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Age at natural menopause and cognition

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Abstract

Objectives: To examine associations between age at natural menopause, childhood IQ and cognition at age 65 years. To determine if lower age at menopause partly mediates the effect of childhood IQ on cognition at age 65 years. *Methods:* Data were provided by a sub-cohort of women participating in a longitudinal study of brain ageing and health. Main variables were childhood IQ from a 1947 national survey of children born in 1936, age at natural menopause and five cognitive tests measured in 2000–2001. *Results:* Age at menopause was associated with childhood IQ ($r = 0.221$, $P = 0.008$) and with general cognitive function age 65 years ($r = 0.246$, $P = 0.004$). Multiple regression showed 44.4% of the reliable variance in cognitive ability age 65 years is contributed by IQ at an age of 11 years to which, years of education contributed an additional 3.9%. Structural equation modelling suggested that childhood IQ differences contribute 4.8% of the variance to age at natural menopause and that the relation between age at menopause and cognition at age 65 years was accounted for by childhood IQ. *Conclusion:* Childhood IQ and age at menopause each have significant relations with general cognitive function age 65 years but the link between cognition age 65 years and age at menopause might be wholly explained by childhood IQ. The association between childhood IQ and age at menopause may be attributed to central neural mechanisms or, as argued here, to the effects of childhood IQ on adult general health.

Keywords: Childhood intelligence; Cognitive function; Ageing; Follow-up study; Natural menopause; Structural equational modelling

1. Introduction

Age at natural menopause and cognitive function across the life span may be related. Richards et al. [1] found in a study of 1548 women, of whom 245 were postmenopausal, that higher childhood cognitive function was associated with later age at menopause. They attributed their findings to the likely effects of gonadal steroids on both neurodevelopment and timing of menopause.

Gonadal steroids have also been linked to better performance on cognitive tests in late life [2] and with postmenopausal estrogen replacement therapy [3]. Decline in estrogen concentrations and cognitive performance after the menopause may be linked to reports of lower AD incidence in women who take estrogen replacement therapy [4,5]. Contrasting evidence is available from the Women's Health Initiative

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trial which is the largest study to date, to assess the effects of estrogen plus progestin on dementia and mild cognitive impairment [6]. The study showed that estrogen plus progestin increased the risk of dementia and did not prevent mild cognitive impairment.

However, these findings may be criticised because the combination therapy used could have increased sex hormone binding globulin and so reduced concentrations of free estrogen. Authors of a meta-analysis [7] suggested that variations in education, health, mood and sleep disturbance might contribute to individual differences in cognitive enhancement by estrogen or in its putative neuroprotective effects. A large-scale study of influences on cognitive functions during the menopausal transition detected slight but significant improvements in cognition that was not explained by differences in age, health, education and income [8,9]. Socioeconomic status is not related to age at menopause but smoking is associated with an earlier menopause and this effect may be more marked in underweight women [10].

We have addressed some of these sources of variation in cognitive ability at age 65 by investigation of a sub-sample of the Aberdeen 1936 birth cohort who took an IQ-type test at about 11 years of age and who have volunteered for a longitudinal study of brain aging and health. We have tested three hypotheses: (1) lower childhood mental ability is associated with lower age at natural menopause; (2) lower age at natural menopause is associated with lower cognitive ability at age about 65 years; and (3) lower age at menopause partly mediates the effect of childhood mental ability on mental ability at age about 65 years.

