**2.14 (1.62 to 2.84)**	21.8 (55)	**2.60 (1.33 to 5.08)**	16.4 (146)	**1.83 (1.14 to 2.94)**	21.8 (202)	**2.53 (1.76 to 3.64)**
Multiple chemical sensitivity†	4.1 (387)	**2.28 (1.34 to 3.86)**						
Respiratory infection								
Bodily distress syndrome	23.2 (560)	**1.62 (1.32 to 2.01)**	29.9 (137)	**2.23 (1.51 to 3.29)**	23.2 (237)	**1.56 (1.13 to 2.14)**	18.7 (225)	1.23 (0.87 to 1.74)
Irritable bowel	5.8 (551)	**1.70 (1.17 to 2.49)**	6.7 (134)	**2.00 (1.00 to 4.01)**	5.9 (236)	1.67 (0.95 to 2.92)	4.1 (220)	1.15 (0.58 to 2.28)
Chronic widespread pain	7.7 (556)	**1.77 (1.26 to 2.49)**	9.6 (136)	**1.91 (1.02 to 3.56)**	7.2 (237)	1.52 (0.90 to 2.55)	6.3 (222)	1.48 (0.84 to 2.60)
Chronic fatigue	13.4 (558)	**1.58 (1.21 to 2.07)**	17.4 (138)	**2.10 (1.30 to 3.40)**	14.4 (237)	**1.67 (1.14 to 2.46)**	9.9 (222)	1.13 (0.71 to 1.79)
Multiple chemical sensitivity†	3.1 (551)	1.63 (0.98 to 2.72)						

Logistic regression analyses of the association between gastrointestinal infection versus no gastrointestinal infection and FSDs, and the association between respiratory infection versus no respiratory infection and FSDs. All analyses were performed for the 17 preceding years, 0–2 years, 2–9 years and 9–17 years and adjusted for sex, age and subjective social status. Numbers marked with bold are significant with a p-value <0.05
*N varies as analyses were done on complete cases; thus, only participants with data on the specific FSD delimitation *and* specific infection were included for analyses.
†Time periods not subdivided due to few cases.
N, number of participants;

Table 4 ORs and 95% CIs of various infections in the preceding 17 years with various pure* functional somatic disorder (FSD) delimitations adjusted for sex, age and subjective social status

| | Pathogen types | | | | | | Infection sites | | | |
| | Bacteria | | Virus | | Other† pathogens | | Respiratory system | | Gastrointestinal system | |
	% FSD (N bacterial infection‡)	OR (95% CI)	% FSD (N viral infection‡)	OR (95% CI)	% FSD (N other pathogen‡)	OR (95% CI)	% FSD (N respiratory infection‡)	OR (95% CI)	% FSD (N gastrointestinal infection‡)	OR (95% CI)
Pure irritable bowel	3.0 (1002)	1.39 (0.93 to 2.07)	2.5 (316)	1.05 (0.51 to 2.17)	3.3 (611)	1.43 (0.89 to 2.30)	3.2 (433)	1.45 (0.83 to 2.54)	4.9 (288)	**2.16 (1.23 to 3.81)**
Pure chronic widespread pain	4.1 (1013)	**1.49 (1.05 to 2.12)**	3.8 (320)	1.68 (0.92 to 3.06)	3.6 (613)	1.35 (0.86 to 2.12)	3.9 (436)	1.41 (0.85 to 2.36)	2.8 (282)	1.09 (0.53 to 2.25)
Pure chronic fatigue	9.2 (1071)	**1.57 (1.24 to 1.98)**	9.7 (341)	1.40 (0.95 to 2.05)	10.3 (659)	**1.55 (1.17 to 2.04)**	9.5 (463)	**1.49 (1.06 to 2.07)**	12.2 (312)	**1.75 (1.21 to 2.53)**
Pure multiple chemical sensitivity	1.3 (985)	0.87 (0.48 to 1.59)	§	§	2.6 (607)	**2.15 (1.26 to 3.69)**	1.9 (427)	1.39 (0.67 to 2.89)	§	§

Logistic regression analyses of the association between specific infection versus no specific infection and FSDs. Analyses were performed for the 17 preceding years and adjusted for sex, age and subjective social status. Numbers marked with bold are significant with a p-value <0.05
*Pure functional somatic disorders are defined as delimitations of functional somatic disorders without comorbidity of another functional somatic disorder.
†Other pathogens include parasites, fungi and unspecified infections. See online supplemental table S1 for specific International Classification of Diseases 10th revision (ICD-10) codes applied.
‡N varies as analyses were done on complete cases; thus, only participants with data on the specific FSD delimitation and specific infection were included for analyses.
§Time periods not subdivided due to few cases.
N, number of participants;

It could be argued that adjustment for only sex, age and subjective social status is inadequate, making the associations vulnerable to underlying confounding factors, for example, personality types. However, more adjustments would increase the risk of over-adjustment, as the aetiology and risk factors for FSD are still poorly understood.

