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Intelligence, health and death

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The field of cognitive epidemiology studies the prospective associations between cognitive abilities and health outcomes. We review research in this field over the past decade and describe how our understanding of the association between intelligence and all-cause mortality has consolidated with the appearance of new, population-scale data. To try to understand the association better, we discuss how intelligence relates to specific causes of death, diseases/diagnoses and biomarkers of health through the adult life course. We examine the extent to which mortality and health associations with intelligence might be attributable to people's differences in education, other indicators of socioeconomic status, health literacy and adult environments and behaviours. Finally, we discuss whether genetic data provide new tools to understand parts of the intelligence–health associations. Social epidemiologists, differential psychologists and behavioural and statistical geneticists, among others, contribute to cognitive epidemiology; advances will occur by building on a common cross-disciplinary knowledge base.

Cognitive epidemiology emerged in the early 2000s; it studies how and why individual differences in intelligence (especially when measured in childhood or young adulthood) associate with later differences in health, illness and death. The first decade of cognitive epidemiology proper went from the discovery of the association between childhood intelligence and survival to old age[1], via overviews and a special journal issue[2–5], to a systematic review of evidence accumulated over the first decade of the field's history[6].

In this review, we take stock of the field's progress over its second decade, examining how our understanding of the association between intelligence and health/mortality has been refined with the advent of new, population-scale data and genetic tools. Following a brief introduction to the use of intelligence as a predictor, we examine the associations between intelligence and, in turn, all-cause mortality, specific causes of mortality, physical illnesses and health-related biomarkers. We then discuss some possible causes of the observed associations (education, health behaviours and literacy, and genetics), which are not mutually exclusive. Although the causes underlying the associations between intelligence and health/mortality remain an open question, research over the past decade has provided results and fingerposts for further progress.

Intelligence as a predictor

A summary of the psychometric structure, life-course stability, heritability, ageing and brain correlates of intelligence test scores is provided in Box 1. Intelligence test scores are used as exposures and outcomes. They are used as outcomes in medical studies to assess, for example, the effects of treatments, illnesses (whether neural or other system based) and ageing on cognitive abilities. Until the recognizable field of cognitive epidemiology began in the early 2000s, intelligence tests were rarely used as long-term predictors of medical outcomes. For much of the twentieth century, though, intelligence tests were used as predictors of social outcomes. Thus, in longitudinal studies, higher intelligence test scores are associated with higher educational attainment, higher-status occupations, more income and upward inter-generational social mobility[7,8]. This is not to ignore that social factors, especially education, might have some influence on later-measured intelligence[9].

Social epidemiology shows that sundry measures of less-advantaged socioeconomic position and lower-level educational attainments are associated with poorer health, more illnesses and risk of earlier death[10–12]. Thus, social factors with which intelligence is associated are also related to health inequalities. How might intelligence fit into this network of life-course social–health associations? One provocative suggestion was expounded in an article entitled "Intelligence: is it the epidemiologists' elusive 'fundamental cause' of social class inequalities in health?"[13]. A counter to this proposal is that it is only by the degree to which intelligence begets educational and social advantage that it relates to health outcomes, and that it is those social variables that hold the causal factors[14,15]. Before such ideas can be tested, however, it is necessary first to find out whether intelligence is associated with health outcomes.

Intelligence and all-cause mortality. Three pioneering studies suggested or showed that higher intelligence was associated with living longer[16–19]. However, none of them was or has been much cited.

In 2011, a systematic review of the association between intelligence measured in youth (7–20 years) and all-cause mortality found 16 studies of independent cohorts of varying sizes (from under 1,000 to almost 1,000,000), all of European descent (a limitation which persists in the field)[6]. The cognitive assessments used (which were provided via national surveys, school records or military conscripts' data) were likely to have been strongly associated with general intelligence (*g*; Box 1). Meta-analysis of the results based on a total of 1,107,022 participants (among whom there were 22,453 deaths) adjusted for age and/or sex found that one standard deviation (15 IQ points) advantage in intelligence in youth was associated with a 24% lower risk of death (from all causes) to the follow-up ages (hazard ratio 0.76, 95% CI 0.75 to 0.77). The effect size translates to an *r* value of approximately 0.2 (ref. [1]), that is, "a *medium* effect that is of some explanatory and practical use"[20]. There was little evidence of publication bias (using funnel plot, Egger's test of asymmetry and trim-and-fill adjustment methods) or heterogeneity among the studies. Cohort size and ascertainment percentage also made little difference to the effect size. Excluding a large Swedish conscripts study[21], which contributed almost 1,000,000 of the participants and over 14,000 deaths, made almost no difference to the effect size.

Turning to the issue of possible confounding variables in the meta-analysis, adjusting for childhood socioeconomic status caused very little attenuation of the intelligence–mortality association[6].

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Box 1 | Psychometric intelligence: an overview

The exposure variable in this review is intelligence, also known as mental ability, cognitive ability, cognitive functioning, intelligence quotient (IQ, which also has a technical, psychometric meaning) and so forth[122]. People's differences in intelligence are measured using psychometric tests of cognitive functions. Individual cognitive epidemiology studies tend to use different tests from each other. Therefore, we now explain the phenotypic structure and some psychometric characteristics of intelligence measures.

The hierarchy of cognitive variation. Cognitive tests are sometimes deliberately broad (those with varied items assessing a number of different cognitive skills) and sometimes narrower (aiming at specific cognitive capabilities). Almost all cognitive tests (both broad and narrow) show positive correlations; people who are good at one type of cognitive test tend also to be good at all the others. This consistent finding led to the widely accepted hierarchical view of variation in human cognitive capabilities[123] (Fig. 1). When a diverse set of cognitive tests is given to a large sample of individuals, the variance can be identified on at least three levels. The universal positive association among cognitive tests' scores means that about 40% of total test variance is general. That is, there is a general tendency for people to do well on all tests, sometimes called general intelligence or just '*g*'. This was discovered[124] and expounded[125] by Spearman. Below that pinnacle of the hierarchy, some tests that assess similar cognitive capabilities correlate better with each other than with tests that assess different capabilities. These pools of variance are called cognitive domains, such as visuospatial reasoning, memory, processing speed, verbal ability and so forth. The domain level of variance accounts for a smaller percentage of individual differences than does *g*. Below *g* and cognitive domains, there is remaining variance that is specific to the ability to carry out individual tests. This level of variance also includes error of measurement. The practical upshot of the hierarchy of variance is that, even when a cognitive test is thought to be assessing a specific cognitive skill, it is still, to a greater or lesser extent, assessing *g* and one or more cognitive domains.

Intelligence's stability, heritability, ageing and brain associations. Whether assessed using a *g* factor created by data reduction from a number of correlated cognitive tests, or from the score on an omnibus intelligence test, or from the score on a test that has a high *g* loading, individual differences in intelligence have some well-established psychometric characteristics. Intelligence test scores are substantially stable across the life course, with about 50% of variance being shared between childhood and the eighth decade[126]; much of that stability is accounted for by genetic factors[112]. They are substantially heritable, with additive genetic contributions to *g* that rise from around 30% or less in childhood[94] to about 70% in adulthood[94,95]. By adulthood, the contribution of shared environment is small. Much of the heritability of cognitive test variance is on the *g* factor[127]. There are mean declines from young adulthood to older age in some cognitive domains, for example, abstract reasoning, processing speed and some aspects of memory[128]. Collectively, they are referred to as 'fluid intelligence'. The effects of age tend substantially to be on the general variance among these capabilities[129]. There is little age-related decline in mean performance in some others, such as vocabulary, general knowledge and some numerical skills[128]. These are known collectively as 'crystallized intelligence'. There is a modest association (around 0.3) between *g* and brain volume and some other aspects of brain structure, such as white-matter health[130].

