

COHORT PROFILE

Cohort profile: The Hertfordshire Ageing Study (HAS)

H E Syddall,* S J Simmonds, H J Martin, Clare Watson, E M Dennison, C Cooper and A Aihie Sayer;
for the Hertfordshire Cohort Study Group

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How did the study come about?

We have previously described the discovery of a unique set of infant records collected in Hertfordshire between 1911 and 1948.¹ The historical data for births between 1911 and 1930 were linked to the NHS central register and showed that small size at birth and during infancy was associated with increased risk of cardiovascular mortality in men and women.^{2,3} These were the first studies based on individual data to suggest that adverse environmental influences acting *in utero* and during infancy might increase the risk of cardiovascular disease mortality in later life. Detailed physiological investigations of surviving men and women born in Hertfordshire between 1920 and 1930 and still living there in the early 1990s were subsequently conducted and allowed investigation of morbidity. Studies based on men and women resident in East Hertfordshire demonstrated that small size at birth and during infancy was associated with increased risk of developing coronary heart disease and type II diabetes mellitus,^{4,5} the metabolic syndrome and insulin resistance⁶ and osteoporosis.⁷ During the same time period (1994–95), 717 men and women resident in North Hertfordshire attended clinics where a wide range of markers of ageing were characterized. These clinics comprised the first follow-up of what will herein be referred to as the Hertfordshire Ageing Study (HAS). This study was the first to demonstrate that size in early life was associated with markers of ageing in older people.⁸

In 2004, mortality studies were extended to include the whole 1911–39 birth cohort⁹ and a second follow-up of the HAS cohort was carried out ~10 years after the first one. Fieldwork for the second HAS follow-up

was conducted at the same time as fieldwork for the larger Hertfordshire Cohort Study¹ (HCS) which comprised 3000 younger men and women who were born in Hertfordshire between 1931 and 1939 and who still lived in the county. The HCS and HAS birth cohorts are completely distinct (with birth years ranging 1931–39 for HCS and 1920–30 for HAS) and have different, although related, research objectives. The principal objective of the HCS is to evaluate the interactions between the genome; the intra-uterine and early post-natal environment; and adult diet and lifestyle in the aetiology of chronic diseases in later life (cardiovascular disease, type II diabetes mellitus and obesity; osteoporosis, osteoarthritis and sarcopenia). The principal objective of the HAS (as described below) is to examine life course influences on healthy ageing, with sarcopenia, frailty, falls, physical performance and cognitive function as the principal outcomes of interest. The rest of this article describes the HAS in detail.

Principal investigators and funding

The HAS was established by Prof. Avan Aihie Sayer (principal investigator) and members of the HCS Group based at the Medical Research Council Epidemiology Resource Centre (MRC ERC), University of Southampton. The Medical Research Council and the University of Southampton were the principal sources of funding.

What does the HAS cover?

The principal objective of the HAS is to examine life course influences on healthy ageing. The outcomes of interest are sarcopenia, frailty, falls, physical performance and cognitive function. The main potential determinants of healthy ageing under investigation are intra-uterine and post-natal size and growth, genetic characteristics and adult physical activity, diet, lifestyle and socioeconomic status. Details of the data collection are provided later in this article.

MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK.

* Corresponding author. E-mail: hes@mrc.soton.ac.uk

Who is in the sample?

The recruitment of participants to the HAS is shown in Figure 1. The ledgers contained records for 6803 live singleton births in North Hertfordshire between 1920 and 1930. The details of these boys and girls were sent for tracing by the National Health Service Central Register (NHSCR) in Southport and 3477 (51.1%) were traced and flagged for ongoing follow-up, including notification of deaths. In 1994, 2621 (75.4%) men and women were identified as still alive in the UK, of whom 1428 (54.5%) were resident in North Hertfordshire; these men and women comprised the target population for the first HAS follow-up. Eight hundred and twenty-four (57.7%) men and women agreed to a home interview with a trained research nurse and 717 (87.0%) subsequently attended a clinic for detailed investigations. Ethical approval for HAS was obtained from the Bedfordshire and Hertfordshire Local Research Ethics Committee and all subjects have given written informed consent.

