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Age-related Changes in Memory and Fluid Reasoning in a Sample of Healthy Old People

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Abstract

Participants in the Healthy Old People in Edinburgh (HOPE) study (N = 398) were assessed on Raven's Progressive Matrices and Logical Memory on up to three occasions. Covariates included education, social class, disease and medication status, blood pressure and study outcome. Raven's score declined linearly with age, whereas decline in Logical Memory was accelerating. There was significant variation in individuals' rates of decline for Ravens but not Logical Memory. Slope–intercept covariances were not significant. Those who later developed dementia already exhibited lower scores, more so for Logical Memory than Raven's. Death and study attrition were related to performance, again greater for Logical Memory. Conclusions: The HOPE approach of progressive screening is a feasible and practical method for studying healthy cognitive ageing. As predicted for an initially healthy sample, rates of decline were relatively homogeneous. The hypothesis of differential decline was not supported, nor was a strict interpretation of the hypothesis that cognitive ageing is entirely pathology driven.

Keywords

Cognitive ageing; Ravens matrices; Logical memory; Physical health

INTRODUCTION

Western societies have increasing numbers of people living to old age, when cognitive functioning is a strong determinant of quality of life and independence. It is important, therefore, to understand the patterns of age-related change in cognitive function and their causes. One distinction that frequently underpins the study of cognitive ageing is that between normal, or healthy, ageing and pathological ageing (Schaie, 2005) – referred to elsewhere as 'normative' and 'nonnormative' ageing (Baltes & Nesselroade, 1979). Normal ageing involves changes that are considered intrinsic to the process of ageing and

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monotonically related to chronological age, whereas pathological ageing denotes changes that are initiated or accelerated by the greater burden of morbidity that is typically associated with older age. Given that such pathological changes would be additional to those of normal ageing, it is understandable that normal ageing should be the primary subject of cognitive ageing research.

However, the full implications of this conceptualization have not always been appreciated. Most representative cohorts of older people have high rates of physical illness and co-morbidity. While researchers have tended to exclude individuals with conditions such dementia or stroke, the influence of physical health on cognitive functioning extends beyond conditions that primarily affect the brain and central nervous system. For example, diabetes has been shown to have negative impacts on cognitive functioning, although the mechanism is not fully established (Strachan, Frier, & Deary, 2003). Then there are other illnesses where the impact on cognitive function may be less a feature of the illness itself than of its treatment. Antihypertensive medication and cardiac surgery are examples.

Furthermore, a disease process may have measurable impact on cognitive functioning before the disease itself is clinically manifest. This is demonstrated by prospective and longitudinal studies that are able to relate disease outcomes measured at later time points to earlier levels of cognitive functioning and to rates of change (Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003).

Sliwinski et al. (2003) suggest that much of the variability in cognitive ageing is due to heterogeneity in the samples studied. They were referring specifically to the effects of dementia. If the effects of physical health more generally are included, the net result could be that many, if not most, studies over-estimate both the rate of cognitive change and the variability between individuals. This would have important implications for theories of cognitive ageing, particularly any derived from observations of health-heterogeneous samples, including population representative samples. One hypothesis that may serve as an exemplar is that of differential decline which posits that cognitive decline is slowest amongst the initially more able (Deary, Starr, & MacLennan, 1999; Richards, Shipley, Fuhrer, & Wadsworth, 2004). Although this has rarely been tested, the evidence would be confounded by physical illness if initial ability and rates of decline were both determined to some degree by concurrent somatic illness.

Despite its widespread currency, the distinction between normal and pathological ageing remains controversial both within the field of cognitive ageing and more widely (Soloman, 1999). For Peto and Doll (1997) ‘old age is associated with disease, but does not cause it’, that is ageing per se has no explanatory power. They give the example of cancer incidence, which increases exponentially with age, but their argument is intended to apply more generally. Rabbitt, Lunn, and Wong (2006) take a very similar stance on cognitive ageing. They found that individuals who completed a 20-year longitudinal study experienced no, or minimal, cognitive change compared with those who died or dropped out of the study. They concluded that ‘age-related variance between individuals is not driven by the simple passage of time or by the progress of poorly understood ‘normal’ or ‘usual’ ageing, but rather by age-related increases in the prevalence and progress of pathologies’. In short, ‘cognitive aging may be little more than a pathology driven phenomenon’ (Backman & MacDonald, 2006).