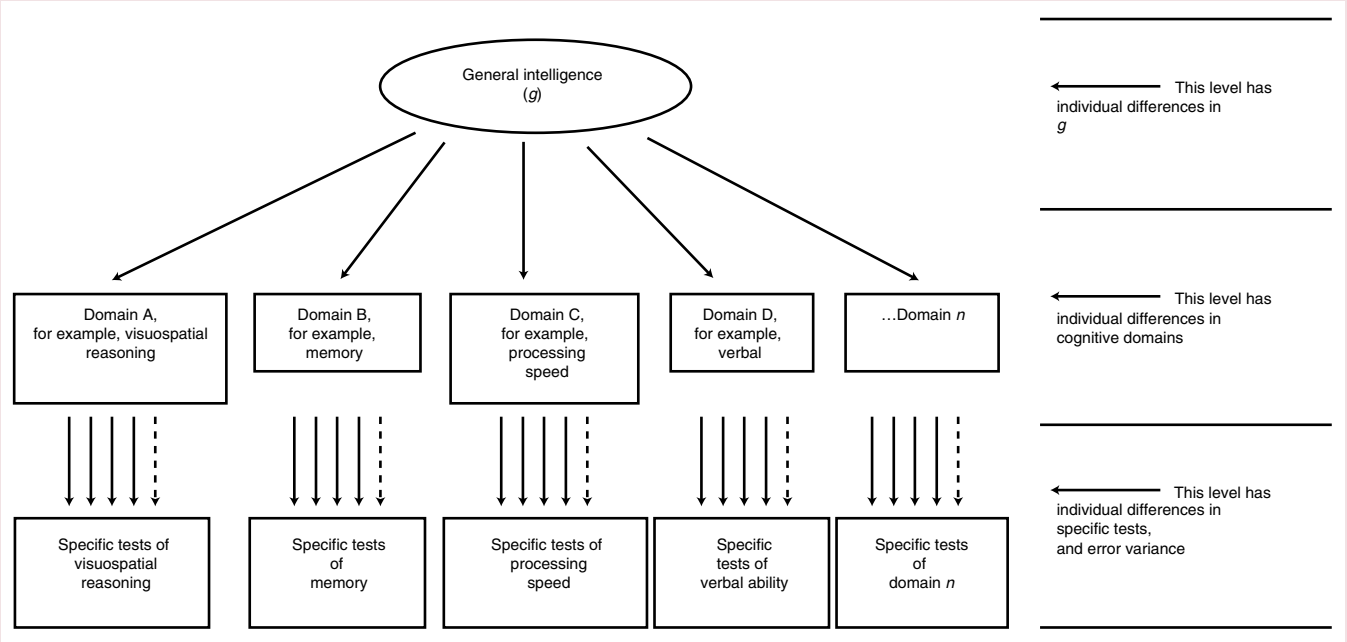

Fig. 1 | The hierarchical model of intelligence. The named domains are examples of those that often appear in analyses of multiple cognitive tests. The arrows from domains to specific tests represent loadings (like correlations) of a variable number of tests. The arrows from general intelligence (*g*) to the domains represent the loadings (like correlations) of the domains on *g*. A key point to understand is that being good at any one specific test (for example, a narrow test of visuospatial reasoning) can mean being generally intelligent, being good at that domain of thinking, just being good at that specific test, and/or having some luck on the day of the test.

Table 1 | Large studies[a] in which intelligence test scores are related to all-cause mortality

Reference	Cohort	Intelligence test	Number in study sample	Number of deaths	Follow-up time	Age- and sex-adjusted hazard ratio (95% CI)[b]	Multivariate-adjusted hazard ratio (95% CI)[b]	Covariates included apart from age/sex
Bratsberg et al.[23]	Norwegian male birth cohorts 1962–1990	Norwegian National Conscript Service IQ test	390,140	12,016	Not specified. 35 years maximum	2.42 (2.22, 2.64) lowest stanine IQ compared with stanine 5 (unadjusted)	2.31 (2.12, 2.52) in lowest stanine compared with stanine 5	Parental socioeconomic position, and birth year
Christensen et al.[24]	Danish Conscription Database; males born 1939–1959	Børge Prien Prøve intelligence test	662,185	117,868	Mean 37 years	1.28 (1.27, 1.29), per SD lower IQ	1.21 (1.20, 1.21)	Educational level at conscription board examination
Cukic et al.[25c]	Scottish Mental Survey 1947	Moray House Test No. 12	66,616	25,460	68 years	0.81[d] (0.80, 0.82), per SD higher IQ	-	-
Lager et al.[26]	Swedish male birth cohorts 1951–1958	Swedish National Conscription IQ test	344,336	12,765	Not specified, approximately 38 years	1.64 (1.55, 1.72), if IQ in lowest 25% (unadjusted)	1.39 (1.33, 1.45), if IQ in lowest 25%	Childhood socioeconomic position and emotional control
Twig et al.[27]	Israeli conscripts	General intelligence test (sum of Otis-R, Similarities-R, Arithmetic-R, Ravens Progressive Matrices-R)	2,277,188	31,268	19.2 years	1.19 (1.18, 1.20), per SD lower IQ	1.08 (1.07, 1.10), per SD lower IQ	BMI, residential socioeconomic status, educational attainment at conscription, country of origin

Note. [a]These studies appeared after the meta-analysis of ref. [6]. [b]Sex included where appropriate, that is, men and women analysed together. [c]This is the most population-comprehensive study to date. The Scottish Mental Survey 1947 (SMS1947) tested 70,805 Scottish schoolchildren born in 1936. It tested about 94% of those who had been born in 1936. The 66,616 here is 94.1% of the SMS1947's participants. [d]If this were expressed as an association per SD lower IQ, the HR would be 1.23.

The absence of confounding by childhood socioeconomic position was also found when members of the population-representative 6-Day Sample of the Scottish Mental Survey 1947 and 1,580 of their younger siblings were studied. After including a random effect of family (which adjusts for those social factors shared within families) the childhood intelligence versus all-cause mortality association was weakened only slightly[22].

Returning to the 2011 meta-analysis[6], adjusting for adult socioeconomic status attenuated the hazard ratio to 0.84 (95% CI 0.78 to 0.90), and education adjustment attenuated it to 0.89 (95% CI 0.86 to 0.91). The discussion of that meta-analysis emphasized the need to identify the meaning of the attenuation by adult socioeconomic status and education (that is, the extent to which these are environmental mediators of the intelligence–mortality association and the extent to which they might be over-adjustments by intelligence-influenced covariates), and the need for more research on how prior intelligence is associated with different causes of death. Both of these and other matters are addressed below in our overview of more recent studies.

A number of remarkable intelligence–death studies have appeared since the systematic review in 2011 (ref. [6]). Five are summarized in Table 1 (refs. [23–27]). The newer studies we present were selected to meet these criteria: they are unusual either in size or population-comprehensiveness, or both, and intelligence was assessed in childhood or early adulthood. This latter criterion is in order, as far as possible, to avoid reverse causation, that is, the possibility that ill health might have reduced cognitive function by the time of its assessment. Similar associations between intelligence and mortality are found, however, when intelligence is first assessed at middle and older ages[28,29]. At the time of writing we are not aware of other studies meeting the above criteria, and especially, we are not aware of studies with null or opposite-direction results.

Putting together the 2011 meta-analysis[6] and these five[23–27] (Table 1) large, post-2011 studies from people born mostly around the middle of the twentieth century, there are fairly consistent effect sizes for the association between intelligence and all-cause mortality. The result is found in men and women, and for deaths at different stages in the life course. The association occurs almost linearly across the normal range of intelligence. Although the studies are from a range of countries, the participants are mainly of European descent.

Despite consistency in this finding, the reasons for the association between intelligence and all-cause mortality are not understood. The next sections are what we consider to be way stations in that process, which is incomplete.

Intelligence and specific causes of mortality

The association between intelligence tested in youth and all-cause mortality is robust-looking and interesting, but also relatively uninformative. There are many causes of death, with their own sets of risk factors, only some of which overlap. One way of finding out more about why intelligence and mortality are related might be to ask whether there are specific causes of death to which intelligence relates. To illustrate this work, Table 2 summarizes findings from three large studies[24,27,28]. Despite the between-cohort differences in geography, and period and age of assessment, the association between intelligence and death from cardiovascular disease (and coronary artery disease within that broader illness group) is quite consistent. There is an approximately 25% lower risk of mortality from these causes in the follow-up periods per standard deviation of higher intelligence test score in youth. After adjustments (including for educational attainment), the risk is still about 20% lower.

