

The Raine Study – Growing into Adulthood

A Green Paper on the Future Development and Directions of the Raine Study

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Introduction

This draft Green Paper has been prepared by the Raine Study Secretariat. Its purpose is to facilitate discussions with the Raine Study Executive regarding future developments and directions of the Raine Study.

Current status

The major assets of the Raine Study in 2014 are:

- Cohort of ~2,000 'active' participants
- Repository of ~20,000 biological samples, ~100,000 phenotypic, environmental, and behavioural variables, ~31 million genetic variables on each participant
 - Participant data collected from 18 weeks gestation to 23 years of age and parental data from participant gestation to 17 years of age
- ~150 researchers and research students engaged in discovery
- Track record of significant research inputs and outputs
 - e.g. \$22million funding and 250+ scientific papers
- Growing national and international reputation
- Experienced data collection and management personnel
- Established governance structure and processes
- Core management funding commitments for next 5 years

The major current challenges identified for the Raine Study are:

- Retaining and re-engaging cohort participants
- Defining and supporting future research foci
- Translating discoveries into interventions, policy and practice
- Curating and securing existing biosamples, hard copy archives and digital data
- Developing an efficient management system for research processes, including review of governance processes
- Funding ongoing management activities, core data collection, and project data collection

Proposals for changes to support Raine Study development over the next few decades

To ensure continuation and development of the Raine Study the following needs must be met:

- I. A broader scientific framework
- II. Better engagement with participants
- III. Increased emphasis on research translation
- IV. Restructured researcher teams and research themes
- V. More efficient infrastructure
- VI. Stable funding

I. A Broader Scientific Framework

Child and adult outcomes. The cohort is now generating health, disease and other outcome measures in early adulthood. This provides opportunities to engage adult health researchers in the Raine Study.

Health and social outcomes. The Raine Study has collected a large amount of social and well-being data at multiple time points. However the Raine research focus to date has been on health and disease. Many potential research opportunities exist for examination of social outcomes including school educational achievement, post-secondary education and training and workforce participation.

Data categorisation (phenotypic, genetic [including epigenetic], behavioural, environmental). To date the Raine Study has broadly categorised data as being either phenotypic or genetic in nature. However a much broader range of information is available and being collected - this needs to be reflected in descriptions of the Raine Study resources. For example, genetic data was initially limited to GWAS, then Exome, and is currently being expanded to epigenetic data, with future plans for full genome sequencing. Phenotype data has been a generic term to describe all measured observable characteristics of participants – such a categorisation does not accurately reflect the environmental and behavioural/lifestyle data. More clearly differentiating these datasets will help clarify the resources available to researchers.

DoHAD and life course approaches. The Raine Study was initiated with a focus on fetal growth. Consequently there has been a strong focus on antenatal exposures and related outcomes, based on the Developmental Origins of Health and Disease (DOHAD) framework. The Raine Study now encompasses other critical time windows in early childhood, childhood, adolescence and young adulthood. A “life course framework” is well suited to include key constructs useful to Raine Study discovery such as trajectories, specific events, transitions, turning points, critical periods, sensitive periods, risk clusters, and chains of risk. Life course epidemiology is also strongly multi-disciplinary, recognising the interlinked developmental pathways for health and well-being (see Figure 1).

Multi-generational themes. The Raine Study has a strong tradition of examining parent factors impacting on child health. There is now the opportunity to expand this to include grandparents, siblings, partners and offspring (see Figure 2).

II. Better Engagement with Participants

Failure to retain (and re-engage) participants will result in a cohort sample whose utility for discovery will be impeded by inadequate size, bias and poor representativeness. This will lead to a loss of interest by researchers and competitive research funding. Improved participant engagement requires a clearer understanding of the needs and values of cohort participants. Initial discussions with participants have indicated value in the Raine Study allowing them to access interesting and useful data about themselves. A preliminary idea is to enable each participant to log in to a secure site to see their own information *e.g.* graphs of their height, weight and BMI over their lives, blood lipid values, immunisation records. Participants have also suggested they would like to upload further clinical data of their own such as scans and blood tests done outside of Raine data collection. Figure 3 shows an illustration of a potential web page for participant access to useful information.

