2016 ACTIVITY REPORT

The Western Australian Pregnancy Cohort (Raine) Study

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Executive Summary

Established in 1989, the Raine Study is one of the largest, most successful prospective cohorts of pregnancy, childhood, adolescence and now adulthood to be carried out anywhere in the world. Over 2,000 of the now young adult participants (Generation 2) remain active, and participated in assessments of work and obesity in 2016. In addition, the original parents (Generation 1) participated in assessments of sleep, obesity and activity this year.

The highlights for the Raine Study in 2016 were:

- The University of Western Australia, Curtin University, Edith Cowan University, Murdoch University, Notre Dame University, Women and Infants Research Foundation and Telethon Kids Institute agreed to become core partners in a new Raine Study Unincorporated Joint Venture,
- The Raine Study led the WA Cohorts Network component of the WAHTN application for AHTRC recognition,
- Over 150 researchers were engaged in Raine Study research and over 50 new research projects within Raine were approved,
- Peer-reviewed publication output remained high in terms of quantity and quality,
- Raine research activity was funded by 6 NHMRC project grants, 1 ARC discovery grant, a Cooperative Research Centre for Living with Autism (Autism CRC) grant and other grants from the WA Department of Health and the National Breast Cancer Foundation. Two further NHMRC project grants (to start in 2017) and one NHRMC CRE grant (to start in 2017) applied for in 2016 were successful.

Activities planned for 2017 represent the next major change in the Raine Study and its operations, the last major change being the appointment of the inaugural Scientific Director and Executive Committee in 2007. In 2017, the Raine Study will see the implementation of: a new strong collaborative governance structure; improved human and technical infrastructure; participation for the first time of three generations of Raine Study participants. These activities will ensure the continued growth of the Raine Study's national and international reputation.

General information about the Raine Study

History of the Raine Study

In 1989 Professor John Newnham and colleagues invited more than 3000 pregnant women to join a National Health and Medical Research Council funded research study at King Edward Memorial Hospital to examine the possible beneficial effects of repeated fetal ultrasound imaging studies. Women were allocated at random into one of two groups – Regular Care or Intensive Care. Those in the Regular Care group had a single ultrasound imaging study at 18 weeks gestation, with further scans only if clinically indicated. The women in the Intensive Care group had ultrasound scans at 18, 24, 28, 34 and 38 weeks gestation. Along with Professor Newnham, a group of prominent investigators (Professor Fiona Stanley, Professor Lou Landau and Professor Con Michael) formed a group to establish these families into a cohort study, focusing on the child, to determine how events during pregnancy and childhood influence health in later life. This was initially supported with funding from the Raine Medical Research Foundation. The original cohort of 2868 children, the Raine Study cohort, is one of the largest, most successful prospective cohorts of pregnancy, childhood, adolescence and now adulthood to be carried out anywhere in the world. The participants have been followed closely over the last 27 years by a collaborative team of researchers from The University of Western Australia, Women and Infants Research Foundation, Telethon Kids Institute, Curtin University, Edith Cowan University, the University of Notre Dame, (and now also Murdoch University), the Lyons Eye Institute, and many other national and international collaborators.

Organisational structure

The Raine Study was initially managed through King Edward Memorial Hospital, then in early childhood management shifted to the then Telethon Institute for Child Health Research. In 2007 a Memorandum of Understanding was signed to establish a clear collaborative governance structure based on an Executive Committee chaired by the Dean of Medicine at the University of Western Australia (initially Professor Ian Puddey) and supported by a Scientific Director (initially A/Professor Craig Pennell).

Raine Study Executive Committee

The Committee includes representatives from the original investigators of the Raine Study, a representative of the Raine Medical Research Foundation and other esteemed researchers with specialist knowledge and expertise relevant to the Raine Study. The Committee is responsible for the protection of the cohort members, upholding the scientific and ethical integrity of the research and overseeing the management of the Raine Study. Research projects and access to cohort resources can only proceed once written approval has been received from the Committee.

In 2016, the Raine Study Executive Committee consisted of:

- Professor Robyn Owens (Chair)
- Professor John Newnham
- Professor Lou Landau

- Professor Lawrie Beilin
- Professor Jennie Blackwell
- Professor Nick de Klerk
- Professor David Mackey
- Professor Leon Straker
- A/Professor Craig Pennell
- Professor Paul Norman
- Professor Susan Prescott

During 2016 the Committee reviewed applications for new projects and collaborations as well as overseeing the governance, leadership and management of the Raine Study. The committee also received advice from two subcommittees, each with specific expertise in technical issues relating to genetic and biological sample curation and research, the Genetics Advisory Subcommittee and the Biological Samples Advisory Subcommittee, respectively.

Raine Study Genetics Advisory Subcommittee

The role of this subcommittee is to provide advice to the Raine Study Executive Committee on issues related to the Raine Study genetic resources. In 2016, the Raine Study Genetics Advisory Subcommittee consisted of:

- Professor Peter Eastwood (Chair)
- Professor Leon Straker (Co-chair)
- Professor Jenefer Blackwell
- A/Professor Craig Pennell
- A/Professor Rae Chi Huang
- Professor David Mackey
- Dr Philip Melton
- Ms Jenny Mountain

Raine Study Biological Samples Advisory Subcommittee

The role of this subcommittee is to provide advice to the Raine Study Executive Committee on access and research issues related to the Raine Study biological samples. In 2016, the Raine Study Biological Samples Advisory Subcommittee consisted of:

- Professor Peter Eastwood (Chair)
- Professor Leon Straker (Co-chair)
- Professor Trevor Mori
- A/Professor Graham Hall
- Professor Pat Holt
- A/Professor Craig Pennell
- Ms Jenny Mountain

Raine Study Scientific Directors

The Scientific Directors are appointed by the Executive Committee and provide leadership and strategic direction for cohort research activities and oversight of Raine Study staff. The positions are funded by the Raine Medical Research Foundation. Since 2014, the Raine Foundation Scientific Director has been Professor Peter Eastwood, and the Raine Foundation Associate Scientific Director has been Professor Leon Straker.

Raine Study Staff

In 2016, the staff of the Raine Study consisted of:

Manager:	Jenny Mountain
Data managers:	Angela Jacques, Louise McKenzie
Co-ordinator:	Diane Wood
Research officers:	Alex D'Vaux
Phlebotomist:	Sue Green
Data entry:	Carolyn Smargiassi
Administration:	Chris Halliday
Research assistant:	Michelle Tickner, Erica Hodgson
Casual research assistants:	Natasha Haynes, Sarah-Finlay-Jones, Upasana Jayaraman, Maddison Jones, Alice O'Connor, Ruth Smith, Renee Wood, Julie Sartori, Jacinta Saldaris, Gemma Peagno, Alyce Russell, Jodie Leslie, Bev Caiacob, Natalie Stein, Cara Lo, Emily Huynh, Annabel Gabb, Racheal Peake, Sean Bryne, Elissa Denton
Sleep scientists:	Anthea Beck, Avijit Bose, Azin Moshtaq, Madeleine Lowe, Gemma Peagno
Overnight assistants:	Alex Burton, Zoe Marsen, Kirsten Smith, Gareth Lingham, Holly Brown

In late 2016 Jenny Mountain retired after around 10 years as Study Manager. Also in late 2016 Angela Jacques ceased work for the Raine Study to undertake more clinical statistics consulting. Their commitment to the Raine Study over many years is greatly appreciated.

Raine Study Students

In 2016, there were 39 students working with the Raine Study, 17 of whom were enrolled for Doctor of Philosophy (PhD) (Figure 1). Three of these students obtained their doctorate degrees in 2016.