Response bias between the HAS target population and participation in the first HAS follow-up

Birth weight and weight at 1 year of age were similar in men and women in the HAS target population but who did not participate in the first follow-up home interview [mean and standard deviation (SD) birth

weight and weight at 1 year: 3.5 kg (0.6), 10.2 kg (1.1) in 318 men and 3.3 kg (0.5) and 9.6 kg (1.0) in 286 women], and among those who were in the target population and did participate in the home interview [mean (SD) birth weight and weight at 1 year: 3.5 kg (0.5), 10.2 kg (1.2) in 459 men and 3.4 kg (0.5) and 9.7 kg (1.0) in 365 women]. In addition, weights at birth and 1 year of age were comparable between men and women who only participated in the first follow-up home interview, or who participated in the home interview and clinic (data not shown).

To further characterize response bias in HAS a short postal questionnaire was mailed to the 604 men and women in the HAS target population who declined the invitation to participate in the study. Two hundred and eighty-six (47%) of these 'non-responders' returned the questionnaire and their characteristics are contrasted with those of the 717 HAS follow-up 1 clinic participants in Table 1. Male 'non-responders' were: more likely to have memory problems; less likely to be of a high social class; and were more likely to state that they felt average rather than young for their age, than participants in the HAS follow-up 1 clinic. Female 'non-responders' were: more likely to have had a heart attack; less likely to have ever smoked; and were more likely to state that they felt old or average rather than young for their age, than participants in the HAS follow-up 1 clinic.

