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INFANCY AND CHILDHOOD INFLUENCES ON LATER HEALTH

Intelligence in youth and all-cause-mortality: systematic review with meta-analysis

Catherine M Calvin,[1] Ian J Deary,[1]* Candida Fenton,[2] Beverly A Roberts,[1] Geoff Der,[2] Nicola Leckenby[1] and G David Batty[1,2,3]

[1]Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, Edinburgh, UK, [2]Medical Research Council Social & Public Health Sciences Unit, Glasgow, UK and [3]Department of Epidemiology & Public Health, University College London, London, UK

*Corresponding author. Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK. E-mail: ian.deary@ed.ac.uk

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Background A number of prospective cohort studies have examined the association between intelligence in childhood or youth and life expectancy in adulthood; however, the effect size of this association is yet to be quantified and previous reviews require updating.

Methods The systematic review included an electronic search of EMBASE, MEDLINE and PSYCHINFO databases. This yielded 16 unrelated studies that met inclusion criteria, comprising 22 453 deaths among 1 107 022 participants. Heterogeneity was assessed, and fixed effects models were applied to the aggregate data. Publication bias was evaluated, and sensitivity analyses were conducted.

Results A 1-standard deviation (SD) advantage in cognitive test scores was associated with a 24% (95% confidence interval 23–25) lower risk of death, during a 17- to 69-year follow-up. There was little evidence of publication bias (Egger's intercept = 0.10, $P = 0.81$), and the intelligence–mortality association was similar for men and women. Adjustment for childhood socio-economic status (SES) in the nine studies containing these data had almost no impact on this relationship, suggesting that this is not a confounder of the intelligence–mortality association. Controlling for adult SES in five studies and for education in six studies attenuated the intelligence–mortality hazard ratios by 34 and 54%, respectively.

Conclusions Future investigations should address the extent to which attenuation of the intelligence–mortality link by adult SES indicators is due to mediation, over-adjustment and/or confounding. The explanation(s) for association between higher early-life intelligence and lower risk of adult mortality require further elucidation.

Keywords Intelligence, mortality, meta-analysis, socio-economic factors, systematic review

Introduction

Individual differences in intelligence (cognitive ability, mental ability) test scores, as measured by standardized IQ-type tests in childhood, show an inverse association with risk of death from all causes throughout adulthood. That is, higher intelligence appears to confer protection. This finding is replicated in prospective cohorts from several Westernized countries,[1] across different ranges of intelligence,[2] and in follow-up periods from early through to late adulthood.[2–4]

Intelligence and somatic health may be inextricably linked throughout the life course. However, longitudinal studies help to establish causal pathway models of the effects of one upon the other. For example, morbidities such as diabetes, cancer, stroke and peripheral atherosclerosis, and/or their treatments, are reported to cause a decline in cognitive function after longitudinal follow-up.[5–10] This illness-to-cognitive ability direction of association is a commonplace finding. The reverse direction of association is studied less often, and has only recently come to be recognized under the term 'cognitive epidemiology'.[11,12] That is, mental ability scores from early life associated with later adulthood morbidities, and before any somatic symptoms or risk factors of disease are manifest, provide evidence that cognitive abilities may be predictive of later health outcomes.

The association between premorbid intelligence and adult all-cause mortality was the subject of a systematic review,[1] in which all nine studies that met the inclusion criteria demonstrated an inverse relationship between intelligence and risk of dying by the time of follow-up. The review did not quantify the association. Furthermore, there were insufficient studies to address comprehensively a number of pertinent questions from this research domain. One issue is whether or not the association between intelligence and mortality is the same in women as in men. For example, it is possible that sex differences in the incidence, age at onset of health behaviours, and the extent to which these act as risk factors for disease,[13,14] could produce sex-specific intelligence–mortality gradients. Data from many more men than women have been included in intelligence–mortality cohort studies to date, mainly due to some studies using military conscript databases. Moreover, when mixed-sex cohorts report mortality risk as predicted by intelligence for men and women separately, they rarely test for statistical difference but, rather, report the observed trend. With more studies now reporting hazard ratios (HRs) for mortality by sex, there is an opportunity to quantify the predictive effects of intelligence on mortality separately for men and women.

A second issue yet to be evaluated systematically is the extent to which intelligence as a predictor of mortality is confounded by early-life environmental influences including socio-economic factors. Socio-economic status (SES) is established as an important determinant of public health inequalities,[15–18] including risk of mortality, and it can carry influence in childhood, via factors such as family income and parental education, to predict individual differences in childhood intelligence.[19,20] In this context, therefore, intelligence may be considered a mediating variable on the pathway between early-life influences and adult health outcomes. If early social factors substantially confound the link between intelligence and longevity, then adjusting for childhood SES would sizeably attenuate the effect size of the association between intelligence and mortality. In their systematic review, Batty *et al.*[1] identified three out of nine studies that adjusted for childhood SES: one of these showed no change from an unadjusted model, and two had modest attenuating effects, suggesting that intelligence has independent effects on risk of mortality from those of early socio-economic influences. Due to this small number of studies, the role of childhood SES in the intelligence–mortality link requires further investigation.

One explanation why intelligence may exert an influence on life expectancy is its ability to predict educational outcomes[21] and occupational class,[22] which can both affect health outcomes via a number of mechanisms; for example, the knowledge and living conditions that contribute to better personal health risk assessment, behaviours and management.[23] In population studies these adult SES factors are themselves inversely associated with risk of mortality.[24–26] Some prospective cohorts take account of the attenuating effects of education and adult SES in estimating the risk of mortality according to intelligence; yet, to date, their influence has not been properly evaluated.

Investigators are giving increasing attention to the issues raised here, with a higher rate of publications reporting risk estimates for all-cause mortality according to differences in intelligence since the first systematic review.[1] There is now an opportunity to re-evaluate this augmented literature, this time with a quantitative, meta-analytic approach. The systematic review by Batty *et al.*[1] reported the overall quality of the nine studies as 'moderate', which was in part related to the weak validity of some measures of premorbid intelligence. Therefore, one important change to the systematic process reported here is the inclusion of studies in which only valid cognitive assessments were used. Kilgour *et al.*[27] also raised a number of methodological considerations that should be addressed in intelligence–mortality studies, including taking account of ascertainment bias, age, sex and education. In this article we address the influence of these factors using subgroup analyses.

Accordingly, the aims of this report are to (i) quantify the association between premorbid intelligence and all-cause mortality, (ii) determine whether there are sex differences in the association and (iii) conduct subgroup analyses on studies that adjust for early-life SES, adult SES and education, to discover their magnitude of influence as potential confounders or mediators of the intelligence–mortality association.

Methods

Systematic review process

An electronic search was conducted of premorbid intelligence and all-cause mortality in all published articles, letters, abstracts and reviews, using the electronic databases MEDLINE, EMBASE and PSYCHINFO (via Ovid). Searches were limited to articles on humans published in the English language. The databases were searched using a cognitive ability-related term ('Aptitude or Cognition'* or 'Cognitive function'* or 'Cognitive ability' or 'Cognitive characteristics' or 'Cognitive style' or 'intellectual ability' or 'Intelligence measures' or 'Intelligence quotient' or 'Intelligence test'* or 'Intelligence'* or 'IQ or Language test'* or 'Memory' or 'Mental ability'* or 'Mental capacity' or 'problem-solving' or 'Problem solving' or 'Psychological performance' or 'Psychometrics') AND a mortality term ('Cause of Death'* or 'Cause of Death trends' or 'Death'* or 'death rate' or 'Incidence' or 'Morbidity' or 'Morbidity trends' or 'Mortality Rate' or 'Mortality risk' or 'Mortality*' or 'Mortality trends'), an asterisk allowing the search term to precede a longer word or phrase.

