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Associations between early infections and childhood cognition in the Newcastle Thousand Families Study birth cohort

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Original Article

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Abstract

Childhood infections have been shown to stunt growth, contribute to malnutrition and reduce cognition in early adulthood. This study aimed to assess relationships between early life infections and childhood cognition at age 11 years in the Newcastle Thousand Families Study (NTFS). The analysis included 741 members from the NTFS who had complete data for infections between birth and 5 years, and the 11-plus examinations. School records from the 11-plus examinations showed cognitive (IQ), English (EQ) and arithmetic (AQ) abilities. Housing conditions, overcrowding, birth order and social class were recorded at birth. *Helicobacter pylori* seropositivity was measured at age 49–51 years. Multivariable linear regression was used to examine relationships between infections and cognition. The total number of infections in the first 5 years of life was not significantly associated with IQ, EQ or AQ, nor were there significant relationships between cognitive outcomes and most infections. Tonsillitis did display a positive, significant association with IQ after adjustment for confounders ($b = 6.43$, 95% CI 0.92, 11.94, $p = 0.022$). Lower respiratory tract infections (LRTIs) showed significant negative relationships with all cognitive outcomes. *H. pylori* seropositivity at age 50 exhibited negative, significant relationships with EQ ($p = 0.014$) and AQ ($p = 0.024$) after adjustment for confounders. Although no significant relationship between overall infections and cognition were found, there were indications that LRTIs and gastrointestinal system infections may limit cognitive development. Given these infections remain prevalent, further research regarding severity and recurrence of infections and how they affect childhood cognition is needed.

Introduction

Childhood cognition at ages 8 and 9 strongly relates to later educational and occupational achievement, independently of factors such as childhood behaviour and family social status.[1] It is therefore important to understand how events in early life impact childhood cognition and the wider implications this may have for both individuals and society. One estimate proposes that more than 200 million children, under 5 years of age, in low- and middle-income countries are not reaching their full developmental potential due to factors such as repeated childhood infection, potentially equating to a 20% deficit in adult income.[2]

Evidence for infection impacting cognition is mixed. In low- and middle-income countries, diarrhoeal diseases are a leading cause of mortality and morbidity in children.[3,4] Research has shown that early childhood diarrhoea (ECD) may impact cognition in later childhood.[3,5] Children who had previously been infected with measles or pertussis were also shown to have lower verbal reasoning scores at age 11 compared to peers, although a lack of adjustment for confounders did limit the validity of that study.[6] Similarly, analysis of the Avon Longitudinal Study of Parents and Children found no strong correlation between infection and intelligence at 8 years of age.[7] Conversely, studies in Swedish and Danish adult males showed that infection was associated with lower IQ at 18 and 19 years of age, respectively.[8,9] The Danish study recorded a dose–response relationship between number of hospitalisations due to infection and cognitive ability.[8] However, these studies were conducted exclusively in males, and cognition was measured later in life[8,9] when compared to the childhood studies mentioned previously.[6,7] The focus, also, was not specifically on childhood infections in the Swedish and Danish studies. These conflicting findings highlight the need for research assessing the effect of infections upon cognition.

An earlier study on the Newcastle Thousand Family birth cohort found that there was a significant positive association between IQ at 11 years and standardised height at ages 9 and 13 years.[10] We have also previously shown that cognition at age 11 in the cohort is associated

with achieved education levels in males, but not females, most likely due to gender inequalities in access to further education in this cohort.[11]

Childhood infections have been shown to be significantly associated with differences in adult height between monozygotic twins.[12] Many infections, especially when recurrent, are known to be a large factor contributing to impaired growth in early childhood.[2,13,14] When infected, children can become malnourished due to lack of appetite, impaired nutrient absorption or increased metabolic needs.[14] The associations between infections and height and the associations between height and IQ suggest that childhood infection may also impact upon cognition.

This study aimed to examine the relationship between early life infections and childhood cognition at age 11 years in the Newcastle Thousand Families Study (NTFS) birth cohort,[15] considering potential confounding factors.

