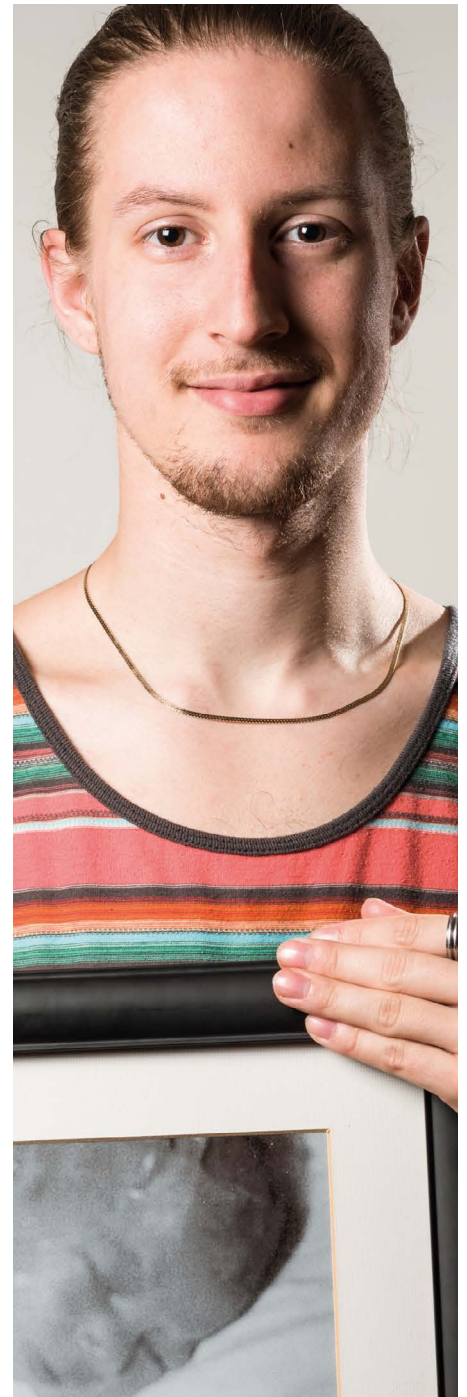


# SURVIVAL OF THE LITTLEST

Babies born before 28 weeks of gestation are surviving into adulthood at higher rates than ever. What are the consequences, in later life, of being born so early? **By Amber Dance**



**T**hey told Marcelle Girard her baby was dead.

Back in 1992, Girard, a dentist in Gatineau, Canada, was 26 weeks pregnant and on her honeymoon in the Dominican Republic.

When she started bleeding, physicians at the local clinic assumed the baby had died. But Girard and her husband felt a kick. Only then did the doctors check for a fetal heartbeat and realize the baby was alive.

The couple was medically evacuated by air to Montreal, Canada, then taken to the Sainte-Justine University Hospital Center. Five hours later, Camille Girard-Bock was born,

weighing just 920 grams (2 pounds).

Babies born so early are fragile and underdeveloped. Their lungs are particularly delicate: the organs lack the slippery substance, called surfactant, that prevents the airways from collapsing upon exhalation. Fortunately for Girard and her family, Sainte-Justine had recently started giving surfactant, a new treatment at the time, to premature babies.

After three months of intensive care, Girard took her baby home.

Today, Camille Girard-Bock is 27 years old and studying for a PhD in biomedical sciences at the University of Montreal. Working with

researchers at Sainte-Justine, she's addressing the long-term consequences of being born extremely premature – defined, variously, as less than 25–28 weeks in gestational age.

Families often assume they will have grasped the major issues arising from a premature birth once the child reaches school age, by which time any neurodevelopmental problems will have appeared, Girard-Bock says. But that's not necessarily the case. Her PhD advisers have found that young adults of this population exhibit risk factors for cardiovascular disease – and it may be that more chronic health conditions will show up with time.

Girard-Bock doesn't let these risks preoccupy



Scientists are watching out for the health of premature babies as they reach adulthood and beyond.

her. "As a survivor of preterm birth, you beat so many odds," she says. "I guess I have some kind of sense that I'm going to beat those odds also."

She and other against-the-odds babies are part of a population which is larger now than at any time in history: young adults who are survivors of extreme prematurity. For the first time, researchers can start to understand the long-term consequences of being born so early. Results are pouring out of cohort studies that have been tracking kids since birth, providing data on possible long-term outcomes; other studies are trialling ways to minimize the consequences for health.

These data can help parents make difficult

decisions about whether to keep fighting for a baby's survival. Although many extremely premature infants grow up to lead healthy lives, disability is still a major concern, particularly cognitive deficits and cerebral palsy.