2. Materials and methods

2.1. The Aberdeen 1936 Birth Cohort Study

On 4 June 1947, the Scottish Council for Research in Education (SCRE) tested 70,531 Scottish schoolchildren born in 1936 and at school that day in the Scottish Mental Survey of 1947. The test was a version of the Moray House Test No. 12 (MHT) which is a valid, group-administered test of mental ability [11]. These archived scores were made available by SCRE for the present study. With the consent of the Local Ethics of Research Committee, in 1999–2001 we matched the 2617 children who took part in the Scottish Mental Survey in Aberdeen with the local health register (~99% coverage) and identified 957 men and women who could be exactly matched by the birth date and name. We next identified 603 of these subjects on the case registers of local family doctors. These 603 subjects were approached in turn until 450 (75%) men and women had agreed to participate in a prospective longitudinal study of brain aging and health. The sample comprised 221 women and 229 men, others refusing outright or deferring participation. Study data include demographic, medical, cognitive, physiological and biochemical information (full details available from authors on request). At the interview, the 221 women reported among which: (1) natural menopause, $n = 159$; (2) hormone replacement therapy (HRT) without hysterectomy, $n = 22$; and (3) surgical menopause with or without HRT $n = 40$. The present report is based on the 144/159 women who had experienced a natural menopause without exposure to hormone replacement therapy and agreed to complete most of the cognitive tests. 15/159 women declined to do this. Cognitive functions were tested in a quiet room without distractions. The following cognitive tests were administered using standard instructions. The mini-mental state examination (MMSE) [12] is a short test of global functioning, often used to screen subjects for dementia. No subjects scored less than 24 points on the MMSE. Non-verbal reasoning was assessed using Raven's Progressive Matrices (RPM) [13]. Verbal learning and memory were tested using the Auditory Verbal Learning Test (AVLT) [14]. Sub-tests from the Wechsler Adult Intelligence Scale-Revised [15] were used to measure visuo-spatial ability by the Block Design sub-test and psychomotor speed was assessed using the Digit Symbol sub-test. Executive function was tested by the 'Uses of Common Objects' (UCO) test [16]. This test requires the subjects to suggest uses of three common objects (a felt hat, a paper clip and a bottle). Responses are coded as correct, incorrect and as perseverative errors. Current mood and anxiety were measured by the hospital anxiety and depression scale (HADS-A and HADS-D) [17]. Using information obtained at interview, age at menopause was defined as the age when menses had not occurred for at least 1 year. Consistency of reproductive history

responses was checked 1–2 years later by telephonic review with a sub-sample of 187/221 subjects.

Authors of a meta-analysis [7] had suggested years of education, health, mood, alcohol consumption and sleep disturbance were sources of estrogen-related variation in cognitive function in women in later life. Informed by earlier studies on variation in age at menopause [18,19], we recorded usual address, years of education, age at menarche and first pregnancy, parity, smoking history, alcohol consumption, body mass index (BMI) at age about 65 and use of hormone replacement therapy as a part of the systematic evaluation of current medical status and past medical history. Usual address provided a "deprivation category" which is an ecological measure of relative socio-economic deprivation based on the small area ecological method devised by Carstairs and Morris [20]. In Scotland, among women and in those aged over 60 years, this ecological method is more informative than socio-economic classification by own occupation or that of husband.

2.2. Statistical methods

Childhood mental ability scores from 1947 were transformed into a conventional IQ-type score (mean 100, S.D. 15) after adjustment for age on the day of testing (4 June 1947). Scores on all cognitive tests administered in 2000–2001 (RPM, AVLT, BD, DS and UCO) were all positively correlated, suggesting the existence of one or more general cognitive factors. Therefore, data from the five cognitive tests at about age 65 were reduced by principal components analysis. Analysis of the scree slope and eigen values suggested only one component, which accounted for 51.5% of the total score variance. Scores on this component were adjusted for age at testing and transformed into IQ-type measures (mean 100, S.D. 15) to facilitate comparison with childhood measures.

Data from those women who had experienced a natural menopause were examined using correlation, multiple regression and survival analyses to estimate the contributions of age at menopause and age-adjusted childhood IQ to the prediction of general cognitive scores at about an age of 65 years. Correlations were also examined between general cognitive function and variables that may have contributed to the relationship between age at menopause and cognitive function aged about 65. These included socio-economic deprivation, HADS anxiety, HADS depression, years of formal education, smoking status, parity and BMI. The EQS structural equation modelling program was next used to construct and test models of association among menopause and mental ability at about an age of 11 and 65 years [21].