For most of the causes of death, there is good agreement between the studies in Table 2. A conundrum is raised by the variety of

Table 2 | Association between intelligence and specific causes of mortality

	Scottish Mental Survey 1947		Danish Conscription Database		Israeli conscripts	
Reference	Calvin et al.[28]		Christensen et al.[24]		Twig et al.[27]	
Overall sample number	65,765	4,031[a]	662,185		2,277,188	
	Age and sex adjusted	Multivariate adjusted[b]	Age adjusted[e]	Multivariate adjusted[c,e]	Age and sex adjusted[e]	Multivariate adjusted[d,e]
Cardiovascular disease	0.76 (0.75, 0.77) *N* = 9,619	0.82 (0.76, 0.89) *N* = 700	0.74 (0.75, 0.72) *N* = 18,505	0.78 (0.79, 0.77)	0.72 (0.75, 0.70) *N* = 3,068	0.82 (0.85, 0.78)
Coronary heart disease	0.75 (0.73, 0.77) *N* = 5,855	-	0.71 (0.72, 0.69) *N* = 9,311	0.76 (0.78, 0.75)	0.73 (0.83, 0.65) *N* = 1,443	0.83 (0.88, 0.78)
Stroke	0.76 (0.73, 0.79) *N* = 2,053	-	0.78 (0.80, 0.75) *N* = 3,685	0.82 (0.85, 0.79)	0.68 (0.74, 0.63) *N* = 514	0.81 (0.89, 0.72)
All cancers	0.86 (0.84, 0.88) *N* = 8,906	0.90 (0.82, 0.98) *N* = 584	0.85 (0.85, 0.83) *N* = 28,678	0.88 (0.90, 0.87)	-	-
Smoking-related cancer	0.82 (0.80, 0.84) *N* = 6,211	0.86 (0.76, 0.95) *N* = 407	-	-	-	-
Non-smoking-related cancer	0.96 (0.93, 1.00) *N* = 2,695	0.98 (0.87, 1.16) *N* = 177				
Lung cancer	0.75 (0.72, 0.77) *N* = 2,602	-	0.73 (0.75, 0.71) *N* = 6,959	0.82 (0.84, 0.80)	-	-
Respiratory disease	0.72 (0.70, 0.74) *N* = 5,313	0.75 (0.68, 0.84) *N* = 367	0.62 (0.65, 0.60) *N* = 3,094	0.69 (0.72, 0.66)	-	-
Digestive disease	0.82 (0.79, 0.86) *N* = 1,868	0.84 (0.70, 1.01) *N* = 122	-	-	-	-
Diabetes	-	-	-	-	0.63 (0.68, 0.58) *N* = 457	0.72 (0.80, 0.65)
Dementia	0.84 (0.78, 0.90) *N* = 786	-	-	-	-	-
External causes	0.82 (0.78, 0.87) *N* = 1,480	-	0.78 (0.79, 0.76) *N* = 15,267	0.86 (0.88, 0.84)	-	-

Note: results are expressed as hazard ratios of death from the specific cause per standard deviation higher intelligence test score, with 95% confidence intervals, and number of deaths (*N*). [a]Covariates were available on only a representative subsample. Only those causes of death with *N* = 100 are included. [b]Adjusted additionally for school, father's or head of household's occupational status, home overcrowding, school absenteeism during 1946–1947, height and physical disability. [c]Adjusted additionally for educational attainment at conscription. [d]Adjusted additionally for BMI, residential socioeconomic status, educational attainment at conscription and country of origin. [e]In these studies, the hazard ratios were originally published as the risk of death per standard deviation lower intelligence score. Here, the hazard ratios have been flipped so that the results are now expressed as risk of death per standard deviation higher intelligence score.

causes of death related to intelligence from youth, that is, all of those listed, with the exception of those cancers that are not associated with smoking. Does intelligence play the same role for each cause of death, or are different explanations needed? Among the strongest effect sizes were those for deaths from respiratory disease. This observation is suggestive of smoking as an environmental partial mediator of the intelligence–mortality association. Deaths related to diabetes had a strong association, with a 37% lower risk per standard deviation of higher intelligence test score in youth. Thus, deaths associated with several major organ systems (cardiovascular, respiratory, digestive, endocrine and neurological) are associated with intelligence tested in youth, as are deaths from external causes, which include accidents, suicide and homicide. Those latter three associations were known from earlier studies[30–32], and attracted their own sets of explanations therein.

Intelligence and physical illnesses and syndromes

Moving proximally in the life course from mortality, we now ask whether intelligence in youth is associated with the onset of physical illnesses in life. A selection of intelligence–morbidity associations for eight health outcomes in ten separate studies[33–42] is provided in Table 3. We chose these as studies that were large and/or population-representative, and had administered cognitive tests in childhood or youth. Moreover, we aimed to exemplify some important health outcomes that mostly had not been covered in the previous section. Higher risk of hypertension, metabolic syndrome, and diabetes (all associated with cardiovascular morbidity and mortality) are associated with lower intelligence tested in youth. Diagnosis of 'arthritis or rheumatism' has a similar association, representing a system that did not appear in mortality analyses. Further work on the National Longitudinal Survey of Youth 1979's hypertension outcomes by age 50 revealed that the links with intelligence from youth were stronger in women, and were accounted for by income as an environmental mediator[43]. Higher dementia risk appears to be related to lower childhood intelligence, too, with some unresolved disagreement about whether there are female–male differences in the effect sizes. We note the association between dementia and prior cardiovascular disease. Table 3 also shows associations between lower prior intelligence and higher risk of schizophrenia and major depression at follow-up.

Possibly in line with this broad association between intelligence and different illnesses is a study of 10,400 children in the Netherlands, tested at age 12 and followed up to age 24. Those with medium and lower intelligence (versus high) had higher general practitioner costs, higher hospital costs and more medication use[44].

Thus far, looking into specific causes of death and specific illnesses and syndromes has not whittled down the intelligence–health associations a great deal. Intelligence appears not to be associated with non-smoking-related cancers[28], but apart from those, it is associated with many major illness groups. Possible environmental mediators, such as education, smoking and income, might have some explanatory role, as suggested by the fact that they partially attenuate intelligence–health associations. Intelligence's associations with these types of variables might be applicable to many different illnesses. This will be explored more below.

Intelligence and biomarkers of health through the adult life course

Before developing a frank illness, we can ask whether intelligence is associated with bodily measures that are associated with future ill health and mortality. Here, we enquire whether prior intelligence is associated with physiological and chemical bodily measures that are associated with diseases. This is, in part, an attempt to gain more objective, detailed and specific indications of why intelligence might relate to illnesses and causes of death. Some of the work overviewed below is from typical cognitive epidemiology studies, that is, those that planned to ask whether intelligence in youth relates to later health-related biomarkers. On the other hand, some of these findings are incidental. For example, associations were discovered between intelligence tested at age 11 and older-age-assessed brain cortical thickness[45], C-reactive protein[46], cytomegalovirus infection[47], glycated haemoglobin (related to diabetes)[48] and allostatic load[49] in the Lothian Birth Cohort 1936 (LBC1936). These associations were mostly found when attempting to use childhood intelligence as a possible confounder of cross-sectional associations between biomarkers and cognitive functions in older age. However, the causal nature of these associations is not clear, not least because the biomarkers are measured only later in life; that is, the possibility of the tracking of these variables with intelligence across the life course could not be tested.

Studies have rarely assessed intelligence and multiple health indicators concurrently in youth. One exception was based on 49,321 Swedish men aged 18–21 years in 1969–1970 (ref. [50]). This cross-sectional study found that lower intelligence test scores were associated with poorer hearing, more hormonal disorders, more back pain, more digestive diseases, lower physical capacity, more indicators of inflammation and poorer subjective health ratings. This raises the possibility that intelligence and health track each other from an early age, which corrects and complicates a model in which intelligence's associations with health are only long-term ones, mediated via adult social factors and health behaviours (Box 2). More evidence for intelligence–biomarker associations within young adulthood came from an Israeli study of 17-year-olds followed up for 6.6 years[51]. It found that lower general intelligence was associated with greater likelihood of having an impaired fasting glucose level.

Next, we move from youth to studies of biomarkers in middle age. In New Zealand's Dunedin study, intelligence measured between 7 and 11 years was significantly associated with perceived facial age (standardized effect size −0.16), a biomarker algorithm from the National Health and Nutrition Examination Survey (NHANES) study (−0.15), Framingham heart age (−0.14) and telomere length (0.073)[52]. The omnibus biomarker variables among these outcomes contain variables whose levels in older age have elsewhere (for example, in the Lothian Birth Cohort 1936 studies mentioned above) been related to childhood intelligence. The biomarker algorithm from NHANES contained C-reactive protein, glycated haemoglobin, total cholesterol, lung forced expiratory volume, systolic blood pressure, serum creatinine, serum albumin, serum urea nitrogen, serum alkaline phosphatase and cytomegalovirus density. The Framingham heart score included total cholesterol, high-density lipoprotein (HDL) cholesterol, systolic blood pressure, treatment for hypertension, diabetes status and smoking status. There was a similar-sized association (−0.19) in the Dunedin study between childhood IQ and a measure called Pace of Aging, which assessed the change of 18 biomarkers measured at 26, 32 and 38 years. Pace of Aging contained "apolipoprotein B100/A1 ratio, blood pressure (mean arterial pressure), body mass index (BMI) and waist–hip ratio, C-reactive protein and white blood cell count, cardiorespiratory fitness (VO2Max), creatinine clearance, forced expiratory volume in one second (FEV1) and forced vital capacity ratio (FEV1/FVC), glycated hemoglobin, high-density lipoprotein (HDL), lipoprotein(a), leukocyte telomere length (LTL), periodontal disease, total cholesterol, triglycerides, and urea nitrogen"[53].