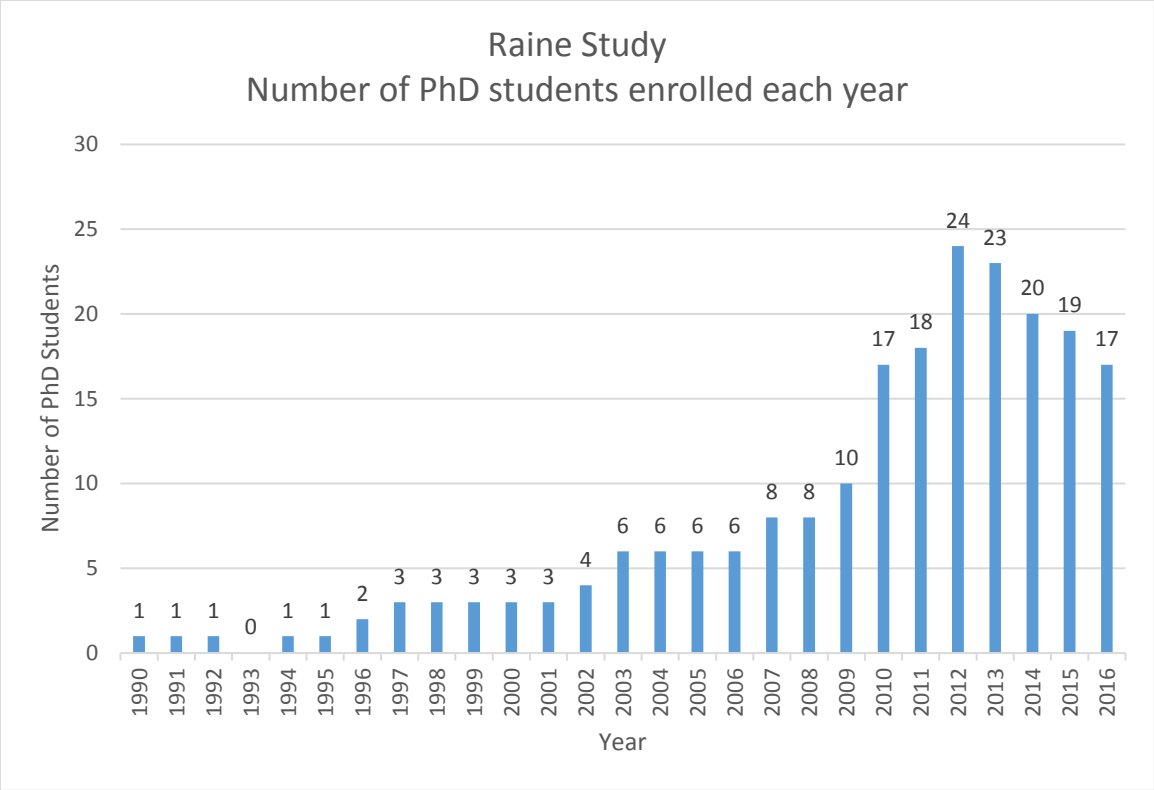

Figure 1 Raine Study PhD students: number of PhD students enrolled each year

Raine Study Representative Group

The Raine Study fosters and encourages participant involvement in decisions about contact or communication with the cohort including assessments, cohort activities and research studies. The Raine Study has an established Representative Group who have met regularly since they were 10 years old. The Raine Study personnel and researchers meet regularly with this group and other cohort members in relation to contact with the cohort and planned research activity.

Raine Study Participants 2016

The original Raine Study fetuses (Generation 2) are now on average 26 years of age. 2,300 of them remain registered as “active” participants, meaning that they have agreed to remain in the study and be contacted for future assessment.

Funding for the Raine Study

Background

In 2014 a five year funding commitment to Raine Study core management costs was obtained from the University of Western Australia (Faculty of Medicine, Dentistry and Health Sciences), University of Western Australia DVC (Research), Curtin University, the Women and Infants Research Foundation, the Telethon Kids Institute and the Raine Medical Research Foundation. A three year commitment was also

generously provided by Edith Cowan University. Additional core funding was obtained from the introduction of a 15% Raine Study access fee applied to all research grant applications.

The cost of core management of the Raine Study is approximately $600K per annum. This cost includes management of the study and maintaining contact with the cohort and facilitating current and future projects. Core funding is separate to the costs associated with cohort assessment and data collection, which requires an additional $500-$700K per annum depending on the specific nature of the cohort assessment research protocols.

Core funding

Core management funding covers the costs associated with:

- Remuneration of the Raine Study core personnel (Scientific Directors, Study Manager, Study Data Managers, administrative support)
- Cohort retention and consumer consultation
- Raine Study PhD top up scholarships
- The Raine Study Annual Scientific Meeting
- The Raine Study website development and maintenance
- Management, curation and storage of previously collected data including biological samples and the purchase of storage freezers
- Other expenses not funded by research grant funding

Grant applications 2015 (for 2016)

Eleven project grant applications totalling $8.4 million were prepared and submitted in 2015 for research projects to commence in 2016. Seven grants proposed the collection of new data (i.e. a new cohort assessment), and four grants proposed utilising previously collected Raine Study data (Appendix 1).

Two grant applications were successful:

- NHMRC 1102106, 2016-2020, T Mori, L Beilin, E Moses, G Watts, L Adams, Genetic and early life predictors of ectopic fat and their association with cardiometabolic health and disease, $1,706,136.
- NHMRC 1109057, 2016-2018, P Eastwood, A Mian, N McArdle, D Hillman, Predicting obstructive sleep apnoea using 3D craniofacial photography, $424,715.

The Raine Study also became involved in the Autism Cooperative Research Centre via a grant awarded to Professor Andrew Whitehouse and colleagues: The creation of the Australian Autism Biobank. Autism Cooperative Research Centre (1.002RC), with a total amount of $130,000 contributing to Raine related activities.

Grant applications 2016 (for 2017)

Thirteen grant applications totalling $11.4 million were prepared and submitted in 2016 for research projects to commence in 2017 (Appendix 2).

Three grant applications were successful:

- NHMRC 1126494, 2017-2020, D Green, L Beilin, L Straker, P Eastwood, T Mori, P Ainslie, Developmental origins of adult cardiovascular disease: Vascular health in the Raine cohort, $1,087,427.
- NHMRC 1121979, 2017-2020, D Mackey, A Hewitt, S MacGregor, C Hammond, Young adult myopia: genetic and environmental associations, $809,270.
- NHMRC CRE1116360, D Mackey, J Craig, A Hewitt, K Burdon, R Jamieson, J Grigg, S Macgregor, F Chen, M Otlowski, D Schofield, NHMRC Centres of Research Excellence - From discovery to therapy in genetic eye diseases (Raine Study is part of this CRE), $2,498,231.5.

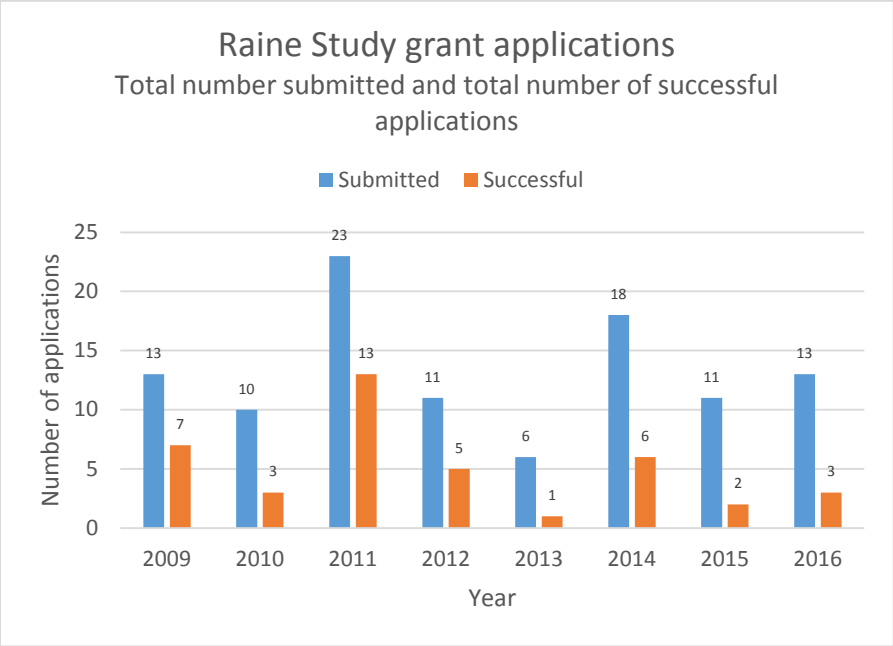

Figure 2 Raine Study grant applications. Total number submitted and total number of successful applications

