
COHORT PROFILE

Cohort Profile: Updating the cohort profile for the MRC National Survey of Health and Development: a new clinic-based data collection for ageing research

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The MRC National Survey of Health and Development: how did the latest NSHD data collection come about?

In a previously published cohort profile,¹ we showed how the MRC National Survey of Health and Development (NSHD), the oldest of the British birth cohort studies, has played an important role in identifying the early origins of adult health and function. The study has a wealth of existing prospective data from birth; and with study members now in their early sixties and approaching conventional retirement age, the NSHD offers the opportunity to investigate how lifetime experience and exposures affect the chance of healthy ageing and reduction of functional decline and chronic disease in later life.

Ageing populations, and the heterogeneity observed among ageing individuals, pose a grand challenge to society. We need to understand better how factors acting across the whole of life can affect the chance of living a long, healthy and independent life.^{2,3} The

NSHD, one of the UK's rich set of longitudinal cohort resources, facilitates a life course approach to the study of ageing, a strategic priority of the Medical Research Council⁴ and the other UK research councils and funders.^{5–7} Evidence is accumulating from the NSHD and from other cohort studies with information from birth, infancy or childhood that adult function and age-related chronic disease have their origins in early life experience and environment and share common risk factors operating across the life course.^{8–13} There is a growing consensus that biological ageing (a progressive, generalized impairment of function resulting in a loss of adaptive response to life challenges) is caused by the rate of accumulation of molecular and cellular damage from the beginning of life.¹⁴ Modifiable factors (such as nutrition and physical activity) and non-modifiable or random factors acting across the life course can alter exposure to sources of damage, and the effectiveness of body systems for maintenance and repair.

The MRC Unit for Lifelong Health and Ageing (LHA) was established in 2008 to maximize the scientific potential of the NSHD and develop it into an

interdisciplinary study of ageing. The LHA research team and their scientific collaborators secured MRC funding to invite study members to take part in their first adult clinic-based data collection to obtain new ageing outcomes, as well as repeat measures of health, function and life circumstances, previously collected by research nurses at home visits. Collection of data took place in 2006–07 in a feasibility study on 10% of the NSHD sample living near the Wellcome Trust Clinical Research Facility (CRF) Manchester, and since 2008 has been taking place on the remainder of the sample at five other UK CRFs (due for completion March 2011).

What does the follow-up at 60–64 years cover and what will be the new areas of research?

The ageing outcomes in the latest NSHD follow-up were chosen to facilitate the testing of life course hypotheses that capitalized on the existing study data, and because they represented important public health problems or intermediate markers of such problems thought to be potentially modifiable. Quantitative ageing traits were preferred over binary outcomes as they provide greater power for analysis, which is important given that the sample contains less than 3500 study members still alive and living in Britain. The choice of outcomes also took into consideration whether the measures would be sufficiently attractive to induce study members in their early sixties to travel a considerable distance for a clinical assessment.

For this data collection between ages 60 and 64 years, we chose to focus on physical and cognitive capability, the capacity to undertake the physical and mental tasks of daily living, as measured by physical performance tests (such as grip strength, chair rises, standing balance) and cognitive performance tests (such as verbal memory and information processing). These tests reflect underlying ageing processes rather than specific diseases *per se*; are the foundation for continued independence and quality of life, as we grow older; and predict future risk of disability, disease, morbidity and mortality.^{15–18}

We also chose to study the structure and function of musculoskeletal and cardiovascular (CV) body systems because age-related changes in these systems threaten capability and account for a major proportion of the disease burden in the ageing population and because there may be opportunities to delay, if not reverse, adverse biological changes. We hypothesize that together these ageing outcomes co-vary in ways that have important practical implications for daily living, and for understanding the ageing process, the development of frailty, disease and longevity.

The existing life course prospective data make this cohort particularly suited to test several hypotheses,

namely: (i) early as well as adult life exposures and risks impact on these aspects of ageing; and (ii) exposure to earlier sources of risk (from gestation to early adulthood) adds substantially to, or is dependent on, the burden of mid-life risk. Our conceptual framework is that NSHD data on earlier life characteristics (such as physical growth and cognitive development, adolescent behaviour and temperament and lifetime socio-economic environment) and on adult functional trajectories (such as changes in blood pressure, lung function and body size) and repeat measures of health behaviours (such as diet, smoking and physical activity) relate to these ageing outcomes via various biological, psychological and social pathways.