From each perspective physical illness is central to the study of cognitive ageing, either as a crucial confounder or as its principal cause. From the first perspective, control for confounding is necessary to adequately assess theories such as that of differential decline. From the second perspective, control for physical health would leave little or no cognitive

decline to be explained. Classical approaches to confounding include data restriction and statistical control. Here we combine the two to describe the age-related changes in non-verbal reasoning and verbal declarative memory in a cohort of older people who were specifically selected to be free from illness and not on any medication. Memory and non-verbal fluid reasoning represent two major domains of cognitive functioning for which a decline in performance with increasing age is typical. The other cognitive measures available for this cohort, the NART and MMSE, exhibit too little age-related change in healthy subjects (McGurn et al., 2004; Spiro & Brady, 2008). To minimise the impact of attrition bias we use growth curve models with maximum likelihood estimation and we control for study outcome.

METHOD

Sample Selection and Screening

The Healthy Old People in Edinburgh (HOPE) cohort comprises 603 community-resident people aged 70 years and over who were initially healthy and not on regular medication. The identification of a sample with these characteristics was achieved by a process of progressive screening. To begin with, a sample aged over 70 was identified from the age registers of 67 general medical practitioners in the city of Edinburgh, Scotland, UK. The potential population from which the sample was selected was estimated to be in the range of 8,600 to 11,000. All available case notes were then scrutinised for evidence of physical or psychological health problems by a research nurse or doctor (JMS). Those who had significant health problems or were on regular prescribed medication were excluded from the study. A health problem was considered significant if it was ongoing (i.e., not resolved such as intercurrent infections, operations for remediable conditions like inguinal herniae) and/or required regular medication. People were included if they took medication as required for intercurrent problems (e.g., paracetamol for acute pain). Full details of the exclusion criteria are given in an earlier report (Starr, Whalley, Inch, & Shering, 1992). Those remaining were reviewed by their general practitioner to allow for information not in the notes and, if still considered eligible, invited to participate in the study. The positive response rate was 70%. Those who replied positively were visited at home by a doctor or research nurse for further screening. Nine hundred people were screened at home and 603 of these had no overt disease and were not on regular medication.

The participants were assessed at baseline in 1990–1991 and at three further occasions over the next 9 years at 4, 7 and 9 years. Health problems, including dementia, and medication use were asked about directly and checked against general practice health records. For those not visited we determined their current status at each occasion, by searching General Practice, Primary Care Division, and General Register Office data. The General Register Office for Scotland is the national repository of death records and was used to determine vital status as at December 31, 2000 (Starr, Deary, & Macintyre, 2003).

MEASURES

Cognitive Measures

Two cognitive measures are modelled: Raven's Standard Progressive Matrices, a non-verbal test of inductive reasoning and a good indicator of general fluid intelligence (Carroll, 1993; Raven, Raven, & Court, 1993); and the Logical Memory subtest from the Wechsler Memory Scale (Wechsler, 1987), a verbal declarative memory test. These measures were collected at waves 2, 3 and 4 of the study.

Predictor Variables

We classify the predictor variables into three categories: variables describing the person; time varying variables; and study outcome variables.

Variables Describing the Person—These are variables which were not expected to change during the course of the study and which were measured only once. They include: occupational social class, education, gender, and deprivation of the area of residence. The social class variable was derived from the subject's main occupation before retirement using the Standard Occupational Classification (HMSO, 1990). We used initial digit of the SOC code comprising nine ordered categories. Education was recorded as the number of years in full time education. Area deprivation is a measure described by Carstairs and Morris (1991), based on household rates of: male unemployment; car ownership; overcrowding and low social class for the postcode sector in which the subject resided.