2.3. Model specification in EQS

An economical model was specified to account for associations among childhood IQ, the timing of natural menopause, and diverse measures of cognitive ability at an age of 65 years. It was hypothesised that the psychometric tests at 65 (Auditory Verbal Learning Test, Block Design, Digit Symbol, Uses of Common Objects and Raven' Progressive Matrices) are all loaded significantly on a latent trait representing general cognitive function. The model hypothesised that childhood IQ had a significant association with mental ability at 65, and that childhood IQ was associated significantly with the timing of the natural menopause. Further, it was hypothesised that the timing of the menopause partly mediated the effect of childhood IQ on cognition in later life.

3. Results

All MMSE scores were in the non-demented range (24–30). Subjects who scored 24 (one) or 25 (four) were reviewed and none met current clinical criteria for dementia. There were missing data on some cognitive tests among 159 women who had experienced natural menopause and had been recruited to the study. These were Block Design (13 subjects), Digit Symbol (8), Uses of Common Objects (11), Auditory Verbal Learning Test (11) and Raven's Progressive Matrices (4). When the 144 women who completed all the tests and thus who form the subjects of this report were compared with those 15 women who did not, the latter group scored significantly lower on childhood IQ $P < 0.001$, MMSE $P < 0.001$, Raven's Progressive Matrices $P < 0.001$, Block Design $P < 0.001$ and Uses for Objects $P < 0.05$ but did not differ in age at menopause.

The age at natural menopause given at recruitment was compared with the age at natural menopause

obtained by a telephonic interview 1–2 years later in 187/221 women, recruited to the study. 131 (of the 144 sub-sample of women who completed most of the cognitive tests) were re-assessed by telephone and of these, 106 gave the same year of menopause, 12 differed by 1 year and 13 differed by 2 or more years (range −8 to +9 years). Ages at menopause reported on two occasions correlated 0.97 $P < 0.001$. Cognitive scores were lower in women who differed by more than one year in age at menopause when compared to those who differed by no more than one year (childhood IQ, $P < 0.01$; Raven's Progressive Matrices, $P < 0.005$; Digit Symbol, $P < 0.05$ and general cognitive score at about age 65 $P < 0.01$. Data from women whose reported ages at menopause did not differ by more than 1 year were analysed separately. Correlations reported below between age at menopause and cognitive scores were similar in size to those correlations obtained for the complete sample (full details available from authors on request).

Table 1 summarises associations between childhood intelligence, age at natural menopause and factors suggested by relevant literature as possible determinants of age at menopause. There were significant correlations between childhood intelligence and length of education ($r = 0.490$, $P < 0.001$) and between childhood intelligence and alcohol consumption ($\rho = 0.18$, $P = 0.034$). There were no significant correlations between age at natural menopause of any of the factors previously found to be associated with age at menopause.

Table 2 presents mean age adjusted IQ age approximately 11 and 65 years, cognitive tests aged about 65 and their correlations with childhood intelligence and age at natural menopause. Childhood IQ significantly correlated with all cognitive tests. Age at natural menopause significantly correlated with childhood IQ; IQ age 65; Raven's Progressive Matrices and Digit Symbol.

A multiple regression model showed that childhood IQ predicted general cognitive score at an age of 65 years (adjusted $R^2 = 0.427$). Addition of years of education improved the model (R^2 change $= 0.039$, d.f. $= 1, 141$; $F = 10.17$, $P = 0.002$) Age at natural menopause, deprivation category, pack years, alcohol consumption, menarche, BMI and HADS-depression or anxiety scores did not significantly improve the model.

Fig. 1 presents Kaplan–Meier survival functions of age at natural menopause by tertile of IQ aged 11 in 144 postmenopausal women. The log rank test statistics showed the unequal survival functions between the tertiles of childhood IQs (statistic $= 8.16$, d.f. $= 2$, $P < 0.02$). A Cox proportional hazards model was then fitted to age at natural menopause first with childhood intelligence as a covariate and then after the stepwise addition of deprivation, education, smoking and parity. The Chi-square statistics was significant with the childhood intelligence entered alone ($\chi^2 = 4.227$, d.f. $= 1$, $P = 0.04$; Wald $= 4.407$, d.f. $= 1$, $P = 0.036$) and with years of education or smoking history but was not significant after addition