The electronic search, conducted on 5 February 2010, yielded 19 236 articles. Two authors (C.C. and N.L.) independently scanned each title and abstract, retrieving articles on the basis of their relevance to intelligence and mortality. The inclusion criteria listed below were applied to their respective shortlists of papers. The reference lists of the selected articles were then examined, along with review papers on intelligence and mortality, and our own personal files, for articles that the electronic search might have missed. Among the final list of articles, when more than one paper reported intelligence–mortality associations from the same cohort, thereby duplicating data, three authors (C.C., D.B. and I.D.) agreed upon those papers to be retained, according to criteria of the following order: (i) the article reported HRs for mortality per 1-standard deviation (SD) difference in IQ-type score; (ii) the cohort size was larger; (iii) it was the original publication to report the data.

Inclusion criteria

We included published cohort data which fulfilled criteria similar to that of the previous systematic review on intelligence and all-cause mortality:[1] (i) to minimize risk of reverse causality, only cohorts where intelligence test score data were collected at a mean age of 24 years or younger were included (the period classified as childhood and youth according to the World Health Organisation Study Group[28]); (ii) the intelligence and mortality data were collected at the level of the individual; (iii) the relationship between intelligence and all-cause mortality was reported quantitatively. We also stipulated that: (iv) the premorbid test should demonstrate an acceptable degree of validity as a measure of intelligence; and (v) the cohort was not selected from a clinical or unrepresentative population.

Statistical analysis

The HR with 95% confidence intervals (CIs) for all-cause mortality per SD advantage in intelligence test score was the principal outcome variable. For HRs expressed per 1SD disadvantage in intelligence, the reciprocal was used. Reported odds ratios (ORs) were treated as HRs, with the caveat that these effect estimates approximate one another[29] when the incidence of an event (i.e. mortality) is low.[30] In case–control studies reporting intelligence test means for living and deceased, we converted the standardized mean difference to an OR using formulae by Chinn.[31] We contacted authors if we were unable to derive an overall effect size from their published data.

Fixed effects models were assumed for the aggregation of HRs based on evidence of a low degree of heterogeneity ($P < 0.10$).[32] Subgroup analyses were conducted by sex group, for those studies to adjust for SES variables, and by study characteristic groupings for the purposes of sensitivity analysis. MIX 1.5 software[33] was used for all analyses and production of plots. The inverse variance method was used to weight studies' effect sizes.

Sensitivity analyses and publication bias

Sensitivity analyses aggregated effect sizes by the following study characteristics: ascertainment rate at follow-up; age at intelligence testing; cohort size; duration of follow-up; average birth year of the cohort; effect size measure (see Table 2 for group parameters). Ascertainment rate may bias the intelligence–mortality effect size if those who emigrate, and are therefore excluded from follow-up, differ on cognitive ability scores compared with those who remain within geographical regions for census. Follow-up rates were estimated based on the proportion of participants from the original cohort that were followed up and included in the final analyses, regardless of whether or not intelligence test scores were available for them. Studies were grouped on the basis of <80% or 80–100% ascertainment rates. We aggregated studies according to age at cognitive testing, first because the likelihood of an effect of bodily insults on intellectual function increases with age and, with it, the risk of reverse causation bias in the intelligence–mortality link. Conversely, the validity of cognitive testing may be greater in older cohorts, and these may reflect more homogeneous results compared with results of younger children at intelligence testing for whom there is more measurement error. For the duration of follow-up, we divided studies on the basis of a median split of the years traced for mortality. Although there may be stronger grounds for assuming causality as the time period between intelligence testing and mortality increases, there is also evidence that, by older adulthood, the intelligence–mortality

association loses significance.[34] The reason for aggregating studies that reported HRs or ORs was to ensure that our treatment of these measures of association did not inflate the overall effect size. We also grouped according to cohort size and decade of birth, as these may also have influenced heterogeneity across the studies. We did not aggregate for population representativeness as one of our criteria ensured the exclusion of clinical samples. However, due to two study cohorts being less representative of the general population (twins and gifted children) than all others, we have reported meta-analytic results with and without their effect sizes.[35,36]

The funnel plot was used to assess publication bias with standard error on the *y*-axis as recommended by Sterne and Egger.[37] Publication bias was further evaluated with Egger's test of asymmetry, and trim-and-fill adjustment methods.

Results

Systematic retrieval of studies

The electronic search resulted in 19 236 publications and, of these, the two reviewers (C.C., N.L.) extracted shortlists of 73 and 69 relevant articles, respectively (<0.4% of total publications), from which 90 non-duplicate publications were retrieved for closer inspection (see Figure 1 for review process). Among these, 64 failed to meet one or more inclusion criteria. A further three studies that met inclusion criteria were identified from the reference lists of the remaining 26 papers, or from review articles or our own records.[38–40] Out of 29 studies, 2 were excluded[39,40] because we were unable to obtain sufficient data to calculate the intelligence–mortality effect sizes. (Table 1 lists the characteristics of the final 27 studies). We excluded 11 articles from the meta-analysis because they overlapped with cohort data of another report.[34,38,41–49] Justification for excluding these data were: (i) the overlapping reports of a sample were generally reported by the same research group resulting in consistent methods of sample selection and data linkage; and (ii) the majority of overlapping cohorts were of similar size and follow-up duration.

Study descriptions for meta-analysis

A total of 16 prospective longitudinal cohort studies included 22 453 deaths among 1 107 022 participants. These were from five countries: UK ($n=7$), USA ($n=5$), Sweden ($n=2$), Australia ($n=1$) and Denmark ($n=1$), ranging in size from 862 to 994 262 participants. Figure 2 illustrates these variables according to year of publication, showing a trend for larger cohorts accumulating in more recent years. Premorbid intelligence test scores were taken from school records ($n=10$), military or national service conscription records ($n=5$), or a research database ($n=1$). The average age at testing ranged from 7 to 20 years, and length of follow-up ranged from 17 to 69 years. Six cohorts were all male (five from conscription databases), and the remainder were mixed sex. A variety of cognitive assessments were used across studies, and we identified evidence for each of them as having validity as standardized measures of intelligence. The concurrent or predictive validity of five tests used across nine of the study cohorts[3,4,35,50–55] have been described elsewhere.[1] Here we describe evidence for psychometric validity among the seven remaining cohorts.

The Binet and Stanford-Binet tests used in two studies[36,56] are well-established, age-standardized intelligence tests for children. Scores on the original Stanford–Binet test contain a single underlying factor of cognitive ability,[57] and the Binet scale has concurrent validity with version 12 of the Moray House intelligence test ($r\sim0.80$).[56] Two studies included selected tests from the well-validated Moray House series.[58] The first study incorporated Moray House tests 57 and 58 in an 11-plus examination that also assessed language and arithmetic.[59] On this exam, total scores have shown well-established associations with childhood height at ages 9 and 13 years.[60] The second[2] used Moray House Picture Tests 1 and 2, which have also shown expected patterns of association with intrauterine and childhood growth.[19] The Härnquist test used in the Danish Metropolit study[61] has shown concurrent validity: a general intelligence factor extracted from scores on the test at age 13 years strongly positively correlated ($r=0.78$) with a military classification intelligence test taken 5 years later.[62] The Armed Forces Qualification Test (AFQT) used in another study[63] strongly correlates with other well-validated IQ tests (median r with seven tests = 0.81), and scores on the four subtests show high loadings on a single g factor, from 0.81 to 0.87.[64] Finally, the Vietnam Experience Study[65] used the Army General Technical test, which strongly correlates with verbal reasoning ($r=0.75$) and visuo-spatial ($r=0.51$) scores from the Weschler Adult Intelligence Scale (WAIS), a standardized and well-validated cognitive ability test battery.

Records of mortality were ascertained prospectively in seven studies, either by linkage of study members to national register databases[4,35,51–52,59] or by individual follow-up with study participants or their families.[36,63] In the remaining studies, incidence of death was ascertained retrospectively by access to national death registers—in Swedish cohorts record linkage used personal identification numbers rather than person names[3,50,53]—with the exception of two studies that did not report methods for extracting death records.[54,65]

Ten papers estimated the intelligence–mortality effect size as an HR with CIs,[2–4,36,50,53,55,56,59,65] two used ORs or logistic regression coefficients,[51,63] and two reported means and SDs that we converted to ORs.[35,54] Authors of the two remaining papers

provided HRs[52,61] in response to email requests, which were unreported in their original publications.

