Leaving a legacy of ill health

The trans-generational effects of smoking

The University of Bristol is a respected authority in research at the intersection of epigenetics and epidemiology. Founded by Jean Golding, Emeritus Professor of Paediatric and Perinatal Epidemiology, the Avon Longitudinal Study of Parents and Children (ALSPAC, also known as Children of the 90s) is one of the world's most comprehensive ongoing data sets spanning generations. Findings from this multi-generational study have influenced policy and practice in healthcare, education, and social services throughout the UK. Its most recent findings, however, are particularly sobering: those who embrace a lifestyle of smoking in childhood may impact the lives of succeeding generations through non-genetic mechanisms.

The dangers of smoking to those who light up are incontrovertible. We also know, through research, that second-hand smoke poses threats to the health of others near smokers and has encouraged restrictions on public smoking. Policing private spaces, such as homes and cars, is nigh impossible, meaning children of smokers can still be directly exposed to the same dangerous chemicals and toxins that smokers inhale. However, there is emerging evidence that children and even grandchildren may be affected by cigarette smoke they never inhaled but was instead inhaled by their parents or grandparents, decades before their birth.

Such inter-generational and trans-generational effects have previously been observed in studies of children whose parents or grandparents endured famine in childhood, effects that may differ according to the sex of the first-generation person exposed or to their age when exposed. Furthermore, sex of the child or grandchild may also play a role. For example, in some cases, effects may be more pronounced in grandsons than granddaughters. Research on this topic is relatively unexplored but has significant implications for human health in a modern world in which humans are faced with a rapidly growing array of novel chemical, biological, radiation, and social exposures.

Findings from ALSPAC have influenced policy and practice in healthcare, education, and social services throughout the UK.

Based in Bristol, the Avon Longitudinal Study of Parents and Children (ALSPAC) was set up in the early 1990s.

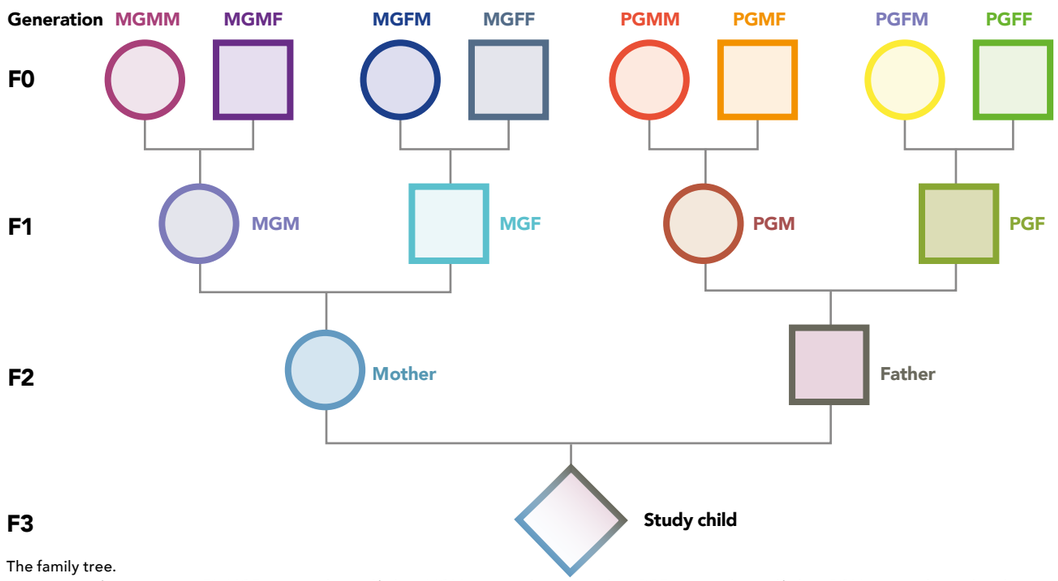
A team of researchers in the UK have ventured deeper into this frontier, drawing from one of the largest, most detailed longitudinal birth cohorts in the world. They are interested in whether environmental exposures in one generation can influence the development of succeeding generations without changing their DNA sequence – a phenomenon they refer to as non-genetic inheritance.

ALSPAC addresses important health questions including childhood obesity, air pollution, and mental health.

