Early life predictors of future multi-morbidity: results from the Hertfordshire Cohort

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Abstract

Background: Multi-morbidity is an increasing challenge in western medicine and has the potential to impact patients’ quality of life, treatment options and compliance with medications. The aim of this study was to identify early life predictors of long-term multi-morbidity in an historical cohort, the Hertfordshire Cohort Study (HCS).

Methods: Perinatal and infant health records were kept on all children born in Hertfordshire between 1931-39. Participants who were still alive in 1998 were recruited to the HCS and data collected on major chronic diseases. They were subsequently followed up in the Clinical Outcomes Study (COS), and data recorded on all major illnesses since HCS, as well as current medications. Ordinal logistic regression analysed the association between early life factors and the number of morbidities in these two surveys as well as medication count.

Results: 2299 participants had data in COS, 1131 (49%) were female, median age (interquartile range (IQR)) at recruitment to HCS was 66 (64-68) years. Higher rates of childhood illnesses were significantly associated with future multi-morbidity (multivariate odds ratio (95% confidence interval (CI)) 1.15 (1.06, 1.25)) and higher medication counts at COS (multivariate OR (95%CI) 1.14 (1.06, 1.23)).

Conclusions: Children who experience more illnesses at a young age may be prone to develop multi-morbidity in later life.

Background

Multimorbidity, defined as the presence of more than one long term condition within an individual, is increasingly prevalent and poses challenges for governments and healthcare services across the world [[1](#_ENREF_1)]. Effective modern treatments for cardiovascular disease, cancer and other previously fatal conditions mean that people are living longer, but with a heavier chronic disease burden. Co-existent conditions can lead to reduced quality of life, limit access to therapies and operative interventions, and put patients at risk through polypharmacy [[1](#_ENREF_1), [2](#_ENREF_2)]. Much of the published literature to date has focused on measuring the prevalence or incidence of multimorbidity in different populations, and quantifying the consequent societal costs [[3](#_ENREF_3)]. For example, in the UK, multi-morbidity contributes significantly to the economic burden within an NHS already struggling to cope with an ageing population [[4](#_ENREF_4), [5](#_ENREF_5)]. Despite this, there is a group of individuals who remain relatively untouched by this problem, even in older age groups. Therefore identifying factors associated with high or low multimorbidity may be important. Lifestyle, environmental and sociodemographic factors such as education, age, smoking, and obesity are recognised predictors of many common chronic conditions and contribute to the multi-morbid burden in individuals [[3](#_ENREF_3), [6](#_ENREF_6), [7](#_ENREF_7)]; in addition there may be specific protective genes within individuals who do not develop multi-morbidity. However it is also possible that factors during the perinatal and early childhood years contribute to the development of multi-morbidity in later life.

The aim of this study therefore, was to investigate the association between early life factors and future multimorbidity in a longitudinal cohort of people in Hertfordshire, UK.

Methods

*Participants and setting:* The study used data from the Hertfordshire cohort study. This cohort has been described previously [[8](#_ENREF_8)]. Briefly, all births in Hertfordshire, United Kingdom from 1931-1939 were reported by the attending midwife and recorded in ledgers, including details of birth weight. Subsequently the children were visited by health visitors throughout infancy who recorded details of weight at 1 year, method of infant feeding and childhood illnesses up to the age of five in the same ledgers. Those participants who were still alive and living in Hertfordshire in 1998-2003 were traced through the NHS Central Register at Southport. With consent from their GP, 6099 of these individuals were contacted with 3225 agreeing to a home visit during which a nurse-administered questionnaire was carried out. These participants formed the original Hertfordshire Cohort study (HCS). The questionnaire covered a wide spectrum of details about lifestyle and bone health, details of major chronic diseases, including ischaemic heart disease, cerebrovascular accidents (CVA), and diabetes. A full list of regular medications was also detailed. The same participants were contacted again in 2007-08 as part of the Clinical Outcomes Study (COS) and 2299 agreed to a follow up postal questionnaire study in which participants were asked for details of hypertension, diabetes, asthma/chronic obstructive pulmonary disease, rheumatoid arthritis, multiple sclerosis, thyroid disease, vitiligo, depression, Parkinson’s disease and cancer. They were also asked to provide details of any other serious illnesses since their last review in the HCS. These data were used to calculate a total multimorbidity count at the time of the COS questionnaire

