Early childhood lower respiratory tract infection and premature adult death from respiratory disease in Great Britain: a national birth cohort study

James Peter Allinson, Nishi Chaturvedi, Andrew Wong, Imran Shah, Gavin Christopher Donaldson, Jadwiga Anna Wedzicha, Rebecca Hardy

Summary

Background Lower respiratory tract infections (LRTIs) in early childhood are known to influence lung development and lifelong lung health, but their link to premature adult death from respiratory disease is unclear. We aimed to estimate the association between early childhood LRTI and the risk and burden of premature adult mortality from respiratory disease.

Methods This longitudinal observational cohort study used data collected prospectively by the Medical Research Council National Survey of Health and Development in a nationally representative cohort recruited at birth in March, 1946, in England, Scotland, and Wales. We evaluated the association between LRTI during early childhood (age <2 years) and death from respiratory disease from age 26 through 73 years. Early childhood LRTI occurrence was reported by parents or guardians. Cause and date of death were obtained from the National Health Service Central Register. Hazard ratios (HRs) and population attributable risk associated with early childhood LRTI were estimated using competing risks Cox proportional hazards models, adjusted for childhood socioeconomic position, childhood home overcrowding, birthweight, sex, and smoking at age 20–25 years. We compared mortality within the cohort studied with national mortality patterns and estimated corresponding excess deaths occurring nationally during the study period.

Findings 5362 participants were enrolled in March, 1946, and 4032 (75%) continued participating in the study at age 20–25 years. 443 participants with incomplete data on early childhood (368 [9%] of 4032), smoking (57 [1%]), or mortality (18 [<1%]) were excluded. 3589 participants aged 26 years (1840 [51%] male and 1749 [49%] female) were included in the survival analyses from 1972 onwards. The maximum follow-up time was 47·9 years. Among 3589 participants, 913 (25%) who had an LRTI during early childhood were at greater risk of dying from respiratory disease by age 73 years than those with no LRTI during early childhood (HR 1·93, 95% CI 1·10–3·37; p=0·021), after adjustment for childhood socioeconomic position, childhood home overcrowding, birthweight, sex, and adult smoking. This finding corresponded to a population attributable risk of 20·4% (95% CI 3·8–29·8) and 179 188 (95% CI 33 806–261 519) excess deaths across England and Wales between 1972 and 2019.

Interpretation In this prospective, life-spanning, nationally representative cohort study, LRTI during early childhood was associated with almost a two times increased risk of premature adult death from respiratory disease, and accounted for one-fifth of these deaths.

Funding National Institute for Health and Care Research Imperial Biomedical Research Centre, Royal Brompton and Harefield National Health Service (NHS) Foundation Trust, Royal Brompton and Harefield Hospitals Charity and Imperial College Healthcare NHS Trust, UK Medical Research Council.

Lancet 2023; 401: 1183–93

Published Online March 7, 2023 https://doi.org/10.1016/S0140-6736(23)00131-9

This online publication has been corrected. The corrected version first appeared at thelancet.com on May 4, 2023

See Comment page 1135

Royal Brompton Hospital, London, UK (J P Allinson PhD); **National Heart and Lung Institute, Imperial College London, London, UK** (J P Allinson, Prof G C Donaldson PhD, Prof J A Wedzicha MD); **MRC Unit for Lifelong Health and Ageing** (Prof N Chaturvedi MD, A Wong PhD, I Shah MSc) **and Social Research Institute** (Prof R Hardy PhD), **University College London, London, UK; School of Sport, Exercise, and Health Sciences, Loughborough University, Loughborough, UK** (Prof R Hardy)

Correspondence to: Dr James P Allinson, National Heart and Lung Institute, Imperial College London, London SW3 6LY, UK **j.allinson@imperial.ac.uk**

Introduction

Respiratory diseases are a major cause of premature adult mortality worldwide.[1–3] Better prevention and control of these often incurable and non-communicable diseases would avoid many of these deaths.[4,5] Current disease prevention strategies mostly focus on harmful adult exposures, such as tobacco smoke.[4–6] Common childhood exposures also influence adult respiratory health,[7–9] but their contribution to premature adult mortality and hence their use as a preventive target remains unclear.[9,10]

Early childhood is a crucial period of lung development.[7,8] Early childhood lower respiratory tract infection (LRTI) can disrupt this development leading to reduced lung function as adults,[7,11,12] and increase the risk of developing chronic airway disease.[12] Historically, these infections were also hypothesised to predispose children to premature adult death from respiratory disease.[13] However, without life-spanning data, investigators could only explore this hypothesis by using ecological methods,[13] asking adults to recall their early life experiences,[14] or by using surrogate markers of childhood

Research in context

Evidence before this study

Respiratory disease is a major driver of premature adult death worldwide. Preventive strategies focus on the avoidance of proven causative adult exposures, such as tobacco smoke, but there might be scope for preventive interventions much earlier in life. Historically, respiratory infection during early childhood lung development was hypothesised to predispose people to adult respiratory disease. Many studies have linked lower respiratory tract infections (LRTIs) in early childhood to reduced adult lung function, but there have been no life-spanning studies quantifying their potential contribution to premature adult mortality from respiratory disease. We searched PubMed on Oct 26, 2022, for articles published in English between database inception and Oct 26, 2022, using the terms (("infant" OR "early-life" OR "child") AND ("respiratory infection" OR "pneumonia" OR "chest infection" OR "respiratory tract infection")) AND ("adult" AND ("mortality" OR "death")) and ("longitudinal" or "cohort"). We identified no studies that prospectively recorded respiratory infection occurrence during early childhood and subsequent mortality across adulthood in the same participants. One study, in 9544 male adult university students, showed that adult participants who recalled having childhood respiratory disease were at 57% greater risk of adult death from respiratory disease. Supportive findings were also provided by studies using ecological methods or surrogate markers of childhood respiratory infection. From these studies, the role of confounding by childhood socioeconomic factors and adult smoking remained unclear, and no studies included nationally representative samples or attempted to estimate the potential contribution of early childhood LRTI to national burdens of premature adult mortality from respiratory disease.

Added value of this study

This study used nationally representative data from, to our knowledge, the longest running ongoing birth cohort study worldwide, following the same participants across eight decades since their birth in 1946. By prospectively linking LRTI recorded during early childhood to adult deaths from respiratory disease recorded by the central National Health Service registry, we showed that LRTI during early childhood (age <2 years) was associated with almost a two times increased risk of death from respiratory disease from age 26 to 73 years. This increased risk remained robust even after adjusting for multiple markers of childhood social disadvantage and adult smoking, and the risk seemed to be specific for respiratory mortality, not for alternative causes of death. This risk would account for one in five (20·4%) premature adult deaths from respiratory disease; by comparison, smoking accounted for almost three in five (57·7%) of these deaths. As mortality in our study closely mirrored nationwide patterns, we estimated that early childhood LRTI was linked to 179 188 excess deaths across England and Wales between 1972 and 2019.