Intelligence–mortality meta-analysis: basic model

In the basic model, the HR from each of the 16 studies was either: unadjusted ($n=2$), adjusted for age ($n=3$), sex ($n=3$), age and sex ($n=3$), or was unspecified ($n=5$) (Table 1). However, there was a low degree of heterogeneity between the effect sizes of these models ($Q=17.7$, $I^2=15.5\%$, $P=0.28$). In a fixed effects model, a 1-SD advantage in intelligence was associated with the lower risk of all-cause mortality (HR 0.76, 95% CI 0.75–0.77) (Figure 3). The exclusion of two studies[35,36] based on selected samples (twins and gifted children) did not alter this estimate; neither did the exclusion of two studies that reported ORs and where incidence of death was between 20 and 40%[35,54] (data not shown). The statistical weight of the largest study[3] was 70.5%; excluding this cohort from the model made a negligible change to the effect of intelligence on risk of mortality (HR 0.77, 95% CI 0.75–0.80).

Sensitivity analyses results are presented in Table 2. Age at intelligence testing may have had a small effect in predicting the risk of mortality. Aggregation of studies in which premorbid intelligence was tested at an average age of between 7 and 12 years resulted in a small attenuation (16%) of the risk of mortality (HR 0.79, 95% CI 0.76–0.82) compared with that of 18- to 20-year olds (HR 0.75, 95% CI 0.74–0.77). Studies of longer follow-up (40–69 years) showed a 20% attenuation of the risk of mortality as predicted by a 1-SD advantage in intelligence (HR 0.80, 95% CI 0.76–0.83), compared with those cohorts of shorter follow-up (HR 0.75, 95% CI 0.74–0.77). Furthermore, there was a trend for cohorts born in the 1910s and 1920s to show an attenuated effect size compared with those cohorts born in the 1930–60s. However, these older age cohorts were also those with a longer duration of follow-up.

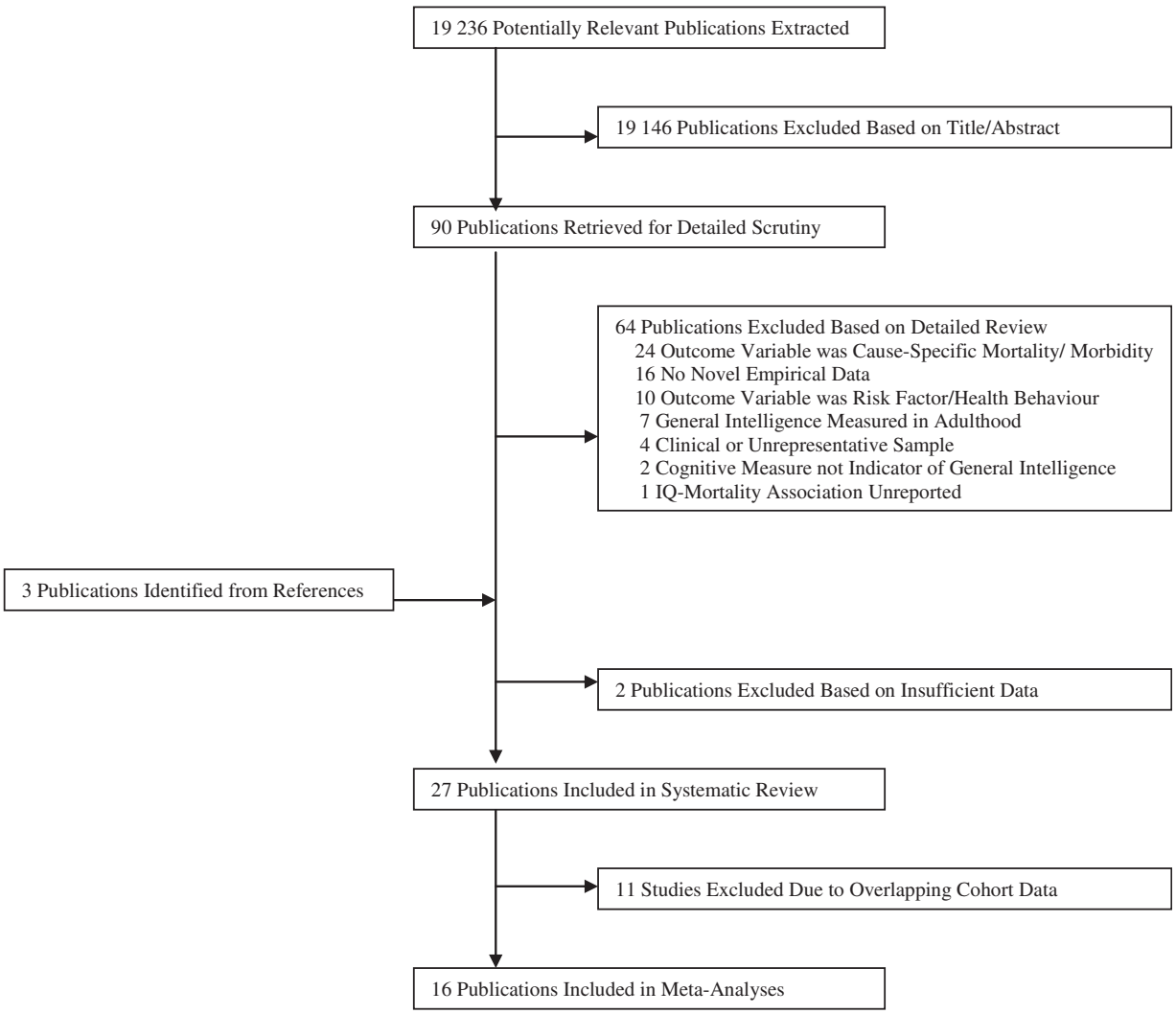

Figure 1 Flow diagram of articles selected for systematic review and meta-analysis

Table 1 Characteristics of 27 longitudinal cohort studies of premorbid intelligence and all-cause mortality

Study references	Country, study name	Sex	Birth year(s)	Age at cognitive test, years (mean)	Years of survival follow-up (*n* years since cognitive test)[a]	Cohort Size, *N*	Deaths, *n*	Intelligence test, cohort type	Model adjustments
*O'Toole *et al.* (1988)[54,b]	Australia, Veterans Health Studies	M	1947–53 (including earlier periods)	⩾18	1967–82 (2–17)	2309	523	AGCT, conscription	Basic model: unspecified Multiple adjustments: post-school course, no. of jobs; and during 2-year service history: AWOL offence, alcohol offence, duration of hospital stay, motor vehicle charge
*Whalley and Deary (2001)[55]	UK, SMS32 Aberdeen Cohort	M/F	1921	11	1932–97 (1–65)	1153 (M) 1032 (F)	646 (M) 438 (F)	Moray House No. 12, school	Basic model: age
Deary *et al.* (2003)[38]	UK, SMS32 Aberdeen Cohort	M/F	1921	11	1932–97 (1–65)	1139 (M) 1032 (F)	633 (M) 438 (F)	Moray House No. 12, school	–
*Hart *et al.* (2003)[4]	UK, SMS32 and Mid-span studies	M/F	1921	11	1970–2001 (38–69)	922	422	Moray House, school	Basic model: sex and age (HR= 0.85 [0.78–0.93]) Adult SES: basic model + adult social class (HR = 0.88 [0.79–0.98]) Multiple adjustments: adult SES model + deprivation
*Osler *et al.* (2003)[61]	Denmark, Metropolit2000	M	1953	12	1968–98 (3–33)	7308	522	Harnquist, school	Basic model: unspecified Childhood SES: father's social class Multiple adjustments: childhood SES model + birth weight
Deary *et al.* (2004)[44]	UK, SMS47 Six Day Sample	M/F	1936	11	1968–2000 (21–53)	908	125	Binet test, school	–
Kuh *et al.* (2004)[46]	UK, National Survey of Health and Development (British 1946 birth cohort)	M/F	1946	8	1971–2000 (17–46)	2192 (M) 2057 (F)	133 (M) 96 (F)	NFER tests, school	–
Hart *et al.* (2005)[34]	UK, SMS32 and Mid-span studies	M/F	1921	11	1970–2001 (38–69)	938	432	Moray House, school	–
*Martin and Kubzansky (2005)[36]	USA, Terman Life Cycle Study	M/F	1903–16	6–18 (11)	1922–86 (1–64)	862	293	Stanford-Binet, school	Basic model: sex Childhood SES: poor health and father's occupation
		M	1949–51	18–20 (19)	1971–2000 (1–31)	49 262	2022		Basic model: unadjusted