Time Varying Variables—These included the presence of any medical condition (yes/no) at waves 2–4; current medication (none/some); systolic and diastolic blood pressure and whether the subject lived alone. Living alone was not recorded at wave 3 so the mean of waves 2 and 4 values was used.

Study outcome variables: These represent the subject's status at the end of the study. The outcome of each wave is coded to the following categories: retested adequately; died; refused; no reply; moved away; untraceable; retested inadequately; and too unwell to participate. If an interview was regarded as inadequately completed, the data were not used. Deaths for the entire cohort were determined centrally, as described above. Where the GP's notes mentioned a diagnosis of dementia, this was recorded, but no formal diagnostic confirmation was performed. A diagnosis of dementia was also ascertained from death certificates, though this is likely to be an underestimate (Thomas, Starr, & Whalley, 1997). These outcomes do not form mutually exclusive categories so a categorical outcome variable was constructed by imposing a hierarchy of outcomes. At the top of the hierarchy were death and study completion. Next came attrition through being 'too unwell', followed by 'refusal' and other outcomes. Study completion was defined as having provided an 'adequate' interview at waves 2, 3 and 4. The onset of dementia was retained as a separate dummy variable in all analyses.

STATISTICAL METHODS

We used linear mixed models which have particular advantages for longitudinal data: they use all measurement occasions, allow for varying intervals between measurements, and make less stringent assumptions about attrition. The term 'linear mixed models' refers to the fact that these models contain both fixed and random effects. A model with only fixed effects would be equivalent to a multiple regression. The addition of random effects serves to take account of the correlated nature of the data. In this case, the random effects are also of substantive interest in their own right. The models were fitted using proc mixed in SAS version 9. (SAS Institute Inc., 2000).

The time dimension for the analyses is age. As the sample was defined to be those over 70 years of age at recruitment and was then followed up prospectively, the age of the participants provides both cross-sectional and longitudinal information on age-related change.

Several variables were centred on their average value at wave 2: age (79 years); systolic blood pressure (159 mmHg), diastolic (87 mmHg), years of education (11 years), and occupational classification (category 4).

The scores from the Raven's Standard Progressive Matrices and Logical Memory tasks comprise the response measures and each is modelled separately. The modelling has four stages beginning with a baseline model in which the overall population rate of change in the cognitive outcome is modelled as polynomial function of age. The centring of age on 79 years means that the intercept term for the baseline model is the estimated mean score at 79 years of age. The coefficients of the terms in age represent the overall change per year of age. The baseline and subsequent models also include random intercepts and random linear slopes in age. In the baseline model the random intercepts can be interpreted as estimated individual differences in test scores, controlling for age. The random slopes in age represent each individual's departure from the overall rate of change. Each model estimates the variances of the individual intercepts and slopes and their covariance. The intercept–slope covariance represents the extent to which the individual slopes converge or diverge over time. The hypothesis of differential decline implies a divergence over time which would manifest itself as a positive intercept–slope covariance.

From the baseline model, person-level variables – gender, education, social class, and area deprivation – were tested and, if significant, entered. In each case the interaction with age was tested. A significant interaction with age would indicate group differences in rates of change. The effects on the random components are noted. The main effects of these variables might account for some of the variance of the random intercepts whereas interactions with age would be more likely to account for individual differences in slopes. For the third stage, the time-varying variables were tested: systolic and diastolic blood pressure, disease status and medication, and whether the person lives alone. Again interactions with age were tested. Finally, study outcome variables were evaluated, including their interactions with age. As these outcome variables are overlapping and correlated, selection of the final model was made on the basis of overall levels of fit amongst candidate models.

RESULTS

Table 1 gives details of the follow up of the initial 603 participants over the subsequent waves of the study. Analyses were based on 398 of the participants having complete data on Raven's matrices, Logical Memory and the covariates for at least one wave of the study. The number included in the analyses is larger than the number that is shown in Table 1 as tested at wave 2 because some of those who were not tested at that wave, or not tested adequately, were tested at a subsequent wave. Table 2 shows the descriptive characteristics of those tested at each wave. Although the sample was selected so as to be free from physical illness, 49% have already developed some illness by wave 2 and this rises to 63% and 76% at waves 3 and 4, respectively.