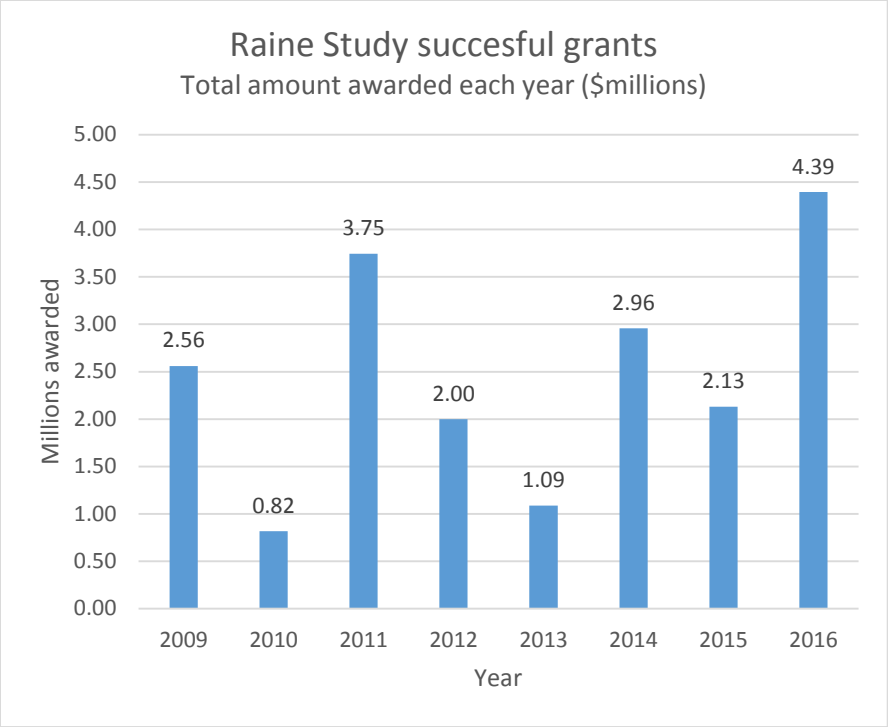

Figure 3 Raine Study successful grants. Total amount awarded each year ($millions)

What happened in 2016?

Grant funded activities update

ARC 150103312, 2015-2018, S Parker, P Dunlop, L Straker, K Parkes, Work design matters: The dynamic interplay of work and person factors, $334,119.

This project aims to examine the working environment and how this affects an individual's health, work performance and behaviour. The study looks at how personality and demographics, and their interactions, shape or constrain individuals' opportunities to undertake high quality work and vice versa. It also examines how family, education, and workplace factors affect the individual and their workplace. The Raine Study participants' contact details were updated and the questionnaires was sent out in May 2016. All active Raine Study participants were contacted and invited to complete an online questionnaire in relation to themselves and their workplace. 472 participants completed their questionnaires. In addition to that 63 managers and 69 peers completed a questionnaire about the Raine participants. To improve participant engagement, feedback workshops were organised and 40 participants attended. Analysis is ongoing, with a follow-up survey scheduled for 2018.

NHMRC 1084947, 2015-2017, P Eastwood, D Hillman, E Moses, N McArdle, P Melton, Prevalence, phenotype and genotype of common sleep disorders, $1,419,000.

This project commenced in January 2015. The grant funded the physical assessment and overnight sleep study of the parents (Generation 1) of the Raine Study index participants (Generation 2). Disturbed sleep is common in the Australian community and the objectives of the study are to establish the prevalence, phenotype and genetic basis of sleep disorders, particularly obstructive sleep apnoea, insomnia, restless legs syndrome and periodic leg movement syndrome in middle aged people. Together the parent and (previously collected) children datasets will determine associations between parent and child sleep disorders and lead to the discovery of genetic variants associated with common sleep disorders.

Parents of Raine Study participants who completed an overnight sleep study during the 22 year cohort follow up are being invited to attend an overnight sleep study at the UWA Centre for Sleep Science. In addition, other tests include eyesight measurements, a DXA scan, lung function testing, pressure and cold pain testing, computer based cognitive functioning test, blood pressure, anthropometric testing, accelerometry and the provision of a fasting blood sample. This testing is conducted in assessment rooms located in the Raine Study House and at the UWA Centre for Sleep Science. At the end of 2016 a total of 831 Generation 1 participants had completed all testing. By the end of data collection in May 2017 we hope to have obtained data from 1000 participants.

NHMRC 1080492, 2015-2017, P Holt, E Hollams, A Bosco, D Strickland, Waxing and waning of asthma during transition from the teens to adulthood, $649,492.

It is now recognized that late onset and persistent (early onset) asthma in young adults represent different forms of the disease that are likely to be driven by different mechanisms, and are therefore likely to need different treatment. However details of the underlying mechanisms driving progression of asthma in this age range, or the spontaneous remission which frequently occurs, are sparse. We are studying these in the Western Australian Pregnancy (Raine) Cohort, using clinical material collected in the 22 year respiratory follow-up of ~1000 participants, complementing a similar follow-up that took place at age 14 years. In addition to collecting clinical data relating to asthma, both follow-ups created an archive of cryobanked viable immune cell samples (peripheral blood mononuclear cells) that were collected from subjects at the time of clinical assessment, at both 14 and 22 years. We are continuing studies at both ages to identify immunological markers associated with remitting asthma, persistent asthma, and late-onset asthma. Data analyses will continue until late 2017, including systems level transcriptomic analyses on aeroallergen specific Th-memory responses to aeroallergens associated with atopic asthma risk, and analysis of IgE-dependent basophil activation.

National Breast Cancer Foundation (NBCF), PS15040, 2015, J Stone, M Hickey, L Lilge, C Saunders, J Hopper, A novel method to measure breast density in young women, $198,931.

Breast density is a strong predictor of breast cancer risk. Evidence of this has been derived from mammography, which is not recommended for younger women. New methods of measuring breast density are therefore needed to bridge large gaps in knowledge regarding breast density in young women. Members of the research team have developed Transillumination Breast Spectroscopy (TiBS) which measures spectral differences in breast composition using visible and near infrared light. It correlates highly with mammographic breast density in women over 40 and is safe and easy to use. This study aims to test the feasibility and acceptability of the TiBS machine to measure breast density. The UWA HREC have granted permission for the study, Raine Study staff have been trained on the use of the TiBS device and recruitment is conducted at the Raine Study house, UWA. The investigators are inviting both volunteers (women aged 18-40) and Raine Study participants to have a TiBS scan. To date, a total of 135 Raine participants and another 400 pilot non-Raine participants have already completed their assessment.

NHMRC 1059711, 2014-2016, RC Huang, K Lillycrop, G Burdge, J Craig, L Beilin, T Mori, W Oddy, K Godfrey, J Holbrook, The cycle of obesity: Two generations of a pregnancy cohort to investigate obesity epigenetics, $1,086,102.

The project commenced in 2014 to examine obesity epigenetics in two generations of the Raine Study. To take advantage of ongoing developments in bioinformatics methodology we have sought and been granted a 6 month extension to this NHMRC grant. (End Feb 2018). Further analyses including use of pathway analyses, DMRcate and Comb-P have been undertaken on these data. We have participated in Pregnancy and Child Epigenetic Consortium (PACE) meta-analyses and papers related to asthma, gestational age, birthweight and maternal BMI. We are still working through the pyrosequencing of hotspots in DNA samples from participants at age 17 and 20 and from parent samples and results are being generated. Multiple manuscripts are currently in preparation and three under review currently. An invited epigenetics review has been submitted.

