Published by Oxford University Press on behalf of the International Epidemiological Association
International Journal of Epidemiology 2009;38:48–52
doi:10.1093/ije/dyn041

COHORT PROFILE

Cohort Profile: The Health In Men Study (HIMS)

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Accepted 11 February 2008

How did the study come about?

The Health In Men Study (HIMS) arose out of a population-based randomized trial of screening for abdominal aortic aneurysms (AAAs) conducted in Perth, Western Australia in 1996–99.[1,2] Only men aged 65 years and over were recruited into the trial as AAAs are uncommon below this age and are six times more common in men than women. The aim of the trial was to assess whether screening reduced mortality from AAA. Secondary outcomes included assessments of the impact of screening on all-cause mortality and quality of life[3] and a study of the rates of expansion of screen-detected AAAs.[4]

Who is in the sample?

The numbers of participants at each phase of the study are summarized in Figure 1. All men were identified from an electronic copy of the electoral roll, enrolment to vote being compulsory for all Australian adults. The target age range was 65–79 years and the potentially available number of men in Perth (the capital of Western Australia) was about 50 000. Of these, 8801 men were not randomized as they were resident in a satellite town (circa 35 km away from Perth). Based on a sample size calculation, we selected 41 000 men who were resident in Perth and were expected to be aged 65–79 years at the projected mid-point of screening. Men were randomized into invited and control groups of equal size, in strata defined by 5-year age-group and postcode of residence. After exclusion of 2296 men dying prior to invitation, 19 352 men were invited and 12 203 (63.1%) attended for baseline screening. As initial versions of the electoral roll only contained age in 5-year strata, some men over the age of 79 years were included. As a result of this, 725 (5.9%) of attending men were aged 80–83 years at the time of screening. The age strata, country of birth and deaths are shown in Table 1. Analyses of all-cause mortality have revealed evidence of response bias with the participating men experiencing about half the mortality of men who did not attend following invitation.[2]

HIMS was initially the name given to a follow-up survey of surviving men undertaken in 2001–04. However, we now use the acronym for investigations of any men in the original study population. Most research in HIMS involves men who participated in the initial screening for AAA (1996–99) and, in particular the follow-up survey when blood samples were obtained (2001–04). However, some outcomes are assessed in men from the control (non-invited) group from the original trial (Figure 1).

What does HIMS cover?

Apart from measuring the diameter of the infra-renal aorta by ultrasound scanning, the trial represented an opportunity to collect demographic and risk factor data relating to wide range of common health conditions in older men. Whilst the focus of the initial study was AAA and other forms of cardiovascular disease (CVD), the follow-up survey undertaken in 2001–04 expanded the scope to include cognitive function and psycho-social elements of health and well-being. Outcomes of participants are being monitored via the Western Australian Linked Data System (described below). This system allows HIMS to assess fatal and most major non-fatal episodes for an indefinite period into the future, and to place these in the context of significant health events affecting

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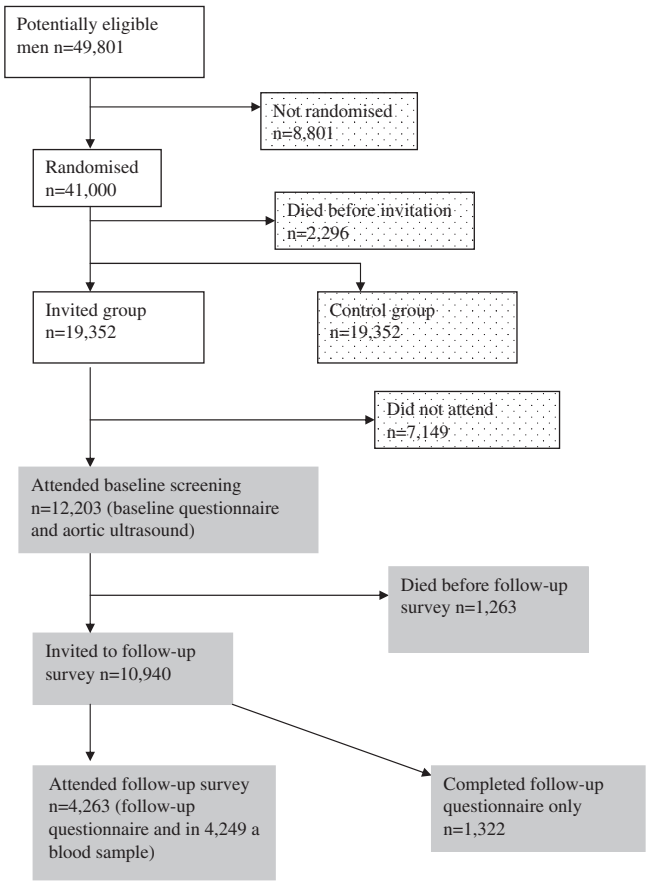