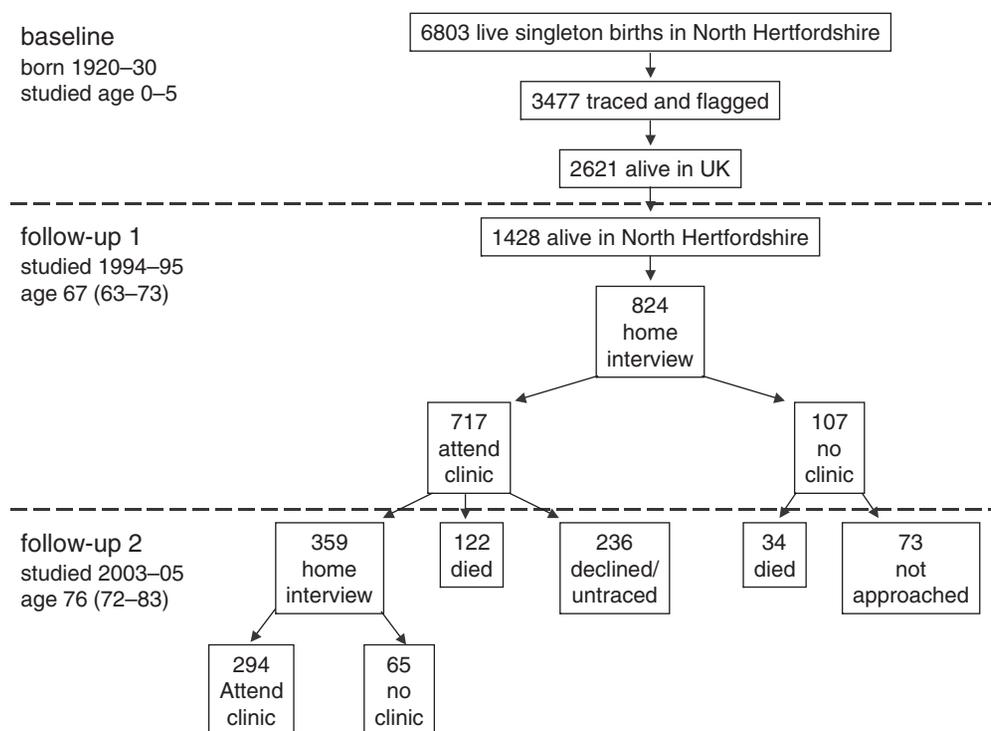


Figure 1 Recruitment of Hertfordshire Ageing Study participants

Table 1 Characteristics of HAS follow-up 1 non-responders vs clinic participants

<i>N</i> (%)	Men		Women	
	Non-responder (<i>n</i> = 139)	Took part in clinic (<i>n</i> = 411)	Non-responder (<i>n</i> = 147)	Took part in clinic (<i>n</i> = 306)
Age (years) ^a	67.3 (2.6)	67.5 (2.4)	67.0 (2.2)	67.5 (2.2)
	<i>P</i> = 0.46		<i>P</i> = 0.05	
How old you feel for your age				
Young	44 (31.4)	238 (57.9)	53 (36.3)	172 (56.2)
Old	3 (2.1)	8 (2.0)	15 (10.3)	7 (2.3)
Average	93 (66.4)	165 (40.2)	78 (53.4)	127 (41.5)
	<i>P</i> < 0.001		<i>P</i> < 0.001	
Ever been diagnosed by a doctor with				
Heart attack	17 (12.4)	53 (13.2)	13 (9.0)	9 (3.0)
	<i>P</i> = 0.82		<i>P</i> = 0.005	
High blood pressure	45 (32.4)	115 (28.4)	62 (43.7)	106 (35.1)
	<i>P</i> = 0.37		<i>P</i> = 0.08	
Under active thyroid	1 (0.7)	2 (0.5)	8 (5.6)	19 (6.3)
	<i>P</i> = 0.74		<i>P</i> = 0.77	
Over active thyroid	2 (1.5)	4 (1.0)	4 (2.8)	17 (5.7)
	<i>P</i> = 0.64		<i>P</i> = 0.20	
Memory problems	22 (15.8)	9 (2.2)	6 (4.2)	5 (1.6)
	<i>P</i> < 0.001		<i>P</i> = 0.10	
Low mood	17 (12.2)	43 (10.5)	24 (17.3)	62 (20.3)
	<i>P</i> = 0.56		<i>P</i> = 0.46	
Glaucoma	5 (3.6)	7 (1.7)	2 (1.4)	5 (1.6)
	<i>P</i> = 0.19		<i>P</i> = 0.85	
Cataract	4 (2.9)	31 (7.6)	12 (8.5)	41 (13.4)
	<i>P</i> = 0.05		<i>P</i> = 0.13	
Fracture	8 (5.8)	30 (7.3)	20 (14.2)	60 (19.6)
	<i>P</i> = 0.54		<i>P</i> = 0.17	
Social Class I or II ^b	23 (19.8)	129 (31.6)	30 (28.3)	89 (29.5)
	<i>P</i> = 0.02		<i>P</i> = 0.67	
Ever smoked	94 (67.6)	309 (75.2)	42 (29.0)	161 (52.6)
	<i>P</i> = 0.08		<i>P</i> = 0.001	

^aMean (SD).^bClasses I (professional) and II (managerial and technical) of the OPCS SOC90 classification of social class, coded from most recent full time occupation for men and never married women, and husband's most recent full time occupation for ever married women. *P*-values for differences in characteristics between non-responders and clinic participants were obtained from two-sample *t*-tests for age, and from chi-squared tests for all other variables.

How often have they been followed up?

Figure 1 shows that the first HAS follow-up was conducted in 1994–95 when the participants ranged in age from 63 to 73 years (mean 67). The cohort is flagged with NHSCR for ongoing notification of deaths, but the second formal follow-up was conducted in 2003–05 after a median time of 9 years between follow-ups (range 8.2–10.0 years) when

participating members of the cohort were aged 72–83 years (mean 76).

What is attrition like?

Figure 1 shows that 359 (50.0%) of the men and women who participated in the first follow-up also took part in the home interview for the second one. One hundred and twenty-two (17.0%) men and

women who participated in the first follow-up had died before the time of the second one. In addition, 236 (32.9%) men and women were lost to follow-up owing to failure to trace them across the intervening period ($n=55$), or because the individual was traced but declined the invitation to take part in the second follow-up ($n=181$).