A project is proposed to consult with participants to determine what they would find useful and attractive for ongoing engagement. Discussions are currently underway with Lotterywest to fund this project.

III. Increased Emphasis on Research Translation

Over the last 6 years there has been a rapid increase in discovery activity, as evidenced by the rapid rise in publications and citation rates. There is now a need for a similar increase in translating the Raine Study discoveries (see Figure 4) – to inform further research, to inform health and social policy and practice and to inform the public. Translation includes informing intervention studies, but also informing improved policy and practice. Lessons learned from the Raine Study can inform other research *e.g.* identifying problems to target, vulnerable groups who require intervention, factors that could be addressed by an intervention, and when in the life course to intervene.

The skills required to change policy and practice are increasingly being realised as different to those required for discovery and research development. Thus the Raine Study needs to attract and support people with policy and practice translation skills.

Informing the public of Raine discoveries to encourage better health and well-being should be a focus of Raine translation. Figure 3 shows how a web page could provide an easy access point for the general public to gain access to Raine information. However a broader plan for translation to the public needs to be developed and implemented.

An initial start has been made with this, with lay summaries of Raine Study scientific publications being prepared, using funding from the Department of Health. However a more detailed plan of translation needs and processes should be prepared and then resourced. Discussions are currently underway with Lotterywest to fund this project.

IV. Restructured Researcher Teams and Research Themes

Currently, Raine Study researchers are organised into 23 research groups. Some groups are based on specific disorders (*e.g.* asthma, eating disorders), some on anatomical structures (*e.g.* otolaryngology, ophthalmology), others on lifestyle behaviours (*e.g.* nutrition, activity), one on environmental exposure (anaesthesia), others on specific variables (*e.g.* vitamin D, HPA axis) and one on DoHAD. Such groupings have aided the Raine Secretariat to manage and administer these groups' activities. Over the past 18 months each group has met with the Secretariat – these reviews have revealed varied levels of organisation, planning, engagement and collaboration. It has become clear that the current group structure is failing to meet both scientific and administrative needs.

To better reflect the research activities across the Raine Study, and to improve management and administrative processes, the Secretariat proposes separating the research collaboration and administrative function groupings. Researchers based in the same organisational unit will select a leader to be responsible for administrative communications with the Raine Study. Roles will include ensuring researchers in the unit have signed data access agreements, obtained ethics approvals, provided copies of grant applications and published papers etc. Example **administrative units** would be: Centre for Sleep Science, University of Western Australia; School of Physiotherapy and Exercise Science, Curtin University; Telethon Kids Institute.

To support research collaboration the Secretariat proposes aligning research activities into themes within clusters focussed on 4 overarching areas: (1) genetics, (2) phenotype, (3) behaviours, and (4) environment matching the revised scientific framework (see Figure 5). **Research clusters** will have a leader and deputy leader who will be responsible for stimulating collaborative development of the area. Cluster meetings can progress shared approached to data analysis, develop joint projects and provide a mechanism for cross-cluster collaborations. Research clusters will also foster expanded national and international collaborations, following the successful models of collaboration developed by Raine Study genetics researchers.

- (1) **Genetics** to include GWA, Exome, epigenetics.
- (2) **Phenotype** to include: cardiometabolic (heart, vessels, liver, kidney), respiratory (asthma, lung structure), immunology/inflammation (allergy), reproduction (testes, ovaries, breasts), hormones (HPA, thyroid, testosterone), musculoskeletal (pain, bones, arthritis), mental (cognition, language, mood, disorders), senses (eyes, ears), body composition (growth, size, adiposity, bone, muscle), fitness (aerobic, muscular), nutrients (iron, Vitamin D).
- (3) **Behaviour** to include: sleep, activity (physical activity, sedentary behaviour), diet, drug use (alcohol, tobacco, other drugs), risky behaviour (sexual behaviour, driving), and perhaps social outcomes of education and work.
- (4) **Environment** to include: microbiome, chemical exposures, noise exposure, sunlight exposure, neighbourhood security, parks, walkability, shops, fast food outlets and social environment (family relationships, peer relationships, work colleague relationships).