Implications of all the available evidence

To our knowledge, this is the first prospective study to quantify the relationship between early childhood LRTI and premature adult death from respiratory disease, showing both the long-lasting sequalae of early childhood respiratory infection and the childhood origins of premature adult respiratory mortality. Although reducing premature respiratory mortality is a key aim of many international organisations, their efforts focus predominantly on avoiding adverse adult exposures, particularly smoking. By showing such a substantial link to early childhood LRTI, this study shows there is scope for much earlier preventive interventions and provides a more rounded explanation for existing inequities in survival. Our findings also challenge historically held assumptions that life-limiting adult diseases, such as chronic obstructive pulmonary disease, result only from choices made as adults.

infection.[15,16] Although these studies provide supportive data, they risked exposure misclassification bias,[13–16] and confounding by both childhood socioeconomic position and adult smoking.[13] Furthermore, it was often unclear how well these study samples represented the populations from which they were recruited.

We aimed to estimate the association between early childhood LRTI and the risk and burden of premature adult mortality from respiratory disease.

Methods

Study design and participants

This longitudinal observational cohort study used data collected prospectively by the Medical Research Council National Survey of Health and Development (NSHD) in a nationally representative cohort of all single births among married women during 1 week in March, 1946, within England, Scotland, and Wales.[17] Cohort participants were contacted 25 times between birth and age 73 years. Ongoing high adult participation has resulted in this cohort remaining broadly representative of men and women of their generation born in Great Britain.[18] Individuals were flagged for notification of date and cause of death on the National Health Service (NHS) Central Register in 1971.[19] Ethics approval was obtained for each of the NSHD study waves (the most recent approval was from the Queen Square Research Ethics Committee [14/LO/1073]). All participants or their parents or guardians gave informed consent to participate in each NSHD study wave.

Procedures

Survival follow-up time was from the middle of the first quarter of 1972 (when participants were aged 26 years), thus minimising immortal time bias, to the middle of the quarter of the year when death occurred or, for survivors,

to the end of 2019, when all study participants reached age 73·9 years. Therefore, the maximum length of follow-up was 47·9 years. Deaths before age 75 years are considered premature.[2]

Using International Classification of Diseases (ICD) codes, we categorised each death by cause as respiratory, circulatory, cancer, externalising (including accidents, suicide, or alcohol-related), or other (appendix p 29). The primary outcome was death from respiratory disease from age 26 through 73 years. Deaths from alternative causes were considered as negative control outcomes. To show how different diseases contributed to respiratory deaths, these were subcategorised accordingly (appendix p 29).

We defined early childhood as the first 2 years of life. In 1948, when study participants reached age 2 years, their parents or guardians were asked by health visitors: "Has this baby ever had a lower respiratory infection—that is, bronchitis, bronchopneumonia, or pneumonia".[11] Infection frequency (before age 2 years) was recorded, together with age (in months) and treatment at the initial infection.

Childhood socioeconomic position (grouped according to paternal manual occupation *vs* non-manual occupation) was recorded at age 4 years (or, if missing, at age 11 or 15 years).[11] The number of household occupants and rooms were also recorded in 1948 and we defined overcrowded homes as homes with more than one person per room.[11] We used pollution exposure estimates based on domestic local coal consumption at birth and 2 years to classify early childhood pollution exposure as high or low.[11] Birthweight was obtained from hospital records within a few weeks of birth and subsequently converted to kg. Participant sex was reported by parents.

At age 20, 25, 36, 43, 53, 60–64, and 68 years, the number of cigarettes participants smoked per day was recorded at interviews or via postal questionnaires. Self-rolled cigarettes were converted on the basis that 1 oz tobacco was equal to 25 manufactured cigarettes. At each survey, participants who reported smoking at least one cigarette per day for at least 1 year were considered active smokers. At age 26 years, participants were classified as either smokers (active smokers at age 20–25 years) or non-smokers (those who only reported non-smoking status at age 20–25 years).

Statistical analysis

Participants with available data on early life and adult smoking who survived to age 26 years were included in our analysis. We excluded participants who had emigrated by age 26 years. We tested whether inclusion versus exclusion at age 26 years differed by early life characteristics (χ^2 tests) and whether birthweight differed by inclusion (independent *t* test). To illustrate the national representativeness of mortality data in this cohort, we compared them with data held by the Office for National Statistics (ONS) documenting all deaths across England and Wales from 1972 to 2019, at age 26–73 years, among those born in 1946, applying the same ICD-based categorisation (appendix p 29).

We used a cause-specific hazard model fitted using Cox regression to estimate the association between early childhood LRTI (yes *vs* no) and premature adult death from respiratory disease occurring between the middle of the first quarter of 1972 and the end of 2019. We censored subsequent emigrations and deaths from non-respiratory causes. This approach assumes that intervention to eliminate competing events is practical, that there is a similar risk factor distribution across censored versus uncensored participants, such competing events are independent of the outcome of interest, and there are a sufficient number of uncensored and censored participants at each level of the common risk factors and exposure.[20] We first considered unadjusted models, and then models were adjusted for early life covariates (father's occupation, home overcrowding, sex, and birthweight) and smoking at age 20–25 years (yes *vs* no), informed by construction of a directed acyclic graph (appendix pp 4–5). Plotting the Schoenfeld residuals against time for each covariate showed no violation of the Cox proportional hazards assumption. We confirmed assumed birthweight linearity as a predictor by including a birthweight squared term (p=0·08) and, separately, using a likelihood ratio to test whether entering birthweight categories (defined using quintiles) versus in continuous form improved the fit of the model (p=0·95). To explore whether unrecognised confounding might explain any association between early childhood LRTI and adult death from respiratory disease, we assessed whether infection was also associated with death from cardiovascular, cancer, external, and other causes, using these as negative control outcomes (appendix p 7).[21] If this explanation was correct, we would expect early childhood LRTI to also predict those causes of mortality that are strongly influenced by childhood socioeconomic position.[10] We also assessed whether early childhood LRTI was associated with all-cause mortality.

To explore how differences in adult smoking behaviour might explain our findings, we adjusted for smoking intensity (mean number of cigarettes smoked per day across ages 20–25 years), both instead of and then alongside binary smoking status. For respiratory-cause mortality, effect modification of early childhood LRTIs by both smoking status and sex was examined and both multiplicative and additive interaction terms were estimated in post-hoc analyses. To explore whether associations between early childhood LRTI and adult survival might reflect differences in smoking behaviour after age 26 years, we assessed whether adult smoking status or intensity among participants differed according to early childhood LRTI as well as father's occupation, home overcrowding, and sex. Within the participants with available data, we adjusted our main analyses for early childhood pollution exposure.

