How did the study come about?

The initial thoughts leading to the development of the *Thousand Families Study* arose through observations made by Sir James Spence, one of the first full-time paediatricians in the United Kingdom and from 1942, the first holder of a University Chair of Child Health in England.

Prior to the Second World War, the city council in Newcastle upon Tyne, the city in Northern England in which Spence was based, became increasingly concerned about the high-infant mortality rate in the city (in 1939 the rate was 62 per 1000 live births). At that time the city council had a responsibility for the health of its citizens. They asked Spence to undertake a review of all deaths of children under the age of 5 years. He concluded that the excess infant mortality was due to death from acute infection. Further research was curtailed by the Second World War.

At the end of the war, the young doctors began to return to take up their former careers. One of those was Fred Miller and in 1946 Spence is reported to have said to him at a weekly departmental meeting ‘Well Freddie, isn’t it time we did something about these infections?’ So began the Newcastle Thousand Families Study. The study was initially planned for only 1 year and aimed to confirm the earlier finding that acute infection was the major cause of infant mortality in the city, and in particular identify which factors put infants at a higher risk of such infections. However, it continued throughout childhood and has evolved into a longitudinal cohort study now in its seventh decade.

The first 15 years of the study were funded jointly by Newcastle City Health Department, the City Health Committee and the Nuffield Foundation. Follow-ups in early adulthood were funded by a variety of sources including the Department for Health and Social Security, The Medical Research Council, the Social Science Research Council, the Joseph Rowntree Trust, the WT Grant Foundation (New York), the Newcastle Inner Cities Fund, the Joel Joffe Trust and the Home Office. Funding for the follow-up at age 50 years and subsequent analyses were primarily provided by the Wellcome Trust with additional contributions from the Newcastle Healthcare Charity, the Sir James Knott Trust and the Minnie Henderson Trust Fund.

What does it cover?

The original study focused on infections in infancy, attempting to identify risk factors within the context of the child’s familial and social environment. During childhood, the study continued not only to focus on infections, but also began to consider other health outcomes, educational performance and family life. The first 15 years of the study are covered in three books. As the children became adults, behavioural factors became of interest with a subsequent follow-up at age 32 focusing on mental health and criminality. This later became the fourth book on the study.

In the early 1990s, with the focus of chronic disease epidemiology shifting to consider the potential for early origins of disease, a further follow-up took place at 50 years and covered a wide range of health outcomes, including cardiovascular, metabolic, musculoskeletal, oral and mental health. Although the outcomes were assessed primarily in relation to size at birth, our approach to analysis, specifically using hierarchical conceptual frameworks, has enabled estimates of the relative importance of different stages of life, which few studies to date have attempted. A later follow-up of the women in the study assessed breast tissue density, lifetime oestrogen exposure and menopause. The study members continued to be flagged at the National Health Service.
Who is in the sample?

All but 4 of the 1146 children born in May and June 1947 to mothers resident in the city of Newcastle upon Tyne were originally recruited, ensuring coverage of the entire social spectrum of the city at that time. The current sample consists of any traceable survivor of the original cohort; at the most recent full follow-up, at age 50 years, 89% of the surviving cohort were traced. Of these, 574 returned lengthy questionnaires and 412 attended for clinical examination. Further details of responders and non-responders are given in the section on attrition.

How often have they been followed up?

Throughout the first years of the children’s lives, all families were visited both on a routine (up to every 6 weeks during infancy and at least quarterly until age 5 years) and ad hoc basis by the study team, which consisted of health visitors and paediatricians. Children were formally examined by a paediatrician at the end of the 1st, 3rd and 5th years. During the school years, visits were made at least once a year to record height, weight and any health problems up to the age of 15 years in 1962. Additional data were provided from GP and hospital consultations, details of which were provided to the study team. Further follow-ups, of subsets of the original cohort took place in 1969 and 1979.