NON-GENETIC INHERITANCE

At the University of Bristol, researchers in epidemiology and epigenetics have combined forces to chart the roles that pre-conception and prenatal environmental exposures can play in the trans-generational transmission of ill-health. The team is led by Jean Golding, Emeritus Professor of Paediatric and Perinatal Epidemiology and Associate Professor Matthew Suderman, and has included Marcus Pembrey, Emeritus Professor of Paediatric Genetics, as well as specialists in epigenetics and data analysis, Dr Sarah Watkins, Yasmin Iles-Caven, and Steven Gregory. Notably this group of researchers is investigating associations between ancestral exposures and health outcomes in one of the world's most comprehensive ongoing data sets spanning multiple generations.

The team asked the question: Can regular smoking prior to puberty or in adolescence impact the health of later generations?



The family tree.
Abreviations for generation F1. MGF: maternal grandfather; MGM: maternal grandmother; PGF: paternal grandfather; PGM: paternal grandmother.
Abreviations for generation F0. MGMM: maternal grandmother's mother; MGMF: maternal grandmother's father; MGFM: maternal grandfather's mother; MGFF: maternal grandfather's father; PGMM: paternal grandmother's mother; PGMF: paternal grandmother's father; PGFM: paternal grandfather's mother; PGFF: paternal grandfather's father.

ALSPAC: A POWERFUL DATA SET

In the early 1990s, Golding set up the Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort study of children born in the former county of Avon, which included Bristol. The area was broadly representative of the UK at the time. It had a mix of urban and rural areas – providing a mixture of urban and rural populations – and a well-established healthcare system, making it easier to collect and manage data. The primary aim of ALSPAC was to understand how genetic and environmental factors influence health and development. By following families from pregnancy onwards, the ALSPAC team could gather valuable insights into a range of health-related issues, from mental health to physical development and chronic diseases from pre-birth into adulthood.

From the outset, ALSPAC was an ambitious project, recruiting 14,541 pregnant women with estimated delivery dates between April 1991 and December 1992. The scope of data collection was extensive, including biological samples, psychological tests, and lifestyle questionnaires. Findings derived from the data have influenced policy and practice in healthcare, education, and social services throughout the UK.

Can regular smoking prior to puberty or in adolescence impact the health of later generations?

A MULTI-GENERATIONAL STUDY

Notably, the Bristol research team have recently expanded on the initial study to collect information from both the children and ancestors of the original study participants, yielding information from up to five generations (four of which are included in these data analyses). This multi-generational study enables research into whether environmental exposures in one generation can influence the development of succeeding generations. In terms of data, ALSPAC is the gift that keeps on giving – thanks to the generosity of the original parents recruited to the study and their children, it is possible to ask questions about our lifestyles, genes, and the environment in which we live, and how these factors affect subsequent generations. Drawing from this data set, Golding and colleagues set out to ask the following question:

A multi-generational study. The primary aim of ALSPAC was to understand how genetic and environmental factors influence health and development.
Photo courtesy of Children of the 90s.

Can regular smoking prior to puberty or in adolescence impact the health of later generations? They have uncovered evidence suggesting a clear response, specifically that regular smoking pre-puberty and in adolescence is associated with higher fat mass in both grandchildren and great-grandchildren.

THE INFLUENCE OF THE GRANDFATHER

Like other developed Western countries, the UK is fighting an obesity epidemic, and children are not spared. The Bristol researchers wanted to know if there was any connection between fat mass in children and whether their male ancestors (fathers and paternal and maternal grandfathers and great-grandfathers) smoked, and if they did smoke, when they started. Of particular interest was whether they began to smoke at a young age – before puberty – or during adolescence. ALSPAC has data from questionnaires on the smoking habits of participating parents, and grandparents and great-grandparents. Fat mass and lean mass measurements were collected during offspring face-to-face clinics at the ages of 17 (at the end of puberty) and 24 years (early adulthood).

The researchers have recently published their findings.

Focusing on pre-pubertal regular smoking in male ancestors, the researchers found that it is associated with extra fat mass during childhood, adolescence, and early adulthood in their grandchildren and great-grandchildren. The father who starts smoking pre-puberty will probably impact his sons; the paternal grandfather, his granddaughters; and the maternal grandfather's father (MGFF), his great-granddaughters. The largest effect was an additional 6kg of body fat in 24-year-old females whose great-grandfathers on their mother's side started smoking before puberty.

Regular smoking pre-puberty and in adolescence is associated with higher fat mass in both grandchildren and great-grandchildren.

TIMING MAKES A DIFFERENCE

A second study showed slightly different effects when grandfathers started regular smoking a little later, during adolescence. This time the data suggested no major differences between sexes, ie, between paternal and maternal grandfathers or between the sexes of the grandchildren. For all familial combinations, fat mass was increased by at least 1.3kg in 24-year-old grandchildren whose grandfathers started smoking in adolescence rather than later in life.

