

Original article

Infections presenting for clinical care in early life and later risk of hay fever in two UK birth cohorts

Background: The 'hygiene hypothesis' proposes that infections in infancy protect against hay fever (HF). We investigated infections during infancy in relation to HF, including rarer ones not previously researched in this context, while examining the role of potential confounding variables.

Methods: From birth cohorts derived within the General Practice Research Database (GPRD) and Doctors Independent Network (DIN) database of computerized patient records from UK general practice, we selected 3549 case-control pairs, matched for practice, age, sex and control follow-up to case diagnosis. Conditional logistic regressions were fitted for each of 30 infections; behavioural problems (BP) acted as a control condition unrelated to HF. Odds ratios (OR), adjusted for consultation frequency were pooled across the databases using fixed effect models. We also adjusted for sibship size in GPRD and a socioeconomic marker in DIN.

Results: Upper respiratory tract infections, diarrhoea and vomiting and acute otitis media in infancy were each related with a moderately increased risk of HF in both databases, as were BP. These associations were lost on adjustment for consultation frequency. Only bronchiolitis was significantly associated with a reduced pooled risk of HF after adjustment for consultations (OR = 0.8). Adjustment for sibship size in GPRD and a socioeconomic marker in DIN had little impact on the OR.

Conclusions: Of 30 infectious illnesses investigated, none had strong or consistent associations with HF after adjustment for consultation frequency. Except for bronchiolitis, possibly a chance finding, none of the clinically apparent infections considered appear to have an important role in allergy prevention.

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The 'hygiene hypothesis' for allergy as originally proposed, suggested that infections caught from older siblings offer protection against hay fever (HF) (1). Many studies have investigated infections in relation to atopic diseases, but the role of specific infections remains unclear. Where associations have been found the mechanisms proposed remain speculative and controversial.

A Canadian study of Saskatchewan Métis and white communities found that IgE levels were higher in the Métis who also experienced a greater burden of infection (2). Helminth infestation increases IgE and induces a Th2 response. However, allergy is less common in developing countries, where infestation is more common. Huang et al. (3) found that pinworm had an inverse association with rhinitis (odds ratio; OR = 0.61). van den Biggelaar et al. (4) concluded that chronic schistosomiasis was key to atopy suppression in Gabonese children. A study in rural Ecuador found that positive skin prick tests were less common in children infested with worms (OR = 0.62), but the overall prevalence of skin prick test positivity was 18% (5).

On the other hand, hepatitis A seropositivity has been associated with reduced atopy in several studies. A cross-sectional study of over 1600 air force students in Italy found that those seropositive for hepatitis-A virus (HAV) had a lower prevalence of atopy (6). A larger USA study by the same author found a much reduced prevalence of HF in HAV-seropositive residents (7). Other seroepidemiological studies support an inverse association of atopic diseases with bacterial infections acquired by the orofaecal route such as *Helicobacter pylori* (8–10), and inverse associations have also been reported with seropositivity to herpes simplex virus and cytomegalovirus (9).

Several studies have investigated measles infection and/or measles vaccination in relation to atopy. The largest such study of around 555 000 Finnish children found an increased prevalence (OR = 1.41) of allergic rhinitis in MMR-recipients who had had measles (11). However, in 6000 British children both measles vaccination and infection were associated with a reduced risk of HF amongst children with multiple older sib contacts (12).

A study of survivors of a measles epidemic in Guinea Bissau reported an extremely low OR of HF of 0.36 (13). It has been suggested that this may be because atopic children are less able to mount a response against infectious diseases rather than an effect of the infection on the developing immune system (14).

Respiratory infections in infancy have been considered in several studies with varying results. A very large Swedish study did not find a convincing association between neonatal respiratory disorders and allergic rhinitis (15). In Tasmania, a prospective study reported no association between upper respiratory tract (URTI) or lower respiratory tract infection and HF 7 years later (16).

A study in one UK General Practice (GP) found increased risk of HF with a number of infections, including croup and chickenpox, which were both statistically significant (17). However, another study based on 53 practices found that associations between infections in early life and HF were largely lost on adjustment for the number of medical visits in each 6-month interval (18). The advantage of using primary care data is that it is possible to examine a broad range of infections presenting to family doctors in early childhood.

In previous work, we examined the relationship of HF to antibiotics. In both our study and in other major epidemiological studies reviewed, no consistent effect was apparent after adjusting for frequency of consultation (19). However, antibiotics may be considered both a marker of infections as well as of a reduced infection burden after administration, including effects on gut flora.

In this paper, we use two large primary care databases, the General Practice Research Database (GPRD) and the Doctors Independent Network (DIN) database, to investigate the association between a variety of childhood infections recorded in GP during infancy and later HF. We focused on HF because: (i) it gave rise to the hygiene hypothesis; (ii) it is specifically an allergic condition, unlike asthma which has allergic and nonallergic components; (iii) its onset is largely distinct in time (mostly after age 2) from the period of exposure of interest (year 1), unlike eczema and asthma and (iv) it is common and well recorded in GP databases. This extends the work of McKeever who addressed similar questions in a regional subset of the GPRD (18). Because we had longer follow up and the whole of GPRD as well as DIN, our study has high statistical power for investigating common infections and allows some rarer conditions to be studied. At the same time, we were able to control for the confounding effect of consultation frequency; in GPRD we also investigated the confounding effect of sibship size while in DIN we investigated the role of socio-economic status using the ACORN (A Classification of Residential Neighbourhoods) index, thus addressing some of the criticisms of earlier studies made by Van Schayck and Knottnerus (20).