Figure 1 Numbers of men at each phase of recruitment and surveys. Follow-up with identified record linkage (solid grey background) or with de-identified aggregated age-standardized outcomes (stippled background)

participants at any time since the beginning of data collection (which ranges from 1966–81 for the various datasets).

What has been measured?

Baseline survey (1996–99)

Each man completed a questionnaire assessing aspects of history and lifestyle relevant to AAA and CVD: smoking status (never, ex-smoker, current smoker and number of cigarettes/cigars or grams of tobacco per day); birthplace; marital status (never married, now married, separated but not divorced, divorced, widowed, *de facto*); education (never attended school, primary school, some high school, completed high school, completed tertiary degree); alcohol [non-drinker, number of standard drinks (each containing 10 g of alcohol) typically consumed for each day of the week]; addition of salt to food (rarely or never, sometimes, almost always or always); usual type of milk consumed (condensed, full cream, full cream and reduced fat, reduced fat, skim or none, other); frequency of eating meat and fish (each 6 + times/week, 3–5/week, 1–2/week, <1/week, never). A history of, or treatment for Coronary Heart Disease (CHD), hypertension, dyslipidaemia or diabetes, a history of aspirin intake, asthma or bronchitis and family history of CVD. Symptomatic peripheral arterial disease (PAD) was assessed using the Edinburgh Claudication Questionnaire (ECQ).[5] Socio-economic status was estimated using the Socio-Economic Indices For Areas (SEIFA), which were derived by the Australian Bureau of Statistics from a set of demographic factors measured in the quinquennial Census.

The greatest transverse and antero-posterior diameter of the infra-renal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW). Height, weight, BP and circumference at waist and hips were measured by a research nurse. Ankle : brachial pressure index (ABI) was measured in 4351 men.

Table 1 The age strata, country of birth and deaths of men participating in HIMS surveys

Survey dates	Baseline survey April 1996–January 1999	Follow-up survey October 2001–August 2004
Age of survey		
65–69 years	4646	0
70–74 years	4261	1560
75–79 years	2571	1848
>80 years	725	855
Country of birth		
Australia	6718	2641
Northern Europe	3392	1139
Mediterranean	1163	221
Other	930	262
Deaths[a]	3677	444
Median (IQR) age of survivors[a]	80.0 (77.4–83.5)	79.8 (77.3–83.0)

[a]At 26 March 2007.

Follow-up survey (2001–04)

Attending men completed a questionnaire that included: medical history, smoking status (as described earlier), ECQ, current medications, Cambridge Mental State Examination of the Elderly, Family and Friends APGAR Scale, SF-36, Sense of Community, Family and Social Role Scale, Geriatric Depression Scale-15 items, Mini-Mental State Examination and various other psycho-social questions. Height, weight, BP and circumference at waist and hips were measured again. The California Verbal Learning Test was used to assess memory function

in a random sub-sample of 693 men. Blood samples were obtained from 4249 men (fasting in 3328 and non-fasting in 921 men). Cholesterol, HDL, LDL, triglycerides, glucose, creatinine, C-reactive protein (CRP) and homocysteine were all measured on the day of blood sampling. Three aliquots (~0.8 ml) each of sera, EDTA plasma, citrated plasma and two of DNA have been archived at −80°C.

Total testosterone, luteinizing hormone, sex hormone binding globulin, insulin and thyroid stimulating hormone have all been measured using archived sera. Assays of other proteins such as insulin-like growth factor and osteocalcin are planned. A large number of single nucleotide polymorphisms have been assessed using a range of genotyping platforms (details available on request).