See Online for appendix

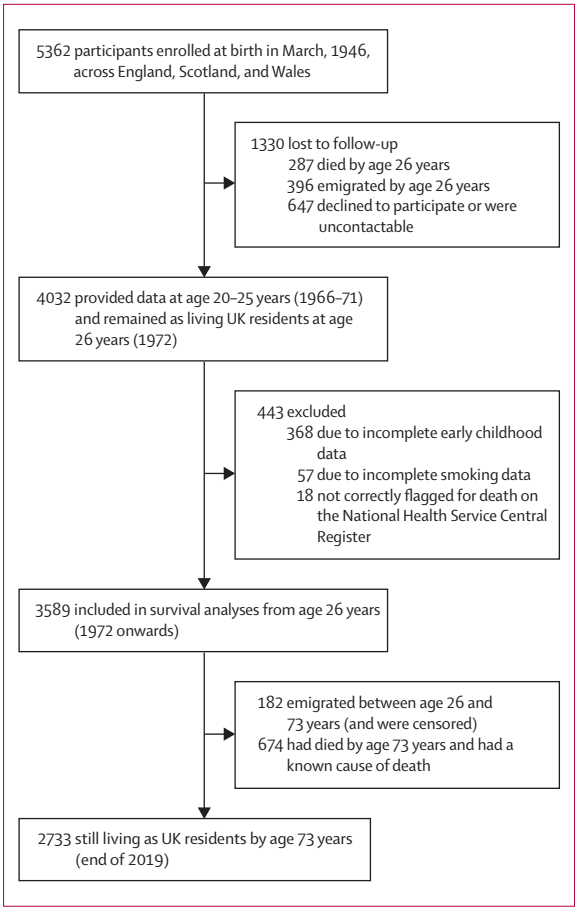


Figure 1: **Study profile**
Further information regarding deaths before age 26 years is provided in the appendix (p 8).

	Participants (n=3589)
Early life characteristics	
Sex	
Female	1749 (49%)
Male	1840 (51%)
Early childhood LRTI before age 2 years	913 (25%)
Father with manual occupation when study participant age 4 years	2090 (58%)
Home overcrowding at age 2 years	1621 (45%)
Birthweight, kg	3·405 (0·515)
Smoker at age 20–25 years	1832 (51%)
Number of cigarettes smoked per day by smokers at age 20–25 years	10 (7–16)
Early childhood LRTI	
LRTI at age <2 years	913 (25%)
Number of LRTIs by age 2 years	
1	596/913 (65%)
2	162/913 (18%)
≥3	155/913 (17%)
Age when first LRTI occurred	
<1 year	648/913 (71%)
≥1 year	256/913 (28%)
Data missing	9/913 (1%)
Treatment of first LRTI	
Untreated	36/913 (4%)
Outpatient treatment	820/913 (90%)
Inpatient treatment	52/913 (6%)
Data missing	5/913 (1%)
Outcome by age 73 years	
Alive	2733 (76%)
Emigrated	182 (5%)
Died	674 (19%)

Data are n (%), n/N (%), mean (SD), or median (IQR). LRTI=lower respiratory tract infection.

Table: **Baseline characteristics and overall outcomes of participants included in the survival analyses**

In supplementary analyses, we explored whether forced expiratory volume in 1 s (FEV_1) at age 43 years (when spirometry was first measured) was a potential mediator of any relationship between early childhood LRTI and respiratory-cause mortality.

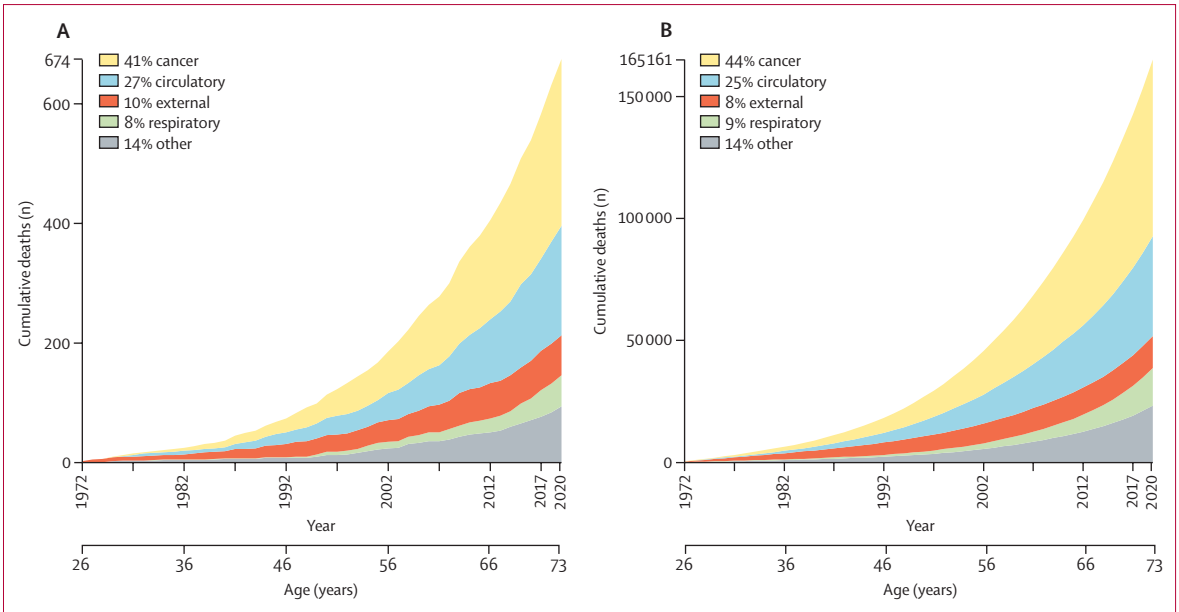
We also explored how early childhood LRTI frequency (one, two, or three or more infections), age at initial infection (<1 year or 1–2 years), and treatment for initial infection (untreated or outpatient *vs* inpatient) influenced mortality, replacing binary infection occurrence with categorical variables in the fully adjusted models.

Using Miettinen's formula, we calculated the population attributable risk fraction and estimated the excess premature adult deaths from respiratory disease across England and Wales between 1972 and 2019, assuming that the association with early childhood LRTI was causal and free from unaccounted confounding, that infection removal would not change other risk factors, and that our data were nationally representative.[22,23]

Analyses were done with SPSS (version 28) and STATA (version 17).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
5362 participants were enrolled in March, 1946, and 4032 (75%) continued participating in the study and completed one or more postal questionnaires at age 20–25 years (1966–71), with withdrawal from the study being due to death (287 [5%]), emigration (396 [7%]), and declined participation or failure to trace (647 [12%]; figure 1). 443 participants with incomplete data on early childhood (368 [9%] of 4032), smoking (57 [1%]), or mortality (18 [<1%]) were excluded. 3589 participants aged 26 years (1840 [51%] male and 1749 [49%] female) were included in the survival analyses from 1972 onwards (table). The maximum and median follow-up times were



Cause of death	Deaths (n=674)
Cancer	278 (41%)
Circulatory	183 (27%)
External	67 (10%)
Respiratory	52 (8%)
Other*	94 (14%)

Cause of respiratory deaths	Deaths (n=52)
Chronic obstructive pulmonary disease	31 (60%)
Acute LRTI	7 (13%)
Interstitial pulmonary disease	4 (8%)
Asthma	4 (8%)
Bronchiectasis	3 (6%)
Respiratory disease due to external agents	2 (4%)
Other respiratory diseases	1 (2%)

