REPORT ON THE FOURTH ANNUAL 45 AND UP STUDY COLLABORATORS' MEETING HELD ON 20 SEPTEMBER 2007

The Fourth Annual Collaborators' Meeting of the 45 and Up Study was held at the John Nielsen Scientia Building, University of New South Wales in Sydney on 20 September 2007. This report summarises the presentations and discussions at the meeting. A wide range of possibilities for work within the Study and future directions were raised; it should be noted that not all of these will necessarily occur.

GOALS

Main meeting
The goals of the main meeting were:

1. To update collaborators and other interested people on the progress of the Study.
2. To inform collaborators and other interested people on research underway using data from the 45 and Up Study.
3. To encourage use of data from the Study for high quality research projects.
4. To inform participants how to access data from the Study.
5. To keep collaborators and funders engaged in the Study.

Workshops
The goals of the workshops were:

1. To inform workshop participants of the priorities and information needs of the relevant policy or funding agency, in relation to the workshop topic.
2. To inform workshop participants of the types of data that will be available and the research potential relevant to the workshop topic.
3. To facilitate the development of research proposals and project working groups using Study data.

PLENARY SESSIONS

KEYNOTE ADDRESS
Presentation: Professor Eugenia Calle, American Cancer Society
From Hammond-Horn to CPS-3: how American Cancer Society cohort studies have shaped our understanding of risk, with particular emphasis on the effects of obesity
Eugenia E. Calle received her PhD (1982) in Epidemiology from the Ohio State University. She worked as an epidemiologist at the Oak Ridge National Laboratory in the area of cancer risk assessment (1979-1984) and at the Centers for Disease Control on the Agent Orange Projects (1984-1989) prior to joining the American Cancer Society in 1989. She is currently the Managing Director of Analytic Epidemiology, a position that she has held since 1994. In this capacity, she oversees all program activities including data collection, management and analyses for the Cancer Prevention Study cohorts. Her research has been primarily in the areas of breast cancer risk factors, hormone replacement therapy and cancers in women, and adiposity and cancer incidence and mortality. Her scientific publications on breast cancer include examinations of associations with weight, weight gain, height, alcohol, physical activity, reproductive factors, active and passive smoking, occupation, family history of cancer, exogenous hormone use, and spontaneous abortion. Her scientific publications on adiposity include analyses of BMI and total mortality, BMI and mortality for the 20 most common cancer sites in men and women, in depth evaluations of BMI and cancers of the

colon, breast, ovary, prostate, lung, and pancreas, and review articles and book chapters on the epidemiology of obesity and cancer.

Main points of presentation:

- Cohort study research within the American Cancer Society (ACS) has relied on a partnership between ACS researchers and volunteers
- These cohort studies began in early 1950s
- Total of around 2.4 million cohort study participants, with biospecimens: 70,000 buccal cell samples; 40,000 blood samples
- These studies have been the basis of important scientific advances in multiple areas, including results on the link between smoking and lung cancer, the impact of obesity on cancer deaths and the link between aspirin and colon cancer
- Cancer Prevention Study 3 is planning to enrol 500,000 participants 30-65 years old, without previous cancer. Participants will provide waist measurement and blood sample and complete baseline survey. This will allow comprehensive investigation of cancer risk in the US.
- Suggestions for research whilst waiting for a cohort study to mature:
    - Cross sectional studies: Predictors of screening; Predictors of weight gain; Any genotype/phenotype association
    - Methodologic Studies: Validate linkage with National Death Index; Validate linkage with state registries; DNA yield and quality from buccal cells; Nutrition Cohort baseline paper; GWS in paired blood and buccal samples; methodological studies relating to blood collection, storage and processing

Discussion points:

- The relative risk of cancer in relation to higher BMI appears to be attenuated by age There is some evidence that weight decreases are protective at older ages but we need to bear in mind that weight decrease in older age is often associated with morbidity. The absolute risk is a better measure than the relative risk in this type of analyses.
- There have not been any issues in the US cancer cohorts around DNA samples being requested by law enforcement agencies to date. All participants sign an extensive confidentiality agreement. Results of blood results are not released to anyone, even the participants themselves.
- It has been suggested that the most recent cancer cohort (recruited through the “Relay for Life”) might have disproportionate participation from people with cancer or relatives with cancer. Comparison with available national rates shows that the cohort and national are similar. The internal validity of the study is not affected as long as you have enough people within the study who have cancer and those who do not.
- Samples are frozen at around -80deg) in liquid nitrogen. There was extensive testing of logistics prior to the national roll-out of the study.
- The new US cancer cohort (CPS3) is going to cost around 36 million dollars. This does not include staff costs as these are covered by the American Cancer Society and much of the data collection is done by volunteers.