Table 3 gives the results of the modelling of Raven's Progressive Matrices. Fixed and random effects are given for the four hierarchically nested models. The fixed effects are interpreted in the same way as the results from a linear regression would be. For each significant effect, the regression coefficient is given together with its standard error and associated p value. As age is centred on 79 years, the fixed effect intercept estimates the mean score at 79 years of age. For the baseline model this is 28 points. The fixed effect of age represents a decline of just over half a point per year. No higher order terms in age were significant so the model includes only a linear trend in age. The random effects are variance and covariance terms. The random intercept term is the variance of the individual intercepts around the overall mean of 28. The slope term is the variance of the individual slopes (in age) around the overall decline of 0.53 points per year. The term labelled 'slope–intercept' is the covariance between the random slopes and intercepts. The 'residual' variance is variance of the observed values around the individually fitted lines. Thus, the residual variance is a

within subject component of the variation, and the other random effects are between subject components. The random intercepts, interpreted as individual differences at age 79, account for 80% of the total variation at that age. As mentioned, the hypothesis of differential decline implies a positive slope–intercept covariance. In the baseline model this term is negative and non-significant, so the baseline model does not provide support for the hypothesis of differential decline.

The second model shows the results of adding significant person level effects. Education, social class and gender all had significant effects, area deprivation did not. There were no significant interactions with age. Gender is added as a dummy variable labelled ‘male’ as women are the reference group. As education and social class are both centred on their mean, the fixed effect estimate in this model is the estimated mean score for a female, aged 79, of average education and social class. The effect of education is an increase of one point per year of education. Social class is coded with higher values indicating lower social class, so the effect is a decrease of around half a point per unit increase in social class. The gender effect shows that, on average, men score 2 points higher than women.

In the person level model the random intercepts term reduced by 28% from the baseline model, indicating that the gender, education and social class, together account for 28% of the individual differences in Raven’s score at age 79. The variance of the random slopes has increased, as has the slope–intercept covariance, although the latter is still not significant.

Among the time-varying variables, there was a significant interaction between living alone and age. At age 79 there was no significant difference between those living alone and those not, but at older ages those living alone scored higher. Diastolic blood pressure was negatively associated with Raven’s score. Neither of the dummy variables indicating disease status and medication was significant.

Among the study outcome variables, dementia was the most powerful predictor, and no others were significant when it was controlled for. Its effect estimate at −9.17 implies that those who went on to be diagnosed with dementia scored 9 points lower at age 79 than those who did not. At just over a standard deviation in size (see Table 2) this is a large effect. The interaction of dementia and age was not significant. This effect should be interpreted in the light of the fact that the diagnosis of dementia was made after the cognitive data were collected and that the participants were all considered healthy at wave 1.

In the final model, the random intercepts remain significant, although 33% of the baseline variance has been accounted for. The random slopes remain significant and have increased somewhat. The slope–intercept covariance remains non-significant.

Table 4 gives the results for Logical Memory. The fixed effects in the baseline model indicate an estimated mean of just over 35 points at age 79. The negative quadratic in age shows that the rate of decline is increasing with age: the expected decline between 79 and 80 years of age would be less than half a point (0.4), but between 85 and 86 it would be nearly 5 points (4.9). Over the decade of age 79 to 89 the expected decline would be just over 8 points, or .57 of a standard deviation. Among the random effects, there is significant variation for the random intercepts, but not for the slopes. The proportion of the total variation attributable to the random intercepts is lower than for Raven’s at 66%.

Among the person level variables, education and social class were both significant predictors, but not gender or area deprivation. None of the four person-level variables interacted with age.

Of the time varying variables, there was a similar interaction of living alone with age, but it was no longer significant after controlling for systolic blood pressure. Again, the variables indicating disease status and medication had no significant effect.