Also with respect to middle age, in a Swedish study of 57,279 men born between 1949 and 1959, higher intelligence at conscription was associated with the following at age 41: lower systolic and diastolic blood pressure, lower heart rate, lower triglycerides and cholesterol, lower body mass index, lower likelihood of smoking and lower likelihood of physical inactivity[54]. Adjusting for education made substantial attenuations to the already-small effect sizes. One standard deviation higher intelligence test score from conscription in the Copenhagen Aging and Midlife Biobank was associated with the following at age 50 years: better rising from a chair, better hand grip strength, better jumping power, better balance control and better low-back force[55]. Respiratory function in midlife was associated with intelligence in young adulthood in a 35-year follow-up study of over 900 men in the Vietnam Era Twin Study (VETS)[56]. The associations did not fall below 0.10 after adjustment for education, smoking, lung disease and occupation.

There are also studies of biomarkers in older ages. In an even longer follow-up than that of the VETS, in the Lothian Birth Cohort 1921, it was found that higher intelligence at age 11 years was correlated 0.10 with better forced expiratory volume in 1 s at age 79 years[57]. Moving to brain-based biomarkers, a meta-analysis of five studies, with a total *N* of 1,512, found that higher intelligence tested in childhood was associated ($r = -0.07$, 95% CI −0.12, −0.02) with having fewer brain white-matter hyperintensities (WMHs) in older age[58]. WMHs are a risk factor for cerebrovascular disease and dementia.

In summary, intelligence measured in childhood or young adulthood is related to many and overlapping health markers from young adulthood, through middle age, to older ages. The effect sizes are often around or slightly more than 0.1, that is, "an effect that is still *small* at the level of single events but potentially more ultimately consequential"[20]. Next, we turn to possible causes of intelligence's associations with health and death. The first paper that described the association between higher childhood intelligence and lower risk of all-cause mortality up to old age[1] offered four non-exclusive possible explanations for the association. These are summarized in Box 2, along with a diagram suggesting some possible pathways.

Possible causes of the intelligence versus health and death associations

Education. Many regression analyses have introduced education as a way of testing for possible confounding and mediation of intelligence–health associations. Typically, education moderately attenuates intelligence–health/mortality associations. Education is an interesting variable: it is substantially heritable, and it is strongly phenotypically and genetically associated with intelligence[59,60]. Yet, researchers view educational differences along a continuum of causal perceptions that ranges from treating them as if they were a genetic proxy for intelligence to conceiving them as an environmental variable that captures much, including certified attainments, social status and learned knowledge[61]. Education is widely used in social epidemiology as one of three indicators of socioeconomic position, alongside income and occupational status. The attenuation

Table 3 | Intelligence's associations with a variety of illnesses and syndromes

Condition	Reference	Cohort	IQ test	Number in study sample	Number of outcomes	Follow-up time (years)	Age- and sex-adjusted effect size (95% CI)[1]	Multivariate-adjusted effect size (95% CI)[1]	Covariates included apart from age/sex
Arthritis or rheumatism	Wraw et al.[33]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	4,012	993	-	OR 0.84 (0.78, 0.90)	OR 1.02 (0.92, 1.13)	Childhood and adult SES
Dementia	Osler et al.[34]	Danish men, brothers and twins born 1939–59	Børge Prien Prøve	666,986	6416	44.1	Unadjusted HR 1.33 (1.30, 1.35)	HR 1.33 (1.30, 1.37)	Height, education, psychiatric hospitalization before conscription
	Nyberg et al.[35]	Swedish Conscript Cohort, born 1950–87	Sum of tests on four cognitive domains	1,172, 190	657	25.7	HR 4.04 (3.18–5.14) lowest three IQ stanines versus highest three	HR 3.82 (2.96–4.93)	Year conscripted, BMI, region, test centre, parental education, cardiovascular fitness at age 18
	Huang et al.[36]	USA high school students in 1960	IQ composite (reading comprehension, reasoning, mathematics)	43,014 men 42,749 women	1,239 men 1,416 women	~52	-	OR 1.17 men (1.04, 1.32) 1.17 women (1.04, 1.31)	Birth year, race, adolescent SES, school region, residence region at follow-up
	Russ et al.[37]	Scottish Mental Survey 1932	Moray House Test No. 12	16,370 men 16,097 women	1,231 men 2,163 women	81	HR 1.02 men (0.97, 1.08) HR 1.14 women (1.09, 1.19)	HR 1.03 men (0.97, 1.09) HR 1.13 women (1.08, 1.18)	School- and county-level overcrowding in childhood
Hypertension	Wraw et al.[33]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	4,010	1,471	-	OR 0.80 (0.75, 0.86) per SD higher IQ	OR 0.85 (0.78, 0.94)	Childhood and adult (SES)
	Schmidt et al.[38]	Danish conscript cohort, born 1955	Børge Prien Prøve	6,502	524	33	Unadjusted HR 1.20 (1.11, 1.31)	HR 1.14 (1.01, 1.27)	Education and BMI
Major depression, onset <60 years	Christensen et al.[39]	Danish conscript cohort, born 1939–59	Børge Prien Prøve	666,804	19,004	40.8	HR 1.23 (1.21,1.24) per SD lower IQ	HR 1.21 (1.18, 1.23)	Birth year and education at time of conscription
Major depression, onset ≥60 years	Christensen et al.[39]	Danish conscript cohort, born 1939–59	Børge Prien Prøve	467,907	6,837	40.8	HR 1.14 (1.11, 1.16) per SD lower IQ	HR 1.17 (1.13, 1.20)	Birth year and education at time of conscription
Metabolic syndrome	Richards et al.[40]	MRC National Survey of Health and Development	Sum of four verbal and non-verbal tests	1,799	380	-	Unadjusted OR 0.86, (0.76, 0.96)	OR 0.93 (0.82, 1.05)	Adult SES
Schizophrenia	Gale et al.[41]	Swedish male conscript cohort born 1950–76	Sum of four tests: verbal, logical, spatial and technical	1,049,663	4,522	22.6	HR 1.60 (1.55, 1.65) per SD lower IQ	HR 1.66 (1.61, 1.71)	Birth year, testing centre, age at test, parental SES, parental age
Diabetes	Twig et al.[42]	Israeli male conscripts	General intelligence test (sum of Otis-R, Similarities-R, Arithmetic-R, Ravens Progressive Matrices-R)	35,500	770	5.5	-	HR 1.1 (1.04, 1.17) per point in the nine-point general intelligence score	Age, BMI, fasting glucose, family history, country, SES, education, physical activity, smoking, TG, breakfast consumption, WBC
Type 2 diabetes	Schmidt et al.[38]	Danish conscript cohort, born 1955	Børge Prien Prøve	6,502	316	33	Unadjusted HR 1.34 (1.21, 1.50) per SD lower IQ	HR 1.18 (1.02, 1.36)	Education and BMI

[1]Sex included where appropriate, that is, men and women analysed together.

Box 2 | Possible, non-exclusive causes of intelligence–mortality associations

These are précis and updates of the suggestions that appeared in the discussion of ref. [1]. They are not mutually exclusive, and there could be more possibilities.

Intelligence confounded by childhood health and deprivation. Intelligence test scores in childhood and young adulthood might be affected by developmental (including prenatal and perinatal), health and other social and environmental factors before cognitive assessment. These factors, in turn, might influence health and lifespan. Note, however, that adjustment for childhood social class tends not to attenuate intelligence–health associations. However, more research with more targeted childhood developmental, health and social factors would be useful.

Intelligence as a marker of general bodily system integrity. Intelligence test scores in healthy children and youths might be related to the efficiency of information processing in the brain. This 'brain health' might be correlated with the health of the body more generally. A theoretical article addressed conceptual issues with this idea of overall bodily 'system integrity'[131]. The system integrity idea has been tested via genetic research, suggesting that it might contribute part of the intelligence–health association. Genetic correlations between intelligence in youth and health outcomes also support some other interpretations listed below, via environmental variables in mediated pleiotropy[132]. This is an example of how these explanations are not only nonexclusive but also partly overlapping.

