

Study of a

LIFETIME

In 1946, scientists started tracking thousands of British children born during one cold March week. On their 65th birthday, the study members find themselves more scientifically valuable than ever before.

BY HELEN PEARSON

On Tuesday 5 March 1946, Patricia Malvern was born in a small flat in Cheltenham, UK, near the boilers that her dad stoked to warm the building above. She weighed in at 9 pounds, 2 ounces (4 kilograms).

The next day, David Ward was “one of the few Catholics born in a Jewish hospital” opposite Hampton Court, near London. Ward doesn’t know exactly what he weighed, although his dad said later that he looked “like a skinned rabbit”.

Throughout the rest of that week, just months after the end of the Second World War, 16,695 babies were born in England, Scotland and Wales. Health visitors carefully recorded the weights of the vast majority on a four-page questionnaire, along with countless other details including the father’s occupation, the number of rooms and occupants (including domestics) in the baby’s home and whether the baby was legitimate or illegitimate. Over subsequent years, the information files on more than 5,000 of these children thickened, then bulged. Throughout their school years and young adulthood and on into middle age, researchers weighed, measured, prodded, scanned and quizzed the group’s bodies and minds in almost every way imaginable.

This week, the group has much to celebrate. They are turning 65, the age at which many in the United Kingdom retire and, as such, a milestone in British life. They will also celebrate being part of the longest-running birth-cohort study in the world. These ordinary men and women are now some of the best-studied people on the planet. And this makes them some of the most scientifically valuable, because it has allowed researchers to track their health and wealth throughout their lives, and to search for factors that could explain their trajectories.

The exercise has revealed some surprises. It has shown that the heaviest babies were most at risk of breast cancer decades later; that children born into lower social classes were more likely to gain weight as adults;

that women with higher IQ reached menopause later in life; and that young children who spent more than a week in hospital were more likely to suffer behaviour and education problems later on.

A generation under study

All told, the results from the 1946 birth cohort — now known as the National Survey of Health and Development and run by the Medical Research Council (MRC) — have filled 8 books and some 600 papers so far. Perhaps more than anything else, the survey has shown that early life matters — a lot. “Ultimately, where you get to in early adulthood is strongly influenced by where you come from,” says Michael Wadsworth, who led the study for nearly 30 years, until 2007.

Children who were born into better socioeconomic circumstances were most likely to do well in school and university, escape heart disease, stay slim, fit and mentally sharp and, so far at least, to survive. (Ward, whose father worked his way up in a Walthamstow-based dry-cleaning business, went on to university and built a career in journalism. Malvern, whose father left home when she was five and who wore third-hand clothes, left school at 16 and “bitterly regrets” the fact that her mother couldn’t afford to pay tuition for her to train as a teacher.)

Those lessons are arguably more urgent today than they were in 1946 when, caught up in post-war optimism, Britain was introducing major educational reforms and a National Health Service (NHS) to ensure that good schooling and health were available to all. The contrast with the

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Diana Kuh leads the UK National Survey of Health and Development, which has compiled thick files on more than 5,000 people since their birth in 1946.

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country's mood this winter couldn't be starker. Students have been rioting to protest against the government's plan to introduce £9,000 (US\$14,600) annual fees for universities; plans are afoot to drastically reform the NHS (eviscerate it, critics say); and sweeping budget cuts are threatening public services — including early childhood support centres, for which the cohort's data once helped provide impetus. “I find these changes very worrying,” says Diana Kuh, who now directs the survey and says she is saving up for her grandchildren to attend university.

“It's unique and groundbreaking in the history of epidemiology. It's the only study to have chased an entire cohort across its life course — and it's not yet finished,” says Ezra Susser, an epidemiologist who works with cohort studies at Columbia University in New York. He says that cohort research has been vital in seeding the idea that disease evolves as a result of events throughout life. “You gain enormous depth of understanding in how that disease came to be by following someone over their life course.”