It could also be argued that subjective social status measured simultaneously with FSD might be affected by, for example, the occurrence of infections and FSD, making it an unstable confounder. Nevertheless, subjective social status 'involve[s] cognitive averaging of standard markers of socioeconomic position, while taking into account one's assessment of current and future prospects',[29] hence providing a more global measurement of social status, making it a stable and valid measurement of social status.

The time dimensions of this study are essential to consider. First, due to the 17-year time span, we lack information on outpatient treatment regarding a small number of participants included in DanFunD in 2011, as outpatient treatment was recorded only from 1995. However, the associated risk of information bias is considered minimal, as we expect this to involve a very small number of cases, and we have information on all severe infections as inpatient treatments. Second, infections might affect the risk of FSD differently over a life course, for example, infections in childhood versus adulthood, which our study does not investigate. Third, we do not know the exact time of FSD onset, so we cannot exclude FSD preceding the infection. This is important as the determination of causality in this study, therefore, remains uncertain. Assessing infections 17 years prior to the DanFunD baseline limits the risk of misinterpretation, yet future studies with incident FSD cases are needed to confirm our findings.

Interpretation and comparison with related studies

The findings of significant associations with FSD across multiple delimitations of FSD, various pathogen types and infection sites may indicate that not one specific pathogen trigger FSD, but rather having a severe infection, in general, may function as a trigger of FSD. This is further supported by our finding of a dose-response association where a number of infections are associated with a higher risk of fulfilling the criteria for BDS. This is also supported in the literature; for example, Hickie et al[30] investigated the associations between Epstein-Barr virus, the bacterium Coxiella burnetii and Ross River virus and CFS (n=28/253) with a 12-month follow-up and found the severity of the infection, not the type of infection to predict CFS, as the different pathogens were associated with the same risk of CFS. Additionally, a recent meta-analysis reported that different bacteria bring with them the same risk of IBS,[6] thus limiting the hunt for one specific pathogen.

A systematic review and meta-analysis found the highest rates of IBS after protozoal/parasitic infectious enteritis, followed by bacterial and, lastly, viral infections. The study

Table 5 The associations between bacterial, viral or infections with other pathogens in the preceding 17 years and subdivided into time periods and various functional somatic disorder (FSD) delimitations expressed as ORs and 95% CIs adjusted for sex, age and subjective social status

	0–17 years before baseline		0–2 years before baseline		2–9 years before baseline		9–17 years before baseline	
	% FSD (N pathogen*)	OR (95% CI)	% FSD (N pathogen*)	OR (95% CI)	% FSD (N pathogen*)	OR (95% CI)	% FSD (N pathogen*)	OR (95% CI)
Bacterial infections								
Bodily distress syndrome	23.2 (1263)	**1.69 (1.46 to 1.96)**	27.1 (262)	**2.07 (1.55 to 2.76)**	23.5 (580)	**1.59 (1.29 to 1.96)**	24.6 (574)	**1.72 (1.40 to 2.11)**
Irritable bowel	4.8 (1245)	**1.41 (1.06 to 1.88)**	5.0 (259)	1.52 (0.86 to 2.71)	4.2 (571)	1.16 (0.76 to 1.78)	5.3 (567)	1.43 (0.97 to 2.11)
Chronic widespread pain	6.4 (1251)	**1.47 (1.13 to 1.90)**	8.4 (261)	**2.12 (1.34 to 3.35)**	5.9 (574)	1.26 (0.85 to 1.80)	6.3 (570)	**1.48 (1.13 to 1.93)**
Chronic fatigue	12.8 (1255)	**1.62 (1.34 to 1.96)**	15.4 (260)	**2.14 (1.49 to 3.06)**	13.0 (575)	**1.51 (1.16 to 1.98)**	12.8 (569)	1.35 (0.94 to 1.94)
Multiple chemical sensitivity†	2.3 (1256)	1.16 (0.77 to 1.74)						
Viral infections								
Bodily distress syndrome	19.0 (390)	1.29 (0.99 to 1.68)	23.2 (69)	1.53 (0.86 to 2.74)	18.5 (162)	1.24 (0.82 to 1.87)	18.8 (186)	1.27 (0.87 to 1.87)
Irritable bowel	3.6 (389)	0.90 (0.52 to 1.56)	†	†	4.4 (161)	1.06 (0.49 to 2.31)	3.8 (186)	0.96 (0.45 to 2.08)
Chronic widespread pain	5.2 (388)	1.37 (0.85 to 2.20)	7.4 (68)	1.89 (0.74 to 4.86)	5.6 (160)	1.56 (0.78 to 3.13)	3.7 (187)	0.92 (0.43 to 2.00)
Chronic fatigue	11.7 (385)	1.23 (0.88 to 1.72)	13.0 (69)	1.30 (0.62 to 2.70)	12.0 (159)	1.20 (0.73 to 1.99)	12.0 (184)	1.28 (0.80 to 2.04)
Multiple chemical sensitivity†	2.3 (388)	1.26 (0.64 to 2.49)						
Other‡ pathogens								
Bodily distress syndrome	25.2 (810)	**1.86 (1.56 to 2.21)**	31.0 (155)	**2.41 (1.68 to 3.45)**	24.0 (346)	**1.70 (1.30 to 2.20)**	25.9 (374)	**1.82 (1.42 to 2.33)**
Irritable bowel	5.9 (799)	**1.65 (1.19 to 2.28)**	7.2 (152)	**2.05 (1.09 to 3.87)**	5.5 (344)	1.48 (0.92 to 2.40)	4.9 (368)	1.25 (0.76 to 2.05)
Chronic widespread pain	8.1 (806)	**1.93 (1 .45 to 2.57)**	9.0 (155)	**1.91 (1.05 to 3.48)**	7.5 (345)	**1.75 (1.14 to 2.68)**	8.1 (371)	**1.85 (1.24 to 2.77)**
Chronic fatigue	15.6 (799)	**1.87 (1.51 to 2.32)**	20.9 (153)	**2.59 (1.69 to 3.97)**	13.7 (342)	**1.55 (1.11 to 2.15)**	17.4 (368)	**2.03 (1.51 to 2.72)**
Multiple chemical sensitivity†	4.1 (797)	**2.41 (1.63 to 3.54)**						