Western Australian Department of Health Future Health G06302, 2014-2016, P Eastwood, L Straker, J Mountain, Western Australian Pregnancy Cohort Study, $200,000.

This funding was secured to (i) analyse blood samples collected during the follow up at 22 years of age. This was completed and the data incorporated into the Raine Study database; (ii) employ a research officer to facilitate the translation of Raine Study research scientific findings and lay summaries of published scientific journal articles – these have been published on the Raine Study website; and (iii) support the management and analyses of accelerometry data which is ongoing.

NHMRC 1042269, 2012-2016, R Hart, C Pennell, D Doherty, M Robinson, R Norman, The long-term consequences of IVF treatment for the offspring - a prospective cohort study using the Raine cohort for comparison, $1,552,096.

The Growing Up Healthy Study (GUHS) aims to determine the long-term consequences of assisted reproduction upon the development of the offspring by comparing their growth, metabolic, respiratory, psychological, immunological and reproductive development at ages 13-15, 16-18 and 20-22 with outcomes from the Raine Study cohort. Teenagers involved in the study were invited to visit the GUHS research team at Raine Study house, UWA to undertake the same age-specific assessments performed on the Raine cohort, focusing on metabolic, respiratory, psychological, immunological and reproductive health. The study is proceeding as planned, with approximately 350 teenagers currently involved. Data collection continued during 2016, and will continue in 2017.

CRC, A Whitehouse, The creation of the Australian Autism Biobank. Autism Cooperative Research Centre (1.002RC). $130,000.

In 2013 the Commonwealth Department of Industry awarded $31 million to establish a Cooperative Research Centre for Autism. One project within this CRC is to establish a detailed comprehensive characterisation of children with Autism Spectrum Disorder (ASD) and children without ASD. The children (Gen3) of the cohort participants (Gen2) were identified as a well-established cohort that could act as control sample of children without ASD. Assessments will include a detailed questionnaire, parent interview and face-to-face testing of developmental ability, as well as assessment of physical activity, and collection of blood samples for later genotyping and biochemistry. As ASD is usually first established at around 2 years of age, all Raine Generation 3 children of 2 years and greater will be included. In 2016 protocols were established and it is anticipated that 150 Raine Gen3 children will be assessed in 2017 and another 150 in 2018.

NHMRC 1102106, 2016-2020, T Mori, L Beilin, E Moses, G Watts, L Adams, Genetic and early life predictors of ectopic fat and their association with cardiometabolic health and disease, $1,706,136.

The grant application has helped fund the 26/27 year old follow-up and will examine the genetic, antenatal and childhood antecedents of ectopic fat depots in young adults, and the relative importance of different depots in relation to cardio metabolic health and novel markers of resolution of inflammation. Ectopic fat depots are best quantified using Magnetic Resonance Imaging (MRI). Project approval from UWA Human Ethics Committee (HREC) was granted in March 2016. All study protocols, materials and resources were created and obtained. New casual research staff were recruited and trained. Online questionnaires with the option of paper copies were created, databases to record assessment data developed and contact details of participants updated. Pilot assessments were conducted and the follow up commenced in May 2016. Eligible participants were invited to participate in a physical assessment at the Raine Study House situated on the UWA campus and an MRI at Envision, Wembley. The physical assessment tests include the core anthropometric measurements of height weight, skinfolds and blood pressure, DXA scan as well as a repeat of some of the eye measurements from the year 20 follow-up. Fasting bloods were also obtained on the day of their assessment and for females a new breast density screening test using Transillumination Breast Spectroscopy (TiBS) was also performed. All participants were also requested to provide urine and faecal samples. In 2016, 237 participants had completed the physical assessment and of these 222 had completed an MRI. Data collection will continue in 2017 and 2018.

NHMRC 1109057, 2016-2018, P Eastwood, A Mian, N McArdle, D Hillman, Predicting obstructive sleep apnoea using 3D craniofacial photography, $424,715.

This project commenced in mid-2016. It is examining the relationships between the structure of the face, head and neck and the development and severity of obstructive sleep apnoea (OSA), a very

common condition associated with snoring and collapse of the upper airway (throat) during sleep. Determining which characteristics of the face and neck are related to the development and severity of OSA could provide important information about the causes of OSA and may allow us to diagnose it using a simple 3-dimensional photograph of the face.

The study leverages off the unique combination of 3D photographs and laboratory-based measurements of OSA that have been obtained in 956 young adults from the 22 year follow up and 1,000 of the parents (currently being studied) of these young adults. These data will be combined with 1,000 data sets from patients attending the Sleep Clinic at Sir Charles Gairdner Hospital (to date 870 patients have been studied). Data collection is ongoing.

Projects and collaborations update

New applications to use Raine Study data

In 2016, there were 53 new project applications (P forms) processed involving 26 new national/international collaborations (C forms) (Figure 4). Additionally there were 47 manuscripts forms reviewed.

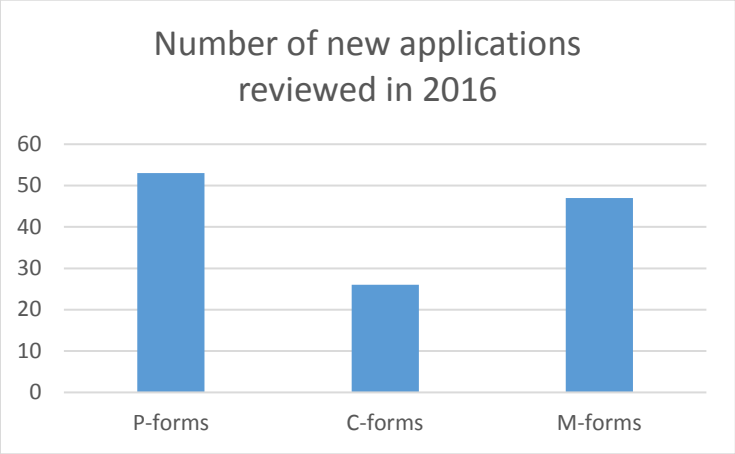

Figure 4 Number of new applications reviewed in 2016

Data linkage

Raine Generation 2 participants' keys for linkage in the Western Australian Department of Health's Data Linkage Unit were maintained. This is important as it will facilitate any future utilisation of WA linked data resources. One data linkage project is active, with Anett Nyaradi, Wendy Oddy and Leon Straker investigating the relationship between nutritional intake, mental health and school educational outcomes.

Additionally, educational outcome data at the end of school were obtained from the Tertiary Institutions Service Centre, Western Australia for Generation 2 participants. This included subject grade scores and Australian Tertiary Admission Rank. Negotiations are also ongoing with the WA School Curriculum and Standards Authority to access school results and with the university sector to access tertiary education participation and outcome data.

Intergenerational studies

With the original parents (Generation 1) being followed-up for the first time independently of their children (Generation 2) with NHMRC grant 1084947, and the offspring (Generation 3) of the original children being followed-up for the first time with Autism Collaborative Research Centre funding, the multi-generation nature of the Raine Study has become prominent. This led to the development of a logical naming convention that will be viable for decades to come – with Generation 0 being the grandparents (Gen0), Generation 1 the parents (Gen1), Generation 2 the index participants (Gen2) i.e. the original fetuses, and Generation 3 the offspring of the index participants (Gen3). This terminology is now being used consistently across Raine research activities.

Western Australian Health Translation Network (WAHTN)

The Raine Study is one of several large successful cohort studies in Western Australia. During 2016 the Raine Study Scientific Directors worked with Professor John Challis (a previous Chair of the Raine Study Executive Committee and current Director of the Western Australian Health Translation Network) to promote the excellent track record of the Raine Study and several other WA cohort studies. This led to the cohorts forming a substantial part of the WAHTN's application for NHMRC recognition as an Advanced Health Research and Translation Centre (AHRTC).

