**Data supplement**

**Methods**

The NSHD is a birth cohort following-up 5362 individuals born during one week in March 1946 in England, Scotland and Wales.[[11](#_ENREF_11),[12](#_ENREF_12)] Representativeness has been maintained over time.[[13-15](#_ENREF_13)] This report uses data collected over 24 assessments from birth. In 1989 (at age 43), of the 3749 participants remaining in the study, 3262 (87%) were assessed;[[11](#_ENREF_11)] the majority of whom (3247) had been flagged for death notification on the National Health Service Central Register. Of these, 3192 (98%) had at least one cognitive assessment of verbal memory or search speed at this follow-up or at subsequent follow-ups at ages 53, 60-64, and 69; this is the overall sample for analysis.[[16](#_ENREF_16)] Ethical approval was obtained from the Multicentre Research Ethics Committee (for data collections up to 2010) and Queen Square Research Ethics Committee (14/LO/1073) and the Scotland A Research Ethics Committee (14/SS/1009) for data collections between 2014 and 2015.

*Visual search speed and verbal memory*

All assessments at each of the four follow-ups (ages 43, 53, 60-64 and 69) were carried out at home or clinic visits by research nurses according to a standardised protocol. The visual search speed task required participants to cross out the letters P and W, randomly embedded within a grid of other letters in one minute. The score represents the total number of letters searched (maximum 600, except for at age 43 where maximum score was 450). Verbal memory was assessed through recall of a 15-item word learning task, where each word was presented for two seconds. The score represents the total number of words correctly recalled over three identical trials (maximum 45). To minimise practice effects, two different word lists were alternated between follow-ups.

*Mortality*

We included deaths from any cause from March 1989 (43 years) until February 2016 (the end of the 69th year) notified through NHS Digital (previously the Office for National Statistics).

*Covariates*

Variables were chosen on the basis of factors previously demonstrated to be associated with adult cognition in NSHD.[[16](#_ENREF_16),[17](#_ENREF_17)] In childhood, paternal education (primary or none, more than primary) was used as a measure of childhood SEP. Childhood cognition was measured at age 8, using a battery of tests administered by participants’ school teachers: reading comprehension, pronunciation, vocabulary, and non-verbal reasoning.[[18](#_ENREF_18)] Childhood cognitive test scores were summed and standardised to the final sample. Where data on childhood cognition were missing at age 8 (n=366), Z-scores from the assessment at age 11 or 15 were used (n=89 and n=42 respectively). Educational attainment by age 26 was classified in three categories: below ordinary secondary qualiﬁcations (vocational); ordinary secondary qualiﬁcations (‘O’ levels and their training equivalents), advanced secondary qualiﬁcations (‘A’ levels and their equivalents) and above.

At age 43, adult SEP was based on participants’ occupational class (I and II; IIINM and IIIM; IV and V). Measures of health status at this age included systolic blood pressure (of two measurements using a sphygmomanometer, the second measure was used if available), body mass index (BMI) calculated by measured height and weight; self-reported diabetes, stroke and cancer, and the World Health Organization Rose angina scale.[[19](#_ENREF_19)] Smoking status (current, former, never) was also recorded.

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**Statistical analyses**

Variables were examined for distribution and completeness. Linear mixed models were used to examine the trajectories of verbal memory and search speed, the intercept being set at age 43. These models allow for the inclusion of random factors (accounting for inter-individual variability in intercept and slope), and estimate the covariance structure prior to testing further associations. Where data were skewed, models were adjusted using the Kenward-Roger procedure to ensure robust type I error rates.1,2 Chronological age since age 43, scaled in a 5-year unit to facilitate the interpretation of possible quadratic terms, was used as the time metric. Linear and non-linear models with random intercepts and slopes were examined and the fit of the models was compared using the Bayesian Information Criterion (BIC). Linear and quadratic models were tested under the assumption that decline begins at age 43 and this decline might be constant over time (linear) or not (quadratic). A spline model with a transition point at 60 was estimated in order to explore whether the decline only begins at 60 (as suggested by data from the Seattle Longitudinal Studies and Whitehall II), or whether there is a difference of the speed of decline before and after this age. The models were estimated using PROC MIXED in SAS 9.3, which automatically handles missing data at random by maximum likelihood.3 Covariance matrices were assumed to be unstructured. Practice effects in search speed were investigated by comparing accuracy of target identification, in addition to the number of letters covered, over each wave. This measure was used to estimate test-retest effects by comparing accuracy of target identification (correct hits minus misses), but not used as a variable in the main analyses.