V. More Efficient Infrastructure

Current Raine Study infrastructure has evolved with the Study, but the facilities and systems are now unable to cope effectively with the complexity and magnitude of Study-related activities. Data curation, research management and governance infrastructure urgently need up-grading. Additionally, there are ongoing requirements for office and laboratory facilities to house Raine staff and data collection activities.

Raine Study **biosamples** are housed at a number of different locations, with different inventories, security arrangements, and access protocols. A plan for secure long term storage and management is required, along with a long term secure storage facilities and a central information management system. An audit of existing biosamples is currently underway, using funding from the Department of Health.

Raine Study **hard copy data** are currently stored in an offsite storage facility managed by the Telethon Kids Institute, with current documentation stored within the Raine Study office space at Telethon Kids. A plan for long term storage and management is required.

Raine Study **phenotypic, behavioural and environmental digital data** are currently stored at the Telethon Kids Institute on secure servers but is not integrated, described and only accessible by the Raine Study manager and data managers. A small project is currently underway to prepare meta-data descriptions of data available at each follow-up, funded by core management funds. A plan for long term data storage and management is required along with a data management system to implement the plan.

Raine Study **genetic digital data** are currently stored on iVEC. A plan needs to be developed to link this securely with other digital data.

Research **management systems** are required to support project and manuscript reviews, approvals and related material and data transfers, along with core business processes such as human resources, and finances. Consistent with the increased Study activities, the governance structures need to be reviewed to ensure appropriate legal foundations are in place along with clear leadership.

Raine Study **office facilities** are currently provided at Telethon Kids Institute. Relocation of the Telethon Kids Institute to new premises places constraints on space available, data collection facilities and ease of access for participants. Opportunities for expanded facilities to meet the ongoing and growing needs are being explored.

VI Stable Funding

To successfully implement the activities outlined above, adequate funding is required for the next decade.

Core facilities funding needs to cover offices for staff and researchers, facilities for data collection, biosample storage, hard copy archive storage, digital data storage and a Raine Study car. Currently

staff offices and financial administration are provided by in-kind support from Telethon Kids Institute.

Core management funding for the next 5 years is secure, with University of Western Australia, Curtin University, Edith Cowan University, Women's and Infant's Research Foundation, Raine Medical Research Foundation and Telethon Kids Institute together providing \$2.8 million.

Core data collection funding for the 25 year follow up is dependent on NHMRC/ARC project grants. NHMRC assessor reports consistently raise concerns about project grants including funding for recruitment and core data collection. In the past successful grants have had their budgets slashed in the misguided belief there is overlap between projects. This issue was not resolved by providing a carefully worded approach for all applications in the recent round. Medium term secure funding to cover core data collection is required. This would ensure the continuation of follow-ups and assist the success of project grants (their budgets could be smaller and could argue high value for NHMRC investment). Options for core data collection funding include the State Government or other philanthropic sources.

Project data collection and discovery funding can continue to be primarily funded by competitive grants. This will ensure the maintenance of high scientific standards resulting in research publications and the protecting the Raine Study profile. Small project funding may be possible from philanthropic sources, and potentially from core management savings which may result from the establishment of more efficient management systems.

Translation funding is currently being discussed with Lotterywest.

Funding for whole genome sequencing is being explored.

Conclusion

The Raine Study has performed strongly, particularly over the past few years, with unprecedented levels of productivity. The maturation of the cohort and rapid growth of research activity present some major challenges which now threaten the continued development and success of the Raine Study. Substantial changes are required to be implemented over the coming years to ensure the survival and growth of the Raine Study as the cohort moves into adulthood. These changes will ensure that the Raine Study continues to deliver on its enormous potential for discovery and translation of outcomes to improve the lives of future generations.