The study has a wealth of life course data to elucidate psychological and social pathways. A priority of this data collection was to obtain new assessments of well-being and quality of life at an age when social roles may be rapidly changing (for example, the supervision of grandchildren), and when retirement, an important life transition, is taking place.

A previous study of this cohort at age 53 years collected blood biomarker information on aspects of metabolic function (HbA1c, total and high-density lipoprotein, triglycerides), and extracted DNA to be used for genotyping and measures of telomere length. Another priority was, therefore, to collect fasting blood and overnight urine samples to facilitate further study of biological pathways linking lifetime risk factors to our ageing outcomes. Of particular interest are markers of dysregulation of homeostatic equilibrium hypothesized to underlie musculoskeletal, CV and cognitive ageing and other aspects of functional decline. They include markers of chronic inflammation, adipocyte, renal and hepatic function and neuro-endocrine function (such as insulin growth factors, cortisol, thyroid function and heart rate variability).

The new data collection was designed to allow LHA scientists and their expert collaborators to meet the objectives of LHA's integrated research programmes (www.nshd.mrc.ac.uk). It also enhances the NSHD resource for the wider scientific community (see below).

Who is in the sample?

The MRC NSHD is the oldest of the UK national birth cohort studies and is based on a nationally representative sample of 5362 births out of all the single, legitimate births that took place in 1 week in March 1946 in England, Scotland and Wales.¹⁹ The whole sample has been followed up 23 times previously, and, at the last visit in 1999, the sample remained broadly representative of native born British men and women.¹⁹

For the new data collection, the initial target sample at the age of 60 years was 3116, excluding 337 who remained untraced despite attempts to trace study members through the health authorities in 2005. Of

the remainder of the original cohort of 5362, 636 had died, 604 had emigrated and 669 were prior refusals.

To accommodate our scattered geographical sample, we chose the CRFs in Manchester, Edinburgh, Birmingham and Cardiff, as well as two CRFs in London, and allocated the target sample to the nearest facility. These CRFs offer high-quality research environments within or close to acute hospital facilities. The NSHD data collection was the first co-ordinated data collection across these clinical facilities.

A 10% sample ($n=348$) of traced and untraced study members was selected for a feasibility study. This was a stratified random sample selected from all target study members whose last known address was closest to the Wellcome Trust Clinical Research Facility (WTCRF) Manchester. The target sample was stratified into those living ≤ 40 miles from the WTCRF Manchester and those living further away with equal numbers being sampled from each group. The main aims of the feasibility study at the WTCRF Manchester were to test: (i) what proportion of the sample would be successfully contacted; (ii) whether study members were prepared to come to a clinic for an assessment and to estimate the overall clinic response rate to within $\pm 5\%$; (iii) whether distance from the clinic was a deterrent to attendance; and (iv) satisfaction with the clinic visit and compliance with the various tests. The feasibility study, therefore, had to involve study members who have a lifelong experience of being part of the study as their response was likely to be different from other members of the population.

What has been measured?

An invitation to attend a clinic at 08.00 h on a specific day was sent out by CRF staff with an accompanying information brochure. Before the visit, a trained research nurse contacted the study member by telephone to discuss any concerns (health, regular medication, fasting etc.). Instructions about the visit and how to collect the overnight urine sample, along with urine collection equipment and a pre-assessment questionnaire, were posted to the study members before the visit.

Study members unwilling or unable to travel to the CRF were offered an alternative home visit, which had fewer assessments. Collection of other information was achieved by an initial postal questionnaire to update socio-demographic, socio-economic and medical information, sent ~ 2 months before the CRF visits began; a pre-assessment questionnaire to capture information on everyday function, attitudes and life events, sent ahead and collected on the day of the visit; and through dietary diaries and activity monitors in the days following the visit.

The measures collected are shown in Table 1. The supplementary data available at *IJE* online describe the main fieldwork processes and the data acquisition

and duty of care protocols. A 4-day training programme and 60-page training manual for the research nurses and the technicians were designed and implemented by the MRC LHA and Human Nutrition Research (HNR) fieldwork teams and their key collaborators.