TRANS-GENERATIONAL IMPACTS

Non-genetic inheritance has become a growing area of research, a frontier of research where the University of Bristol is a respected authority. Having said that, and even with the wealth of rich data within ALSPAC, Golding's team are circumspect about the findings of these studies. Proving causality of outcomes across generations must negotiate a wealth of variables; consider the many social and cultural factors, such as parenting practices, family dynamics, and socioeconomic status, that could impact outcomes. However, if the studies' outcomes are confirmed in other datasets and relevant laboratory models, according to Golding, they will be one of the first human demonstrations of trans-generational effects of environmental exposure across four generations and will significantly add to our understanding of how environmental effects can be passed on to later generations.

Behind the Research

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Research Objectives

ALSPAC is a one-of-its-kind multi-generational study. The breadth and depth of its data has already informed more than 3,000 research papers that address important health questions including childhood obesity, air pollution, and mental health. Since 2010, research has explored whether environmental exposures in one generation can influence the development of succeeding generations.

Detail

Funding
- Medical Research Council
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- Wellcome Trust

Collaborators
Matthew Suderman, Marcus Pembrey, Yasmin Iles-Caven, Sarah H Watkins, Steven Gregory

References

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Personal Response

With respect to your recent work examining whether smokers in one generation can influence succeeding generations, are there any findings that came as a surprise to you?

Our transgenerational research has produced several surprises. One of our first discoveries was that grandchildren, particularly boys whose grandmothers smoked during pregnancy, had over 1kg of additional lean mass compared to children with non-smoking grandmothers. Given that exposure to cigarette smoke is generally associated with poor health, we were surprised to find that it could have such a positive effect, since lean mass is mainly an indicator of muscle mass. We were then equally surprised at the findings described in this article, that grandfathers who started smoking pre-puberty had grandchildren with higher fat mass but no evidence of different lean mass.

Are you able to tell us more about your future plans for this project?

Since the ancestors we are studying were children at a time when smoking rates were as high as 90% of men and 50% of women, we have been concentrating on phenotypes that have increased in prevalence over time, thus reflecting the changes in smoking rates over time. We have recently explored, for example, the associations with asthma and autism, each of which has increased over time, and of religious belief which has decreased. All three outcomes showed relationships with ancestral smoking. Future projects will explore whether there are also ancestral smoking links to mental health, since the prevalence of depression in particular has increased dramatically over time. Our future plans are to continue to explore the relationships between ancestral smoking preconception and during pregnancy on later generations in regard to features of their development, health and behaviour. The modern world is full of novel exposures about which we know little, so we will continue to look at ancestral smoking as an example of the extent to which an exposure in one generation may have positive or negative consequences for later generations.

The Avon Longitudinal Study of Parents and Children (ALSPAC) has provided such a rich and valuable source of data. When you founded the study, did you imagine it would be so successful?

No – this has exceeded my wildest dreams. The success has, of course, been due to the many families that have taken part. Their enthusiasm and cooperation have been vital. All of us who work on the study cannot thank them enough.

Although the focus in the early years of the study was on the children, and particularly on the environmental influences that impact their development, I am becoming increasingly interested in the ways in which the early circumstances of childhood can influence the development of problems in middle and old age. Because of the wealth of data collected on several generations, ALSPAC is in a prime situation to be able to determine influences on outcomes over time. The study has always concentrated on relatively common health challenges, whether of menopausal symptoms, anxiety, or dementia. The continuing aim is to identify the causes and determine ways of preventing distress and disorders.

Over 3,000 research papers have drawn from the ALSPAC's data and samples. Can you tell us a bit more about some of the collaborations that have come about through this data set?

All over the world there are scientists who have taken part in many of the projects that have used information that was collected by ALSPAC. Collaboration is ongoing, and more and more information is being collected. There have been a number of studies which have resulted in long-lasting collaborations and friendships. They have arisen when distinguished scientists had a theory to test – such as that of Professor Gideon Lack, who wanted to determine whether common baby lotions and creams may be responsible for initiating peanut allergy. We were able to show that he was correct – the products that contained peanut oil have now been taken off the market. Professor Joseph Hibbeln wished to assess whether fish consumption in pregnancy benefitted the developing brain of the foetus – we were able to show that this was clear, with results that have been quoted worldwide, and which are responsible for changing the advice given to pregnant mothers.

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