Researchers are working on novel interventions to boost survival and reduce disability in extremely premature newborns. Several compounds aimed at improving lung, brain and eye function are in clinical trials, and researchers are exploring parent-support programmes, too.

Researchers are also investigating ways to help adults who were born extremely prematurely to cope with some of the long-term

health impacts they might face: trialling exercise regimes to minimize the newly identified risk of cardiovascular disease, for example.

"We are really at the stage of seeing this cohort becoming older," says neonatologist Jeanie Cheong at the Royal Women's Hospital in Melbourne, Australia. Cheong is the director of the Victorian Infant Collaborative Study (VICS), which has been following survivors for four decades. "This is an exciting time for us to really make a difference to their health."

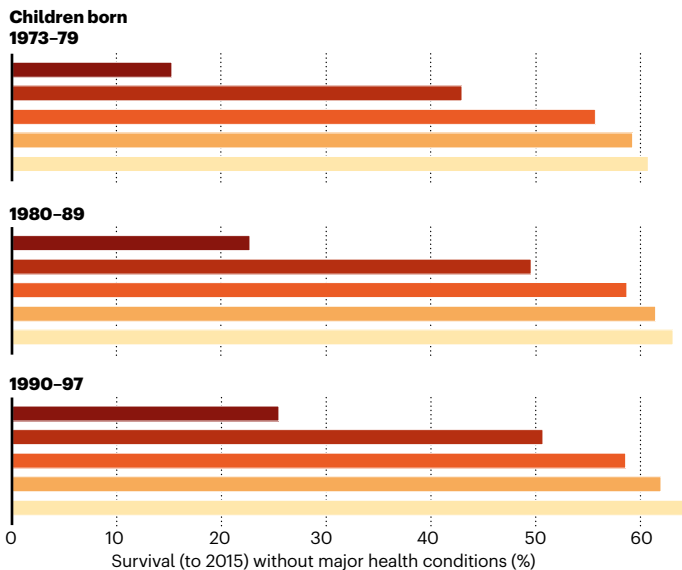
The late twentieth century brought huge changes to neonatal medicine. Lex Doyle, a paediatrician and previous director of VICS, recalls that when he started caring for preterm

## THE EFFECTS OF BEING EARLY

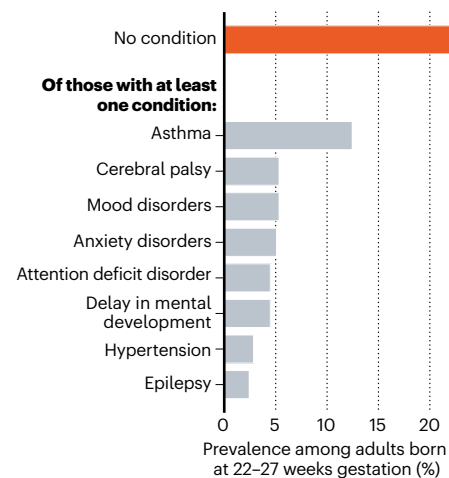
Data from a large Swedish cohort show the proportion of babies that live beyond age 18 without major health problems. Survival rates increased from the 1970s to the 1990s, especially for babies born extremely prematurely.

Gestational age at birth (weeks)

- 22–27
- 28–33
- 34–36
- 37–38
- 39–41



More than three-quarters of the babies born extremely preterm — at or before 27 weeks — had at least one chronic health condition when they reached adolescence or adulthood.



infants in 1975, very few survived if they were born at under 1,000 grams — a birthweight that corresponds to about 28 weeks’ gestation. The introduction of ventilators, in the 1970s in Australia, helped, but also caused lung injuries, says Doyle, now associate director of research at the Royal Women’s Hospital. In the following decades, doctors began to give corticosteroids to mothers due to deliver early, to help mature the baby’s lungs just before birth. But the biggest difference to survival came in the early 1990s, with surfactant treatment.

“I remember when it arrived,” says Anne Monique Nuyt, a neonatologist at Sainte-Justine and one of Girard-Bock’s advisers. “It was a miracle.” Risk of death for premature infants dropped to 60–73% of what it was before<sup>1,2</sup>.

Today, many hospitals regularly treat, and often save, babies born as early as 22–24 weeks. Survival rates vary depending on location and the kinds of interventions a hospital is able to provide. In the United Kingdom, for example, among babies who are alive at birth and receiving care, 35% born at 22 weeks survive, 38% at 23 weeks, and 60% at 24 weeks<sup>3</sup>.