Feedback to participants and their general practitioners (GPs) about clinically relevant results is summarized in Table 2 and detailed in the supplementary data available at *IJE* online.

Ethical approval was given by the Central Manchester Research Ethics Committee for the data collection taking place in Manchester, Birmingham, Cardiff and London. Ethical approval was given by the Scottish A Research Ethics Committee for the data collection taking place in Edinburgh. These approvals covered the extensive duty of care protocols that were needed because of the clinical feedback from the assessments.

What is attrition like?

Manchester feasibility sample

The response in the feasibility sample is shown in Table 3. Within the feasibility target sample of 348, the postal questionnaire was returned undelivered for 13 because the study member was no longer at the address, and 3 were found to have recently died. Of the remaining sample of 332, 276 (83%) completed a postal questionnaire.

The valid target sample for the clinic assessment of the feasibility study excluded 5 who had moved outside the catchment area, 3 who died before the visit and 13 where the clinic invitations were returned undelivered, or there was no response either to two invitations or to recent birthday cards and repeated attempts by CRF staff to make contact by telephone failed. Of the remaining sample of 311, 241 (78%) participated in a clinic or home visit: 190 (62.1%) attended the CRF, 51 (16.4%) had a home visit and a further 7 (2.3%) completed the pre-assessment questionnaire only. In total, 298 (85.6% of the original target sample for the feasibility study) provided some information to the research team.

Information from the feasibility study was used to estimate the number of expected visits for the main study, and for statistical power calculations. Our estimated overall clinic response rate was 62.1% with a 95% confidence interval of 57.7–67.5%.

In the feasibility study, there was no difference in the overall response rate depending on distance from the clinic (Table 4). However, distance from the clinic had a modest effect on the choice of clinic or home visit; of those having a visit, 81% of those living within 40 miles of the clinic attended the clinic compared with 71% of those living further than 40 miles away ($P=0.06$). There were no differences in overall response, or in the choice of a clinic or home visit, by

Table 1 Measurements taken in the NSHD at the age of 60–64 years

CV assessment	<p>Vascular structure and function: carotid intima-medial thickness (IMT) and arterial distensibility (GE Vivid-I), carotid/femoral pulse wave velocity (Vicorder) and central blood pressure and pulse wave analysis (Sphygmocor)</p> <p>Cardiac structure and function: echocardiography (GE Vivid-I). Images from parasternal long axis and short axis views, apical 5-chamber, 4-chamber, 3-chamber, 2-chamber and aortic views (plus conventional and tissue Doppler in 4-chamber view).</p> <p>Brachial blood pressure (Omron HEM-705), 12 lead ECG (Burdick Eclipse 850i), including 6 min heart rate and respiration recordings by ECG for heart rate variability measurements.</p>
Musculoskeletal assessment	<p>DXA (Hologic QDR 4500 Discovery): hip (total, femoral neck, trochanter, Ward's), lumbar spine (L1-4), whole body and region BMD, fat and lean mass, vertebral fracture assessment, aortic calcification score.</p> <p>pQCT (Stratec XCT 2000) radius: 4% site (trabecular, cortical and subcortical BMD), 50% site (endosteal/periosteal circumference, cortical CS area and thickness, BMC and BMD, CS muscle and fat area, stress strain index, moment of inertia).</p>
Tests of functional capacity, biological function and anthropometric measures	<p>Verbal memory, search speed and concentration, simple and choice reaction time, standing balance, grip strength, chair rises, get up and go test, spirometry.</p> <p>Standing and sitting height, weight, chest, upper arm, waist and hip circumference.</p>
Assessment of free-living physical activity	Five continuous days by combined heart rate and movement sensor (Actiheart) with individual calibration.
Cardio-respiratory fitness	Heart rate response to an incremental step test.
Overnight fasting 50-ml blood sample	Thyroid-stimulating hormone (TSH), free thyroxine (T4), free Triiodothyronine (T3) (Reflex request), insulin, sodium, potassium, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), γ -glutamyl transferase (GGT), urea, creatinine, urate, phosphate, total bilirubin, C-reactive protein, triglyceride, HDL cholesterol, cholesterol, calcium, corrected calcium, total protein, albumin, globulin, iron, total iron binding capacity (TIBC), glucose, vitamin C, HbA1c, full blood count (including white cell Count). DNA extraction, lithium Heparin, EDTA, citrate and fluoride plasma and serum aliquots stored at -80°C .
Overnight fasting urine sample	Dipstick, spun and unspun aliquots stored at -80 and -20°C .
Salivary samples	One salivary sample was collected at the visit and a further three during the following 24 h (evening, next day waking and 30 min later).
Scales or questions	<p>Rose angina, intermittent claudication, bronchitis, chest pain, doctor diagnosed CVD events and test for chest pain/heart disease, osteoarthritis symptoms, back pain, knee injuries, functional limitations, fracture history, prescribed and non-prescribed regular medication, hospital admissions, day surgery, outpatients.</p> <p>Dietary and alcohol assessment (5-day diary), CAGE, smoking, physical activity assessment (EPAQ2), GHQ28, the Close Person Questionnaire, life events, SF36, Edinburgh wellbeing scale, life satisfaction, neighbourhood satisfaction, spare time activities, parental death, time spent caring for others, updated marital and fertility histories.</p> <p>Household income and sources, perceived financial hardship, periods of unemployment, household size and housing tenure, own/partner's occupation and work status.</p>