Methods

We designed nested case-control studies within a GPRD cohort of 76 310 children born between 1989 and 1993 from 464 practices and within a DIN cohort of 40 183 children born between 1989 and 1997 from 141 GP. All children had at least 5 years of continuous follow-up from birth and had been registered with the practice within 3 months of birth. For each case of HF, we randomly selected one control child, matched for GP, sex, birth month and follow-up of control to at least date of case diagnosis. Analysis was based on fitting conditional logistic regression models using *proc phreg* in SAS (version 8.1 for SunOS) (21). A more detailed account can be found in Bremner et al. 2003 (19). The advantages of using the two separate databases are: (i) we can assess consistency of results across databases; (ii) pooling data from both databases increases power and (iii) we can adjust for confounders only available in one or other database. Estimates from the two databases were pooled using a fixed-effects model by way of the *meta* command in STATA (version 9.0 for Windows) (22, 23).

We explored a wide variety of infections from commonly recorded, such as diarrhoea and vomiting, to infrequently recorded such as measles, as defined in DeWilde et al. 2003 (24). The common childhood infections presented therein were supplemented with fever/pyrexia, abscesses, boils and nail infections, meningitis, septicaemia and warts to enable a more comprehensive investigation. Children were flagged as either having been diagnosed or not with any particular infection in the first year of life, based on relevant Read and OXMIS codes. The vast majority of these diagnoses would have been made in primary care at the time of a consultation. However, hospital admissions for conditions, such as pneumonia or bronchiolitis would also be included. As a control condition, we also included behavioural problems (BP) in our selection as these are common and there is no evidence linking them to the risk of developing HF.

The rationale behind adjusting for consultation frequency is that regular attenders are more likely to have any infectious diseases recorded and more likely to be diagnosed with HF if they suffer from the symptoms. Thus, there is likely to be positive confounding between infections and HF, which might mask any protective effect. The challenge is to define the most appropriate adjustment for consultation frequency. An association could be reversed if we over-adjust and this could easily arise, given that definitions of consultation frequency potentially incorporate information on the infections we wish to study as exposures as well as consultations for HF. To define an appropriate measure of consultation frequency it seemed logical to prefer consultations during years 2–5 rather than in year 1 given our interest in measuring exposure to infections during year 1. We also wished to consider: (i) the bias arising if the control was a potential ghost (by ghosts we mean controls still registered with a practice, but who have moved away); (ii) the effect of adjusting for consultations in year 1, except consultation for URTI/cold, diarrhoea and vomiting or BP (because these are major reasons for consulting in year 1 as well as being exposures of interest) and (iii) the confounding effect of sibship size and socio-economic factors. Finally, in previous work (19, 25) we adjusted for all consultations in years 1–5, and so include it here for completeness and comparability.

To address these issues, we considered a spectrum of adjustments for consultation frequency:

- 1 Univariate (no adjustment).
- 2 Exclude pairs where the control is a potential ghost.
- 3 Exclude potential ghosts and adjust for consultations in year 1, except if for upper respiratory tract infection/cold, diarrhoea and vomiting or BP.

Table 1. Unadjusted odds ratios for hay fever by diagnosed infections in year 1, separately for GPRD and DIN