Table 1
Correlations between IQ age 11, age at menopause, and demographic variables in 144 postmenopausal women aged about 65 years (r = Pearson's, ρ = Spearman's)

Variable	Mean	S.D.	Range	IQ age 11	P value	Age at menopause	P value
Education (years)	11.2	2.0	10–18	$r = 0.490$	0.000	$r = 0.100$	0.234
Deprivation category	3.1	1.5	1–6	$r = -0.092$	0.281	$r = 0.081$	0.343
Smoking (pack years)	14.1	18.7		$\rho = -0.11$	0.186	$\rho = -0.076$	0.364
Alcohol (units per week)	3.8	4.8	0–21	$\rho = 0.18$	0.034	$\rho = 0.086$	0.307
Parity[a]	2.4	1.2	0–6	$r = 0.036$	0.702	$r = 0.116$	0.230
Age at first child[a]	24.6	4.3	18–41	$r = 0.076$	0.381	$r = 0.030$	0.88
Menarche (years)	13.3	1.6	10–17	$r = -0.155$	0.136	$r = 0.039$	0.71
HADS anxiety	6.3	3.2	0–15	$r = -0.071$	0.397	$r = 0.065$	0.440
HADS depression	3.0	2.3	0–11	$r = -0.089$	0.293	$r = -0.122$	0.146
BMI	26.9	5.3	16.6–44.0	$r = -0.077$	0.360	$r = 0.024$	0.772

Deprivation category is an ecological measure derived from the postal address and based on small area census returns; 1: most affluent, 6: most deprived.
[a] $n = 123$.

Table 2
Pearson's correlations between childhood intelligence, age at menopause and cognitive variables in 144 postmenopausal women aged about 65 years

Cognitive variable	Mean	S.D.	Range	IQ age 11	*P* value	Age at menopause	*P* value
IQ age 11	100	15	63–135	–	–	$r = 0.221$	0.008
IQ age 65	100	15	65–145	$r = 0.654$	0.001	$r = 0.246$	0.004
Raven's Progressive Matrices	36.5	8.0	15–53	$r = 0.586$	0.001	$r = 0.213$	0.01
Auditory Verbal Learning Test	64.1	12.2	30–113	$r = 0.369$	0.001	$r = 0.157$	0.07
Block Design	23.4	7.8	1–43	$r = 0.555$	0.001	$r = 0.083$	0.35
Digit Symbol	46.6	10.6	24–75	$r = 0.530$	0.001	$r = 0.260$	0.002
Uses of Objects Test	12.4	4.7	3–24	$r = 0.442$	0.001	$r = 0.133$	0.13

of years of education $P = 0.051$; none these factors were significant predictors of age at menopause when entered alone.

3.1. Structural equation model fit and structure

The hypothetical model which was fitted to the data is shown in Fig. 2. The fit indices were as follows: average of the off-diagonal absolute standardised residuals = 0.04; Chi-square = 14.5, d.f. = 14, $P = 0.41$; Bentler–Bonett normed fit index = 0.95; Bentler–Bonett non-normed fit index = 0.99, comparative fit index = 0.99. The Wald test indicated that the path between age at menopause and the general cognitive factor at an age of 65 years (F1 in Fig. 1) should be dropped. This parameter was not significantly greater than zero. The Lagrange Multiplier Test indicated that there were no additional paths that might significantly improve the model.

Measures of cognitive function at about 65 years of age loaded significantly—between 0.58 and 0.68—on the latent trait representing general cognitive function (Fig. 1). There was a significant association between the Moray House Test score at 11 years and the