Of the study outcome variables, later dementia was associated with a large difference in scores with those who went on to develop dementia scoring nearly 22 points, around 1.5 standard deviations, lower at age 79. The hierarchically coded outcome variable was also significant, suggesting that those who went on to complete the study (the reference group) had scores 6–7 points higher than those who died, refused or were too unwell to continue. In the final model the random intercepts remain significant, with 21% of the variation in the baseline model having been explained. The variability of the random slopes has increased, but is still non-significant. The slope–intercept covariance remains non-significant throughout. As with the model for Raven's matrices, there is no support for the hypothesis of differential decline.

DISCUSSION

Through the age range of the sample, change in fluid intelligence is best described as a linear decline with age, whereas verbal memory exhibits a pattern of accelerating decline. Both effects are of reasonable magnitude: the expected decline in the 10 years of age from 79 to 89 would be around .6 of a standard deviation (.6 for Raven's, .57 for Logical Memory). These findings would tend to contradict the speculation that all age-related cognitive decline is pathology driven (Backman & MacDonald, 2006; Rabbitt et al., 2006) which was prompted by a finding of little or no change in persons who completed 20 years of follow-up (Rabbitt et al., 2006).

There was the expected significant variation in individual ability levels as represented by significant variation in the random intercepts. But there was no evidence that rates of decline were associated with initial ability. Neither Logical Memory nor Raven's exhibited the predicted positive slope–intercept covariance; hence the hypothesis of differential decline was not supported. Formulating this hypothesis in terms of the intercept–slope covariance makes explicit some technical and theoretical problems. In mixed effects models the statistical significance of the intercept–slope covariance is known to depend on the position of the overall intercept. This is one of the reasons why age was centred at 79 years – the mean age at wave 2 – although the conclusions were unaffected when age was centred at other points in the range of the sample (results not shown).

The variation in individual rates of change was statistically significant for Raven's but not for Logical Memory scores. This is in line with the suggestion (Sliwinski et al., 2003) that much of such variation arises from the heterogeneity of the samples studied. Including persons with extant illness increases the variability and more homogeneous, healthier samples, like the HOPE sample, would be expected to exhibit less variability. With the exception of the effect of living alone on Raven's score, none of the variables had significant interactions with age – another indicator of relative homogeneous rates of change.

Those members of the sample who went on to develop dementia already exhibited lower level of cognitive functioning prior to the diagnosis, as has been previously found, even in studies that specifically screened for dementia (Jacobs et al., 1995; Rubin et al., 1998). Other studies have shown effects of dementia ten (Elias et al., 2000) or even twenty (La Rue & Jarvik, 1987) years prior to diagnosis. However, such apparently long lead times may be the result of risk factors for dementia which also impact on cognitive functioning prior to onset. For example, *APOE* status has been shown to predict cognitive functioning levels in non-

demented samples (Blair et al., 2005; Carmelli et al., 2000; Hofer et al., 2002) and the *ε*4 allele is a well established risk factor for dementia. The fact that the effect on Logical Memory was much greater than on Raven's score is a characteristic shared both by preclinical dementia and the deficits observed for *APOE ε*4 status.

That said, the lead times in this study are shorter so it is quite possible that the results do reflect the early stages of dementia. If so, the impact would be expected to intensify as the dementia developed and lead to an interaction between dementia and age in our models. However, the relatively small number of dementia cases in the sample ($N = 21$) means that the study has little power to detect these interactions.

Aside from dementia, there were also signs that other study outcomes had a prior influence. As is commonly found (Schaie & Hofer, 2001), those who completed the study performed better throughout than those who did not. For Logical Memory, the effect remained significant even after controlling for dementia. Moreover, the size of the effect was similar for those who died, those who were too unwell to continue in the study and those who simply refused. This adds support to the suggestion (Rabbitt et al., 2006) that neglecting death and drop out would underestimate change. The effect observed for living alone, we also interpret as a type of outcome effect indicating the continued ability to live independently and the fact that more cognitive reserves are needed to do so with increasing age.