For babies who survive, the earlier they are born, the higher the risk of complications or ongoing disability (see ‘The effects of being early’). There is a long list of potential problems — including asthma, anxiety, autism spectrum disorder, cerebral palsy, epilepsy and cognitive impairment — and about one-third of children born extremely prematurely have one condition on the list, says Mike O’Shea, a neonatologist at the University of North Carolina School of Medicine in Chapel Hill, who co-runs a study tracking children born between 2002 and 2004. In this cohort, another one-third have multiple disabilities, he says, and the rest have none.

“Preterm birth should be thought of as a chronic condition that requires long-term follow-up,” says Casey Crump, a family physician and epidemiologist at the Icahn School

of Medicine at Mount Sinai in New York, who notes that when these babies become older children or adults, they don’t usually get special medical attention. “Doctors are not used to seeing them, but they increasingly will.”

### Outlooks for earlyies

What should doctors expect? For a report in the *Journal of the American Medical Association* last year<sup>4</sup>, Crump and his colleagues scraped data from the Swedish birth registry. They looked at more than 2.5 million people born from 1973 to 1997, and checked their records for health issues up until the end of 2015.

Of the 5,391 people born extremely preterm, 78% had at least one condition that manifested in adolescence or early adulthood, such as a psychiatric disorder, compared with 37% of those born full-term. When the researchers looked at predictors of early mortality, such as heart disease, 68% of people born extremely prematurely had at least one such predictor, compared with 18% for full-term births — although these data include people born before surfactant and corticosteroid use were widespread, so it’s unclear if these data reflect outcomes for babies born today. Researchers have found similar trends in a UK cohort study of extremely premature births. In results published earlier this year<sup>5</sup>, the EPICure study team, led by neonatologist Neil Marlow at University College London, found that 60% of 19-year-olds who were extremely premature were impaired in at least one neuropsychological area, often cognition.

Such disabilities can impact education as well as quality of life. Craig Garfield, a paediatrician at the Northwestern University Feinberg School of Medicine and the Lurie Children’s Hospital of Chicago, Illinois, addressed a basic question about the first formal year of schooling in the United States: “Is your kid ready for kindergarten, or not?”

To answer it, Garfield and his colleagues

analysed standardized test scores and teacher assessments on children born in Florida between 1992 and 2002. Of those born at 23 or 24 weeks, 65% were considered ready to start kindergarten at the standard age, 5–6 years old, with the age adjusted to take into account their earlier birth. In comparison, 85.3% of children born full term were kindergarten-ready<sup>6</sup>.

Despite their tricky start, by the time they reach adolescence, many people born prematurely have a positive outlook. In a 2006 paper<sup>7</sup>, researchers studying individuals born weighing 1,000 grams or less compared these young adults’ perceptions of their own quality of life with those of peers of normal birthweight — and, to their surprise, found that the scores were comparable. Conversely, a 2018 study<sup>8</sup> found that children born at less than 28 weeks did report having a significantly lower quality of life. The children, who did not have major disabilities, scored themselves 6 points lower, out of 100, than a reference population.

As Marlow spent time with his participants and their families, his worries about severe neurological issues diminished. Even when such issues are present, they don’t greatly limit most children and young adults. “They want to know that they are going to live a long life, a happy life,” he says. Most are on track to do so. “The truth is, if you survive at 22 weeks, the majority of survivors do not have a severe, life-limiting disability.”

### Breathless

But scientists have only just begun to follow people born extremely prematurely into adulthood and then middle age and beyond, where health issues may yet lurk. “I’d like scientists to focus on improving the long-term outcomes as much as the short-term outcomes,” says Tala Alsadik, a 16-year-old high-school student in Jeddah, Saudi Arabia.

When Alsadik’s mother was 25 weeks

pregnant and her waters broke, doctors went so far as to hand funeral paperwork to the family before consenting to perform a caesarean section. As a newborn, Alsadik spent three months in the neonatal-intensive-care unit (NICU) with kidney failure, sepsis and respiratory distress.

The complications didn't end when she went home. The consequences of her prematurity are on display every time she speaks, her voice high and breathy because the ventilator she was put on damaged her vocal cords. When she was 15, her navel unexpectedly began leaking yellow discharge, and she required surgery. It turned out to be caused by materials leftover from when she received nutrients through a navel tube.

That certainly wasn't something her physicians knew to check for. In fact, doctors don't often ask if an adolescent or adult patient was born prematurely – but doing so can be revealing.

Charlotte Bolton is a respiratory physician at the University of Nottingham, UK, where she specializes in patients with chronic obstructive pulmonary disease (COPD). People coming into her practice tend to be in their 40s or older, often current or former smokers. But in around 2008, she began to notice a new type of patient being referred to her owing to breathlessness and COPD-like symptoms: 20-something non-smokers.