	GPRD				DIN			
	2 × 2 tables		Crude odds ratios		2 × 2 tables		Crude odds ratios	
	(C−)(X−) (C−)(X+)	(C+)(X−) (C+)(X+)	OR 95% CI	P-value	(C−)(X−) (C−)(X+)	(C+)(X−) (C+)(X+)	OR 95% CI	P-value
Upper respiratory tract	1021	987	1.22 (1.11–1.34)	<0.0001	1281	626	1.28 (1.14–1.44)	<0.0001
	807	1384			489	506		
Conjunctivitis	2031	897	1.12 (1.02–1.23)	0.02	1336	648	1.09 (0.98–1.22)	0.13
	803	465			594	324		
Diarrhoea and vomiting	2149	880	1.16 (1.05–1.28)	0.003	1476	658	1.35 (1.20–1.52)	<0.0001
	759	408			487	281		
Acute otitis media	2605	722	1.21 (1.08–1.35)	0.0007	1817	501	1.18 (1.03–1.34)	0.01
	598	271			426	158		
Bronchitis and chest infection	2906	569	1.09 (0.97–1.23)	0.16	2281	297	1.16 (0.98–1.37)	0.08
	522	199			256	68		
Candidiasis	2900	563	0.99 (0.88–1.12)	0.91	2051	395	1.11 (0.96–1.28)	0.16
	567	166			356	100		
Viral illness	3489	329	1.06 (0.91–1.24)	0.45	2703	97	1.76 (1.23–2.46)	0.0008
	310	68			55	47		
Fever/pyrexia	3480	358	1.22 (1.04–1.42)	0.01	2727	85	1.04 (0.77–1.40)	0.82
	294	64			82	8		
Sore throat	3818	186	1.08 (0.87–1.32)	0.49	2565	169	1.17 (0.94–1.47)	0.16
	173	19			144	24		
Bronchiolitis	3789	194	1.04 (0.85–1.27)	0.13	2496	183	0.94 (0.77–1.15)	0.54
	187	26			195	28		
Laryngitis and croup	3922	141	1.15 (0.90–1.46)	0.27	2690	95	0.90 (0.69–1.19)	0.48
	123	10			105	12		
Chickenpox	3941	121	0.93 (0.73–1.19)	0.57	2724	104	1.44 (1.07–1.95)	0.02
	130	4			72	2		
Other viral rash	4043	89	1.44 (1.04–1.99)	0.03	2804	46	0.98 (0.65–1.47)	0.92
	62	2			47	5		
Impetigo	4098	52	1.16 (0.78–1.72)	0.48	2821	50	1.61 (1.03–2.53)	0.04
	45	1			31	0		
Otitis externa	4108	50	1.32 (0.86–2.01)	0.20	2863	19	0.95 (0.51–1.78)	0.87
	38	0			20	0		
Chronic otitis media	4115	47	1.38 (0.89–2.15)	0.15	2863	24	1.60 (0.84–3.05)	0.15
	34	0			15	0		
Measles	4111	45	1.15 (0.75–1.77)	0.51	2850	28	1.17 (0.68–2.01)	0.58
	39	1			24	0		
Rubella	4118	35	0.81 (0.52–1.27)	0.37	2831	36	1.03 (0.65–1.64)	0.91
	43	0			35	0		
Urinary tract infections	4101	51	1.24 (0.82–1.88)	0.30	2844	30	1.11 (0.66–1.87)	0.69
	41	3			27	1		
Threadworms	4144	20	0.65 (0.37–1.13)	0.13	2878	11	0.85 (0.38–1.89)	0.68
	31	1			13	0		
Influenza	4142	23	0.92 (0.52–1.62)	0.77	2827	48	1.85 (1.15–2.98)	0.01
	25	6			26	1		
Hand, food and mouth	4171	12	1.00 (0.45–2.23)	1	2872	18	1.50 (0.72–3.11)	0.28
	12	1			12	0		
Lice	4170	13	1.00 (0.46–2.16)	1	2894	3	0.60 (0.14–2.51)	0.48
	13	0			5	0		
Dermatophytosis	4167	17	1.42 (0.68–2.97)	0.36	2855	23	0.96 (0.54–1.70)	0.88
	12	0			24	0		
Abscess/boil/nail infections	4162	19	1.36 (0.68–2.71)	0.39	2876	14	1.17 (0.54–2.52)	0.7
	14	1			12	0		
Meningitis	4176	10	1.00 (0.42–2.40)	1	2984	5	1.67 (0.40–6.97)	0.48
	10	0			3	0		
Scabies	4180	6	0.60 (0.22–1.65)	0.32	2889	8	1.60 (0.52–4.89)	0.41
	10	0			5	0		
Molluscum contagiosum	4189	5	2.50 (0.49–12.87)	0.27	2899	2	2.00 (0.18–22.05)	0.57
	2	0			1	0		

Table 1. (Continued)

	GPRD				DIN			
	2 × 2 tables		Crude odds ratios		2 × 2 tables		Crude odds ratios	
	(C-)(X-) (C-)(X+)	(C+)(X-) (C+)(X+)	OR 95% CI	P-value	(C-)(X-) (C-)(X+)	(C+)(X-) (C+)(X+)	OR 95% CI	P-value
Septicaemia	4189 3	4 0	1.33 (0.30–5.94)	0.71	2894 2	6 0	3.00 (0.61–14.82)	0.18
Warts	4190 3	3 0	1.00 (0.20–4.96)	1	2890 3	9 0	3.00 (0.81–11.05)	0.1
Behavioural problems	3933 101	153 9	1.51 (1.18–1.95)	0.001	2605 119	167 11	1.40 (1.11–1.78)	0.005

GPRD, General Practice Research Database; DIN, Doctors Independent Network.

(C-), unexposed case; (C+), exposed case; (X-), unexposed control; (X+), exposed control.

4 Exclude potential ghosts and adjust for all consultations in years 2–5, except if only for HF.

5 Further adjust (4) for sibship in GPRD or ACORN in DIN.

6 Exclude potential ghosts and adjust for all consultations in years 1–5.

The effect of these adjustments is presented in relation to the commonest condition of interest, URTIs and our control condition, BP. *A priori* we expected models 1–4 to successively reduce the magnitude of ORs between HF and both URTIs and our control condition. We were unsure of the effects of model 5. On theoretical grounds, we felt model 6 was likely to overadjust as it included consultations for infections during year 1.

Results

Table 1 shows unadjusted OR for HF for each of the conditions separately for GPRD and DIN [together with 95% confidence intervals (CI) and *P*-values]; these matched pair OR can also be calculated by dividing the upper-right cell in each 2 × 2 table by the lower-left cell. The conditions are ordered by the descending totals of discordant pairs (shown in bold) in GPRD.

In GPRD (Table 1), the unadjusted OR for HF amongst those infants presenting with infections compared with those not presenting were positive (i.e. > 1) for 20 of the 30 infections, the OR was 1.0 for four infections and negative for six infections. There was a strong positive association between BP and HF. In DIN, 23 of the unadjusted OR were positive and seven were negative; BP were strongly and positively related with HF. Strong positive associations were also noted for URTIs, diarrhoea and vomiting and viral illness, among others. For 10 conditions, associations were opposite in direction between GPRD and DIN though there was considerable overlap in the CI.

The importance of consultation frequency as a potential confounding variable is emphasized by the strong positive relationship between HF and number of consultations in years 2–5: those with over 10 consultations had an OR of HF of 8.5 in GPRD and 9.6 in DIN

compared with those with only one consultation. A strong association remained even when diagnostic codes were excluded, emphasizing that it is likely to be behaviour in presenting children that underpins this relationship. We therefore considered how to adjust for consultation frequency in more detail.