Cause of death	Deaths (n=165161)
Cancer	72399 (44%)
Circulatory	40920 (25%)
External	13153 (8%)
Respiratory	15321 (9%)
Other*	23368 (14%)

Cause of respiratory deaths	Deaths (n=15321)
Chronic obstructive pulmonary disease	7781 (51%)
Acute LRTI	4162 (27%)
Interstitial pulmonary disease	1356 (9%)
Asthma	511 (3%)
Bronchiectasis	486 (3%)
Respiratory disease due to external agents	399 (3%)
Other respiratory diseases	626 (4%)

Figure 2: **Premature adult death (from age 26 to 73 years) according to cause from 1972 to 2019**
(A) All deaths in the NSHD 1946 birth cohort (current study). (B) All deaths across England and Wales among individuals born in 1946 (ONS data). According to ONS data, 9 589 309 premature adult deaths occurred across England and Wales from 1972 to 2019, and 878 951 (9%) of these deaths were caused by respiratory disease. Among the 9 589 309 premature adult deaths, 165 161 were in people born in the same year as the NSHD study participants (1946). LRTI=lower respiratory tract infection. NSHD=National Survey of Health and Development. ONS=Office for National Statistics. *Includes any death not due to cancer, circulatory disease, external causes, or respiratory disease.

both 47·9 years, as 2733 (76%) participants survived to the end of 2019. By the end of 2019, 182 (5%) of 3589 participants had emigrated and 674 (19%) had died.

Among 674 premature adult deaths, 52 (8%) participants died from respiratory disease, mostly caused by chronic obstructive pulmonary disease (31 [60%]), but also due to acute LRTI (seven [13%]), interstitial lung disease (four [8%]), asthma (four [8%]), bronchiectasis (three [6%]), respiratory disease due to external agents (two [4%]), and other respiratory disease (one [2%]; figure 2). There was no relationship between early life exposures or sex and inclusion in the analytical sample (appendix pp 31–32). Birthweight was higher in participants who were included in the analytical sample than in those who were excluded as adults (mean 3405 g [SD 515] *vs* 3318 g [589]; p<0·0001; appendix pp 31–32). During the follow-up period across England and Wales, 9 589 309 adults died prematurely (from age 26 through 73 years), 165 161 of whom were born in 1946. Respiratory disease caused 878 951 (9%) of all premature adult deaths and 15 321 (9%) of premature adult deaths among people born in 1946. Distribution of cause-specific deaths was very similar in the study cohort and in the national data (figure 2).

913 (25%) of 3589 participants had one or more LRTIs in early childhood (596 [65%] had one infection, 162 [18%] had two infections, and 155 [17%] had three or more infections; table). The first infection mostly occurred before age 1 year (648 [71%] participants) and most participants (872 [96%]) received treatment, with a minority (52 [6%]) requiring inpatient treatment (table). The first infection mostly

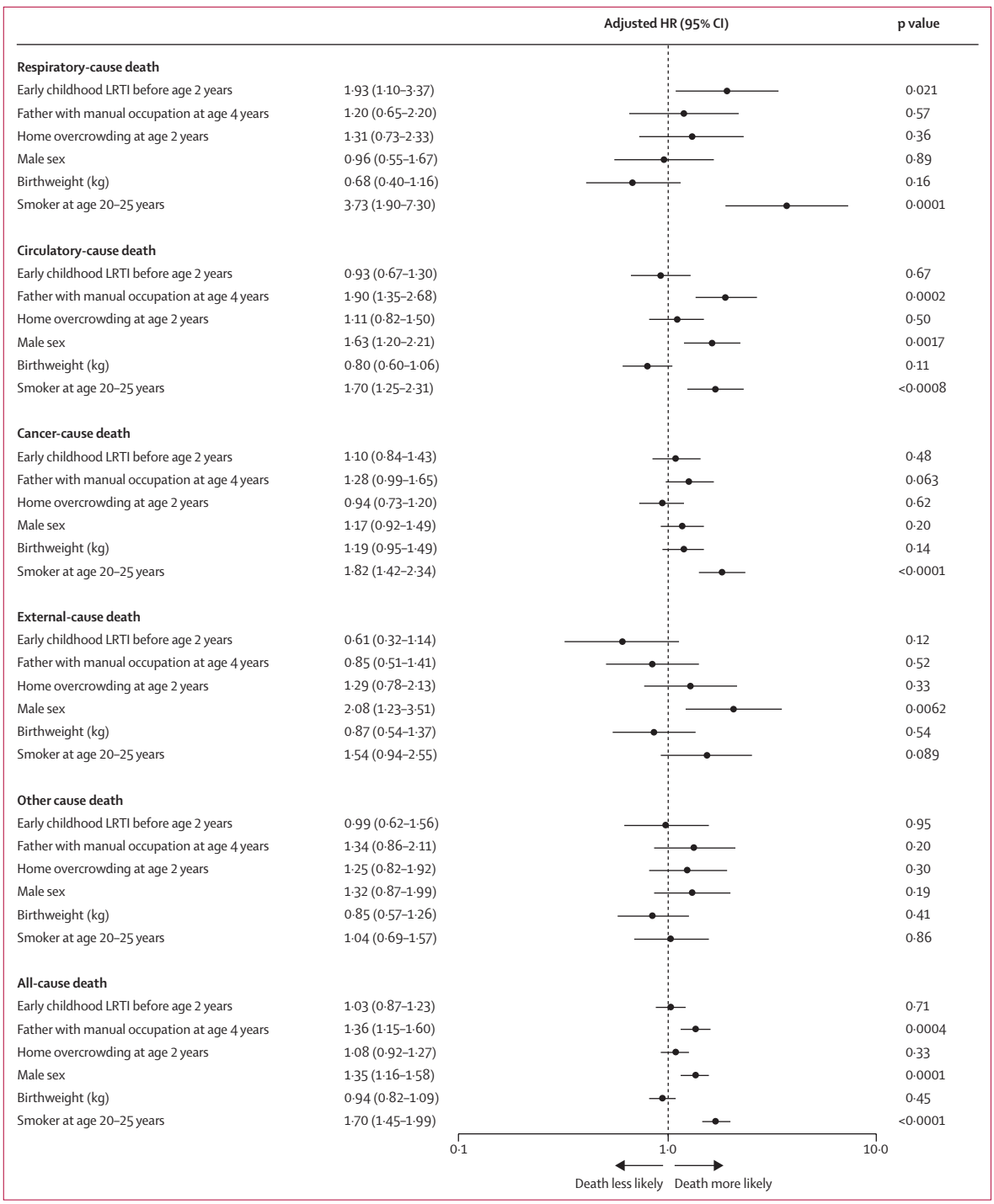


Figure 3: **Adjusted HRs for premature adult death from respiratory causes, negative control outcome causes (circulatory, cancer, external, and other), and all causes**

3589 participants were included in each model. Unadjusted HRs are shown in the appendix (p 11). HR=hazard ratio. LRTI=lower respiratory tract infection.

occurred in autumn or winter (appendix p 10). 2090 (58%) of 3589 participants had fathers with a manual occupation at age 4 years and 1621 (45%) lived in overcrowded homes at age 2 years. By age 20–25 years, 1832 (51%) participants were smokers (table).