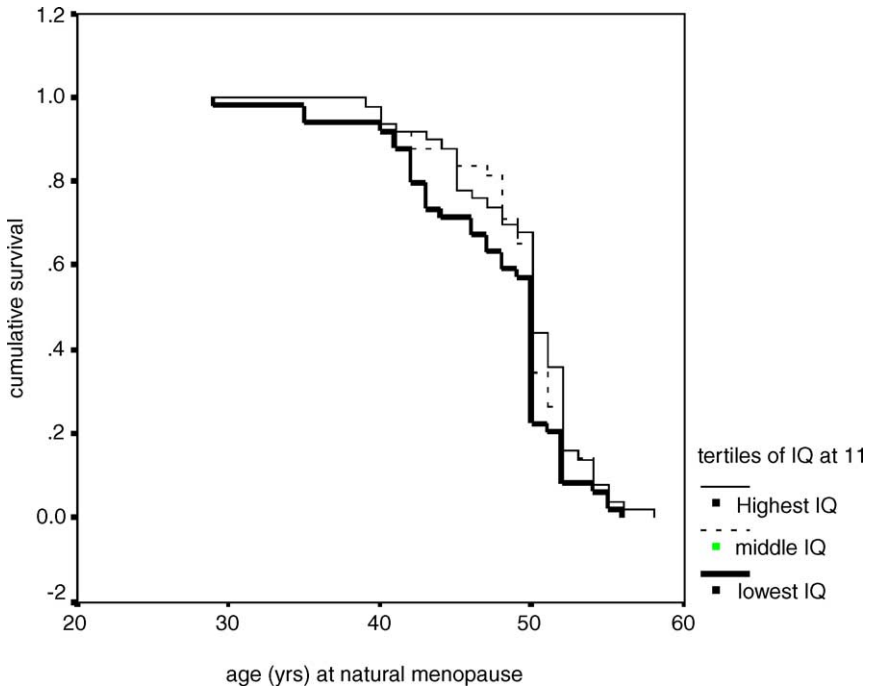

Fig. 1. Kaplan–Meier survival functions of age at natural menopause by tertile of IQs aged about 11 in all the 144 women.

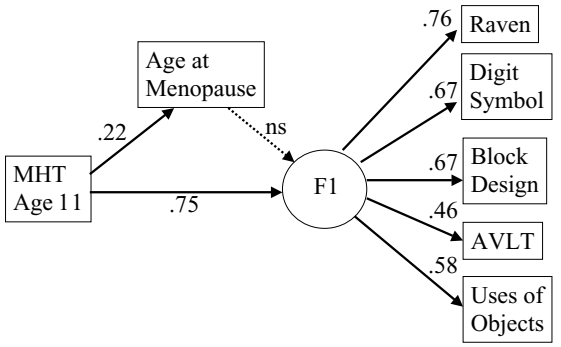

Fig. 2. Structural equational model of childhood mental ability (MHT), age at menopause and cognitive function (F1).

timing of the natural menopause (standardised regression weight = 0.22), but not between the menopause timing and the general cognitive function age of 65 years (non-significant parameter). As expected, there was a significant, direct association between age 11 test scores and general cognitive function age 65 (standardised regression weight = 0.75). There were no significant paths between the age of 11 years IQ or timing of the natural menopause and the specific cognitive test scores.

4. Discussion

Age at natural menopause was associated with lower childhood IQ and lower performance on tests of cognitive ability at an age of 65 years. The first finding strengthens that of Richards et al. [1] who showed that childhood mental ability contributes to individual differences in age at menopause in a UK 1946 birth cohort aged about 49. The finding that cognitive ability aged about 65 is significantly associated with age at menopause is novel. Therefore, we examined this using two different methods.

First, after entering IQ at age 11 into a multiple linear regression model, addition of years of education contributed 3.9% ($P = 0.002$) significant independent variance to mental ability age 65. Age at natural menopause, deprivation category, pack years smoked, alcohol consumption, age at menarche, BMI aged about 65, and HADS depression or anxiety scores did not improve the prediction of cognitive ability age of 65 years.

Second, structural equation modelling optimised statistical testing of competing explanations of these associations and the results were consistent with the findings of multiple regression. The strong association between the IQ age of 11 years and later the cognitive function was expected. However, once the association between the childhood IQ and the age at menopause was taken into account, the association between the age at menopause and the ability age of 65 years was no longer significant. Therefore, age at menopause does not mediate the association between childhood and 65 years mental ability scores.