Response bias between the first and second HAS follow-ups

The ageing, medical, lifestyle and socioeconomic characteristics of the cohort at the first follow-up were compared according to subsequent mortality status between follow-ups. Unsurprisingly, among men, mortality in the intervening period was associated with: poorer cognition (AH4 and Mill Hill); poorer grip strength; greater likelihood of having no teeth; and a higher prevalence of smoking, memory problems, fracture since the age of 50 years and slow walking speed at the first follow-up (data not shown). Among women, mortality was associated with: somewhat poorer cognition on the AH4 and Mill Hill tests; a higher hearing threshold; and a poorer assessment of how the woman felt for her age at the first follow-up (data not shown).

We also examined response bias by contrasting the follow-up 1 characteristics of surviving men and women at the time of recruitment for follow-up 2 ($n=595$) according to whether ($n=359$) or not ($n=236$) they agreed to participate in follow-up 2. Among surviving men, higher social class, better cognition (AH4 and Mill Hill) and a greater number of teeth at follow-up 1 were associated with participation in follow-up 2 (data not shown). Among surviving women, the only characteristic from follow-up 1 which was associated with agreement to participate in follow-up 2 was better cognition (data not shown).

Comparison of participants in the second HAS follow-up and the 2005 Health Survey for England

We have described attrition and response bias at all stages of the HAS study and, as in any epidemiological study, the representativeness of the participants in the second HAS follow-up is open to question, not least because we have unsurprisingly demonstrated the presence of a healthy participant/survivor bias in HAS. We have addressed this by comparing the ageing characteristics of participants in the second HAS follow-up with those in the nationally representative Health Survey for England (HSE).

We accessed the 2005 HSE dataset¹⁰ (www.data-archive.ac.uk). We restricted the HSE dataset to match the age range of participants in the second HAS follow-up and focused attention on ageing markers that were assessed using comparable questionnaire items and measurement protocols in the two studies (namely grip strength, falls in the past year, prescribed medications and chair rises time).

The ageing characteristics of the second HAS follow-up and HSE study populations were compared using *t*, Mann–Whitney and chi-squared tests. Analyses were carried out using Stata 10.¹¹

Overall, the ageing characteristics of the participants in HAS and HSE were broadly comparable. Table 2 shows that the prevalence of falls in the past year, and number of prescribed medications, were not significantly different between participants in HAS and HSE. Grip strength was slightly higher among the HAS participants, but this could have been partly due to use of the Jamar dynamometer in HAS and the Smedley in HSE. Finally, chair rises times were slightly slower in HAS than HSE. Hence, overall there was no evidence to suggest that participants in HAS were consistently more or less aged than their counterparts in the HSE.

What has been measured?

Table 3 outlines the extensive range of ageing, medical, lifestyle and socioeconomic data available in the HAS cohort study. The characteristics of the participants in the follow-up 1 home interview ($n=824$) and clinic ($n=717$) have been described previously.⁸

What has it found? Key findings and publications

The first HAS follow-up showed that lower birth weight was related to sarcopenia⁸ in later life, and lower weight at 1 year of age was related to sarcopenia, lens opacity, skin thickness and hearing threshold.⁸ This phase of the study also demonstrated that different systems of the same individual do not age together, suggesting that further research was, and still is, needed to identify the different processes underlying ageing.¹² Further work explored whether chronological age or grip strength might function as useful single markers of frailty¹³ and concluded that, within the relatively narrow age range studied, grip strength was associated with more markers of frailty than chronological age; raising the possibility that grip strength might serve as a useful marker of frailty in clinical practice. The first HAS follow-up included a detailed eye examination (visual acuity using LogMAR chart; intra-ocular pressure using tonometry and nuclear lens opacity using LOCSIII grading and retinal photography). These data were used to demonstrate that reduced growth in the first year of life was associated with age-related nuclear lens opacities¹⁴ and retinal vasculature¹⁵ but no associations were identified between early size and growth and intra-ocular pressure¹⁶ or visual acuity.¹⁷ Finally, analysis of HAS follow-up 1 data showed that polymorphism of the IGF2 gene and birth weight have independent effects on adult grip strength in men.¹⁸

Table 2 Characteristics of participants in the HAS second follow-up in comparison with those in the HSE