Intelligence mediated by healthy behaviours. Intelligence test scores in childhood and youth might be associated with the subsequent uptake of health-related behaviours, such as not smoking, keeping fit, staying slim and taking precautions to avoiding injury and illness. There are known to be widespread associations between intelligence tested in youth and health behaviours. Adjusting for smoking, for example, attenuates some but not all of the intelligence–illness association.

Intelligence mediated by entry to safer environments. Intelligence test scores in childhood and youth might be associated with higher educational attainments and, partly thereby, entry to types of employment that are safer. These types of employment might also be better remunerated, leading to less-deprived living conditions. There is partial attenuation of intelligence–health associations by indicators of the person's own adult social class, but the reason for the attenuation is not yet understood (Fig. 2).

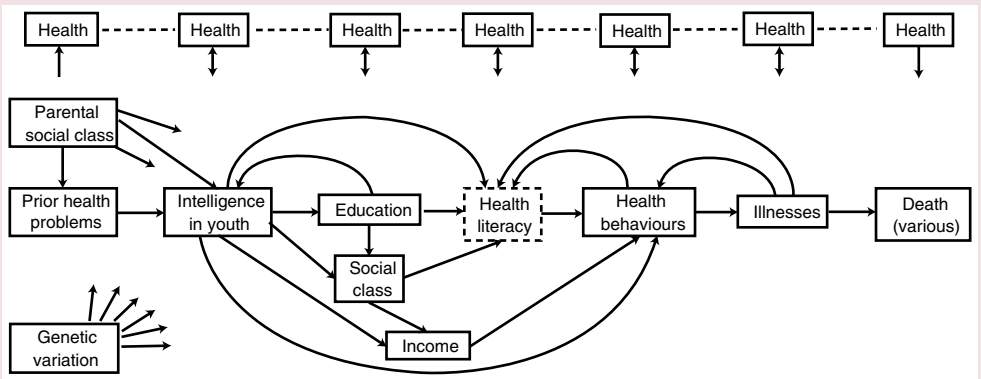

Fig. 2 | Why is higher intelligence in youth associated with better health and living longer?. A diagram to help think about why higher intelligence in youth is associated with living longer, and with diverse indicators of better health in life. The reader is encouraged to suggest some constructs that could be added, removed or changed, and some associations that could be added and/or changed in direction. Here are a few of our comments on the diagram. (1) Many of the constructs (including health outcomes) are partly heritable. There are genetic correlations between some constructs, consistent with the notion that many of the same genetic variants are linked with each of the constructs, and supporting 'system integrity'. Some of the constructs are probably linked to genetic differences via mediated pleiotropy (Box 3). (2) The focus of this piece is how intelligence tested in youth is associated with later health, illnesses and death, but we recognize that there is a reciprocal dynamic association between intelligence and health through life. (3) Health literacy has a dashed outline box because some authors have suggested that it merely assesses cognitive functions by another name[91]. (4) Note the nexus of forward and feedback associations in some parts of the diagram. For example, developing an illness could lead to change in behaviours and becoming more health-literate about that illness. (5) The fact that illnesses and death have only one box each should not be taken to suggest that there is the same series of paths and explanations for each of them. (6) The horizontal line of health boxes tries to represent the fact that the health of the body changes continuously and reciprocally, during the life course, with many of the variables listed here. (7) Parental social class is known to relate to a child's education and eventual occupational social class. It might relate to other outcomes shown here. To draw them all would clutter the diagram; however, adjusting for parental social class rarely attenuates associations between intelligence tested in youth and health and death outcomes.

of intelligence–mortality/health associations after adjusting for education has seen a range of interpretations. To some[21], it is at least partly an over-adjustment, that is, adjusting for education might, to an extent, be removing some intelligence variance, including some shared genetic effects. At an extreme, this is known as 'Everest regression' (attributed to the macroeconomist Garrett Jones: "adjusting for altitude, Everest is room temperature"). To others, the attenuation is a sign of a selection effect. According to this view, there is selection into educational streams based on cognitive performance, but the causal effects on health are via what education gifts the person, not what cognitive resources they had. Thus, some have concluded that the attenuations of intelligence–health associations by education suggest that, "It may not be IQ per se that is directly linked to health, but the conditions of adult life to which IQ

Box 3 | Molecular genetic methods used in cognitive epidemiology

Genome-wide association study (GWAS). A GWAS is used to identify genetic variants associated with a phenotype or disease. These genetic variants (usually SNPs) are used as markers for a region of the genome. A significant association between a genetic variant and a trait is evidence that the region in which the marker is located harbours a variant that might be causally related to the phenotype under investigation.

Heritability. Heritability means the proportion of the variation in a trait measured in a given population at a given time that is accounted for by genetic variation[133]. It can be assessed using behavioural methods, such as twins' data, or molecular genetic methods, such as genome relatedness-based restricted maximum likelihood-single component (GREML-SC)[134,135] and linkage disequilibrium score regression (LDSC)[136].

Genetic correlation. Genetic correlations describe the average genetic effect that is shared between traits. It can be conceptualized as the correlation between the genetic associations of one trait with the genetic associations of another trait. Genetic correlations may be computed using bivariate GREML-SC[112] (the variables must be from the sample sample) or LDSC (which can be done in independent samples, though it copes with sample overlap)[136].

Pleiotropy. The presence of genetic correlations between traits (for example, between intelligence and health traits) can be due to multiple, and non-exclusive, forms of pleiotropy[137]. Genetic correlations can be due to biological pleiotropy, which can take three forms. First, biological, or horizontal, pleiotropy can occur at the level of the allele and describes instances where a single causal variant has two independent effects that act on two phenotypes. Second, two causal variants can have separate effects on two phenotypes, but each of these causal variants is in high LD with the same SNP. This SNP, measuring both independent effects of each of the two causal variants, would show an association with each of the phenotypes. Third, biological pleiotropy can occur at the level of the gene, whereby two causal variants, each associated with different phenotypes, co-localize within the same gene. In addition to these forms of biological pleiotropy, mediated pleiotropy might also account for some of the genetic correlations found between intelligence and health. Mediated, or vertical, pleiotropy occurs in instances where one phenotype is associated with a second phenotype. Any genetic variant that is associated with the first trait will also show association with the second.

Mediated pleiotropy also provides a probable partial explanation for the apparently 'genetic' link between educational attainment, intelligence, and socioeconomic position and health in the UK. One study used a regional GWAS to examine whether the SNP-based heritability for traits, including educational attainment, correlated with systematic differences in geographically clustered alleles that are associated with health, beyond what would be expected from differences in ancestry[138]. It reported that the geographic clustering of alleles was consistent with the hypothesis that regional allele frequencies were influenced by a recent movement of people and that this was most consistent with a migration of individuals with a high polygenic load for education away from areas with low average socioeconomic position. Further studies have also found that the apparently 'genetic' association between intelligence and socioeconomic position (SEP) is most likely to be explained in terms of mediated pleiotropy[139,140] (see also ref. [132]).

Finally, genetic correlations can appear through instances of spurious pleiotropy which can occur because of the misclassification of a phenotype. For example, if the low mood observed in individuals suffering from bipolar disorder is misclassified as major depressive disorder, then this sample contamination could result in a genetic correlation between these two phenotypes. Spurious pleiotropy can also occur in instances where a single SNP is found to be associated with two traits, but this variant is in fact tagging two independent causal variants, each of which is located in a different gene. This is most likely to occur in regions of the genome with high LD. Importantly, because genetic correlations are based on all the SNPs within a data set, multiple forms of pleiotropy might be contributing to any apparent genetic correlation between pairs of traits.

Mendelian randomization. Mendelian randomization (MR) is used to examine the causal effects of one phenotype on another, using genetic data[141,142]. MR is argued to be an example of a natural 'experiment' in which random variation in the exposure of interest (in our case, intelligence) is used to estimate potentially causal effects on outcomes, such as health. The specific combination of an individual's genetic variants is a random draw from each parent's genotype. Therefore, because genetic variation is associated with intelligence differences[95,96], intelligence is viewed, in MR, as, in part, randomly assigned at conception. Furthermore, because an individual's genotype is invariant after conception (ignoring somatic mutation, for now), this frees Mendelian randomization methods from the problems of reverse causation.