Content provided by the Directors and utilised in the AHRTC application include:

- "Western Australia has a strong history in developing and maintaining substantial cohorts. These cohorts cover the whole life-course from pre-natal to older people. They are typically richly characterised with data collection involving not only questionnaire/interview data but also clinical assessments, biosamples and linkage to administrative databases. Data collected includes genetics, extensive biobanks, physical and mental health status, behaviours, environment, hospital admissions, health service utilisations and deaths. A very broad range of health issues are investigated, along with important social outcomes including education and work."
- "There are four major community cohorts and a number of clinical cohorts and registries. *The Busselton Health Study* was initiated in 1966, with 3,394 participants. Since then there have been 15 further waves of data collection involving over 20,000 participants. Major foci for the Busselton Health Study have included: lung disease, diabetes, cardiovascular disease, gene discovery and multi-morbidity. *The Raine Study* was initiated in 1989 and recruited 2,900 women at around 18 weeks gestation. Further assessments were completed at 34 weeks, birth, and 1, 2, 3, 5, 8, 10, 17, and 22 years of age. Major foci for the Raine Study have included: developmental origins, gene discovery, vision, cardio-metabolic, respiratory, allergic, musculoskeletal and hormonal disorders, lifestyle behaviours and health and behavioural

trajectories. *The Health in Men Study* was initiated in 1996 and recruited 12,203 men aged 65-84 years. The participants have been followed-up on 5 more occasions. Major foci for the Health in Men Study have included: cardiovascular disease, mental health, testosterone and other biochemical and hormones, genetics, and physical activity. *The ORIGINS project* is just commencing and aims to recruit 10,000 families over the next 5 years at first antenatal contact. *The Fremantle Diabetes Study* phase 1 was initiated in 1993 and recruited 1426 people with diabetes, with a subsequent phase 2 initiated in 2008 recruiting 1,732 (some overlap). Other cohorts include: *Wittenoom*, *WA HIV cohort study*, *WA young driver cohort study*, *WA sleep health OSA cohort*, *WA family connections genealogical project* with clinical registries for many disorders including childhood diabetes, autism, developmental anomalies and in-vitro fertilisation."

- "Together these cohorts have been very successful in generating new knowledge that can change practice and improve societal health outcomes (examples provided). The five major cohorts outlined have published over 1,100 peer reviewed papers in total and over 580 in the 2011-2016 period."
- "The substantial discovery has had considerable impact on policy and practice (examples provided)."
- "The cohorts have provided excellent research capacity building opportunities. For example they have been the basis for many research students and early career researchers. They have also enabled local researchers to establish collaborations with leading national and international research groups."
- "This research activity has been supported with funding in 2011-present totalling $30 million, including $24 million from NHMRC. Lifetime cash funding support totals $55 million, with $49 million from NHMRC."

Translation, dissemination, impact

Publications

In 2016 50 peer-reviewed papers were published, with 78% of these in journals with impact factors of 2 or greater (Figure 5). High impact publications included Nature, Nature Communications, and Journal of Allergy and Clinical Immunology. (Appendix 3: List of publications)

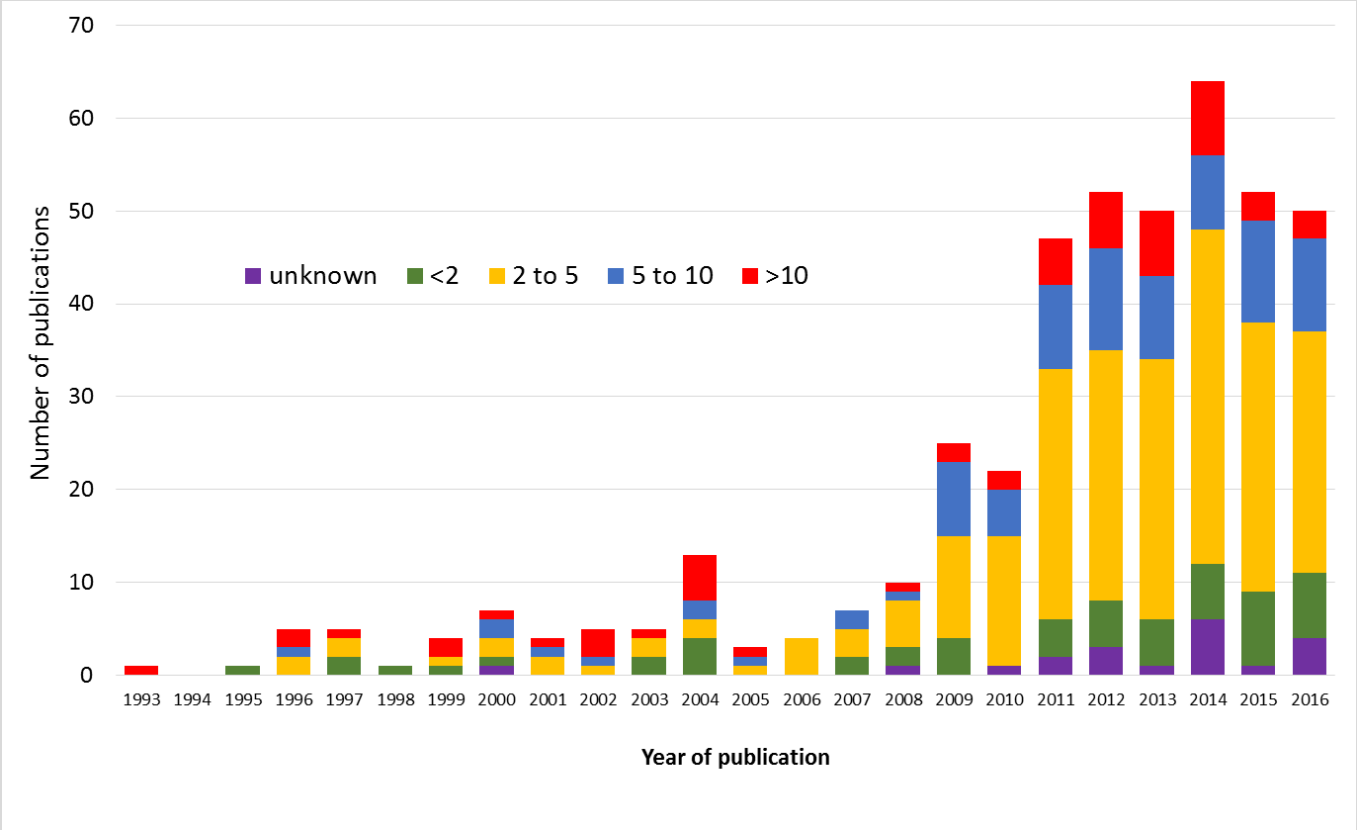

Figure 5 Number of Raine Study publications by year and impact factors

Raine Study Annual Scientific Meeting

A very successful 9th Raine Study Annual Scientific meeting was held on Friday 30 September 2016, at the University Club UWA. The meeting was formally opened by Her Excellency the Honourable Kerry Sanderson AC, Governor of Western Australia and patron of the Raine Study. Professor John Newnham gave an excellent and entertaining talk about Mary Raine, and presented Her Excellency with a biography on Mary Raine, signed by the author, Meg Sangster.

Sixteen presentations were delivered over the course of the day that covered a wide variety of research areas. The Raine Medical Research Foundation prizes for the two best presentations by early career researchers were present by Emeritus Professor Lou Landau to Niamh Troy for her talk on predicting causes of gene expression changes in T-helper memory responses in asthma, and to Karen Richards for her presentation on the association of neck posture and neck pain in adolescents.