Attrition is a problem for all longitudinal studies, especially attrition due to the response of interest, cognitive functioning in this case. Incorporating socio-demographic, health and study outcome variables into the statistical models is one way of reducing the bias due this type of attrition (Hedeker & Gibbons, 1997). The likelihood based methods of estimation used for the models, whilst they make the assumption of data missing at random, tend to perform well in most practical situations even when the assumption is not appropriate (Collins, Schafer, & Kam, 2001; Schafer & Graham, 2002). A surprising aspect of the results is that the onset of illness or uptake of medication during the study does not appear to have had any effect. One possible explanation is that the onset of more serious conditions might have resulted in dropout from the study. While only 3–4% of those eligible for waves 2–4 explicitly mentioned ill health as the reason for not participating, illness may also have played a part in a similar number of refusals. If so, the effects of study outcome on Logical Memory would be due in part to incident illness. The corollary of this would be that illnesses not severe enough to cause drop out would not have a measurable effect.

The rates of illness and medication use increased more rapidly between waves 1 and 2 than in the subsequent two intervals. Part of this excess could be because the first interval was the longest: 4.2 years on average, compared with 2.9 years and 2.6 years. Part of the difference could also be due to regression to the mean – a common phenomenon where an extreme group is selected and subsequently re-measured on the attribute used for selection.

The study has some limitations. In particular, dementia was not systematically assessed, but ascertained from general practice case notes and death certificates, with the result that rates are likely to be underestimated. There were only three waves at which Logical Memory and the Raven's progressive matrices were assessed and only half of the eligible participants completed all three.

The HOPE approach of progressive screening is a feasible and practical method for studying healthy cognitive ageing. Many other studies of 'normative' ageing seek only to exclude dementing individuals. We would argue that this is insufficient because of the many direct and indirect ways in which physical illness and its treatment can impact on cognitive functioning (Hassing et al., 2004a, 2004b; Spiro & Brady, 2008; Starr et al., 2003; van Dijk

et al., 2000). Even with thorough screening, the preclinical effects of dementia will be evident although these may be partly due to common risk factors for both cognitive decline and dementia. Other study outcomes, such as death and dropout should be taken account of in modelling change (Rabbitt et al., 2006). As predicted for an initially healthy sample, rates of decline were relatively homogeneous. The hypothesis of differential decline was not supported, although this needs an explicit time frame to be fully testable.

Nor was there support for the hypothesis that cognitive ageing is 'little more than a pathology-driven phenomenon' (Backman & MacDonald, 2006): the rates of decline manifest in the sample could not be regarded as 'minimal'. However, this would be a strict interpretation and one that relies on the assumption that the HOPE screening has identified all relevant illness. A broader version of the hypothesis might include the impacts on cognitive functioning made by sub-clinical illness. A plausible example would be sub-clinical cardiovascular disease which is present in a large proportion of older people presumed to be disease free (Kuller et al., 2006) and is associated both with cerebral lesions (Vermeer, Koudstaal, Oudkerk, Hofman, & Breteler, 2002) and with cognitive functioning (Soderlund et al., 2006). Testing such a hypothesis would require intensive and detailed assessments of physical illness and its precursors which, in turn, might be made more feasible but a process of screening such as that used here.

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Table 1

Details of Follow Up

	Wave		
	2	**3**	**4**
Tested	387	287	201
Dead	69	57	31
Refused	46	44	33
no reply	19	1	4
moved away	12	9	2
not traced	13	2	0
inadequate test	42	14	9
too unwell	15	16	7
Total	603	430	287

Table 2

Descriptive Details of Tested Sample at each Wave

	Wave			
	1	**2**	**3**	**4**
Age	75.7 (4.2)	79.3 (3.9)	81.3 (3.8)	83.5 (3.6)
Years of education	10.9 (2.6)	11.0 (2.6)	11.2 (2.7)	11.2 (2.6)
Area deprivation	−1.9 (3.0)	−2.1 (2.8)	−2.1 (2.8)	−2.1 (2.8)
Systolic BP	159.7 (23.4)	159.7 (20.9)	162.2 (23.6)	155.3 (25.0)
Diastolic BP	86.0 (10.4)	86.6 (10.3)	86.2 (9.8)	78.4 (11.6)
Logical Memory		33.6 (14.0)	35.1 (15.0)	35.1 (14.4)
Raven's		27.9 (8.8)	27.1 (8.8)	27.8 (8.9)
Male (%)	39	39	35	35
Living alone (%)	40	68	54	54
Physical illness (%)	0	49	63	76
On medication (%)	0	42	59	63
N	603	387	287	201

Entries are mean (*SD*) for continuous variable.

