Birth of a cohort — the first 20 years of the Raine study

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Participant engagement and careful planning are key to a successful cohort study

In the beginning there was an idea ... and funding. The project might never have started if not for a serendipitous meeting between an accountant for the Raine Medical Research Foundation and a young obstetrician. The Foundation had been established 30 years earlier by the bequest of Mary Raine (Box 1), a successful businesswoman who left her property empire to the University of Western Australia (UWA) for medical research. The accountant mentioned that the Foundation had decided to award a large sum of money to one big, visionary project, and the very next day the grant application was underway.

The obstetrician's big idea, the Western Australian Pregnancy Cohort, had two objectives: to investigate the hypothesis that complications of pregnancy might be prevented by frequent ultrasound scans, and to develop a long-term cohort to study the role that early life events have on later health.

From 1989 to 1991, 2900 pregnant women were randomly assigned to either routine obstetric ultrasound or multiple scans.[1] Extensive data were collected during pregnancy and the children were assessed at birth and at ages 1, 2, 3, 5, 8, 10, 14, 17, 18 and 20 years (Box 2). Questionnaire data, physical measurements and biological samples were collected looking at growth, cardiovascular, respiratory, immunological, musculoskeletal, nutritional, psychiatric, neurocognitive and ophthalmic health. The current dataset contains more than 85 000 measures on each participant, as well as 2.5 million genetic variants, with an exponential increase in publication output over time. Selected findings are summarised in Box 3.

Charlotte M McKnight
MB BS,
Clinical Lecturer,
Lions Eye Institute, Centre for Ophthalmology and Visual Science

John P Newnham
MB BS, MD, FRANZCOG,
Head of School/Winthrop Professor,
School of Women's and Infants' Health

Fiona J Stanley
MB BS, MD, MSc,
Distinguished Research Professor,
Telethon Institute for Child Health Research

Jenny A Mountain
MBA, MClinEpi,
Raine Study Manager,
Telethon Institute for Child Health Research

Louis I Landau
MB BS, MD, FRACP,
Emeritus Professor,
School of Paediatrics and Child Health

Lawrence J Beilin
MB BS, MD, FRACP,
Senior Honorary Research Fellow,
School of Medicine and Pharmacology

Ian B Puddey
MB BS, MD, FRACP,
Dean/Winthrop Professor,
Faculty of Medicine, Dentistry and Health Sciences

Craig E Pennell
MB BS, PhD, FRANZCOG,
Associate Professor,
School of Women's and Infants' Health

David A Mackey
MB BS, MD, FRANZCO,
Managing Director/Winthrop Professor,
Lions Eye Institute, Centre for Ophthalmology and Visual Science

University of Western Australia, Perth, WA.

craig.pennell@uwa.edu.au

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1 Mary Raine (1877–1960) bequeathed her property empire to the University of Western Australia for medical research

Lessons learned: ingredients for a successful cohort study

Start with a good idea

The original "good idea" for this study was Mary Raine's bequest to investigate "the nature, origin and cause of disease in human beings". The obstetrician's grant application made many references to fetal origins of adult illness, although it preceded the "developmental origins of health and disease" (DOHaD) theory by several years.

Initial funding

Projects requiring ongoing financial support, where the most important research outcomes may take decades, do not intrinsically appeal to funding bodies. How then to fund the establishment of a cohort? The Raine researchers designed the cohort as the follow-up of a randomised controlled trial (RCT) funded by the National Health and Medical Research Council (NHMRC). An RCT structure has funding appeal with potential for novel findings in a defined period, and allows simultaneous recruitment and collection of baseline cohort data. Participants in each arm of the RCT have had the same cohort involvement.

Planning for future work

The RCT was well designed, but the practicalities of cohort follow-up were initially ill defined. In the early years, volunteer staff maintained the cohort on a shoestring budget until ongoing funding was established. Planning for the future should engage not only investigators and institutions relevant to the initial phase, but also those who will be involved later as the cohort ages and the research focus changes.

Ongoing funding

A cohort cannot survive on short-term project grants; ongoing funding is necessary for staff and infrastructure. Initially, core funding was provided through NHMRC program grants to the Telethon Institute for Child Health Research. More recently, core funding has been obtained through "institutional buy-in", whereby universities and research foundations associated with the study each contribute a set amount of funds over a 5-year period. Beyond the financial benefit, "investment" in the cohort encourages institutional research commitment. Multiple

funding sources ensure that no single organisation "owns" the cohort or has exclusive access. Further funding is obtained by charging collaborators for data access.