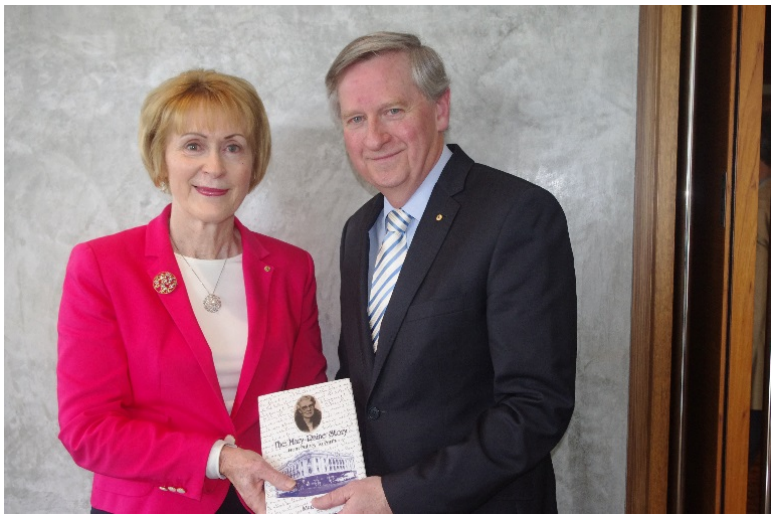

Figure 6 Her Excellency the Governor and John Newnham

Figure 6 Graham Hall, Joanne McVeigh, Her Excellency, the Governor, Anu Bharadwaj, Nigel McCardle

Figure 8 Lou Landau with Karen Richards and Niamh Troy

What will happen in 2017?

Organisational structure changes

During 2015 and 2016 the Scientific Directors worked with stakeholders to examine ways to improve the governance, efficiency of the human and technical infrastructure, engagement of researchers, translation and engagement of participants. LotteryWest provided funding for an external consultant to assist with this process. In 2016 the Raine Study Executive Committee approved a number of major initiatives proposed by the Scientific Directors including: the establishment of the Raine Study as an Unicorporated Joint Venture (UJV); restructuring of the organisation under a UJV; and the development of improved digital infrastructure for Raine study data and management processes.

In the second half of 2016 in principle agreement to join a collaborative partnership to govern the Raine Study was obtained from: the University of Western Australia (to be the centre agent), Curtin University, Edith Cowan University, Murdoch University and the University of Notre Dame, Telethon Kids Institute, and the Women and Infants Research Foundation. In 2017 the UJV will be established, a chair and board appointed and detailed processes and terms of reference will be established.

The approved restructure of staff, participants and portfolios is represented in Figure 9. During 2017 an Operations Manager, Scientific Officer and Data Manager will be appointed, along with other staff to support the communications, translation, participant engagement and cohort follow-up portfolios and corporate support. Professor Eastwood will become the inaugural Director and Professor Straker the Scientific Director.

The scientific advisory role of the previous Executive Committee along with the advisory roles of the Genetics and Biosamples Advisory Subcommittees will be merged into a single committee, to be known as the *Scientific Review Committee*.

The approved plan for researcher engagement with the Raine Study will be implemented in 2017 following announcement of the Special lnterest Groups (SIG) and their leaders in late 2016. The SIG leaders will be responsible for stimulating collaborative development of the area. SIG leaders will guide researchers interested in their area to expand activities, look for new expertise/researcher talent to attract to their SIG (local, national and international), look for opportunities to collaborate with other SIGs, look for new research projects, look for new funding opportunities, and look for student research opportunities. SIG leaders will work with the Data Manager to ensure that all SIG related data is up to date and will be responsible for maintaining the currency of the brief summary of the SIG's activities.

The 15 Special Interest Groups and their leaders are:

1. Genetics - Phil Melton, Craig Pennell
2. Cardiometabolic - Koya Ayonrinde, Trevor Mori
3. Respiratory, Immunology, Inflammation - Elysia Hollams, Graham Hall
4. Hormonal & Reproduction - Melanie Walls, Roger Hart, Martha Hickey
5. Musculoskeletal - Darren Beales, Peter Kent

6. Psychological - Ashleigh Lin, Andrew Whitehouse, Romola Bucks
7. Senses - Chris Brennan-Jones, Rob Eikelboom, David Mackey
8. Bio - Peter Eastwood, Leon Straker
9. Sleep & Activity - Jo McVeigh, Nigel Mcardle
10. Diet - Therese O'Sullivan, Gina Ambrosini
11. Risky behaviour - Robert Tait, Rachel Skinner
12. Perinatal & Life course Environmental Exposures - Megan Galbally, Jeff Keelan
13. Built & Social Environment - Gina Trapp, Hayley Christian
14. Education & Work - Michael Dockery, Sharon Parker
15. Biostatistics - Angela Jacques, Max Bulsara

Digital infrastructure developments will include an online project/forms management process to better manage the growing number of projects, a restructuring of the digital database to contemporary best practice standards and to support semi-autonomous data extraction for projects, and trialling of secure virtual analysis spaces for Raine researchers.

The approved plan to better engage participants is being supported by Anne McKenzie from the Consumer Community Health Research Network. Participants will be selected and trained for multiple roles within the new structure from the UJV Board through scientific and operations portfolios. An app will also be developed to enable participants to access selected longitudinal data of theirs and provide a platform for further engagement.

Projects and follow-ups

Generation 0

A scoping project will be conducted to determine the number and availability of potential Gen 0 participants.

Generation 1

Data collection for NHMRC grant 1084947 led by Professor Peter Eastwood will be completed in May 2017, with data quality control to follow then initial analyses.

Generation 2

In 2017, the Raine Study will continue with the data collection for the 27 year follow-up funded from various sources including a NHMRC grant 1102106. At the end of 2016 a total of 831 cohort members had participated. The expected total when data collection ceases in May 2018 will be approximately 1000 participants.

A new data online-only 'snapshot' collection of data for a project examining the influence of testosterone on financial risk taking behaviour will be conducted in the first half of the year. European economics researchers Doctors Paul Smeets (Maastricht University, the Netherlands) and Boris van Leeuwen (Tilburg University, the Netherlands) are leading the project in collaboration with Raine research Professors Andrew Whitehouse, Peter Eastwood and Leon Straker.

Data collection will start for the next full follow-up of Gen2, funded by NHMRC grants 1126494 and 1121979 (focussed on cardiovascular function and vision) in late 2017.

Generation 3

In 2017, data collection will commence on the Autism CRC funded first follow-up of Generation 3, examining a broad range of issues in children aged 2 years and older. It is anticipated that 150 children will participate in 2017 and a similar number in 2018.

Focus on research impact

A part time communications expert will be appointed to develop a comprehensive external communications plan for the Raine study and its activities. This officer will also work with the media departments of UJV partners to increase the presence of Raine across institutions and across traditional media and social media.

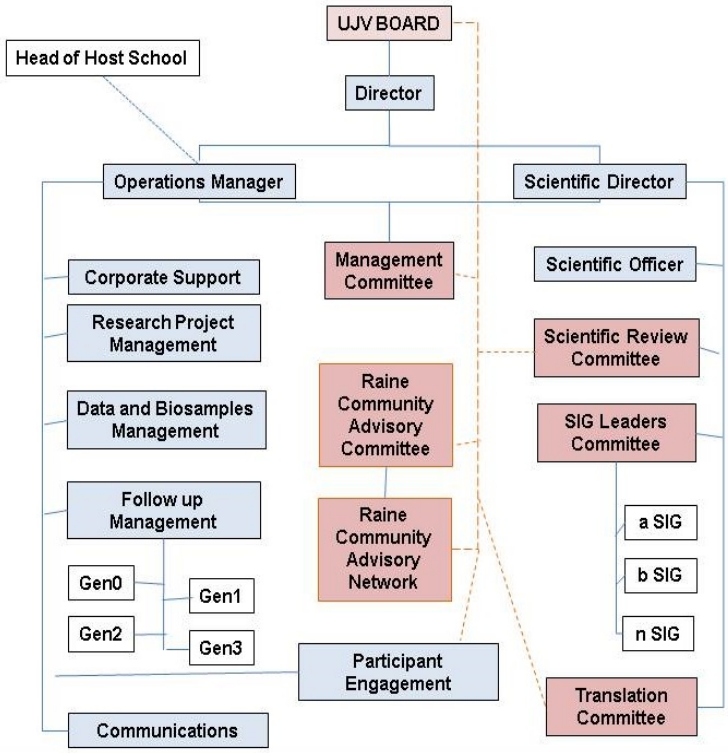

Figure 9The new structure of staff, participants and portfolios

Summary

Activities planned for 2017 represent the next major change in the Raine Study and its operations, the last major change being the appointment of a Scientific Director and Executive Committee in 2007. These changes will position the Raine Study for accelerated growth and impact over the coming decades. The Raine Study in 2017 will be characterised by: a new strong collaborative governance structure; the development and implementation of improved human and technical infrastructure; the participation for the first time of three generations of Raine Study participants; and continued growth of the Raine Study's national and international reputation.