Follow-up via the Western Australian linked data system

The Linked Data System in Western Australia brings together name-identified records for all inpatient hospital admissions, all births, all registered cancers (except non-melanocytic skin cancer), all deaths and all public sector mental health services in (but not outside) that State, from the late 1960s onwards (for the mortality and mental health datasets), 1970 onwards (for the morbidity data) and from 1981 (for the cancer registrations).[6] The capacity it offers for longitudinal, population-based research into the health trajectories of individuals is unrivalled in the Southern Hemisphere and duplicated in only a handful of communities in Europe and North America. Within this collection, the electronic records of inpatient admissions include fields for principal and other conditions treated, and, separately, principal and other procedures undertaken. With updated linkages undertaken every 6–12 months, this system allows us to monitor a wide range of fatal and non-fatal outcomes in the cohort.

What is attrition like?

The crude participation fraction at baseline screening was 63.1% (12 203/19 352) although the denominator includes 543 invitations returned to sender and 238 men who were away for the duration of the study. Of the 10 940 surviving men who were invited to the follow-up survey, 4263 (39.0%) attended with an additional 1322 (12.1%) men completing questionnaire only (Figure 1). At the time of writing, we are planning a new postal survey and a telephone interview of surviving participants. Comprehensive follow-up is assured as outcomes can be monitored via the Western Australian Linked Data System and very few residents die outside of the State[7] (see above).[7]

What has it found?

Abdominal aortic aneurysm

As the cohort arose from a trial of screening for AAAs, a large number of the initial publications focused on this condition. The prevalence of AAAs ($\geqslant$30 mm in diameter) was 7.2% (95% CI 6.7%, 7.6%), although only 10% of these AAAs were large enough to consider surgical intervention.[1] We demonstrated that although screening for AAAs reduced the mortality from AAA, the reduction was not significant (mortality ratio 0.61, 95% CI 0.33, 1.11).[2] Other publications report risk factors for AAAs,[8,9] the influence of screening on quality of life measures,[3] and rates of expansion of AAAs.[4,10] In addition, we have recently demonstrated an inverse association between glucose levels and aortic diameter.[11]

Peripheral arterial disease

The baseline survey included assessment of PAD with the ECQ (in 12 203 men) and measurement of ABI (in 4351 men). The prevalence of PAD was 15.6% (95% CI 14.5%, 16.6%) and there was evidence that previous smoking remains a risk of PAD.[12] A randomized controlled trial of 882 men with early PAD revealed that a simple regime of exercise and smoking cessation had the potential to improve walking distance.[13]

Cardiovascular risk

An example of the type of analysis that can be undertaken within HIMS is the novel observation that aortic diameter is an independent marker of subsequent all-cause mortality.[14] The relationship between diameter (measured at the time of screening for AAA, $n = 12\,203$) and subsequent mortality was explored using Cox proportional hazard models. The cumulative all-cause mortality increased in a graded fashion with increasing aortic diameter. Using the diameter interval 19–22 mm as the reference, the adjusted hazard ratio for all-cause mortality rose from 1.26 (95% CI 1.09, 1.44; $P = 0.001$) for aortic diameters of 23–26 mm to 2.38 (95% CI 1.22, 4.61; $P = 0.011$) for aortic diameters of 47–50 mm. Subsequent analysis of causes of death indicates that CVD is the most important cause of the increased mortality (unpublished data).

We have also demonstrated that a simple lifestyle score based on dichotomous answers to eight items (covering smoking, physical activity, alcohol consumption, self-reported BMI and consumption of fish, meat, salt and milk) in the original questionnaire from the AAA trial has considerable predictive significance for mortality from all causes both in men without clinically-evident CVD[15] and those with established vascular symptoms.[16] Over 5 years of follow-up, the mortality ratio for all causes for men with scores below the median compared with above it was 1.3 (95% CI 1.1, 1.5). Provided this pattern of

results persists with longer follow-up, the 'lifestyle score' has the potential to be a very useful health promotion tool, especially as it can be self-administered.