We interpreted the multiple regression analysis as exclusion of potential confounding by socio-economic deprivation, concurrent anxiety and depression, years of education (always continued beyond age 13) and reproductive history. From this combined approach using multiple regression and structural equation modelling, we conclude that the association between age at menopause and cognition age 65 is attributable to effects of IQ at age 11 on both.

Although our finding of a significant correlation between age at menopause and age 65 cognitive scores at first appears consistent with observed associations between exogenous estrogen on general health and cognitive function in well-educated postmenopausal women, there should be caution before accepting this interpretation. Once the contribution of childhood IQ to mental ability age about 65 is accounted for, the relationship between age at menopause and later mental ability falls to a non-significant value. Post-menopausal estrogen depletion is, therefore, not implicated by this finding.

Some of the variance shared between menopause and childhood ability might be attributable to earlier influences shared by both IQ age 11 and timing of menopause. Variation in age at menopause has been partly attributed to lower weight gain in the first year of life [22] which is also associated with lower childhood ability [23]. Impaired growth in utero and later in childhood is associated with lower academic and occupational achievements [24,25]. It is plausible, therefore, that early menopause and lower childhood mental ability share exposures to factors that impair early growth.

In addition to simple oocytic depletion, Wise [26] have provided extensive experimental data derived from a rat model of menopause which proves that

the timing of menopause is influenced by age-related changes in central neuroendocrine regulatory systems. She argues their observations have the potential to link the timing of human menopause to brain aging through age-related changes in multiple biological pacemakers (clocks) that disrupt reproductive cycles, decrease fertility and lead ultimately to a post-reproductive state.

The present study is strengthened by the availability of valid estimates of childhood intelligence but is limited by uncertainty about the reliability of recall of age at menopause. Mean age at menopause in this sample of 144 women (48.1 years) was lower than figures quoted elsewhere for the UK population [27] and this may be a birth cohort-specific effect. Hahn et al. [28] compared the responses made at first and second interviews by 2545 women participants in the US National Health and Nutrition Survey and follow-up study and found that reliability (around 70%) fell with time from menopause. Likewise, den Tonkelaar [29] reported that the age at natural menopause was accurately reported by about 70% of a sample of Dutch women and that accuracy declined with time since menopause. We addressed this issue by repeat telephone enquiry after 1–2 years and found high overall high agreement within subjects. A minority gave ages at the second occasion more than 2 years earlier or later than on the first occasion. The overall effect of discrepant reporting (as with decreasing reliability with increasing age) is to underestimate the contribution of age at menopause to disorders with late onset. Further uncertainty was raised by about 10% of women eligible for inclusion but who declined to complete some cognitive tests. They were seen to be less able age about 11 and 65 and this may have biased the study towards the more able. The most likely effect of this, if any, would be to attenuate the range of ability scores in this sample and to lead to the correlations here being slight underestimates of the true values.

These findings may not be relevant to AD. In the Rotterdam study [30] the incidence of late onset dementia was not associated with earlier menopause: a longer reproductive period was associated with an increased risk of dementia. The findings in the Rotterdam study are not inconsistent with those recent studies [7] which report insufficient evidence to link exposure to exogenous estrogens with risk of dementia.

Genetic factors play a part in the timing of age at menopause [31], and the same genetic factors might contribute to individual differences in postmenopausal cognitive ability. For example, polymorphisms in the estrogen receptor (ER) gene may influence age at menopause [32] and also be associated with AD [33] though, if present, this association is probably complex [34]. Midlife exposures to risk factors for vascular disease probably contribute to late onset AD [35]. Some risk factors for earlier age at menopause might also increase risk of later vascular disease. These include smoking history [36], potentially hazardous changes in serum lipids and lipoproteins [37] and impaired glucose tolerance [38]. These associations suggest possible links to the impaired foetal growth hypothesis of adult cardiovascular disease [39]. A complex interaction seems likely between intra-uterine disadvantage [22], lower childhood IQ, earlier menopause and lower mental ability in late life. Shared disease mechanisms might explain associations between lower age at menopause and increases in total mortality and risk of cardiovascular disease [40,41] and possibly, with increased cancer-related mortality [42].