Table 2 Feedback to participants and GPs

Tests	Results	Feedback to GP ^a	Feedback to Study Member (SM) ^b
Blood samples listed in Table S2	Action level	Telephone call from survey doctor (SD), results normally faxed the day results available.	Telephone call from SD advising seeing GP ASAP
	Out of normal range	Results posted to GP	Letter with results advising seeing GP ASAP or at next routine visit ^c
	Normal		Letter advising results are normal
Bone scan	Osteoporotic	Full report sent to GP	Letter advising seeing GP
	Osteopenic		Letter advising GP may wish to give lifestyle advice
	Normal		'Normal' letter
ECG criteria listed in Table S1	Abnormal	Copy of ECG annotated as 'normal' or 'abnormal'	'Abnormal' letter to GP and letter advising SM to visit GP
	Normal		'Normal' letter to GP and SM
Cardiac echo	Abnormal and full echo done	Letter from CRF cardiologist with clinical advice	Local cardiologist may send copy of letter to SM
	Normal	None	None
Carotid intima media thickness	Abnormal	Letter from JD advising referral for full clinical assessment	Letter advising seeing GP
	Normal	None	None
Blood pressure	Severely raised	BP results sent to GP	Advised at CRF to see GP within 5 days
	Moderately raised		Advised at CRF to see GP within 2–3 weeks
	Mildly raised		Advised at CRF to see GP within 3 months
GHQ or other documentation	Suicidal ideation or significant mental health concerns	None	Telephone call from research team counsellor. SM encouraged to see GP if appropriate.
Urine dipstix	Significant blood, glucose or protein	None	SM advised at CRF to see GP ASAP

^aFeedback to GP only with SM permission. If permission not given and SMs do not agree to have survey doctor contact them blood samples are not done.

^bIf SM requests feedback (most do).

^cDecision as to which letter made at blood sample monthly review meeting.

ASAP=as soon as possible; BMC=bone mineral content; BMD=bone mineral density; BP=blood pressure; CAGE=CAGE questionnaire; CS=cross sectional; DXA=dual energy X-ray absorptiometry; ECG=electrocardiogram; GHQ=general health questionnaire; HDL=high density lipoprotein.

gender, previously recorded physical performance or most health indicators. There was weak evidence that those reporting coronary heart disease and associated hospital procedures on the postal questionnaire were more likely to have a clinic or home visit compared with others ($P=0.1$). The level of educational qualifications had the strongest effect on these response rates, with those having no qualifications less likely to be a participant ($P<0.001$) or attend a clinic visit ($P=0.01$). There were no other significant socio-demographic differences in these response rates.

Participant satisfaction with the clinic visit was very high; 76% were very satisfied and 21% were satisfied with their visit to the WTCRF, many making positive

comments about the staff and the comprehensive screening, or how special the clinic experience made them feel. About half specifically mentioned how valuable they found the echocardiogram, ECG and bone scans.