Summary statistics by study	Men		Women	
	HSE	HAS	HSE	HAS
Age (years) ^a	76.3 (3.0) <i>n</i> = 873	76.2 (2.4) <i>n</i> = 208	76.6 (3.2) <i>n</i> = 1097	75.8 (2.1) <i>n</i> = 151
	<i>P</i> = 0.60		<i>P</i> = 0.002	
Grip strength (kg) ^a	34.7 (7.4) <i>n</i> = 629	38.4 (8.1) <i>n</i> = 172	20.4 (5.4) <i>n</i> = 747	23.7 (6.6) <i>n</i> = 120
	<i>P</i> < 0.0001		<i>P</i> < 0.0001	
Falls in the past year ^b	191 (21.9) <i>n</i> = 873	50 (24.2) <i>n</i> = 207	323 (29.5) <i>n</i> = 1095	50 (33.1) <i>n</i> = 151
	<i>P</i> = 0.48		<i>P</i> = 0.36	
Number of prescribed medications ^c	3 (2,6) <i>n</i> = 649	4 (2,6) <i>n</i> = 208	3 (1,5) <i>n</i> = 782	3 (2,5) <i>n</i> = 151
	<i>P</i> = 0.92		<i>P</i> = 0.54	
Time to complete five chair rises (s) ^c	13.0 (10.9,16.3) <i>n</i> = 502	18.4 (15.8,21.9) <i>n</i> = 162	13.9 (11.2,17.2) <i>n</i> = 162	20.1 (17.1,24.1) <i>n</i> = 110
	<i>P</i> < 0.0001		<i>P</i> < 0.0001	

^aMean and SD.^bNumber and percentage.^cMedian and interquartile range.

P-values for comparisons between study participants were obtained from two-sample *t*-tests for age and grip strength, from the chi-squared test for falls in the past year, and the Mann–Whitney test for prescribed medications and chair rises time. Adjustment for age made no substantive difference to the findings.

Preparation of the HAS follow-up 2 dataset was completed in 2007 and analyses are currently underway. The principal purpose of ongoing research using these data is to examine life course influences on healthy ageing, with a particular focus on sarcopenia, frailty, physical performance, cognitive function and falls as the outcomes of interest, and intra-uterine and post-natal size and growth, genetic characteristics, and adult physical activity, diet, lifestyle and socioeconomic status as potential determinants of healthy ageing.

What are the main strengths and weaknesses?

Strengths

First, a detailed ageing, medical, lifestyle and socio-economic characterization of HAS participants is available, including data for two follow-ups in later life. HAS therefore provides the opportunity to explore lifecourse determinants of both cross-sectional ageing markers and longitudinal rates of ageing. Secondly, sera are stored for future measurements and DNA has been extracted. Thirdly, prospectively collected data on birth weight, weight at 1 year and infant feeding and illnesses, in a cohort who are now aged,

are a unique resource for examining lifecourse influences on healthy ageing. Fourthly, follow-up for mortality is ongoing and follow-up for incident clinical events is feasible. Fifthly, survivor and responder biases mean that the cohort are no longer representative of the wider HAS target population, but the participants do nonetheless constitute a group of men and women who are ageing relatively successfully and in whom the determinants of healthy ageing can be studied. Lastly, all measurements were made by a trained research team working to strict study protocols. Data entry, record keeping, computer processing and statistical analyses have been carried out to an exceptionally high standard and an experienced multidisciplinary research team has ensured preparation of a high quality research database. Overall, the HAS constitutes a high quality resource with which to explore lifecourse determinants of healthy ageing.

Weaknesses

First, HAS participants are local to Hertfordshire and losses have occurred at several stages of follow-up (Figure 1). However, we have previously shown that mortality patterns in the wider Hertfordshire cohort are broadly similar to England and Wales as a whole⁹ and, where comparison was possible, the ageing characteristics of HAS participants are broadly

