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The genomic potential of the Aspirin in Reducing Events in the Elderly and Statins in Reducing Events in the Elderly studies

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Abstract

Human genetic studies are continuing to increase in size and scale, but the availability of well-phenotyped longitudinal cohorts remains rare. Significant infrastructure, investment and effort are required to establish and maintain high-quality cohorts with bio-banking, genetic consent and repeated clinical data measurements. Australia currently has two such cohorts established by Monash University as part of community-based clinical trials in the elderly. Both studies involve capture of demographic, mood, cognitive performance, physical function, neuroimaging, audiometry and various clinical data types over an average of 5 years. The ASPirin in Reducing Events in the Elderly (ASPREE) cohort is comprised of 16 703 Australians aged over 70 years and 2411 Americans aged over 65 years – recruited and randomised to either daily low-dose aspirin or placebo to examine the preventative benefit of aspirin on a range of clinical outcomes. The STAtins in Reducing Events in the Elderly (STAREE) study uses a similar model, and is currently recruiting 10 000 men and women aged over 70 years across Australia randomised to either low-dose statins or placebo. Both cohorts involve bio-banking and consent for genetic research, with recruitment through a network of general practitioners in the community. A combination of whole-genome and targeted sequencing approaches will allow gene–phenotype relationships to be explored within the context of detailed longitudinal data. Genetic risk factors for late-onset high-burden conditions, such as cardiovascular disease and dementia will be investigated, plus research into other areas, such as healthy ageing and disease resilience will be possible due to unique phenotypes of health.

Keywords

genomics; public health; epidemiology; biobank

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Genomics, the study of DNA and genomes, has already led to major advances in the areas of cancer medicine,¹ rare disease² and infectious disease³; however, whether it will have comparable impact for the prevention of common, chronic conditions remains to be seen. Most known genetic risk factors for common diseases infer only minimal risk based on current models,^{4,5} bringing into question whether genomic risk will add value over traditional risk factors for common, polygenic diseases, such as cardiovascular disease, diabetes, autoimmune disease and late-onset cancers.⁵

Genetic association studies for complex disease are trending towards increasing sample size to achieve more statistically significant associations,^{6,7} which can sometimes be carried out at the expense of quality phenotyping and longitudinal clinical data collection.⁸ Alternative study designs involving more in-depth clinical profiling may help improve our understanding of gene–phenotype relationships for diseases where hundreds or thousands of genetic variants plus environment factors contribute to disease risk.^{8–10}

The resources required to conduct large-scale longitudinal cohort studies involving deep phenotyping are significant. They necessitate major investment and infrastructure in sample collection, storage, processing, data analysis, bioinformatics and linkage over many years¹¹ and must ensure a consistently high standard of phenotypic and medical data collection. Such cohorts are generally established for epidemiology, rather than for genetics. However, if quality longitudinal studies can involve biobanking to enable genetic measures, they become particularly powerful resources for genetics, allowing the study of many different phenotypes and diseases together without ascertainment bias.^{12–15}

Two significant cohort-based genomic resources are now becoming available in Australia to help provide valuable opportunities to study genetics alongside deep longitudinal phenotyping data. The ASPIrin in Reducing Events in the Elderly (ASPREE) study¹⁶ is a large clinical trial conducted in general medical practices throughout Australia involving high-quality medical data collection accompanied by sample biobanking and consent for genetic analyses. ASPREE is a study of health outcomes in 16 703 Australians aged over 70 years and 2411 Americans aged over 65 years (including in ‘US minorities’) to examine the potential primary prevention benefits of low-dose aspirin in older healthy individuals. ASPREE also acts as a broader epidemiological study of healthy ageing.¹⁶

ASPREE participants’ health is tracked longitudinally over an average of 5 (and up to 7) years capturing detailed clinical events as well as demographic, lifestyle, cognitive, physical function and neuroimaging data. The primary study endpoint is a composite of death, dementia or persistent physical disability with secondary endpoints, including cardiovascular and cerebrovascular disease, stroke, cancer, depression and clinically significant bleeding. All clinical events and dementia are adjudicated by expert committees, ensuring a particularly high standard of phenotypic data quality, and rare clinical research potential not usually seen in genetics and healthy ageing research.

The ASPREE Healthy Ageing biobank is a biorepository of blood, saliva and urine samples collected from more than 13500 ASPREE study participants who consented for medical and genetic research. In addition to these baseline samples, 3-year follow-up blood samples will

be collected from 75 to 80% of biobank participants for longitudinal bio-marker studies. The sample resource will allow molecular data to be integrated into Australia's largest clinical trial.

The STAREE study is a related study of healthy ageing which is a randomised controlled trial of a statin involving 10 000 men and women over 70 years of age also conducted in general medical practices across Australia. The objective of the STAREE study is to determine the effect of statin therapy (40 mg atorvastatin) versus placebo, over an average 5-year treatment period, for the prevention of major cardiovascular events as well as mortality, disability and dementia. STAREE also involves collection of biospecimens and consent for genetic studies, including RNA collection for gene expression analysis.

Together, the ASPREE and STAREE studies will provide the rare opportunity to combine high-quality medical record data with genetic data on large numbers of older Australians, many of whom are still in good health beyond their 70s. This will allow research by Australian and US investigators into genetic risk factors for diseases of ageing, including dementia, cancer, stroke, diabetes and cardiovascular disease. The research can be conducted in a controlled longitudinal research setting where all personal data and results will be de-identified. Genetic data can also be used for the pharmacogenomic analysis of aspirin, statins and other drugs to identify potential biomarkers for drug efficacy and/or adverse reactions within the elderly. The study will also facilitate research into the genetics of healthy ageing and disease resilience by studying those who remain free of disease to an advanced age, even despite possibly carrying what are thought to be pathogenic mutations.¹⁷

The ASPREE and STAREE studies have the potential to become significant resources for public health research internationally, and help drive the field of genetic epidemiology forward to deliver translational impact to address the growing public health challenge of an ageing population. In particular they will offer an unusual opportunity to make genetic measurements on thousands of otherwise healthy individuals, making studies into gene penetrance, genetic resilience and healthy ageing possible.

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