STUDY UPDATE AND DISCUSSION OF PROJECTS UNDERWAY IN THE 45 AND UP STUDY

Presenters:Associate Professor Emily Banks, the 45 and Up Study
Dr Sonia Wutzke, the 45 and Up Study
Professor Julie Byles, University of Newcastle

Main points of presentations:

- The 45 and Up Study is a large scale cohort study aiming to recruit 250,000 NSW men and women aged 45 and over by end of 2009. It is a state-wide, long-term, open resource for policy and practice relevant research on healthy ageing. The study includes self-reported information plus consent for data linkage and potential for providing biological samples in the future
- The **independent review** of Study after the first 18-months of operation was conducted by Professors Dallas English and Michael Hobbs and recognised the high quality science of the study and that funding milestones had been met. The study governance and management structures were described as exemplary.
- The study has **new partners**: *beyondblue: the national depression initiative* and the NSW Department of Ageing, Disability and Home Care; new supporters: The Macquarie Bank Foundation and the Baxter Charitable Foundation and Alma Hazel Eddy Trust (both managed by Perpetual Ltd) and funding from MBF Foundation to fund a three-year Policy in Action Roundtable
- The **study team** has expanded: Scientific Director, Director Policy and Operations, Data Manager, Data Analyst, 2 project Officers and casual Helpline staff
- 36,645 individuals have been recruited to the cohort giving informed consent for follow-up and linkage. Rolling recruitment is underway; full 250,000 will be recruited by end of 2009
- The **Community and Ethical Oversight Committee**, chaired by Philippa Smith, continues to meet 4 times a year and the Consumer and Community Committee conveyed, chaired by Betty Johnson, to provide comment and advice on issues of participant and potential participant interest
- The study has ethical approval for inclusion in the Master Linkage Key for the NSW Centre for Health Record Linkage. Negotiations underway with Medicare Australia for access to PBS and MBS data for cohort
- The study plans to link routinely to data from: Medical Benefits Scheme (+ veterans), Pharmaceutical Benefits Scheme (+ veterans), NSW Admitted Patients Data Collection, NSW Central Cancer Registry, NSW Deaths. A wide range of more specialised linkages will be possible on a project by project basis.
- The **first paper** from the study has been published: 45 and Up Study Collaborators. Cohort profile: The 45 and Up Study. *International Journal of Epidemiology*. 2007 (advance open access).
- Researchers are encouraged to apply to the 45 and Up Study Scientific Advisory Committee to use data from the study for their projects. More information and forms at: www.saxinstitute.org.au
- There have been 17 projects approved by the Scientific Advisory Committee. 6 are underway and 7 are awaiting funding decisions. The 5 projects that have already received study data are:

1. Economic impacts of disease on older workers: costs to government and individuals and opportunities for intervention: Deborah Schofield, Arul Earnest, Simon Kelly, Megan Passey, Richard Percival
2. Understanding risk factors for cancer in the 45 and Up Study cohort: Freddy Sitas, Emily Banks, Karen Canfell, Dianne O'Connell, David Smith, Marianne Weber
3. The correlates of poor memory, mental health and wellbeing in ageing: are they different in the old-old (aged > 80 years)? Gavin Andrews, Tracy Anderson, Henry Brodaty, Perminder Sachdev
4. Sun exposure and its correlates in the NSW 45 and up cohort study: Bruce Armstrong, Anne Kricker

5. The relationship between oral health, diet and systemic health outcomes in the 45 and Up Study Cohort: Manish Arora, Bradley Christian, Wendell Evans, Pathik Mehta, Shanti Sivaneswaran

