Markers of early life infection in relation to adult diabetes: prospective evidence from a national birth cohort study over four decades

Mark Hamer,[1] PhD (m.hamer@ucl.ac.uk; ORCID: 0000-0002-8726-7992)

G. David Batty[2,3] DSc, PhD (david.batty@ucl.ac.uk; ORCID: 0000-0003-1822-5753)

[1]Division Surgery and Interventional Science, Faculty Medical Sciences, University College London, UK

[2]Department of Epidemiology & Public Health, University College London, UK

[3]School of Biological & Population Health Sciences, Oregon State University, USA

Corresponding author: Professor Mark Hamer, Division Surgery and Interventional Science, Faculty Medical Sciences, University College London, UK. E-mail. m.hamer@ucl.ac.uk

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To The Editor,

Pathogen burden has been linked to the occurrence of selected non-communicable 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 there is a scarcity of longitudinal studies. Existing data on acquired infections and diabetes risk has been inconsistent, which may be ascribed to methodological weaknesses such as small sample sizes ($n<150$) 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 utilize data from a national birth cohort of the general population where exposure to infection was assessed in childhood before the onset of diabetes which was ascertained some 35 years later.

We utilized data from the 1970 British Cohort Study [4] in which participants have been surveyed on a regular basis throughout childhood (age 5, 10) and adulthood. Participants provided informed consent and the study received full ethical approval from NRES Committee South East Coast - Brighton & Sussex (Ref 15/LO/1446). Early life infections were derived from three different sources. Firstly, at the age 10 survey, childhood hospital admissions were recorded during parental interviews and data provided by the community medical officer or school nurse following enquiries about child's use of health services. These data were later coded according to International Classification of Diseases 9th revision (ICD-9), using codes 460-488 to denote admission for infections (e.g., pneumonia and influenza); the remainder were designated as non-infectious. Secondly, we used overcrowding in childhood, indexed by

number of siblings, as a proxy of *Helicobacter pylori*. Prior work has indicated elevated levels of *Helicobacter pylori* at a threshold of four or more siblings [5]. Lastly, during the age 46 biomedical examination, cytomegalovirus (CMV) antibodies were measured from serum samples with an electro chemiluminescent immunoassay (Roche E170 analyser). At age 46, diabetes ascertainment was based on self-report of physician diagnosis and/or elevated A1C (≥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 body mass index age 10. We computed odds ratios (OR) with accompanying 95% confidence intervals (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 mid-life. Combined markers of early life infection were related to higher odds of diabetes in male (odds ratio 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 were examined individually, childhood overcrowding was most strongly associated with diabetes (Table 1). We used non-infection 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. The data for men suggested no association between non-infection related hospital admission and diabetes (OR=0.92; 95 % CI, 0.62, 1.37) and a stronger, if statistically non-significant link for infection-related admission

(OR=1.62; 0.98, 2.66). In women, there was no apparent association between diabetes and either infection- or non-infection-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 were studied in middle age (all 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.

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Data availability: Data are publicly available at UK Data Archive https://www.data-archive.ac.uk/

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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	134/2628	1.0 (Ref)	Ref	89/3064	Ref	Ref
Non-infection	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	52/1062	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	167/3409	1.0 (Ref)	Ref	106/3652	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	120/2784	1.0 (Ref)	Ref	89/2924	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 following covariates: father's social occupational group, parental smoking, childhood public care, childhood body mass index. OR, odds ratio; CI, confidence interval