(continued)

Table 1 Continued

Study references	Country, study name	Sex	Birth year(s)	Age at cognitive test, years (mean)	Years of survival follow-up (*n* years since cognitive test)[a]	Cohort Size, *N*	Deaths, *n*	Intelligence test, cohort type	Model adjustments
*Hemmingsson *et al.* (2006)[50]	Sweden, Army Conscripts							SEB 1967, conscription	Childhood SES: father's occupation at age 9–11 Adult SES: adulthood socio-economic position Multiple adjustments: all above models
Vagero *et al.* (2006)[48]	Sweden, Army Conscripts (Stockholm Birth Cohort Study)	M	1953	(18)	1980–2002 (9–31)	6318	204	SEB, conscription	–
*Pearce *et al.* (2006)[59]	UK, Newcastle Thousand Families	M/F	1947	11	1959–2003 (1–45)	357 (M) 360 (F)	30 (M) 19 (F)	Moray House Nos. 57 & 58, school	Basic model: unspecified Childhood SES: father's social class at birth (mother's if unavailable)
*Holsinger *et al.* (2007)[35,c]	USA, NAC-NRC Twin WWII Veterans	M	1917–27	17–21 (19)	1967–2004 (22–59)	984	385	AGCT/GCT, conscription	Basic model: unspecified
Batty *et al.* (2008)[41]	USA, Vietnam Experience Study	M	1947	(19)	1985–2000 (18–33)	4157	231	Army General Technical, conscription	–
*Batty *et al.* (2008)[65,d]	USA, Vietnam Experience Study	M	1947	(20)	1985–2000 (18–33)	4316	241	Army General Technical, conscription	Basic model: age Education: educational level attained Adult SES: occupational prestige, educational grade and family income Multiple adjustments: basic model + adult SES model + rank, ethnicity, depression, body mass index, pulse rate, posttraumatic stress disorder, somatic disease, martial status, alcohol consumption, blood pressure, blood glucose, generalized anxiety disorder, smoking, FEV1
*Deary *et al.* (2008)[56]	UK, SMS47 Six Day Sample	M/F	1936	11	1968–2003 (21–56)	1181	193	Binet test, school	Basic model: with and without sex (no difference) Education: years of education Adult SES: occupational social class Multiple adjustments: sex and dependability

(continued)

Table 1 Continued

Study references	Country, study name	Sex	Birth year(s)	Age at cognitive test, years (mean)	Years of survival follow-up (*n* years since cognitive test)[a]	Cohort Size, *N*	Deaths, *n*	Intelligence test, cohort type	Model adjustments
Starr *et al.* (2008)[47]	UK, SMS32 Aberdeen Cohort	M/F	1921	11	1932–2007 (1 – 75)	202 (M) 152 (F)	102 (M) 56 (F)	Moray House No. 12, school	–
Batty *et al.* (2008)[42]	USA, Vietnam Experience Study	M	1947	(20)	1985–2000 (18–33)	14437	769	Army General Technical, conscription	–
Batty *et al.* (2008)[43]	USA, Vietnam Experience Study	M	1947	(20)	1985–2000 (18–33)	4166	233	Army General Technical, conscription	–
*Batty *et al.* (2009)[3]	Sweden, Army Conscripts	M	1950–76	16–26 (18)	1971–2001 (1–30)	994 262	14498	SEB, conscription	Basic model: age, year of birth, conscription testing centre Childhood SES: parental socio-economic index (highest of either parent) height Education: educational level attained + multiple adjustments (see below) Multiple adjustments: basic model + childhood SES model + body mass index, blood pressure, psychiatric and somatic illness
*Jokela *et al.* (2009)[63]	USA, National Longitudinal Study of Youth	M/F	1957–64	16–23 (19)	1980–2004 (0–24)	5682 (M) 5639 (F)	248 (M) 112 (F)	AFQT, research sample	Basic model: sex, birth year, ethnicity, health status Education: basic model + years of education and marital status Multiple adjustments: education model + household income
*Kuh *et al.* (2009)[52]	UK, National Survey of Health and Development (British 1946 birth cohort)	M/F	1946	8, 11, 15	1971–2005 (10–51)	4128	195 (M) 137 (F)	NFER tests, school	Basic model: sex Multiple adjustments: basic model + father's social class, mother's and father's education, care of house and child, adult housing quality and tenure, adult social class, household income, smoking, education
Weiss *et al.* (2009)[49]	USA, Vietnam Experience Study	M	1947	(20)	1985–2000 (18–33)	4200	234	Army General Technical, conscription	–

(continued)

Table 1 Continued

Study references	Country, study name	Sex	Birth year(s)	Age at cognitive test, years (mean)	Years of survival follow-up (*n* years since cognitive test)[a]	Cohort Size, *N*	Deaths, *n*	Intelligence test, cohort type	Model adjustments
Hemmingsson *et al.* (2009)[45]	Sweden, Army Conscripts	M	1949–51	18–20 (19)	1990–2003 (19–36)	43 834	Not reported	SEB 1967, conscription	–
*Jokela *et al.* (2009)[51,e]	UK, National Child Development Survey (British 1958 birth cohort)	M/F	1958	11	1969–2004 (1–35)	14 132	213 (M) 116 (F)	NFER tests, school	Basic model: unspecified Childhood SES: father's occupational class Adult SES: occupational class Education: educational level attained Multiple adjustments: all previous models + child covariates (family difficulties, family size, problem behaviour, birth weight, height, mother's interest in child education, father's interest in child education), and adult covariates (marital status, psychosomatic symptoms, smoking, alcohol consumption, body mass index)
*Leon *et al.* (2009)[2]	UK, ACONF	M/F	1955	7	1970–2007 (8–45)	11 603	426 (M) 235 (F)	Moray House Picture Tests Nos 1 & 2, school	Basic model: age, sex Childhood SES: perinatal factors (which did not alter the basic model), father's social class at birth, family size Multiple adjustments: all previous models + childhood height and weight
*Lager *et al.* (2009)[53]	Sweden, Malmö Longitudinal Study	M/F	1927–28	10	1939–2003 (1–65)	832 (M) 698 (F)	363 (M) 176 (F)	Hallgren test, school	Basic model: unadjusted Childhood SES: father's education Education: educational level attained

Studies appear in publication date order; those marked with an asterisk are included in the meta-analysis. ACONF = Aberdeen Children of the 1950s; AGCT = Army General Classification Test; AWOL = absent without leave; FEV1 = forced expiratory volume (1 second); GCT = General Classification Test; NFER = National Foundation for Educational Research; SMS32 = Scottish Mental Surveys of 1932; SMS47 = Scottish Mental Surveys of 1947; SEB = Swedish Enlistment Battery; M = male; F = female.

[a]If years of follow-up and/or dates were not reported, these were estimated according to the longest theoretical time period.

[b]Study included all deceased and a random sample of survivors from the original cohort, twice as large as the deceased group.

[c]Years since cognitive testing is an estimate: in correspondence Holsinger *et al.* reported that the vast majority of conscripts would have been 17–21 years old at testing.

[d]Years since cognitive testing and birth year are approximations based on the mean age of participants at the beginning of follow-up in 1985–86.

[e]Models for sex groups and those that adjusted for adult SES and multiple variables are based on a shorter follow-up period (2346 years) and, therefore, a smaller sample size ($n = 10\,620$).