*Statistical analysis:* Demographic characteristics of those participants completing the COS follow up questionnaire were compared with those not completing it. Differences in these groups were assessed using χ2 tests for categorical variables and Student’s t-tests or Mann-Whitney tests for continuous variables. Ordinal logistic regression was used to determine the association between each early-life factor and (i) the total number of multi-morbid conditions, and (ii) the number of medications reported at the time of the COS questionnaire univariately. Multivariate models were then constructed adjusting for all early life factors as well as baseline age, gender, smoking status, alcohol consumption, BMI, and a validated measure of physical activity[[9](#_ENREF_9)]. The models were also adjusted for time within the cohort (between HCS and COS) and year of recruitment to the HCS to account for secular changes in healthcare.

Results

The median age (interquartile range (IQR)) of the participants at recruitment to HCS was 66 (64-68) years and 1131 (49%) were female. Demographic details are shown in table 1. Those participants who completed the follow-up COS questionnaire (n = 2299) were statistically significantly more likely to be female (p = 0.011), less likely to be current smokers (p<0.001), more active (p<0.001), had a lower BMI (p = 0.003) and were more likely to have a non-manual paternal social class (p = 0.011) than those that did not participate in COS (n = 926). There were no statistically significant differences in their age, alcohol consumption, birth weight, weight at 1 year, conditional 1 year growth, number of childhood illnesses, method of infant feeding, maternal age at birth or whether they’d been immunised against diphtheria.

Four hundred and fifty five (22%) participants reported no comorbidities with a similar number reporting three or more comorbidities (452 (22%)). The median (IQR) number of medications at COS was 4 (2-6).

Of the early life factors, immunisation against diphtheria, paternal social class and the number of childhood illnesses were univariately associated with the multimorbidity count at COS (table 2); in the fully adjusted model only the number of childhood illnesses remained significant, odds ratio (OR) (95% confidence interval (CI)) 1.15 (1.06, 1.25), p = 0.001. Immunisation against diphtheria and the number of childhood illnesses along with a mixed pattern of infant feeding were also associated with medication count at the time of the COS questionnaire (table 2). The number of childhood illnesses and mixed infant feeding remained significant in the fully adjusted model (OR (95%CI) 1.14 (1.06, 1.23), p<0.001 for the number of childhood illnesses and OR (95%CI) 0.82 (0.69, 0.96), p = 0.017 for mixed infant feeding). Of the adult factors, age, BMI, physical activity and being an ex-smoker were also significantly associated with both outcomes (table 2), whereas alcohol consumption showed no association.

**Table 1:** Characteristics of participants

|  |  |  |
| --- | --- | --- |
| COS characteristics: |  | N |
| No. comorbidities *n (%)* |  | 2096 |
| 0  1  2  ≥3 | 455 (22%)  643 (31%)  546 (26%)  452 (22%) |  |
| No. medications *med (IQR)* | 4 (2-6) | 2299 |
|  |  |  |
| Baseline demographics at HCS: |  | **N** |
| Age at HCS (years) *med (IQR)* | 66 (64-68) | 2299 |
| Female *n (%)* | 1131 (49%) | 2299 |
| Smoking status *n (%)*  Never  Ex  Current | 1141 (50%)  907 (39%)  249 (11%) | 2297 |
| Alcohol consumption (units per week) *med(IQR)* | 4 (0.5-11.5) | 2298 |
| Physical activity *mean (SD)1* | 60.5 (15.1) | 2299 |
| BMI *med (IQR)* | 26.7 (24.3-29.6) | 2293 |
|  |  |  |
| Ledger characteristics: |  | **N** |
| No. of childhood illnesses 0-5 yrs *n (%)* |  | 2299 |
| 0  1  2  ≥3 | 974 (42%)  742 (32%)  398 (17%)  185 (8%) |  |
| Birth weight (kg) *mean (SD)* | 3.43 (0.53) | 2299 |
| Weight (kg) *mean (SD)* | 10.01 (1.05) | 2299 |
| Conditional 1 year growth *z-score* *mean (SD)2* | 0.08 (0.98) | 2299 |
| Immunised against diphtheria (y/n) *n (%)* | 291 (13%) | 2299 |
| Infant feeding *n (%)* |  | 2299 |
| Breast  Bottle  Mixed | 1407 (61%)  198 (9%)  694 (30%) |  |
| Paternal social class *n (%)* |  | 2165 |
| I-IIINM  IIIM-V | 372 (17%)  1793 (83%) |  |
| Maternal age at birth (years) *med (IQR)* | 29 (25-33) | 2238 |