- The Social, Economic and Environmental Factors in health (SEEF) project has received an NHMRC Strategic Award of $1.8 million to gather additional information on social, economic and environmental factors in first 100,000 45Up participants. It has themes around socioeconomic disadvantage, social connectedness, retirement and economic factors and environment
- **The 45 and Up Study Research Network** replaces the old system of theme committees and includes researchers, policy makers and others with an interest in the 45 and Up Study. It aims to facilitate high quality practice- and policy-relevant research within the Study and includes: email updates;vevents, including Collaborators' meeting; information on research and opportunities for collaboration; and technical assistance when preparing grant applications. To join, please contact 45andUp@saxinstitute.org.au
- **The MBF Foundation Policy in Action Roundtable** comprises senior policymakers from government and non-government organisations and the private sector and senior researchers. It aims to foster high-quality research using the 45 and Up Study that is relevant to health policy and to the community and enhance collaboration and mutual learning among policymakers and researchers
- **Future priorities for the study include:** Data management infrastructure and processes; linkage; biospecimens and more detailed measures; research proposals in the priority areas of study partners and the MBF Foundation Policy in Action Roundtable

Information on the Kessler-10

- The K10 is a score of current/recent psychological distress
- 17% of participants missing one or more items on the K10. This drops to 16% using logical checks and 13% with imputation, however the implications of this imputation are unclear.
- Groups with high mean scores on the K10 include those who: did not complete school; are unemployed or on a disability pension; need help with everyday tasks, have a family history of depression; report currently receiving treatment for depression or anxiety; those who are separated.

Discussion points:

Q: Clearly the strength of the 45and up study is in the linkage. What validation will be done of the linkage?
A: PBS & MBS will not be probabilistic as mailing was done via Medicare therefore the link is already theoretically established. Validation of other linked datasets will be done in association with CHeReL. Lee Taylor added that it is possible to do manual checks/reviews of 500 records per day.

Q: Suggestion made to J. Byles that the K10 might be able to be condensed to K6 format.
A: Thought there was likely to be only a small gain in doing this. E. Calle mentioned that in scales such as these it is often worthwhile having a "don't know" option. Julie also mentioned that is was interesting that the SF36 question on emotions had been answered well with a very low missing rate.

Q: What are the strategies in 45 and Up for understanding selectivity and any inherent biases?
A: Cohort studies are not generally designed to be strictly representative of the general population, and selection bias does not apply in the same way as it does to case-control studies. What we are aiming for is generalisability of results, through internal comparisons within the study, rather than representativeness. Thus if the relative risk from the study are applied to rates of morbidity in the general population an absolute risk can be calculated. The study population will be compared with other data sources such as the NSW health survey and the Census.

Q: What is the spread across the age groups? What is potential for follow-up beyond 10 years?
A: There is a fairly even spread across age groups (please see the newly published methods paper for details). The plan is to follow participants up beyond 10 years but this will be subject to funding.

Valerie Beral commented that the important point regarding selection of the cohort is that you can generalise from your data. It is almost impossible to get a representative sample. She also stated that we should also consider what was the uniqueness of the 45 & Up study. In her opinion it was the record linkage, in particular with PBS, and also that it was an Australian study and therefore allowed for comparison with US and UK studies. She also mentioned that it was important to put every effort into establishing the cohort before attempting to collect bio. samples. Others commented that the diversity (CALD & rurality) of the NSW population added to the uniqueness of the study.

WORKSHOPS

CANCER WORKSHOP
Facilitator: Associate Professor Rosemary Knight.