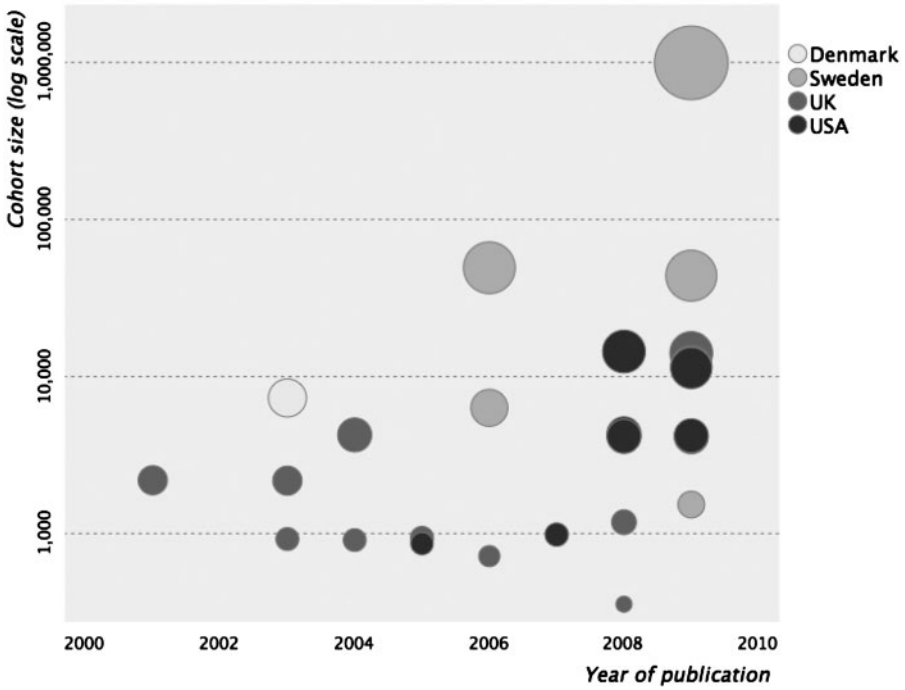

Figure 2 Publication rate of longitudinal cohort studies on intelligence in childhood and youth, and all-cause-mortality ($n = 27$). Circles are shaded to represent country of origin and scaled proportionately to cohort size. One study is missing;[54] its publication precedes 2000

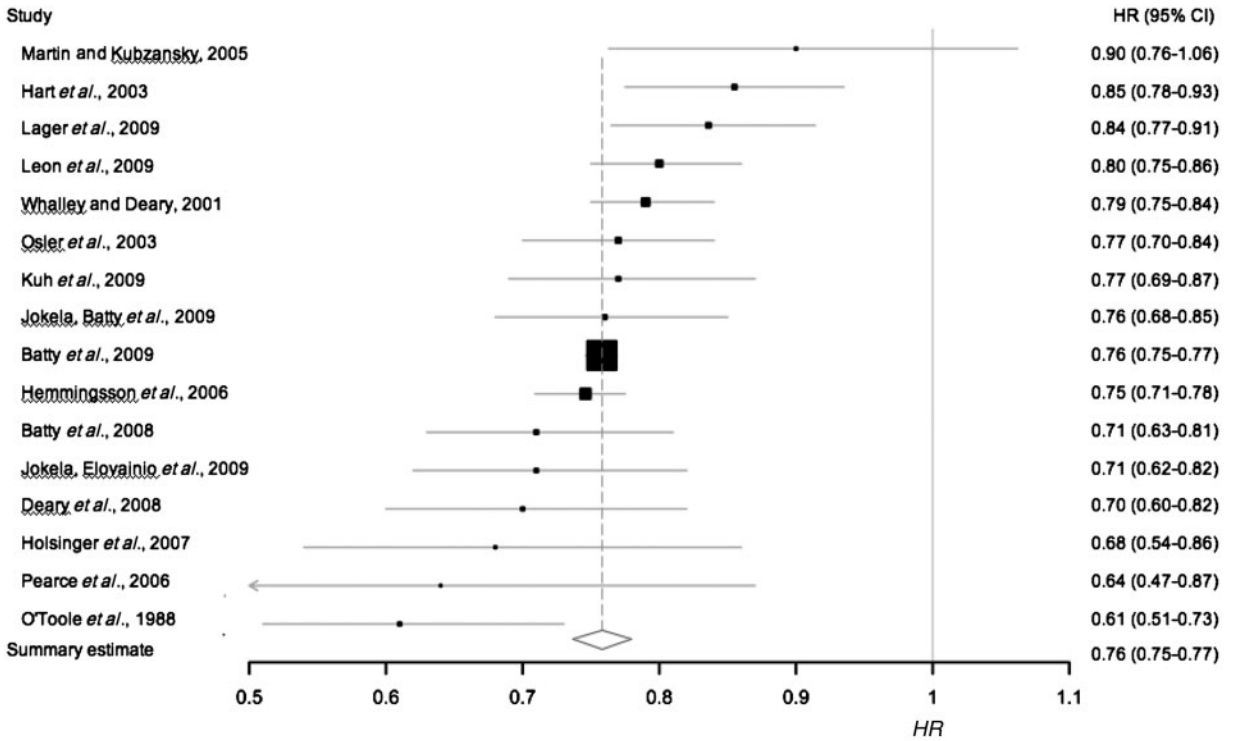

Figure 3 Risk of all-cause-mortality per 1-SD advantage in intelligence test scores ($n = 16$), in a basic model. Squares mark cohort-specific effect sizes, which are proportional to the statistical weight (i.e. inverse variance), and the diamond indicates the aggregate effect size. Horizontal lines represent 95% CIs. ORs from four studies[35,51,54,63] are treated as HRs; excluding the two studies with 20–40% risk of death[35,54] made no change to the summary estimate

Table 2 Summary of HRs for all-cause mortality in relation to a 1-SD advantage in intelligence in 16 longitudinal cohort studies

Subgroups	Studies, *n*	References	Deaths, *n*	HR (95% CI)	Heterogeneity		Risk attenuation from basic model
					P	I^2 (%)[a]	
Basic model	16	2–4, 35, 36, 50–56, 59, 61, 63, 65	22 453	0.76 (0.75–0.77)	0.28	15.5	–
Mean age at cognitive testing							
7–12 years	10	2, 4, 36, 51–53, 55, 56, 59, 61	4424	0.80 (0.77–0.83)	0.61	0.0	–
18–20 years	6	3, 35, 50, 54, 63, 65	18 029	0.75 (0.74–0.77)	0.54	0.0	–
Percentage ascertainment							
<80%	7	3, 4, 52, 55, 59, 61, 65	17 148	0.76 (0.75–0.78)	0.39	5.4	–
⩾80%	7	2, 36, 50, 51, 53, 63	4397	0.77 (0.74–0.80)	0.25	23.7	–
Invalid[b]	2	35, 54	908	–	–	–	–
Effect size							
HR	12	2–4, 36, 50, 52, 53, 55, 56, 59, 61, 65	20 856	0.76 (0.75–0.78)	0.24	21.1	–
OR	4	35, 51, 54, 63	1597	0.71 (0.64–0.79)	0.57	0.0	–
Cohort size							
<1000	4	4, 35, 36, 59	1149	0.83 (0.76–0.91)	0.26	25.3	–
1000–10 000	7	52–56, 61, 65	3638	0.77 (0.74–0.81)	0.30	17.4	–
>10 000	5	2, 3, 50, 51, 63	17 870	0.76 (0.74–0.77)	0.70	0.0	–
Follow-up duration							
<40 years	7	3, 50, 51, 54, 61, 63, 65	18 495	0.75 (0.74–0.77)	0.71	0.0	–
40–69 years	9	2, 4, 35, 36, 52, 53, 55, 56, 59	3958	0.80 (0.77–0.83)	0.50	0.0	–
Cohort birth year							
1910–20s	5	4, 35, 36, 53, 55	2723	0.82 (0.77–0.86)	0.41	0.0	–
1930–40s	4	52, 56, 59, 65	815	0.73 (0.65–0.80)	0.80	0.0	–
1950–60s	7	2, 3, 50, 51, 54, 61, 63	14 858	0.76 (0.74–0.77)	0.56	0.0	–
Sex[c]							
Female	7	2, 51–53, 55, 59, 63	1086	0.78 (0.73–0.84)	0.17	33.4	–
Male	7	2, 51–53, 55, 59, 63	1771	0.80 (0.76–0.85)	0.88	0.0	–
Adjusted for							
Childhood SES	9	2, 3, 36, 50, 51, 53, 56, 59, 61	18 733	0.77 (0.75–0.79)	0.48	0.0	4.0%[d]
Adult SES	5	4, 50, 51, 56, 65	3070	0.84 (0.78–0.90)	0.52	0.0	33.5%
Education	6	3, 51, 53, 56, 63, 65	16 023	0.89 (0.86–0.91)	0.53	0.0	54.2%[d]