Figure 1: The Life Course Approach

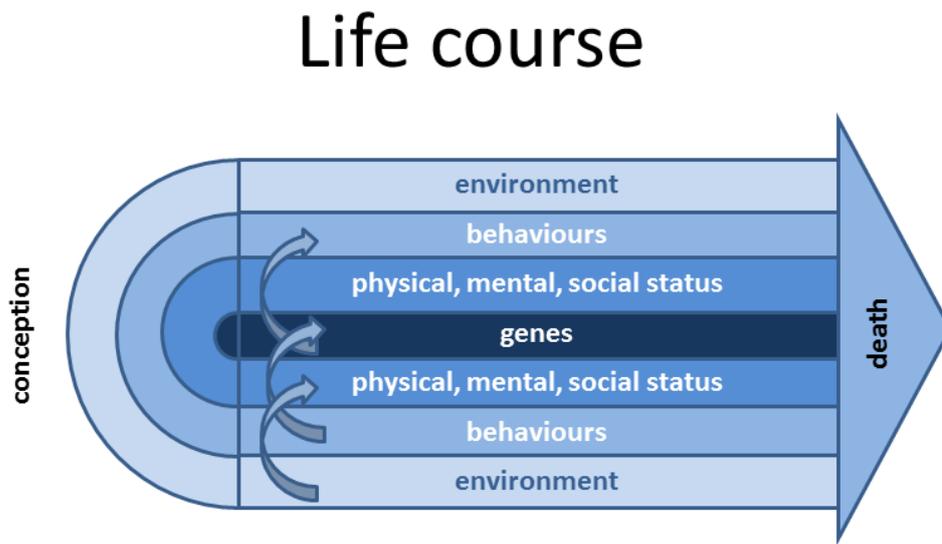


Figure 2: Multi-generational Life Course Approach

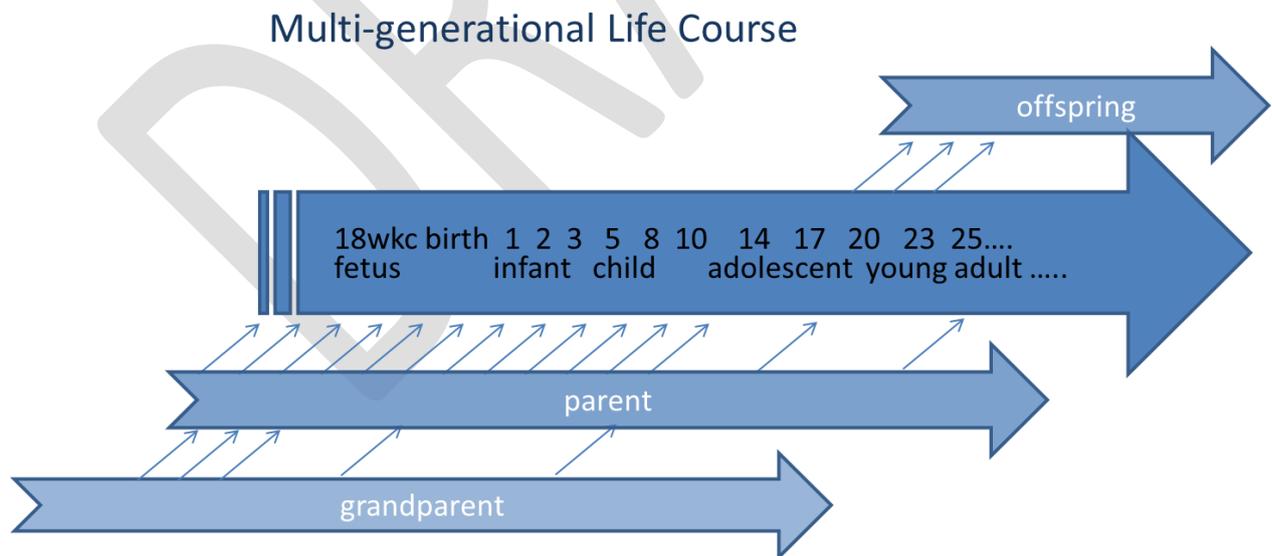


Figure 3: Sample of better participant and public access to Raine data/discoveries (web site, person clicks on topic of interest and links to lay summaries of Raine discoveries and tips for health)