Associations with both intercept and slope were sequentially estimated for sex, early life, socio-economic and health factors using a forward-stepwise procedure. We tested factor-by-slope interactions but did not include these in subsequent models if there was no evidence of such an effect. Fit was compared by selecting the model with the lowest Bayesian Information Criterion. *Model 1*: adjusted for sex. *Model 2*: additionally adjusted for early life factors (parental education, childhood cognition and educational attainment). *Model 3*: additionally adjusted for adult socio-economic position. *Model 4*: additionally adjusted for health factors (smoking, BMI, systolic blood pressure, diabetes, stroke, rose angina and cancer). We used cases where complete data were available for all covariates. Sensitivity analyses to quantify differences due to selective attrition through death were undertaken by re-estimating models restricted to only those who remained alive throughout the study period. Stata version 12.1 and SAS 9.3 was used for all statistical procedures.

**Table S1.** Average cognitive scores recorded at each assessment between ages 43 and 69.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **N** | **Mean** | **SD** | **Missing** | **%** |  | **Mean where complete cognitive data** | **SD** |  |
| **Search speed** |  |  |  |  |  |  |  |  |  |
| Age 43  | 3143 | 344 | *77* | 104 | *3.2* |  | 344 | *77* |  |
| Age 53  | 2922 | 281 | *76* | 102 | *3.4* |  | 286 | *75* |  |
| Age 60-64  | 2173 | 266 | *72* | 50 | *2.2* |  | 268 | *71* |  |
| Age 69  | 2099 | 262 | *74* | 48 | *2.2* |  | 262 | *72* |  |
|  |  |  |  |  |  | **1642** |  |  |
| **Verbal memory** |  |  |  |  |  |  |  |  |  |
| Age 43  | 3045 | 24.7 | *6.4* | 203 | *6.2* |  | 24.7 | *6.0* |  |
| Age 53  | 2876 | 23.9 | *6.3* | 148 | *4.9* |  | 25.1 | *6.0* |  |
| Age 60-64  | 2141 | 24.3 | *6.1* | 82 | *3.7* |  | 25.8 | *6.1* |  |
| Age 69  | 2062 | 22.2 | *6.1* | 85 | *4.1* |  | 22.4 | *6.0* |  |
|  |  |  |  |  |  | **1592** |  |  |
| Search speed is in number of letters searched out of 600 (except at age 43 where it was out of 450) Verbal memory scores are words recalled out of 45. |

**Table S2.** Change in accuracy in search speed task over time.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Age** | **N** | **Mean accuracy** | **SD** | **Lowest score** | **Highest score** |
| 43 | 3151 | 17.5 | 6.7 | -14 | 37 |
| 53 | 2933 | 22.1 | 7.6 | -30 | 46 |
| 60-64 | 2182 | 21.7 | 5.9 | -50 | 38 |
| 69 | 2102 | 20.0 | 6.6 | -21 | 44 |
| Accuracy defined by: (number of correct targets) – (number of targets missed) in scanned area. Lowest score refers to worst accuracy (more targets missed than hit), highest score refers to best accuracy. |

**Table S3.** Change in midlife performance in search speed (number of letters scanned) from age 43 in 2293 individuals (7542 observations) who remained alive throughout the follow-up period (comparable to Model 4 in Table 2).