Executive governance

The Raine Executive is chaired by the Dean of the UWA Faculty of Medicine, Dentistry and Health Sciences and includes the original investigators, a Raine Medical Research Foundation representative, an Emeritus Professor of Medicine and a scientific director. The Executive controls data access, and all proposed research projects, manuscripts and collaborations must be submitted in writing. The aim is a transparent, centralised approval process, led by an independent body prioritising the interests of the cohort. It ensures that research is not duplicated, all projects are of scientific merit, authorship issues are addressed early, and cohort data are protected. The Executive also determines which data are collected at each follow-up, and develops a long-term plan for the cohort. The Executive was formed when the cohort was aged 15, but the lesson from the Raine study experience is that it is important to establish a governance structure from the outset.

Avoiding participant loss to follow-up[3,4]

Initial data collection: As much demographic data as possible should be recorded. Many families will move house while their children are young, so grandparents' details must be collected. A process for checking and updating contact information, including email, mobile phone and even Facebook, should be established.

Engagement: The families need to feel that they are "part of something". The Raine study management maintains contact with the cohort through newsletters, birthday cards, a kids' club and social networking websites. Large functions were organised for the cohort's 10th and 21st birthdays. Engagement must be age-specific and relies on energetic staff involvement.

Cohort overload: The "burden" of research activity is carefully controlled, including length of questionnaires,[5] use of invasive procedures, frequency of assessments (every 2–4 years) and even the number of attempts to contact participants to rebook appointments. Investigators must be aware of what else is happening in participants' lives; an extensive follow-up in the year of the cohort's final high school examinations may not be advisable.

Consultation: Feedback and consultation ensures research remains relevant and acceptable to participants. A small group of cohort members are selected as representatives, and they work closely with Raine study management (Box 4). Participant workshops are used to plan new research (such as projects in fertility and genetics), identify what information should be given back (retinal photographs and dual-energy x-ray absorbtiometry [DEXA] scan results) and gauge what the cohort would (or would not) be prepared to do.

Record linkage: Linking the cohort to total population datasets is an effective and inexpensive way to increase information on the cohort, including those lost to follow-up. These data may be obtained from hospitalisation, disability and mental health contacts and specific disease registers. Linking back into total birth information can assess how well the cohort reflects the general population. As the Western Australian linkage capacity includes data from educational, child protection and justice agencies, the cohort can be tracked in all contacts with these services, with further potential in linkage to national datasets such as the Pharmaceutical Benefits Scheme.

> "Every question must have a valid reason for being asked"

2 Number of participants attending each follow-up assessment during the first 20 years of the Western Australian Pregnancy Cohort (Raine) Study

* Only volunteers for the Trier social stress test[2] attended the 18-year follow-up; no overall cohort assessment was held at this time. ◆

Impeccable ethics

Confidentiality must be maintained, and only de-identified data distributed to researchers. An auditing process should be established to ensure database integrity. When findings are potentially controversial, they must be managed carefully; the facts do not change, but presentation might. Every question must have a valid reason for being asked, with prioritisation of scientific rigour and research output.

What does the future hold? The next 20 years of the Raine study

Twenty-three research groups currently work with the Raine cohort, and international collaborations are expanding. The value of the Raine cohort will increase over time, particularly in later adult life when the major chronic diseases have developed, allowing assessment of genetic and environmental influences across the lifespan. At that point we will truly be fulfilling Mary Raine's philanthropic request in "seeking, diagnosing and investigating the nature, origin and cause of disease in human beings ... and the prevention, cure, alleviation and combating of such diseases".