Remaining sample

Based on a successful feasibility study, all remaining members of the target sample were sent the postal questionnaire. Overall, the response was 2452 out of a valid sample of 3071 (80%).

All remaining members of the sample still alive and with a known postal address in England, Scotland

Table 3 Manchester feasibility study: response

Manchester feasibility study	No.	N (%)
Feasibility sample sent postal questionnaire	348	
Postal questionnaire returned undelivered	-13	
Study member had died	-3	
Valid sample for postal questionnaire		332 (100)
Postal questionnaire not returned or not completed		56 (16.9)
Postal questionnaire completed		276 (83.1)
Moved out of catchment area	-5	
Study member died before visit	-3	
Not known at address	-13	
Valid sample for clinic invitation		311 (100)
Declined clinic or home visit		63 (20.3)
Self completion questionnaires only		7 (2.3)
Home visit completed		51 (16.4)
Clinic visit completed		190 (61.1)
Information from postal and/or visit	298	

or Wales were invited to one of six CRFs (two in London and one in Manchester, Edinburgh, Cardiff and Birmingham). As of the end of September 2010, data collection is complete in Manchester, Edinburgh and Birmingham. Of the valid sample in these centres of 1383, 1067 (77.1%) had a clinic or home visit: 796 (57.5%) attended the CRF, and 271 (19.6%) had a home visit.

Data collection at the other three CRFs will be completed by the March 2011. As of the end of August 2010, 1550 clinic and 394 home visits have been made. On the basis of the traced and responding population for the Manchester, Edinburgh and Birmingham catchment area, we anticipate that there will be approximately 2176 visits in the overall sample (1623 clinic visits and 553 home visits).

What are the main strengths and weaknesses?

One of the weaknesses of the data collection was its length (almost 5 years from the start of the feasibility study to the anticipated end of the main data collection). This raised challenges of maintaining staff skills, dealing with staff turnover, servicing and technical updates of equipment, keeping morale high and costs contained. This length was determined by funding requirements, and because no more than two study members a day could be accommodated by the clinic schedule, given the time restrictions

imposed by fasting and blood sampling, the time taken for the assessments and for participant travel, the availability of specialist technicians and the number of CRF study sessions available. Also, undertaking a comprehensive health assessment on a scattered geographical sample required the team to set up six data collection centres. However, this balanced the need to keep the travelling required by study members to a minimum with the need for standardization of the data collection. To maintain quality control, equipment and training across the centres was comparable and, in most cases, data were acquired at the CRFs but analysed in core laboratories (see supplementary data available at *IJE* online). The data collection was also made more complex by the increased regulatory environment in the wake of media coverage of losses of government data.

To set against these limitations, this study has a number of strengths. First is the intensive phenotyping of an already well-characterized British national cohort. The new NSHD data set will enrich UK longitudinal resources and is designed to test not only the initial hypotheses that form LHA's scientific strategy with existing expert collaborators but also hypotheses that emerge from new collaborations with the wider scientific community.

A second strength is the collection of data by home visit, generally by the same set of research nurses, if the study member could not attend the clinic. This will help to maintain the representativeness of the NSHD study sample against the social and health bias associated with attending the clinic. We will report separately on the representativeness of the complete sample, and on the factors associated with response to the postal questionnaire and the visit. One of the benefits of a longitudinal study is that any bias in the remaining sample can be identified and will be taken into account before generalizing to the UK population of the same age.

A third strength of the study was the duty of care protocols developed specifically for an older population. The need to respond to clinical problems identified during the comprehensive assessment raised ethical issues analogous to those invoked by asymptomatic screening.²⁰ If scientists subject volunteers to clinical research investigations, there is an imperative to do no harm, just as there is in a clinical consultation. The duty of care protocols (Table 2) required at least 1 day a week of a survey doctor on the fieldwork team to deal with resulting queries raised by participants or their GPs. The survey doctor ensured that participants were appropriately referred to their GP (rather than offering advice on individual clinical care), reassured participants, facilitated their retention in the study, ensured appropriate clinical follow-up where necessary, avoided unnecessary work for the GP and avoided leaving GPs uncertain as to what to do as a consequence of tests that they had not ordered. While responding to queries about the results