Method

The NTFS is a prospective birth cohort study which initially enrolled all 1142 children born to mothers resident in the city of Newcastle upon Tyne in May and June 1947.[15] During childhood, the health, growth and development of study members were recorded by the study team, including health visitors and paediatricians.[15]

Visits were routine and on an *ad hoc* basis in the first 5 years of life.[15] Once in school, the children were visited at least once a year to record height, weight and other health measures until the age of 15 years.[15]

Infections included in these analyses and recorded between birth and age 5, by health visitors, included measles, mumps, scarlet fever, pertussis, rubella, chicken pox, tuberculosis, influenza, ear infections and lower (LRTIs) and upper respiratory infections (URTIs). Tonsillitis, pertussis, diarrhoea and otorrhea in the first year of life were also recorded and included in these analyses. *Helicobacter pylori* (*H. pylori*) seropositivity at age 49–51 years of age was measured as part of an adult follow-up of the cohort. Although recorded much later in life, *H. pylori* is commonly acquired in very early life and seropositivity can persist into adulthood.[15] Hence, we treat this measure as a proxy for *H. pylori* infection in early childhood.

Access to school records allowed for the analysis of 11-plus examinations results from 1958. Four tests were used during these examinations in Newcastle: Moray House Tests 57 and 58 (verbal reasoning) and two standardised tests of English (EQ) and Arithmetic (AQ) ability.[16] The average of these four tests was used to give an IQ score for each child, being a combination of verbal reasoning as well as English and arithmetic ability.[10] IQ, EQ and AQ were the cognitive outcomes in this study.

In addition to clinical data, social class and housing data were recorded at birth and throughout childhood.[15] Social class at birth was recorded relative to paternal occupation using the contemporary United Kingdom Registrar General's Standard Occupational Classification.[15] The five categories of social class were I (professional), II (managerial), III (skilled manual or clerical), IV (semi-skilled) and V (unskilled), where I (professionals) were assumed to be the most advantaged.[17,18] Housing conditions at birth were recorded by the city's Public Health Department using a scoring system.[17,19] A score of 0 denoted no adverse conditions and 4 denoted more than three adverse conditions. Adverse conditions consisted of overcrowding, lack of hot water, shared toilet, dampness and poor repair. Overcrowding was also recorded separately, being defined as more than two persons in a dwelling with one room, three persons in two rooms, five in three rooms, eight or more in four rooms and more than two people per room in dwellings of five or more rooms. Birth order was also recorded. These variables were treated as potential confounders and were included in the multivariable analysis.

Statistical analysis

A total infection variable was generated, indicating the total number of infections in the first 5 years for each participant including, tonsillitis, pertussis, ear infections, mumps, measles, scarlet fever, tuberculosis, flu, chicken pox, rubella, LRTI and URTI. For infections which participants had contracted repeatedly (e.g., tonsillitis) the recorded data indicated the number of infections. Therefore, binary variables were also created, yes/no variables simply denoted whether participants had experienced, e.g., tonsillitis or not, regardless of repeated infection.

The representativeness of the study sample used in this investigation was compared to the remainder of the original birth cohort using chi-squared tests. The median and interquartile range were calculated for continuous, non-normal data. Participants missing complete data for cognitive outcomes or infection data at 5 years were excluded from the analyses.

Relationships between IQ, EQ or AQ and each infection were estimated using linear regression. Univariate linear regression was first used to determine initial relationships between cognitive outcomes and each infection with significant relationships recorded when $p < 0.05$. This was followed by multivariable linear regressions allowing for identification of confounding variables. Social class, housing score, overcrowding and birth order were added individually to determine whether they were confounders. Results were stratified by sex to identify sex interactions between infection and cognition. Stratified models showing significant sex interaction ($p < 0.05$) were then adjusted for confounders. The statistical software package Stata, Version 17.0, was used for all statistical analyses (StataCorp, College Station, TX).

Results

Of the 1142 children in the original cohort, 747 (65%) had complete IQ data. Of these 747 children, 741 had complete data for infections recorded between ages 0 and 5 years. Two of these children were missing data for pertussis and tonsillitis from the first year of life but remained in the study sample (Table 1). Data for *H. Pylori* seropositivity at 50 years and diarrhoea in the first year of life were more limited with only 45.75% ($n = 339$) and 4.86% ($n = 36$) of the study sample having these data available, respectively.