In unadjusted (univariable) analyses, early childhood LRTI was associated with higher respiratory-cause mortality by age 73 years (hazard ratio [HR] 2·15, 95% CI 1·24–3·72; p=0·0065), but there were no similarly sized estimates of increased risk for any of the alternative causes

(appendix p 11). Relative to early childhood LRTI, father's occupation (HR 1·54, 95% CI 0·86–2·74; p=0·15) and home overcrowding (1·58, 0·92–2·74; p=0·10) showed smaller unadjusted estimated associations with respiratory-cause mortality. The association between father's occupation and circulatory-cause mortality was larger than that for respiratory-cause mortality, whereas the associations with cancer mortality and mortality from other causes were similar to that for respiratory-cause mortality, but the 95% CIs were narrower due to the higher number of deaths (appendix p 11). Cigarette smoking was associated with all-cause mortality and cause-specific mortality except for deaths from other causes, although the estimated effect size was strongest for respiratory mortality (HR 3·81, 95% CI 1·96–7·41; p<0·0001; appendix p 11).

Figure 3 shows HRs for each cause of death according to early childhood LRTI occurrence, adjusted for father's occupation, home overcrowding, sex, birthweight, and adult smoking status (appendix pp 33–34). In the fully adjusted model, participants who had an LRTI during early childhood were at higher risk of premature adult death from respiratory disease by age 73 years than those with no LRTI during early childhood (HR 1·93, 95% CI 1·10–3·37; p=0·021). This estimate was only slightly attenuated compared with the unadjusted association. By contrast, we found no evidence that early childhood LRTI conferred a similarly increased risk of circulatory, cancer, external, other-cause, or all-cause mortality (figure 3).

Our main findings were unchanged after adjustment for intensity of smoking at age 20–25 years (appendix p 12). For respiratory-cause mortality, the estimated relative excess risk due to interaction between early childhood LRTI and smoking was 2·77 (95% CI –1·41 to 6·95; p=0·20), and between early childhood LRTI and sex was 0·54 (–0·98 to 2·06; p=0·49); neither were significant (appendix pp 35–36). Participants who remained alive at age 25–68 years and who had fathers in manual occupations at age 4 years and who lived in overcrowded homes at age 2 years were more likely to be smokers than those from more advantaged backgrounds. The difference in smoking prevalence by early childhood LRTI was smaller at all ages. Among smokers, there was little difference in the number of cigarettes smoked daily at age 25–68 years by early childhood LRTI (appendix pp 13–14). Adjustment for early childhood pollution exposure did not alter our main findings, and pollution was not associated with adult mortality from respiratory disease even in an unadjusted model (appendix pp 15–16). Early childhood LRTI was associated with lower adult FEV_1 (appendix pp 17–24), and adults who subsequently died from respiratory disease had lower mean FEV_1 at age 43 years than those who remained alive or those who died from alternative causes (appendix p 22). The direct effect of early childhood LRTI on addition of FEV_1 to the model was considerably lower than the total effect, which suggests that FEV_1 is a potential mediator (appendix p 23).

After adjustment, risk of respiratory-cause mortality was increased when early childhood LRTI occurred more frequently (three or more infections, HR 2·87, 95% CI 1·18–7·02), occurred before age 1 year (2·12, 1·16–3·88), or needed inpatient treatment (4·35, 1·31–14·5), compared with no infection (figure 4).

The population attributable risk of premature adult death from respiratory disease due to early childhood LRTI was 20·4% (95% CI 3·8–29·8), corresponding to an estimated 179 188 (95% CI 33 806–261 519) excess premature adult deaths across England and Wales between 1972 and 2019 (appendix pp 26–28). The population attributable risk of premature adult death from respiratory disease due to adult smoking was 57·7% (95% CI 37·3–68·0), corresponding to 507 223 (95% CI 328 272–598 085) excess deaths.

Discussion

This study, which spanned eight decades, found that people who had an LRTI by age 2 years were 93% more likely to die prematurely from respiratory disease as adults than people who did not have early childhood LRTI. If the association was causal, early childhood LRTI would account for one-fifth (20·4%) of respiratory-cause deaths between age 26 and 73 years, and an estimated 179 188 excess deaths across England and Wales between 1972 and 2019.

Childhood LRTIs have been shown to be linked to the development of adult lung function impairments, asthma, and chronic obstructive pulmonary disease,[7,8,11,12] but no previous study has had long enough follow-up to prospectively connect these early childhood infections to adult mortality. Although an association with mortality has been inferred by ecological studies[13] and studies using adult recollections[14] or surrogate markers of early childhood exposures,[15,16] these approaches risked exposure misclassifications, which were likely to be avoided by our use of prospective data. We also showed that early life social circumstances did not explain the association detected between early childhood LRTI and adult premature respiratory-cause mortality. This association remained robust after adjusting for markers of childhood social disadvantage, including socioeconomic position, home overcrowding, and pollution exposure. Although adult smoking varied according to childhood socioeconomic position and home overcrowding, as hypothesised, our findings remained robust after adjustment for smoking. Furthermore, if our main findings were due to residual confounding by early life socioeconomic factors or consequent differences in adult smoking, we would also expect early childhood infection to be associated with circulatory-cause mortality and cancer mortality, as these conditions show strong patterning with smoking and socioeconomic factors.[10] However, early childhood LRTI was only associated with premature adult death from respiratory disease.