Table 3 Data available from the HAS baseline and follow-ups

	Baseline	Follow-up 1	Follow-up 2
Year	1920–30	1994–95	2003–05
Age	0–5	63–73	72–83
<i>n</i>	2621	824/717 ^m	359/294 ⁿ
Early life measures			
Weight at birth	✓		
Method of infant feeding	✓		
Weight at 1 year of age	✓		
Illnesses and development to age 5	✓		
Ageing markers			
Grip strength (kg)		✓ ^a	✓ ^b
Cognitive function			
AH4 IQ and Mill Hill vocabulary tests		✓	✓
Abbreviated mental test and mini mental state exam			✓
Skin thickness ^c		✓	
Eye examination			
Visual acuity		✓	✓
Intraocular pressure, macular degeneration, lens opacity		✓	
Audiometry ^d		✓	✓
Falls in the past year			✓
Frailty ^c			✓
Medical characteristics			
Anthropometry			
Height, weight, waist and hip circumferences		✓	✓
Skinfolds (triceps, biceps, subscapular, suprailiac)			✓
Prescribed medication		✓	✓
Blood pressure ^f		✓	✓
Blood samples		✓ ^g	✓ ^h
Stored for posterity		✓	✓
Extracted DNA		✓	✓
Cardiovascular symptoms ⁱ		✓	✓
Lung function: FEV ₁ and FVC ^j			✓
Respiratory symptoms		✓	✓
Urine samples			✓
Hand examination for osteoarthritis			✓
Reproductive history		✓	✓
SF36 self assessed health			✓

(continued)

similar to those in the nationally representative HSE (Table 2). On this basis, we suggest that it is not unreasonable to generalize results from HAS to the wider population of older men and women in England. Secondly, ‘healthy’ survivor and responder biases were apparent in HAS; this was unsurprising.^{19,20} Such response bias would only be a major concern if the relationships between potential

lifecourse determinants and ageing outcomes differed systematically in men and women who participated fully in HAS and those who did not; this seems unlikely. Thirdly, the cohort is fairly small and the number of men and women available for future follow-ups will inevitably decrease over time. However, the HAS database is a rich research resource as it stands and will inform studies of ageing in

Table 3 Continued

	Baseline	Follow-up 1	Follow-up 2
Lifestyle, socioeconomic characteristics and physical performance			
Social class ^k		✓	✓
Diet assessed by food frequency questionnaire			✓
Physical performance			
Questionnaire assessment		✓	✓
Battery of tests ^l			✓
Smoking and alcohol habit		✓	✓
Occupational history		✓	✓

^aHarpenden hand grip dynamometer.

^bJamar hand grip dynamometer.

^cDermotronics DM70 A-scan ultrasound system.

^dHughson Westlake method.

^eFried, Townsend and Strawbridge scores.

^fDinamap recorder.

^gRandom.

^hFasted.

ⁱIncluding Rose questionnaire.

^jMicro spirometer, MicroMedical.

^kOPCS SOC90 classification of social class, coded from most recent full time occupation for men and never married women, and husband's most recent full time occupation for ever married women.

^lComprising quadriceps strength, timed 6 m up-and-go test, timed 3 m walk, chair rises, timed one-legged stand and functional reach test.

^m824 men and women participated in the follow-up 1 home interview and 717 participated in the clinic.

ⁿ359 men and women participated in the follow-up 2 home interview and 294 participated in the clinic.

younger birth cohorts such as the HCS¹ and the National Survey of Health and Development (the 1946 birth cohort).²¹ Fourthly, birth weight is only a proxy for adaptations that a foetus may make to its body's structure, physiology and metabolism in response to undernutrition *in utero*. Finally, with the benefit of hindsight it would have been desirable to include a broader panel of items that were measured at both follow-ups, in particular to have asked about falls, SF-36 self-assessed health, physical activity and performance at the first HAS follow-up. However, research themes develop and are in themselves informed by previous studies; hopefully our experience will help future researchers to decide which measurements to include in their studies.

Data access and further information

The HCS Group has a long and successful history of conducting collaborative research^{5,14,22–24} and we welcome specific and detailed proposals for new collaborations. Initial enquiries should be made to Prof. Avan Aihie Sayer (Principal Investigator, E-mail: aas@mrc.soton.ac.uk). Further information about the research work conducted by the MRC ERC, including the HAS and the HCS, may be found on the MRC ERC website (<http://www.mrc.soton.ac.uk>) and an information booklet is available on request.

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Conflict of interest: None declared.

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