5. Conclusion

A link between childhood mental ability and age at menopause was not unexpected. Epidemiological studies of age at menopause previously showed that fewer years of education are associated with earlier menopause [18,19] later confirmed by Richards et al. [1] who explained this association as the effect of gonadal steroids on both neurodevelopment and timing of menopause. It is possible that the effect is mediated through a contribution of childhood IQ to adult health. Previously, we showed that longevity is linked to childhood mental ability [43], and have implicated increased susceptibility to disease or increased disease-specific mortality in those with lower mental ability [44]. Age at natural menopause might reflect lifelong health status and differences in rates of ageing [45] and, in light of our earlier work, this might be partly determined by childhood mental ability. In our proposed model of age-related cognitive decline, indices of morbidity and mortality in late life (linked to childhood mental ability and to earlier menopause)

would provide a source of individual variation in cognitive performance amongst the old people.

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References

[1] Richards M, Kuh D, Hardy R, Wadsworth M. Lifetime cognitive function and timing of the natural menopause. Neurology 1999;53:308–14.
[2] Yaffe K, Lui LY, Grady D, Cauley J, Kramer J, Cummings SR. Cognitive decline in women in relation to non-protein bound oestradiol concentrations. Lancet 2000;356:708–12.
[3] Polo-Kantola P, Portin R, Polo O, Helenius H, Irjala K, Erkkola R. The effect of short-term estrogen replacement therapy on cognition: a randomized, double-blind, cross-over trial in postmenopausal women. Obstetr Gynecol 1998; 91:459–66.
[4] Tang M, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, et al. Effects of estrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348:429–32.
[5] Kawas C, Resnick S, Morrison A, Brookmeyer R, Corrada M, Zonderman A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48:1517–21.
[6] Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 2003;289:2651–9.
[7] LeBlanc ES, Janowsky J, Chan BKS, Nelson HD. Hormone replacement therapy and cognition—systematic review of meta-analysis. JAMA 2001;285:1489–99.
[8] Meyer PM, Powell LH, Wilson RS, Everson-Rose SA, Kravitz HM, Luborsky JL, et al. A population-based longitudinal study of cognitive functioning in the menopause transition. Neurology 2003;61:801–6.
[9] Brett KM, Cooper GS. Associations with menopause and menopausal transition in a nationally representative US sample. Maturitas 2003;45(2):89–97.
[10] Hardy R, Kuh D, Wadsworth M. Smoking, body mass index, socio-economic status and the menopausal transition in a British national cohort. Int J Epidemiol 2000;29:845–51.
[11] Deary IJ, Whalley LJ, Lemmon HA, Crawford JR, Starr JM. The stability of individual differences in mental ability from childhood to old age. Follow-up of the 1932 Scottish mental survey. Intelligence 2000;28:49–55.
[12] Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State" a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[13] Raven JC. Revised manual for Raven's Progressive Matrices and vocabulary scale. Windsor, Berks, UK: NFER-Nelson; 1982.
[14] Rey A. L'examen clinique en psychologie. Paris: Presses Universitaires de France; 1964.
[15] Wechsler D. WAIS-R manual. New York: The Psychological Corporation; 1981.
[16] Guilford JP, Christensen PR, Merrifield PR, Wilson RC. Alternate uses: manual of instructions and interpretation. Orange, CA: Sheridan Psychological Services; 1978.
[17] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scan 1983;67:361–70.
[18] Do KA, Treloar SA, Pandeya N, Purdie D, Green AC, Heath AC, et al. Predictive factors of age at menopause in a large Australian twin study. Hum Biol 1998;70:1073–91.
[19] Treloar SA, Sadrzadeh S, Do KA, Martin NG, Lambalk CB. Birth weight and age at menopause in Australian female twin pairs: exploration of the fetal origin hypothesis. Hum Reprod 2000;15:55–9.
[20] Carstairs V, Morris P. Socioeconomic deprivation in Scotland. Aberdeen University Press; 1990.
[21] Bentler PM. EQS structural equations program manual. Encino, CA: Multivariate Software Inc.; 1995.
[22] Cresswell JL, Egger P, Fall CHD, Osmond C, Fraser RB, Barker DJP. Is the age of menopause determined in utero? Early Hum Dev 1997;49:143–8.
[23] Deary IJ. Looking down on human intelligence: from psychometrics to the brain. Oxford psychology series number 34. Oxford University Press; 2000.
[24] Van der Meulen JH. Commentary: early growth and cognitive development. Int J Epidemiol 2001;30(1):72–4.
[25] Richards M, Hardy R, Kuh D, Wadsworth ME. Birthweight, postnatal growth and cognitive function in a national UK birth cohort. Int J Epidemiol 2002;31(2):342–8.
[26] Wise PM. Neuroendocrine modulation of the "menopause": insights into the aging brain. Am J Physiol Endocrinol Metab 1999;277:965–70.
[27] McKinlay S, Jefferys M, Thompson B. An investigation of the age at menopause. J Biosoc Sci 1972;4:161–73.
[28] Hahn RA, Eaker E, Rolka H. Reliability of reported age at menopause. Am J Epidemiol 1997;146:771–5.
[29] den Tonkelaar I. Validity and reproducibility of self-reported age at menopause in women participating in the DOM-project. Maturitas 1997;27:117–23.
[30] Geerlings MI, Ruitenberg A, Witteman JCM, van Swieten JC, Hofman A, van Duijn CM, et al. Reproductive period and risk of dementia in postmenopausal women. JAMA 2001;285:1475–81.
[31] Snieder H, MacGregor AJ, Spector TD. Genes control the cessation of a woman's reproductive life: a twin study of