Quizzing them, Bolton discovered that many had been born before 32 weeks. For more insight, she got in touch with Marlow, who had also become concerned about lung function as the EPICure participants aged. Alterations in lung function are a key predictor of cardiovascular disease, the leading cause of death around the world. Clinicians already knew that after extremely premature birth, the lungs often don't grow to full size. Ventilators, high oxygen levels, inflammation and infection can further damage the immature lungs, leading to low lung function and long-term breathing problems, as Bolton, Marlow and their colleagues showed in a study of 11-year-olds<sup>9</sup>.

VICS research backs up the cardiovascular concerns: researchers have observed diminished airflow in 8-year-olds, worsening as they aged<sup>10</sup>, as well as high blood pressure in young adults<sup>11</sup>. "We really haven't found the reason yet," says Cheong. "That opens up a whole new research area."

At Sainte-Justine, researchers have also noticed that young adults who were born at 28 weeks or less are at nearly three times the usual risk of having high blood pressure<sup>12</sup>. The researchers figured they would try medications to control it. But their patient advisory board members had other ideas – they wanted to try lifestyle interventions first.

The scientists were pessimistic as they began a pilot study of a 14-week exercise programme. They thought that the cardiovascular risk

factors would be unchangeable. Preliminary results indicate that they were wrong; the young adults are improving with exercise.

Girard-Bock says the data motivate her to eat healthily and stay active. "I've been given the chance to stay alive," she says. "I need to be careful."

### From the start

For babies born prematurely, the first weeks and months of life are still the most treacherous. Dozens of clinical trials are in progress for prematurity and associated complications, some testing different nutritional formulas or improving parental support, and others tar-



**THIS IS AN EXCITING TIME FOR US TO REALLY MAKE A DIFFERENCE TO THEIR HEALTH."**

geting specific issues that lead to disability later on: underdeveloped lungs, brain bleeds and altered eye development.

For instance, researchers hoping to protect babies' lungs gave a growth factor called IGF-1 – which the fetus usually gets from its mother during the first two trimesters of pregnancy – to premature babies in a phase II clinical trial reported<sup>13</sup> in 2016. Rates of a chronic lung condition that often affects premature babies halved, and babies were somewhat less likely to have a severe brain haemorrhage in their earliest months.

Another concern is visual impairment. Retina development halts prematurely when babies born early begin breathing oxygen. Later it restarts, but preterm babies might then make too much of a growth factor called VEGF, causing over-proliferation of blood vessels in the eye, a disorder known as retinopathy. In a phase III trial announced in 2018, researchers successfully treated 80% of these retinopathy cases with a VEGF-blocking drug called ranibizumab<sup>14</sup>, and in 2019 the drug was approved in the European Union for use in premature babies.

Some common drugs might also be of use: paracetamol (acetaminophen), for example, lowers levels of biomolecules called prostaglandins, and this seems to encourage a key fetal vein in the lungs to close, preventing fluid from entering the lungs<sup>15</sup>.

But among the most promising treatment programmes, some neonatologists say, are social interventions to help families after

they leave the hospital. For parents, it can be nerve-racking to go it alone after depending on a team of specialists for months, and lack of parental confidence has been linked to parental depression and difficulties with behaviour and social development in their growing children.

At Women & Infants Hospital of Rhode Island in Providence, Betty Vohr is director of the Neonatal Follow-Up Program. There, families are placed in private rooms, instead of sharing a large bay as happens in many NICUs. Once they are ready to leave, a programme called Transition Home Plus helps them to prepare and provides assistance such as regular check-ins by phone and in person in the first few days at home, and a 24/7 helpline. For mothers with postnatal depression, the hospital offers care from psychologists and specialist nurses.

The results have been significant, says Vohr. The single-family rooms resulted in higher milk production by mothers: 30% more at four weeks than for families in more open spaces. At 2 years old, children from the single-family rooms scored higher on cognitive and language tests<sup>16</sup>. After Transition Home Plus began, babies discharged from the NICU had lower health-care costs and fewer hospital visits – issues that are of great concern for premature infants<sup>17</sup>. Other NICUs are developing similar programmes, Vohr says.

With these types of novel intervention, and the long-term data that continue to pour out of studies, doctors can make better predictions than ever before about how extremely premature infants will fare. Although these individuals face complications, many will thrive.

Alsadik, for one, intends to be a success story. Despite her difficult start in life, she does well academically, and plans to become a neonatologist. "I, also, want to improve the long-term outcomes of premature birth for other people."

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