Table 4 Manchester feasibility study

	N (row per cent)			N (row per cent)		
	Clinic/ home/SC N = 248	Refusal/non response N = 63	P-value (χ^2)	Clinic N = 190	Home/SC N = 58	P-value (χ^2)
Distance from clinic						
≤40 miles	129 (80.1)	32 (19.9)	0.9	105 (81.4)	24 (18.6)	0.06
>40 miles	119 (79.3)	31 (20.7)		85 (71.4)	34 (28.6)	
Missing	0	0		0	0	
Gender						
Male	134 (80.7)	32 (19.3)	0.6	100 (74.6)	34 (25.4)	0.4
Female	114 (78.6)	31 (21.4)		90 (79.0)	24 (21.1)	
Missing	0	0		0	0	
Own social class 53 years						
Manual	65 (81.3)	15 (18.8)	0.2	39 (60.0)	26 (40.0)	<0.001
Non-manual	164 (87.2)	24 (12.8)		141 (86.0)	23 (14.0)	
Missing	19	24		10	9	
Highest qualification by the age of 26 years						
None	84 (69.4)	37 (30.6)	<0.001	55 (65.5)	29 (34.5)	0.01
Up to GCE	69 (89.6)	8 (10.4)		56 (81.2)	13 (18.8)	
A level and above	86 (86.0)	14 (14.0)		72 (83.7)	14 (16.3)	
Missing	9	4		7	2	
Employment (from postal questionnaire)						
Full time	75 (86.2)	12 (13.8)	0.8	57 (76.0)	18 (24.0)	0.2
Paid part-time	46 (85.2)	8 (14.8)		41 (89.1)	5 (10.9)	
Not in paid work	101 (82.8)	21 (17.2)		77 (76.2)	24 (23.8)	
Missing	26	22		15	11	
Hospital procedures for CHD and doctor-diagnosed CHD (from postal questionnaire)						
No	174 (82.5)	37 (17.5)	0.1	135 (77.6)	39 (22.4)	0.6
Yes	52 (91.2)	5 (8.8)		42 (80.8)	10 (19.2)	
Missing	22	21		13	9	
Doctor diagnosed BP problems (from postal questionnaire)						
No	169 (84.9)	30 (15.1)	0.6	135 (79.9)	34 (20.1)	0.3
Yes	57 (82.6)	12 (17.4)		42 (73.7)	15 (26.3)	
Missing	22	21		13	9	
Grip strength at the age of 53 years						
Lowest quartile	55 (85.9)	9 (14.1)	0.6	42 (76.4)	13 (23.6)	0.8
2nd to 4 th quartile	158 (83.2)	32 (16.8)		123 (77.9)	35 (22.2)	
Missing	35	22		25	10	

Overall response and choice of clinic or home visit by study member characteristics.

SC = self completion.

of routine clinical tests that are normally seen by GPs is straightforward, it requires considerable time and effort. Responding to queries about clinical investigations that are not routinely reported to GPs, e.g. carotid scans, raises additional issues, as the clinical significance and the most appropriate management

plan in an asymptomatic patient is not clear. In this case, it is important that there is an expert who is familiar with the investigation, and the possible clinical course associated with any finding, available to discuss the result with the GP or the participant if required.

A final strength of this study is increased capacity building in the research community. It has developed the skill base of the research nurses in the UK CRFs and led to the development of home visit services, at a time when demand for including biological measures in health and social surveys is high and supply of suitably trained nurses limited. The model of scientific collaboration has also developed the skill base of the research team and has enabled specialist measures to be collected within reasonable costs.

This pioneering clinic data collection may provide a model for other UK national birth cohort studies which, like the NSHD, have traditionally relied on sending trained interviewers and nurses on home visits to these scattered samples living across England, Scotland and Wales.

Can I get hold of the data? Where can I find out more?

Facilitated collaborations with the scientific and data collection teams by bona fide scientists are welcome; they are encouraged to become principal or co-investigators on grants to raise additional funding for new research projects based on the new data or samples. In parallel with the data collection, a secure web-based tool to facilitate working with shared scientific data and resources is being developed.²¹ Enquiries should be made to swiftinfo@nshd.mrc.ac.uk

Through these collaborations, we aim to maximize the scientific potential of the new data collection.

Supplementary Data

Supplementary data are available at *IJE* online.

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