3 Selected research findings from the Western Australian Pregnancy Cohort (Raine) Study and related publications

Discipline and key findings	References
Obstetrics and women's health	
Additional ultrasound scans in the second and third trimesters did not improve pregnancy outcomes. This study established the standard for routine prenatal ultrasound scanning worldwide.	*Lancet* 1993; 342: 887-891
Children in the intensive ultrasound group had higher rates of intrauterine growth restriction, but no change in physical characteristics, behaviour or neurocognitive development during childhood. This remains the major study showing the safety of prenatal ultrasound throughout adolescence and into early adulthood.	*Lancet* 2004; 364: 2038-2044
Birthweight and weight gain during childhood were found to predict age at menarche, with implications for polycystic ovarian syndrome.	*J Clin Endocrinol Metab* 2007; 92: 46-50
Cardiovascular disease, metabolic syndrome and obesity	
Normal ranges for weight and blood pressure in childhood were established and are now used clinically, with recording of biochemical measurements including serum glucose, lipid levels and inflammatory markers.	*Obes Facts* 2009; 2: 302-310 *J Paediatr Child Health* 2000; 36: 41-46 *Nutr Metab Cardiovasc Dis* 2010; 20: 274-283 *Diabetes Care* 2009; 32: 695-701
A U-shaped relationship between birth weight and metabolic risk, previously only described in the developing world, was shown.	*Int J Obes (Lond)* 2007; 31: 236-244
Maternal smoking during pregnancy, shorter duration of breastfeeding and rapid childhood weight gain were associated with metabolic risk, lending further evidence to the benefits of breastfeeding and the need for public health interventions in the prenatal and early childhood periods.	*Int J Obes (Lond)* 2007; 31: 236-244
Asthma, allergy and atopy	
Largest study measuring lung function and bronchial responsiveness in preschool-aged children, finding that preterm babies had persistently impaired lung function at age 6 years.	*Am J Respir Crit Care Med* 2004; 169: 850-854
Respiratory allergy was of central importance in the progression and consolidation of asthma in teenage years.	*J Allergy Clin Immunol* 2009; 124: 463-470, 470.e1-470.e16
Pseudo-allergic immune responses to respiratory bacteria were associated with protection against asthma.	*Eur Respir J* 2010; 36: 509-516
Mental health, cognition and language	
Maternal factors during pregnancy including stress, hypertension and weight were found to influence offspring behaviour, language and emotional development. The finding that prenatal stress can affect offspring development has led to involvement of perinatal mental health specialists as an essential part of the obstetric team.	*J Child Pschol Psychiatry* 2008; 49: 1118-1128 *Early Hum Dev* 2010; 86: 487-492 *Dev Psychopathol* 2011; 23: 507-520
Biological risk factors, such as fetal head circumference and androgen exposure, were associated with neurodevelopmental disorders.	*Arch Dis Child* 2012; 97:49-51 *Psychoneuroendocrinology* 2010; 35: 1259-1264
Musculoskeletal	
Findings from the study raised clinician awareness that spinal pain in adolescence is not trivial, but results in school absenteeism and burden on health services. Comorbid conditions of spinal pain were also identified, including poor mental health, drug use and obesity, with implications for management of adolescents presenting with back and neck pain.	*BMC Public Health* 2012; 12: 100 *Int J Pediatr Obes* 2011; 6:e97-e106 *BMC Public Health* 2011; 11: 382 *J Health Psychol* 2011; 16: 688-698
Genetics	
In conjunction with other cohorts, the Raine study identified new genetic loci influencing lung function, birth weight and age at menarche.	*Nat Genet* 2011; 43: 1082-1090 *Lancet* 2011; 378: 1006-1014 *Nat Genet* 2010; 42: 430-435 *Nat Genet* 2010; 42: 1077-1085
Targeted genetic studies have investigated otitis media, neurodevelopmental disorders and metabolic risk.	*Genes Immun* 2011; 12: 352-359 *Genes Brain Behav* 2011; 10: 451-456 *Genes Brain Behav* 2011; 10: 158-165 *Am J Clin Nutr* 2011; 93: 851-860 *Diabetes* 2011; 60: 1805-1812

4 Western Australian Pregnancy Cohort (Raine) Study representatives

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1 Newnham JP, Evans SF, Michael CA, et al. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet* 1993; 342: 887-891.

2 Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 1993; 28: 76-81.

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4 Hunt JR, White E. Retaining and tracking cohort study members. *Epidemiol Rev* 1998; 20: 57-70.

5 Edwards P, Roberts I, Clarke M, et al. Methods to increase response rates to postal questionnaires. *Cochrane Database Syst Rev* 2007; (2): MR000008. ❑