Now, as the cohort members enter old age, the study offers a precious opportunity to understand how a lifetime of experiences might hasten or slow their decline — an urgent question for countries such as the United Kingdom and United States, whose populations are rapidly ageing and sickening. In the latest round of data collection, running from 2006 to 2010 and costing £2.7 million, study members underwent almost every modern biomedical test, including echocardiograms, measures of blood-vessel function, whole-body bone, muscle and fat scans, and tests of blood, memory and how quickly they could get up from a chair.

The data will provide a detailed starting point from which to measure the cohort members' inevitable decline, and the opportunity to analyse the information is already swelling an extensive network of collaborators. Some are testing how genes interact with a lifetime of experiences to lead to obesity or disease; others plan to scan participants' genomes for 'epigenetic' marks — molecular traces left, perhaps, by early birth

weight or by life's inequalities — that alter gene expression and might provide a molecular explanation for effects in later life. Greg Duncan, an economist at the University of California, Irvine, who studies the impact of child poverty, hopes that follow-up studies could help to answer a question arising from the earlier findings on socioeconomic status and health: “What are the active ingredients in social class?”

It is this ability to draw associations between biological data, from blood pressure right down to genes, and life as it is actually lived that makes the cohort study so unusual, say its leaders. “These are real people,” says Kuh. “This is what it is to be human and normal.”

Next Steps in Making Motherhood Easier

The first few decades of the twentieth century found Britain acutely concerned about its falling birth rate and stagnant infant mortality. (The thought at the time, as Kuh puts it, was “how are we going to maintain Britain and its empire?”) A Population Investigation Committee recommended a maternity survey to explore whether the social and economic costs of childbearing were discouraging prospective parents. James Douglas was appointed to head it.

Douglas, a physician, had spent part of the war conducting vast studies of air-raid casualties. He set about launching an investigation that today would be ethically difficult, logistically nightmarish and financially prohibitive: sending health visitors to interview the mothers of every child born in that March week. He reached 13,687 of them. “It was crazily ambitious,” says Wadsworth, who inherited the study leadership from Douglas more than three decades later. Yet “he pulled it off”.

In 1948, when Douglas's book about the study's results appeared, the baby boom was in full swing and concerns about birth rate had mostly dissipated. But the volume, *Maternity in Great Britain*, made a stir by revealing shocking disparities between rich and poor in infant survival and women's care. One widely reported result showing that only 20% of women who gave birth at home were offered pain relief, and that the poor suffered most, spurred a parliamentary bill allowing more midwives to deliver gas and air.

Douglas decided to turn the study into a tool for documenting social inequality and gauging the impact of newly minted welfare reforms such as the NHS. In particular, he realized that he had the perfect weapon for testing the success of the 1944 Education Act, which had introduced a nationwide system of exams for 11-year-olds — the 11+ — intended to channel the brightest, regardless of background, into elite 'grammar' schools. He selected a sample of the original 13,687 children spanning geography and social class, ending up with 5,362, whose health, growth and other data were regularly recorded and then transferred onto punch cards. Douglas also tested the children's cognition as they reached 8, 11 and 15, and tracked their course through school.

BRITAIN'S SQUANDERED

TREASURY OF TALENT

To the architects of the welfare state, the results were discouraging. Bright children from the middle classes were more likely to pass the 11+ and do well at school than were equally bright working-class children, although supportive parents and good teachers could better a child's odds. The attrition of smart but poor boys (girls counted for less) became known as the 'waste of talent', turning Douglas's next two books — *The Home and the School* (1964) and *All Our Future* (1968) — into must-read educational references and contributing to the introduction of non-selective 'comprehensive' schools in the 1960s.

While Douglas was studying the group's diverging paths, the children were walking them. Malvern, who was cripplingly embarrassed by taking free school meals, failed her 11+. She blames a class teacher so violent that Malvern would sleep without covers in order to catch a cold and avoid school, and who "walloped me across the head" on the day of the exam. After she left school, Malvern went to learn typing at Government Communications Headquarters in Cheltenham. Ward's father, meanwhile, was planning to buy a house, and his mother tested him on Latin vocabulary over the ironing. He was one of 4 children out of 66 in his school's top two classes who passed the 11+ exam, and he and his sister were the first in their family to attend university.