In a MR study, SNPs that have attained genome-wide significance are used as instrumental variables for the trait of interest (for example, intelligence). Valid instrumental variables must meet three assumptions: that they are associated with the risk factor under investigation, in this case intelligence (the relevance assumption); that they do not share a common cause with the outcome of interest, in this instance health outcomes (the independence assumption); and, finally, that they do not affect the outcome except through their influence on the risk factor (the exclusion restriction assumption)[116].

Pleiotropy, a genetic variant being associated with multiple traits, represents a potential violation of the exclusion restriction assumption. This can be seen with genetic variants that display biological pleiotropy, for example, in instances where a genetic variant makes independent contributions to both intelligence and health outcomes. However, mediated pleiotropy does not violate this assumption and would be seen in instances where a genetic variant is associated with both intelligence and health outcomes but only through its effect on intelligence.

A further problem for MR is dynastic effects. This describes instances whereby the genotype of the parent, including alleles that are not passed from parent to offspring, influences the phenotype of the offspring ('genetic nurture'), which appears to occur for education[143]. This can take the form of influencing the environment that a child is raised in, including their socioeconomic status. In instances where the environment provided by the parent was the causal factor in health outcomes, this would result in a bias of the causal estimate of intelligence on health outcomes due to dynastic effects, violating the independence assumption[144]. MR analysis conducted within families can however avoid issues arising from dynastic effects[145].

Using the MR method, it is also possible to test for bi-directional relationships where each phenotype is used as the outcome and the exposure. Recent extensions to the MR method include multivariable MR as a means to test the independent causal effects of two highly correlated phenotypes (for example, intelligence and education) on an exposure, such as health outcomes[119].

predisposes"[62]. In fact, this is similar to one of the suggestions made in 2001[1] (Box 2), that is, that childhood intelligence might predict entry to safer environments. Others have suggested, more strongly, that the attenuations, "highlight structural inequalities over individual capabilities when studying health behaviors"[14]. In a different way, it has been suggested that one does not need to be intelligent to obtain its health benefits. Rather, one should 'phenocopy' intelligent people, that is, by noticing and copying what smart people do with respect to health behaviours, one might stay healthier and live longer[5].

Those who suggest that education (as an environmental variable) might be the cause (rather than its correlate, intelligence) sometimes recount childhood environmental circumstances that might explain some of the intelligence–health associations. Thus we read the suggestion that, "early conditions, ranging from foetal programming to parental interest in child's education… influence both IQ and subsequent risk of disease… [IQ] remains a bystander in the causal drama"[62]. Whereas these suggestions should be taken seriously and tested empirically, we note two things that we develop below. First, there are massive twin-based and DNA-based genetic studies showing that educational attainments are substantially heritable and highly genetically correlated with intelligence, and that they are also modestly genetically correlated with some health outcomes[59,60]. Second, there is possible partial genetic confounding of some of the variance in these 'environmental' circumstances[63,64].

Whereas many intelligence–health studies examine possible confounding and mediation by education and childhood and adult socioeconomic position, less has been done to investigate moderation/interaction effects. Analyses of the UK's 1970 British Cohort Study and 1958 National Child Development Study (NCDS) found that intelligence tested in childhood moderated the associations between social disadvantage and all-cause mortality (NCDS only), self-rated health and psychological distress[65]. The moderation was such that the health variables' associations with social disadvantage were weaker in those with higher intelligence. It is possible that childhood intelligence might also weaken the association between genetic predisposition to type 2 diabetes and glycaemic control in older age. In the Lothian Birth Cohort 1936, those with higher prior intelligence were less likely to have higher HbA1c for a given type 2 diabetes polygenic score[66]. This is an instance of intelligence's acting as a possible environmental moderator of the association between genetic predisposition and a health outcome; more simply, it is possible that higher intelligence makes a contribution to freeing people from their genetic predisposition to illness. Mendelian randomization analysis of the UK Biobank sample found that there is lower risk of smoking, independent of any association between intelligence and smoking, in people with greater educational attainment[67].

The last decade's results make it difficult to separate the contributions made by intelligence and education (and adult social class) to later health outcomes. Statistical mediation of intelligence–health associations (which education partially achieves) does not afford the simple conclusion that education is therefore an important mechanism through which intelligence contributes to health, though, of course, it is possible.

Health behaviours and health literacy. An influential suggestion about one possible route for intelligence to be associated with health outcomes is via health-related behaviours (Box 2). Smoking, diet, alcohol consumption and exercise are behaviours related to health and illness. As part of filling in the association between intelligence and mortality, studies have examined longitudinal associations between intelligence in youth and later-assessed health behaviours. Table 4 provides examples of these associations, related to five health behaviours (alcohol drinking, diet, exercise, oral care and smoking) from six different studies[68–73]. In a follow-up study of the USA's National Longitudinal Survey of Youth 1979, a standard deviation higher intelligence score between about 18 and 22 years was associated at about age 50 with: having fewer sugary drinks in the last week, being more able to engage in vigorous cardiovascular exercise and strength training and using dental floss[68]. Alcohol was more complex; higher intelligence test scorers had fewer alcohol-drinking sessions in the past month in which six drinks were taken, though they drank alcohol more frequently, and more overall in the previous month. Twenty-year follow-up studies of the 1970 British Cohort Study found that those with a higher childhood intelligence score were more likely to be vegetarian[70], ate fruit more frequently[71], ate chips (French fries) less frequently[71] and were more likely to have given up smoking[73]. A 33-year follow-up study in Denmark found that higher intelligence in youth was associated with a 33% lower risk of smoking[72]. Table 4 shows that all of these associations were substantially attenuated after adjustment for markers of socioeconomic status.

A three-cohort study including the Wisconsin Longitudinal Study from the USA, and National Survey of Health and Development (NSHD; the UK's 1946 birth cohort) and National Child Development Study (the UK's 1970 birth cohort) found that higher cognitive test scores from adolescence were associated with not smoking and less physical inactivity in midlife[14]. All of these associations were rendered non-significant, and were substantially or fully attenuated after adjusting for whether or not subjects had achieved a university degree.

As stated above, the relationship between intelligence in early life and subsequent use of alcohol is probably complex. Evidence from cohorts in both the USA and the UK suggests that higher intelligence is associated with an increased likelihood of being an alcohol drinker rather than a non-drinker as an adult[68,69]. Higher intelligence has also been associated in UK National Birth Cohorts with drinking more frequently and having a higher intake of alcohol[69]; however, in Swedish men, the reverse pattern was seen[74]. Higher adolescent cognitive scores in the NSHD were associated with drinking more alcohol at midlife[14]. This survived adjustment for university degree status, with little attenuation. People with higher intelligence in childhood tended to drink more alcohol, at moderate levels, at age 70 in the Lothian Birth Cohort 1936[75]. In part, this might be because some unhealthy people follow medical advice not to consume alcohol. Problem drinking seems to have a different association with intelligence. In cohorts from both the USA and Europe, people with higher early-life intelligence were found to be less likely to engage in risky alcohol use as indicated by less binge drinking, fewer hangovers and lower risk of being hospitalized or dying from an alcohol-related illness[76–79].

Among people who grew up at a time when the dangers of smoking were not yet recognized, there was no association between early-life intelligence and the likelihood of ever having smoked, although it was associated with quitting later in life[80]. However, in cohorts exposed from youth to public health information about smoking, higher intelligence tends to correlate with a lower likelihood of being a current smoker and greater likelihood of quitting[72,81,82].

Contrary to the above evidence of less physical inactivity among those with higher intelligence, a Finnish study with data on objectively measured activity found that higher childhood cognitive ability was associated with greater physical inactivity in young adults, perhaps because many of them were still studying[83].

Most of the above-mentioned health behaviours are factors associated with illness outcomes in studies of mostly healthy people. Intelligence might also relate to people's behaviours when illness has occurred. A study of Swedish men found that intelligence tested at conscription at 18–20 years was associated with 2-year adherence to statin medication after a first myocardial infarction at age under 60 (HR 1.14, 95% CI 1.02, 1.27)[84]. The importance of this example is that, although it is tempting and simpler to draw static box and

arrow models (say, intelligence → health behaviours → illness), in fact, the life course almost certainly involves dynamic associations. For example, developing an illness might elicit individual differences in health behaviours that were not apparent previously, and some of those individual differences might be related to intelligence (Box 2).

A special mention is required for the concept of health literacy and whether it is an intervening, distinct and causal variable in intelligence's and/or education's associations with illness and mortality. A review found that low health literacy was associated with many health outcomes, including greater use of services, less screening uptake, poorer interpretation of health information, less optimal medication use, worse health status and earlier death[85].