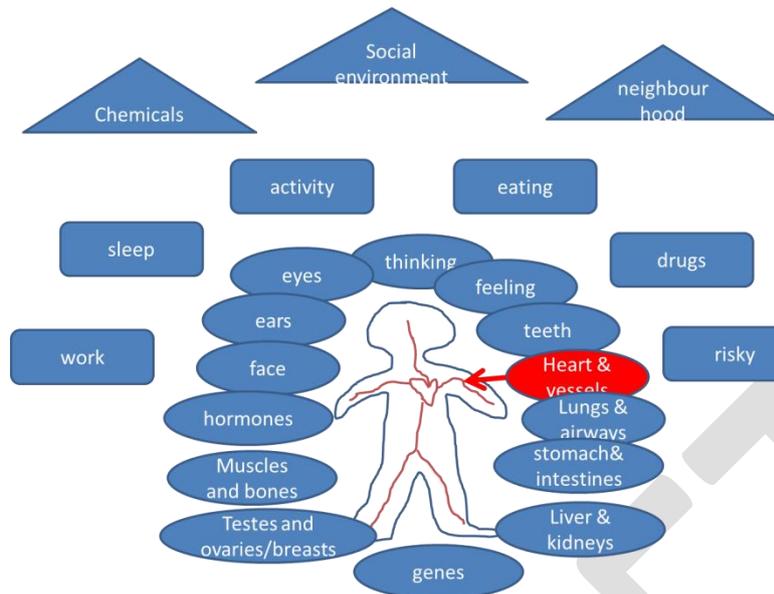


Figure 4: Representation of data collection, analysis and discovery and translation activity in the Raine Study (illustrating ongoing need for data collection, rapidly expanding discovery and need for increased translation)

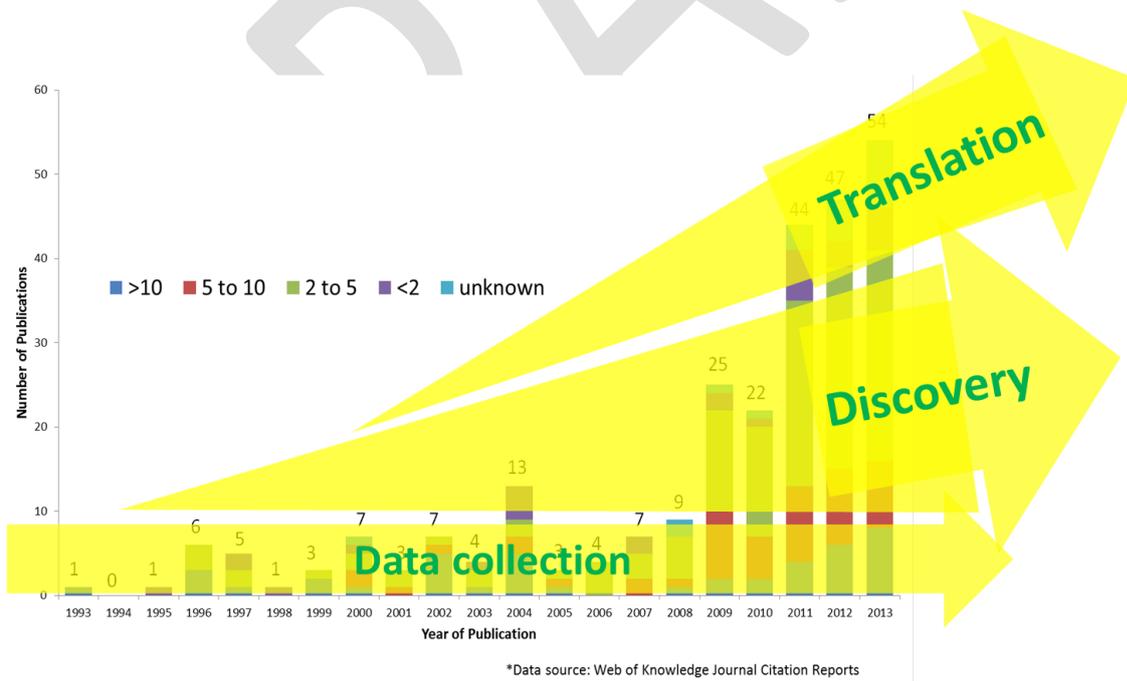


Figure 5: Research themes and larger clusters (4 larger groups, with smaller more focussed groups)