Descriptive characteristics for the study sample and original cohort can be seen in Tables 1 and 2. The study sample was representative of the remainder of the original cohort for sex, overcrowding, tonsillitis, otorrhea, pertussis, LRTIs, tuberculosis, flu, rubella and diarrhoea (Table 1). The mean IQ at age 11 from the Medical Research Council National Survey of Health and Development cohort born in the year 1946 was 102.1,[20] slightly higher than the median calculated in this study (Table 2).

The most common infection amongst the study sample was URTIs with a frequency of 97.44%. Reports of measles and LRTIs were also high relative to other infections with over 50% of the sample having experienced at least one of these infections (Table 1).

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Table 1. Descriptive characteristics for the categorical variables for the original cohort and the study sample used in this investigation including the p-values obtained from a chi-squared test to determine whether the study sample is representative of the original cohort

		Original cohort ($n = 1142$)		Study sample ($n = 741$)		X^2 test
Variable		*n*	%	*n*	%	*p*-value
Sex	Male	583	51.05	370	49.93	0.304
	Female	559	48.95	371	50.07	
Social class at birth	1 – most advantaged	32	2.8	10	1.35	<0.001
	2	93	8.14	44	5.94	
	3	602	52.71	421	56.82	
	4	172	15.06	117	15.79	
	5 – least advantaged	163	14.27	123	16.6	
	Unknown	80	7.01	26	3.51	
Housing score at birth	0	458	40.11	301	40.62	0.001
	1	270	23.64	202	27.26	
	2	164	14.36	125	16.87	
	3	111	9.72	93	12.55	
	4	23	2.01	17	2.29	
	Unknown	116	10.16	3	0.4	
Birth order	1st born	868	76.01	507	68.42	<0.001
	2nd born	162	14.19	133	17.95	
	3rd born	65	5.69	56	7.56	
	4th born	20	1.75	20	2.7	
	>4th born	27	2.36	25	3.37	
Overcrowding	Yes	326	28.55	254	34.28	0.076
	No	666	58.32	484	65.32	
	Unknown	150	13.13	3	0.4	
Tonsillitis in first year	Yes	32	2.8	23	3.1	0.867
	No	978	85.64	716	96.63	
	Unknown	132	11.56	2	0.27	
Otorrhea in first year	Yes	64	5.6	50	6.75	0.355
	No	946	82.84	689	92.98	
	Unknown	132	11.56	2	0.27	
Pertussis in first year	Yes	104	9.11	81	10.93	0.252
	No	906	79.33	658	88.8	
	Unknown	132	11.56	2	0.27	
Ear infection 0–5 years	Yes	202	17.69	163	22	0.028
	No	790	69.18	578	78	
	Unknown	150	13.13	0	0	
LRTI* 0–5 years	Yes	487	42.64	376	50.74	0.074
	No	505	44.22	365	49.26	
	Unknown	150	13.13	0	0	
URTI** 0–5 years	Yes	939	82.22	722	97.44	<0.001
	No	53	4.64	19	2.56	
	Unknown	150	13.13	0	0	

(*Continued*)

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Table 1. (*Continued*)

Variable		Original cohort (*n* = 1142)		Study sample (*n* = 741)		X^2 test
		n	%	*n*	%	*p*-value
Measles 0–5 years	Yes	541	47.37	443	59.78	<0.001
	No	451	39.49	298	40.22	
	Unknown	150	13.13	0	0	
Mumps 0–5 years	Yes	117	10.25	104	14.04	<0.001
	No	875	76.62	637	85.96	
	Unknown	150	13.13	0	0	
Scarlett fever 0–5 years	Yes	25	2.19	23	3.1	0.044
	No	967	84.68	718	96.9	
	Unknown	150	13.13	0	0	
Pertussis 0–5 years	Yes	415	36.34	333	44.94	0.001
	No	577	50.53	408	55.06	
	Unknown	150	13.13	0	0	
Tuberculosis 0–5 years	Yes	67	5.87	55	7.42	0.156
	No	925	81	686	92.58	
	Unknown	150	13.13	0	0	
Influenza 0–5 years	Yes	26	2.28	23	3.1	0.102
	No	966	84.59	718	96.9	
	Unknown	150	13.13	0	0	
Chicken pox 0–5 years	Yes	242	21.19	205	27.67	<0.001
	No	750	65.67	536	72.33	
	Unknown	150	13.13	0	0	
Rubella 0–5 years	Yes	118	10.33	95	12.82	0.122
	No	874	76.53	646	87.18	
	Unknown	150	13.13	0	0	
Helicobacter pylori seropositivity status[a]	Yes	161	14.1	139	18.76	0.183
	No	246	21.54	200	26.99	
	Unknown	735	64.36	402	54.25	
Diarrhoea	Yes	34	2.98	27	3.64	0.862
	No	11	0.96	9	1.21	
	Unknown	1097	96.06	705	95.14	

*LRTI = lower respiratory tract infections.
**URTI = upper respiratory tract infections.
[a]*H. Pylori* seropositivity measured at age 50 years.