Data from the Hertfordshire Cohort Study (HCS) and the Clinical Outcomes Study (COS)

1Standardised score ranging 0–100 derived from frequency of gardening, housework, climbing stairs, and carrying loads in a typical week. Higher scores indicate greater level of activity

2conditional growth at 1 year based on birthweight and weight at 1 year

**Table 2:** Association between early life factorsand multimorbidity count

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Multimorbidity count | | | | Medication count | | | |
|  | **Univariate** | | **Multivariate**  **(n = 1923)1** | | **Univariate** | | **Multivariate**  **(n = 2105)1** | |
|  | N | OR (95% CI) | | OR (95% CI) | N | OR (95% CI) | | OR (95% CI) |
| Diphtheria immunised | 2096 | 0.67 (0.54, 0.84)\* | | 0.96 (0.72, 1.26) | 2299 | 0.74 (0.60, 0.91)\* | | 1.07 (0.82, 1.39) |
| No. of childhood illnesses | 2096 | 1.11 (1.03, 1.19)\* | | 1.15 (1.06, 1.25)\* | 2299 | 1.08 (1.01, 1.16)$ | | 1.14 (1.06, 1.23)\* |
| Paternal social class *I-IINM*  *IIIM-V* | 1979 | ref  1.36 (1.10, 1.68)\* | | ref  1.15 (0.93, 1.43) | 2165 | ref  1.07 (0.88, 1.30) | | ref  0.92 (0.75, 1.13) |
| Maternal age at birth (yrs) | 2040 | 0.99 (0.98, 1.01) | | 1.00 (0.98, 1.01) | 2238 | 1.00 (0.98, 1.01) | | 1.00 (0.98, 1.01) |
| Feeding *Breast*  *Bottle*  *mixed* | 2096 | ref  0.94 (0.72, 1.24)  0.92 (0.78, 1.09) | | ref  1.05 (0.78, 1.40)  0.95 (0.79, 1.14) | 2299 | ref  0.82 (0.63, 1.06)  0.83 (0.71, 0.97)$ | | ref  0.83 (0.63, 1.09)  0.82 (0.69, 0.96)\* |
| Birth weight (kg) | 2096 | 0.97 (0.84, 1.13) | | 1.29 (0.58, 2.89) | 2299 | 0.93 (0.81, 1.07) | | 0.79 (0.37, 1.67) |
| Weight at 1 year (kg) | 2096 | 1.01 (0.94, 1.09) | | 0.52 (0.17, 1.63) | 2299 | 1.00 (0.94, 1.07) | | 1.13 (0.39, 3.28) |
| Conditional growth 0-1 yrs2 | 2096 | 1.02 (094, 1.10) | | 1.88 (0.61, 5.74) | 2299 | 1.04 (0.97, 1.12) | | 0.93 (0.33, 2.63) |
| Age (yrs) | 2096 | 1.06 (1.03, 1.09)\* | | 1.10 (1.06, 1.14)\* | 2299 | 1.07 (1.04, 1.10)\* | | 1.11 (1.07, 1.15)\* |
| Gender *Male*  *Female* | 2096 | ref  1.00 (0.86, 1.16) | | ref  0.74 (0.45, 1.22) | 2299 | ref  1.27 (1.10, 1.46)\* | | ref  1.35 (0.85, 2.15) |
| BMI (kg/m2) | 2091 | 1.13 (1.11, 1.16)\* | | 1.12 (1.10, 1.15)\* | 2293 | 1.09 (1.07, 1.11)\* | | 1.08 (1.06, 1.10)\* |
| Activity score | 2096 | 0.99 (0.98, 0.99)\* | | 0.99 (0.98, 0.99)\* | 2299 | 0.98 (0.98, 0.99)\* | | 0.98 (0.98, 0.99)\* |
| Smoking *Never*  *Ex*  *Current* | 2094 | ref  1.56 (1.32, 1.84)\*  1.20 (0.93, 1.55) | | ref  1.41 (1.18, 1.70)\*  1.26 (0.95, 1.67) | 2297 | ref  1.25 (1.08, 1.46)\*  1.02 (0.80, 1.31) | | ref  1.23 (1.04, 1.45)$  1.17 (0.90, 1.52) |
| Alcohol consumption (units per wk) | 2095 | 1.00 (0.99, 1.00) | | 0.99 (0.99, 1.00) | 2298 | 1.00 (0.99, 1.00) | | 1.00 (0.99, 1.00) |