As the 1970s rolled on and the participants entered their thirties, Douglas was losing steam. Most of his questions about the cohort members' education, occupations and social mobility had been answered, and Douglas was heading towards retirement. Medical epidemiologists thought that the cohort should be mothballed until its members got

interesting again, when they started to sicken and die. The MRC, which had been funding the project since 1962, dithered about what to do with it; even Douglas thought the project was finished.

LIFE'S PATTERN DECIDED-

AT THE AGE OF SEVEN

For Wadsworth, a social epidemiologist who had joined Douglas's team in 1968, it was just getting going. "I thought the changing pattern of health of these people would be interesting over life," he says.

After he took the helm in 1979, Wadsworth convinced the MRC to fund a new round of data collection as the cohort reached 36, then again at 43 and 53. He started assessing the group's physical capabilities and health, including blood pressure, heart and lung function, diet and exercise. He wanted to see how these indicators had been influenced by earlier life — and then chart them into the future.

Correlations tumbled out of the data. In 1985, Wadsworth and his team reported that cohort members whose birth weight had been low had higher blood pressure as adults¹. It was an early hint that fetal and infant growth shape adult health, a link that became known as the Barker hypothesis after David Barker, an epidemiologist at the University of Southampton, UK, who published a 1989 analysis of birth weight and health in a different cohort². He found that babies with the lowest birth weights had the highest risk of heart disease as adults.

Study after study from the 1946 cohort supported the link, showing a tangle of connections between infant and child growth or development and adult traits from cognitive ability to frailty, diabetes, obesity, cancer and schizophrenia risk. "It isn't the same story every time, but we find an endless stream of long-term associations in quite 'noisy' data," says Kuh. "Big babies were more likely to get breast cancer. Small babies were more likely to have poor grip strength. Those who grew fast postnatally have more cardiovascular risk." (Says Ward: "I find that quite extraordinary, almost in a poetic way, that there is something that spans all those years, that something was set down, determined at that stage.")

A major question for scientists today is how to explain these connections: which biological systems in infants are so important, and how

are lasting scars laid down on them? One possible answer lies in epigenetics: the chemical footprints, such as methyl groups, stamped on DNA by early life events that alter gene-expression patterns and might contribute to later disease. Martin Widschwendter, an oncologist at University College London (UCL), for example, is planning to analyse tens of thousands of possible methylation sites in the cohort's DNA, looking for changes that could explain the link between birth weight and breast-cancer risk. The detailed life-course information that can be combined with the DNA "is really only available via these cohorts", says Widschwendter.



David Ward as a baby in 1947 with his mother and sister; and in 1976 with his son and daughter.

COURTESY OF D. WARD

The doctor's son does better than a dustman's

Yet Kuh and others emphasize that fates are not fixed by early life. "I don't ever want the findings to be interpreted as purely deterministic," says Kuh; she prefers the more optimistic idea that disease risks result from an accumulation of experiences throughout life, and that education, diet or other factors can shift poor trajectories to better ones. Marcus Richards, an epidemiologist who is leading the cognition studies on the group, points to evidence from the 1946 cohort — and supported by many other studies — that regular physical exercise in a person's thirties and forties can slow their cognitive decline with age. "We can take that research and say, here is very clear-cut evidence of something you can do to protect your cognitive health as you get older, and this is how you should do it," says Richards.

The 1980s brought a vivid lesson in the power of environment. Hardly any of the Douglas babies, nourished on post-war rations, were fat as children — a sharp contrast to those of today — and they had maintained a healthy weight throughout young adulthood. But now incomes were climbing, eating out was more affordable, and cars were the way to get around. As the cohort approached their thirties, the line plotting the proportion who were obese edged upwards; in their late thirties it soared³. And although those in lower socioeconomic brackets did get fatter faster, no social class was immune.