Presentation: Professor Jim Bishop, Cancer Institute NSW
Current policy drivers include:

- Increased numbers of cancer patients
    - Can cancers be prevented?
    - Can they be detected earlier?
    - Can we re-design services?
- Increased numbers of cancer survivors
    - Survivorship issues (biased sample – eg more breast cancer than lung cancer survivors)
- Increased cost of health care and indirect costs (eg productivity)

- Potential of the 45 and Up Study:
    - Interplay of cancer risk
    - New prevention strategies
    - Patterns of risky behaviour
    - Balanced duty of care for programs and reporting

Presentation: Associate Professor Freddy Sitas and Dr Marianne Weber, Cancer Council NSW

- The large degree of heterogeneity in NSW (23% of population born outside of Australia) provides great opportunity for etiological research
- Cancer trends in NSW are good but there are pockets of the population that could benefit (eg in relation to country of birth)
- Work program of the Cancer Epidemiology Research Unit at TCCNSW:
    - Smoking (and migrants)
    - Hormonal factors and cancer
    - Determinants of screened / unscreened populations
    - Epidemiology of colorectal polyps
    - Natural history of ‘prostate dysfunction’

- Preliminary work on 45 and Up dataset is exploring smoking rates by country of birth

Discussion

- Priority must be establishing the cohort. Costs should be cut wherever possible to ensure the full mail-out is achieved as soon as possible and the 250,000 participants are recruited quickly. More time can be taken later to process and analyse the data
- Great potential for studies using linked data. Much work is required to ensure 100% linkage (eg to exclude reported deaths from cancer without a cancer notification). For 45 and Up data, initial validation work would include identifying those who report a history of cancer, referring them to the registry for matching, following up on those where no match is found etc. Because good quality data is being collected good linkage is expected but thorough validation should be encouraged. One challenge is how to deal with people with a history of cancer who move overseas; unless they are removed from the dataset they will be 'immortal'

Potential research projects

- Studies of factors that are associated with survival (eg age of diagnosis, treatment); this will be one of the last type of study conducted as it will take time to gather data on etiological factors
- Study of health promotion for survivorship (i.e. if the goal is to change behaviour post-diagnosis). As a cross-sectional study this could be flawed because the behaviour of cohort survivors may not represent all cancer survivors; however, 45 and Up offers a good opportunity to identify participants for a survivorship intervention trial
- Studies of women with a previous breast cancer diagnosis – lifestyles, use of exogenous hormones etc.
- Profiles of people not attending cancer screening (although in 45 and Up a high proportion do screen)
- Identification of populations (including geographical location) of people engaging in behaviours most likely to lead to increased cancer risk
- Genetic profiling using tissue samples (eg paraffin slice). Currently cost is prohibitive; there are some small tissue banks in operation in Australia but these are uncoordinated
- Study of the behaviours of people regarding the improvement of relative risk (i.e. in relation to the amenability of cancers to prevention, early identification, or treatment); eg HPV vaccine (but long lead time required)
- Study of changes over time as the colorectal screening program ratchets up; there is potential to link to the national database over time
- Access to health services, especially regional differences and barriers to access
- Skin cancers – the cohort will have more numbers than any other dataset and it provides a great opportunity to learn more about behaviours in relation to sun exposure
- Interrelationships between mental health conditions and cancer; eg as a prospective study, follow up people with poorer mental health to identify cancer-related outcomes

CARDIOVASCULAR DISEASE WORKSHOP
Facilitator: Associate Professor Emily Banks

Presentation: Ms Julie Anne Mitchell, National Heart Foundation
Priority areas in the 2008-2012 National Heart Foundation Strategic Plan:
- Chest pain
- Women and heart disease
- Access and prevention, especially among indigenous population
- Healthy weight
- Strategic research with partners

The National Heart Foundation has a keen interest in seeing the 45 and Up Study used for cardiovascular disease (CVD) research.

Presentation: Professor Mark Harris, University of NSW
Use of linked data for cardiovascular research
- Multivariate models to explore risk and prescribing and how this association is influenced by other factors
- Variables could include: diagnosis of diabetes, CVD, hypertension, PBS prescribing, age, smoking, alcohol, BMI, hospitalisation, SES, ethnicity, rurality etc.
- Preliminary data show large numbers of participants in each variable.
- Types of research questions including, quality of care in terms of what is prescribed for CVD, trends in prescribing over time, inequalities in prescribing.