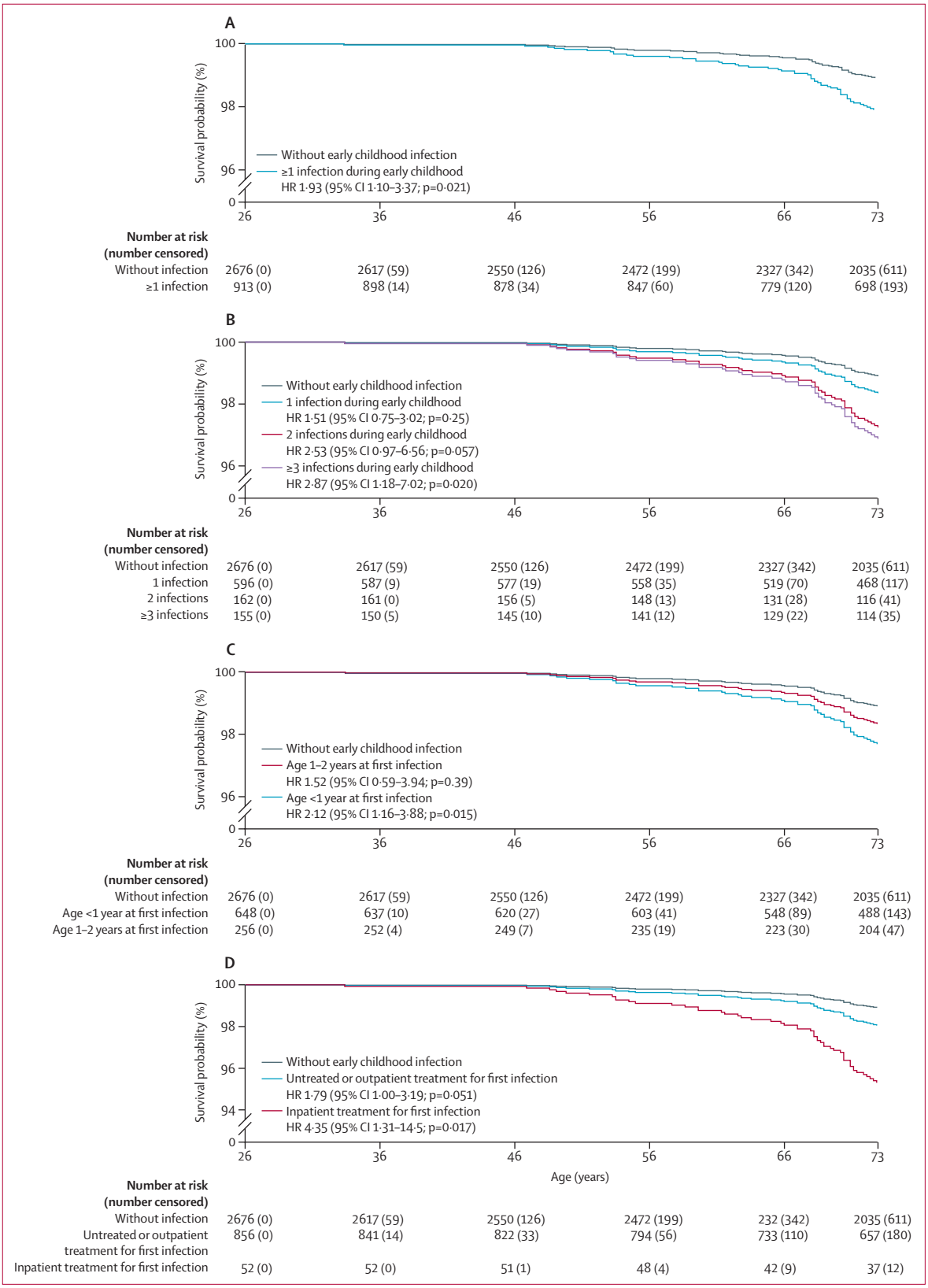


Figure 4: **Survival probabilities by age and adjusted HRs for premature adult death from respiratory disease from age 26 to 73 years according to LRTI during early childhood**

All models are adjusted for father's occupation, early childhood home overcrowding, sex, birthweight, and smoking at age 20–25 years. (A) Any LRTI during early childhood (≥1 infection *vs* without any infection). (B) Frequency of LRTI during early childhood (1 infection, 2 infections, or ≥3 infections *vs* without any infection). (C) Timing of the first early childhood LRTI (first infection before age 1 year or at age 1–2 years *vs* without any infection). (D) Treatment received for the first early childhood LRTI (untreated or outpatient treatment, or inpatient treatment, *vs* without any infection). This figure shows the results of the adjusted Cox proportional hazards models (A–D) described in the appendix (p 25). The HRs for each group shown are calculated relative to participants without any LRTI during early childhood. HR=hazard ratio. LRTI=lower respiratory tract infection.

Overall, our analyses indicate plausible differences in the early life origins of adult diseases, with a specific association between early childhood LRTI and adult respiratory disease development or survival. This specific link is further suggested by increased adult respiratory-cause mortality following more frequent early childhood LRTI, infection requiring inpatient treatment, or infection before age 1 year, which could reflect the consequences of cumulative damage from multiple infections, more severe infection, or a greater vulnerability to developmental disturbance earlier in infancy.

A major strength of this study is that the NSHD recruited a nationally representative sample at birth in 1946.[17] Inclusion in analyses from age 26 years and follow-up using centralised NHS mortality data meant only people who had emigrated (5%) were then lost from survival analyses. The resemblance to nationwide ONS mortality data confirms this study is well placed to estimate the national proportion of premature adult respiratory deaths attributable to specific exposures. Smoking caused almost three-fifths (57·7%) of these deaths. Not smoking is essential to optimising respiratory health, and approaches to prevent and understand the development of diseases such as chronic obstructive pulmonary disease have focused predominantly upon this avoidable adult exposure.[7,8,9] However, one-fifth (20·4%) of respiratory-cause adult deaths were linked to early childhood LRTI, equating to 179 188 excess deaths across England and Wales during the analysis period, assuming the association is causal. Linking such a large proportion of adult respiratory deaths to early childhood infection should help challenge the smoking-related stigma attached to death from these diseases[24] and drive preventive strategies targeting risk well before adulthood.

Impaired adult lung function is a plausible mediator linking early childhood infection to respiratory-cause adult mortality. Infection might disrupt or reflect already disrupted childhood lung development, leading to children reaching lower peak lung function as adults,[8,11] increasing the risk of respiratory morbidity and mortality.[7,25,26] In the NSHD, early childhood LRTI led to lowered adult lung function trajectories, predisposing individuals to developing more severe-grade respiratory disease.[11] Our mediation analyses suggested lower adult lung function could explain much of the association between early childhood LRTI and premature adult respiratory-cause death. Importantly, the relationship between early childhood LRTI and adult lung function appears modifiable by adolescent smoking and asthma, which perhaps prevent naturally occurring catch-up growth during adolescence.[11,27–30] Therefore, identifying young children with LRTIs and actively optimising their health as they and their lungs grow into adulthood might be one way to break the connection between poor respiratory health in childhood and adulthood.

If early childhood LRTIs are causally linked to premature adult respiratory-cause mortality, preventing these infections or, possibly, lessening infection severity (given that we found higher mortality in participants who required inpatient treatment) might offer an earlier interventional opportunity. Many of these infections are caused by viruses, such as respiratory syncytial virus and human rhinovirus,[31,32] and we observed an infection prevalence and seasonal variation closely resembling virally triggered bronchiolitis.[32] Most children have encountered respiratory syncytial virus by age 2 years and the minority who develop bronchiolitis more commonly develop chronic respiratory disease,[29,33] but it remains unclear whether chronic disease is caused by respiratory syncytial virus and is therefore preventable by vaccination.[34] Despite existing vaccination programmes, bacteria remain major drivers of childhood respiratory infection, often complicating viral infection during severe infections. Bacterial dysbiosis is also a potential target for intervention because bacterial–viral interactions and aeroallergen sensitisation during childhood immune maturation is implicated in the development of longer-term asthma-like symptoms.[35]

In some people, early childhood LRTI, impaired adult lung function, and premature adult respiratory-cause death might reflect already impaired lung function at birth due to impaired intrauterine lung development or genetic variation.[8] Within the Tucson Children Respiratory Study,[36] functional residual capacities at age 2 months were lower among children who later developed intermittent wheeze, and these deficits explained up to 14% of lung function variation in early adulthood.[37] More recently, the number of genetic variants linked to both impaired lung function and adult respiratory disease has rapidly expanded, hopefully foreshadowing further preventive and therapeutic opportunities.[38] With regard to the lifelong consequences we report, the extent to which early childhood LRTI represents a marker of underlying susceptibility in need of greater recognition, or a cause to be targeted therapeutically, remains to be determined.