The moderately raised risk of HF, having had an URTI or a common cold (OR = 1.22 in GPRD, 1.28 in DIN) by 12 months of age was highly significant. Figure 1 shows the OR (log-odds scale) and 95% CI for HF amongst those diagnosed with an URTI in year 1 compared with those undiagnosed subject to a variety of adjustments for consultation frequency. Each consecutive adjustment tends to reduce the OR, initially towards the null hypothesis, but eventually reversing the effects.

A similar pattern is seen for the control condition, BP (lower half of Fig. 1). The significant unadjusted associations were markedly attenuated on controlling for the various measures of consultation frequency. None of the estimates, however, changed direction.

On the basis of these analyses we chose adjustment 4 as the appropriate method to present for all conditions in Table 2 and Fig. 2. Further adjustment for sibship size or ACORN score are also presented in Table 2, but have minimal effect. On the basis of our control condition, we might have chosen method 6 as being least biased. However, there was serious concern that for URTIs and other common problems this would result in over adjustment.

Apart from the rarer infections, the adjusted OR in both GPRD and DIN in Table 2 did not substantially differ from unity, and none of these are significant at *P* = 0.05. For 11 of the 30 conditions the OR was greater in GPRD, for 18 it was greater in DIN. The difference in OR between the databases was significant at *P* = 0.05 for only two conditions: viral illness and chickenpox. Because of multiple testing, we would have expected 1.5 to be significant by chance, if there were no real differences. We therefore used a fixed effects method to pool the results (22).

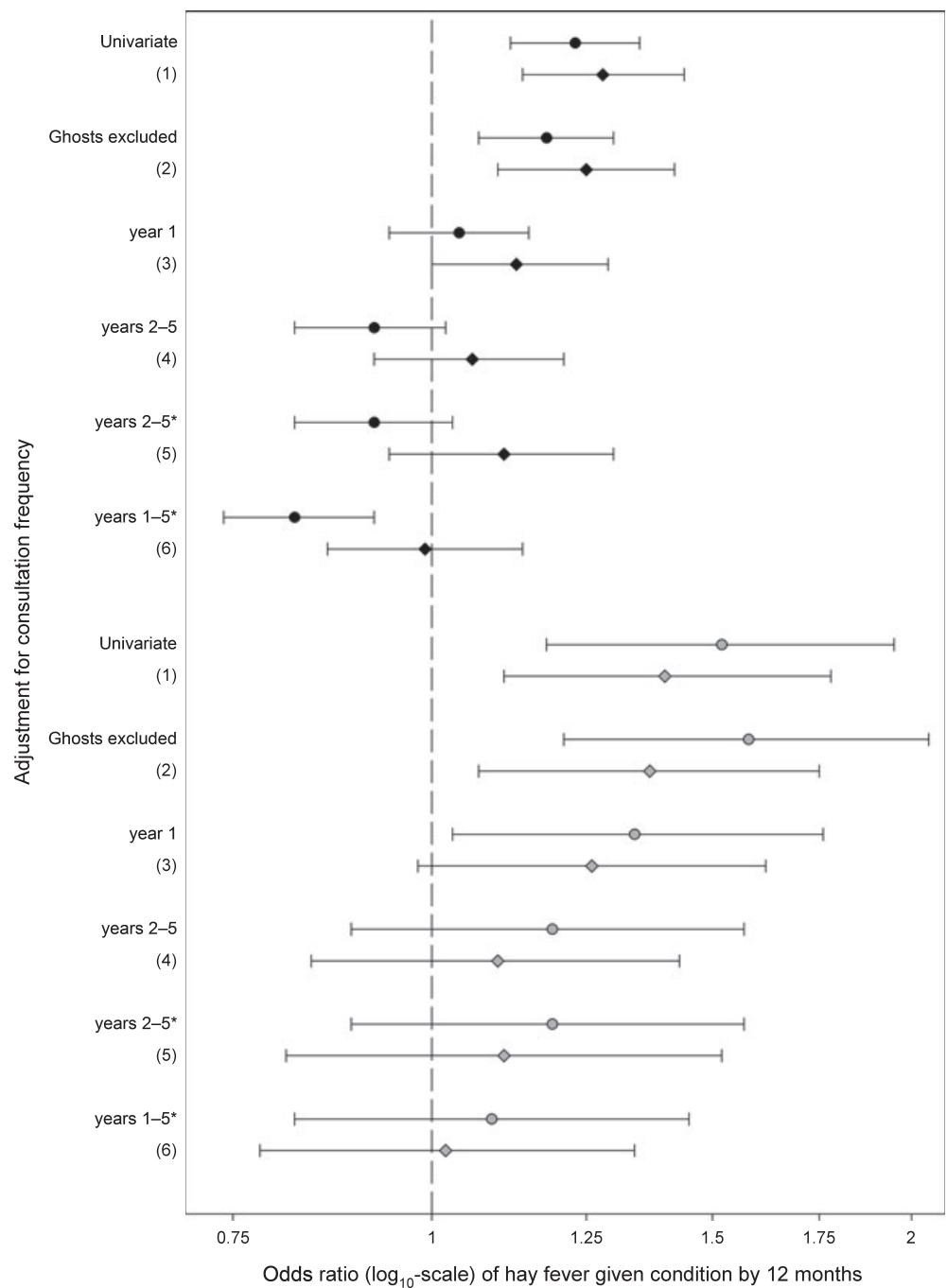


Figure 1. Odds ratios for hay fever given URTI or behavioural problems in year 1 adjusting for a variety of measures of consultation frequency. (●) GPRD: URTI; (◆) DIN: URTI; (○) GPRD: behavioural problems; (◇) DIN: behavioural problems. Adjustments (1) to (6) are detailed in the Methods section.