If it has construct validity and is also related to intelligence, health literacy is obviously relevant in cognitive epidemiology. Health literacy's conceptual structure and how it might influence health-related actions were reviewed[86]. As an example, in the 7,000+ participants of the English Longitudinal Study of Ageing (ELSA), low scores on a health literacy test (comprising just four reading-comprehension-based items to do with understanding instructions on a medicine bottle) were associated with greater mortality risk, after adjusting for socioeconomic position and some health behaviours[87]. This was replicated in ELSA with a longer follow-up[88]. Low scores on two out of three tests of health literacy in the 700+ 73-year-olds of the Lothian Birth Cohort 1936 (LBC1936) predicted earlier mortality[89]. These associations were attenuated to non-significance after adjusting for concurrent fluid cognitive ability (intelligence) but not intelligence assessed in childhood. In the same LBC1936 sample, better scores on three tests of health literacy were significantly associated with health markers such as walking speed, lung function, grip strength, BMI (lower) and number of teeth[90]. However, almost all associations were accounted for by intelligence measured at age 11, education, occupational class and concurrent cognitive function.

Despite its large number of associations with health outcomes, there is discussion as to whether 'health literacy' is a distinct construct, or mostly just cognitive abilities by another name. One student-based study found that three so-called health literacy tests loaded on different domains of cognitive function, did not form a coherent health literacy factor, and had little incremental validity on health outcomes beyond measures of intelligence[91]. The authors suggested that "measures of health literacy are simply domain-specific contextualized measures of basic cognitive abilities". The question about whether health literacy is an example of the jangle fallacy[92] is moot.

Genetic variation. For those unfamiliar with statistical-genetic methods and terminology, we provide short descriptions in Box 3. Intelligence differences and health differences are partly heritable traits. For intelligence test scores, using behavioural methods (that is, pedigree, family or twin-based studies), heritability is ~50% when studies of all ages are included; it is lower in childhood and higher in adulthood[93–95]. Using molecular-genetic methods, SNP-based heritability of intelligence in adulthood is ~25% if only common variants are used to make the estimate[96–98], and higher if rarer variants are included[99]. The difference in the estimates is because behavioural and molecular-genetic methods differ with regard to the genetic variants they capture. For example, molecular-genetic methods using genome-wide association (GWAS) data typically capture only relatively common genetic variants; more technically, they capture additive variance associated with genetic variants in linkage disequilibrium (LD) with common single-nucleotide polymorphisms (SNPs)[100]. Pedigree- and family-based methods can capture causal variants from across the allele frequency spectrum.

Physical health, mental health, health behaviours and mortality are partly heritable. Self-rated health's heritability using molecular genetic methods was estimated at 13% (s.e. 0.6%)[101], and its behavioural genetic methods-based heritability at 32.5% (95% CI 28.8%, 36.1%)[102]. Subjective wellbeing's heritability using molecular genetic methods was estimated at 4.7% (s.e. 0.4%)[103], and its behavioural genetic methods-based heritability at about 40% (ref. [104]). Genetic influences are also evident for health-related variables such as smoking[105], and all-cause mortality[106]. Finding that intelligence and also health, health behaviours and mortality are partly heritable affords the investigation of whether they are partly associated with the same genetic variants.

In a pedigree-based analysis of the Generation Scotland cohort, additive genetic effects accounted for 81% of the phenotypic correlation between intelligence and smoking status, 80% of the correlation between intelligence and fruit and vegetable intake and 46% of the level of physical activity outside of work[107]. Analysis of four independent twin studies found that genetic factors accounted for between 84% and 95% of the phenotypic intelligence–longevity correlation[108].

Molecular genetic data from GWASs has provided information about the nature of the relationship between intelligence and physical health, illness and mortality[109], and between intelligence and mental health[110]. This is due to large GWASs now having the statistical power to identify loci associated with intelligence[96–98]. Furthermore, GWASs of educational attainment (used by some as a proxy for intelligence) have attained a sample size in excess of one million[60]. These GWASs enable a comparison of the genetic loci associated with intelligence (and education[96,111]) with those genetic loci associated with health, health behaviours and longevity. Furthermore, techniques exist to examine whether genetic variation at multiple single-nucleotide polymorphisms is associated with more than one phenotype. These analyses can therefore be used to determine whether intelligence and health are correlated because genetic variation associated with intelligence is also partly the same genetic variation associated with health and related phenotypes.

Molecular genetic correlations capture overlapping genetic variation accounting for part of any phenotypic associations. Thus, associations between intelligence and physical and mental health, as well as with longevity, appear to be accounted for, in part, by shared associations with genetic variants[96,109,110]. Specifically, intelligence has negative genetic correlations with, for example, coronary artery disease, type 2 diabetes, obesity and Alzheimer's disease, and positive correlations with FEV1 and self-rated health.

The phenotypic link between the age of death for all-cause mortality and intelligence is to some extent accounted for by shared associations with genetic variants, as evidenced by their genetic correlation ($r_g = 0.37$, s.e. 0.06, $P = 0.009$)[96]. However, the genetic signal for intelligence in this computation was obtained from samples in adulthood, sometimes in older age. We should ask whether it would make a difference if the genetic signal for intelligence had come from children because, in cognitive epidemiology, we are primarily trying to explain phenotypic associations between childhood or young-adult intelligence, health and death. Many of the same genetic variants are, in fact, associated with childhood intelligence and older-age intelligence as evidenced by a strong genetic correlation of $r_g = 0.62$ (s.e. 0.22) between intelligence assessed at age 11 years and intelligence measured in the same individuals at age 70 or more[112]. When examining across large old and young cohorts (that is, the 'young' intelligence test scores and the 'old' intelligence test scores are not from the same individuals), the genetic correlation between intelligence in childhood older age is $r_g = 0.71$ (s.e. 0.10)[113]. Both of these studies, each using different methods and data to derive genetic correlations, support a conclusion that many of the same genetic variants that are associated with childhood intelligence are also associated with intelligence in older age. One study, using data from two different GWASs, found a genetic correlation of 0.35 (s.e. 0.14, $P = 0.01$) between childhood intelligence and longevity[114]. Two points should be noted about it: first, the longevity

GWAS was performed on the phenotype of parental longevity, and second, the GWAS of childhood intelligence was, for this type of analysis, relatively small (N ~ 12,000). Using education instead of intelligence, many of the same genetic correlations can be recovered for longevity and physical health outcomes. Overall, the behavioural and molecular genetic correlations with physical health indicate a consistent pattern that some of the genetic variants associated with a higher level of intelligence are also associated with a higher level of physical health, fewer instances of disease and being less likely to engage in some behaviours that put one at risk of illness (for example, smoking, poor diet and lack of exercise).

Some mechanisms by which the same genetic variants might be associated with different phenotypes (intelligence and health, for example) are described in Box 3. Evidence of a shared genetic association, be it from behavioural or molecular methods, is not, on its own, informative as to the existence of a causal relationship between traits. Indeed, genetic loci are likely to show an association between two traits if those two traits are phenotypically linked (Box 3). In addition to the difficulty in extracting meaning from genetic correlations, a further limitation lies, potentially, in the samples used. Data sets such as UK Biobank, which is included in many GWAS, suffer from ascertainment bias whereby healthier, more educated individuals are over-represented[115]. This might bias genetic correlations.

Progress in asking about causality between traits is being made with the Mendelian randomization (MR) method. MR is not used to identify the presence of a genetic effect on a trait but, rather, under a number of assumptions, uses genetic variation as a natural 'experiment' to investigate putative causal relationships between phenotypic traits. MR can be used to examine potential causal relations as it can, under certain assumptions, overcome unmeasured confounding in observational data[116]. However, as with any technique, the findings garnered through the use of MR depend on a number of assumptions being met. These are described in Box 3.

This ability of MR studies to test for causal relationships between measures of cognitive ability and physical health, mental health and mortality makes it even more important to be able to ascertain correctly the independent contributions of intelligence and of education. The importance of this is apparent when one considers the possibilities of interventions intended to improve health: it is arguably a simpler matter to increase the school leaving age than it is to increase intelligence.

Using univariate MR analyses, intelligence and education appear to be causal factors in the aetiology of Alzheimer's disease. A standard deviation higher score, for intelligence and education, respectively, resulted in a 35% (95% CI 25–43%) and a 37% (95% CI 23–49%) lower Alzheimer's disease risk[117]. However, a multivariate MR analysis found that there is little evidence that education makes a causal contribution to Alzheimer's disease that is independent of the contribution from intelligence[118]. In contrast, intelligence did make a causal contribution to Alzheimer's disease that was independent of education, where a standard deviation higher intelligence test score was associated with 38% (95% CI 12–56%) lower odds of Alzheimer's disease.