Appendix 1. Grant applications submitted in 2015 for funding in 2016

1. NHMRC 1102106, T Mori, L Beilin, E Moses, G Watts, L Adams, Genetic and early life predictors of ectopic fat and their association with cardiometabolic health and disease, $1,956,136. **Funded**
2. NHMRC 1109057, P Eastwood, A Mian, N McArdle, D Hillman, Predicting obstructive sleep apnoea using 3D craniofacial photography, $424,715. **Funded**
3. NHMRC 1102223, M Hickey, J Stone, C Saunders, M Sabin, N Warrington, D Taylor, G Colditz, How does the early life environment modify breast cancer risk? A prospective cohort study, $545,258.
4. NHMRC 1108020, A Teichtahl, A Smith, Y Wang, D Urquhart, Does the risk of hip osteoarthritis begin in childhood? Implications for prevention, $301,451.
5. NHMRC 1102101, D Green, L Beilin, L Straker, P Eastwood, Developmental origins of adult cardiovascular disease: Vascular health in the Raine Cohort, $1,164,955.
6. NHMRC 1101032, D Mackey, A Hewitt, C Hammond, S Macgregor, K Rose, E Milne, F Chen, M He, J Guggenheim, Young adult myopia: genetic and environmental associations, $1,394,728.
7. NHMRC 1104349, G Ambrosini, J Scott, G Trapp, W Oddy, F Bull, Identifying opportunities to reduce non-communicable diseases: a prospective analysis of novel determinants of dietary intake and eating behaviours in the Raine Study, $508,091.
8. NHMRC 1102574, P O'Sullivan, J Karppinen, A Borthakur, L Straker, A Smith, D Beales, K Cheung, F Williams, Understanding lumbar spine degenerative changes and their relationship to back pain and disability in young adults, $579,306.
9. NHMRC 1099700, R Mattick, E Sillins, J Horwood, G Patton, J Najman, J Toumbourou, D Hutchinson, R Tait, R Skinner, R Hayatbakhsh, Continuity and discontinuity of cannabis use: Predictors and outcomes into contemporary adulthood, $782,024.
10. NHMRC 1104506, W Oddy, T Mori, G Ambrosini, R Chi Huang, L Adams, Nutritional predictors of cardio-metabolic risk from infancy to adulthood, $348,014.
11. ARC DE160101012, I Heinonen, D Green, P Eastwood, L Beilin, L Straker, Effect of maternal physical activity on adult arterial phenotype in humans, $403,437.

Appendix 2. Grant applications submitted in 2016 for funding in 2017

1. NHMRC 1126494, D Green, L Beilin, L Straker, P Eastwood, T Mori, P Ainslie, Developmental origins of adult cardiovascular disease: Vascular health in the Raine cohort, $ 1,087,427. **Funded.**
2. NHMRC 1121979, D Mackey, A Hewitt, S MacGregor, C Hammond, Young adult myopia: genetic and environmental associations, $809,270. **Funded.**
3. NHMRC CRE1116360, D Mackey, J Craig, A Hewitt, K Burdon, R Jamieson, J Grigg, S Macgregor, F Chen, M Otlowski, D Schofield, NHMRC Centres of Research Excellence - From discovery to therapy in genetic eye diseases (Raine Study year 20 part of this CRE), $2,498,231.5. **Funded.**
4. NHMRC 1124825, G Ambrosini, J Scot, G Trapp, B Boruss, F Bull, W Oddy, Why do young adults eat what they eat? Identifying determinants of dietary intake and eating behaviours in young adults to reduce chronic disease, $781,638.
5. NHMRC 1102574, P O Sullivan, A Smith, J Karppinen, D Beales, L Straker et al, Understanding the role of lumbar spine structure in disabling low back pain MRI scan, $1,188,982.
6. NHMRC 1127991, M Teichtahl, A Smith, Y Wang, L Straker, D Urquhart, I Ackerman, Obesity during the “growth spurt” – A window of preventive opportunity for femoroacetabular impingement, $851,068.
7. NHMRC 1130187,P Cistulli, D Hillman, P Eastwood, A Pack, K Sutherland, N McArdle, B Singh, B Keenan, P de Chazal, Phenotypic characterisation of obstructive sleep apnoea (OSA): a pathway to precision medicine, $668,707.
8. NHMRC 11288440, M Kavurma, L Adams, C Hawkins, T Griffith, On the trail of a fatty liver, $359,930.
9. NHMRC 1120430, E Silins, J Horwood, W Hall, G Gatton, J Najman, J Toumbourou, R Skinner D Hutchinson, Informing universal risk assessment for persistent substance use and dependence in adulthood using population-based, integrated data from five Australasian cohorts, $636,885.
10. NHMRC 1129411, R Skinner, J Mario, B Liu, D Doherty, M Hickey, F Zepf, Lifecourse determinants of sexual and other risky behaviours in young adulthood, $539,200.
11. NHMRC 1125416, W Oddy, T Mori, G Ambrosini, K Smith, A Lin, K Sanderson, S Gall, RC Huang, G Trapp, C Blizzard, Nutritional pathways to adult depression via obesity, cardio-metabolic disease and inflammation: a collaborative study, $488,739.
12. NHMRC 1127285, B Erbas, P Sly, P Holt, G Hall, The role of environmental exposures in the development of lung function in children and adolescents: a prospective study of 3 birth cohorts, $227,707.
13. NHMRC 1120430, R Mattick, E Silins, J Horwood, G Patton, J Najman, J Toumbourou, S Skinner, D Hutchinson, W Hall, Informing universal risk assessment for persistent substance use and dependence in adulthood using population-based, integrated data from five Australasian cohorts, $636,885.2.

Appendix 3. Publication list 2016

1. Allen KL, Byrne SM, Crosby RD, Stice E. Testing for interactive and non-linear effects of risk factors for binge eating and purging eating disorders. Behaviour Research and Therapy. 2016;87:40-7.
2. Ambrosini GL, Oddy WH, Robinson M, O'Sullivan TA, Hands BP, de Klerk NH, et al. Adolescent dietary patterns are associated with lifestyle and family psycho-social factors. Public Health Nutrition. 2016;19(3):765-765.
3. Ayonrinde OT, Adams LA, Doherty DA, Mori TA, Beilin LJ, Oddy WH, et al. Adverse metabolic phenotype of adolescent girls with non-alcoholic fatty liver disease plus polycystic ovary syndrome compared with other girls and boys. Journal of Gastroenterology and Hepatology. 2016;31(5):980-7.
4. Black LJ, Burrows S, Lucas RM, Marshall CE, Huang RC, Chan She Ping-Delfos W, et al. Serum 25-hydroxyvitamin D concentrations and cardiometabolic risk factors in adolescents and young adults. British Journal of Nutrition. 2016;115(11):1994-2002.
5. Carrion-Castillo A, van Bergen E, Vino A, van Zuijen T, de Jong PF, Francks C, et al. Evaluation of results from genome-wide studies of language and reading in a novel independent dataset. Genes, Brain, and Behavior. 2016;15(6):531-41.
6. Demmer DL, Beilin LJ, Hands B, Burrows S, Cox KL, Straker LM, et al. Effects of muscle strength and endurance on blood pressure and related cardiometabolic risk factors from childhood to adolescence. Journal of Hypertension. 2016;34(12):2365-2375.
7. Demmer DL, Beilin LJ, Hands B, Burrows S, Pennell CE, Lye SJ, et al. Dual energy x-ray absorptiometry compared with anthropometry in relation to cardio-metabolic risk factors in a young adult population: is the 'gold standard' tarnished? PloS ONE. 2016;11(9):e0162164.
8. Fan Q, Guo X, Tideman JW, Williams KM, Yazar S, Hosseini SM, et al. Childhood gene-environment interactions and age-dependent effects of genetic variants associated with refractive error and myopia: The CREAM Consortium. Scientific Reports. 2016;6:25853.
9. Fan Q, Verhoeven VJ, Wojciechowski R, Barathi VA, Hysi PG, Guggenheim JA, et al. Meta-analysis of gene-environment-wide association scans accounting for education level identifies additional loci for refractive error. Nature Communications. 2016;7:11008.
10. Felix JF, Bradfield JP, Monnereau C, van der Valk RJ, Stergiakouli E, Chesi A, et al. Genome-wide association analysis identifies three new susceptibility loci for childhood body mass index. Human Molecular Genetics. 2016;25(2):389-403.
11. Gaillard R, Welten M, Oddy WH, Beilin LJ, Mori TA, Jaddoe VWV, et al. Associations of maternal prepregnancy body mass index and gestational weight gain with cardio-metabolic risk factors in adolescent offspring: A prospective cohort study. BJOG: An International Journal of Obstetrics and Gynaecology. 2016;123(2):207-16.
12. Grace T, Bulsara M, Robinson M, Hands B. Early life events and motor development in childhood and adolescence: a longitudinal study. Acta Paediatrica. 2016;105(5):e219-27.