Mental health and cognitive function

We have demonstrated that increasing age, diabetes and regular use of full-cream milk are associated with a 5-year risk of cognitive impairment in older men, whereas mild alcohol consumption and physical activity appear to have a protective effect on cognition.[17] We reported that treatment with B-vitamins decreases total plasma homocysteine by 4 μmol/l on average[18] and reduces the serum concentration of β-amyloid,[19] a peptide thought to play an important role in the pathogenesis of Alzheimer's disease. Our studies have also shown that CVD and risk factors (particularly diabetes, a history of cardiovascular events, elevated triglyceride and homocysteine concentrations) are associated with an increased prevalence of depression (assessed with Geriatric Depression Scale-15 items).[20] Depression in this cohort was also associated with elevated CRP concentration and greater physical comorbidity,[21] with a low concentration of free testosterone being associated with almost a tripling of the risk of depression in older men.[22] Finally, data from HIMS have revealed that education, physical activity and a diet low in saturated fat appear to decrease the risk of poor mental health outcomes after the age of 80 years.[23]

Metabolic and endocrine studies

Analyses of testosterone and free testosterone levels have demonstrated that free testosterone levels are lower, and luteinizing hormone levels higher, in advanced age, mainly due to higher levels of sex hormone binding globulin.[24] There was also an association between higher levels of free testosterone and cognition, although the effect was relatively modest in size.[25] We now plan to assess the effects of lifestyle factors on circulating levels of testosterone, and whether androgen and growth hormone function play important roles in regard to cardiovascular outcomes and mortality.

Genotypic studies

Genetic association studies assessing candidate genes for AAA have recently been published including an example of a collaborative study with replication of associations in other cohorts.[26–28] We have also contributed data to an ongoing meta-analysis of CRP genotype and CHD. Similar analyses with various phenotypic outcomes (e.g. mental health and colon cancer) are planned, and a genome-wide screen is under consideration.

What are the main strengths and weaknesses of HIMS?

Very importantly, HIMS is located in a community served by one of the most comprehensive, electronic health record systems available anywhere. The existence of the Linked Data System means that at entry into HIMS each man had a minimum of 15 years of health records available. We have a very unusual ability to track non-responders ($n = 7149$) and their health experience using this system (Figure 1). Moreover, because it arose from the randomized trial, the HIMS cohort also has a control group that is subject to exactly the same 'surveillance' and therefore provides a ready check on the external validity of any findings related to endpoints recorded within the WA Linked Data System.

Weaknesses are: that the cohort only includes men who were resident in one major metropolitan area; and there is some participation bias as men needed to be able to travel to screening clinics—those who were unwell or immobile and lacked transportation were less likely to attend. Although, some outcomes may be missed in men admitted to hospital or dying outside Western Australia, this is estimated to occur in a small proportion (<1%).[7] Some outcomes cannot be captured by the various administrative databases at our disposal, particularly for conditions that do not result in a hospital admission (e.g. minor strokes). Analyses involving genetic associations may be limited by the number of men from whom blood samples were obtained ($n = 4249$).

What rules govern access to HIMS?

The study has wide-ranging scope for collaborative studies of most aspects of health and illness in older men. We will continue to add biochemical and genotypic data and monitor outcomes in participants via the Western Australian Linked Data System. The HIMS investigators already participate in numerous collaborative studies. Examples include Asia Pacific Cohort Studies Collaboration,[29] Collaborative Aneurysm Screening Study Group,[30] Australian Longitudinal Study of Women's Health (http://www.alswh.org.au/) and the Ankle Brachial Index Collaboration. Potential collaborators are invited to contact the HIMS investigators via http://www.wacha.org.au/.

Acknowledgements

Special thanks to all men who participated in the Western Australian Abdominal Aortic Aneurysm Programme. Thanks to the staff and investigators of the original screening trial. The authors are also grateful for assistance received from the State Electoral Commission, the Australian Bureau of Statistics, the Registrar General of Births, Deaths and Marriages, and the Data Linkage Unit of the Health Department of Western Australia, and to

hospitals in Perth for providing space in which to conduct screening. The research was supported by NHMRC Project Grants 964145, 139093, 403963 and 455811 with additional funding from the National Heart Foundation and the Western Australian Health Promotion Foundation (Healthway).

Conflict of interest: None declared.

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