Markers of Early Life Infection in Relation to Adult Diabetes: Prospective Evidence From a National Birth Cohort Study Over Four Decades

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Pathogen burden has been linked to the occurrence of selected noncommunicable health events, particularly coronary heart disease (1). In addition to an inflammatory hypothesis, pathogen burden may contribute to features of immune senescence, such as the accumulation of differentiated cytotoxic T cells that are associated with impaired glucose homeostasis (2). This raises the possibility of a link between early life infection and diabetes, although longitudinal studies are scarce. Existing data on acquired infections and diabetes risk have been inconsistent, which may be ascribed to methodological weaknesses such as small sample sizes ($n < 150$) in studies largely on patient groups rather than the general population and a scarcity of prospective cohort studies. In the only prospective evidence of which we are aware, childhood illness of sufficient severity to warrant hospitalization was associated with markers of metabolic health, including fasting glucose (3). In the present analysis we use data from a national birth cohort of the general population in which exposure to infection was assessed in childhood before the onset of diabetes that was ascertained some 35 years later.

We used data from the 1970 British Cohort Study (4), in which participants have been surveyed on a regular basis throughout childhood (ages 5 and 10 years) and adulthood. Participants provided informed consent and the study received full ethical approval from the National Research Ethics Service (NRES) Committee South East Coast – Brighton and Sussex (Ref. 15/LO/1446). Data on early life infections were derived from three different sources. First, at the age 10 survey, childhood hospital admissions were recorded during parental interviews and data were provided by the community medical officer or school nurse following inquiries about the child's use of health services. These data were later coded according to ICD-9 using codes 460–488 to denote admission for infections (e.g., pneumonia and influenza); the remainder were designated as noninfections. Second, we used overcrowding in childhood, indexed by number of siblings, as a proxy of *Helicobacter pylori*. Prior work has indicated elevated levels of *H. pylori* at a threshold of four or more siblings (5). Last, during the biomedical examination at age 46 years, cytomegalovirus (CMV) antibodies were measured from serum samples with an electrochemiluminescent immunoassay (Roche E170 analyzer). At age 46, diabetes ascertainment was based on self-report of physician diagnosis and/or elevated A1C ($\geq$48 mmol/mol). Covariates included occupational social class of parents, history of public child care as a marker of major childhood adversity, parental smoking, and BMI at age 10 years. We computed odds ratio (OR) with accompanying 95% CI to summarize the relation of diabetes with early life infection, both for the individual exposures and a combination. Analyses were conducted using SPSS version 26.

Despite attrition, the adulthood sample of the birth cohort remains broadly representative. The analytic sample comprised 7,396 participants (51.9% women). Early life infection was evident in 22.8% of the analytical sample and was more prevalent in female participants, people from lower socioeconomic groups, and families of smokers. Diabetes was apparent in 4% of the sample in midlife. Combined markers of early life infection were related to higher odds of diabetes in male participants (OR 1.84; 95% CI 1.29, 2.64) but not female participants (0.60; 0.34, 1.06) after adjustment for covariates (Table 1). When each of the exposure markers was examined individually, childhood overcrowding was most strongly associated with diabetes (Table 1). We used noninfection-related hospital admission as a negative control (6), hypothesizing that it would have a similar confounding structure to admissions for infection yet no biologically or socially plausible link to later diabetes.

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Table 1—Association between markers of early life infection and diabetes in middle age: the 1970 British Cohort Study

	Men			Women		
	N diabetes cases/*N* at risk	Age-adjusted OR (95% CI)	Multiply-adjusted OR (95% CI)	*N* diabetes cases/*N* at risk	Age-adjusted OR (95% CI)	Multiply-adjusted OR (95% CI)
Hospitalization in childhood						
None	134/2,628	1.0 (Ref)	Ref	89/3,064	Ref	Ref
Noninfection	32/679	0.92 (0.62, 1.37)	0.95 (0.61, 1.48)	19/505	1.31 (0.79, 2.16)	1.22 (0.69, 2.17)
Infection	19/238	1.62 (0.98, 2.66)	1.60 (0.91, 2.83)	7/229	1.05 (0.48, 2.31)	0.95 (0.40, 2.22)
CMV exposure						
Negative	52/1,062	1.0 (Ref)	Ref	34/962	Ref	Ref
Positive	34/478	1.49 (0.95, 2.32)	1.47 (0.87, 2.47)	20/610	0.93 (0.53, 1.62)	0.53 (0.26, 1.11)
Childhood overcrowding						
<4 siblings	167/3,409	1.0 (Ref)	Ref	106/3,652	Ref	Ref
≥4 siblings	15/153	2.11 (1.21, 3.68)	2.20 (1.16, 4.16)	8/182	1.54 (0.74, 3.20)	0.47 (0.12, 1.96)
Combined infection						
None	120/2,784	1.0 (Ref)	Ref	89/2,924	Ref	Ref
Any	62/778	1.92 (1.40, 2.64)	1.84 (1.29, 2.64)	25/910	0.93 (0.62, 1.40)	0.60 (0.34, 1.06)

Adjusted models contain the following covariates: father's social occupational group, parental smoking, childhood public care, childhood BMI. Ref, reference.

The data for men suggested no association between noninfection-related hospital admission and diabetes (OR 0.92; 95% CI 0.62, 1.37) and a stronger, if statistically nonsignificant, link for infection-related admission (1.62; 0.98, 2.66). In women, there was no apparent association between diabetes and either infection- or noninfection-related admissions.

In conclusion, infections acquired in early life were related to higher likelihood of developing diabetes in adult men over four decades later, although associations were more marked for less severe infection such as *H. pylori*. The strengths of our study include its size and the availability of various markers of early life infection in a cohort that was followed for over four decades. Our sample was studied in middle age (all participants born in 1970) before the onset of significant physical decline, thus allowing associations

between infection and diabetes to be studied more clearly in the absence of other major comorbidities.

References

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