Logistic regression analyses of the association between bacterial infection versus no bacterial infection and FSDs, the association between viral infection versus no viral infection and FSDs and the association between infection with other pathogens versus no infection with other pathogens and FSDs. All analyses were performed for the 17 preceding years, 0–2 years, 2–9 years and 9–17 years and adjusted for sex, age and subjective social status. Numbers marked with bold are significant with a p-value <0.05

*N varies as analyses were done on complete cases; thus, only participants with data on the specific FSD delimitation *and* specific pathogen were included for analyses.

†Time periods not subdivided due to few cases.

‡Other pathogens include parasites, fungi and unspecified infections. See online supplemental table S1 for specific International Classification of Diseases 10th revision (ICD-10) codes applied.

N, number of participants;

was based on 45 cohort studies comprising 21 421 individuals with infectious enteritis followed from 3 months to 10 years port infection. The risk of IBS decreased to that of the general non-diseased population 1 year post viral exposure.[4] Similarly, we found GI infections, bacterial infections and other pathogens in the preceding 17 years to be significantly associated with IB but not viral infections. As our shortest time span was 0–2 years post infection, the lack of an association between IB and viral infections might reflect the decrease identified in the meta-analysis.[4]

In a 10-year population-based follow-up study, an elevated risk of IBS after bacterial infection was insignificant 5 years post infection and was similar to controls at 10-year follow-up.[31] In contrast, another study found bacterial infections to be associated with subsequent IBS 8 years post infection in another population-based study.[32] We did not find consistent associations with IB when subdividing the periods. This might be due to fewer cases but may also be explained by our periods having large time spans, thus reflecting a decrease in the risk of IB with time.

Multiple infections were associated with CWP. In contrast to previous studies,[11 12] we do not find a significant association with viral infections. However, our findings support previous studies[11 12] on associations between bacterial agents and CWP, with bacterial infections being significantly associated with both CWP and pure CWP.

Supporting the findings of Hickie et al,[30] we consistently find multiple types of infection associated with CF and pure CF, indicating infection in general, not merely the pathogen type, to be important. Larger overlaps between the delimitations have previously been found.[33] When assessing the pure profiles and thus eliminating FSD comorbidity, we notice CF standing out by still being associated with other pathogens, respiratory infections and GI infections. This indicates CF comorbidity might play a part in the association between these infections and other FSD delimitations.

Meaning of the study and unanswered questions

Former infections have previously been associated with subsequent mood disorders.[34 35] Direct consequences of infection and inflammation such as dysregulation of the immune system[36 37] and altering the microbiota[37–39] could explain the association between infections and FSD, but indirect consequences, for example, treatment with antibiotics[40] or the interpretation and experience of being sick might also play part in the development of specific FSDs. Psychological factors, that is, personality, mental state and illness-related behaviour, have previously been associated with FSD[41 42] and might affect the association, for example, as effect modifiers or even mediators. Thus, infections could act as a precipitating factor, which 'may initiate a process of sensitization in predisposed individuals, which is then maintained and reinforced by perpetuating factors',[42] such as health-expectations, personality or coping strategies.

Importantly, a common vulnerability to infections or diseases in general could also explain the association. As such, a genetic predisposition has been proposed in the development of IBS,[43] but the common vulnerability could also be psychological or social for example through illness-related behaviour. Future studies assessing the association of other severe physical diseases (eg, cardiovascular disease, diabetes mellitus, cancer) with the development of FSD would be valuable in understanding infections compared with other severe physical diseases in general.

Conclusion and perspectives

Previous severe infections were associated with a higher risk of having FSD showing more pronounced associations with multisystemic FSD. Higher numbers of infections were associated with a higher risk of FSD, and former bacterial, but not viral, infection was consistently significantly associated with FSD. These results tend to support the idea that infections could play a role in FSD, but further prospective population-based studies are needed to confirm our findings.

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