hysterectomy and age at menopause. J Clin Endocrinol Metab 1998;83:1875–80.
[32] Weel AEAM, Uitterlinden AG, Westerdorp IC, Burger H, Schuit SC, Hofman A, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. J Clin Endocrinol Metab 1999;84:3146–50.
[33] Ji Y, Urakami K, Wada-Isoe K, Adachi Y, Nakashima K. Estrogen receptor gene polymorphisms in patients with Alzheimer's disease, vascular dementia and alcohol associated dementia. Dement Geriatr Cogn Disord 2000;11:119–22.
[34] Lambert JC, Harris JM, Mann D, Lemmon H, Coates J, Cumming A, et al. Are estrogen receptors involved in Alzheimer's disease? Neurosci Lett 2001;306:193–7.
[35] Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population-based study. BMJ 2001;322:1447–51.
[36] Bromberger JT, Matthews KA, Kuller LH, Wing RR, Meilahn EN, Plantinga P. Prospective study of the determinants of age at menopause. Am J Epidemiol 1997;145:124–33.
[37] Stevenson JC, Crook D, Godsland IF. Influence of age and menopause in serum-lipids and lipoproteins in healthy women. Atherosclerosis 1993;98:83–90.
[38] Wu SI, Chou P, Tsai ST. The impact of years since menopause on the development of impaired glucose tolerance. J Clin Epidemiol 2001;54:117–20.
[39] Barker DJ, Eriksson JG, Forsen T, Osmond C. Fetal origins of adult disease: strength of effects and biologic basis. Int J Epdemiol 2002;31(6):1235–9.
[40] Snowdon DA, Kain RL, Beeson WL, Burke GL, Sprafka JM, Potter H, et al. Is early natural menopause a biologic marker of health and aging? Am J Public Health 1989;79:709–14.
[41] vanderSchouw YT, vanderGraaf Y, Steyerberg EW, Eijkemans MJC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714–8.
[42] Cooper GS, Sandler DP. Age at natural menopause and mortality. Ann Epidemiol 1988;8:229–35.
[43] Whalley LJ, Deary IJ. Longitudinal cohort study of childhood IQ and survival up to age 76. BMJ 2001;322:818–22.
[44] Starr JM, Deary IJ, Lemmon HA, Whalley LJ. Mental ability age 11 years and health status age 77 years. Age Ageing 2000;29:523–8.
[45] Sayer AA, Cooper C, Evans JR, Rauf A, Wormald RP, Osmond C, et al. Are rates of ageing determined in utero? Age Ageing 1998;27(5):579–83.