Somewhere on one of those curves is Malvern, who found her own weight creeping up when she moved to Luxembourg in 1992 and stopped work as a school bursar. She weighed 11 ½ stone (73 kilograms) when she moved. "When I came back in 2000 I was horrified: I was 15 stone. It was the pâté and the baguettes and the cheese and having visitors," she thinks — on top of the menopause. Malvern has since lost weight, and Ward has kept himself trim, he says, by living in the Peak District, where "you can't get anywhere without going up and down a hill".

Cleverness 'delays the menopause'

As women in the study reached their fifties, a more mysterious pattern emerged: those who had performed well on childhood intelligence tests tended to reach menopause several years later than those who had performed poorly⁴. "We tested almost to destruction every social and behavioural pathway; we threw almost everything we had at that to see if we could make that association go away and it didn't," says Richards. But once the researchers considered the association, it began to make sense. Their theory now is that childhood cognition provides a readout of brain development, including that of some areas that respond to hormones or are responsible for hormone production. In short, high IQ scores could indicate a brain that was well-developed all round, and so was able to sustain reproduction

for longer. Kuh says that she has been testing whether genes are responsible, "so far without success".

In 2005, as the cohort neared 60 and Wadsworth neared the end of his scientific career, the project's future was again in jeopardy. The MRC was pondering whether to keep paying for it and, if it did, who should lead it. "We didn't know if the study would be closed down — and Mike was retiring. It was a very unstable period," says Kuh.

Kuh — who had trained in economics — wanted to build up the biomedical data that Wadsworth had been collecting. Until that time, all the examinations had been performed at the study members' homes, but by this stage the nurses were staggering under all the equipment. To really understand the participants' physiology and biology, Kuh argued, the study needed to get them to a clinic. "People appreciate a free bone scan," she says. By 2008 she had convinced the MRC to pay for every willing cohort member to visit one of a number of clinics around the country and had established a dedicated research unit, now housed in a Georgian terrace in central London.

Ward went to a clinic in Manchester for his exam. He learned that he has signs of osteoporosis in his spine, and that he can no longer stand on one leg for long with his eyes closed. "You wobble rather more and I ended up hopping about the place." He recalls the food diary he had to prepare as a "serious challenge". "You don't want to admit that you had that extra glass of plonk or another slice of cake, but you say, hang on, this is science, I've got to tell the truth".

Kuh and her colleagues — the study now has about 25 full-time researchers and support staff and 100 collaborators — are still compiling such truths about their thousands of participants. "Now the cohort is one of the most phenotyped in the world," says Kuh. Once her paper summarizing the latest data goes public⁵, Kuh is expecting the queue of epidemiologists, geneticists and other scientists who want to collaborate to lengthen, and last November she hired someone for three years especially to cope with the increased data sharing. As the cohort ages and falls ill, the study will continue monitoring participants' health and trying to tease out the influence of early experience. "One big question we can ask is, are these life effects we see in mid life going to wane?" says Kuh. Or will they, as some epidemiologists expect, get more dramatic with age?

Kuh is also thinking about how best to exploit genomic and other biomedical analyses. At least one study has hinted at the power of the cohort's life-course data combined with genetics. Last year, Rebecca Hardy, a statistician with the survey, published a study of two hot genes called *FTO* and *MC4R*, variants of which have been identified as risk factors for obesity⁶. When she analysed DNA collected from the cohort in 1999, she found that the association of those variants with body mass index increased in early adult life, then weakened as the cohort grew older. Perhaps, Hardy speculates, any effects of the genes on appetite or fat storage were overwhelmed by that onslaught of fat-promoting influences in the 1980s, a possibility that might become clearer when she tests a further panel of obesity-linked genes.

Ever protective of her study members and the limited DNA samples



Patricia Malvern aged 16; and aged 51, holding one of her grandchildren.



The research team never forgets to send birthday cards to the cohort.

CARDS & CALLS

How to keep a cohort together — for 65 years

After tracking its subjects' health and well-being for longer than any other study, the 1946 British birth-cohort study has lessons to offer its younger siblings. British birth cohorts were started in 1958, 1970 and 2000, and another is provisionally planned. In the United States, children are being enrolled in the National Children's Study, which aims to follow some 100,000 children from before birth to age 21. Yet other cohort studies have been felled by bureaucratic infighting, spiralling costs or a lack of sustained funding. Diana Kuh, director of the 1946 survey, attributes its survival to having fairly autonomous, dedicated leaders and a relatively low budget. "We've always had to offer good value for money."