As the early and middle adult years are generally of less interest to epidemiologists than other stages of life, due to the relatively low frequency of disease, the study went into abeyance and the data were stored in the Newcastle City Archive. A large-scale follow-up of the cohort took place at age 50 years in 1997, with sub-groups followed up for specific hypotheses in 2001 and 2005. A further follow-up is scheduled to start in 2008 with additional follow-ups planned for regular points in the future.

What has been measured?

Descriptions of the data collected to date are given in Table 1.

A detailed social study was made of each of the families recruited covering each study members first 15 years of life. A red spot was put on the child’s general practitioner medical record so that the doctor could notify the study team if the child became unwell. For this reason the children became known as the ‘Red Spot Babies’ and still today refer to themselves as ‘Red Spots’.

Data collection began with the antenatal chart for those mothers who attended clinics and continued through the reports of midwives at the birth. Special investigations, such as a housing survey, were completed specifically for the study, as was a summary of the circumstances of the family at the time of the start of the study. The core information from these was updated regularly by the health visitors at the routine visits. Each health visitor kept a detailed record of each of the families she covered, enabling details of the study members and other household members to be obtained prospectively. Further information from schools included both educational and growth data.

In 1969, a study of growth from birth to adulthood took place. A limited study of 272 of the cohort was undertaken with the cohort aged 32 years, focusing on the relationship between deprivation and psychological development and the transmission of socioeconomic disadvantage between generations.

In the 1997 follow-up, all traceable surviving cohort members were asked to complete a lengthy health and lifestyle questionnaire and invited to attend a clinical examination from which serum, urine and DNA samples remain stored for further use.

At the age of 54 years, 74 study members were recruited into a sub-study, which required measurement of endothelial function. In 2005, the women who had returned questionnaires at the age of 50 years were asked to return a further questionnaire asking for permission to access their mammography scans, to allow estimation of breast tissue density, and a more detailed assessment of their reproductive history.

What is attrition like?

Of the original 1142 babies in the cohort, 967 were followed through to the end of their first year; 44 babies died in the first year and 126 left the study area. Despite the high mobility of the British population throughout the country after the Second World War, few of the original cohort were lost when the cohort was restricted to those remaining within the city; 847 were followed until the end of their 5th year of life and 750 were followed throughout their school years.

Of the original 1142 cohort members, 832 (89% of the surviving cohort) were traced at age 50 years, 574 returned lengthy questionnaires and 412 attended for clinical examination. Those followed up at age 50 have been shown to be representatives of the original cohort for all early life factors considered so far, with the exception of gender. In addition, inclusion of study members no longer resident in the study region (18% of those attending a health check were resident outside of the Northern Region of England) increased the representativeness of the population attending. We anticipate that with increased regional
<table>
<thead>
<tr>
<th>Years</th>
<th>Cohort ages (years)</th>
<th>Participants</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1947</td>
<td>Birth</td>
<td>1142</td>
<td>Antenatal charts, midwives reports (including birthweight, gestational age and infant feeding). SES of the family, housing survey</td>
</tr>
<tr>
<td>1947–62</td>
<td>Birth to the age of 15</td>
<td>1142 falling to 750 by 1962</td>
<td>SES and welfare of the family, further housing surveys, changes in familial circumstances. Physical examination by paediatrician at end of 1st, 3rd and 5th years. Measures of height and weight (at ages 3, 5, 9, 13, 14 and 15 years). Infections and other illnesses, accidents, attendance at child welfare centres. Clinical notes. Further housing surveys (1948, 1949 and 1961). Behaviour and criminality. School performance, including school reports, examination results and the results of the Moray House 57 and 58 Tests, standardized tests of English and Arithmetic (giving IQ at age 11), Mill Hill vocabulary tests and the Raven standard progressive matrix tests. Spirometry data on 300 study members at age 14 years. Home and leisure activities at age 13 years, including hobbies.</td>
</tr>
<tr>
<td>1966</td>
<td>18</td>
<td>750</td>
<td>Entry to employment and further education. Height and weight.</td>
</tr>
<tr>
<td>1979–80</td>
<td>32</td>
<td>266(^a) (interview)</td>
<td>Educational history. Employment and residential history (at ages 15, 25, 35 and 50 years) and household net income at age 50. Family history (including marriage and children and health of other family members). Smoking and alcohol (at ages 15, 25, 35 and 50 years). Self-reported health, including Oral Health Impact Profile at age 50. Women’s health at age 50 (menopausal status and symptoms, HRT history). Diet (EPIC food frequency questionnaire) and exercise (MRC Physical Activity Questionnaire) at age 50. Work and social life characteristics at age 50. McMaster Family Assessment Device, the Parental Bonding Instrument and the General Health Questionnaire 28 item at age 50.</td>
</tr>
<tr>
<td>1997–99</td>
<td>49–51</td>
<td>574</td>
<td>Cardiovascular and metabolic measures (carotid artery intima media thickness, systolic and diastolic blood pressure, ECG, oral glucose tolerance test, measurements of lipids and clotting factors). Anthropometric measures (height, weight, skin folds, waist and hip circumferences and bioelectrical impedance). Bone mineral density, bone mineral content, skeletal size and femoral geometry. Respiratory function measured by spirometry. Dental examination (tooth retention and loose teeth). (H. pylori) seropositivity. Telomere length from stored DNA. Sex hormones and bone turnover (in males only) from stored serum.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>412 (physical assessment)</td>
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</table>
assessments and the decreasing working population within this cohort future follow-ups will be able to include greater numbers of participants.