Table 2. Descriptive characteristics for the continuous, non-normal variables for the original cohort and the study sample used in this investigation, including the median and interquartile range (IQR) for each cognitive outcome

Test	Original cohort		Study sample	
	n	Median (IQR)	*n*	Median (IQR)
IQ at 11-plus	747	100 (87–110)	741	100 (87–110)
AQ at 11-plus	747	102 (91–112)	741	102 (91–112)
EQ at 11-plus	747	100 (89–111)	741	100 (89–111)

Regression analysis

Univariate analyses showed no significant associations between any of the cognitive outcomes and pertussis in the first year, or ear infections, URTIs, measles, mumps, scarlet fever, flu, chicken pox or rubella in the first 5 years. Further, few infections showed significant associations to cognitive outcomes. Otorrhea in the first year, as a binary variable, was negatively associated to both IQ ($p = 0.038$) and AQ ($p = 0.035$). Similarly, pertussis in the first 5 years was negatively associated with EQ ($p = 0.04$) and TB was negatively associated with AQ

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Table 3. Results of multivariable linear regressions relating IQ at age 11 to different infections. The models were adjusted for different combinations of 4 confounding variables: social class at birth (~), housing score at birth (†), birth order (‡) and overcrowding (¤)

	Results of linear regression with IQ (adjusted)		
Exposure	Coefficient	95% CI	*P*-value
Total infection 0–5 years ~†	0.015	−0.178 to 0.207	0.822
Tonsillitis in first year ~	5.416	0.235 to 10.597	0.04
Tonsillitis in first year (binary) ~	6.426	0.917 to 11.935	0.022
Otorrhea in first year ~†‡¤	−1.813	−5.097 to 1.471	0.279
Otorrhea in first year (binary) ~†‡¤	−2.467	−6.275 to 1.341	0.204
Pertussis in first year ~†‡¤	2.618	−0.463 to 5.699	0.096
Ear infection 0–5 years †‡¤	−0.475	−1.549 to 0.599	0.386
Ear infection 0–5 years (binary) ~†¤	−0.043	−2.344 to 2.258	0.971
*LRTI 0–5 years ~†¤	−0.632	−1.344 to 0.080	0.082
*LRTI 0–5 years (binary) ~†	−1.892	−3.818 to 0.035	0.054
**URTI 0–5 years ~†‡¤	0.091	−0.160 to 0.342	0.476
**URTI 0–5 years (binary) ~†‡¤	2.545	−3.741 to 8.831	0.427
Measles 0–5 years ~†‡¤	−0.194	−2.164 to 1.776	0.847
Mumps 0–5 years ~†‡¤	0.117	−2.625 to 2.860	0.933
Scarlet fever 0–5 years ~†‡¤	−1.133	−6.537 to 4.270	0.681
Pertussis 0–5 years ~†¤	−1.166	−3.09 to 0.759	0.235
Tuberculosis 0–5 years ~¤	−2.788	−6.417 to 0.841	0.132
Influenza 0–5 years ~†‡¤	−0.312	−5.402 to 4.778	0.904
Influenza 0–5 years (binary) ~†‡¤	0.041	−5.377 to 5.458	0.988
Chicken pox 0–5 years ~†‡¤	0.473	−1.675 to 2.622	0.666
Rubella 0–5 years ~‡¤	1.991	−0.832 to 4.814	0.167
H. Pylori[a] seropositivity ~†¤	−2.497	−5.463 to 0.468	0.099
Diarrhoea in first year ~†‡¤	−6.811	−15.601 to 1.978	0.124

*LRTI = lower respiratory tract infections.
**URTI = upper respiratory tract infections.
[a]*H. Pylori* seropositivity measured at age 50 years.