In Fig. 2, we present the pooled adjusted OR from the two databases for each of the 30 infections plus BP. The estimates and CI are plotted on the log-odds scale to make the comparison between estimates easier to visualize. The dotted vertical line corresponds to no association (i.e. an OR = 1). All of the CI cross the line of no association, with the exception of bronchiolitis. As we

move down through the plot, the intervals become successively wider.

The pooled OR for fever/pyrexia was 0.95 and not significant (see Fig. 2). Behavioural problems were not significantly associated with HF (pooled OR = 1.14). Although an infrequently recorded condition, the pooled OR for molluscum contagiosum was 3.32 (not

Table 2. Adjusted odds ratios for GPRD and DIN separately and pooled for hay fever amongst those diagnosed with infection in year 1, vs those not diagnosed

GPRD and DIN to age 1 in all CC pairs	*GPRD			†GPRD (adj. sibs)			*DIN			†DIN (adj. ACORN)			Pooled fixed-effects			P-value for diff in OR between databases
	OR 95% CI	P-value		OR 95% CI	P-value		OR 95% CI	P-value		OR 95% CI	P-value		OR 95% CI	P-value		
Upper respiratory tract	0.92 (0.82–1.02)	0.12		0.92 (0.82–1.03)	0.13		1.06 (0.92–1.21)	0.43		1.11 (0.94–1.30)	0.21		0.97 (0.89–1.06)	0.51		0.11
Conjunctivitis	0.99 (0.89–1.11)	0.89		1.04 (0.93–1.17)	0.50		0.97 (0.85–1.09)	0.58		0.90 (0.77–1.05)	0.17		0.98 (0.90–1.07)	0.65		0.81
Diarrhoea and vomiting	0.97 (0.87–1.09)	0.63		0.95 (0.84–1.07)	0.38		1.13 (0.99–1.29)	0.08		1.02 (0.87–1.20)	0.81		1.03 (0.95–1.13)	0.44		0.09
Acute otitis media	0.98 (0.86–1.11)	0.72		0.98 (0.86–1.12)	0.74		0.91 (0.78–1.05)	0.19		0.85 (0.71–1.02)	0.08		0.95 (0.86–1.05)	0.3		0.46
Bronchitis and chest infection	0.92 (0.80–1.05)	0.92		0.98 (0.85–1.13)	0.74		1.04 (0.86–1.26)	0.66		1.12 (0.89–1.41)	0.33		0.96 (0.86–1.07)	0.46		0.31
Candidiasis	0.88 (0.77–1.00)	0.05		0.88 (0.76–1.01)	0.07		1.02 (0.87–1.20)	0.8		0.98 (0.81–1.20)	0.87		0.93 (0.84–1.03)	0.18		0.16
Viral illness	0.86 (0.73–1.03)	0.1		0.85 (0.71–1.02)	0.08		1.46 (1.00–2.12)	0.05		1.41 (0.89–2.25)	0.15		0.94 (0.81–1.10)	0.44		0.01
Fever/pyrexia	0.97 (0.81–1.16)	0.75		1.00 (0.83–1.20)	0.96		0.89 (0.63–1.25)	0.5		0.66 (0.45–0.98)	0.04		0.95 (0.81–1.12)	0.55		0.66
Sore throat	0.84 (0.67–1.06)	0.14		0.95 (0.74–1.23)	0.70		0.98 (0.76–1.25)	0.86		1.02 (0.76–1.36)	0.91		0.90 (0.76–1.07)	0.23		0.37
Bronchiolitis	0.80 (0.64–1.01)	0.06		0.77 (0.60–0.99)	0.04		0.80 (0.63–1.00)	0.05		0.80 (0.61–1.06)	0.12		0.80 (0.68–0.94)	0.007		1
Laryngitis and croup	1.06 (0.81–1.40)	0.67		1.08 (0.81–1.45)	0.60		0.82 (0.61–1.12)	0.21		0.74 (0.51–1.07)	0.11		0.94 (0.77–1.16)	0.58		0.22