What has it found? Key findings and publications

Findings from the first 33 years of the study have been summarized in four books. References to subsequent publications, particularly those since the age 50 follow-up began are on the study’s website at http://www.ncl.ac.uk/plerg/Research/1000F/1000publications.htm and only selected references are given here.

Health and development in childhood

The results at the end of the first year of the study suggested that poverty, family structure and maternal education all played an important role in influencing the health of the infants, particularly ‘mothering skills’. However, a later re-analysis of the data with modern multivariable statistical techniques demonstrated that living in an economically deprived household was the greatest risk factor, and that even those mothers scoring highly in terms of mothering skills could do little to mitigate the effects of poverty. Analyses in childhood continued to show strong socio-economic gradients in health, growth and school achievement. Childhood growth was also positively associated with earlier menarche.

Cardiovascular and metabolic health

Our results for carotid artery-intima media thickness, suggest that, in this cohort, adult lifestyle and adult biological risk markers are the main influence on cardiovascular health, as opposed to factors in early life, including birthweight, particularly in men. Birthweight and socio-economic circumstances at birth accounted for 2% of the variation in intima media thickness in both men and women, although when all early life factors were included the total variation explained by them and their mediating effects through factors and biological risk markers in later life this rose to 9% in men and 4% in women. Around 13% of the variation was explained by adult lifestyle and adult biological risk markers. In terms of central metabolic syndrome risk, we showed an association between childhood catch-up growth on risk at the age of 50 years in men, but that for both men and women the most important factors in predicting ‘central metabolic syndrome’ were related to diet and physical activity in adulthood. Similar results were shown for components of the central metabolic syndrome, with differential associations seen between birthweight and later health status for men and women. Parental diabetes was reported in the self-completion questionnaires at age 50 and used to test the hypothesis that genetic or inherited factors confound or mediate the association between low birthweight and risk of diabetes in adulthood. A subsequent paper reported no association between the birthweight of study members and whether their parents had ever been diagnosed with diabetes.

Obesity

Obesity and health has become a key research question in modern times. We were able to show that BMI at age 9 years was significantly associated with BMI at age 50 years, but not with percentage body fat. The Thousand Families Study data were also considered alongside a younger cohort, again from Newcastle upon Tyne, to assess whether the effects of deprivation on height and weight had changed over a 40-year period. No evidence of a change in the influence of deprivation on growth during childhood was found, despite increases in average height over the same time period.