Note. All sub-analyses refer to fixed effects models.
[a]I^2 (%) = percentage of variation across studies due to heterogeneity.
[b]Insufficient data prevented estimation of ascertainment rate at follow-up.
[c]Number of deaths reported for men and women exclude data from Jokela *et al.*,[63] which were unreported.
[d]Removing the influence of by far the largest cohort by Batty *et al.*[3] gave attenuation effects by childhood SES of 0.0% and by education of 45.8%.

Ascertainment bias was unlikely to have affected the total aggregate HR. That is, studies of low ascertainment (62–79%) showed a similar aggregate effect size (HR 0.76, 95% CI 0.75–0.78) to that of studies with 80–100% ascertainment (HR 0.77, 95% CI 0.74–0.80). There was also no observable effect of cohort size on the magnitude of the intelligence–mortality association.

The aggregate effect size for studies reporting ORs resulted in a higher risk of mortality as predicted by intelligence (0.71, 95% CI 0.64–0.79) compared with the aggregate effect size from studies reporting HRs (0.76, 95% CI 0.75–0.78). However, the four studies reporting ORs had among the lowest weightings of the 16 cohorts (0.42–1.08%), which may explain why their inclusion in the basic model was less likely to have incurred statistical bias.

Publication bias was first addressed by examination of the funnel plot, which revealed one study[4] on the outside of 95% CI parameters (Figure 4). Egger's test of asymmetry supported a low risk of publication bias (intercept = 0.10, 95% CI 0.72–0.91, $P = 0.81$), as did application of trim and fill adjustments in which only one missing study was estimated, and its imputation made no difference to the magnitude of the risk estimate (HR 0.76, 95% CI 0.75–0.78).

Stratification by sex

Seven studies reported intelligence–mortality effect sizes for men and women separately, and their follow-up spanned 24–65 years.[2,51–53,55,59,63] During this period the absolute risk of death was 5.6% for women and 8.2% for men. Four out of the seven studies reported negligible sex differences[2,51,52,63] (two of these formally tested intelligence × sex interaction effects), two reported a stronger effect for men (one reported a null effect in women with an intelligence × sex interaction effect),[53,59] and one reported a stronger effect in women.[55] However, fixed effects models were applied to aggregate the sex-specific HRs, given the evidence for low heterogeneity (Table 2). A 1-SD advantage in intelligence among women was associated with a 22% lower risk of all-cause mortality (HR 0.78, 95% CI 0.73–0.84), whereas among men there was a 20% reduced risk of mortality per 1-SD advantage in intelligence (HR 0.80, 95% CI 0.76–0.85). Nevertheless, there was a high degree of overlap in the CIs of these respective effect sizes. Egger's test of asymmetry supported a lack of publication bias among sex-specific cohorts.

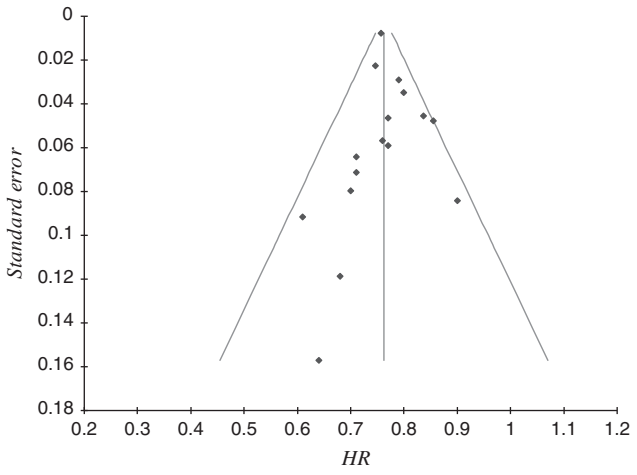

Figure 4 Funnel plot of HRs and standard errors to assess publication bias. Diagonal lines indicate 95% CIs of the aggregate HR (shown by vertical line) from all studies combined. One study[4] is an outlier of the CI parameters

Adjustment for childhood SES

Nine studies that included 18 733 deaths, reported effect-size models adjusted for childhood SES, measured either by father's occupation or income,[2,36,50,51,56,59,61] the highest socio-economic index recorded for either parent,[3] or father's education.[53] Heterogeneity was very low in unadjusted ($Q = 8.56$, $I^2 = 6.6\%$, $P = 0.38$) and adjusted models ($Q = 7.49$, $I^2 = 0.0\%$, $P = 0.48$). In a fixed effects basic model the HR for this subgroup of papers did not deviate from the HR for the 16 studies (HR 0.76, 95% CI 0.75–0.77). However, even after adjustment for childhood SES there was a very small attenuation (by 4%) of the effect size (HR 0.77, 95% CI 0.75–0.79) (Figure 5). Excluding the large study of over one million Swedish men had no effect on the aggregate effect size of the childhood SES-adjusted model, except to slightly widen the 95% CI parameters (HR 0.77, 95% CI 0.74–0.80). Compared with the unadjusted model of this smaller group of studies in which there were 4608 deaths (HR 0.77, 95% CI 0.74–0.80), controlling for childhood SES had no effect on the intelligence–mortality gradient when the influence of this largest weighted study was removed.

A 10th publication[46] from the systematic review, which could not be included in meta-analysis, reported data consistent with this finding: early-life socio-economic inequalities do little to explain the inverse association between intelligence and all-cause-mortality.

Controlling for adult SES and education

There was no evidence for publication bias among studies that controlled for adult SES or education. In five studies that adjusted for adult SES, there were 3070 deaths among 66 301 participants. SES was measured either by occupational social class,[4,50,51,56] or income.[65] The unadjusted effect size for this subgroup of studies (HR 0.76, 95% CI 0.72–0.79) matched that of all 16 studies. After adjustment for adulthood SES, the lower risk of mortality predicted by higher intelligence was attenuated by 33.5% from the basic model (HR 0.84, 95% CI 0.78–0.90) (Figure 5).

Among the six studies that adjusted for educational attainment, there were 16 023 deaths out of 1026 742