Chickenpox	0.83 (0.63–1.10)	0.2		0.95 (0.70–1.27)	0.71		1.33 (0.95–1.85)	0.1		1.61 (1.08–2.39)	0.02		1.01 (0.81–1.25)	0.94		0.03
Other viral rash	1.29 (0.90–1.87)	0.17		1.34 (0.91–1.98)	0.14		0.95 (0.60–1.49)	0.81		0.90 (0.53–1.53)	0.69		1.14 (0.86–1.52)	0.36		0.3
Impetigo	1.02 (0.65–1.59)	0.94		1.04 (0.65–1.66)	0.87		1.68 (1.01–2.78)	0.04		1.72 (0.95–3.11)	0.07		1.27 (0.91–1.77)	0.16		0.15
Ortitis externa	1.13 (0.71–1.81)	0.6		1.31 (0.78–2.20)	0.31		0.86 (0.43–1.70)	0.65		0.83 (0.37–1.85)	0.65		1.04 (0.70–1.53)	0.86		0.52
Chronic otitis media	1.05 (0.64–1.73)	0.84		1.17 (0.70–1.95)	0.56		1.27 (0.61–2.65)	0.52		0.80 (0.35–1.82)	0.59		1.11 (0.74–1.68)	0.61		0.67
Measles	1.03 (0.65–1.65)	0.89		1.18 (0.71–1.94)	0.53		0.94 (0.50–1.76)	0.84		0.62 (0.29–1.31)	0.21		1.00 (0.69–1.45)	0.99		0.82
Rubella	0.77 (0.47–1.28)	0.31		0.80 (0.48–1.34)	0.40		1.04 (0.61–1.77)	0.88		1.15 (0.60–2.21)	0.68		0.89 (0.62–1.28)	0.52		0.42
Urinary tract infections	0.89 (0.55–1.43)	0.62		0.87 (0.53–1.45)	0.60		0.98 (0.53–1.83)	0.96		1.12 (0.52–2.41)	0.77		0.92 (0.63–1.35)	0.68		0.81
Threadworms	0.74 (0.39–1.40)	0.35		0.77 (0.39–1.51)	0.44		0.69 (0.27–1.73)	0.43		0.48 (0.15–1.54)	0.22		0.72 (0.43–1.22)	0.23		0.9
Influenza	1.20 (0.63–2.26)	0.58		1.15 (0.59–2.24)	0.68		1.63 (0.95–2.80)	0.08		1.38 (0.70–2.70)	0.35		1.43 (0.95–2.17)	0.09		0.47
Hand, food and mouth	0.95 (0.40–2.28)	0.92		0.72 (0.28–1.85)	0.49		1.48 (0.66–3.32)	0.34		0.82 (0.26–2.64)	0.74		1.21 (0.67–2.18)	0.54		0.46
Lice	0.98 (0.42–2.29)	0.96		1.26 (0.52–3.07)	0.61		0.43 (0.07–2.80)	0.38		1.53 (0.13–17.41)	0.73		0.85 (0.39–1.83)	0.68		0.43
Dermatophytosis	1.09 (0.47–2.52)	0.85		1.03 (0.42–2.54)	0.94		0.77 (0.40–1.46)	0.42		0.92 (0.43–1.95)	0.83		0.88 (0.53–1.46)	0.61		0.52
Abscess/boil/nail infection	1.03 (0.47–2.26)	0.94		1.00 (0.43–2.32)	1		1.17 (0.49–2.79)	0.73		1.89 (0.53–6.80)	0.33		1.09 (0.61–1.95)	0.77		0.83
Meningitis	0.95 (0.35–2.60)	0.92		1.20 (0.41–3.56)	0.74		1.17 (0.27–5.14)	0.84		0.77 (0.16–3.66)	0.74		1.02 (0.44–2.33)	0.97		0.82
Scabies	0.61 (0.21–1.81)	0.37		0.70 (0.23–2.13)	0.53		1.73 (0.52–5.74)	0.37		1.35 (0.34–5.32)	0.67		0.97 (0.44–2.16)	0.94		0.21
Molluscum contagiosum	6.82 (0.70–66.97)	0.1		N/E	N/E		1.41 (0.13–15.92)	0.78		1.33 (0.12–15.14)	0.82		3.32 (0.62–16.91)	0.16		0.35
Septicaemia	1.51 (0.28–8.21)	0.64		0.98 (0.16–6.11)	0.98		2.98 (0.55–16.12)	0.2		1.15 (0.16–8.27)	0.89		2.12 (0.64–7.00)	0.22		0.58
Warts	0.55 (0.10–2.98)	0.49		0.54 (0.09–3.10)	0.49		3.02 (0.75–12.15)	0.12		4.63 (0.42–50.63)	0.21		1.52 (0.52–4.47)	0.44		0.13
Behavioural problems	1.19 (0.89–1.57)	0.24		1.18 (0.87–1.60)	0.30		1.10 (0.84–1.43)	0.51		1.11 (0.81–1.52)	0.51		1.14 (0.94–1.39)	0.18		0.69