Table 3

Raven's Progressive Matrices – results of Mixed Effects Modelling

	Model											
	Baseline			Person Level			Time Varying			Outcome (Final)		
	Estimate	*SE*	*p*	Estimate	*SE*	*p*	Estimate	*SE*	*p*	Estimate	*SE*	*p*
Fixed effects												
Intercept	28.05	0.43	<.001	27.41	0.49	<.001	27.20	0.66	<.001	27.71	0.65	<.001
Age	−0.53	0.07	<.001	−0.58	0.06	<.001	−0.84	0.10	<.001	−0.82	0.10	<.001
Education				1.01	0.16	<.001	1.02	0.16	<.001	0.98	0.15	<.001
Social class				−0.63	0.17	<.001	−0.63	0.17	<.001	−0.63	0.17	<.001
Male				2.37	0.77	.002	2.53	0.78	.001	2.57	0.75	<.001
Living alone							0.20	0.61	.741	0.08	0.60	.895
Living alone*age							0.38	0.12	.002	0.36	0.12	.003
Diastolic BP							−0.04	0.02	.040	−0.04	0.02	.035
Dementia										−9.17	1.65	<.001
Random effects												
Intercept	58.12	5.12	<.001	41.66	3.96	<.001	42.37	4.00	<.001	39.05	3.74	<.001
Slope–Intercept	−0.39	0.61	.525	0.07	0.51	.889	0.05	0.49	.927	−0.26	0.48	.592
Slope	0.28	0.13	.017	0.34	0.13	.004	0.30	0.13	.009	0.33	0.12	.003
Residual	14.27	1.34	<.001	13.90	1.27	<.001	13.62	1.25	<.001	13.46	1.20	<.001

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Table 4

Logical Memory – results of Mixed-effects Modelling

	Model											
	Baseline			Person Level			Time Varying			Outcome (Final)		
	Estimate	*SE*	*p*	Estimate	*SE*	*p*	Estimate	*SE*	*p*	Estimate	*SE*	*p*
Fixed effects												
Intercept	35.09	0.72	<.001	35.34	0.70	<.001	35.26	0.69	<.001	38.83	0.83	<.001
Age	−0.35	0.14	.015	−0.41	0.14	.004	−0.37	0.14	.010	−0.35	0.14	.013
Age^2	−0.05	0.02	.008	−0.05	0.02	.010	−0.05	0.02	.005	−0.05	0.02	.012
Education				0.95	0.27	<.001	0.97	0.27	<.001	0.84	0.24	<.001
Social class				−0.75	0.30	.013	−0.73	0.30	.015	−0.77	0.27	.004
Systolic BP							0.08	0.02	<.001	0.06	0.02	<.001
Dementia										−21.84	2.76	<.001
Outcome: died										−6.67	1.52	<.001
Outcome: refused										−5.79	1.67	<.001
Outcome: unwell										−6.37	3.22	.050
Outcome: other										−1.70	2.21	.441
Random effects												
Intercept	131.14	13.02	<.001	117.10	12.10	<.001	117.35	12.04	<.001	88.51	9.82	<.001
Slope–Intercept	2.66	1.59	.094	2.23	1.52	.143	2.04	1.53	.183	0.56	1.35	.679
Slope	0.15	0.39	.346	0.25	0.38	.256	0.38	0.38	.159	0.36	0.34	.144
Residual	66.13	5.29	<.001	65.73	5.23	<.001	62.31	5.07	<.001	62.28	4.90	<.001

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