Data from the Hertfordshire Cohort Study (HCS) and the Clinical Outcomes Study (COS)

1multivariate models also adjusted for time in cohort (between HCS and COS) and year of recruitment to HCS to account for secular changes in disease management.

2this is a measure weight aged 1 year, adjusted for birth weight

3Standardised score ranging 0–100 derived from frequency of gardening, housework, climbing stairs, and carrying loads in a typical week. Higher scores indicate greater level of activity

$p<0.05, \*p<0.01

Discussion

In this study we have demonstrated that the people who experience childhood illnesses are more likely to develop multimorbidity and have a higher medication burden later in life. This association remained significant after adjustment for socio-demographic factors in child hood (such as paternal class) and lifestyle factors later in life, such as smoking, obesity and alcohol consumption. Interestingly birth weight and infant growth were not associated with total burden of multimorbidity, despite their known association with common chronic diseases late in life such as heart disease, COPD and diabetes which has been demonstrated within the HCS [[10-13](#_ENREF_10)] and other longitudinal studies [[14](#_ENREF_14), [15](#_ENREF_15)]. Higher rates of childhood infections (which constitute the majority of early childhood diseases included here), have previously been associated with respiratory disease in later life and autoimmunity [[11](#_ENREF_11), [16](#_ENREF_16), [17](#_ENREF_17)]; it may be that these diseases contribute more to the overall burden of disease seen in this study. To our knowledge, this is the first study to investigate prospectively collected early life health factors as predictors of total burden of multi-morbidity in later life. Pavela et al investigated trajectories of multimorbidity in the Health and Retirement study in the US, and found that, similar to our data, poor childhood health was independently associated with increased numbers of chronic conditions [[18](#_ENREF_18)]. However their data on childhood economic status and childhood illness were collected retrospectively and childhood illness was assessed by a single question asking whether they could recall health under the age of 16 as good or poor. These data are therefore susceptible to recall bias, and it might be reasonable to suspect that adults with poorer current health might more readily recall poor health in childhood. Childhood SES has been more widely investigated as a predictor of adult health, and shown to influence burden of multi-morbidity [[19](#_ENREF_19)]. Notably in both our study and the study by Pavela et al, markers of childhood SES were associated with multi-morbidity univariately, but not in multivariate models, suggesting the influence occurs through other factors such as later lifestyle habits or childhood illness.

It should also be noted that the majority of the childhood illnesses recorded in the Hertfordshire ledgers are now vaccine preventable illnesses. Given recent resurgences in such infections [[20](#_ENREF_20), [21](#_ENREF_21)], our data further highlights the importance of public health efforts to ensure as wide a vaccine coverage as possible.

There are limitations to this study. Not all chronic diseases were captured in the first HCS questionnaire, and data captured later in COS only pertained to illnesses occurring since the original study. Therefore it is possible some outcomes were not captured, which may have underpowered our results, but is unlikely to have biased the results in one direction or another. Importantly, the literature around multimorbidity suggests the impact relates primarily to common and high impact diseases such as CVD, diabetes and depression [[22](#_ENREF_22)], all of which were captured in the HCS. In addition, the outcomes we used to define multimorbidity (a multimorbid count and number of medications) are relatively crude measures to capture a complex construct. For example, they do not take into account the severity of individual diseases and may not account for non-linear associations. Finally we were not able to include individuals who died between the two surveys (or even before they could be recruited to HCS) in our study. However, these individuals potentially had greater levels of multimorbidity and therefore their absence will have underpowered our study. This might have contributed to the lack of association seen with birth weight and conditional growth in infancy.