Musculoskeletal health

An investigation of the lifecourse determinants of bone health suggested a limited impact of early life on bone mineral density and that any such impact is likely to be mediated through achieved adult height. We did, however, find an association between size at birth and bone area in adulthood. A weak association between a polymorphism of the vitamin D receptor gene and lumbar spine bone mineral density was also found.

Oral health

The major factor in tooth retention was shown to be adult socio-economic position and lifestyle.
(in particular cigarette smoking), with little influence of early life.\textsuperscript{24} In men, oral health-related quality of life was mostly explained by factors in early life, particularly early socio-economic disadvantage, while in women the number of teeth retained had a more prominent impact.\textsuperscript{25}

**Mental health and cognition**

Socio-economic gradients were also found with risk of major depression by age 33, with continuities of this association across generations.\textsuperscript{26} A later analysis of the school data showed a positive association between growth throughout childhood and IQ scores from the examinations of IQ at age 11 years.\textsuperscript{27} The childhood IQ data were also assessed in relation to early mortality, with an increasing risk of early mortality, primarily from cardiovascular disease, seen in men with decreasing childhood IQ scores, but not in women.\textsuperscript{28} Self-reported mental health at age 50 was shown to be associated with socio-economic mobility across the lifecourse. In particular, a downward social trajectory was associated with poorer self-reported mental health in men, but not in women.\textsuperscript{29} Again in men, lower current income and a downward social trajectory across the lifecourse were associated with a negative perception of family functioning.\textsuperscript{30}

**Respiratory health**

Adult lung function was showed to be influenced, both directly and indirectly, by a range of factors during an individual’s lifetime. As expected, sex, achieved adult height and smoking were the most influential predictors, but birthweight, breast-fed duration and childhood lower respiratory tract infections also contributed significantly.\textsuperscript{31}

**Helicobacter pylori**

Data on \textit{H. pylori} seropositivity in the cohort members were used, along with data from other sources to demonstrate that while children and adults in the Gambia appear to have the same IgG sub-class response to \textit{H. pylori} infection, the response in the Thousand Families Study was different to that seen in a contemporary UK paediatric population, as well as being different from the two Gambian populations.\textsuperscript{32} Increased duration of exclusive breastfeeding in infancy was suggested to have a long-term protective effect against chronic \textit{H. pylori} infection,\textsuperscript{33} while in contrast to cross-sectional studies relating \textit{H. pylori} infection to risk of periodontal disease, we were able to suggest that the proposed relationship between the two outcomes may be simply due to confounding by social class.\textsuperscript{34}

**Telomere length**

In our studies to date on telomere length, as a putative marker of biological ageing, we have shown no association with markers of socio-economic status, but did find longer telomeres in men than in women.\textsuperscript{35}

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**References**


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**What are the main strengths and weaknesses?**

The obvious weakness of this study is the sample size when compared with a number of other birth cohorts. However, this is offset by the rich data available at different stages of life on the study cohort and we have relatively low levels of attrition in a cohort that are keen to participate and maintain the study’s profile, particularly within the North of England. The study has prospectively collected data on birthweight, infant feeding, growth, illness, educational performance and familial and social circumstances during childhood. From the 1997 follow-up, detailed health and lifestyle measures for a large, and representative, portion of the cohort were measured, including a wide range of health outcomes with further samples, including DNA stored for future use. As to be expected with a cohort study of this age, there are also measures that we would have liked to have from early life, particularly body size measures over and above weight in very early life, that were either not measured or were and the data destroyed.

**Can I get hold of the data? Where can I find out more?**

We welcome suggested collaborations to use the existing data held by the Thousand Families Study team in Newcastle upon Tyne. Potential collaborators should contact the study director [see contact details of corresponding author (M.S.P.)]. The study has a website at http://www.ncl.ac.uk/plerg/Research/1000F/1000_home.htm.

**Acknowledgements**

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