($p = 0.016$). Diarrhoea was negatively associated with IQ ($p = 0.036$) and EQ ($p = 0.014$). None of these relationships remained significant once adjusted for confounding variables (Tables 3–5).

Univariate analysis found tonsillitis in the first year (binary) to be positively associated with IQ ($p = 0.048$). This remained significant following adjustment for social class (Table 3). The number of tonsillitis infections was not significantly associated with IQ ($p = 0.072$) however following adjustment for social class the relationship became significant (Table 3).

LRTIs in the first 5 years in both the binary and ordinal form showed negative associations with all cognitive outcomes during univariate analysis ($p < 0.005$). After adjustment for confounding variables such as social class, housing score and overcrowding, these significant relationships only remained between LRTIs and AQ (Table 5).

H. pylori seropositivity at 50 years was also negatively associated with IQ ($p = 0.003$), EQ ($p < 0.001$) and AQ ($p < 0.001$) during univariate analyses. Following adjustment *H. pylori* was only significantly associated with EQ and AQ (Tables 3–5).

Interactions

Sex interactions were found to be significant in the regression models for tuberculosis and IQ ($p = 0.047$), EQ ($p = 0.008$) and AQ ($p = 0.005$). Females showed significant, negative relationships between tuberculosis and IQ, AQ and EQ whereas there were no significant relationships between tuberculosis and the cognitive outcomes in males who showed weaker relationships between tuberculosis and cognitive outcomes. These sex interactions remained significant for the regression models for tuberculosis and IQ, EQ and AQ following adjustment (Table 6). For regressions between cognitive outcomes and tonsillitis, otorrhea, pertussis, ear infections, LRTIs, URTIs, measles, mumps, scarlet fever, flu, chicken pox, rubella and diarrhoea, no significant sex interactions were found.

H. pylori seropositivity significantly interacted with sex in the regressions between IQ and *H. pylori* ($p = 0.015$) and EQ and *H. pylori* ($p = 0.048$). When *H. pylori* was regressed against IQ and EQ for each sex, males showed significant, negative associations whereas females showed no significant associations. This interaction remained significant in the regressions between

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Table 4. Results of multivariable linear regressions relating EQ at age 11 to different infections. The models were adjusted for different combinations of 4 confounding variables: social class at birth (~), housing score at birth (†), birth order (‡) and overcrowding (¤)

	Results of linear regression with EQ (adjusted)		
Exposure	Coefficient	95% CI	*P*-value
Total infection 0–5 years ~†‡¤	−0.006	−0.209 to 0.198	0.957
Tonsillitis in first year ~	4.123	−1.322 to 10.199	0.131
Tonsillitis in first year (binary) ~¤	4.438	−1.307 to 10.365	0.128
Otorrhea in first year ~†‡¤	−1.029	−4.512 to 2.453	0.562
Otorrhea in first year (binary) ~†‡¤	−1.726	−5.763 to 2.312	0.402
Pertussis in first year ~†‡¤	2.922	−0.342 to 6.186	0.079
Ear infection 0–5 years †¤	−0.559	−1.700 to 0.581	0.336
Ear infection 0–5 years (binary) ~†‡¤	0.338	−2.099 to 2.776	0.785
*LRTI 0–5 years ~†¤	−0.719	−1.473 to 0.035	0.062
*LRTI 0–5 years (binary) ~†	−1.901	−3.943 to 0.141	0.068
**URTI 0–5 years ~†‡¤	0.153	−0.113 to 0.418	0.260
**URTI 0–5 years (binary) ~†‡¤	3.075	−3.586 to 9.735	0.365
Measles 0–5 years ~†‡¤	−0.83	−2.916 to 1.257	0.435
Mumps 0–5 years †¤	0.193	−2.774 to 3.159	0.899
Scarlet fever 0–5 years ~†‡¤	−0.557	−6.283 to 5.169	0.849
Pertussis 0–5 years ~†	−1.229	−3.284 to 0.826	0.241
Tuberculosis 0–5 years ~¤	−1.868	−5.714 to 1.979	0.341
Influenza 0–5 years ~†‡¤	−1.164	−6.557 to 4.229	0.672
Influenza 0–5 years (binary) ~†‡¤	−0.864	−6.604 to 4.876	0.769
Chicken pox 0–5 years ~†‡¤	−0.509	−2.786 to 1.767	0.661
Rubella 0–5 years ~¤	2.152	−0.834 to 5.139	0.158
H. Pylori[a] seropositivity ~†¤	−3.684	−6.789 to 0.579	0.014
Diarrhoea in first year ~¤	−6.811	−15.601 to 1.978	0.124

*LRTI = lower respiratory tract infections.
**URTI = upper respiratory tract infections.
[a]*H. Pylori* seropositivity measured at age 50 years.