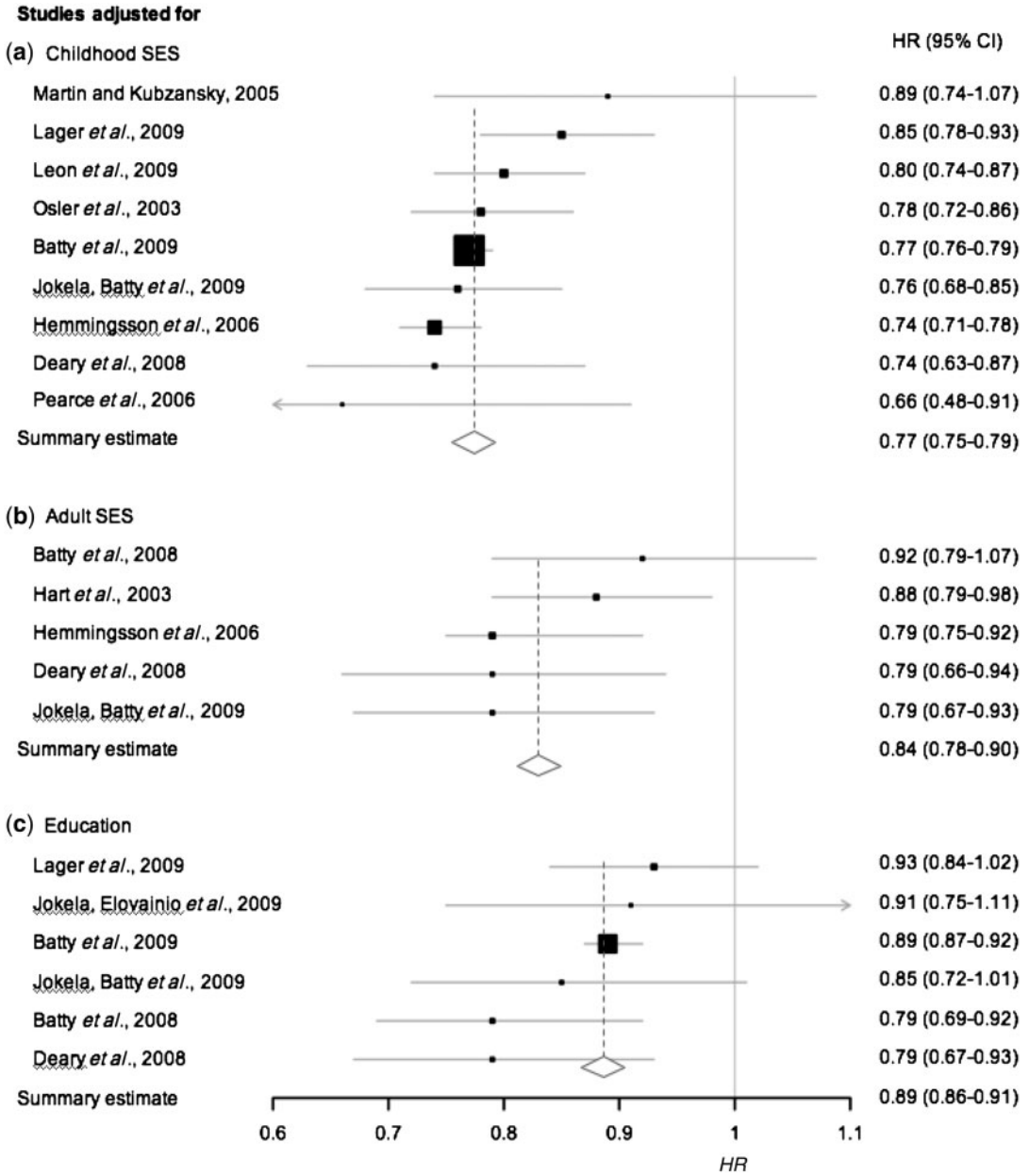

Figure 5 Risk of all-cause-mortality per 1-SD advantage in intelligence test scores after adjustment for: (a) childhood SES, (b) adult SES and (c) education. Squares mark cohort-specific effect sizes, which are proportional to the statistical weight (i.e. inverse variance), and diamonds indicate the aggregate effect sizes for studies adjusted for each covariate. Horizontal lines represent 95% CIs

participants.[3,51,53,56,63,65] Again, the aggregate effect size for this subgroup of studies in an unadjusted model (HR 0.76, 95% CI 0.74–0.77) was no different from that for all 16 studies. After adjustment for education (HR 0.89, 95% CI 0.86–0.91), the effect of intelligence on mortality was reduced by 54.2% (Figure 5). Exclusion of the large Swedish cohort[3] from the model, as expected, widened the CI parameters (HR 0.87, 95% CI 0.81–0.93), but still reduced the intelligence–mortality gradient by 45.8% from the unadjusted model.

Two further studies from the systematic review,[45,46] excluded from meta-analysis due to the type of statistics reported, are consistent with our result. They observed attenuation effects by education of over one third, of the intelligence–mortality association.

Multiple covariates

Eleven studies, including 15 148 deaths, reported effect sizes for the risk of mortality according to intelligence while adjusting for multiple

variables[2–4,50–52,54,56,61,63,65] (see Table 1 for covariates). Among these cohorts, four showed entire attenuation of the intelligence–mortality effect size from unadjusted (or basic) models.[51,52,63,65] These studies tended to adjust for adult SES variables with the addition of other important covariates, including education[63] or smoking[52] among other cardiovascular disease risk factors.[51,65] The remaining studies reported a smaller degree of attenuation from unadjusted models. Due to the varying number and nature of covariates across the studies it was not appropriate to aggregate their effect sizes in meta-analyses.

Discussion

The present meta-analysis of 16 published prospective cohort studies, comprising over 1.1 million participants and 22 453 deaths, demonstrates and quantifies the consistently-reported association between higher premorbid intelligence and lower mortality risk. A 1-SD advantage in intelligence in childhood and youth was associated with a 24% lower risk of mortality. The effect was similar in men and women, and was not explained by socio-economic differences in early life, as indicated by parental occupation or income. The association was attenuated by approximately a third after adjusting for adult SES and by approximately a half after adjusting for educational experience. Intelligence remained a predictor of mortality after these attenuating effects, and removal of one study that carried by far the largest weighting in the models[3] did little to change the magnitude of these effects.

This is the first meta-analysis of studies examining the relationship between premorbid intelligence and all-cause mortality. A recent systematic review, which was based on nine identified at that time, reported the inverse association.[1] Since then the number of publications of the intelligence–mortality association has grown, and the 16 unrelated cohorts we identified represent more than four times as many deaths. We found little evidence of publication bias, and so the estimated risk of mortality according to a 1-SD advantage in intelligence may be generalized to cohorts beyond those included in this meta-analysis, at least to those of the five countries included in the analyses. Our treatment of ORs as HRs in two studies where the absolute risk of death was >5%, which could have incurred statistical error, was not found to inflate the aggregate effect size.

Heterogeneity was not apparent across the studies despite most using different assessments of premorbid intelligence. This may be because most omnibus intelligence tests of the types used in the identified studies show strong loadings on general intelligence, *g*.[66] The intelligence–mortality association was, however, slightly weaker among cohorts of younger ages at cognitive testing, and those of longer follow-up duration. As it was the same cohorts that were followed up beyond 40 years who were the youngest at intelligence testing, it is difficult to establish which factor would make the larger contribution to attenuating the intelligence–mortality association. However, it seems less likely to have been due to differences in the validity of intelligence tests taken at younger and older ages, given the equally low heterogeneity among these two cohort groupings. It may be that older cohorts at cognitive testing show a steeper intelligence–mortality gradient because of the increased likelihood of bodily insults, or, it is still possible that the association varies according to age at mortality, most likely due to cause of death.

Lack of confounding by sex and early-life SES

Our observation of negligible differences between men and women in the relative risk of mortality as predicted by intelligence, may be surprising given well-documented sex differences in patterns of risk factors, onset and prevalence of specific diseases and life expectancies.[67] However, there were exceptions in individual studies, with differences between men and women reported, although there seem to be cohort-specific explanations for these. In one study[55] the lower relative risk among men was probably due to the rise in deaths of higher intelligence servicemen during World War II.[68] In another, the lower relative risk among women could have resulted from a lack of statistical power due to the small number of female deaths.[59] The result from an older birth cohort study[53] of a null association among women, could have been influenced by a relatively higher incidence of smoking among well-educated women during an era before the health hazards of smoking were widely known. In general, however, data from large post-war birth cohort studies show negligible sex differences in the effects of intelligence in relation to risk of mortality, and results from our meta-analyses support this. Equivalent effect sizes by sex still do not mean that the mechanisms that explain the intelligence–mortality association act in equal measure for men and women, and it continues to be of interest to study sex differences in cognitive epidemiology. Differences in health behaviours, risk patterns and medical interventions should also be considered when comparing ethnic groups or diverse countries. However, there is currently a lack of cohort data to evaluate how such group differences influence the risk of all-cause mortality as predicted by premorbid intelligence.