N/E, not estimable.

* Adjustment excludes potential ghosts and adjusts for frequency of all consultations in years 2–5, except if only for hay fever (method 4 in methods).

† Further adjusted for number of sibs in GPRD or ACORN in DIN.

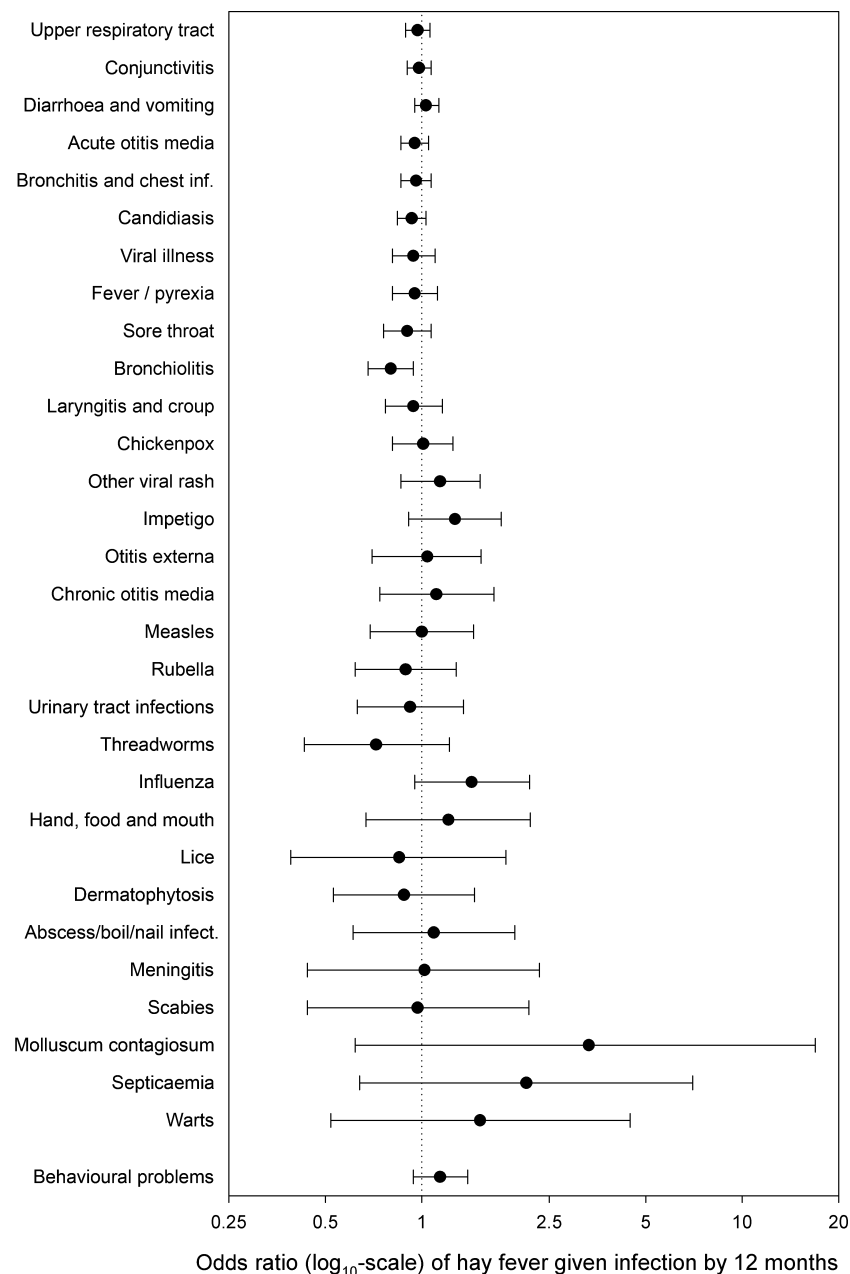


Figure 2. Risk of later hay fever among children diagnosed with condition in year 1 vs those not diagnosed with condition. Odds ratios are adjusted for consultation frequency in years 2–5 using model 4 and then pooled across GPRD and DIN.

significant). In summary, 14 of the pooled ORs were >1, 16 were <1 and 1 was =1. Bronchiolitis was associated with a reduced pooled OR of HF of 0.8; this reduction was statistically significant because bronchiolitis also had a relatively high incidence. We note that the pooled estimate for influenza almost attained statistical significance and was associated with an increased risk of later HF. None of the other exposures were significantly associated with later HF.

Despite pooling estimates, having applied the chosen adjustment for consultation frequency, statistical power was limited for the rarer infections. For example, the CI for warts spanned 0.52–4.47 (Fig. 2). A few other CI estimates were substantially less precise. Figure 3 further documents the relationship of HF and the 30 infections to sibship size within GPRD, plotting for each condition the OR per additional older sib. While the risk of HF fell with increasing number of older sibs, there was no clear pattern with infections. Only one