Presentation: Dr Emma Heeley, The George Institute
Example of research using data from 45 and Up Study
Around 25,000 men in the Study will report erectile dysfunction
Proposed research
- Are PDES's cardioprotective? Use baseline questionnaire data, RPBS and hospitalisations.
- Is erectile dysfunction an early warning sign for CVD? Use baseline questionnaire data, linked with PBS and/or hospitalisation
- Which factors are associated with erectile dysfunction (e.g. age, medication use)? Using questionnaire data only.

Discussion points
- There is difficulty conducting traditional cardiovascular disease research without information on measures such as blood pressure and lipids. While the protocol for biospecimens and physical measures is being developed, large amounts of resources are required for these.
- Although it is theoretically possible to link to records of blood pressure through the GPRN, this would only cover a small number of GPs
- A high level CVD research champion is needed to stimulate research using 45 Up and develop robust research proposals.
- The group would like the following measures: blood biochemistry (lipids, glucose etc), blood pressure, height, weight, waist circumference, urine. These should be collected and samples stored to be used mainly for nested studies.
- Some members of the group expressed the opinion that researchers are interested in learning about the effects of interventions, rather than about aetiological questions. The 45 and Up Study was seen as useful for health services research.

MENTAL HEATH AND COMORBIDITY WORKSHOP
Facilitator: Professor Gavin Andrews
Presenters: Professor David Clarke, Professor Julie Byles, Dr Tracy Anderson

- Gavin Andrews' study (published in the Lancet) found that co-morbidity of depression with a physical disease was more disabling than any two or more physical diseases combined
- Workshop attendants questioned the validity of measuring depression in a survey; discussion noted that all measures of ill mental health were self reported; that the K10 is a measure of psychological distress, not a proxy for depression or other mental illness
- Question of whether the measure was clinically significant? Discussion noted that mental health is dimensional in nature, and many illnesses, not just mental (such as asthma) have criteria that are not always reliable
- It was noted that the K10 section of the 45 and Up questionnaire could identify people at risk, and could use each person as their own control in follow up studies. Re: missing data, could they be used as a special group – explore correlations, look at their linked data, perhaps invite them to another study/survey?
- Question was raised regarding the percentage of 45 and Up participants with internet access – approx 50%. Suggestion that PC interventions and cost effective treatment could be administered to those at risk. There are people currently being treated over the net for anxiety and depression
- Suggestion was made to use the PHQ9 as it can be administered over the internet, and it would enrich the sample
- Question was raised regarding cross section of population if response rate is only 20%, and that it is possible that small range of those over 95 years are exceptionally fit and healthy. Suggested that the longitudinal data collected over the course of the study will provide further info.
- A suggestion was made to follow up the over 80s sooner rather than waiting 5 years
- Question was raised regarding self-reporting of stress and depression – perhaps the more recent the incident, the more likelihood of reporting; also younger people may feel more inclined to admit to mental health issues than older generations. Could there be a cohort effect, or is it actually representative of the population?
- Recall effects were discussed – a study had been done comparing hospital admissions 4 depression with self reporting 25 years after the incident, and half of the respondents said they had not been hospitalised when in fact they had been.
- It was suggested that retirement information was not sufficiently covered in the study, in terms of what the participant's mental health was before retirement, and specific contributing factors such as own choice or forced, and whether they were prepared for retirement or not. It was noted that the impact of retirement on mental health may not be equal between genders, and different occupations and the nature of the work may have different impacts, e.g. a UK study found that many teachers retired early due to poor mental health. It was suggested that it would be interesting to survey other household members of the participants to enquire about the impact on them.
- Question was asked about the progress of the SEEF study – it was noted that the questionnaire is in the process of being developed with 5 themed committees.

DATA LINKAGE WORKSHOP
Facilitator: Professor Louisa Jorm
Presenters: Pamela Rutledge, Justine Waters, Katie Irvine, Elizabeth Comino

Research ideas using data linkage

- Baseline methodological papers
  - Process: CHeReL and 45 and Up
  - Validation of linkage
  - Quality of data
- Aged care service usage
- Validation of self-report and other within projects?
- Boost indigenous cohort (College GPs)

Other suggestions:

1) Sax Institute to distribute research ideas on website
2) Feedback to build capacity of data repository
3) Explore opportunities for DADHC grants
4) Investigate methodology around self-reported measures in 45 and Up