When examining health phenotypes, it has been suggested that intelligence makes genetic contributions independently of those made by education, with inferred positive causal effects on socioeconomic position (measured using income) and negative effects on physical activity[119]. In the same study, education was suggested to make independently-of-intelligence genetic contributions to health, with inferred positive causal effects identified for socioeconomic position (measured using income) and negative causal effects identified for smoking, BMI and sedentary behaviour. Overall, the results of multivariable MR to date suggest that both intelligence and education make independent contributions to health.

The results of this latter study[119] contrast with those of ref. [117] insofar as education, rather than intelligence, had the greater implied direct causal genetic effect on health differences. This is consistent with the idea that intelligence is linked with health as it is a predictor of access to safer environments through the association of intelligence with education, or perhaps as an indicator of future, learned healthy behaviours (Box 2). These MR studies highlight that the relationship between intelligence and health outcomes is likely to differ depending on the specific health outcomes examined. Furthermore, the possible explanations listed in Box 2 are unlikely to act in isolation. Different combinations of these four, and possibly other, explanations will be needed to describe the relationship between intelligence and any health outcome. Finally, whereas both of the above-mentioned MR studies examined the total and direct effects of intelligence and education on health, they have not quantified the total indirect effect (the genetic overlap between intelligence and education). This hampers interpretations of how intelligence and education might be causally related to health. In addition, by examining only the direct effects, any overall causal effect of intelligence on health outcomes may be underestimated. This would occur should causal effects of intelligence on health outcomes also be shared with education.

Conclusions and implications

The accumulated findings of almost two decades of cognitive epidemiology research have afforded a fairly panoptic description of how higher intelligence associates (modestly) with better health and later death. Confounding expectations that there might be specificity in the causes of death, the illnesses, the health biomarkers and the health behaviours with which intelligence is associated, in fact it has widespread associations. There are notable exceptions, for example, in deaths from non-smoking-related cancers not being associated with intelligence. Another interesting exception is the association with alcohol drinking; in those cultures yet studied, people with higher intelligence tend to drink slightly more and slightly more regularly, but report fewer problems with drinking.

Intelligence's associations with health should be seen as something to be explained, that is, as an explanandum rather than explanans. The advance in the last ten years is that we are now clearer on what needs to be explained, as well as having some partial explanations. There has been a substantial amount of phenotypic mediation, to find out those variables that account for some or all of intelligence's health links. The results point to education and adult social class (and to health behaviours such as smoking). Testing whether these are mostly just outcomes of intelligence (that is, to some extent statistical over-adjustments) or the key factors (for example, what matters is to be educated, whether or not one is a high intelligence test scorer) has taken a genetic turn, with large-scale genetic correlations and Mendelian randomization studies. However, one must remember that intelligence, education and health variables are only partly heritable, and that the genetic correlations account for only a part of any phenotypic associations. Therefore, potentially dazzling as they might be in study size and analytical complexity, genetic studies are addressing only part of the intelligence–health correlation puzzle.

Among the implications of the research are the personal and societal returns to improving childhood predictors of later-life health and other outcomes. Linkages between intelligence in youth and health and death outcomes are remarkable enough, but some nations' data linkages extend to what are called non-health administrative data, such as censuses, care registers, justice records, etc. For example, the Scottish Mental Surveys have been linked to census data, to reveal associations between childhood intelligence and various functional limitations and how these change from age 55 to 75 (ref. [120]). These additional types of linkages enhance the outcomes and covariates that can be studied in cognitive epidemiology. With even more linkages in place, a longitudinal follow-up analysis of New Zealand's Dunedin study found that those with lower childhood intelligence were more

Table 4 | Intelligence's associations with health behaviours

Health behaviour	Reference	Cohort	IQ test	Number in study sample	Number of outcomes	Follow-up time (years)	Age- and sex-adjusted effect size (95% CI)[1]	Multivariate-adjusted effect size (95% CI)[1]	Covariates included apart from age/sex
Alcohol									
Drunk alcohol in last 30 days	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	5,336	3,115	-	OR 1.58 (1.47, 1.69), per SD higher IQ	OR 1.23 (1.14, 1.34) per SD higher IQ	Childhood and adult SES
Drinks alcohol more frequently	Batty et al.[69]	1970 British Cohort Study	British Ability Scales	Male 3,040 Female 2,896	-	20	Male OR 1.36 (1.29, 1.45) per SD higher IQ; female OR 1.54 (1.43, 1.66)	Male OR 1.18 (1.10, 1.27) per SD higher IQ; female OR 1.26 (1.16, 1.36)	Childhood and adult SES, income, qualifications, whether has children
Had six or more drinks on one occasion in last 30 days	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	3,112	801	-	OR 0.67 (0.61, 0.74) per SD higher IQ	OR 0.83 (0.74, 0.94) per SD higher IQ	Childhood and adult SES
Dietary habits									
Vegetarian	Gale et al.[70]	1970 British Cohort Study	British Ability Scales	8,170	366	20	OR 1.42 (1.28 to 1.59) per SD higher IQ	OR 1.20 (1.06, 1.36) per SD higher IQ	Childhood and adult SES, qualifications
Had sugary drinks in last week	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	5,341	2786	-	OR 0.75 (0.71 to 0.80) per SD higher IQ[2]	OR 0.96 (0.89 to 1.03) per SD higher IQ	Childhood and adult SES
Eats fruit more frequently	Batty et al.[71]	1970 British Cohort Study	British Ability Scales	8,282	-	20	OR 1.30 (1.25, 1.35) per SD higher IQ	OR 1.09 (1.03, 1.14)	Childhood and adult SES, income, qualifications
Eats chips more frequently	Batty et al.[71]	1970 British Cohort Study	British Ability Scales	8,282	-	20	OR 0.74 (0.71, 0.77) per SD higher IQ	OR 0.91 (0.87, 0.97)	Childhood and adult SES, income, qualifications
Exercise									
Able to engage in vigorous cardiovascular activity	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	5,151	4,963	-	OR 1.67 (1.41, 1.99) per SD higher IQ	OR 1.33 (1.08, 1.65) per SD higher IQ	Childhood and adult SES
Able to engage in strength training	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	4,989	4,776	-	OR 1.61 (1.37, 1.90) per SD higher IQ	OR 1.40 (1.14, 1.71) per SD higher IQ	Childhood and adult SES
Oral care									
Use dental floss	Wraw et al.[68]	National Longitudinal Survey of Youth 1979	Armed Forces Qualification Test	5,093	4,010	-	OR 1.47 (1.35, 1.59) per SD higher IQ	OR 1.18 (1.07, 1.30) per SD higher IQ	Childhood and adult SES
Smoking									
Current smoker	Osler M et al.[72]	Metropolit cohort, men born 1953	Børge Prien Prøve	6,292	2,287	33	Unadjusted OR 0.67 (0.63, 0.70) per SD increase in IQ	OR 0.82 (0.71, 0.90)	Father's SES, education, divorced by 30, in labour market at 22
Given up smoking	Batty et al.[73]	1970 British Cohort Study	British Ability Scales	8,171	1,550	20	OR 1.25 (1.18, 1.34) per SD increase in IQ	OR 1.02 (0.93, 1.11) per SD increase in IQ	Childhood and adult SES, income, qualifications

[1]Sex included where appropriate, that is, men and women analysed together. [2]Also adjusted for ethnicity

likely, as adults, to be in a 'high-cost economic burden group' for social welfare, fatherless children, smoking, excess weight, hospital stays, prescription fills and crime[121]. It is notable, however, that, in their multivariable models, other variables often nudged intelligence to below significance levels.

Therefore, with respect to the implications, we should ask: how can we make people healthier and happier overall, and reduce inequalities? In asking that, we may rehearse what the regularities are, that is that, in the studies described herein, intelligence–health associations are substantially attenuated by education and other indicators of adult socioeconomic position. Therefore, helpful things might be to optimize cognitive development in the early years, to raise educational attainments for all, to make health literacy messages accessible and widespread, to improve workplace and home conditions for all and/or to ensure that people have more and more equal incomes. It has been suggested that childhood intelligence is one of a number of personal history predictors of later ill health, accelerated ageing and earlier mortality that might be used to identify those most in need for recruitment into so-called healthspan-extension trials[53]. For now, focussing on intelligence and education and the still-unsettled causal story they have with health inequalities, it seems prudent to promote more and better education and health literacy for all.

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Competing interests

The authors declare no competing interests.

Additional information

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