In conclusion we have demonstrated that higher rates of early childhood illness contribute to the burden of multimorbidity later in life. This may be important for future public health policy.

References

1. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012 Jul 7; 380(9836):37-43.

2. Brilleman SL, Salisbury C. Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study. Family practice. 2013 Apr; 30(2):172-178.

3. Palladino R, Tayu Lee J, Ashworth M, Triassi M, Millett C. Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. Age and ageing. 2016 May; 45(3):431-435.

4. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. The British journal of general practice : the journal of the Royal College of General Practitioners. 2011 Jan; 61(582):e12-21.

5. Fund Ks. Long-term conditions and multi-morbidity. 2016 [cited; Available from: <http://www.kingsfund.org.uk/time-to-think-differently/trends/disease-and-disability/long-term-conditions-multi-morbidity>

6. Kadam UT, Croft PR. Clinical multimorbidity and physical function in older adults: a record and health status linkage study in general practice. Family practice. 2007 Oct; 24(5):412-419.

7. Wikstrom K, Lindstrom J, Harald K, Peltonen M, Laatikainen T. Clinical and lifestyle-related risk factors for incident multimorbidity: 10-year follow-up of Finnish population-based cohorts 1982-2012. Eur J Intern Med. 2015 Apr; 26(3):211-216.

8. Syddall HE, Aihie Sayer A, Dennison EM, Martin HJ, Barker DJ, Cooper C. Cohort profile: the Hertfordshire cohort study. International journal of epidemiology. 2005 Dec; 34(6):1234-1242.

9. Dallosso HM, Morgan K, Bassey EJ, Ebrahim SB, Fentem PH, Arie TH. Levels of customary physical activity among the old and the very old living at home. Journal of epidemiology and community health. 1988 Jun; 42(2):121-127.

10. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989 Sep 9; 2(8663):577-580.

11. Barker DJ, Godfrey KM, Fall C, Osmond C, Winter PD, Shaheen SO. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. Bmj. 1991 Sep 21; 303(6804):671-675.

12. Fall CH, Vijayakumar M, Barker DJ, Osmond C, Duggleby S. Weight in infancy and prevalence of coronary heart disease in adult life. Bmj. 1995 Jan 7; 310(6971):17-19.

13. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, et al. Fetal and infant growth and impaired glucose tolerance at age 64. Bmj. 1991 Oct 26; 303(6809):1019-1022.

14. Rich-Edwards JW, Stampfer MJ, Manson JE, Rosner B, Hankinson SE, Colditz GA, et al. Birth weight and risk of cardiovascular disease in a cohort of women followed up since 1976. Bmj. 1997 Aug 16; 315(7105):396-400.

15. Rich-Edwards JW, Colditz GA, Stampfer MJ, Willett WC, Gillman MW, Hennekens CH, et al. Birthweight and the risk for type 2 diabetes mellitus in adult women. Annals of internal medicine. 1999 Feb 16; 130(4 Pt 1):278-284.

16. Edwards CJ, Cooper C. Early environmental factors and rheumatoid arthritis. Clinical and experimental immunology. 2006 Jan; 143(1):1-5.

17. Edwards CJ, Goswami R, Goswami P, Syddall H, Dennison EM, Arden NK, et al. Growth and infectious exposure during infancy and the risk of rheumatoid factor in adult life. Ann Rheum Dis. 2006 Mar; 65(3):401-404.

18. Pavela G, Latham K. Childhood Conditions and Multimorbidity Among Older Adults. The journals of gerontology Series B, Psychological sciences and social sciences. 2016 Sep; 71(5):889-901.

19. Tucker-Seeley RD, Li Y, Sorensen G, Subramanian SV. Lifecourse socioeconomic circumstances and multimorbidity among older adults. BMC public health. 2011; 11:313.

20. Eaton L. Measles cases in England and Wales rise sharply in 2008. Bmj. 2009; 338:b533.

21. Amirthalingam G. Strategies to control pertussis in infants. Archives of disease in childhood. 2013 Jul; 98(7):552-555.

22. Diederichs C, Berger K, Bartels DB. The measurement of multiple chronic diseases--a systematic review on existing multimorbidity indices. The journals of gerontology Series A, Biological sciences and medical sciences. 2011 Mar; 66(3):301-311.