H. pylori and IQ and EQ after adjustment for social class, housing score and overcrowding (Table 6).

Discussion

Principal findings

In this study, we found a limited number of significant associations between cognitive outcomes and recognised infections. Tonsillitis in the first year of life was significantly associated with IQ even after adjustment for social class. This relationship was positive, suggesting an increase in IQ in children who had experienced tonsillitis. As such, it is likely that reporting of tonsillitis was better in mothers who were more educated and tied to care seeking behaviours, perhaps explaining this relationship. LRTIs from 0 to 5 years were negatively associated with all three cognitive outcomes. However, only the relationship with AQ remained significant after adjustment. *H. pylori* seropositivity at 50 years was also negatively associated with all three cognitive outcomes, yet only the associations with EQ and AQ remained significant following adjustment. Significant sex interaction was seen in the regressions between cognitive outcomes and *H. pylori* and tuberculosis.

Comparisons with other studies

A study on children born in Birmingham during the early 1950's by McKeown *et al.* showed a relationship between lower verbal reasoning scores at age 11 and children who had previously been infected with pertussis or measles in the first 5 years of life.[6] It was proposed that these infections may interfere with the central nervous system.[6] For example, in extreme cases measles can cause encephalitis whilst critical pertussis can result in convulsions and encephalopathy.[21,22] Childhood encephalitis has been linked to lower IQ later in childhood (mean age at time of cognitive assessment was 11.3 years).[23] The results of the present investigation were not reflective of McKeown *et al.,* study on children in Birmingham, as measles was not significantly associated to cognitive outcomes. However, McKeown *et al.* noted that adjustment was limited and as such there was a possibility that the relationships between cognition and infections were not completely valid.[6] All regression models between cognitive outcomes and measles in this study were adjusted for confounders, perhaps explaining the difference in conclusions.

In the present study, pertussis from 0 to 5 years showed a negative relationship with EQ scores which was lost to adjustment

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Table 5. Results of multivariable linear regressions relating AQ at age 11 to different infections. The models were adjusted for different combinations of 4 confounding variables: social class at birth (~), housing score at birth (†), birth order (‡) and overcrowding (¤)

	Results of linear regression with AQ (adjusted)		
Exposure	Coefficient	95% CI	*P*-value
Total infection 0–5 years ~†	−0.004	−0.194 to 0.186	0.966
Tonsillitis in first year ~	4.527	−0.619 to 9.673	0.085
Tonsillitis in first year (binary) ~	5.424	−0.049 to 10.896	0.052
Otorrhea in first year ~†‡¤	−1.727	−4.972 to 1.518	0.296
Otorrhea in first year (binary) ~†‡¤	−2.647	−6.408 to 1.114	0.167
Pertussis in first year ~†‡¤	3.042	0.001 to 6.084	0.05
Ear infection 0–5 years ~†¤	−0.543	−1.579 to 0.493	0.304
Ear infection 0–5 years (binary) ~†¤	−0.575	−2.846 to 1.096	0.619
*LRTI 0–5 years ~†¤	−0.959	−1.661 to −0.259	0.007
*LRTI 0–5 years (binary) ~†	−2.537	−4.434 to −0.640	0.009
**URTI 0–5 years ~†‡¤	0.093	−0.155 to 0.341	0.462
**URTI 0–5 years (binary) ~†‡¤	0.959	−5.254 to 7.171	0.762
Measles 0–5 years ~†‡¤	−0.199	−2.145 to 1.747	0.841
Mumps 0–5 years ~†‡¤	1.036	−1.672 to 3.744	0.453
Scarlet fever 0–5 years ¤	−4.584	−10.134 to 0.966	0.105
Pertussis 0–5 years ~†¤	−1.225	−3.124 to 0.675	0.206
Tuberculosis 0–5 years ¤	−3.678	−7.356 to 0.000	0.050
Influenza 0–5 years ~†¤	0.118	−4.907 to 5.143	0.963
Influenza 0–5 years (binary) ~†¤	0.327	−5.021 to 5.675	0.905
Chicken pox 0–5 years ~†‡¤	0.643	−1.479 to 2.766	0.552
Rubella 0–5 years ~‡¤	1.475	−1.325 to 4.276	0.301
H. Pylori[a] seropositivity ~†¤	−3.361	−6.269 to 0.453	0.024
Diarrhoea in first year ~†¤	−6.675	−17.707 to 4.358	0.226