Socio-economic conditions in early life, determined by parental occupation or income, were also unlikely confounders. Individual differences in cognitive ability appear to act independently of childhood social inequalities in predicting all-cause mortality. There may of course be alternative early-life factors contributing to confounding that were not covariates of the cohorts we reviewed. Among three studies that

adjusted for birth weight in multivariate-adjusted models, one reported no change from unadjusted models,[2] and two reported a risk attenuation of 1 and 4%, respectively, compared with models that adjusted for childhood SES[61] and education.[51] However, recent evidence suggests that birth weight may not be the ideal indicator for exposures in the intrauterine environment, which carry their most critical influence on neurological and physiological development during the early prenatal period.[69] Other qualitative characteristics in early childhood may further explain the relationship between premorbid intelligence and longevity,[27] including style of parenting and cognitive stimulation at home,[70] or the effects of diet. However, so far, the potential confounding of these early-life factors have not been demonstrated, and these other suggested variables are likely to be associated with parental intelligence.

Attenuation of the intelligence–mortality association

Education and adult SES were found partially to attenuate the risk of mortality according to a 1-SD advantage in intelligence. Premorbid cognitive ability may act via occupational status and wealth to reduce the risk of mortality, by providing a less hazardous work environment, a safer and more comfortable home environment, and the material means to access better and more immediate medical care. Furthermore, intelligence may be mediated by education to reduce the likelihood of death, perhaps by increasing a person's receptivity to health education messages (thereby reducing negative behaviours such as smoking and excess alcohol consumption, and promoting exercise and healthy eating), and by improving comprehension of medical terminology and instruction that impacts on disease management and prevention. Nevertheless, the results to date cannot tell us for certain whether education and adult SES are simply partial mediators of the association between intelligence and mortality, or whether the results reflect over-adjustments if both factors are partial surrogates for intelligence, or if these variables confound intelligence–mortality associations.[71] Structural equation modelling can examine for statistical mediation, and one study to employ this technique reported that the effect of a general intelligence factor on mortality was entirely mediated by income, education and poor physical health in adulthood.[49] However, in this study, with cognitive ability measured at age 20 years, the association between intelligence and mortality could also have been partially confounded by education. In our meta-analyses, two out of five studies that adjusted for adult SES,[50,65] and three out of six studies adjusting for education,[3,63,65] had intelligence test scores measured in later youth (19–20 years of age), when most people have completed education. There is evidence for a causal association from childhood intelligence scores to later educational achievement in longitudinal studies, and it is also likely educational experience can boost cognitive test scores to some extent.[72] Therefore reciprocal dynamic pathways between intelligence, education and adult SES need to be considered.

Few studies in the meta-analysis adjusted for both education and adult SES in the same model. It is suggested that both factors may overlap in their attenuation effects on the intelligence–mortality association,[40] but there is also evidence to show that they are not interchangeable, and have independent effects on health outcomes.[73,74] Among three studies to control simultaneously for adult SES and education, the relative risk of mortality was entirely attenuated.[51,52,63] Interpretation of these findings should also consider the likelihood of over-adjustment. In studies that reported complete attenuation effects of the intelligence–mortality gradient after multivariate adjustments, in addition to controlling for socio-economic and educational variables, it was noted that three studies adjusted for smoking,[51,52,65] two adjusted for alcohol consumption,[51,65] and there were further adjustments made for psychiatric illness,[65] parental interest in a child's education,[51] or the quality and care of a household.[52] These potential explanatory factors are worthy of further investigation, particularly as two of these (smoking and alcohol consumption) are important risk factors for various chronic diseases.

Future directions

The present meta-analysis was unable to consider cause of death in the intelligence–mortality association, but this would seem an important area for future systematic review, particularly as it was likely to have driven the stronger effect sizes of cohorts followed to younger ages in adulthood. For example, it may be that intelligence has a stronger relation to mortality caused by external events such as accidents,[54] more prevalent among younger adults, than cause-specific mortalities more typical in later life.[4] Studies have already replicated the inverse association between premorbid intelligence and cardiovascular disease-related mortality, with increased effect size magnitudes for coronary heart disease-related deaths[3,75–78] compared with stroke-related deaths.[75,77,78] The relationship between childhood cognitive ability and risk of cancer mortality is also likely to vary by type.[4] For example, smoking-related cancers might carry a stronger association with intelligence[4,79,80] than other cancer types.[79] Specific causes of death are therefore likely to be crucial in providing explanations as to why intelligence predicts life expectancy, and larger cohorts with increased numbers of cause-specific mortalities will help to clarify this issue.

In the present study we found that education and social position in adulthood are factors that may help to account for the intelligence–all-cause mortality association. However, the extent to which these SES indicators act as partial surrogates for intelligence, or mediators and/or confounders of the intelligence–mortality association requires formal testing. Future longitudinal studies of mortality risk with repeated measures of intelligence, education, and adult SES, spanning childhood to adulthood could contribute to do this. Twin studies to determine the extent to which intelligence shares genetic and environmental causes with health, education, and social class, in predicting mortality, will also help to inform this issue. With evidence of associations between cognitive performance and education showing substantial heritability,[81,82] it is possible that these variables may share some genetic effects in predicting death.

Although early-life SES did not help to explain the intelligence–mortality association and birthweight is another unlikely confounder, future studies could explore alternative early-life variables, in particular the intrauterine environment, and how these might simultaneously determine neurological and physiological integrity, in interaction with genetic influences, leading to lifelong effects on cognition and health.

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KEY MESSAGES

- Higher intelligence test scores measured in youth are associated with the reduced risk of mortality by mid-to-late adulthood.
- The intelligence–mortality association does not appear to be confounded by gender or early-life socio-economic inequalities.
- Adult SES and education attenuate the intelligence–mortality association by a third and a half, respectively. Improved study design can contribute to a better understanding of the mechanisms involved in this effect, including: lifetime repeated measures of intelligence and SES indicators; detailed early-life and adult covariate data, and specific causes of mortality; twin studies that estimate the environmental and genetic contributions to intelligence–SES–mortality associations.

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Commentary: Intelligence in youth and all-cause mortality: some problems in a recent meta-analysis

Denny Vågerö

CHESS, Centre for Health Equity Studies, Stockholm University/ Karolinska Institutet, SE-196 91 Stockholm, Sweden.
E-mail: denny.vagero@chess.su.se

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I would like to congratulate Cathrine Calvin and co-authors for their meta-analysis, recently published by *IJE*.[1] Research addressing the relation between social circumstances, cognitive ability and health has grown rapidly. The association between early IQ and all-cause mortality is an excellent place to start. Their review will benefit all working in the field. I will highlight some of its problems in order to help us to move forward, both in understanding whether cognitive ability has any causal effect on health and in addressing the public health consequences of this knowledge.

Early intelligence or pre-morbid intelligence?

There is some inconsistency in the way the authors think and define the causal factor in focus: is it intelligence in youth or pre-morbid intelligence? Both terms are used and in fact treated as equivalent. However, they can hardly be equivalent if one at the same time sees IQ as a measure of 'bodily insult', as some of the authors do.[2]

Bodily insult is a somewhat vague concept, but I assume that it refers to external influences on the body which influence a person's development negatively. Malnutrition in utero (resulting in low birthweight), infection in infancy or physical abuse as a child, may influence physiological, emotional and cognitive development, thus constituting 'bodily insult'. IQ in youth would already have been affected (reduced) by such early events, and should therefore not be described as pre-morbid intelligence. And as far as I understand there is no information about morbidity, or exclusion of persons reporting morbidity in childhood, adolescence or early adulthood, in any of the studies included in the meta-analysis.

The concept of pre-morbid intelligence may be borrowed from studies of cognitive decline, where 'pre-morbid intelligence' often refers to intelligence before the ageing process affects the mind severely. It can simply mean intelligence measured in a person with no disease diagnosis, in which case it clearly differs from early intelligence.

Cognitive ability and health probably develop together from Day 1 (conception) and influence each other mutually during the fetal, infant, childhood and adult periods. At the end of life they decline together. A mutual, reciprocal, influence between health and intelligence need not look the same early and late in life; the predominant causal direction could change