Most respiratory-cause deaths within this study were due to chronic obstructive pulmonary disease, and it is possible that our findings reflect childhood health influencing the development of this disease. However, consideration of chronic obstructive pulmonary disease as an outcome would risk substantial misclassification, as diagnostic criteria recognise only already well-established disease, and diagnosis is often conferred only later in life or missed altogether.[39] Background nationwide underdiagnosis, coupled with study participation inadvertently increasing disease recognition, known as Hawthorne effect,[40] might explain the higher proportion of deaths in the NSHD attributed to underlying chronic obstructive pulmonary disease. However, because our study has mortality as its outcome, the wider effect of early childhood LRTI on adult respiratory health and wellbeing remains unquantified and is likely to have been underestimated.

All population survival studies suffer limitations from inbuilt bias (outcome-susceptible participants are progressively selected out) and unmeasured confounding. Using direct acyclic graphs, we highlight our analytical assumptions and avoid overadjustment of total effect estimates for factors on the causal pathway. Although we adjusted for important socioeconomic factors and smoking, some adverse exposures remained unrecognised, and therefore unrecorded, in the 1940s. Prospective investigation of unrecorded factors, including parental smoking and prematurity, awaits the maturation of subsequently initiated studies. However, we also used negative control outcomes, to assess whether unmeasured confounding might explain our findings. We found it did not, as the association appeared to be specific to respiratory-cause mortality. This approach also has structural limitations. Specifically, circulatory-cause death has a similar confounding structure to respiratory-cause mortality, but a causal relationship might be possible, whereas the opposite applies to cancer-cause and external-cause mortality.

During this life-spanning study, concurrent societal change might have also driven secular change across subsequent birth cohorts, altering both lung function[41] and future adult survival. Since 1946, average UK living conditions, nutrition, and health care have improved, including the introduction of universal health care and childhood vaccination strategies. New exposures have also emerged, including electronic cigarettes, and our follow-up period also preceded the first UK COVID-19 case. Furthermore, advanced health care might lead to some people who would not have survived childhood previously reaching adulthood, albeit in poorer health. Poor preterm birth survival in the 1940s would explain the association between study inclusion and birthweight. Since then, premature birth survival rates have been transformed, but respiratory complications might nevertheless shorten adult lifespans among people who survive.[7,42] Expansion of this survivor group, and declining adult smoking rates, could mean childhood health makes an even greater relative contribution to future premature adult mortality in the UK. In more disadvantaged areas, for example in low-income and middle-income countries, where hospitalisation, morbidity, and mortality from early childhood LRTI remains high,[31] their contribution to premature adult mortality might be even greater than we report. Childhood poverty, a broad driver of childhood respiratory disease,[4] remains common globally,[43–45] and although this does not explain the link between early childhood LRTI and subsequent adult mortality, poorer environmental conditions predisposed children in the NSHD to develop respiratory infection in the first place.[11] Addressing childhood poverty worldwide, besides improving child health, could help avoid the perpetuation of health inequities across life, down generations, and between communities.

In conclusion, our results suggest that children who had an LRTI by age 2 years were almost twice as likely to die prematurely from respiratory disease as adults, and these infections accounted for one-fifth of these deaths. This association was not explained by early life socioeconomic circumstances or adult smoking, and early childhood LRTI was not associated with other causes of death, suggesting a specific link between early childhood LRTI and the development or prognosis of adult respiratory diseases, such as chronic obstructive pulmonary disease. To avoid the development of these adult diseases and the perpetuation of child health inequities, preventive strategies spanning the whole life course are required.

Contributors

JPA conceived the study and did the statistical analysis. All authors contributed to the content and writing of the manuscript. JPA wrote the first draft of the manuscript. AW, IS, RH, and NC contributed to the curation, preparation, and collection of data. NC is the principal investigator of the NSHD. JPA, AW, and IS had access to and verified the underlying data. All authors contributed to the scientific content of the manuscript, critically reviewed it, and approved the final version. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

NC has participated in an advisory board for AstraZeneca. GCD has received institution grants or contracts from Genentech and AstraZeneca; has participated in advisory boards for AstraZeneca and Novatis; and has authored a book chapter for Elsevier. JAW has received institution grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Genentech, and 37 Clinical; has received consulting fees from AstraZeneca, Epiendo, GlaxoSmithKline, Gilead, Novartis, Pieris, and Pulmatrix; has received speaker fees from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Recipharm, and Novartis; has participated as data safety monitoring board chair for Virtus; and was the Editor-in-Chief of the *American Journal of Respiratory and Critical Care Medicine* until March, 2022. RH has received an institution grant from the Economic and Social Research Council. All other authors declare no competing interests.

Data sharing

Data sharing must be within the bounds of consent given previously by study members and meet rigorous Medical Research Council data security standards. Data sharing is dependent on the project being approved by the NSHD Data Sharing Committee, a data sharing agreement being in place between University College London and the academic institution that employs the researcher, and Medical Research Council Unit for Lifelong Health and Ageing resources being available to meet the requests for data sharing. Further details can be found at http://www.nshd.mrc.ac.uk/data, https://doi.org/10.5522/NSHD/Q101, https://doi.org/10.5522/NSHD/Q102, and https://doi.org/10.5522/NSHD/Q103.

Acknowledgments

This study was supported by the National Institute for Health and Care Research Imperial Biomedical Research Centre; Royal Brompton and Harefield NHS Foundation Trust; Royal Brompton & Harefield Hospitals Charity; and Imperial College Healthcare NHS Trust. The views expressed are those of the authors and not necessarily those of the National Institute for Health and Care Research, NHS, or the Department of Health and Social Care. The Medical Research Council NSHD is funded by the UK Medical Research Council (MC_UU_00019/1, MC_UU_00019/2, and MC_UU_00019/4). We wish to thank the NSHD study members for their lifelong participation, and the past and present members of the NSHD study team who helped to collect and curate the data presented. This manuscript also includes data prepared and provided by the ONS, licensed under the Open Government Licence (version 3.0).

References

1 Collaborators GBDCRD. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020; **8:** 585–96.

2 Organisation for Economic Co-operation and Development. Avoidable mortality: OECD/Eurostat lists of preventable and treatable causes of death (January 2022 version). Paris: Organisation for Economic Co-operation and Development, 2022.

3 Organisation for Economic Co-operation and Development. Mortality from respiratory diseases. Health at a glance: Europe 2018: state of health in the EU Cycle. Brussels: Organisation for Economic Co-operation and Development, 2018.