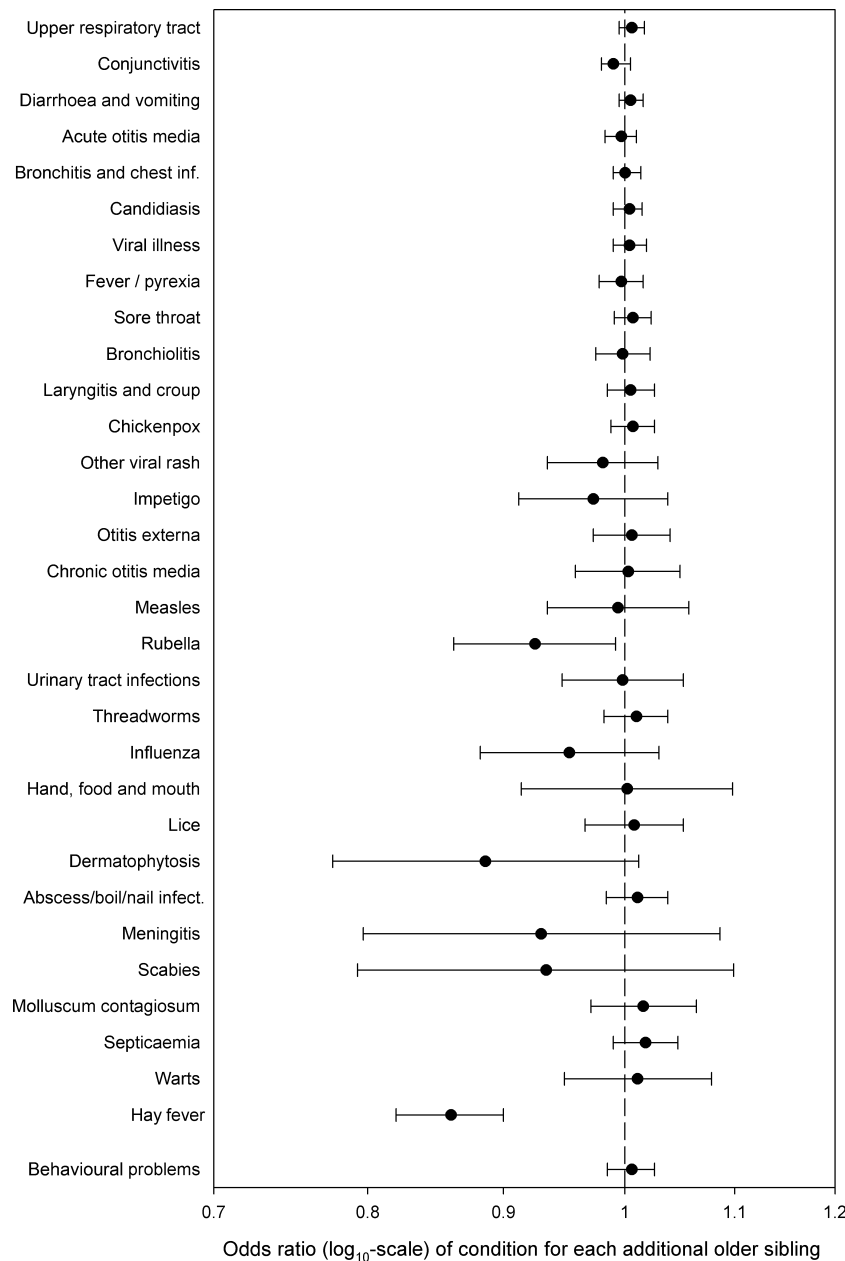


Figure 3. Odds ratio of being diagnosed with condition (by age 1) or hay fever (by age 5) in the GPRD birth cohort for each additional older sibling.

infection, rubella was significantly related with older sibs and the relationship was negative rather than positive.

Discussion

Having defined 30 infections (plus one control condition) using different clinical coding systems, tested them in two large independent samples, and controlled for consultation frequency, we found little evidence of any associations between HF and a wide variety of acute infectious illnesses presenting to primary care in infancy. The

findings were equally negative for conditions which were likely to be routinely reported to the health care system, such as conjunctivitis, measles, influenza, meningitis and septicaemia, as well as for conditions which were less likely to be reported, such as URTIs. Not only were these infections unrelated to HF, but they were unrelated to sibship size in GPRD, while HF was clearly inversely related with number of older sibs consistent with many earlier publications. We believe this to be a robust and comprehensive demonstration that the inverse association of HF with sibship size is not explained by clinically apparent infectious illness in infancy.

How does the disparate literature described in the introduction fit with this resoundingly negative result? Four factors are likely to explain this: (i) publication and selection bias; (ii) lack of control for confounding variables, particular behavioural; (iii) some infections are simply too rare in the UK and (iv) clinical infections presenting in primary care may not well characterize microbial exposures that do induce immunomodulation.

Our concern, in trying to define a sensible adjustment for consultation frequency, was that a large proportion of consultations in early life were for the exposures under consideration. Including such consultations in any adjustment would potentially over-adjust. What we have demonstrated is that the relationships between early infection and later HF are sensitive to consultation behaviour and this has to be addressed in any study based on health service records. On the other hand, sibship size and socioeconomic status did not emerge as important confounding variables, after allowance was made for consultation frequency. The lack of effect of adjustment for sibship size was consistent with the lack of any clear associations between sibship size and infections (26). Our findings are similar to those of Davey et al. (27) who reported strong positive associations between migraine and asthma which were entirely removed on adjustment for consultation frequency. The generality of this problem needs to be more widely appreciated by those analysing primary care databases.

Several of the infections studied were uncommon and the estimated OR had wide CI; for instance infestations, some skin infections and serious systemic infections. We do not have the power to rule out effects for these conditions. However, these infections are so rare that even if they were implicated in the aetiology, they would not play an important role in determining the distribution of HF in the UK, in particular the inverse association with HF.

Timing of exposure may be crucial. Although this study showed few associations between infection in infancy and later HF, the possibility remains that a more specific critical period in year 1 could be important. In another paper, we have looked at these same infections in the grass pollen season vs outside it, proposing that an atopic response is triggered by the combination of exposure to infection and grass pollen simultaneously. No effect was found (28).

We are driven to conclude that if infections do play any important role in the aetiology of HF in the UK, it must arise from common milder infections which do not present to the GP. This would dilute any true association between such infections and HF in our study, which focussed on infections that presented for clinical care. The positive, though nonsignificant association with influenza we found (Fig. 2) is in keeping with what Umetsu reported (29). We had hypothesized in a previous paper that intercurrent febrile illnesses may offer some protection against atopic disease (28). Collectively, mild intercurrent febrile illnesses could be responsible for a protective effect against HF. Certainly these were not reported in a sufficiently regular way to GPs to be investigated under our study design. In addition, for several years there has been interest in the possibility that the commensal intestinal microflora acquired in the neonatal period may influence the long-term risk of developing allergic disease (30, 31), but the most definitive test of this 'gut flora' hypothesis showed little evidence that the pattern of intestinal colonization with culturable bacteria in the first year of life predicted subsequent allergic sensitization in European children (32). We conclude that supporters of the hygiene hypothesis need to look beyond acute infectious illnesses, perhaps towards longer-term immune challenges for an explanation of the increase in atopic diseases in developed countries.

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