*LRTI = lower respiratory tract infections.
**URTI = upper respiratory tract infections.
[a]*H. Pylori* seropositivity measured at age 50 years.

with social class and housing score. These results were reflected in a study by Johnston *et al.*[24] The study found that children hospitalised with pertussis had significantly lower reading ages as a percentage of their real age when compared to controls, but these results were no longer significant once models were adjusted for social class and parental smoking.[24]

ECD in the first 2 years of life has been correlated with poorer cognitive abilities 4–7 years later in children in Brazil.[3,5] The present investigation also found diarrhoea to be associated with lower cognitive abilities albeit, in a different study setting. However, this did not remain following adjustment for confounders. Conversely, Niehaus *et al.* found a significant relationship between cognition and ECD, which remained despite adjustment for maternal education and breastfeeding.[3] A later, larger study on Peruvian children found diarrhoea in the second year of life to be significantly associated to cognitive test scores at age nine, this was lost after adjustment for confounding variables, similar to the present study.[25] A number of studies have provided a link between enteric infections, diarrhoea and reduced cognitive outcomes[3,5,25,26] however the cause of this is uncertain. Some hypothesise that damage to the intestine reduces nutrient uptake and thus cognitive development is impaired by malnutrition,[2,27] yet Pinkerton *et al.* found diarrhoea in children to affect cognition independent of malnutrition.[5] As such, this area requires more research, particularly investigating causes of diarrhoea such as specific enteric pathogens and how they interact with cognitive development. In light of findings in more recent studies, it would also be useful to improve measures of childhood infections (with and without overt symptoms) and of intestinal or systemic inflammation, for example using quantitative molecular pathogen detection and biomarkers, respecitively,[28] and assess how they may interact with cognitive development.

Studies on the effect of *H. pylori* seropositivity on cognition in children are limited. One study carried out in an Israeli Arab population found that *H. pylori*-positive children between the ages of 6 and 9, living in one of the more affluent villages in the study, had lower IQ, non-verbal and verbal reasoning scores than their uninfected peers.[29] The present study also showed significant relationships between *H. pylori* seropositivity and cognitive outcomes. Studies have shown associations between *H. pylori* seropositivity and iron deficiency in children.[30,31] This may provide an explanation for the reduced cognitive abilities seen in

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Table 6. Adjusted stratified analysis of linear regressions relating cognitive outcomes to infections which were found to have significant interactions with sex prior to adjustment, along with the results of a test for interaction between sex and each infection in the relevant regression models. The linear regressions in these stratified analyses were adjusted for confounding variables as marked on the table: social class at birth (~), housing score at birth (†) and overcrowding (¤)

Regression	Males			Females			Test for interaction	
	Coefficient	95% CI	*p*-value	Coefficient	95% CI	*p*-value	95% CI	*p*-value
IQ × TB* ~¤ 0 to 5 years	1.371	−3.514 to 6.256	0.581	−7.704	−13.101 to −2.307	0.005	−15.883 to −1.372	0.020
IQ × *H. Pylori* ~†¤ seropositivity[a]	−6.248	−10.655 to −1.840	0.006	0.644	−3.308 to 4.597	0.748	1.409 to 12.941	0.015
EQ × TB* ~¤ 0 to 5 years	3.908	−1.239 to 9.054	0.136	−8.606	−14.301 to −2.911	0.003	−19.735 to −4.433	0.002
EQ × *H. Pylori* ~†¤ seropositivity[a]	−6.819	−11.499 to −2.139	0.005	−0.993	−5.111 to 3.125	0.635	0.126 to 12.220	0.045
AQ × TB* ¤ 0 to 5 years	1.167	−3.991 to 6.324	0.657	−9.881	−15.091 to −4.671	*P*<0.001	−17.778 to −3.053	0.006

*TB = Tuberculosis.
[a]*H. Pylori* seropositivity measured at age 50 years.