13. Grace T, Bulsara M, Robinson M, Hands B. The impact of maternal gestational stress on motor development in late childhood and adolescence: A longitudinal study. Child Development. 2016;87(1):211-20.
14. Hands B, Parker HE, Rose E, Larkin D. Gender and motor competence affects perceived likelihood and importance of physical activity outcomes among 14 year olds. Child: Care, Health and Development. 2016;42(2):246-52.
15. Hart RJ, Doherty DA, Keelan JA, McLachlan R, Skakkebaek NE, Norman RJ, et al. Early life events predict adult testicular function; data derived from the Western Australian (Raine) birth cohort. The Journal of Clinical Endocrinology and Metabolism. 2016;101(9):jc20161646.
16. Henley D, Brown S, Pennell C, Lye S, Torpy DJ. Evidence for central hypercortisolism and elevated blood pressure in adolescent offspring of mothers with pre-eclampsia. Clinical Endocrinology. 2016;85(4):583-9.
17. Herbison CE, Henley D, Marsh J, Atkinson H, Newnham JP, Matthews SG, et al. Characterization and novel analyses of acute stress response patterns in a population-based cohort of young adults: influence of gender, smoking, and BMI. Stress. 2016;19(2):139-50.
18. Holt PG, Strickland D, Bosco A, Belgrave D, Hales B, Simpson A, et al. Distinguishing benign from pathologic TH2 immunity in atopic children. The Journal of Allergy and Clinical Immunology. 2016;137(2):379-87.
19. Horikoshi M, Beaumont RN, Day FR, Warrington NM, Kooijman MN, Fernandez-Tajes J, et al. Genome-wide associations for birth weight and correlations with adult disease. Nature. 2016;538(7624):248-52.
20. Howie EK, McVeigh JA, Smith AJ, Straker LM. Organized sport trajectories from childhood to adolescence and health associations. Medicine and Science in Sports and Exercise. 2016;48(7):1331-9.
21. Huynh E, Bukowska DM, Yazar S, McKnight CM, Mian A, Mackey DA. Quantification of sun-related changes in the eye in conjunctival ultraviolet autofluorescence images. Journal of Medical Imaging. 2016;3(3):034001.
22. Ing C, Wall MM, DiMaggio CJ, Whitehouse AJ, Hegarty MK, Sun M, et al. Latent class analysis of neurodevelopmental deficit after exposure to anesthesia in early childhood. Journal of Neurosurgical Anesthesiology. Published online 13 April 2016. Epub ahead of print.
23. Jones AC, Troy NM, White E, Hollams EM, Gout AM, Ling K-M, et al. Persistent activation of interlinked Th2-airway epithelial gene networks in sputum-derived cells from aeroallergen-sensitized symptomatic atopic asthmatics. BioRxiv. Published online 13 July 2016.
24. Le-Ha C, Herbison CE, Beilin LJ, Burrows S, Henley DE, Lye SJ, et al. Hypothalamic-pituitary-adrenal axis activity under resting conditions and cardiovascular risk factors in adolescents. Psychoneuroendocrinology. 2016;66:118-24.
25. McVeigh J, Smith A, Howie E, Straker L. Trajectories of television watching from childhood to early adulthood and their association with body composition and mental health outcomes in young adults. PloS ONE. 2016;11(4):e0152879.
26. McVeigh JA, Winkler EA, Healy GN, Slater J, Eastwood PR, Straker LM. Validity of an automated algorithm to identify waking and in-bed wear time in hip-worn accelerometer data collected with a 24 h wear protocol in young adults. Physiological Measurement. 2016;37(10):1636-52.

27. McVeigh JA, Winkler EA, Howie EK, Tremblay MS, Smith A, Abbott RA, et al. Objectively measured patterns of sedentary time and physical activity in young adults of the Raine Study cohort. The International Journal of Behavioral Nutrition and Physical Activity. 2016;13:41-53.
28. McVeigh JA, Zhu K, Mountain J, Pennell CE, Lye SJ, Walsh JP, et al. Longitudinal trajectories of television watching across childhood and adolescence predict bone mass at age 20 years in the Raine Study. Journal of Bone and Mineral Research : the official journal of the American Society for Bone and Mineral Research. 2016;31(11):2032-2040.
29. Middeldorp CM, Hammerschlag AR, Ouwens KG, Groen-Blokhuis MM, St. Pourcain B, Greven CU, et al. A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. Journal of the American Academy of Child & Adolescent Psychiatry. 2016;55(10):896-905.e6.
30. Mountain JA, Nyaradi A, Oddy WH, Glauert RA, de Klerk NH, Straker LM, et al. Data linkage in an established longitudinal cohort: the Western Australian Pregnancy Cohort (Raine) Study. Public health Research & Practice. 2016;26(3):e2631636.
31. Nyaradi A, Li JH, Foster JK, Hickling S, Jacques A, O'Sullivan TA, et al. Good-quality diet in the early years may have a positive effect on academic achievement. Acta Paediatrica. 2016;105(5):E209-E18.
32. O'Sullivan TA, Bremner AP, Mori TA, Beilin LJ, Wilson C, Hafekost K, et al. Regular fat and reduced fat dairy products show similar associations with markers of adolescent cardiometabolic health. Nutrients. 2016;8(1):22-38.
33. Pang J, Martin AC, Mori TA, Beilin LJ, Watts GF. Prevalence of familial hypercholesterolemia in adolescents: potential value of universal screening? The Journal of Pediatrics. 2016;170:315-6.
34. Pappa I, St Pourcain B, Benke K, Cavadino A, Hakulinen C, Nivard MG, et al. A genome-wide approach to children's aggressive behavior: The EAGLE consortium. American Journal of Medical Genetics Part B, Neuropsychiatric Genetics : the official publication of the International Society of Psychiatric Genetics. 2016;171(5):562-72.
35. Parmar PG, Taal HR, Timpson NJ, Thiering E, Lehtimaki T, Marinelli M, et al. International genome-wide association study consortium identifies novel loci associated with blood pressure in children and adolescents. Circulation Cardiovascular genetics. 2016;9(3):266-78.
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38. Richards KV, Beales DJ, Smith AJ, O'Sullivan PB, Straker LM. Neck posture clusters and their association with biopsychosocial factors and neck pain in Australian adolescents. Physical Therapy. 2016;96(10):1576-1587.
39. Sanfilippo PG, Huynh E, Yazar S, Hewitt AW, Mackey DA. Spectral-domain optical coherence tomography-derived characteristics of bruch membrane opening in a young adult Australian population. American Journal of Ophthalmology. 2016;165:154-63.

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Report Ends