4 Bousquet J, Kaltaev N. Global surveillance, prevention and control of chronic respiratory disease: a comprehensive approach. Geneva: World Health Organization, 2007.

5 Watkins DA, Msemburi WT, Pickersgill SJ, et al. NCD Countdown 2030: efficient pathways and strategic investments to accelerate progress towards the Sustainable Development Goal target 3.4 in low-income and middle-income countries. *Lancet* 2022; **399:** 1266–78.

6 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2020 report). Fontana, WI: Global Initiative for Chronic Obstructive Lung Disease, 2020.

7 Stocks J, Hislop A, Sonnappa S. Early lung development: lifelong effect on respiratory health and disease. *Lancet Respir Med* 2013; **1:** 728–42.

8 Martinez FD. Early-Life origins of chronic obstructive pulmonary disease. *N Engl J Med* 2016; **375:** 871–78.

9 Kuh D, Ben-Shlomo Y. A life course approach to chronic disease epidemiology: tracing the origins of ill-health from early to adult life. Oxford: Oxford University Press, 2004: 3–14.

10 Galobardes B, Lynch JW, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiol Rev* 2004; **26:** 7–21.

11 Allinson JP, Hardy R, Donaldson GC, Shaheen SO, Kuh D, Wedzicha JA. Combined impact of smoking and early-life exposures on adult lung function trajectories. *Am J Respir Crit Care Med* 2017; **196:** 1021–30.

12 Shaheen S. The beginnings of chronic airflow obstruction. *Br Med Bull* 1997; **53:** 58–70.

13 Barker DJ, Osmond C. Childhood respiratory infection and adult chronic bronchitis in England and Wales. *Br Med J (Clin Res Ed)* 1986; **293:** 1271–75.

14 Galobardes B, McCarron P, Jeffreys M, Davey Smith G. Association between early life history of respiratory disease and morbidity and mortality in adulthood. *Thorax* 2008; **63:** 423–29.

15 Hart CL, Davey Smith G. Relation between number of siblings and adult mortality and stroke risk: 25 year follow up of men in the Collaborative study. *J Epidemiol Community Health* 2003; **57:** 385–91.

16 van Dijk IK, Janssens A, Smith KR. The long harm of childhood: childhood exposure to mortality and subsequent risk of adult mortality in Utah and the Netherlands. *Eur J Popul* 2018; **35:** 851–71.

17 Wadsworth M, Kuh D, Richards M, Hardy R. Cohort Profile: the 1946 national birth cohort (MRC national survey of health and development). *Int J Epidemiol* 2006; **35:** 49–54.

18 Stafford M, Black S, Shah I, et al. Using a birth cohort to study ageing: representativeness and response rates in the National Survey of Health and Development. *Eur J Ageing* 2013; **10:** 145–57.

19 Dehbi HM, Blangiardo M, Gulliver J, et al. Air pollution and cardiovascular mortality with over 25 years follow-up: a combined analysis of two British cohorts. *Environ Int* 2017; **99:** 275–81.

20 Mansournia M, Nazemipour M, Etminan M. A practical guide to handling competing events in etiologic time-to-event studies. *Glob Epidemiol* 2022; **4:** 4.

21 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21:** 383–88.

22 Counil E. Contribution of causal factors to disease burden: how to interpret attributable fractions. *Breathe (Sheff)* 2021; **17:** 210086.

23 Khosravi A, Nielsen RO, Mansournia MA. Methods matter: population attributable fraction (PAF) in sport and exercise medicine. *Br J Sports Med* 2020; **54:** 1049–54.

24 Woo S, Zhou W, Larson JL. Stigma experiences in people with chronic obstructive pulmonary disease: an integrative review. *Int J Chron Obstruct Pulmon Dis* 2021; **16:** 1647–59.

25 Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; **373:** 111–22.

26 Agustí A, Noell G, Brugada J, Faner R. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017; **5:** 935–45.

27 Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018; **6:** 535–44.

28 Allinson JP, Hardy R, Donaldson GC, Wedzicha JA. Childhood exposures, asthma, smoking, interactions, and the catch-up hypothesis. *Ann Am Thorac Soc* 2018; **15:** 1241–42.

29 Voraphani N, Stern DA, Wright AL, Guerra S, Morgan WJ, Martinez FD. Risk of current asthma among adult smokers with respiratory syncytial virus illnesses in early life. *Am J Respir Crit Care Med* 2014; **190:** 392–98.

30 Dharmage SC, Bui DS, Walters EH, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med* 2022; published online Oct 14. https://doi.org/10.1016/S2213-2600(22)00364-2.

31 Zar HJ, Nduru P, Stadler JAM, et al. Early-life respiratory syncytial virus lower respiratory tract infection in a South African birth cohort: epidemiology and effect on lung health. *Lancet Glob Health* 2020; **8:** e1316–25.

32 Reeves RM, Hardelid P, Gilbert R, Warburton F, Ellis J, Pebody RG. Estimating the burden of respiratory syncytial virus (RSV) on respiratory hospital admissions in children less than five years of age in England, 2007–2012. *Influenza Other Respir Viruses* 2017; **11:** 122–29.

33 Sørensen KG, Øymar K, Dalen I, Halvorsen T, Mikalsen IB. Asthma, atopy and lung function in young adults after hospitalisation for bronchiolitis in infancy: impact of virus and sex. *BMJ Open Respir Res* 2022; **9:** e001095.

34 Driscoll AJ, Arshad SH, Bont L, et al. Does respiratory syncytial virus lower respiratory illness in early life cause recurrent wheeze of early childhood and asthma? Critical review of the evidence and guidance for future studies from a World Health Organization-sponsored meeting. *Vaccine* 2020; **38:** 2435–48.

35 Pijnenburg MW, Frey U, De Jongste JC, Saglani S. Childhood asthma: pathogenesis and phenotypes. *Eur Respir J* 2022; **59:** 2100731.

36 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995; **332:** 133–38.

37 Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007; **370:** 758–64.

38 Shrine N, Guyatt AL, Erzurumluoglu AM, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. *Nat Genet* 2019; **51:** 481–93.

39 Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. *Lancet Respir Med* 2017; **5:** 426–34.

40 McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J Clin Epidemiol* 2014; **67:** 267–77.

41 Allinson JP, Afzal S, Çolak Y, et al. Changes in lung function in European adults born between 1884 and 1996 and implications for the diagnosis of lung disease: a cross-sectional analysis of ten population-based studies. *Lancet Respir Med* 2022; **10:** 83–94.

42 Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. *Postgrad Med J* 2015; **91:** 712–18.

43 Wickham S, Anwar E, Barr B, Law C, Taylor-Robinson D. Poverty and child health in the UK: using evidence for action. *Arch Dis Child* 2016; **101:** 759–66.

44 The Lancet Respiratory Medicine. Health inequality: a major driver of respiratory disease. *Lancet Respir Med* 2017; **5:** 235.

45 Marmot M, Bell R. Fair society, healthy lives. *Public Health* 2012; **126** (suppl 1)**:** S4–10.