H. pylori-positive children as iron deficiency anaemia in early life has been linked with reduced cognitive performance later in childhood.[32] A study looking at ferritin levels in children with and without *H. pylori*, a greater percentage of the seropositive females had lower ferritin levels than seropositive males.[31] The present study found males to have a much stronger negative correlation between *H. pylori* seropositivity and cognitive outcomes than females. These opposing results may suggest that iron deficiency is not the only factor contributing to reduced cognition because of *H. pylori* infection. Alternatively, the present study measured *H. pylori* at 50 years and although research suggests this infection is commonly contracted in early life,[33] the studies mentioned above measured seropositivity in childhood likely providing more accurate results.[29–31] Further, we cannot rule out an element of reverse causation whereby *H. pylori* infection risk is higher in those with lower cognition.

There was also significant sex interaction in the relationships between tuberculosis and cognitive outcomes in the present study. Females had more pronounced negative correlations between tuberculosis and cognitive outcomes. Many studies recognise that tuberculous meningitis, a severe complication associated with tuberculosis, can have implications for cognitive development in children.[34–36] Data from the present study did not specify the severity of tuberculosis infections in study members, thus limiting comparability with other studies. The studies on the effects of tuberculous meningitis on cognition did not stratify results for each sex,[34–36] although in one study mortality in females was higher. This indicates a need for more research on the effects of tuberculosis between sexes.

There is little data on how LRTIs impact cognition. One study showed that children with LRTIs in the first year of life had significantly decreased lung function at age 11,[37] whilst another showed that better lung function in children was associated with increased cognitive test scores (mean age 9.9 years).[38] It could therefore be proposed that LRTIs may be linked to reduced cognition by diminishing lung function in infected individuals. More research should be carried out to determine whether these deficits may result in cognitive delays later in childhood, as well as the potential long-term consequences on factors such as respiratory health, as well as education, employment and income.

Since the beginning of the NTFS the number of childhood vaccinations offered in the UK has vastly increased,[39] leading to reduction, and in some cases eradication, of many infectious diseases.[40,41] This provides promise that the impact of infections upon cognition may be limited, in time, by the wider availability of vaccinations. Studies have shown that children who had received vaccinations against common childhood infections such as measles and pertussis had better cognitive outcomes than their unvaccinated counterparts.[42,43] This highlights the wider importance of vaccination against childhood infections, including the need for better control of infections that we do not currently have vaccines for.

Strengths and weaknesses

The NTFS is a prospective study, therefore, data collected at birth such as social class and housing score were not reliant on recall. Furthermore, childhood infection data were collected regularly over the first 5 years of life, also limiting any bias due to recall. However, some of the infections recorded have varied symptoms and do not always require medical attention or professional diagnosis. For example, tonsillitis and ear infections may have

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been reported by some parents or health visitors and not by others due to different interpretations of symptoms. Similarly, *H. pylori* seropositivity was recorded at 50 years, therefore, we cannot be sure that every seropositive study member was infected during childhood. Further, data on diarrhoea in the first year was extremely limited. We cannot rule out residual confounding. For example, maternal education and breastfeeding have been reported to impact upon cognitive development in children[44,45] and may have influenced the relationship between infections and cognition. We were also unable to account for potential mediators between early infections and childhood cognition, such as associations with brain injury, or infection rates later in childhood, which may in turn be related to factors such as absence from school. Finally, this study generated several regression models, and false positives may have occurred due to multiple testing.

Conclusion

In this investigation, LRTIs and *H. pylori* seropositivity showed significant, negative relationships with cognitive outcomes which, in some cases remained even after adjustment for confounding variables. This research suggests that specific childhood infections, particularly those which affect the gastrointestinal and pulmonary systems, may impair cognitive development resulting in reduced cognitive performance at 11 years. Further research should address how infections impact cognition in more detail, focusing on the severity and recurrence of specific infections, including more accurate exposure data, and the potential mediating pathways.

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Ethical standard. This study was performed in line with the principles of the Declaration of Helsinki. Approval for data collection was granted by the appropriate Local Research Ethics Committees and anonymised data were used for this analysis.

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