|  |  |
| --- | --- |
|  | **Model 4** |
|  | **beta** | **LCI** | **UCI** | **p** |
| **Intercept** |  |  |  |  |
| Intercept  | 413.42 | 395.40 | 431.44 | <.001 |
| Sex (Male) | -22.36 | -29.08 | -15.63 | <.001 |
| Father’s education | 8.76 | 3.24 | 14.29 | .001 |
| Childhood cognition | 4.11 | 1.16 | 7.07 | .001 |
| Education attainment |  |  |  |  |
|  | < ordinary | [ref] |  |  |  |
|  | Ordinary | 2.14 | -4.43 | 8.71 | .64 |
|  | Advanced | 12.48 | 5.28 | 19.67 | <.001 |
| Smoking |  |  |  |  |
|  | Never | [ref] |  |  |  |
|  | Former | -.85 | -6.66 | 4.94 | .77 |
|  | Current | -12.29 | -18.80 | -5.78 | <.001 |
| BMI | -0.75 | -1.37 | -0.13 | .01 |
| Diabetes | -33.18 | -65.58 | -0.78 | .04 |
| **Slope** |  |  |  |  |
| Slope (linear)/year | -48.82 | -51.92 | -45.71 | <.001 |
| Slope (quadratic)/year2 | 4.50 | 4.07 | 4.94 | <.001 |
| Sex  | 1.67 | 0.30 | 3.04 | .01 |
| Fathers education (primary cf. > primary); childhood cognition (per SD); BMI body mass index at age 43 (per kg/m2); diabetes at age 43 (yes cf. no). No associations with stroke, systolic BP or occupational class at age 43 were evident, therefore not included |

**Table S4.** Change in midlife performance in verbal memory (words recalled) from age 43 in 2293 individuals (7542 observations) who remained alive throughout the follow-up period (comparable to Model 4 in Table 3).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **beta** | **LCI** | **UCI** | **p** |
| **Intercept** |  |  |  |  |
| Intercept  | 23.93 | 22.55 | 25.32 | <.001 |
| Sex (Male) | -2.11 | -2.48 | -1.73 | <.001 |
| Father’s education | 0.61 | 0.20 | 1.01 | .003 |
| Childhood cognition | 1.89 | 1.66 | 2.11 | <.001 |
| Education attainment |  |  |  |  |
|  | < ordinary | [ref] |  |  |  |
|  | Ordinary | 2.14 | 1.63 | 2.65 | <.001 |
|  | Advanced | 3.37 | 2.80 | 3.95 | <.001 |
| Occupational class |  |  |  |  |
|  | IV + V | [ref] |  |  |  |
|  | III NM+M | 0.74 | 0.18 | 1.30 | .008 |
|  | I+II | 1.42 | 0.80 | 2.05 | <.001 |
| Smoking |  |  |  |  |
|  | Never | [ref] |  |  |  |
|  | Former | -0.73 | -1.21 | -0.24 | .002 |
|  | Current | 0.07 | -0.34 | 0.50 | .71 |
| BMI | 0.1 | -0.06 | -0.10 | -0.01 |
| Stroke | -3.8 | -3.80 | -7.47 | -0.13 |
| **Slope** |  |  |  |  |
| Before 60 | -0.18 | -0.28 | -0.08 | <.001 |
| After 60 | -0.97 | -1.19 | -0.75 | <.001 |
| Education (after 60) |  |  |  |  |
|  | < ordinary | [ref] |  |  |  |
|  | Ordinary | -0.25 | -0.53 | -0.01 | .06 |
|  | Advanced | -0.31 | -0.57 | -0.06 | .01 |
| Fathers education (primary cf. > primary); childhood cognition (per SD); BMI body mass index at age 43 (per kg/m2); diabetes at age 43 (yes cf. no). No associations with diabetes, systolic BP or occupational class at age 43 were evident, therefore not included |