The 1946 study also shows that building a strong relationship with the participants is vital. Every year, the members receive a birthday card, signed by the research team and telling them about the latest results. One participant, Patricia Malvern, says that the card means a lot to her. "Somehow, over the years I began to feel I knew the team members, although I had never met any." One year the

card showed a sunset, and some recipients complained about the suggestion that they were entering the evening of life. Kuh and her colleagues responded to those complaints, like every other enquiry from the participants, with personal letters or calls. Kuh says that this relationship has been crucial to keeping an average of 80% of the original cohort in the study. When leaders of other studies hear that figure, she says, "people are amazed".

But some factors in its success can't be duplicated today. In 1946, recruitment and consent issues were a lot simpler: "If someone was willing to see you, that was consent," says Kuh, "and the response rates were over 90% probably because people didn't think they could choose not to participate." Those simpler days also brought constraints. In the early years of the study, questions about money and sex were "off the table", illegitimate children were turfed out of the study, and mothers were not asked whether they smoked in pregnancy because "the minister for health was telling the soldiers to smoke," says Kuh. "But that's part of being the history of science, really." **H.P.**

she has, Kuh says that she views the latest molecular biology techniques with caution. "I feel a huge responsibility to deliver," she says. Quite often, she says, outside researchers have an attitude of "give us all the cohort data and we'll rush this through and find millions of associations. I say, well, that sounds very interesting; can you come back with a hypothesis?" Even so, when Kuh compiles a plan for the MRC's five-yearly review of the survey in 2012, she knows that working out how to incorporate these technologies "is going to be key". The falling cost of DNA sequencing means that ploughing through participants' entire genomes is an almost inevitable step, she acknowledges. "The questions are, when is the best time — and what would we learn from it?"

A survey taking on

a life of its own

For now, Kuh has more immediate planning concerns: five 65th-birthday parties, at which the study members will meet each other for the first time. The parties are causing her some anxiety. Wadsworth had considered and rejected the idea of a 50th- or 60th-birthday bash, in case the get-together ended up influencing the participants' life course in some way. "Basically, we thought people might leave their partners and get off with someone in the study," he says. But Kuh decided that recognizing and rewarding the members was worth the risk. (She even wrote to Buckingham Palace to request a garden-party invitation for the study members. "I wrote such a nice letter. I learned all about how to address the Queen, and I'm still hoping to get a reply.")

Ward and Malvern are pleased to have been part of the study. "It gives me a fair old bit of pride in a way," says Ward. "Just things like bed-wetting. What did I contribute to the nation's store of knowledge on bed-wetting?" Neither is perturbed by the idea of the researchers watching them until they crumble and die. "I suppose," says Ward, "it helps you accept that you're mortal, you're not going to last forever."

Some 13% of subjects have died so far — and the study already has something to say about the fate of the rest. Kuh flips open some graphs of survival rates that she has calculated. They show the proportion of the survey members surviving up to age 60, separated by father's social class. And they reveal yet another curious correlation for Kuh and her colleagues to dig into. Kuh points out a blue line representing a group of women from better-off backgrounds, whose death rate is about half that of everyone else⁷. Kuh has not been able to attribute the effect to less smoking or other obvious factors, and she suspects that these women took advantage of the educational and health opportunities afforded by post-war Britain to improve themselves. "They really changed their lives with education. The girls, if they got through, they did really well."

Yet the study is lending a touch of immortality to all its participants, whether men and women, born into comfort or poverty. Traces of them will live on in preserved DNA, cell lines frozen in liquid nitrogen — and in their records, now all transferred from punch cards to computers. "You're very aware that your memory is going," says Ward. "But you also know that in the archive is a version of you."

"I often call it an alternative biography in there," he adds, "and that I'd quite like to get my hands on." ■ [SEE EDITORIAL P.5](#)

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